



**MONASH** University

**Polypharmacy in the heart failure patient:  
Are all prescribed drug classes required?**

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# Abstract

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**Background and aims:** Heart failure (HF) is a complex disease process with high mortality and high costs to the community. Major inroads have been made in reducing the high morbidity and mortality associated, largely by the use of drug therapies that focus on key neurohormonal systems activated in HF with demonstrated mortality benefits. Other therapies are also employed in the HF setting that do not have mortality benefits, and contribute to polypharmacy in HF patients. Polypharmacy, defined herein as the use of five or more prescription medications, is increasing in HF patients. This thesis aims to explore the issue of polypharmacy in the HF patient, and whether all prescribed drug classes are required.

**Methods:** A systematic review of the medical literature on drug withdrawal trials was performed to identify which drugs could and could not be withdrawn in HF. Three randomised clinical trials were conducted investigating the effect of withdrawing digoxin, aspirin or statin in stable HF patients. Qualitative methods were used to explore attitudes of clinician prescribers and HF patients to medications, looking in particular at withdrawal of medications.

**Results:** This thesis examined the available data on medication withdrawal in HF patients and translated it into practical recommendations for prescribers; demonstrated that with contemporaneous background HF therapies, withdrawal of digoxin worsens HF clinical status and that withdrawal of statins or aspirin does not; found that HF patients with polypharmacy are largely not dissatisfied with the number of medications they take, and that prescribing clinicians recognise polypharmacy as important but address it infrequently in clinical practice.

**Conclusions:** It is expected that polypharmacy will increase in HF patients. This research provides an evidence base with which clinicians can address polypharmacy in HF in their clinical practice.

# Declaration

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This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.



## Publications during enrolment

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1. **Hopper I**, Kotecha D, Chin KL, Mentz RJ, von Lueder TG. Comorbidities in heart failure: are there gender differences? *Current Heart Failure Reports*. Submitted manuscript.
2. **Hopper I**, Skiba M, Windebank E, Brack J, Tonkin A, Krum H. Polypharmacy in heart failure – is reducing medication safe? *International Journal of Cardiology*. 2015. In press.
3. Power A, Graudins LV, McLean C, **Hopper I**. Probable fenofibrate-induced acute generalized exanthematous pustulosis. *American Journal of Health Systems Pharmacy*. 2015. In press.
4. Graudins L, Chen F, **Hopper I**. Warfarin Brands. Letter to the editor. *Australian Prescriber*. 2015; 38: 150-1.
5. Krum H, **Hopper I**. The ongoing evolution of optimal endpoints for heart failure trials. *Journal of the American College of Cardiology: Heart Failure*. 2015; 3: 615-7.
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18. **Hopper I**, Billah B, Skiba M, Krum H. Prevention of Diabetes and Reduction in Major Cardiovascular Events in Studies of Subjects with Impaired Glucose Tolerance: Meta-Analysis of Randomized Controlled Clinical Trials. *European Journal of Cardiovascular Prevention and Rehabilitation* 2011; 18: 813-23.

# Thesis including published works General Declaration

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I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes three original papers published in peer reviewed journals and one unpublished publication. The core theme of the thesis is Polypharmacy in Patients with Heart Failure. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the School of Public Health and Preventive Medicine under the supervision of Professor Henry Krum.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

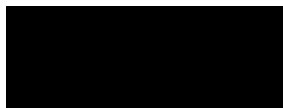
In the case of chapters 2, 3 and 4, my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status*	Nature and extent (%) of students contribution
2	Can medications be withdrawn in patients with stable chronic heart failure? Systematic review and meta-analysis.	Published	95%
3	Digoxin withdrawal worsens clinical status in heart failure patients receiving optimal contemporaneous therapy – a randomised controlled trial.	Published	85%
4	Polypharmacy in heart failure – is reducing medications safe?	Accepted	95%

\* e.g. 'published' / 'in press' / 'accepted' / 'returned for revision'

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

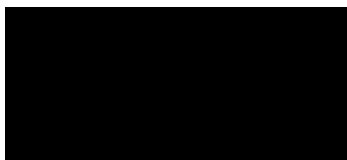
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**Date: November 2015**

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student and co-authors' contributions to this work.

**Main Supervisor signature:**



**Date: November 2015**

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# Table of Contents

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<b>Abstract .....</b>	<b>iii</b>
<b>Declaration .....</b>	<b>iv</b>
<b>Publications during enrolment.....</b>	<b>v</b>
<b>Thesis including published works General Declaration .....</b>	<b>vii</b>
<b>Acknowledgements.....</b>	<b>ix</b>
<b>Table of Contents.....</b>	<b>xi</b>
<b>List of Tables.....</b>	<b>xiv</b>
<b>List of Figures .....</b>	<b>xv</b>
<b>List of Abbreviations.....</b>	<b>xvii</b>
<b>Chapter 1 : Introduction and literature review.....</b>	<b>1</b>
<b>1.1 General introduction .....</b>	<b>1</b>
<b>1.2 HF definition .....</b>	<b>2</b>
<b>1.3 HF classification .....</b>	<b>2</b>
<b>1.4 Types of HF .....</b>	<b>3</b>
<b>1.5 Diagnosis of HF.....</b>	<b>3</b>
<b>1.6 Epidemiology of HF.....</b>	<b>4</b>
<b>1.7 Prevalence .....</b>	<b>4</b>
<b>1.8 Incidence.....</b>	<b>5</b>
<b>1.9 Hospital admissions .....</b>	<b>5</b>
<b>1.10 Costs.....</b>	<b>6</b>
<b>1.11 Risk factors for HF.....</b>	<b>6</b>
<b>1.12 Non-cardiac comorbidities.....</b>	<b>7</b>
<b>1.13 Prognosis .....</b>	<b>8</b>
<b>1.14 Pathophysiology of HFREF.....</b>	<b>9</b>
1.14.1 The Frank-Starling mechanism .....	9
1.14.2 Neurohormonal activation .....	10
1.14.3 Ventricular remodelling .....	11
<b>1.15 Pathophysiology of HFPEF .....</b>	<b>11</b>
<b>1.16 Therapeutics in HF.....</b>	<b>11</b>
<b>1.17 Non-pharmacological treatments.....</b>	<b>12</b>
<b>1.18 Drugs conferring a mortality benefit.....</b>	<b>12</b>
1.18.1 RAAS inhibitors .....	13
1.18.2 Beta-adrenergic receptor antagonists (beta-blockers) .....	15
1.18.3 Mineralocorticoid Receptor Antagonists.....	15
1.18.4 Angiotensin-neprilysin inhibition.....	16
1.18.5 Other treatments with mortality benefits .....	16
<b>1.19 Therapeutics in HF – drugs not conferring a mortality benefit.....</b>	<b>16</b>
1.19.1 Digoxin.....	17
1.19.2 Aspirin .....	17
1.19.3 HMG CoA Reductase inhibitors (Statins).....	18
1.19.4 Loop diuretics .....	18

1.19.5	Other treatments without mortality benefit .....	18
<b>1.20</b>	<b>Drug therapies in HFPEF .....</b>	<b>19</b>
<b>1.21</b>	<b>Polypharmacy in heart failure .....</b>	<b>19</b>
<b>1.22</b>	<b>Thesis aims and questions.....</b>	<b>21</b>
<b>Chapter 2 : Can medications be safely withdrawn in patients with stable chronic heart failure?</b>		
.....		22
<b>Declaration for Thesis Chapter 2 .....</b>		<b>22</b>
<b>2.1</b>	<b>Abstract .....</b>	<b>24</b>
<b>2.2</b>	<b>Introduction .....</b>	<b>25</b>
<b>2.3</b>	<b>Methods .....</b>	<b>26</b>
2.3.1	Trial Design .....	26
2.3.2	Agents Investigated .....	26
2.3.3	Outcomes Evaluated.....	26
2.3.4	Search Methodology.....	26
2.3.5	Statistical Methods .....	27
<b>2.4</b>	<b>Results.....</b>	<b>28</b>
2.4.1	Renin-Angiotensin-Aldosterone System inhibitors.....	30
2.4.2	Beta-blockers.....	31
2.4.3	Digoxin .....	32
2.4.4	Diuretics .....	37
2.4.5	Vasodilators.....	38
2.4.6	Ancillary agents used in HF .....	38
2.4.6.1	Aspirin .....	38
2.4.6.2	HMG CoA Reductase inhibitors (Statins).....	39
<b>2.5</b>	<b>Discussion .....</b>	<b>39</b>
<b>2.6</b>	<b>Conclusion .....</b>	<b>43</b>
<b>Chapter 3 : Digoxin withdrawal worsens clinical status in stable heart failure patients receiving optimal contemporaneous therapy – a randomised controlled trial .....</b>		<b>44</b>
<b>Declaration for Thesis Chapter 3.....</b>		<b>44</b>
<b>3.1</b>	<b>Abstract .....</b>	<b>47</b>
<b>3.2</b>	<b>Introduction .....</b>	<b>48</b>
<b>3.3</b>	<b>Methods .....</b>	<b>48</b>
<b>3.4</b>	<b>Results.....</b>	<b>50</b>
<b>3.5</b>	<b>Discussion .....</b>	<b>59</b>
<b>3.6</b>	<b>Conclusion .....</b>	<b>62</b>
<b>Chapter 4 : Polypharmacy in heart failure – is reducing medications safe? .....</b>		<b>63</b>
<b>Declaration for Thesis Chapter 4.....</b>		<b>63</b>
<b>4.1</b>	<b>Abstract.....</b>	<b>66</b>
<b>4.2</b>	<b>Introduction .....</b>	<b>67</b>
<b>4.3</b>	<b>Methods .....</b>	<b>67</b>
<b>4.4</b>	<b>Aspirin withdrawal results .....</b>	<b>68</b>
<b>4.5</b>	<b>Statin withdrawal results.....</b>	<b>72</b>
<b>4.6</b>	<b>Discussion .....</b>	<b>75</b>
<b>4.7</b>	<b>Conclusion .....</b>	<b>77</b>
<b>Chapter 5 : Attitudes of patients and prescribing clinicians to polypharmacy and medication withdrawal in heart failure.....</b>		<b>78</b>



<b>Declaration for Thesis Chapter 5</b> .....	<b>78</b>
<b>5.1 Abstract</b> .....	<b>79</b>
<b>5.2 Introduction</b> .....	<b>80</b>
<b>5.3 Methods</b> .....	<b>81</b>
5.3.1 Design of the survey .....	81
5.3.2 Study Setting .....	81
5.3.3 Participants .....	82
5.3.4 Administration .....	82
5.3.5 Statistical analysis .....	83
<b>5.4 Results</b> .....	<b>83</b>
5.4.1 Patients .....	83
5.4.1.1 Patient satisfaction with medications .....	83
5.4.1.2 Ceasing medications .....	85
5.4.2 Prescribing clinicians .....	85
5.4.2.1 Prescribing practice .....	86
5.4.2.2 Prescribing priorities .....	87
<b>5.5 Discussion</b> .....	<b>89</b>
<b>5.6 Conclusion</b> .....	<b>91</b>
<b>Chapter 6 : Conclusions and future directions</b> .....	<b>92</b>
<b>Bibliography</b> .....	<b>96</b>
<b>Appendices</b> .....	<b>110</b>
<b>Appendix 1</b> .....	<b>111</b>
<b>Appendix 2</b> .....	<b>128</b>
<b>Appendix 2.1</b> .....	<b>129</b>
<b>Appendix 2.2</b> .....	<b>141</b>
<b>Appendix 2.3</b> .....	<b>149</b>
<b>Appendix 2.4</b> .....	<b>153</b>
<b>Appendix 3</b> .....	<b>162</b>
<b>Appendix 3.1</b> .....	<b>165</b>
<b>Appendix 3.2</b> .....	<b>176</b>
<b>Appendix 3.3</b> .....	<b>188</b>
<b>Appendix 3.4</b> .....	<b>197</b>
<b>Appendix 3.5</b> .....	<b>205</b>
<b>Appendix 3.6</b> .....	<b>218</b>
<b>Appendix 3.7</b> .....	<b>226</b>
<b>Appendix 3.8</b> .....	<b>232</b>
<b>Appendix 3.9</b> .....	<b>235</b>
<b>Appendix 3.10</b> .....	<b>239</b>
<b>Appendix 3.11</b> .....	<b>245</b>
<b>Appendix 3.12</b> .....	<b>250</b>
<b>Appendix 3.13</b> .....	<b>278</b>
<b>Appendix 3.14</b> .....	<b>280</b>
<b>Appendix 3.15</b> .....	<b>283</b>

# List of Tables

---

Table 2.1 – Characteristics of included studies.....	29
Table 2.2 – Digoxin withdrawal trials: meta-analysis results .....	34
Table 3.1 – Baseline characteristics .....	53
Table 3.2 – Cardiac dimensions and functions by echocardiography.....	58
Table 5.1 – Patient and prescribing clinician rating of importance of prescribing issues.....	88

# List of Figures

---

Figure 1.1 – Heart failure and oedema prevalence, by age and sex, 2007-2008. Source: Australian Institute of Health and Welfare. ....	5
Figure 1.2 – Heart failure and cardiomyopathy death rates in Australia, by sex, 1987-2007. Source: Australian Institute of Health and Welfare.....	8
Figure 1.3 - Heart failure and cardiomyopathy death rates, by age and sex, 2007. Source: Australian Institute of Health and Welfare. ....	9
Figure 1.4 – Pathophysiological mechanisms of heart failure and major sites of drug action. From Brunton et al. Goodman & Gilman’s The Pharmacological Basis of Therapeutics 12 <sup>th</sup> ed. Reproduced with permission from McGraw-Hill Education. ....	13
Figure 1.5 – The renin-angiotensin-aldosterone axis. From Brunton et al. Goodman & Gilman’s The Pharmacological Basis of Therapeutics 12 <sup>th</sup> ed. Reproduced with permission from McGraw-Hill Education. ....	14
Figure 2.1 – Study flow diagram.....	28
Figure 2.2 – Heart failure hospitalisations: digoxin withdrawal versus digoxin continuation.....	35
Figure 2.3 – Heart rate: digoxin withdrawal versus digoxin continuation. ....	35
Figure 2.4 – Funnel plot of digoxin withdrawal versus digoxin continuation for mortality, demonstrating no publication bias.....	36
Figure 3.1 – CONSORT Flow Diagram.....	52
Figure 3.2 – Plasma BNP levels on and off digoxin .....	54
Figure 3.3 – 6MWD on and off digoxin.....	54
Figure 3.4 – CDS on and off digoxin .....	55
Figure 3.5 –MLHFQ on and off digoxin.....	55
Figure 3.6 – SF-36 health survey on and off digoxin.....	56
Figure 4.1 – Plasma BNP levels on and off aspirin.....	69
Figure 4.2 – 6MWD on and off aspirin .....	69
Figure 4.3 –MLHFQ on and off aspirin .....	70
Figure 4.4 – CDS on and off aspirin .....	70
Figure 4.5 – SF36 health survey on and off aspirin .....	71
Figure 4.6 – Plasma BNP levels on and off statin.....	73
Figure 4.7 – 6MWD on and off statin .....	73

Figure 4.8 – MLHFQ on and off statin .....	74
Figure 4.9 – CDS on and off statin.....	74
Figure 5.1 – Patient satisfaction with number of medications .....	84
Figure 5.2 – HF guidelines followed most closely by prescribing clinicians .....	87

# List of Abbreviations

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ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
AF	Atrial fibrillation
AHA	American Heart Association
AHR	Adjusted hazard ratio
AngII	Angiotensin II
ANP	Atrial natriuretic peptide
ARB	Angiotensin receptor blocker
AT <sub>1</sub>	Type 1 angiotensin receptor
BP	Blood pressure
BPM	Beats per minute
BMI	Body mass index
BNP	Brain natriuretic peptide
CAD	Coronary artery disease
CDS	Cardiac Depression Scale
CI	Confidence interval
CORONA	Controlled Rosuvastatin Multinational Trial in Heart Failure trial
COX	Cyclo-oxygenase enzyme
CRT	Cardiac Resynchronisation Therapy
CSANZ	Cardiac Society of Australia and New Zealand
CV	Cardiovascular
DIG	Digitalis Investigation Group
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
HbA1c	Glycated haemoglobin

HDL	High-density lipoprotein
HF	Heart failure
HFREF	Heart failure with reduced ejection fraction
HFPEF	Heart failure with preserved ejection fraction
ICD	Implantable cardioverter-defibrillator
IDCM	Idiopathic dilated cardiomyopathy
LDL	Low-density lipoprotein
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MRA	Mineralocorticoid receptor antagonist
No ATT	No anti-thrombotic arm
NT pro-BNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OR	Odds ratio
QoL	Quality of life
PROVED	Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin study
RAAS	Renin-Angiotensin-Aldosterone System
RADIANCE	Randomized Assessment of [the effect of] Digoxin on Inhibitors of the Angiotensin-Converting Enzyme study
RCT	Randomised controlled trial
RevMan	Review Manager
RR	Risk ratio
SD	Standard deviation
SF-36	Short Form 36 Health Survey

SR	Sinus rhythm
TIA	Transient ischaemic attack
6MWD	Six minute walk distance

# Chapter 1: Introduction and literature review

---

## 1.1 General introduction

Heart failure (HF) is a complex disease process associated with high mortality, frequent hospitalisation and major healthcare cost to the community [1]. Approaches to the management of this condition have made major inroads into the high morbidity and mortality. Drug therapies have been developed that reduce mortality and morbidity, with relatively few side effects. Device-based strategies augment drug therapies, and non-pharmacological measures are also employed, such as salt and alcohol restriction and exercise. For a minority of patients ventricular assist devices and cardiac transplantation may be offered.

Drug therapies shown to be of significant mortality benefit have generally focussed on inhibition of key neurohormonal systems activated in the HF disease process: agents that block the renin-angiotensin-aldosterone system (RAAS) including angiotensin-converting enzyme (ACE) - inhibitors, angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs), as well as agents that block the sympathetic nervous system (beta-blockers). These medications are the cornerstone of life-saving drug therapies in HF. However, in addition to these agents, many other therapies are employed in the HF setting. This is often but not necessarily because of the co-morbidities that are common accompaniments of this condition. Furthermore, in some cases, the evidence base supporting the use of particular agents was derived before the advent of other now proven therapies. This introduces the possibility that not all therapies are needed in contemporary practice.

This thesis examines the polypharmacy that is being routinely prescribed to patients with HF and addresses the question of whether certain therapies can be withdrawn without affecting overall efficacy or compromising safety.



## 1.2 HF definition

HF describes a complex clinical syndrome in which the heart is incapable of maintaining cardiac output that is adequate to meet metabolic requirements and accommodate venous return. Multiple aetiologies lead to this final common pathway. Definitions of HF describe typical symptoms, including dyspnoea, orthopnoea, fatigue, and signs including pulmonary and peripheral oedema, with objective evidence of impaired cardiac function. HF is a syndrome and not a disease. The diagnosis relies on a clinical examination and can be challenging.

## 1.3 HF classification

HF can be classified using the New York Heart Association (NYHA) classification [2], which assigns one of four classes according to the physical disability caused by HF. Patients without any limitations or symptoms with ordinary activity are NYHA Class I. Patients with a slight limitation in physical activity are NYHA Class II. NYHA Class III patients are comfortable at rest but have marked limitation in physical activity with symptoms occurring at less than ordinary physical activity. NYHA Class IV patients may have symptoms at rest and are unable to carry out any physical activity without symptoms. The National Heart, Lung and Blood Institute estimate that approximately 35% of HF patients are Class I, 35% are Class II, 25% Class III and 5% Class IV. Mortality rises with NYHA class [3].

The American College of Cardiology (ACC) and the American Heart Association (AHA) have developed another system which emphasises the evolution and progression of the HF disease process [4]. Patients in Stage A are at high risk of developing HF but do not have structural disorders of the heart. Stage B patients have structural disorder without any symptoms of HF. Stage C patients have past or current symptoms of HF and associated underlying structural heart disease. Stage D patients have end-stage HF and require specialised treatment strategies. Stage A represents pre-HF, Stage B corresponds to NYHA Class I, Stage C to NYHA Class II and III as well as previously symptomatic HF now in NYHA Class I (usually following treatment), and Stage

D to NYHA Class IV HF. This four-stage classification emphasises that therapeutic intervention before the development of left ventricular (LV) dysfunction can improve the course of the HF.

## **1.4 Types of HF**

HF is broadly classified by left ventricular ejection fraction (LVEF) which is derived from imaging studies. Various ejection fraction (EF) thresholds have been recommended, including 40% [5,6], 50% [7] and 55% [8], above which HF with preserved EF (HFPEF) is diagnosed, and below which HF with reduced EF (HFREF) is diagnosed. Approximately half of HF patients have HFREF and half have HFPEF [9], and they are indistinguishable at presentation with acute HF.

## **1.5 Diagnosis of HF**

Several diagnostic criteria for HF have been developed, including Framingham, Boston, Gothenburg and the European Society of Cardiology (ESC) [10]. These criteria use typical symptoms and elevated filling pressures in combination with the medical history, physical examination and chest X-ray. Diagnostic modalities used routinely in HF include echocardiography to evaluate cardiac structure and function including diastolic function and measurement of LVEF. Twelve-lead electrocardiograph is used to determine rhythm and QRS morphology and duration as well as detect other abnormalities. Chest X-ray is useful to exclude other causes of dyspnoea, identify congestion and assess for cardiomegaly. Natriuretic peptides, including brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP), can distinguish HF from other causes of dyspnoea in the Emergency Department [11] and can be used to guide HF therapy [12]. Other investigations which can be considered include cardiac magnetic resonance imaging with gadolinium enhancement to provide further information on cardiac structure and function, and characterise cardiac tissue [13], although its use may be limited by the presence of devices. Other investigations to assess ischaemia may be appropriate, including coronary angiography, myocardial perfusion scanning and exercise testing.

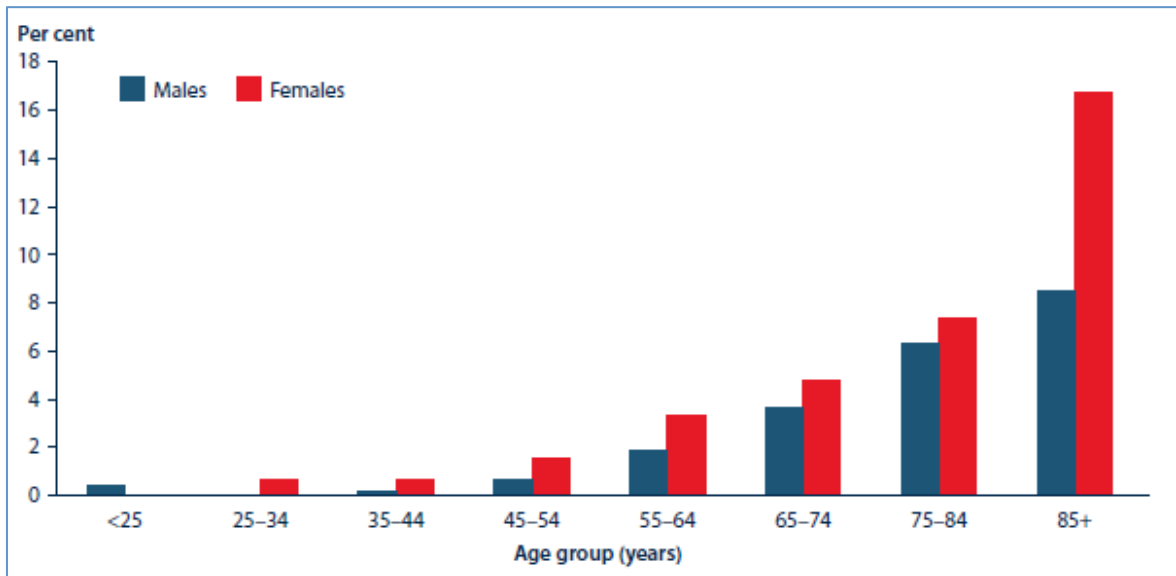
## 1.6 Epidemiology of HF

HF is increasingly common in both the developed and developing worlds, and has been described in terms of an epidemic [14,15]. This epidemic reflects increased prevalence, which may be due to increased awareness and diagnosis of HF, the aging of the population, improvements in patient survival or a combination of these factors. Accurate information, however, is difficult to obtain as data are derived from hospital discharge records, self-report or administrative databases, for which consistent definitions of HF are not used. There are no national registers or administrative datasets which record the prevalence or incidence of HF in Australia [16].

## 1.7 Prevalence

Prevalence of HF in the United States is estimated at over 5.7 million people [17], in Europe over 15 million people [18] and in Australia, approximately 277,800 people are estimated to have HF [19]. These numbers represent about 1-3% of the population. An increase in the prevalence of HF is suggested from population studies. A cohort study of over 600,000 US Medicare beneficiaries found that HF prevalence grew from 90 to 120 per 1,000 between 1994 and 2003 [20]. Canadian linked health care data show an increase in prevalence of HF from 1585 to 2510 per 100,000 population between 2000 and 2006 [21].

HF is more prevalent in females, especially so over the age of 85 (Figure 1.1) [19]. HF prevalence also rises with age. The Rotterdam cohort study found a HF prevalence of 1% in age 55 to 64 years, rising to 10% in those aged over 80 years [22]. Similarly in Olmstead County, Minnesota prevalence was 0.7% in age 45 to 54 years, and 8.4% in those aged over 75 years [23]. HF is also a disease of social disadvantage, being 1.6 times more prevalent in the lowest socioeconomic group than the highest in Australia, with a disproportionate burden of hospitalisation for HF in remote regions of Australia [19]. The prevalence in Aboriginal and Torres Strait Islanders is 1.7 times higher than non-Indigenous populations [19]. Additionally the type of HF is changing, with prevalence of HFPEF rising while that of HFREF falling [9]. HF prevalence is projected to rise further in the future [24,25].



**Figure 1.1 – Heart failure and oedema prevalence, by age and sex, 2007-2008. Source: Australian Institute of Health and Welfare.**

## 1.8 Incidence

An estimated 870,000 cases of incident HF are diagnosed in the United States annually [17]. By applying findings from overseas it has been estimated that 30,000 new cases of HF are diagnosed each year in Australia [19]. The incidence of HF appears to be falling. A study of a community-based cohort in Olmsted County, Minnesota saw a reduction in incident HF from 316 to 219 cases per 100,000 in the decade from 2000 to 2010, with greater reductions in HFREF than HFPEF [26]. Data from the Framingham Heart Study showed that between 1950 and 1999 the incidence of HF in males was stable and decreased in females [27]. Population-based studies from Canada demonstrated a decrease in incident HF from 455 to 306 cases per 100,000 people between 1997 and 2007 [28], and a study from Scotland found that rates of first hospitalisation for HF had declined [29]. The lifetime risk of HF is 20% at age 40 years [30] and this risk increases with age [31,32].

## 1.9 Hospital admissions

Admissions where HF was the principal diagnosis account for 0.6% of all hospitalisations in Australia, with over 49,000 separations. HF was listed as an additional diagnosis in a further

95,000 admissions [19]. The HF hospitalisation rate appears to have peaked and is now declining. A US study of Medicare beneficiaries demonstrated a relative decline in HF admissions of 29.5% between 1998 and 2008 [33]. In Australia, a data linkage study in New South Wales showed reductions in age-standardised hospitalisation rates for HF between 2002/3 and 2006/7 [34]. Data from the Australian Institute of Health and Welfare show that length of stay has reduced, from 11.2 days in 1993/4 to 8.9 days in 2007/8 [19]. However readmission rates are high. The study from New South Wales found all-cause readmission at 28 days was 27%, and at one year 73%, and that readmission for HF was 11% at 28 days and 32% at one year [34]. Readmission rates have also been demonstrated to be increasing in the United States [35].

## **1.10 Costs**

HF is associated with a substantial economic burden, with about two-thirds of costs accounted for by hospitalisations [36,37]. For the United States, a recent estimate of the direct cost of HF as the primary diagnosis was calculated at \$60 billion per annum, and \$115 billion when HF was considered as one of the admission diagnoses [38]. Costs are predicted to increase by 75% over the coming 40 years as “baby boomers” born following World War II continue to age [39]. Studies from a number of OECD countries including New Zealand, USA, Sweden and the UK, suggest that HF is responsible for 1-2% of total health care expenditure [36]. Data for Australia is not directly available, however extrapolations suggest that HF costs the Australian health care system over \$1 billion dollars annually and contributes to over 1.4 million hospitalisation days per year [14].

## **1.11 Risk factors for HF**

The most common risk factors which precede the development of HF in both men and women include coronary artery disease (CAD), hypertension, diabetes, obesity and smoking. The combined population attributable risk for these five risk factors is 52% [40]. Hypertension is the commonest risk factor (present in 66% of HF patients), however the risk of HF is highest for CAD and diabetes mellitus (odds ratios (OR) and 95% confidence intervals (CI) of 3.05 (2.36-3.95) and 2.65 (1.98-3.54) respectively) [40]. Although the risk of HF from hypertension is less, it contributes equally to the population burden of HF as CAD, due to its greater prevalence [40].

Obesity (body mass index (BMI) > 30 kg/m<sup>2</sup>) doubles the risk of HF after adjustment for associated risk factors [41]. The frequency of CAD and smoking is higher in men, and women have a higher frequency of hypertension [40]. The epidemiology of these risk factors is evolving, and all are increasing in prevalence, particularly hypertension and obesity [9,40].

Risk factors for the development of HFPEF differ from those of HFREF. The Framingham study found that independent predictors of incident HFPEF included elevated systolic blood pressure (BP) (OR 1.13 per 10mmHg), atrial fibrillation (AF) (OR 4.23), female sex (OR 2.29), whereas reduced odds of HFPEF were seen with prior myocardial infarction (MI) (OR 0.32) and left bundle branch block morphology (OR 0.21) [42]. The cardiovascular (CV) risk factors of diabetes, smoking and hypertension preceded the development of both HFPEF and HFREF.

Multiple other risk factors increase the risk of HF in addition to those already described [43]. These include, but are not limited to, age, male sex, valvular heart disease, chronic kidney disease, sleep-disordered breathing, sedentary lifestyle, psychological stress, low socio-economic group, immune mediated conditions such as peripartum cardiomyopathy, infectious agents, toxic agents such as chemotherapy, alcohol and illicit drugs such as cocaine and amphetamines and genetic predisposition.

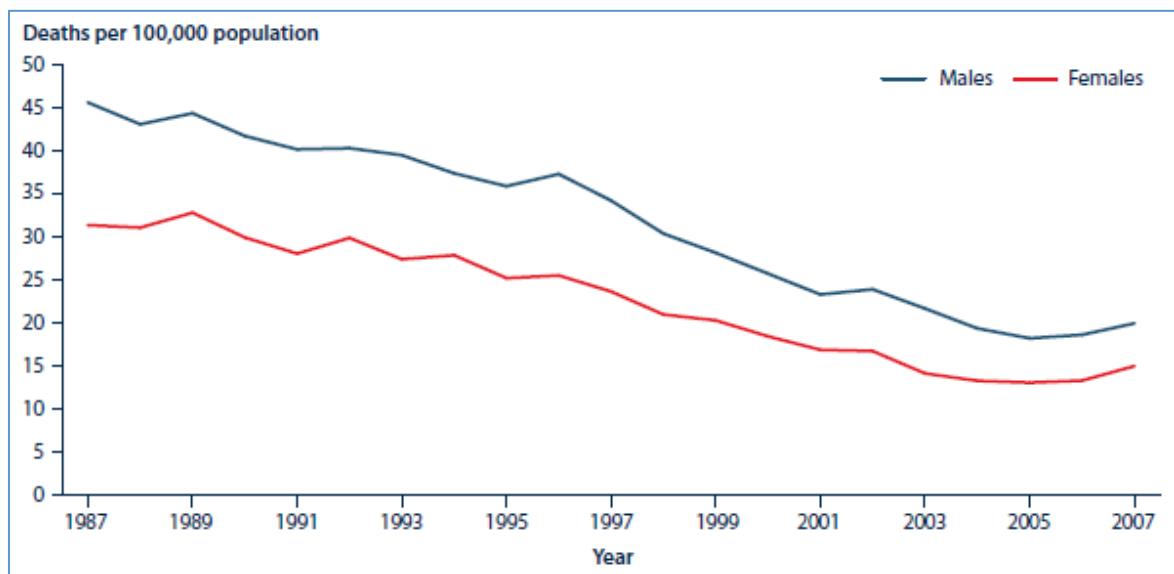
## **1.12 Non-cardiac comorbidities**

As HF is a disease of the elderly, comorbid conditions are common, and contribute to reduced quality of life (QoL) and increased mortality [44]. Comorbidities are a frequent cause of hospitalisation, and non-cardiac causes for hospitalisation outnumber those for HF [45]. A population-based study in the US demonstrated that the risk of hospitalisation increased with the number of comorbidities, and that chronic obstructive pulmonary disease, renal failure, diabetes mellitus and depression were the comorbidities most strongly associated with adverse outcomes in HF patients [46]. Sleep disordered breathing, anaemia, cognitive dysfunction and arthritis are also common [47]. HFPEF patients have a higher rate of non-cardiac comorbidity than HFREF, leading

to a greater rate of non-HF hospitalisations, but the overall hospitalisation rate for HFPEF and HFREF is the same [48].

## 1.13 Prognosis

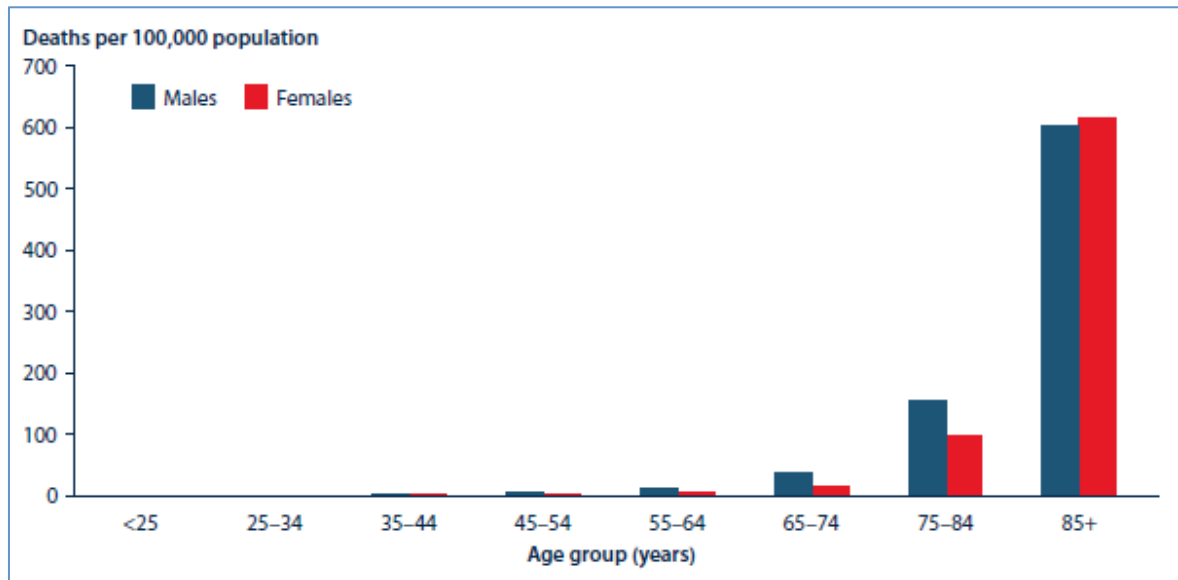
Survival following a diagnosis of HF has improved substantially over the previous decades [33,49]. In Australia, the age-standardised death rate from HF fell by close to half in the twenty years from 1987 to 2007, from 38 to 17 deaths per 100,000 (Figure 1.2) with nearly 90% of deaths occurring in those aged over 75 years (Figure 1.3) [19]. However HF remains highly lethal. The Rotterdam study estimated an age-adjusted mortality twice that of persons without HF (hazard ratio 2.1, 95% CI 1.8-2.7) and risk of sudden death even higher (hazard ratio 4.8, 95% CI 2.6-8.7) [50]. A study from Scotland estimated the overall population rate of expected life-years lost to be 6.7 years/1000 in males and 5.1 years/1000 in females [51].



**Figure 1.2 – Heart failure and cardiomyopathy death rates in Australia, by sex, 1987-2007.**  
Source: Australian Institute of Health and Welfare.

Mortality rises after a hospital admission for HF. Administrative data from Australia showed a mortality rate of 28% one year after HF admission [34]. A community-wide study in the US showed a 75% five year mortality after first hospitalisation for HF [52]. Mode of death was determined in 1383 patients in the ATLAS trial (high vs low dose of lisinopril in NYHA II-IV HF),

and classified as sudden death (43%), progressive HF (32%) and other causes (25%) [53]. Overall mortality risk is similar for HFREF and HFPEF, but HFPEF patients are more likely to die of non-CV causes, while those with HFREF more likely to die from ischaemic heart disease [54].



**Figure 1.3 - Heart failure and cardiomyopathy death rates, by age and sex, 2007. Source: Australian Institute of Health and Welfare.**

## 1.14 Pathophysiology of HFREF

The syndrome of HF is the end result of a number of different pathophysiologic processes in which there is injury to the heart with loss or impairment of functioning myocardial cells. A number of compensatory mechanisms are then activated in order to maintain adequate cardiac function and tissue perfusion. These include i) increasing cardiac output through the Frank-Starling mechanism, and ii) augmentation of mean arterial pressure via neurohormonal activation, including both the sympathetic nervous system and the RAAS and iii) increasing ventricular volume and wall thickness through ventricular dilatation. With time these factors mediate adverse changes in myocardial structure, function and electrical stability, initiating a progressive cycle of deterioration with worsening of HF clinical status and arrhythmogenesis resulting in sudden death.

### 1.14.1 The Frank-Starling mechanism

As preload (LV end diastolic volume) increases in the failing heart, LV end diastolic pressure increases causing myocardial stretch, and a consequent increase in cardiac output. This is the



Frank-Starling mechanism, and is important in the early stages of HF for maintaining tissue perfusion. There is a limit to how much cardiac output can increase, and eventually the heart muscle decompensates, with pulmonary congestion and depressed cardiac output [55].

#### **1.14.2 Neurohormonal activation**

Several compensatory mechanisms are activated with myocardial injury, including the sympathetic nervous system and RAAS. Inflammatory mediators are also activated, which are responsible for cardiac repair and remodelling (described below). Sympathetic nervous system activation occurs early in the course of HF, and an increase in circulating catecholamines is seen (noradrenaline and adrenaline levels) which stimulate  $\beta_1$ ,  $\beta_2$  and  $\alpha_1$  receptors. Early in the course of HF this stimulation results in cardiac effects, including increased heart rate and contractility, effects on the peripheral vasculature to increase BP including RAAS stimulation resulting in vasoconstriction and sodium retention [55,56]. Prolonged overstimulation of the sympathetic nervous system however leads to cardiac toxicity which includes decreased EF, arrhythmias and tachycardia.

The RAAS is key in regulating electrolyte levels and fluid balance. The RAAS is activated later than the sympathetic nervous system in LV dysfunction. The kidneys secrete renin in response to increased sympathetic activation, and in response to reduced renal blood flow from reduced mean arterial pressure. Renin then acts on angiotensinogen to make angiotensin I in the liver, which is then converted by ACE in the lungs to angiotensin II, increasing vasoconstriction and promoting the release of aldosterone. The end result is to facilitate release of noradrenaline, increase sodium reabsorption, stimulate vasopressin release from the hypothalamus to further increase vasoconstriction and water retention, and increase cardiac contractility [55].

A further important neurohormonal mechanism is the natriuretic peptides, including atrial (ANP), BNP and C-type natriuretic peptides. These hormones counteract the vasoconstricting effects of the sympathetic nervous system and RAAS. ANP and BNP are found in the atria and ventricles respectively, and are released in response to atrial or ventricular stretch. They act directly on blood vessels to cause vasodilatation, salt and water excretion, inhibition of secretion of renin, aldosterone and vasopressin [55,56].

### **1.14.3 Ventricular remodelling**

Ventricular remodelling occurs in response to chronic haemodynamic stresses. A sequence of changes including cell proliferation, apoptosis, hypertrophy and atrophy result in changes in ventricular mass, composition, volume and geometry [57]. The heart becomes less elliptical and more spherical, which initially allows the failing heart to accommodate a greater stroke volume and higher cardiac output. Greater myocardial wall thickness and ventricular mass lead to increased contractility. However this is ultimately detrimental, resulting in increased wall tension and fibrosis, which impairs contractility and also results in contractile dyssynchrony and less effective pumping.

## **1.15 Pathophysiology of HFPEF**

HFPEF is defined by the presence of preserved LV systolic function with impaired diastolic LV function with prolonged LV relaxation, slow LV filling and increased diastolic LV stiffness [58]. In the absence of endocardial or pericardial disease, diastolic LV dysfunction is the result of increased myocardial stiffness. The extracellular matrix and the cardiomyocytes form two compartments, and stiffness in one is transmitted to the other. Stiffness in the extracellular matrix is determined by collagen through regulation of its total amount, relative abundance of collagen type 1, and degree of cross-linking, all of which can be altered with HFPEF. Intrinsic cardiomyocyte stiffness is also elevated in HFPEF patients. Systolic function is also impaired in HFPEF, with a decreased ability to enhance contractility, resulting in exercise intolerance. Age, hypertension and diabetes all contribute to increased ventricular and vascular stiffening, leading to increased lability of BP. Pulmonary hypertension occurs secondary to increased left heart pressures as well as pulmonary vascular dysfunction [58].

## **1.16 Therapeutics in HF**

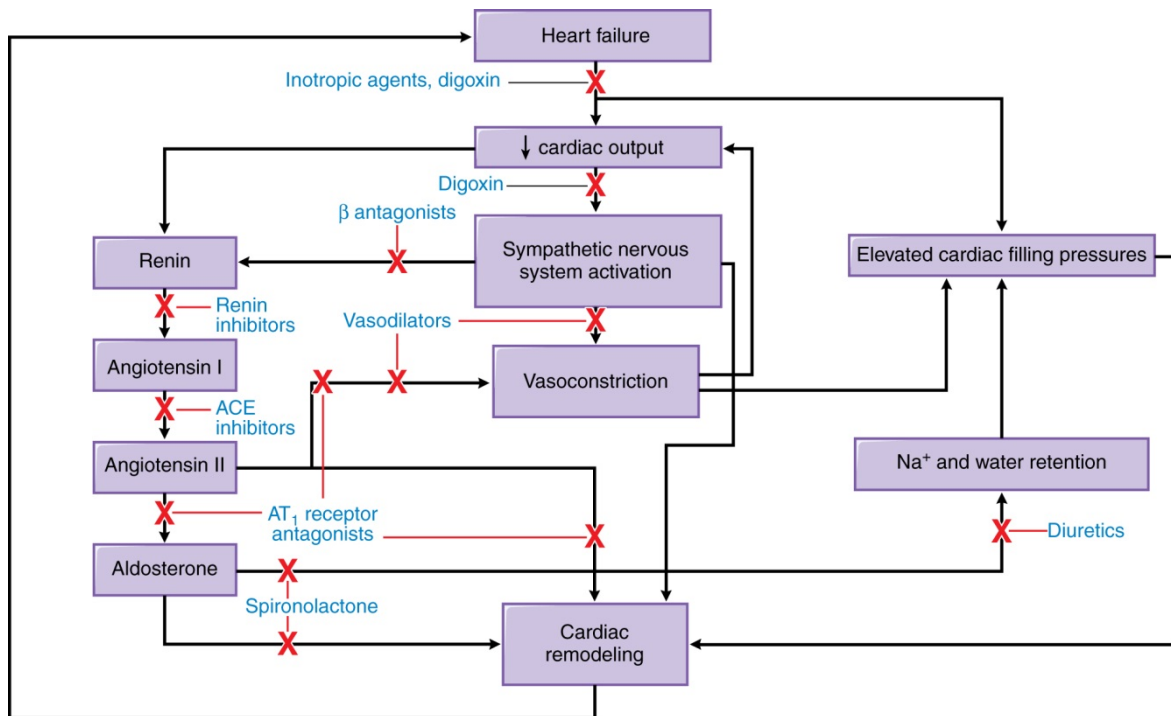
The goals of management in HF are to control symptoms, prevent progression of LV dysfunction and improve survival. This is achieved using a combination of education, lifestyle change and pharmacological therapies.

## **1.17 Non-pharmacological treatments**

Various non-pharmacological therapies have been demonstrated to be beneficial in HF, and are employed in conjunction with pharmacological approaches [7,18]. Importantly, education of the patient in self-care improves outcomes [59], addressing such issues as symptoms, diet, physical activity and medications. Dietary recommendations include sodium restriction in symptomatic HF however there is a lack of evidence from trials and no specific level of intake is recommended [60]. Restriction of fluid is recommended, especially if fluid overload is present. Overweight and obesity portends a better prognosis than normal or underweight patients in HF (the obesity paradox [61]) thus intentional weight loss is recommended only for those with significant obesity ( $\text{BMI} > 40 \text{ kg/m}^2$ ) in order to improve pump function and QoL. Other measures which have been shown to improve outcomes include exercise training [62] and cardiac rehabilitation [63].

## **1.18 Drugs conferring a mortality benefit**

Drug therapies have significant mortality benefit in HFREF only. These therapies have generally focus on inhibition of key neurohormonal systems activated in the HF disease process including agents that block the RAAS (ACE inhibitors, ARBs and MRAs), and agents that block the sympathetic nervous system (Figure 1.4). These medications act to unload the failing LV and reduce the damaging effects of neurohormonal activation, decreasing myocardial energy requirement and electrical instability. These will be discussed first, followed by an outline of other medications used in HF.

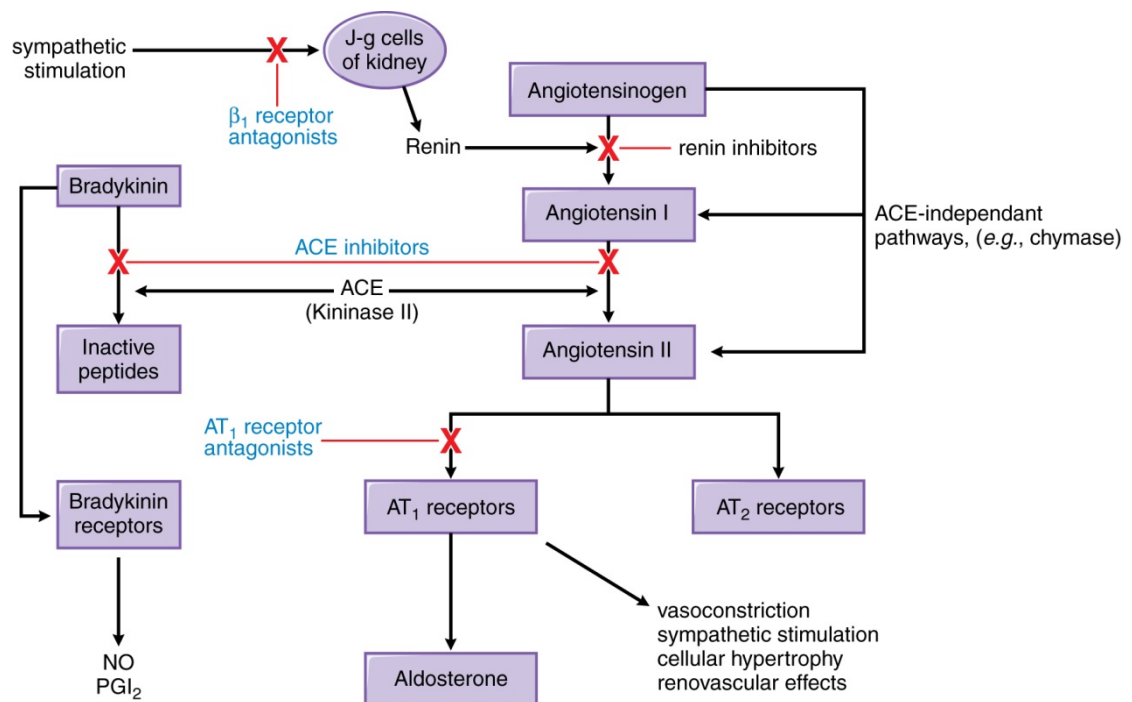


**Figure 1.4 – Pathophysiological mechanisms of heart failure and major sites of drug action.** From Brunton et al. Goodman & Gilman’s The Pharmacological Basis of Therapeutics 12<sup>th</sup> ed. Reproduced with permission from McGraw-Hill Education.

### 1.18.1 RAAS inhibitors

ACE inhibitors act by suppressing the conversion of Angiotensin I to Angiotensin II (AngII) (Figure 1.5). Stimulation of the type 1 angiotensin (AT<sub>1</sub>) receptors by AngII causes arterial vasoconstriction, sympathetic stimulation, cellular hypertrophy and renovascular effects including sodium and water retention and aldosterone secretion. Inhibition of ACE reduces afterload and systolic wall stress, cardiac output increases, BP falls, heart rate declines, renal blood flow increases and natriuresis occurs. Additionally ACE inhibitors increase the production of kinins, which are important regulators of prostaglandin production and nitric oxide synthesis, both of which play a beneficial counter-regulatory in HF. ACE inhibitors have been demonstrated in numerous trials comprising over 100,000 patients to have beneficial effects in mild through to severe HF [64-66], and in the post-MI setting [67-70] on outcomes including all-cause mortality, hospitalisation, progressive HF and other CV endpoints. ACE inhibitors are considered mandated therapy in HFREF [7,18].

ARBs inhibit most of the biological effects of AngII described above, by binding with high affinity to the AT<sub>1</sub> receptor (Figure 1.5). The CHARM-Alternative (Candesartan in Heart failure – Assessment or moRtality and Morbidity-Alternative) trial investigated candesartan compared with placebo in patients who were ACE inhibitor intolerant with NYHA II-IV symptoms and LV dysfunction, and demonstrated a relative risk reduction of 23% for CV death and HF hospitalisation [71]. Other trials have demonstrated improved outcomes with the addition of ARB to ACE inhibitor [72,73], and non-inferiority head-to-head with ACE inhibitor [74]. However results have been inconsistent and thus this class of medication is considered an alternative to ACE inhibitors in HF, particularly if ACE inhibitor intolerance is an issue, as incidence of cough and angio-oedema is less than that with ACE inhibitors.



**Figure 1.5 – The renin-angiotensin-aldosterone axis. From Brunton et al. Goodman & Gilman's The Pharmacological Basis of Therapeutics 12<sup>th</sup> ed. Reproduced with permission from McGraw-Hill Education.**

### **1.18.2 Beta-adrenergic receptor antagonists (beta-blockers)**

The introduction of beta-adrenergic receptor antagonists, or beta-blockers, reflected one of the most startling paradigm shifts seen in modern medicine. Previously it was believed that the failing heart depended upon sympathetic nervous system activation to support circulatory function, and beta-blockers were absolutely contraindicated [75]. Recognition that a pathological response to sympathetic stimulation was likely to be an aetiological factor in the development of HF led to the introduction of beta-adrenergic blockade for chronic use in HF [76].

Beta-blockers inhibit beta-adrenergic receptor activation by catecholamines. In HF they inhibit and can reverse LV remodelling, they confer anti-arrhythmic effects, improve myocardial diastolic perfusion, and reduce myocardial oxygen consumption [77]. Beta-blockers are a heterogeneous group of agents with differences in relative potency on beta-1 and beta-2 receptors, and not all beta-blockers have been shown to be useful in HF [78]. The beneficial effects of beta-blockers have been observed in mild through to severe HF with carvedilol [79,80], sustained-release metoprolol succinate [3] and bisoprolol [81]. They are considered to be a cornerstone of HF treatment in combination with ACE inhibitors [7,18].

### **1.18.3 Mineralocorticoid Receptor Antagonists**

Aldosterone levels are markedly elevated (up to 20 fold above normal) in HF. Aldosterone stimulates fibroblast proliferation, which augments collagen deposition and fibrosis, and results in cardiac remodelling as well as conduction abnormalities. Aldosterone promotes sodium and water retention, and also causes electrolyte imbalances including hypokalaemia, which together with the fibrosis predispose to cardiac arrhythmias [82]. MRAs are weak potassium sparing diuretics, and act by competitively inhibiting the binding of aldosterone to the mineralocorticoid receptor in the distal tubule and collecting duct [83].

MRAs have been shown to reduce mortality, sudden death and HF hospitalisation in patients with  $EF \leq 35\%$  with severe systolic HF with background ACE inhibitors [84], and in mild HF with background ACE inhibitor and beta-blocker [85], as well as post-acute MI LV

dysfunction ( $EF \leq 40\%$ ) with background diuretics, ACE inhibitor and beta-blocker [86]. MRAs should be instituted in patients with a sufficiently reduced EF [7,18].

#### **1.18.4 Angiotensin-neprilysin inhibition**

A new treatment paradigm was heralded in 2014 with the landmark PARADIGM-HF trial [87]. This trial used the angiotensin receptor-neprilysin inhibitor (ARNI) LCZ-696, which comprises a neprilysin inhibitor (sacubitril) and an ARB (valsartan). Compared to enalapril, LCZ-696 reduced CV death and HF hospitalisation by 20%, as well as improved symptoms. The neprilysin inhibitor component (sacubitril) blocks the degradation of natriuretic peptides and enhances their beneficial effects including reductions in sympathetic tone, serum aldosterone levels, myocardial fibrosis and hypertrophy, and increased natriuresis [88]. The combination with an ARB theoretically reduces the risk of angio-oedema caused by increased bradykinin levels. This new compound has received fast track approval by the US Food and Drug Administration, and has already been incorporated into the Canadian HF Guidelines [89].

#### **1.18.5 Other treatments with mortality benefits**

Other treatments which have been demonstrated to confer mortality benefits include the combination of hydralazine and isosorbide dinitrate in African-American patients [90], polyunsaturated fatty acids [91] and the sinus node inhibitor ivabradine [92].

### **1.19 Therapeutics in HF – drugs not conferring a mortality benefit**

All of the above agents have mortality benefits in HF and are recommended in HF treatment guidelines [7,18,93]. Several other therapies are also employed in the HF setting. Registry and clinical trial derived lists of drug therapies include agents such as digoxin, aspirin, statins and amiodarone given for various putative reasons. The HEAAL (The Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan) trial in HFREF involved 3846 patients, of whom 42% were taking digoxin, 50% aspirin, 39% statins and 12% anti-arrhythmic agents [94]. The OPTIMIZE-HF (The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry showed similar prescribing patterns in a sample of over 20,000

patients, with 38% on digoxin, 51% on aspirin, 42% on statins and 15% on anti-arrhythmics [95]. None of these therapies has been shown to improve survival in HF.

### **1.19.1 Digoxin**

Digoxin has been in use for over 200 years for HF, and is derived from the herb Foxglove. Digoxin inhibits the sodium-potassium adenosine triphosphatase (ATPase) pump, which results in increased intracellular calcium levels, improved myocardial contractility and a positive inotropic effect. Digoxin also has beneficial neuroendocrine effects and a slowing of sinus rate by its parasympathomimetic action [96].

The only large scale randomised controlled trial (RCT) of the use of digoxin in HF in sinus rhythm (SR) was published in 1997. The Digitalis Investigation Group (DIG) trial demonstrated the safety of digoxin and decrease in HF hospitalisations and symptoms, although no mortality benefit was seen (a small increase in sudden death was balanced by a reduction in death from worsening HF) [97]. Following the major benefits seen with beta-blockers and MRAs, digoxin use declined, despite it being used as concurrent background medication in trials of those drugs [96]. Digoxin currently is recommended for reducing hospitalisations in the ACCF/AHA guidelines [7] and is recommended for symptomatic HF with LVEF $\leq$ 40% in the ESC guidelines [18].

### **1.19.2 Aspirin**

The key mechanism of action of aspirin is believed to be irreversible inhibition of the cyclooxygenase enzyme (COX). COX is required for synthesis of thromboxanes, which promote clotting, and prostaglandins which are pro-inflammatory. Aspirin inhibits COX, thus blocking thromboxane A<sub>2</sub> production, which reduces platelet aggregability and thrombosis [98]. However, aspirin has a detrimental effect on vascular function by inhibiting production of vascular prostacyclin, which has a powerful vasodilator effect, causing vasoconstriction [99]. Aspirin blocks the counter-regulatory effects of nitric oxide, natriuretic peptides and prostaglandins, and adversely affects renal function and sodium balance [100].



Aspirin is widely prescribed in HF, although the evidence for its use is controversial [99,101]. In HF, aspirin does not reduce mortality compared with warfarin, clopidogrel or placebo [102-104], and its use was associated with increased HF hospitalisations in some studies [102,104]. Aspirin has been shown to increase BNP levels in HF compared with clopidogrel [105,106], and an interaction with ACE inhibitors may reduce the latter's mortality benefit [107,108]. Major HF guidelines do not clearly address the question of aspirin use [7,18].

### **1.19.3 HMG CoA Reductase inhibitors (Statins)**

Statins exert their major effect of reducing low-density lipoprotein (LDL) through a mevalonic acid-like moiety that competitively inhibits HMG-CoA reductase, thereby inhibiting the conversion of HMG-CoA to mevalonate and with it the rate limiting step in cholesterol biosynthesis. Statins also improve endothelial function as well as platelet function, stabilise atherosclerotic plaque and reduce vascular inflammation [109]. Despite conferring significant benefits in secondary prevention of ischaemic heart disease [110-112] and in prevention of HF [113,114], a mortality benefit has not been demonstrated with statins once HF is established. Two large scale RCTs trialled rosuvastatin against placebo, and both trials failed to achieve their primary endpoint in participants with ischaemic HF [115] and a mixed ischaemic and non-ischaemic group [116]. Guidelines do not support the initiation of statin therapy in HF [7,18].

### **1.19.4 Loop diuretics**

Loop diuretics are central to the pharmacologic management of congestive symptoms. Loop diuretics including frusemide and bumetanide inhibit the sodium-potassium-chloride co-transporter in the ascending limb of the loop of Henle, increasing sodium and fluid delivery to the distal nephron segments, and enhance potassium secretion. Loop diuretics have not been demonstrated to be associated with reduced mortality [117].

### **1.19.5 Other treatments without mortality benefit**

Other medications which have been studied but not been shown to have a mortality benefit in patients with HF include amiodarone [118], sustained release moxonidine [119], dofetilide [120]. Increased mortality has been found with dronedarone [121].

## 1.20 Drug therapies in HFPEF

Most treatments in HFPEF are general measures similar to those employed for HFREF, including monitoring weight, diet and lifestyle, and patient education. Risk factors are aggressively managed, including hypertension, tachycardia and other potential precipitants of acute HF are addressed such as AF and anaemia [122]. Diuretics are used to address fluid symptoms and exercise training [123] is beneficial in HFPEF patients.

Trials of medications that are beneficial in HFREF have failed to achieve their primary endpoints in HFPEF. ACE inhibitors and ARBs show modest reductions in hospitalisations [124] [125,126]. Trials of beta-blockers to reducing heart rate and extending diastolic filling time as well as reduce ischaemia have been negative [127,128]. Ivabradine has been shown to increase exercise capacity [129]. Trials of MRAs have shown an improvement in diastolic function but without an associated clinical improvement [130], and a modest reduction in hospitalisation without mortality benefit [131]. Further research is required.

## 1.21 Polypharmacy in heart failure

It is not difficult to see how patients with HF swiftly gain a substantial medication list, and that polypharmacy becomes an issue. Polypharmacy is defined as the use of multiple prescription medications. Arbitrary cut-points for the number of medications that constitute polypharmacy have been suggested as four [132,133] or five [134] medications, however other authors have noted that an arbitrarily defined cut-point is of limited value [135]. Hyperpolypharmacy has been defined as the use of ten or more medications [136]. The number of five medications has been arbitrarily selected as the definition of polypharmacy for the purposes of this research.

Polypharmacy is becoming increasingly common amongst HF patients, reflecting their advancing age and increased co-morbidities. A study in a community-based HF population found that the average number of medications taken increased from 4.1 to 6.4 over two decades, accompanied by a doubling of the proportion of patients aged over 80 [137]. Another community-based study found the median number of unique medications taken by HF patients was 11 [138].

The majority of HF patients have four or more comorbidities which command their own medications [137,139,140].

Polypharmacy is not necessarily bad, and the use of multiple medications has resulted in the substantial decreases in mortality described earlier. The costs of medications for HF has been estimated at \$3.2 billion per year in the United States [37], accounting for 9% of the costs of HF treatment, however the incremental cost is easily justified by the added benefits, and can indeed be cost saving [37].

However, polypharmacy can present problems for patients. In ambulatory older patients CV drugs are the most common cause of adverse drug events [141]. Studies of hospitalised patients have shown that the number of drug-related problems increases with the number of drugs used [135,142,143], which may reflect increased drug-drug interactions. Polypharmacy has been associated with reduced drug adherence, which is often related to the cost of the medication [138,144]. High levels of potential drug-drug interactions have been observed amongst HF patients [145-147] and medication use has been observed to be excessive in the final stages of life in patients with HF [148]. Medications with uncertain benefit may be contributing to the polypharmacy that accompanies HF.

Polypharmacy is a significant burden in aged care and much of the work addressing this issue started there. A number of different tools have been developed by expert consensus to identify potentially inappropriate medications used in older persons [149], including Beer's Criteria [150] and the Screening Tool of Older Persons' Prescriptions (STOPP) [151]. Medication withdrawal in the elderly has become accepted practice, and the term "deprescribing" has been coined to describe "cessation of long-term therapy supervised by a clinician" [152]. Issues of polypharmacy and deprescribing are increasingly relevant to the HF setting.

In this thesis I will examine whether the medications that are commonly prescribed in HF are contributing to polypharmacy and whether they can be safely reduced or withdrawn.

## 1.22 Thesis aims and questions

The purpose of this thesis is to investigate the issue of polypharmacy in HF and whether medications can be safely reduced, or deprescribed, without compromising the clinical status of HF patients.

In the first chapter a general overview of the condition and its complexities, as well as other issues such as epidemiology, causes and aims of therapy have been presented. A general consideration of the issue of polypharmacy has also been presented.

In Chapter 2 the literature on medication withdrawal in HF is presented in order to illustrate the impact of withdrawal of various medications in HF. This review has been published in the *Journal of Cardiac Failure* [153].

In Chapter 3 a RCT of digoxin withdrawal in HF in SR is described. This is the first RCT examining digoxin in the era of contemporaneous neurohormonal blockade, and was published as a research letter in the *Journal of Cardiac Failure* [154]. It is presented in this thesis as a full paper.

Chapter 4 describes two other RCTs examining the effect of statin and aspirin withdrawal in stable HF. These have been grouped together because these medications are often co-prescribed in ischaemic HF and not indicated in non-ischaemic HF. This work has been accepted by the *International Journal of Cardiology* [155], and is presented with an expanded discussion.

Chapter 5 explores the experience of polypharmacy amongst patients and their attitudes to their medications and also the experiences and attitudes of prescribing clinicians to polypharmacy, and their approach to prescribing and deprescribing.

Chapter 6 summarises the issues and conclusions that have arisen by the investigations presented in this thesis. There is also a discussion of what remains to be answered and the future directions that may be undertaken to further investigate these, as well as other issues.

## Chapter 2: Can medications be safely withdrawn in patients with stable chronic heart failure?

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### Declaration for Thesis Chapter 2

#### Declaration by candidate

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Designed and performed literature review, extracted data, performed meta-analysis, wrote the paper.	95%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
R Samuel	Assisted in verification of data extraction and intellectual contribution through drafting the paper	
C Hayward	Assisted in identifying references, assisted in intellectual content by interpreting the literature and developing the arguments, and in drafting the paper.	
A Tonkin	Supervision throughout project and assisted in intellectual content through drafting the paper.	
H Krum	Supervision throughout project and assisted in intellectual content through drafting the paper.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

Candidate's  
Signature

	Date November 2015
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Main  
Supervisor's  
Signature

	Date November 2015
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The following article “Can medications be safely withdrawn in patients with stable chronic heart failure? Systematic review and meta-analysis” has been published in the international peer-reviewed medical journal “*Journal of Cardiac Failure*”.

Citation of the article [153]:

Hopper I, Samuel R, Hayward C, Tonkin A, Krum H. Can medications be safely withdrawn in patients with stable chronic heart failure? Systematic review and meta-analysis. *Journal of Cardiac Failure*. 2014; 20: 522-532.

## 2.1 Abstract

**Background:** HF therapy involves use of multiple medications. There is little guidance on the safety and impact on clinical outcomes of stopping HF medications.

**Methods:** Comprehensive systematic search for studies of drug therapy withdrawal in HF. Meta-analysis of the risk ratio (RR) using the Mantel-Haenszel random effects model for all-cause mortality and CV outcomes.

**Results:** Twenty-six studies met inclusion criteria. Studies on withdrawal of RAAS inhibitors and beta-blockers in HF are scarce and small, however show relatively convincingly that such withdrawals will have untoward effects on cardiac structure, symptoms and major outcomes. Meta-analysis of seven studies of digoxin withdrawal (2987 participants) without background beta-blocker showed increased HF hospitalisations (RR 1.30, 95% CI 1.16, 1.46  $p<0.0001$ ), but no impact on all-cause mortality (RR 1.00, 95% CI 0.90-1.12,  $p=0.06$ ) nor reduction in all-cause hospitalisation (RR 1.03, 95% CI 0.98, 1.09,  $p=0.27$ ). Diuretic withdrawal trials demonstrated an ongoing need for these agents in chronic HF. Studies in peripartum cardiomyopathy showed that medications could be successfully withdrawn following recovery.

**Conclusion:** Current evidence discourages any attempt to discontinue RAAS inhibitors or beta-blockers in patients with stable HF, regardless of clinical and/or echocardiographic status. Formal withdrawal trials of other classes are needed.

## 2.2 Introduction

Chronic HF patients generally require lifelong pharmacologic therapy involving multiple medications. Studies have shown a median of six to 11 prescription medications taken daily by patients with HF [137,138,156]. Polypharmacy, defined as the use of five or more medications [135] is also becoming more common [157,158] with associated increased risk of drug-drug interactions [145] and reduced medication adherence, often for reasons of cost to the patient [138]. However, when considering a reduction in use of multiple agents, there is a paucity of literature available on the effects of actually withdrawing HF medications and little guidance regarding evidence-based decisions on their reduction.

There are a number of clinical scenarios in which medication withdrawal may be considered. First, HF with recovered LVEF is becoming increasingly common. [159,160] Such patients are generally younger and healthier than the usual HF population, and following therapeutic response to ACE inhibitors and beta-blockers, may request cessation of their medications. Peripartum cardiomyopathy is also associated with a return of normal ventricular function in over half of patients and in them, withdrawal of medications is also a consideration [161]. Furthermore as the population ages and co-morbidities increase, it is useful to review individual HF drug regimens for possibly unnecessary agents.

We therefore performed a systematic review and where possible, meta-analysis of studies of withdrawal of drug therapies in HF. These data might also inform which withdrawal trials are feasible in light of these preliminary experiences and ethical considerations.



## **2.3 Methods**

The study was performed according to recommendations from the Cochrane Collaboration and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statements [162].

### **2.3.1 Trial Design**

We searched for any study in which a drug for HF was withdrawn in which the population was adult, and patients had HF with recovered EF, or stable HFREF. Chronic HF was defined as a clinical syndrome in which patients have typical symptoms such as breathlessness, ankle swelling and fatigue, and signs such as elevated jugular venous pressure, pulmonary crackles and displaced apex beat resulting from an abnormality of cardiac structure or function [18]. Study designs included double-blind, RCTs, cross-over trials, open label prospective trials, observational studies, retrospective case series and case reports.

### **2.3.2 Agents Investigated**

Interventions included therapies with proven mortality benefit, including blockers of the RAAS, beta-blockers, and the combination of hydralazine/nitrates. Withdrawal trials involving diuretics were also investigated. Guideline recommended medication for co-existing conditions in HF were also evaluated, including digoxin, HMG CoA reductase inhibitors (statins), aspirin and nitrates.

### **2.3.3 Outcomes Evaluated**

Where possible, outcomes including all-cause mortality, HF hospitalisation and all-cause hospitalisation were examined. We also aimed to assess the effect of drug withdrawal on clinical status, NYHA class, haemodynamic measures, echocardiographic parameters, exercise capacity and quality-of-life measures, hormones and haemodynamic parameters assessed by right heart catheterisation.

### **2.3.4 Search Methodology**

Searches took place up to January 2014. We searched Medline (1966-January 2014), Embase (1980-January 2014), the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled trials, as well as ClinicalTrials.gov and abstracts from major international

cardiology meetings from 2007 to 2013. The search strategy combined keywords and MeSH terms related to removing medications (deprescribing, withdraw\*, cessation, cease\*, discontinue\*, stop\*, interrupt\*), with terms related to HF (HF, cardiomyopathies, dilated cardiomyopathy, left ventricular dysfunction, myocarditis, peripartum cardiomyopathy, CV pregnancy complications) and cross-linked with classes of drugs as well as individual drug names. Extensive manual reference checking was also undertaken. Studies were limited to those reported in English.

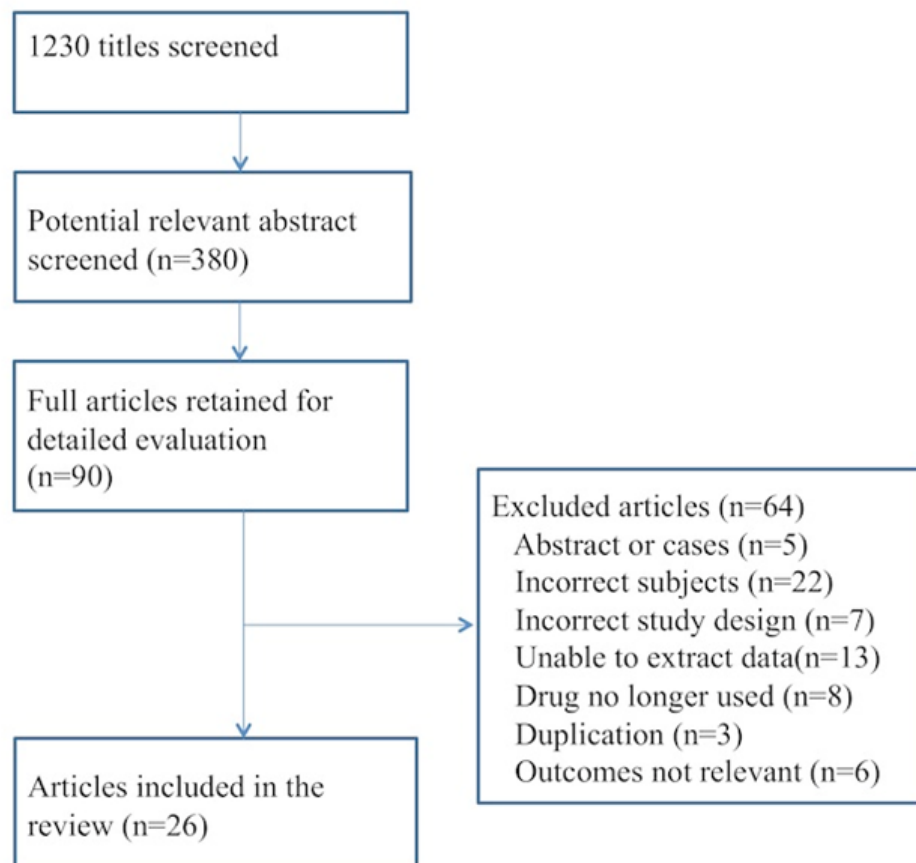
Initially studies were limited to RCTs, but due to the low number of studies identified, the search criteria were broadened to include studies published or unpublished, in full articles, abstracts or letters. All abstracts and letters identified through our searches were assessed to determine relevant full text articles for retrieval. Studies were excluded from the final analysis if they reported on medications that were no longer available or no longer used in the treatment of HF. Abstracts or letters without an accompanying peer-reviewed article, case studies and case series were not included in the final analysis but are listed in the supplementary appendix. Studies were reviewed by two authors (IH and RS).

### **2.3.5 Statistical Methods**

The statistical analysis was performed using Review Manager (RevMan) version 5.2.5 [163]. Meta-analysis was performed if three or more papers examined the same pre-specified endpoint. Mantel-Haenszel random effects models were used for data analysis, given the clinical heterogeneity of the studies found. The significance of RR was assessed using the Z-test with a statistical significance of 0.05. RR with 95% CI was derived for each study and also for overall outcome. A weighting was calculated for each study in accordance with the number of events that occurred in that study to enable derivation of an average overall outcome statistic and 95% CI. To examine potential publication bias, symmetry of individual study estimates around the overall estimate was assessed with funnel plots in which standard error of log RR were plotted against their corresponding RR [164].

## 2.4 Results

The literature search identified 1230 relevant titles from databases and hand-searches. 867 were excluded at the title level, and 273 at abstract level (Figure 2.1). Full text articles were retrieved for 90. A total of 64 full text articles were excluded (see supplementary material in appendix for list of excluded studies). Twenty-six drug withdrawal studies were identified (Table 2.1). 11 were RCTs, 4 were cross-over trials and 11 were observational trials. One observational trial instituted several medication changes sequentially, and each is dealt with separately [165]. There were no studies of withdrawal of aldosterone antagonists or statins from patients with HF.



**Figure 2.1 – Study flow diagram**

**Table 2.1 – Characteristics of included studies.**

Study	Year	Drug withdrawn	Population	# pts	Follow-up (weeks)	Background Therapy	Study Design	Random allocation	Control group
de Silva	2007	ACE	HFRD, ICM (81%)	68	4	ACE/ARB, BB	OB	N	Y
de Silva	2007	DIU	HFRD, ICM (81%)	68	4	ACE/ARB, BB	OB	N	Y
de Silva	2007	ASP	HFRD, ICM (81%)	32	4	ACE/ARB, BB	OB	N	Y
Nicholls et al	1982	ACE	ICM	5	0.5	DIG DIU	OB	N	N
Maslowski et al	1981	ACE	ICM	5	0.5	DIG DIU	OB	N	N
Pflugfelder et al	1993	ACE	ICM (63%)	224	16	DIG	RCT	Y	Y
Remme et al	2004	ACE	ICM (67%)	572	78	ACE DIG DIU	RCT	Y	Y
Swedberg et al	1980	BB	NICM	15	16	DIG	OB	N	N
Waagstein et al	1989	BB	NICM	24	52	NS	OB	N	N
Morimoto et al	1999	BB	NICM	13	16	NS	OB	N	N
Moon et al	2009	ACE/ARB ±BB	NICM	7	192	ACE/ARB, BB	RET OB	N	N
Amos et al	2006	ACE, BB	PPCM	11	116	ACE, BB	RET OB	N	N
PROVED	1993	DIG	ICM (60%)	88	12	DIU	RCT	Y	Y
RADIANCE	1993	DIG	ICM 60%	178	12	DIU, ACE	RCT	Y	Y
DIG trial	1997	DIG	ICM (68%)	3365	160	ACE	RCT	Y	Y
Fleg et al	1982	DIG	ICM (63%)	30	12	DIU	XO	Y	X
Guyatt et al	1988	DIG	ICM (85%)	20	7	DIU	XO	Y	X
Lee et al	1982	DIG	ICM (60%)	25	9	DIU	XO	Y	X
Taggart et al	1983	DIG	ICM (77%)	22	12	DIU	XO	Y	X
Shammas et al	2001	DIG	NICM	8	68	ACE, BB	OB	N	N
Khand et al	2003	DIG	ICM + AF	47	24	BB	RCT	Y	Y
Richardson et al	1987	DIU	ICM (53%)	14	8	ACE, DIG	RCT	Y	X
Grinstead et al	1994	DIU	ICM (75%)	41	12	DIG NIT	OB	N	N
Magnani et al	1988	DIU	ICM (44%)	64	52	DIG	RCT	N	N
Walma et al	1997	DIU	NS	84	26	NS	RCT	Y	Y
Galve et al	2005	FRU	ICM (52%)	26	12	ACE, DIG	OB	N	N
Braunschweig et al	2002	FRU	ICM (75%)	4	2	ACE, BB, DIG	OB	N	N
Wieshammer et al	1993	NIT	ICM	29	6	ACE, DIG	RCT	Y	Y
WASH	2004	ASP	ICM (64%)	279	108	ACE, DIG, DIU	RCT	Y	Y

ACE, Angiotensin Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; ASP, Aspirin; BB, Beta-Blocker; DIG, Digoxin; DIU, Diuretics; FRU, Frusemide; ICM, Ischaemic cardiomyopathy; NICM, Non-ischaemic cardiomyopathy; NIT, Nitrates; NS, not stated; OB, Observational Trial; PPCM, Peripartum cardiomyopathy; RCT, Randomised Controlled Trial; HFRD, Heart Failure with Renal Dysfunction; RET, Retrospective; XO, Cross-over trial.

### 2.4.1 Renin-Angiotensin-Aldosterone System inhibitors

Data on the withdrawal of RAAS inhibitors are scarce. However, the small studies reported are relatively convincing in showing that such withdrawals are likely to have untoward effects on cardiac structure and patients' symptoms and outcomes. Two studies of RAAS inhibitor withdrawal were identified. Withdrawal of captopril was associated with a sharp increase in RAAS activity within a day [166,167]. Marked increases in angiotensin II and aldosterone, a decrease in plasma renin activity, and increases in plasma and urinary cortisol excretion were observed, together with increases in heart rate and arterial BP. However no worsening in clinical status was observed in this short time frame. Pflugfelder et al [168] found higher rates of worsening HF in the quinapril withdrawal group compared with the continuation group (33% vs 19%,  $p = 0.003$ ) in 224 participants with stable chronic HF. Exercise tolerance, NYHA class, QoL and clinical status of HF deteriorated, which occurred gradually over a four to six week period.

Dose reduction however appears to be tolerated in the setting of renal dysfunction at least. De Silva [165] studied 68 patients with HF and renal dysfunction (serum creatinine  $> 130\mu\text{mol/l}$  ( $1.5\text{mg/dl}$ ) and estimated glomerular filtration rate (eGFR)  $< 60\text{ml/min}$ ). ACE inhibitors or ARBs were taken by this group at 75% of maximum recommended dose. No increase in symptoms of HF was seen after the dose was halved (or stopped in four participants on low doses). Mean BP was unchanged, although BP rose by  $> 10\text{mmHg}$  in 22 (32%) patients. Mean serum creatinine also fell from  $170 (\pm 55) \mu\text{mol/l}$  to  $164 (\pm 46) \mu\text{mol/l}$ .

Cessation of ACE inhibitor and use of beta-blocker in its place may also be safe. The CARMEN (The Carvedilol and ACE-inhibitor Remodelling Mild Heart Failure Evaluation Trial) study [169] compared enalapril, carvedilol and enalapril/carvedilol combination in mild HF. Participants randomised to the carvedilol group ( $n=191$ ) had their ACE inhibitor ceased prior to the trial (62% were taking an ACE inhibitor). Compared to the enalapril group, the carvedilol group showed a non-significant reduction in left ventricular end systolic volume index determined by transthoracic echo, and an improvement in LVEF at 6 and 12 months which was not present at 18 months. The combination enalapril/carvedilol however was superior to either alone.

### 2.4.2 Beta-blockers

Beta-blockers were withdrawn in three small uncontrolled open-label observational trials in idiopathic dilated cardiomyopathy (IDCM) with stable HF, with all trials observing deterioration in clinical signs of HF and reduction in LVEF. Swedberg and colleagues [170] withdrew beta-blockers from 15 patients whose HF had improved following six to 50 months of beta-blocker use, with continuation of background digitalis and diuretics. Clinical features of HF recurred in nine of the 15, with one sudden death. Echocardiography demonstrated an overall reduction in LVEF from  $46\pm3\%$  to  $35\pm3\%$  ( $p<0.01$ ) after a mean of 72 (range 7-119) days following beta-blocker withdrawal. Waagstein et al [171] withdrew metoprolol in 24 patients, with 16 deteriorating (four of whom died) after an average 5.8 (range 1-12) months. Mean LVEF on echocardiography before withdrawal was  $41\pm12\%$ , decreasing to  $32\pm13\%$  after withdrawal ( $p<0.01$ ). The remaining eight patients remained stable for a follow up period ranging from 2.5 to 6.5 years. Morimoto et al [172] withdrew metoprolol (mean dose of  $61.5\pm34.1\text{mg/day}$  for  $46.8\pm9.8$  months) in a stepwise fashion over a period of 14 weeks in 13 patients, ten of whom were NYHA class I. Seven patients deteriorated (two sudden deaths and two deaths from worsening HF) during the four month follow-up period. Six patients remained stable. Overall LVEF fell from  $38.3\pm14$  to  $33.9\pm14\%$  ( $p<0.05$ ).

Medication cessation was the only identified predictor of recurrence of HF in a retrospective study by Moon et al [173] of 42 patients with IDCM and recovered LVEF. All patients were on ACE inhibitors and about half beta-blockers. Recovery was considered to be LVEF  $\geq 40\%$  and a net increase in LVEF of  $\geq 10\%$ . Of the 42 patients studied, eight experienced recurrence of HF, defined as LV systolic dysfunction with LVEF  $< 40\%$ . Of the eight with recurrence, five had ceased “anti-heart failure medications”. The OR for recurrence of HF with cessation of anti-HF medications was 26.7 (95% CI 3.5 – 201.5,  $p<0.007$ ) and was the only significant predictor of recurrence. The investigators also described two patients who ceased medications who did not experience a recurrence of HF at nine and 72 months.

Amos and colleagues [174] retrospectively studied the outcomes of 55 patients with peripartum cardiomyopathy, 22 (45%) of whom had recovery of normal LVEF during mean follow up of  $38\pm28$  months. Baseline LVEF was  $23\pm10$  at initial presentation, and improved to LVEF 43

(no standard deviation (SD) available) by 2 months. The authors state that this group of 22 patients thereafter normalised their LVEF (considered to be LVEF > 50%, exact figure not available). Fifteen patients then had further echocardiography, and of them, 11 had ceased either ACE inhibitor or beta-blocker, and in five both were ceased. No deterioration in LVEF was observed an average of 29 (range 5-63) months after recovery.

### **2.4.3 Digoxin**

Studies of digoxin withdrawal were commenced in the 1960s. These were heterogeneous in nature, with diverse patient selection including patients with atrial arrhythmias, and were mostly uncontrolled and poorly designed. These early trials have been reviewed [175], with the conclusion that responses to digoxin and its withdrawal were highly variable.

Two larger-scale RCTs of digoxin withdrawal demonstrated its importance in patients with HFREF and SR in the pre-beta-blocker era. The PROVED (Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin) [176] and RADIANCE (Randomized Assessment of [the effect of] Digoxin on Inhibitors of the Angiotensin-Converting Enzyme) Study [177] were both 12-week double-blind RCTs of digoxin withdrawal. In PROVED patients received background diuretics without ACE inhibitors, and in RADIANCE diuretics and ACE inhibitors.

In PROVED, a total of 88 patients with baseline LVEF  $28 \pm 1\%$ , were randomised to digoxin continuation or withdrawal. Three of the four primary end-points worsened on digoxin withdrawal. Maximal exercise performance deteriorated ( $p=0.003$ ), “treatment failures” (defined as increased diuretic requirement, need for addition of new medications for HF or emergency visit / hospitalisation or HF-related death) were higher (39% vs 19%,  $p=0.039$ ) and time to treatment failure was less when digoxin was withdrawn ( $p=0.037$ ). No difference was observed in sub-maximal (6 minute walk) exercise test. RADIANCE randomised 178 patients to digoxin continuation or withdrawal, with baseline LVEF  $27 \pm 0.01\%$ . The RR of withdrawal from the study due to worsening HF in the digoxin withdrawal group was 5.9 (95% CI 2.1-17.2,  $p<0.001$ ) compared to continued use. Significant deterioration in maximal treadmill exercise tolerance and exercise endurance was also observed after digoxin withdrawal ( $p=0.033$ ).

Statistically significant small reductions in LVEF in the digoxin withdrawal groups (4% in PROVED, 3% in RADIANCE) ( $p < 0.05$ ) were observed compared to the digoxin continuation groups. Meta-analysis demonstrated that even patients with clinically mild HF with few or no symptoms and signs of HF at randomisation deteriorated after digoxin withdrawal [178]. Multivariate analysis found that participants who were not receiving an ACE inhibitor at randomisation were more likely to deteriorate after digoxin withdrawal [179].

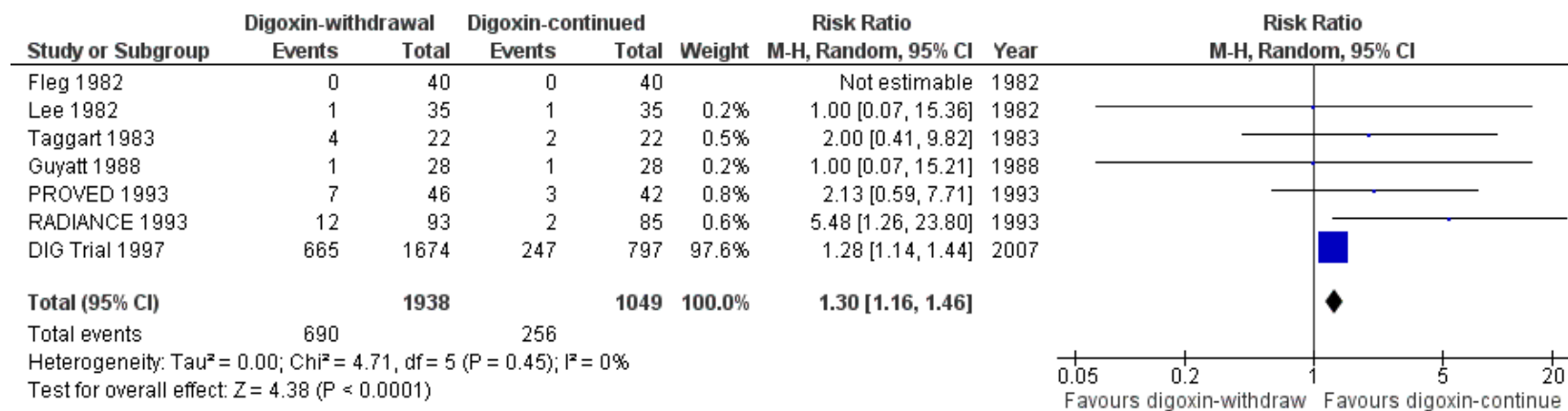
A sub-group analysis of the DIG study ( $n = 3,365$ ) examined participants taking digoxin at enrolment, who were then randomised to digoxin withdrawal. They were compared to participants taking digoxin at enrolment who were continued on it [180]. Background medications included ACE inhibitors and diuretics. Mean LVEF overall was  $31 \pm 12\%$ , with 10% having an LVEF  $> 45\%$ . Compared with continuing digoxin ( $n = 1,666$ ), its cessation ( $n = 1,699$ ) resulted in significant increases in hospitalisation, both all-cause hospitalisation (adjusted hazard ratio (AHR) 1.18, 95% CI 1.09 to 1.28,  $p < 0.0001$ ) and hospitalisation related to HF (AHR 1.35, 95% CI 1.20 to 1.51,  $p < 0.0001$ ). However all-cause mortality was not significantly different over a median 39.7 months follow up (AHR 1.06, 95% CI 0.95 to 1.19,  $p = 0.272$ ).

We performed meta-analysis of all available (seven) RCTs of digoxin withdrawal in SR [97,176,177,181-184] including a total of 2987 participants (Table 2.2). On withdrawal of digoxin, there was an increase in HF hospitalisations (RR 1.30, 95% CI 1.16, 1.46  $p < 0.0001$ ) (Figure 2.2), but no change in all-cause mortality (RR 1.00, 95% CI 0.90-1.12,  $p = 0.95$ ) nor any change in all-cause hospitalisation (RR 1.03, 95% CI 0.98, 1.09,  $p = 0.27$ ). These results were dominated by the DIG trial, which accounted for 95% of the weighting. Sensitivity analysis excluding the DIG trial did not alter the results. A significant rise in heart rate was seen after withdrawal of digoxin (reported in 5 studies,  $n = 416$ , mean difference 6.57 (3.74, 9.41) beats per minute (bpm),  $p < 0.00001$ ) (Figure 2.3) as well as a fall in systolic BP (mean difference -5.13 (-9.83, -0.42) mmHg  $p = 0.03$ ). No significant mean differences were seen in LVEF, left ventricular end-diastolic diameter, body weight, cardio-thoracic ratio, or diastolic BP (Table 2.2). No publication bias was evident on visual inspection of the funnel plot (Figure 2.4).

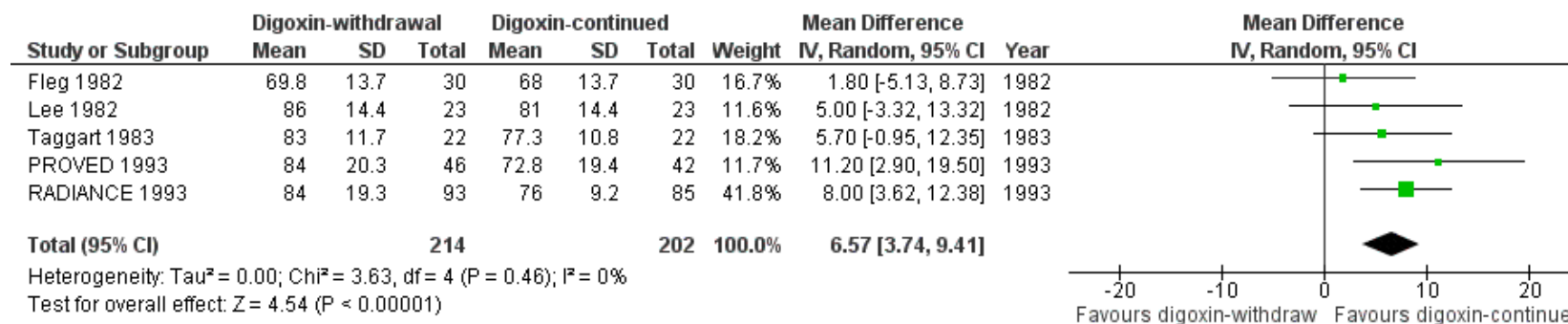


**Table 2.2 – Digoxin withdrawal trials: meta-analysis results**

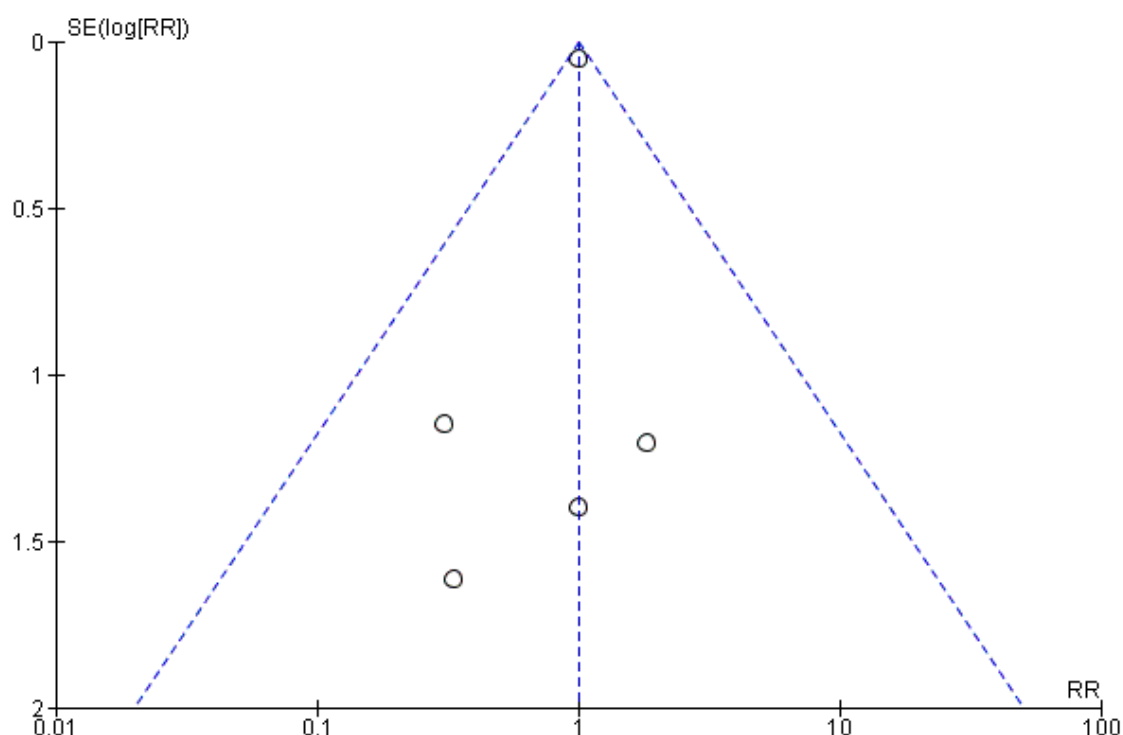
<b>Outcome or Subgroup</b>	<b>Studies</b>	<b>Participants</b>	<b>Effect Estimate</b>
1.1 Hospitalisation - heart failure	7	2987	1.30 [1.16, 1.46]
1.2 Mortality	7	2987	1.00 [0.90, 1.12]
1.3 Hospitalisation - all cause	4	2677	1.03 [0.98, 1.09]
1.4 Left Ventricular Ejection Fraction	3	316	0.01 [-0.05, 0.06]
1.5 Left Ventricular End-Diastolic Dimension	4	308	0.23 [-1.95, 2.41]
1.6 Heart rate	5	416	6.57 [3.74, 9.41]
1.7 Body weight	5	420	4.24 [-0.24, 8.72]
1.8 Cardio-thoracic ratio	5	326	0.00 [-0.02, 0.02]
1.9 Systolic Blood Pressure	3	282	-5.13 [-9.83, -0.42]
1.10 Diastolic Blood Pressure	3	282	1.74 [-0.52, 4.01]
1.11 Hospitalisation - heart failure (without DIG trial)	7	516	2.41 [1.13, 5.14]
1.12 Mortality (without DIG trial)	7	516	0.68 [0.19, 2.43]
1.13 Hospitalisation - all cause (without DIG trial)	3	206	1.11 [0.20, 6.25]



**Figure 2.2 – Heart failure hospitalisations: digoxin withdrawal versus digoxin continuation.**



**Figure 2.3 – Heart rate: digoxin withdrawal versus digoxin continuation.**



**Figure 2.4 – Funnel plot of digoxin withdrawal versus digoxin continuation for mortality, demonstrating no publication bias.**

Shammas et al [185] examined digoxin withdrawal with background ACE inhibitors and beta-blockers in a single-arm observational trial with eight patients with IDCM and normalised EF >50%. Mean baseline LVEF measured with isotope ventriculography at initial presentation was  $28.5 \pm 8.3\%$ , and improved to  $56.1 \pm 4.7$  over  $17.3 \pm 5.4$  months. On digoxin withdrawal, LVEF fell to  $51.0 \pm 7.35$  ( $p=0.05$ ) at mean follow-up of  $7.0 \pm 4.3$  months, although this remained in the normal range. No comment was made on the clinical status of the patients.

The CAFÉ (Carvedilol in Atrial Fibrillation Evaluation) trial enrolled 47 participants with AF and HF, taking background ACE inhibitors [186]. When digoxin was withdrawn and carvedilol continued, a significant increase of 22 bpm in mean heart rate ( $65.2 \pm 15$  to  $88.8 \pm 18.7$  bpm) and a 9% decline in LVEF ( $30.6 \pm 9.6$  to  $21.6 \pm 11$ ) were seen. Participants in the digoxin withdrawal / carvedilol continuation arm rated their symptoms better than the digoxin arm, however three subjects withdrew from the study after digoxin withdrawal due to worsening symptoms associated with HF due to increased heart rate. Greater control of ventricular response with digoxin was considered beneficial but this has recently been challenged [187,188].

#### 2.4.4 Diuretics

Diuretics cause contraction of intravascular volume leading to short-term relief from symptoms of congestion, but have been shown to stimulate the RAAS [189,190] and worsen renal function in the short term. The safety of diuretics has not been established [117]. Seven studies of diuretic withdrawal were identified. Deterioration was more frequent in the diuretic withdrawal group throughout, indicating an ongoing need for this class of drug in stable, chronic HF.

Three trials withdrew diuretics, commencing ACE inhibitors concomitantly in subjects with euvolaemic HF, in an attempt to determine whether ACE inhibitors could replace diuretics in subjects with mild to moderate HF. Richardson et al performed a 16 week, double-blind, cross-over trial [191]. Four of 14 participants (29%) developed pulmonary oedema when diuretics were withdrawn and captopril started, compared with none in the diuretic (frusemide with amiloride) continuation arm. On withdrawal of diuretic and randomisation to lisinopril or placebo, Grinstead et al found that 29 of 41 participants (71%) required diuretic after a median 15 (range 2-42) days [192]. Independent predictors of the need to restart diuretics included a history of hypertension, baseline daily frusemide dose of more than 40mg and LVEF less than 27%. Magnani et al withdrew diuretics from 64 participants who were then randomised to captopril or placebo in a 12 month trial in mild-to-moderate HF (NYHA class II or III) [193]. Background medication was digoxin. This study found that 34% required diuretics to be restarted, and that captopril was associated with reduced need for diuretics.

Significant failure rates were seen on withdrawal of diuretics in HF. Walma et al performed a 6 month double-blind randomised trial withdrawing or continuing diuretics in 202 subjects with various indications aged over 65 years recruited from general practice [194]. Of the subjects with HF, diuretic withdrawal was poorly tolerated, with 30 (65%) subjects in the withdrawal group (n=46) requiring diuretics to be restarted, whereas only 4 (11%) subjects randomised to diuretic continuation (n=38) required further diuretics during the trial. The risk difference was 57% (36% to 78%). De Silva halved the doses of diuretic in 50 patients with HF and renal dysfunction, with doses of frusemide ranging from 40mg to 160mg daily, and 36% were unable to tolerate such a reduction [165]. Diuretics were ceased in 18 patients on a 20mg dose, and 39% were unable to tolerate cessation of even this small dose. Reasons for recommencement of diuretics included shortness of breath, ankle swelling

and weight gain. Of the 42 participants who could tolerate cessation, modest improvements in serum creatinine were seen. Higher baseline serum creatinine was associated with worse tolerance of diuretic withdrawal, and less marked improvements in serum creatinine.

Two trials investigated the neurohormonal effects of diuretic withdrawal. Galve et al withdrew diuretics from 26 subjects with stable HF (mean LVEF 34%) on background ACE inhibitor [195]. At three months, 9 (35%) required diuretics to be restarted (median time to reinitiation 33 days, range 2-83), and 17 (65%) tolerated withdrawal successfully with no deterioration in exercise tolerance or NYHA class (15 of whom remained off diuretics without deterioration out to 12 months). Importantly, diuretic withdrawal was associated with improvement in renal function parameters and glucose metabolism, with no change in heart rate or systolic BP and a rise in diastolic BP observed. A decrease in plasma renin activity was noted, but no change in aldosterone, arginine-vasopressin, endothelin-1 and norepinephrine seen. ANP levels increased. Braunschweig et al withdrew frusemide from four patients with stable severe HF, with LVEF ranging from 21 to 33%, receiving both ACE inhibitors and beta-blockers, using implantable haemodynamic monitoring devices to allow continuous haemodynamic monitoring [196]. Right ventricular systolic and diastolic pressures, and estimated pulmonary artery pressures increased over the two week study period in all four patients, in parallel with increasing symptoms of HF, reduction in exercise tolerance and increase in BNP levels, demonstrating the rapidity of fluid accumulation on diuretic cessation.

### **2.4.5 Vasodilators**

Withdrawal of isosorbide dinitrate alone was compared with withdrawal of a placebo in HF patients [197]. At rest, withdrawal of nitrates had no effect on LV chamber size, however during exercise, nitrate withdrawal was associated with a reduction in LVEF (mean change: 0.8 vs -2.7%,  $p < 0.02$ ). No studies were identified which tested the withdrawal of combination hydralazine and nitrates.

### **2.4.6 Ancillary agents used in HF**

#### **2.4.6.1 Aspirin**

Aspirin's use in both ischaemic and non-ischaemic HF to reduce thrombotic risk is mired by evidence of worsening of HF status with this drug [64]. The WASH (Warfarin/Aspirin Study in Heart Failure)

study included 279 participants randomised to no anti-thrombotic (No ATT), aspirin or warfarin in HF in SR [102]. Baseline aspirin was withdrawn in the No ATT (46% of the group) and warfarin (56% of the group) arms. Overall there were no significant differences in the primary outcomes of death, non-fatal MI and non-fatal stroke across the three groups. However a pre-specified secondary analysis found that aspirin was associated with a significantly increased risk of CV hospitalisation mainly for worsening HF, suggesting that aspirin may exacerbate HF, and its withdrawal reduce its occurrence.

Withdrawal of aspirin may also improve renal function. The study by De Silva et al of participants with HF and renal dysfunction also withdrew aspirin and substituted clopidogrel in 32 participants, with a resultant fall in serum creatinine by 8 (SD 19)  $\mu\text{mol/l}$  ( $p=0.05$  within the group) [165]. No comment on symptoms of HF was made.

#### **2.4.6.2 HMG CoA Reductase inhibitors (Statins)**

RCTs of statins have shown no mortality benefit in HF [115,116]. However there have been no trials investigating the effects of statin withdrawal in the HF setting, when they are not considered otherwise indicated.

## **2.5 Discussion**

In patients with chronic stable HF, the studies reviewed here indicate that continuation of RAAS inhibitors and beta-blockers is mandatory, given the deterioration in clinical status seen on withdrawal of these medications, and also their known survival benefit. This assessment also likely extends to aldosterone antagonists and combination hydralazine/nitrates, despite the absence of withdrawal trials. Limited data reviewed shows that patients with HF with normalised LVEF increase their risk of recurrent HF if neurohormonal blockade is withdrawn. This can occur many years later, suggesting that the underlying pathology continues despite normalisation of the LVEF. Indeed recurrence has been well documented in subsequent pregnancies in patients with peripartum cardiomyopathy [198].

This methodical and comprehensive review of the literature has demonstrated the scarcity of robust evidence to guide withdrawal of medications in HF. The majority were observational trials or cross-over trials, and only a minority were RCTs. Follow-up in most studies was less than one year. The studies reflect a different era of HF therapeutics, with most trials performed with digoxin as

background therapy. The relative absence of high quality data has precluded meta-analysis, other than that of digoxin withdrawal, and even here, no contributing trials involved patients receiving background beta-blockers. Pragmatic reasons also contribute to the inadequacy of the available data. Objections from physicians and ethics committees, poor recruitment and difficulty in obtaining funding all may have resulted in RCTs too small to adequately answer the question they were designed to address. In essence new medications developed for patients with HF have been added to existing therapies, as it has been considered unethical to remove older medications with possible benefit.

Withdrawal trials can be difficult to interpret. There may be weaknesses inherent in their design, and interpretation can be ambiguous. Withdrawal trials may introduce bias in favour of the drug, as participants who cannot tolerate the drug are not included in the trial and therefore participants represent a group who benefit from, or at least tolerate, the drug, consequently deteriorating on its withdrawal. The effect of medication withdrawal is also complex, and may be influenced by a number of factors that cannot be addressed in this review, such as the aetiology, duration and severity of HF symptoms, degree of systolic dysfunction, patient age and method of withdrawal whether abrupt or stepped. Withdrawal of drugs without manipulation of other medications may not be a fair test of a therapeutic strategy [199]. Cross-over designs assume that there will not be a “carry over” effect from the intervention from first to second phase of the trial. The long-term benefits of neurohormonal antagonists may occur far out from their time of initiation and it is reasonable to expect that the effects of withdrawal may also be delayed. Additionally the rationale for withdrawing medications varies between trials, with confounding by indication problematic, especially in observational trials.

In light of these caveats, which trials of medication withdrawal would be important to inform clinicians considering reducing HF therapies in patients? A prospective trial of withdrawal of neurohormonal blockade in patients with HF with recovered LVEF would be difficult to justify because of the evidence presented here, and it is possible that such a trial would not have sufficient follow-up to capture late deterioration. However there may be a role for trials of dose reduction in this population, and in such a trial, an important element would be to investigate possible markers which

could predict recurrence of HF. Further, trials of medication withdrawal after normalisation of LVEF in patients with peripartum cardiomyopathy would be a relatively safe clinical situation in which to consider such trials.

There are questions relating to both efficacy and safety of digoxin that mean its role in HF remains unresolved. It has been suggested that the benefits of modern HF therapies including ACE inhibitors, beta-blockers and aldosterone antagonists may overwhelm any benefit seen with the use of digoxin [200]. While the DIG trial, which was performed prior to beta-blockers being established as a standard of care in HF, did not show an overall mortality benefit with digoxin compared with placebo [97], statistically significant reductions in HF hospitalisations were observed and *post-hoc* analysis suggested a potential mortality benefit at low serum concentrations [201]. Recent retrospective studies failed to show any benefit with digoxin, but issues of confounding by indication and patients receiving digoxin having more severe HF, made interpretation difficult [202,203]. Higher quality data comes from a *post-hoc* analysis of the Val-HeFT trial which demonstrated no benefit from the addition of digoxin to ACE inhibitors, beta-blockers and diuretics, but also suggested a possible detrimental interaction between digoxin and beta-blockers, however participants were not randomised to digoxin [204]. Further safety issues arise from digoxin's modest positive inotropic effects, as drugs with such effects have been associated with poorer outcomes and increased risk of sudden death in HF [205]. However, digoxin continues to be used in clinical practice, albeit with calls for further trials [200,206,207]. An important question to address is whether there continues to be a role for digoxin in such patients on optimal background HF pharmacotherapy, and a randomised digoxin withdrawal trial could inform this.

The overall quality of the diuretic withdrawal trials identified was poor, with three studies introducing an ACE inhibitor at the same time as withdrawing diuretic, the type of diuretic (whether potassium sparing or not) poorly specified, and background therapies not optimised according to current guideline recommendations. A key question is whether diuretics confer benefit or risk in the setting of chronic euvoaemic HF in patients prescribed optimal neurohormonal blockade. A diuretic withdrawal study could be designed, comparing continuation of higher or withdrawal to lower doses



as well as complete cessation of diuretic, and an important element would be to attempt to identify accurate predictors of sustained clinical stability following diuretic withdrawal.

Despite statins failing to confer a survival benefit in large RCTs in patients with HF [115,116], they are still commonly prescribed. Reasons to continue statins include their purported beneficial pleiotropic properties including anti-inflammatory effects and improvement in endothelial function [109], other potential benefits which may be important in patients with ischaemic cardiomyopathy including reduced risk of coronary heart disease events, primary and secondary stroke [208], and in those with peripheral arterial disease, improvement in symptoms and reduced progression of disease [209,210]. Although the proportion of patients with side effects from statin usage is low, the number of patients taking them means that side effects are encountered commonly in practice [211]. Statins are the class of drug which HF patients themselves identify as causing the greatest frequency of side-effects [212]. Coenzyme Q10 depletion potentially exacerbates poor myocardial contractility [213], and also impairs the ability of cholesterol rich lipoproteins to detoxify bacterial lipopolysaccharides [214]. Statins have not been abandoned in HF, despite evidence lacking for their efficacy. A trial of statin withdrawal in patients with ischaemic HF would inform clinicians on the safety of doing so.

Aspirin is commonly used in patients with HF as an anti-thrombotic, although there is no evidence for a reduction in MI or stroke or of a mortality benefit in this context [102,104,215]. The anti-prostaglandin effects of aspirin result in sodium and water retention, and indeed early trial evidence suggested a worsening of HF status with aspirin [102,104] although recent evidence from the WARCEF (The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction) study in mild HF found otherwise [215]. There is also potential for an interaction with ACE inhibitors which might negate their mortality benefit [216,217]. An aspirin withdrawal trial in patients with ischaemic cardiomyopathy is warranted.

## 2.6 Conclusion

In summary, the database regarding drug withdrawal is incomplete, however it does demonstrate specific risks with withdrawal of neurohormonal blocking agents. Medication cessation in patients with HF and recovered EF increases risk of late recurrence of HF. Based on the above, there clearly is a need for high quality RCTs examining the discontinuation of medications without proven mortality benefit in HF, specifically digoxin, statins and aspirin.

*Appendix 2.2– trials excluded from meta-analysis*

# Chapter 3: Digoxin withdrawal worsens clinical status in stable heart failure patients receiving optimal contemporaneous therapy – a randomised controlled trial

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## Declaration for Thesis Chapter 3

### Declaration by candidate

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

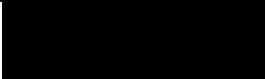
Nature of contribution	Extent of contribution (%)
Designed study, obtained ethics approval, obtained funding, screened, recruited and consented patients, collected data including blood samples and 6 minute walk tests, cleaned and analysed data, wrote paper, archived documents.	85%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
<b>M Skiba</b>	Advised on the following: design of study, ethics application, costings, pathology and pharmacy, assisted in management of patient medications to retain blinding, cross-checked data entry, assisted in intellectual content and drafting of the paper.	
<b>TG von Lueder</b>	Assisted in performing the echocardiograms, cleaned and analysed the echo data, assisted in intellectual content and drafting of the paper.	
<b>M Watanabe</b>	Assisted in performing the echocardiograms, and intellectual content and drafting of the paper.	
<b>R Funston</b>	Assisted in design of the case report form, assisted in the data collection and on-study care of the patients, assisted in intellectual content and drafting of the paper.	
<b>A Tonkin</b>	Supervisor throughout the study, assisted with conception and planning of the study, analysis of results, drafting of paper.	
<b>H Krum</b>	Supervisor throughout the study, assisted with conception and planning of the study, analysis of results, drafting of paper.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

**Candidate's  
Signature**

	<b>Date</b> <b>November 2015</b>
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**Main  
Supervisor's  
Signature**

	<b>Date</b> <b>November 2015</b>
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The following article “Digoxin withdrawal worsens clinical status in stable heart failure patients receiving optimal contemporaneous therapy – a randomised controlled trial” has been published as a Research Letter in the international medical journal “*Journal of Cardiac Failure*”.

It is presented here in expanded form.

Citation of the article [154]:

Hopper I, Skiba M, von Lueder TG, Watanabe M, Funston R, Tonkin A, Krum H. Digoxin withdrawal worsens clinical status in stable heart failure patients receiving optimal contemporaneous therapy – a randomised controlled trial. *Journal of Cardiac Failure*. 2015; 21: 779-81.

### 3.1 Abstract

**Background:** Digoxin's role in HFREF patients in SR is unclear. We investigated digoxin withdrawal in HF patients receiving digoxin with optimal ACE inhibitor/ARB and beta-blocker.

**Methods:** Prospective, randomised, single-blind, placebo-controlled, two-arm cross-over trial. Participants were randomised to digoxin continuation ("dig-on") or unmatched placebo ("dig-off") and crossed over after three months. Standard HF clinical status and QoL endpoints were evaluated. Dig-on vs dig-off results were compared using a two-tailed paired *t*-test.

**Results:** The 16 participants were aged  $61.3 \pm 11.0$  years, 81% were male, the mean duration of HF was  $5.6 \pm 3.3$  years and mean EF was  $33 \pm 10\%$ . HF aetiology was ischaemic (7) and non-ischaemic (9). All participants completed the dig-on arm, and two withdrew from the dig-off arm early due to deterioration in HF (assessments included). Digoxin withdrawal resulted in a 50% increase in plasma BNP (dig-on:  $405 \pm 587$  vs dig-off:  $604 \pm 843$  ng/L,  $p=0.019$ , 95%CI 39-361), reduced 6 minute walk distance (dig-on:  $474 \pm 69$  vs dig-off:  $455 \pm 64$  m,  $p=0.015$ , 95%CI 4-34) but no worsening in QoL measures. Echocardiographic parameters were unchanged.

**Conclusion:** Withdrawal of digoxin in stable HFREF patients in SR on optimal contemporaneous therapy worsens HF clinical status with increased BNP and reduced submaximal exercise capacity but did not worsen QoL.

## 3.2 Introduction

The role of digoxin in patients with HFREF in SR and receiving contemporary evidence-based neurohormonal blocking therapies, including ACE inhibitors or ARBs, MRAs and beta-blockers is not clear. Since the establishment of ACE inhibitors, beta-blockers and MRAs as standard of care in HF [18], there have been no RCTs of digoxin in this context [218]. The largest RCT of digoxin, performed against a background of ACE inhibitors (but not beta-blockers or MRAs), showed that overall digoxin reduced hospitalisations but had a neutral effect on mortality [97]. A post-hoc analysis of this trial found that a serum digoxin concentration of 0.5-0.9ng/ml was associated with a mortality which was lower than average, and higher concentrations were associated with higher than average mortality [219]. Digoxin use is generally associated with poorer outcomes in contemporary non-randomised observational and retrospective studies [202,204,220]. However these results are confounded by indication, with sicker patients more likely to be prescribed digoxin [200].

We therefore sought to determine whether digoxin has an ongoing therapeutic role in HF patients receiving optimal background neurohormonal blockade including ACE inhibitors/ ARB and beta-blockers. Our hypothesis was that digoxin no longer has a clinical effect in the era of modern HF pharmacotherapy and could thus be safely withdrawn without adverse short or medium term clinical worsening.

## 3.3 Methods

This study was designed as a prospective, randomised, open-label blinded end-points, placebo-controlled, cross-over trial. Participants were recruited from the HF Clinic of the Alfred Hospital, which is a large outpatient clinic in a tertiary referral centre in Melbourne, Australia and the regional centre for heart transplantation. Eligibility criteria included patients over the age of 18, in SR at the time of randomisation, LVEF $\leq$ 45%, taking digoxin for at least three months at a dose aiming for digoxin plasma levels of between 0.5 and 0.9ng/ml, and documented stable HF with one of BNP $\geq$ 100ng/L, evidence of pulmonary congestion on chest X-ray or evidence of HF on echocardiogram. Initially an EF $\leq$ 40% was required for inclusion, however at one year this was

altered to EF  $\leq 45\%$  due to slow recruitment. Participants were also required to be on a stable dose for at least four weeks of both an ACE inhibitor/ARB and a beta-blocker, and a diuretic dose unchanged for at least two weeks. MRA use was not mandated in this study. Implantable cardioverter-defibrillators (ICD) and cardiac resynchronisation therapy (CRT) devices were permitted. Exclusion criteria included uncorrected primary valvular disease, active myocarditis, obstructive or restrictive cardiomyopathy, exercise capacity limited by factors other than cardiac dyspnoea, MI in the previous six months, stroke in the previous 12 months, hospitalisation within one month of randomisation and severe primary pulmonary, renal or hepatic disease.

Participants were randomised to either digoxin continuation (“dig-on”) or digoxin withdrawal (using placebo, “dig-off”) for 12 weeks, and then crossed over to the opposite arm for a further 12 weeks. A safety visit was performed six weeks after commencement of each treatment arm. This was a pragmatic trial, and the dose of digoxin already prescribed by the HF physician when the participant was recruited from clinic was the dose used within the trial.

The randomisation schedule was designed using a random number generator, and kept (blinded to the study investigators) in the Alfred Hospital Pharmacy. The blinding was not broken during the trial. Medications were dispensed by the pharmacy in opaque bags. Questions about trial medications were answered by other study investigators in order to fully maintain the blinding of the study lead investigator (IH). Trial medications were not matched, and included digoxin, which was coloured blue and placebo, which was a commercial unmarked saccharine tablet Natvia™. Participants were not fully blinded to treatment allocation; specifically they were not explicitly told which arm they were in, and agreed not to un-blind themselves. IH or HK performed all clinical assessments and were fully blinded to treatment group allocation.

Endpoint evaluations and plasma digoxin levels were performed at baseline, at cross-over at three months, and the end of the trial at six months. The primary efficacy endpoint of this study was change in plasma BNP levels between digoxin control and withdrawal groups. An increase in BNP of  $\geq 50$  pg/ml was considered clinically significant (with estimated mean baseline BNP of 200 pg/ml) and to indicate potential destabilisation of patients’ clinical status, and that it was unlikely that digoxin could be safely withdrawn. A sample size of 16 patients has 95% power to detect a minimum



difference of 50 pg/ml with alpha of 0.05 and based on a SD of the difference in plasma BNP of 50 pg/ml which was derived from a comparable patient group [221]. Plasma BNP levels were determined by Chemiluminescent Microparticle ImmunoAssay using the Abbott Architect ci16200 machine, which can detect plasma BNP to a lower level of 10ng/L.

Other end-point evaluations included 6 minute walk distance (6MWD), standard laboratory evaluations, Cardiac Depression Scale (CDS), Minnesota Living with Heart Failure Questionnaire (MLHFQ), and Short Form 36 Health Survey (SF-36). Two-dimensional- and Doppler echocardiography was also included, which was performed by expert sonographers in the left decubitus position using a commercially available system (GE Vingmed Vivid I, Horten, Norway) with a M3S probe. Frame rates (60-100 frames/s) were adjusted at end-expiratory breath holding for optimal image acquisition. Conventional echocardiographic and Doppler data were measured as recommended by the American Society of Echocardiography [8]. Recordings were analysed offline by blinded cardiologists without knowledge of the study groups.

Statistical analysis: GraphPad Prism version 6 was used for statistical analysis. Differences between dig-on and dig-off groups were assessed by two-tailed paired *t*-test. An unpaired *t*-test was used to determine whether a treatment order effect was present. A two-tailed *p*-value <0.05 was regarded as significant. Data are expressed as mean  $\pm$  SD unless otherwise stated.

Ethics approval was obtained from the Alfred Hospital Ethics Committee and the Monash University Human Research Ethics Committee. This research conformed to Principles of the Declaration of Helsinki, and each participant provided written informed consent. The ClinicalTrials.gov registration number was NCT01398371.

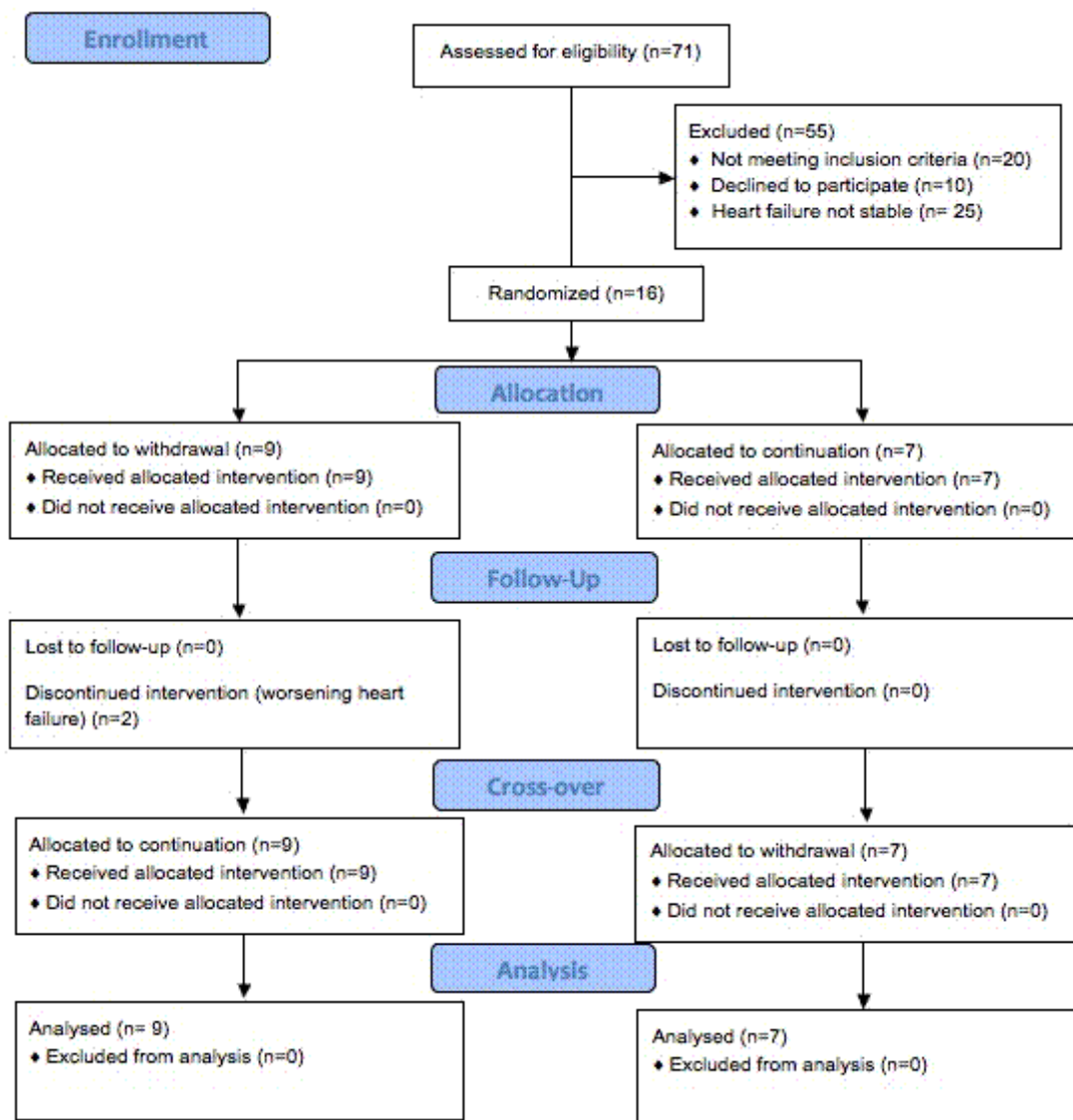
### 3.4 Results

The first study participant was recruited in February 2012 and the final participant seen in February 2015. A total of 16 participants were randomised, all received the intended treatments and all were analysed for the primary outcome by intention-to-treat (Figure 3.1). Two participants withdrew from the dig-off arm due to deterioration in HF symptoms. Their final endpoint evaluations were performed early and are included in the analysis.

Baseline characteristics of the individual participants are described in Table 3.1. Mean age was  $61.3 \pm 11.0$  years, 81% were male and the mean duration of HF was  $5.6 \pm 3.3$  years. The mean LVEF for the group was  $33 \pm 10\%$ . HF aetiology was ischaemic in seven patients and non-ischaemic in nine. Background treatments reflect a high compliance with guideline mandated therapies. All participants were on both ACE inhibitor/ARB and beta-blockers. A total of nine were on MRA, 11 had an ICD and two had CRT defibrillators (CRT-D).

The mean plasma digoxin level during the active phase was  $0.5 \pm 0.2$  ng/ml. Three participants fell below the therapeutic range of serum digoxin, with two at 0.3 ng/ml and one 0.2 ng/ml. One participant had digoxin levels above 1.0 ng/ml. None of the participants had detectable digoxin levels during the placebo phase. During the dig-off arm, four participants required an increase in diuretic compared with one participant in the dig-on arm. Two participants withdrew early from the dig-off arm due to worsening HF symptoms. No participants were hospitalised during the trial.

Compared to taking digoxin (dig-on), withdrawal of digoxin (dig-off) resulted in a significant approximately 50% increase in plasma levels of BNP (dig-on:  $405 \pm 587$  vs dig-off:  $604 \pm 843$  ng/L,  $p=0.019$ , 95% CI 39 to 361) (Figure 3.2) and reduced 6MWD (dig-on:  $474 \pm 69$  vs dig-off:  $455 \pm 64$  m,  $p=0.015$ , 95% CI 4 to 34) (Figure 3.3). CDS improved slightly (dig-on:  $82 \pm 20$  on vs dig-off:  $72 \pm 22$ ,  $p=0.005$ , 95% CI 4 to 17) (Figure 3.4) but no significant change was seen in MLHFQ score (dig-on:  $29 \pm 19$  vs dig-off:  $25 \pm 16$ ,  $p=0.105$ , 95% CI -1 to 9) (Figure 3.5), nor in SF-36 (dig-on:  $98 \pm 15$  vs dig-off:  $97 \pm 14$ ,  $p=0.714$ , 95% CI -5 to 7) (Figure 3.6). Minor changes were seen in body weight (dig-on:  $87.3 \pm 13.2$  vs dig-off:  $88.2 \pm 13.1$  kg,  $p=0.064$ , 95% CI 0.1 to 1.8), and there was a non-significant change in heart rate (dig-on:  $66 \pm 8$  to dig-off:  $69 \pm 9$  bpm  $p=0.060$ , 95% CI 0 to 6) and no change in systolic BP (dig-on:  $115 \pm 15$  to dig-off:  $115 \pm 17$  mmHg  $p=0.896$ , 95% CI -7 to 7). No change was observed in serum creatinine (dig-on:  $105 \pm 37$  to dig-off:  $108 \pm 40$   $\mu$ mol/L,  $p=0.350$ , 95% CI -8 to 3) or eGFR (dig-on:  $65 \pm 20$  to dig-off:  $64 \pm 19$  mL/min/1.73m<sup>2</sup>,  $p=0.716$ , 95% CI -3 to 5).



**Figure 3.1 – CONSORT Flow Diagram**

**Table 3.1 – Baseline characteristics**

No.	Age	Sex	Primary	Duration of	NYHA	Baseline	Background therapy							
			diagnosis	HF (years)	Class	EF (%)	ACE/ARB	Dose (mg)	BB	Daily dose (mg)	MRA	Dose (mg)	ICD	CRT
1	68	M	ICM	2.5	2	31	RAMI	10	BISO	10	SPIRO	25	Y	N
2	66	M	ICM	6	2	29	CAND	2	BISO	3.75	EPLER	50	Y	N
3	68	F	NICM	10	2	43	RAMI	10	BISO	1.25	SPIRO	25	N	N
4	54	F	ICM	2.5	2	30	RAMI	5	CARV	50	EPLER	12.5	Y	N
5	69	M	NICM	1.7	1	35	IRB	300	BISO	5	N	.	N	N
6	45	M	NICM	2.25	2	24	CAND	8	BISO	5	SPIRO	25	Y	N
7	74	M	ICM	6	2	32	CAND	32	BISO	5	N	.	Y	N
8	62	M	ICM	6	2	32	IRBE	300	SOTA	80	N	.	N	N
9	74	M	ICM	10	3	20	ENAL	2.5	CARV	50	N	.	Y	Y
10	61	M	NICM	7	3	30	RAMI	10	CARV	50	SPIRO	25	N	N
11	50	F	NICM	5	2	50	PERI	10	CARV	50	SPIRO	25	N	N
12	37	M	NICM	1.5	1	48	CAND	8	BISO	10	N	.	Y	N
13	68	M	NICM	5	1	48	PERI	8	METOP	142.5	N	.	Y	N
14	57	M	ICM	7	2	38	CAND	2	BISO	5	SPIRO	25	Y	N
15	54	M	NICM	4	2	26	PERI	4	CARV	75	SPIRO	25	Y	N
16	74	M	NICM	13	1	19	LISI	10	CARV	50	N	.	Y	Y

ACE/ARB, angiotensin converting enzyme/angiotensin receptor blocker; BB, beta-blocker; BiV, biventricular pacing; BISO, bisoprolol; CAND, candesartan; CARV, carvedilol; EF, ejection fraction; ENAL, enalapril; EPLER, Eplerenone; ICD, implantable cardioverter-defibrillator; ICM, ischaemic; IRB, irbesartan; HF, heart failure; LISINO, Lisinopril; METOP, Metoprolol; MRA, mineralocorticoid receptor blocker; NICM, Non-ischaemic; NYHA, New York Heart Association; PERI, perindopril; RAMI, ramipril; SPIRO, spironolactone.

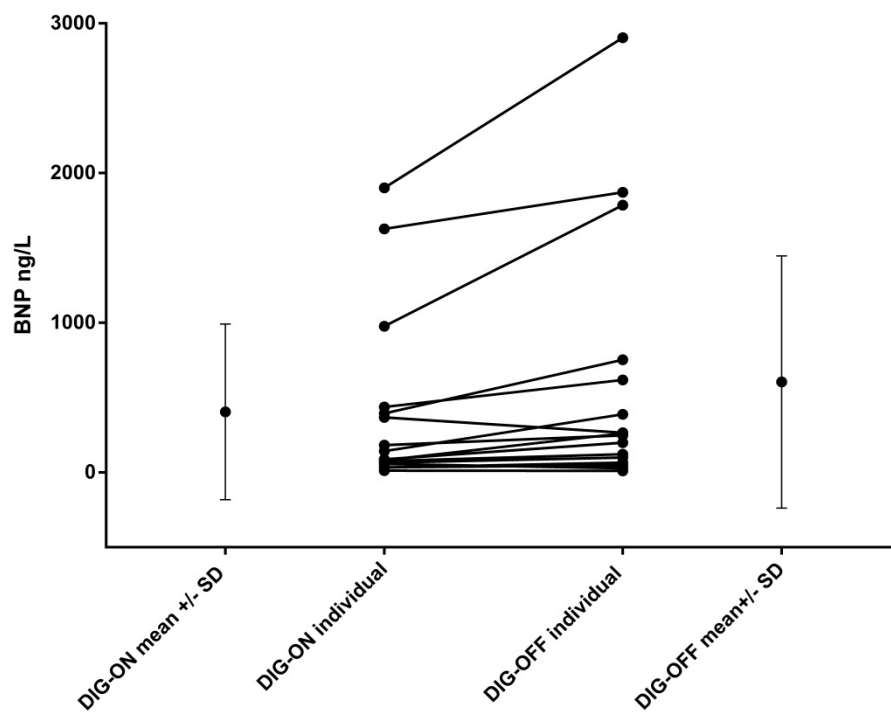


Figure 3.2 – Plasma BNP levels on and off digoxin

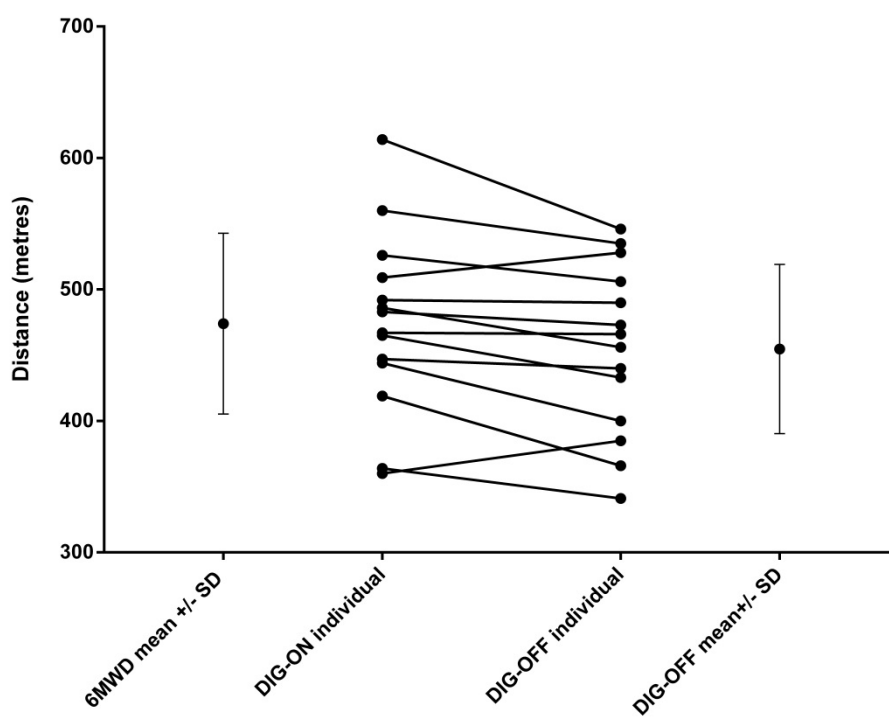


Figure 3.3 – 6MWD on and off digoxin

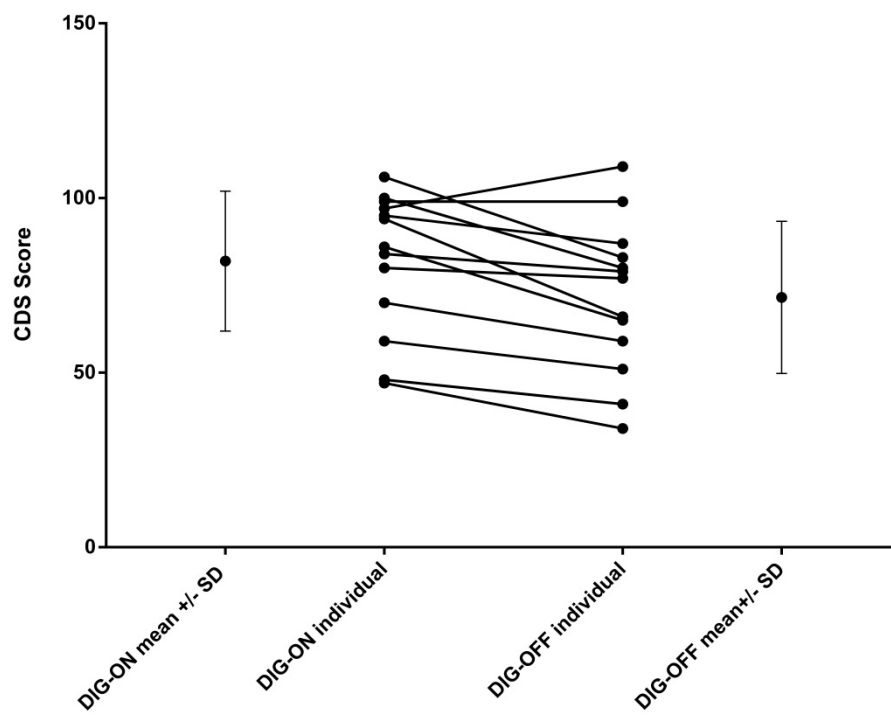


Figure 3.4 – CDS on and off digoxin

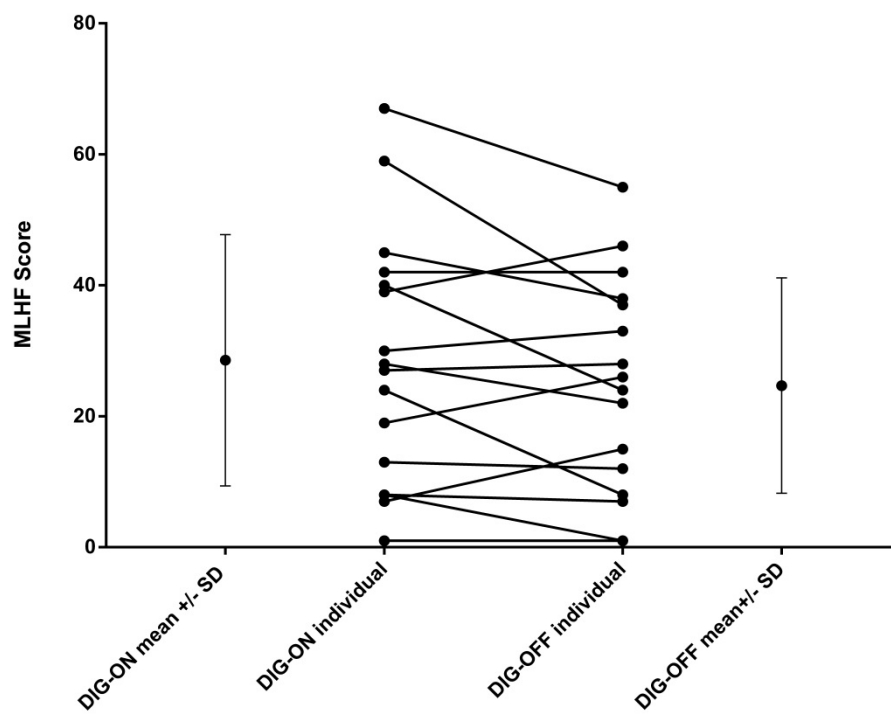
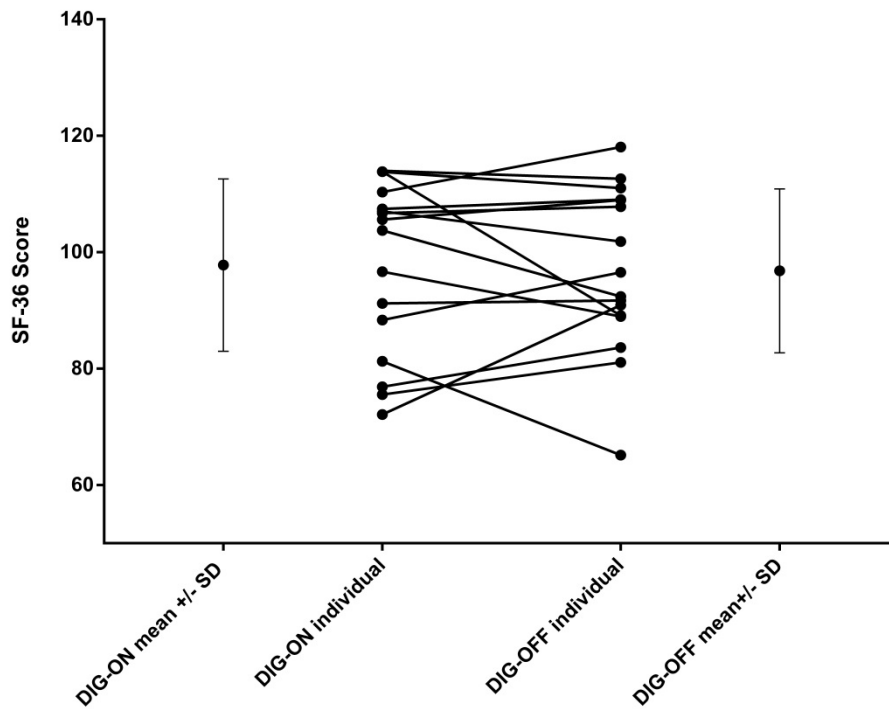


Figure 3.5 –MLHFQ on and off digoxin



**Figure 3.6 – SF-36 health survey on and off digoxin**

No significant differences for any echocardiographic parameters could be discerned between the dig-on and dig-off groups (Table 3.2) although there was a noteworthy non-significant trend towards increases in LV end-diastolic and systolic volumes in the dig-off group. Of note, we found a significant positive correlation between changes in plasma BNP and changes in LV end-diastolic ( $r=0.68$ ,  $p=0.045$ , 95% CI 0.03-0.93) and systolic volumes ( $r=0.73$ ,  $p=0.025$ , 95% CI 0.13-0.94), respectively. There was no evidence of a treatment order effect ( $p=0.6$ ).

Sub-group analysis on participants with EF 40% or less ( $n=11$ ) was performed as per the original planned analysis. In those subjects, even greater differences between dig-on vs dig-off were seen in plasma levels of BNP (dig-on:  $560\pm656$  vs dig-off:  $842\pm929$  ng/L,  $p=0.019$ , 95% CI 58 to 508) and 6MWD (dig-on:  $462\pm72$  vs dig-off:  $434\pm63$ m,  $p=0.015$ , 95% CI 6 to 45). No significant change in QoL scores were seen in this group (CDS dig-on:  $88\pm18$  to dig-off:  $78\pm21$ ,  $p=0.079$ , 95% CI -1 to 21; MLHFQ dig-on:  $32\pm18$  dig off:  $29\pm15$ ,  $p=0.373$ ; 95% CI -4 to 10, SF-36 dig-on  $97\pm15$  to dig-off  $94\pm1$ ,  $p=0.4536$ , 95% CI -5 to 11).

The median digoxin level was 0.5ng/ml. Sub-group analysis comparing participants with plasma digoxin level <0.5ng/ml (n=7) vs plasma digoxin level  $\geq$ 0.5ng/ml (n=9) was performed. Above the median digoxin level, there was a statistically significant difference in BNP (dig-on: 603 $\pm$ 722 vs dig-off: 940 $\pm$ 1004 ng/L, p=0.019, 95% CI 73 to 600). There was no statistically significant difference in BNP below the median (dig-on: 149 $\pm$ 175 vs dig-off: 173 $\pm$ 213 ng/L, p=0.500, 95% CI -103 to 56).



	DIG-ON	DIG-OFF	p-value
Left Atrial Area (cm <sup>2</sup> )	31±11	32±12	0.154
EF Biplane (%)	36±8	36±8	0.740
LVEDV Mod BP (ml)	175±42	195±42	0.092
LVESV Mod BP (ml)	111±37	126±35	0.093
FS (%)	17.4±4.1	17.5±5.3	0.932
IVSd (mm)	9.5±2.0	8.9±1.4	0.061
RWT	0.27±0.1	0.26±0.0	0.239
Heart rate (bpm)	64±9	68±10	0.642
MV E Vel (m/s)	0.66±0.23	0.65±0.20	0.712
MV A Vel (m/s)	0.54±0.25	0.52±0.22	0.969
MV Dec T (ms)	141±35	133±49	0.602
MV E/A Ratio	1.8±1.0	1.4±0.76	0.340
E/e'	16.4±7.9	14.6±7.1	0.176
Tei index	0.5±0.2	0.5±0.2	0.941
MV S' (cm/s)	4.8±1.1	4.5±1.4	0.916
TR Max PG	29.8±11.3	31.0±15.6	0.755
TAPSE (mm)	19±4	12±7	0.209

LA, left atrium; EF, ejection fraction; LVEDV, LV enddiastolic volume; LVESV, LV systolic volume, FS, fractional shortening, IVSd, enddiastolic interventricular septum thickness, RWT, relative wall thickness; HR, heart rate; MV E vel, peak transmitral E wave velocity; MV A peak transmitral A wave velocity; TR Max PG, tricuspid regurgitation maximum pressure gradient; TAPSE, tricuspid annular plane systolic excursion.

Values are presented as mean±SD.

**Table 3.2 – Cardiac dimensions and functions by echocardiography.**

### 3.5 Discussion

This is (to our knowledge) the first prospective RCT on the effects of digoxin withdrawal in stable HFREF patients in SR to be performed in the era of contemporaneous HF therapeutics. This included background therapies of ACE inhibitors/ARBs and beta-blockers, as well as high utilisation of MRAs and ICD/CRT. This study demonstrated overall deterioration in objective measures of HF status, including marked increases in plasma BNP levels. There was a modest decrease in 6MWD, and no deterioration in QoL on withdrawal of digoxin, with an overall trend towards improvement in HF specific QoL measures. Echocardiography parameters did not change significantly, however a correlation between changes in BNP and changes in LV volumes was seen. The results of this trial suggest that digoxin may provide benefits (at least in those stabilised on the drug), in particular in patients with LVEF 40% or less, and with digoxin levels above 0.5ng/ml, and that while some participants can be safely withdrawn from digoxin, deterioration in HF status as well as measures of adverse LV remodelling and LV filling pressures may occur despite modern HF therapy.

Digoxin exerts its actions by inhibiting membrane-bound sodium/potassium adenosine triphosphatase, increasing intracellular calcium and exerting weak positive inotropic activity on the myocardium [222]. Digoxin also exhibits beneficial neurohormonal effects by increasing parasympathetic tone [223] and decreasing activation of the sympathetic nervous system [224]. Current thinking is that the pharmacological and clinical effects of digoxin are likely to be overwhelmed by those of ACE inhibitors, beta-blockers and MRAs, rendering it redundant in the contemporary era [200]. However, some studies suggest that digoxin may have add-on benefits in HF in synergy with other drugs, including carvedilol and spironolactone [84,186]. Conversely, digoxin use has been associated with worse outcomes in retrospective studies [202], healthcare databases [220] and within clinical trials [204]. Of note, digoxin use in all of these studies was not randomised, thus the role of digoxin remains unclear.

The plasma digoxin levels of the participants in this study were mostly within the recommended range, and the mean plasma level was 0.5ng/ml. Therefore, plasma digoxin levels were considered to be generally optimal by today's standards in this group of participants [18,225].

However optimal dosing of digoxin remains somewhat uncertain. Digoxin has arrhythmogenic potential and a narrow therapeutic window. A reduction in HF-related deaths was offset by an increase in sudden deaths in the DIG study, thus resulting in an overall neutral effect on mortality [97]. The DIG study used much larger doses than are currently employed, and aimed for a plasma digoxin level of 0.8-2.5ng/mL, with mean digoxin concentration of 0.86ng/mL. Post-hoc analysis of the DIG trial found that serum digoxin concentrations between 0.5-0.9ng/L were associated with reduced mortality [219] and led to the lowering of guideline recommended doses [7]. Other studies have also shown that clinical benefits can be obtained with lower doses of digoxin [226,227]. However, it is worth noting that the recommended levels are derived from post-hoc analyses, not RCTs, and it has been suggested that higher serum digoxin concentrations may be a marker for higher-risk HF that cannot be corrected for in multivariate analysis [96].

A further change in the landscape of HF therapeutics is the widespread use of beta-blockers and MRAs additional to ACEi, both of which have been shown to reduce sudden death [228,229]. The addition of these classes of medications may favourably alter the risk/benefit ratio for digoxin [200]. All participants on our trial were taking background beta-blockers and over half were on MRAs. MRA use was not mandated in the protocol as use of this medication is generally restricted to those with a lower EF. The doses of beta-blockers and MRAs were highly variable, and were selected by the treating physicians in an effort to balance efficacy with off-target effects. Thus, this can be considered a pragmatic trial, reflecting current clinical use of digoxin and other medications in a large HF centre and outside of usual clinical trial restrictions and exclusions.

We observed a substantial 50% increase in plasma BNP levels upon digoxin withdrawal. This key finding of our study indicated deterioration in HF status across the entire spectrum of systolic LV function. However confidence intervals were wide and findings should therefore be interpreted in this light. Digoxin withdrawal did not induce significant changes in parameters of LV dimensions or function, which is consistent with previous studies of digoxin withdrawal over a similar time period [153]. It may be that the 12 week time period was insufficient to see LV remodelling. Yet, the clinical relevance of marked increases in plasma BNP level after digoxin withdrawal was corroborated by significant correlation with changes in LV volumes.

Despite the marked changes in plasma BNP levels, changes in 6MWD and QoL measures were modest. The 19m reduction in 6MWD was statistically significant, although this distance is not considered clinically significant [230]. Previous trials have found deterioration in 6MWD on digoxin withdrawal [177,182], while others have not [176]. Despite worsening in overall HF status, QoL measures remained stable or improved. Previous digoxin withdrawal studies have demonstrated either no effect [176] or a deterioration [177] in QoL, and addition of digoxin to background therapy was associated with only a modest short-term improvement in QoL [231]. Many patients with HF are asymptomatic, and increases in LV filling pressures may precipitate worsening which is not necessarily paralleled perfectly by these measures. Examination of the individual data in Figures 3.4-3.6 demonstrates substantial inter-individual variability, with some participants indicating considerable improvement in QoL on withdrawal of digoxin. This may suggest that QoL assessments can be influenced by the absence or presence of common drug-related side effects, or indeed by simply participating in a trial [232].

Withdrawal trials were a commonly used approach to investigate the utility of digoxin when its use was more widespread in HF [176,177,180], but have important limitations. Withdrawal of digoxin may overstate its efficacy by selecting stable patients who are benefitting from its use, and are thus more likely to deteriorate on its removal. Additionally, the selection of other HF treatments is made concomitantly with digoxin use, and thus it may be unreasonable to withdraw digoxin without subsequent adjustment of other medications. One of the strengths of this study is the cross-over design, in which each patient acts as their own control, reducing variation and the potential for type-II error. There was no effect of treatment order on the results, indicating that background worsening, or improvement, of the HF disease process, did not affect intra-individual comparisons. Analysis of previous digoxin withdrawal trials demonstrated that deterioration in HF status occurred at around 4-6 weeks [176,177], thus the length of each arm of the trial at 12 weeks was designed to mitigate any potential cross-over effect of drug or withdrawal effect into the other arm, and a wash-out period was considered unnecessary.

As this trial is relatively small in size, it is considered a pilot study to inform a more definitive evaluation. Additionally these patients reflect prescribing patterns in a single centre only.

Yet, we assume that our findings are generalisable to HF patients optimally treated with neurohormonal blockade. A further limitation of this trial was the lack of a matching placebo tablet. It is possible that some patients were aware of which medication they were taking, and that may have impacted the QoL questionnaires. In addition, the 6MWD performance can also be affected by training [233]. However, evaluation of the primary endpoint of plasma BNP is objective and all other endpoints was performed fully blinded by the investigators.

### **3.6 Conclusion**

In summary, this RCT observed that digoxin withdrawal resulted in an overall worsening of HF clinical and functional status but no worsening in QoL measures. Although the magnitude of benefit relative to comparator of ACE inhibitor/ARB, beta-blockers and MRAs may have surpassed those of digoxin, this finding demonstrates that withdrawing digoxin in patients with HFREF in SR with optimised background neurohormonal blockade worsens HF status, as reflected by a 50% increase in plasma BNP. Large prospective RCTs in patients with symptomatic HF using low-dose digoxin are needed to determine the role of this old but apparently still useful drug.

# Chapter 4: Polypharmacy in heart failure – is reducing medications safe?

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## Declaration for Thesis Chapter 4

### Declaration by candidate

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Designed study, obtained ethics approval, screened, recruited and consented patients, collected data including blood samples and 6 minute walk tests, cleaned and analysed data, wrote paper, archived documents.	95%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
<b>M Skiba</b>	Advised on the following: design of study, ethics application, costings, pathology and pharmacy, assisted in management of patient medications to retain blinding, cross-checked data entry, assisted in intellectual content and drafting of the paper.	
<b>E Windebank</b>	Assisted in design of the case report form, assisted in the data collection and on-study care of the patients, assisted in intellectual content and drafting of the paper.	
<b>J Brack</b>	Assisted in design of the case report form, assisted in the data collection and on-study care of the patients, assisted in intellectual content and drafting of the paper.	
<b>A Tonkin</b>	Supervisor throughout the study, assisted with conception and planning of the study, analysis of results, drafting of paper.	
<b>H Krum</b>	Supervisor throughout the study, assisted with conception and planning of the study, analysis of	

	results, drafting of paper.	
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The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

**Candidate's  
Signature**

	<b>Date</b> <b>November 2015</b>
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**Main  
Supervisor's  
Signature**

	<b>Date</b> <b>November 2015</b>
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This paper “Polypharmacy in the heart failure – is reducing medications safe?” has been accepted as a Research Letter in the international, peer-reviewed medical journal “International Journal of Cardiology”.

It is presented in this thesis with an expanded discussion. This chapter describes two randomised controlled drug withdrawal trials, one in which aspirin was withdrawn, and the other in which a statin was withdrawn. The methodology used for these trials was the same as that used in the digoxin withdrawal trial (chapter 3) and thus a detailed description is not included in this chapter. These aspirin and statin withdrawal trials are combined together in one chapter because these medications are often prescribed together for patients with ischaemic cardiomyopathy. However separate trials of drug withdrawal were undertaken for this thesis.



## 4.1 Abstract

**Background** - The role of aspirin and statins in HFREF is unclear. We performed two pilot studies investigating the effects of withdrawing aspirin and statins in stable HF patients while maintaining optimal doses of proven HF medications. We hypothesised that withdrawal of these medications would not alter HF clinical status.

**Methods** – Two prospective, randomised, placebo-controlled, single-blind cross-over trials, in which participants were randomised to either aspirin continuation (asp-on) or unmatched placebo (asp-off), or statin (statin-on) or placebo (statin-off) and crossed over at 3 months. Stable optimised doses of ACE inhibitor/ARB and beta-blockers were required. Standard HF clinical status and QoL endpoints were evaluated. Groups were compared using two-tailed paired *t*-test.

**Results** – Aspirin was withdrawn from 12 study participants with non-ischaemic HF, with a mean age of  $58 \pm 10$  years and 75% were male. The mean duration of HF was  $5.9 \pm 4.8$  years and the mean EF was  $37.3 \pm 9.5\%$ . Two participants withdrew during the trial. Compared with taking aspirin, withdrawal of aspirin resulted in no change in BNP (asp-on:  $110 \pm 82$  vs asp-off:  $97 \pm 102$  ng/L,  $p=0.526$ , 95% CI -66 to 36) or 6MWD (asp-on:  $562 \pm 94$  vs asp-off:  $563 \pm 104$  m,  $p=0.532$ , -25 to 14). QoL measures were unchanged. A statin was withdrawn from 13 study participants, with a mean age of  $64 \pm 11$  years and 62% were male. The duration of HF was  $7.7 \pm 5.7$  years and mean EF was  $38.1 \pm 10.4\%$ . Compared with taking statin, withdrawal of statin resulted in no significant changes in plasma BNP (stat-on:  $130 \pm 175$  vs stat-off:  $129 \pm 180$  ng/L,  $p=0.924$ , -23 to 21) or 6MWD (stat-on:  $455 \pm 172$  vs stat-off:  $450 \pm 182$  m,  $p=0.802$ , -19 to 23). QoL measures were unchanged.

**Conclusion** - Withdrawal of aspirin and statin in stable HFREF patients receiving optimal background HF therapy did not alter HF clinical status including plasma BNP levels, submaximal exercise capacity or QoL measures.

## 4.2 Introduction

Polypharmacy is increasing in HF patients, due in part to the widespread adoption of medications recommended in guidelines for HF [234], and the multiple comorbidities that accompany aging [137]. However there is scant evidence to guide physicians when considering reduction of medications for HF. A recent review of studies in which medications were withdrawn in HF demonstrated that cessation of ACE inhibitors and beta-blockers, and to a lesser extent diuretics, was associated with worsening of HF clinical status [153]. Other classes of medications which have been shown to lack benefit in HF could be withdrawn.

Two such classes include aspirin and HMG CoA reductase inhibitors (statins). These are accepted therapies for ischaemic heart disease, which is the cause of over 50% of cases of HF. However aspirin has been shown to reduce neither mortality nor CV events in HF [235], and has been associated with increases in plasma BNP in HF patients [105]. In addition, increased HF hospitalisations have been observed in some studies [102,104]. Statins have been shown to have a neutral effect on mortality in HF, in both ischaemic [115] and mixed ischaemic and non-ischaemic HF cohorts [116]. Therefore we performed pilot studies investigating the safety of withdrawing aspirin and statins in stable HF patients while maintaining optimal doses of proven HF medications. We hypothesised that withdrawal of these medications would not affect HF clinical status.

## 4.3 Methods

These studies were prospective, randomised, placebo-controlled, single-blind cross-over trials, in which participants were randomised to either aspirin (asp-on) or placebo (asp-off), or statin (stat-on) or placebo (stat-off) with cross-over after three months. These studies shared the same design as the digoxin withdrawal trial described in the previous chapter, except a six week safety phone call was substituted for the safety visit, and an echocardiographic assessment was not included.

Stable optimised doses of ACE inhibitor / ARB and beta-blockers were required. Standard HF clinical status and QoL endpoints were evaluated, including the CDS, MLHFQ and SF-36 Health Survey. Groups were compared using two-tailed paired t-test. Institutional ethics approval

was obtained, each patient provided informed consent, and the studies conformed to the ethical guidelines of the Declaration of Helsinki. The registration numbers for the trials are NCT01534026 and NCT01554592.

## 4.4 Aspirin withdrawal results

Aspirin was withdrawn from participants with documented non-ischaemic cardiomyopathy who were in SR at randomisation, with LVEF  $\leq 45\%$ . Participants were excluded if they had a past history of, or were at high risk for thromboembolism including if AF was present. Ischaemic HF was excluded as it was considered unlikely that treating physicians would consent to withdrawal of aspirin in these patients.

The 12 study participants had mean age  $58 \pm 10$  years, 75% were male, duration of HF was  $5.9 \pm 4.8$  years, and mean LVEF was  $37.3 \pm 9.5\%$ . Two participants withdrew, one due to transient ischaemic attack (TIA) with visual symptoms who had been randomised to placebo (not included in the analysis) and another due to onset of new AF (results included).

Compared with taking 100mg aspirin, withdrawal of aspirin resulted in no change in plasma BNP (asp-on:  $110 \pm 82$  vs asp-off:  $97 \pm 102$  ng/L,  $p=0.526$ , 95% CI -66 to 36) (Figure 4.1) or 6MWD (asp-on:  $562 \pm 94$  vs asp-off:  $563 \pm 104$  m,  $p=0.532$ , -25 to 14) (Figure 4.2). QoL measures were unchanged, including MLHFQ (asp-on:  $28 \pm 21$  vs asp-off:  $26 \pm 21$ ,  $p=0.284$ , -2 to 7) (Figure 4.3), CDS (asp-on:  $71 \pm 20$  vs asp-off:  $70 \pm 19$ ,  $p=0.373$ , -3 to 7) (Figure 4.4) and SF-36 (asp-on:  $99 \pm 11$  vs asp-off:  $102 \pm 11$ ,  $p=0.396$ , -3-6) (Figure 4.5).

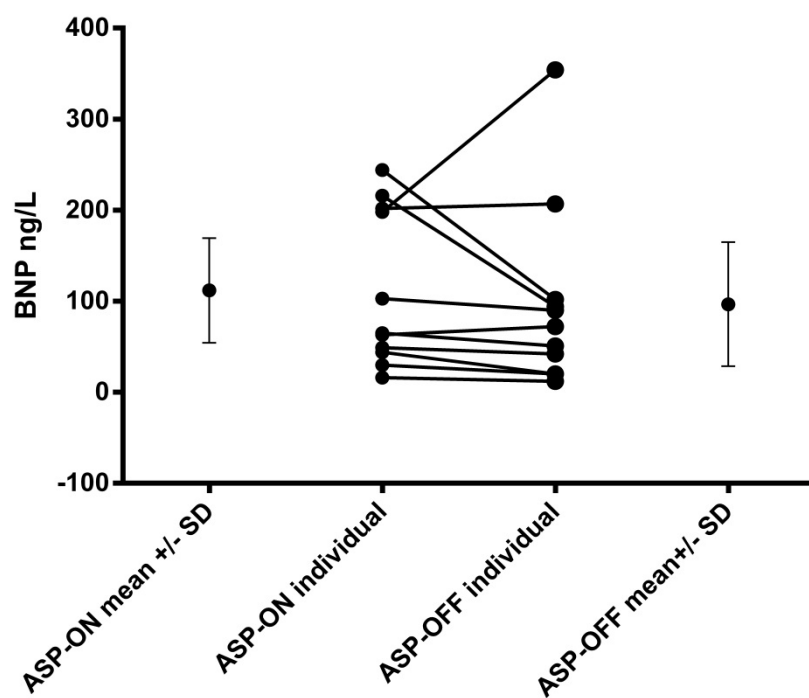


Figure 4.1 – Plasma BNP levels on and off aspirin

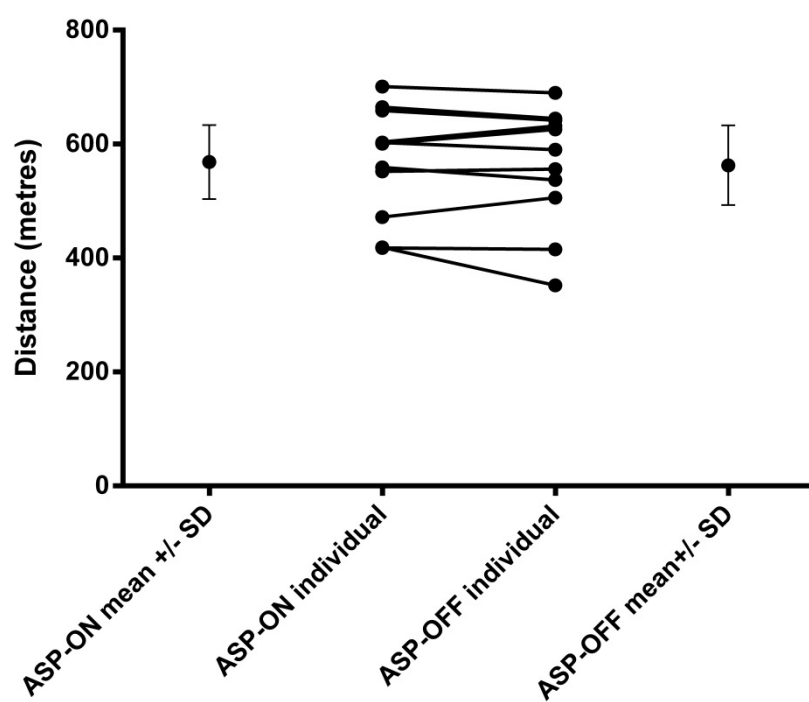


Figure 4.2 – 6MWD on and off aspirin

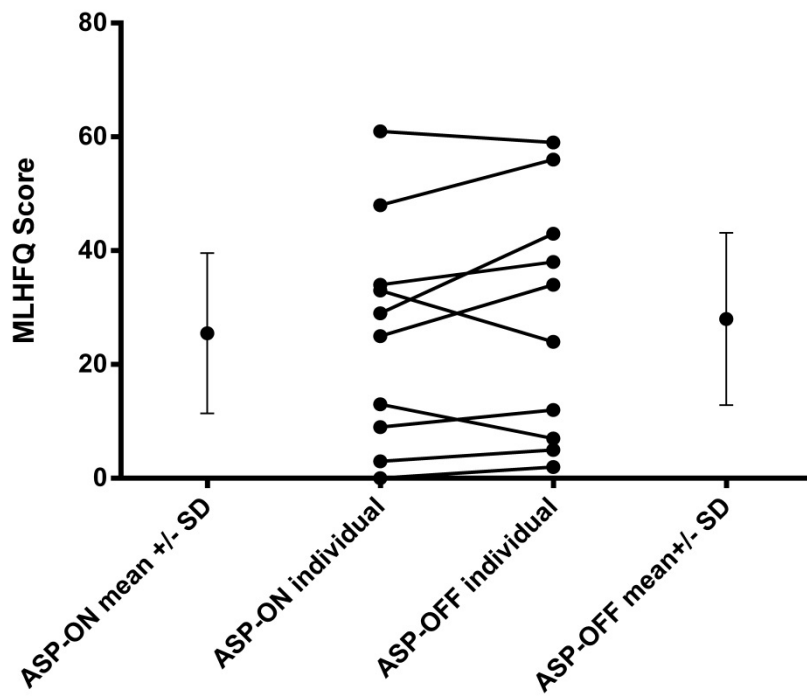


Figure 4.3 –MLHFQ on and off aspirin

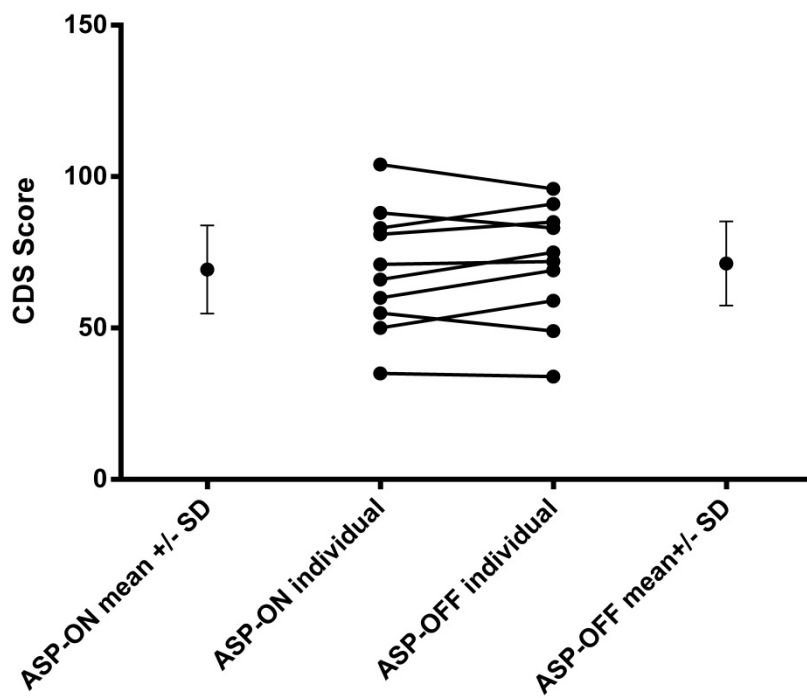
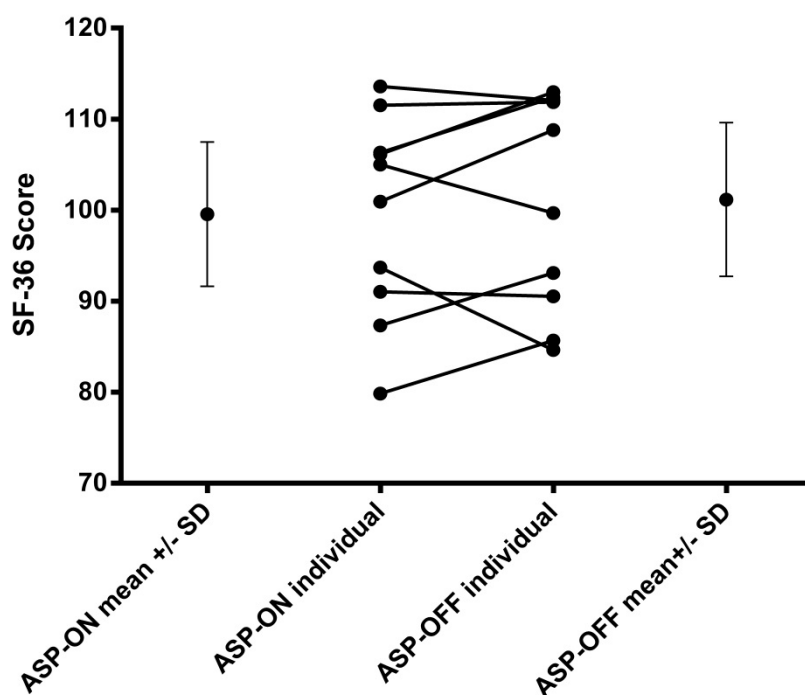


Figure 4.4 – CDS on and off aspirin



**Figure 4.5 – SF36 health survey on and off aspirin**

Results were unchanged in a sensitivity analysis in which the participant with TIA was assigned the worst score. This patient was withdrawn from the study and commenced on clopidogrel, and a further TIA occurred eight months later.

There were no changes in serum creatinine (asp-on:  $98 \pm 31$  vs asp-off:  $114 \pm 74 \mu\text{mol/L}$ ,  $p=0.255$ , -14 to 46), eGFR (asp-on:  $68 \pm 19$  vs asp-off  $65 \pm 24$  ml/min/ $1.73\text{m}^2$ ,  $p=0.323$ , -9 to 3), heart rate (asp-on:  $69 \pm 9$  vs asp-off:  $73 \pm 13$  bpm,  $p=0.458$ , -6 to 12), systolic BP (asp-on:  $122 \pm 17$  vs asp-off:  $115 \pm 23$  mmHg,  $p=0.512$ , -25 to 13) or weight (asp-on:  $90 \pm 24$  vs asp-off:  $91 \pm 24$  kg,  $p=0.602$ , -2 to 3).

## 4.5 Statin withdrawal results

Statin was withdrawn from participants with idiopathic (12) or ischaemic (1) HF with LVEF $\leq$ 40%. Exclusion criteria related to high absolute risk, and included treatment with statins primarily for severe hypercholesterolaemia or unstable ischaemic heart disease. The trial statin was that prescribed by their treating physician.

The 13 study participants had a mean age of  $64\pm 11$  years, 62% were male, the duration of HF was  $7.7\pm 5.7$  years, and mean EF was  $38.1\pm 10.4\%$ . Compared with taking statin, withdrawal of statin resulted in significant rises in LDL cholesterol (stat-on:  $2.4\pm 0.7$  vs stat-off:  $4.4\pm 1.4$  mmol/L,  $p<0.0001$ , 1.3 to 2.7) and non-significant changes in high-density lipoprotein (HDL) cholesterol (stat-on:  $1.2\pm 0.5$  vs stat-off  $1.2\pm 0.4$  mmol/L,  $p=0.265$ , -0.2 to 0.1) and triglycerides (stat-on:  $1.3\pm 0.6$  to stat-off:  $1.7\pm 0.7$  mmol/L,  $p=0.079$ , 0.0 to 0.7). Serum uric acid (stat-on:  $0.41\pm 0.1$  vs stat-off:  $0.40\pm 0.1$  mmol/L,  $p=0.789$ , -0.03 to 0.03), serum glucose (stat-on:  $5.0\pm 0.6$  vs stat-off:  $4.9\pm 0.5$  mmol/L,  $p=0.465$ , -0.5 to 0.2) or HbA1c (stat-on:  $5.6\pm 0.3$  vs stat-off:  $5.6\pm 0.4\%$ ,  $p=0.488$ , -0.1 to 0.2) were also unchanged.

There were no significant changes in BNP (stat-on:  $130\pm 175$  vs stat-off:  $129\pm 180$  ng/L,  $p=0.924$ , -23 to 21) (Figure 4.6), 6MWD (stat-on:  $455\pm 172$  vs stat-off:  $450\pm 182$  m,  $p=0.802$ , -19 to 23) (Figure 4.7) or QoL measures, including MLHFQ (stat-on:  $32\pm 26$  vs stat-off:  $31\pm 30$ ,  $p=0.406$ , -17 to 8) (Figure 4.8), CDS (stat-on:  $77\pm 20$  vs stat-off:  $81\pm 22$ ,  $p=0.445$ , -4 to 8) (Figure 4.9) and SF-36 (stat-on:  $93\pm 18$  vs stat-off:  $94\pm 19$ ,  $p=0.248$ , -2 to 7) (Figure 4.10).

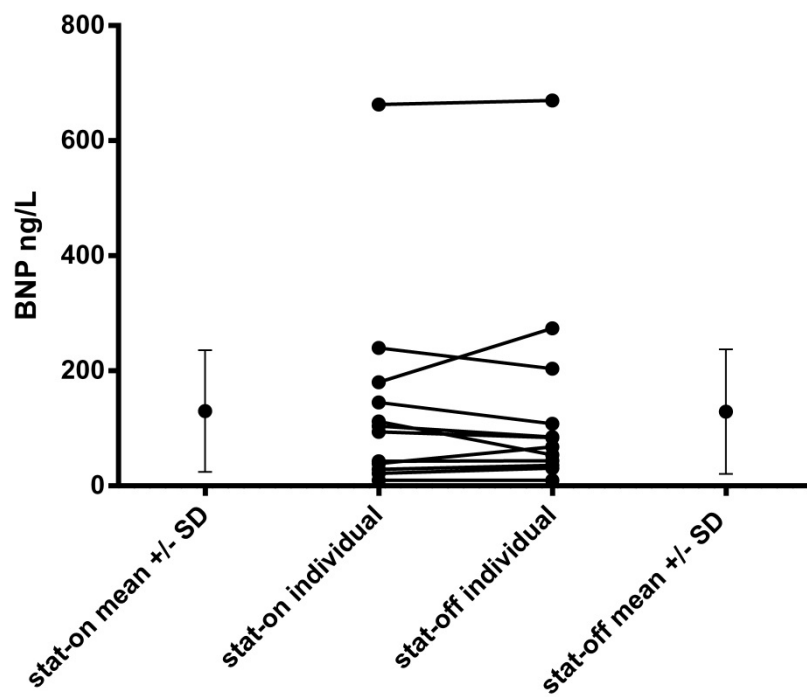


Figure 4.6 – Plasma BNP levels on and off statin

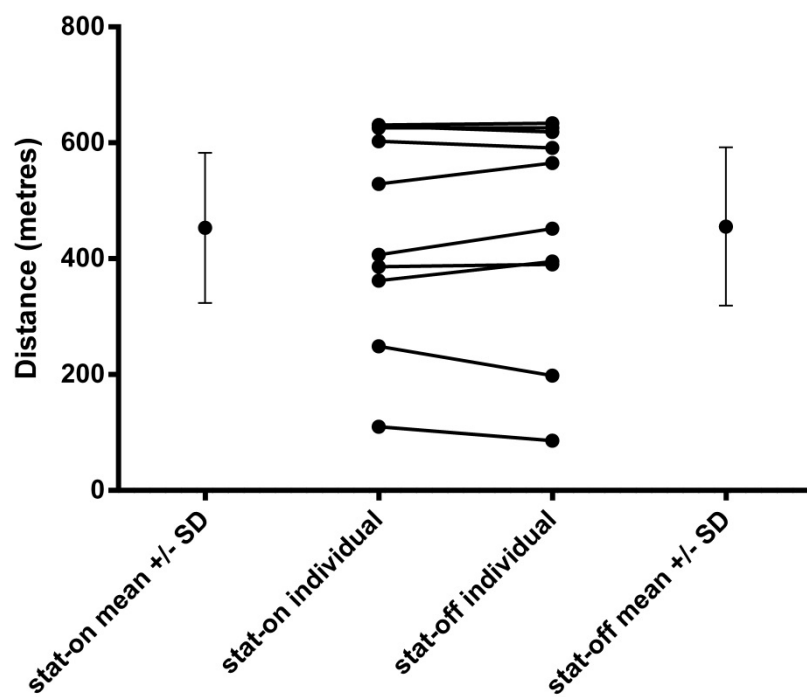


Figure 4.7 – 6MWD on and off statin



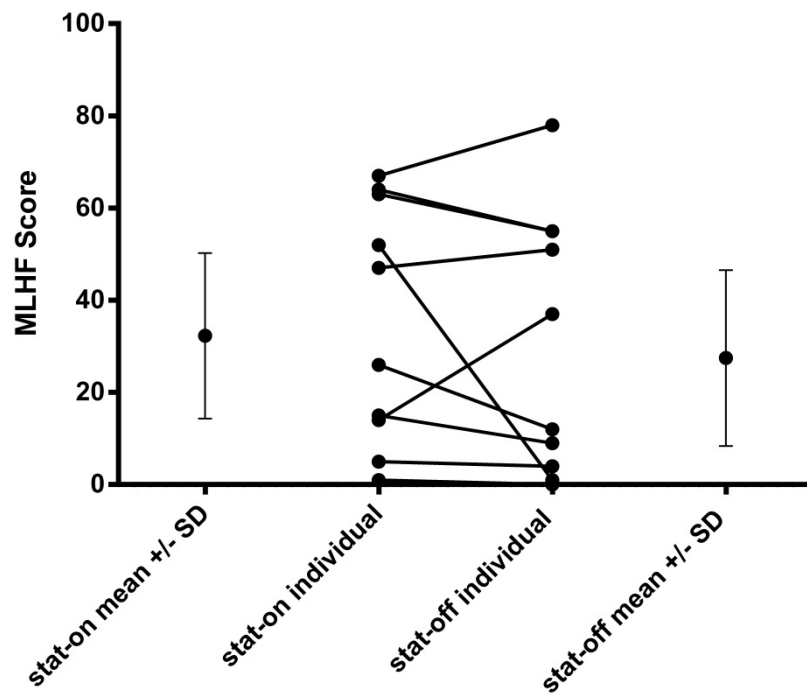


Figure 4.8 – MLHFQ on and off statin

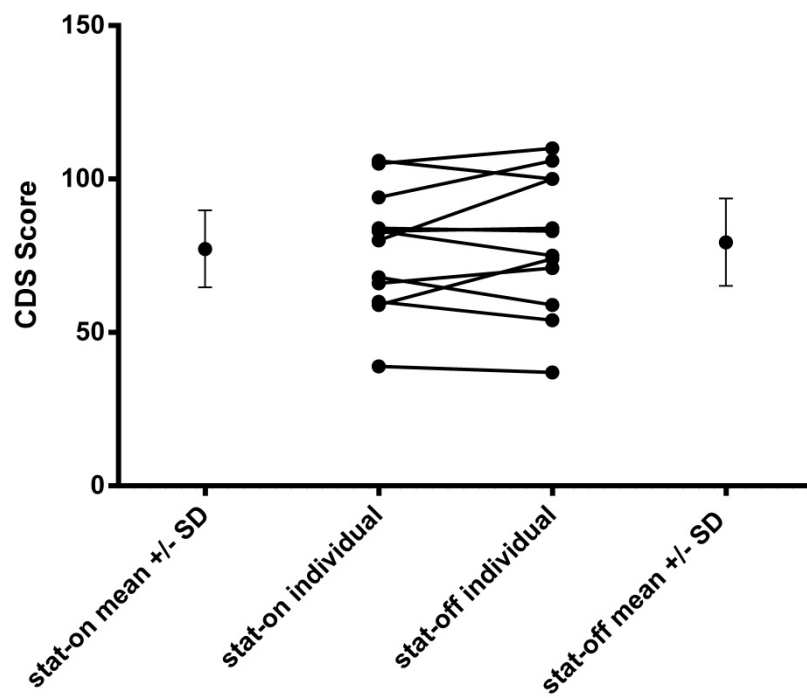
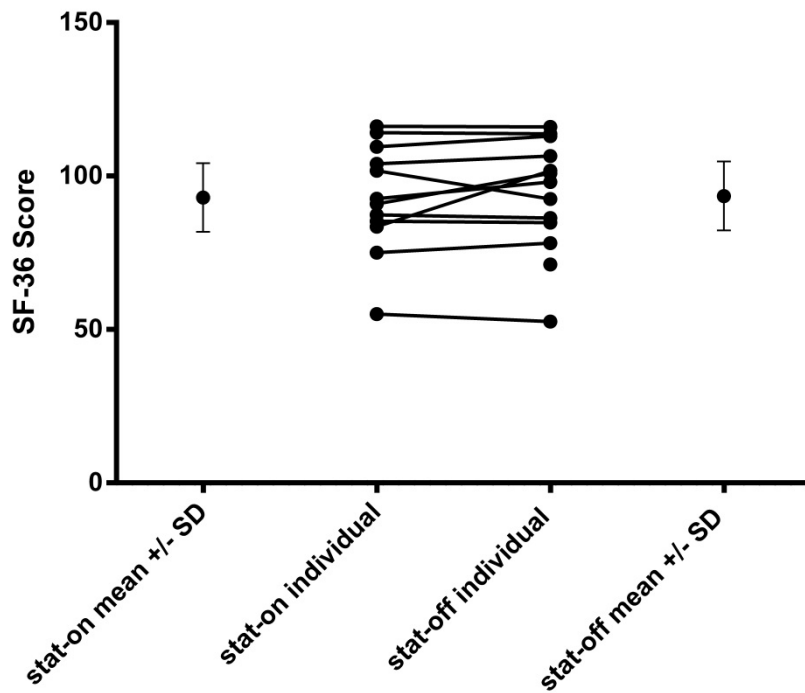


Figure 4.9 – CDS on and off statin



**Figure 4.10 SF-36 Health Survey on and off statin**

## 4.6 Discussion

These small pilot studies demonstrate that withdrawal of aspirin or statins did not result in change to the HF status either clinically or biochemically. The main limitation of these two studies is that a change in the endpoints measured over such a short timeframe would not be expected, given that neither treatment has a haemodynamic effect. Whether statins and aspirin have a role in the management of HF continues to be debated. HF guidelines do not recommend their use [7], yet physicians are reluctant to discontinue them, as reflected in a recent large scale clinical trial in systolic HF involving 3846 patients, among whom 50% were taking aspirin and 39% statins [94].

Physician reluctance to cease medications may relate to concern about the risk of an outcome which could relate to drug cessation, such as the TIA seen in a patient in the aspirin withdrawal study. Interestingly this recurred when the same patient was later taking clopidogrel, suggesting that it may have been unrelated to specific medication use. A recent meta-analysis suggested that aspirin use may not be associated with increased HF hospitalisations, as had been

previously observed [236], however there remains a question of an interaction between aspirin and ACE inhibitors which is thought to reduce the effectiveness of the latter [100]. Trials on the use of aspirin in HF in SR have been hampered by lack of funding and poor recruitment, thus the data concerning aspirin in HF patients in SR is inadequate to determine whether or not absence of aspirin in the HF drug regimen is safe [236]. Further, AF occurs in up to one quarter of HF patients [237], and there is increased risk of thromboembolism while transitioning between AF and SR. Although aspirin was found on meta-analysis of 29 trials to reduce the risk of stroke in AF by approximately 20% [238], the significance of this conclusion has been called into question [239]. Thus the role of aspirin in HF in SR remains unclear.

The role of statins in HF is also controversial. Two landmark randomised placebo-controlled trials of rosuvastatin, the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial [115] in elderly ischaemic HF, and GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca Heart Failure) [116] in patients with ischaemic and non-ischaemic HF, were negative for their primary endpoint, although a reduction in the pre-specified secondary outcome of hospitalisation for CV causes was seen with statins in CORONA. *Post-hoc* analysis of the CORONA trial together with data from the Heart Protection Study demonstrated a beneficial effect of statins in the group with the lowest NT-pro-BNP levels, with no effect when HF was more severe with NT-pro-BNP levels of 800pg/mL or higher [240]. This generated a hypothesis that there may be a transition point of HF severity when statin therapy becomes ineffective. There are purported pleiotropic effect of statins in HF, including beneficial anti-inflammatory effects which might improve myocardial function, encourage repair, reduce fibrosis and increase electrical stability [241]. However these appear not to be supported by clinical evidence [213]. Reducing cholesterol may also have detrimental effects. Lowered cholesterol may impair circulating lipid fractions which are thought to bind endotoxins absorbed from the gut, impairing this natural defence mechanism and leading to cytokine activation, inflammation and progression of HF [241]. Also synthesis of coenzyme Q10 is impaired with statin use, which is an essential component of the mitochondrial respiratory chain. It has been suggested that the lipophilic statins including atorvastatin and simvastatin may have potential benefit that

rosuvastatin, which is not lipophilic, does not [241,242], but this remains to be demonstrated in large scale clinical trials. Other complicating issues are the difficulty in recognising ischaemic heart disease as a cause of death in HF [243], and the paradoxical finding that lower serum cholesterol is associated with worse prognosis in HF (the obesity paradox) [244]. However the latter observation may reflect “reverse causality” with lower LDL cholesterol levels occurring in the sicker individuals.

Practical issues may contribute to polypharmacy. Physicians may be reluctant to cease medications commenced by someone else [245], or have inadequate time to thoroughly review the medication list during consultations. Reducing medications may not be considered a priority compared with reaching target doses of medications with mortality benefits. However as polypharmacy continues to rise in the HF population [146], there will be potential for treatment interactions with comorbid disease [156] as well as increased potential for drug interactions [145], and the incidence of hospital admissions caused by adverse drug events will likely rise.

## **4.7 Conclusion**

These small pilot trials demonstrate no deterioration in HF clinical status or biochemical status on withdrawal of aspirin or statin. Proper randomised, adequately powered trials of withdrawal of medications for which mortality benefit has not been demonstrated are needed to inform consideration of the risks and benefits of reducing polypharmacy.

# Chapter 5: Attitudes of patients and prescribing clinicians to polypharmacy and medication withdrawal in heart failure.

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This paper has not yet been submitted for publication.

## Declaration for Thesis Chapter 5

### Declaration by candidate

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:


Nature of contribution	Extent of contribution (%)
Designed surveys, obtained ethics approval, obtained funding, screened, recruited and consented patients, collected data, cleaned and analysed data, wrote paper.	90%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
M Skiba	Advised on the following: design of surveys, ethics application, assisted in intellectual content and drafting of the paper.	
C de Silva	Assisted in the design and piloting of the study, assisted with data collection and data entry, intellectual content and drafting of the paper.	
A Tonkin	Supervisor throughout the study, assisted with conception and planning of the study, analysis of results, drafting of paper.	
H Krum	Supervisor throughout the study, assisted with conception and planning of the study, analysis of results, drafting of paper.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

Candidate's  
Signature

	Date November 2015
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Main  
Supervisor's  
Signature

	Date November 2015
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## 5.1 Abstract

**Background** – Patients frequently comment that they take too many medications and polypharmacy is commonplace in HF. We sought to explore the attitudes of patients with HF towards their medications and also attitudes of prescribing clinicians.

**Methods** – Two surveys were developed, one for patients and one for prescribing clinicians. Both groups were asked questions related to medication use and prescribing, and to rate the importance of a number of prescribing issues. Patients were surveyed in the waiting room of the HF clinic, and prescribing clinicians while attending a HF symposium, through emails and a web-link.

**Results** – The survey was completed by 84 patients (response rate 93%), of whom 72% were male with mean age  $62 \pm 13$  years. The time since diagnosis of HF was  $11 \pm 9$  years. An average of  $8.3 \pm 2.8$  medications were taken daily in  $10.8 \pm 6.2$  doses, of which  $5.9 \pm 1.6$  were for cardiac reasons. Patients were generally satisfied with the number of medications they took (16% were unsatisfied or very unsatisfied). Fewer than half (39%) said there was a medication they would stop if they could, with frusemide being the most common. Responses were received from seventy-four prescribing clinicians (response rate not able to be calculated). Although clinicians regarded reducing medications as valuable in HF patients, they rarely addressed it in clinical consultation but had clear views on which medications could be reduced and which should not. Patients and prescribing clinicians had similar views on priorities in prescribing, with cost and number of medications being the least important issues.

**Conclusion** – Patients with HF and polypharmacy are largely not dissatisfied with the number of medications they take. Prescribing clinicians value reducing medications but rarely address it in clinical practice.

## 5.2 Introduction

“I’m taking too many medications” is a common complaint that clinicians hear from their patients. Patients with HF take a large number of medications and polypharmacy is thus commonplace. Remarkable reductions in mortality and increases in longevity have been brought about by effective HF therapies, including ACE inhibitors, beta-blockers and MRAs, at the cost of increasing complexity of medication regimens. Illustrating this, a recent study demonstrated an increase in average number of medications from 4.1 to 6.4 in a community-based population of HF patients over a 20 year period [137]. Polypharmacy may be appropriate [246] and indeed the advances in HF therapeutics and mortality reductions seen could not have been achieved in the HF setting without it. However polypharmacy is not without risk, including increased side effects from the HF medications [247], potential drug-drug interactions [145] as well as potential treatment interactions [156], and polypharmacy has been associated with reduced medication compliance [248].

Little is known about the attitudes of HF patients or physicians to polypharmacy and ceasing medications, or deprescribing, a term which indicates the withdrawal of medications under clinical supervision [152]. Patient attitudes to deprescribing have been examined in a multidisciplinary outpatient setting, not specific to HF, and were found to be favourable [249]. Previous qualitative studies in patients with HF have examined knowledge and understanding of medications, often in relation to medication adherence [250-253]. Attitudes towards prescribing and medication withdrawal have been comprehensively examined in physicians treating older populations [254-256]. Studies of physician attitudes in the treatment of HF have examined reasons for under-prescribing medications [257,258] but none has examined physician opinion on reducing medications.

We sought to explore the attitudes of patients with HF towards their medications, and also attitudes of prescribing clinicians.

## **5.3 Methods**

### **5.3.1 Design of the survey**

Two questionnaires were developed, one for patients (Appendix 1.1) and one for prescribing clinicians (Appendix 1.2). The title of the surveys was “Heart Failure Patients and Medications.” This was chosen so as not to alert respondents to the issue of polypharmacy, or bias their views on withdrawing medications. The survey needed to be brief in order to be completed in the clinic waiting room or by busy clinicians. Surveys were piloted on 8 patients and 5 cardiologists, all of whom were randomly selected to be approached in a tertiary hospital HF clinic, and changes made in response to feedback to improve the clarity of the questions before the final version received approval.

Patients were asked about their satisfaction with the number of medications they were taking, and whether they would cease a medication if they could. They were also asked to rate the importance of a number of issues related to prescribing.

Prescribing clinicians were also asked about their perception of polypharmacy in their patients, a number of questions about their practice of prescribing, and asked to rate the importance of the same issues related to prescribing using appropriate language. They were then asked what they would do in some clinical scenarios not covered in the HF guidelines.

### **5.3.2 Study Setting**

Patients with HF were recruited from the Alfred Heart Failure Clinics, located within the Alfred Hospital which is a tertiary referral centre in Melbourne, Victoria and the regional heart transplant centre. The Heart Failure Clinic is a multidisciplinary HF service, staffed by cardiologists, specialist HF nurses, pharmacists and dietitians. The patient population comprises complex HF patients from across Victoria and the region, as well as less complex patients within the local catchment area. Data collection occurred between January and July 2015 (inclusive). This HF clinic supports a great deal of research and patients are familiar with being approached to be involved in trials.



Prescribing clinicians, including physicians and HF nurse practitioners, were recruited from two sources. Firstly, the Alfred Heart Centre ran a Heart Failure Symposium on Friday 10<sup>th</sup> October 2014, during which participation was invited. Secondly, a survey link was attached to one weekly newsletter of the Cardiac Society of Australia and New Zealand (CSANZ) with information about the survey and a web-link, and this was emailed to all members of CSANZ and members of the Heart Failure Council of CSANZ.

Institutional ethics approval was obtained from the Alfred Hospital Ethics Committee and Monash University Human Research Ethics Committee, and consent was implied through completion of the survey.

### **5.3.3 Participants**

To be eligible, patients needed to have HF as diagnosed by their cardiologist and be taking five or more medications specifically for cardiac indications. These could include, but was not limited to, an ACE inhibitor, ARBs, MRAs, beta-blocker, other antihypertensive agents, antiplatelet agents, or oral anticoagulant. Sublingual nitrates were not included in the list of cardiac medications due to the irregular nature of their intake. Potassium supplementation was not considered a cardiac medication but was included in the total medication count. Injected insulin was included in the total medication count. Eye drops, topical ointments and *as required* medications such as paracetamol or temazepam were not included in the total medication count. Exclusion criteria included dementia, insufficient English language skills to participate and age less than 18 years. Prescribing clinicians were identified as they entered the HF Symposium, or were self-identified through the CSANZ newsletter and email. A convenience sample for both groups of between 70 and 80 surveys was chosen.

### **5.3.4 Administration**

Consecutive patients were approached individually in the HF clinic waiting room by a HF research nurse and invited to participate in a confidential questionnaire. If consent was obtained, they were given the option to complete the questionnaire with the investigator, or complete alone. The research nurse was trained to ask questions without leading respondents to an answer.

Questionnaires were returned anonymously by participants into a sealed collection box in the HF clinic.

Prescribing clinicians were invited to complete a written survey as they entered the HF symposium. They completed the questionnaire by themselves and returned them anonymously in sealed collection boxes. The email link was anonymous.

### **5.3.5 Statistical analysis**

Survey data was entered into Qualtrics survey software (Provo, Utah, USA, copyright 2015) was used to collate the data. The data were cleaned and survey responses were reviewed for incomplete or missing data. Three prescriber surveys were deleted after none of the questions were completed. Descriptive statistical analysis was conducted on the complete data set. The analysis approached the data generated from the five-point Likert scale questions as interval data, which assumes that the differences between each point are equal. Frequencies, proportions, means and SDs were used to analyse and present the data.

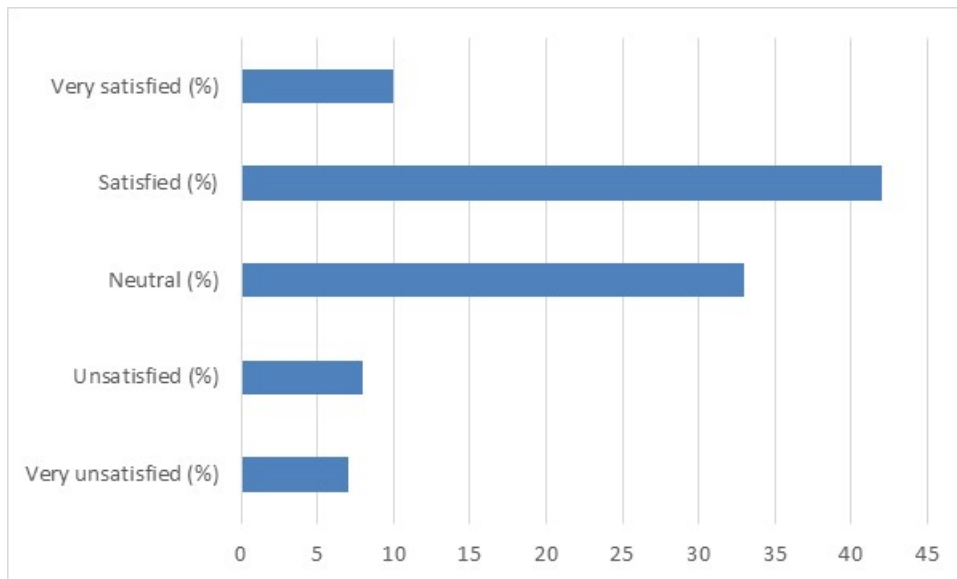
## **5.4 Results**

### **5.4.1 Patients**

A total of 90 patients were approached, and 84 surveys were completed. The response rate was 84/90 (93%). The respondents were mean age of  $62 \pm 13$  years, and 72% were male. The time since diagnosis of HF was  $11 \pm 9$  years. An average of  $8.3 \pm 2.8$  medications were taken daily. Of these,  $5.9 \pm 1.6$  medications were cardiac medications. The total number of medication doses daily (pill count) was  $10.8 \pm 6.2$ .

#### **5.4.1.1 Patient satisfaction with medications**

Patients were generally satisfied with the number of medications they were taking. A total of 43 (51%) indicated they were satisfied or very satisfied, 26 (32%) were neutral, and the minority of 13 (16%) indicated they were either unsatisfied or very unsatisfied with the number of medications they were taking (Figure 5.1).



**Figure 5.1 – Patient satisfaction with number of medications**

Respondents were asked to comment in free text on the number of medications they were taking. There were 30 comments indicating satisfaction, such as “I am happy with the present situation” and “they are doing the job” and “happy to take them as they keep me alive and feel better”. There were comments acknowledging the high number of medications but acceptance of this, for example “the quantity is high but the result satisfactory” and “[I] don’t care about the number of medications so long as medication is effective.”

There were 27 negative comments, such as “I wish I could come off some of them”, “rather not take any” and “unsatisfied but have to take them”. These comments highlighted issues such as “[It’s] hard to keep track sometimes of which ones to take and when to get scripts refilled”, “swallowing them is difficult, [with] restricted water, 800ml each day to take tablets”, “it’s easier to omit medication than hassle with supply and scripts.” A number of comments suggested that a polypill would be advantageous, such as it “would be nice if four individual medications could be dispensed as one tablet”. Cost was mentioned only twice, one respondent stated “cost is not an issue at this stage” and another that “the cost of medication should be spread evenly across the year.”

#### **5.4.1.2 Ceasing medications**

When asked if there was a medication they would stop if they could, the majority 51/84 (61%) of patients said “no”, and 33/84 (39%) said “yes”. Of these, 17 nominated one medication they would stop if they could, and 16 nominated two medications. Four options were offered for reasons for wanting to stop a medication. “This medication gives me side effects” and “I am taking too many medications” were selected. “The price is too high” was selected only once for Valium™. No respondents nominated “the directions are too difficult to follow” as a reason for wanting to stop a medication.

Of the medications which participants nominated as wanting to stop, frusemide was the most frequently mentioned (11 times), with complaints of “constantly needing the toilet” and “makes me dry”. Warfarin was mentioned five times, due to “frequent blood tests” and “skin thinning side effects”. ACE inhibitors and beta-blockers were mentioned five times each, with the main concerns being side effects and taking too many medications. Potassium supplements were also mentioned four times, as being “too large” and “difficult to swallow”, and statins were mentioned three times in the context of “read some bad news about statins”. Other medications causing concern with side effects included amiodarone, ivabradine, verapamil and oral hypoglycaemics.

#### **5.4.2 Prescribing clinicians**

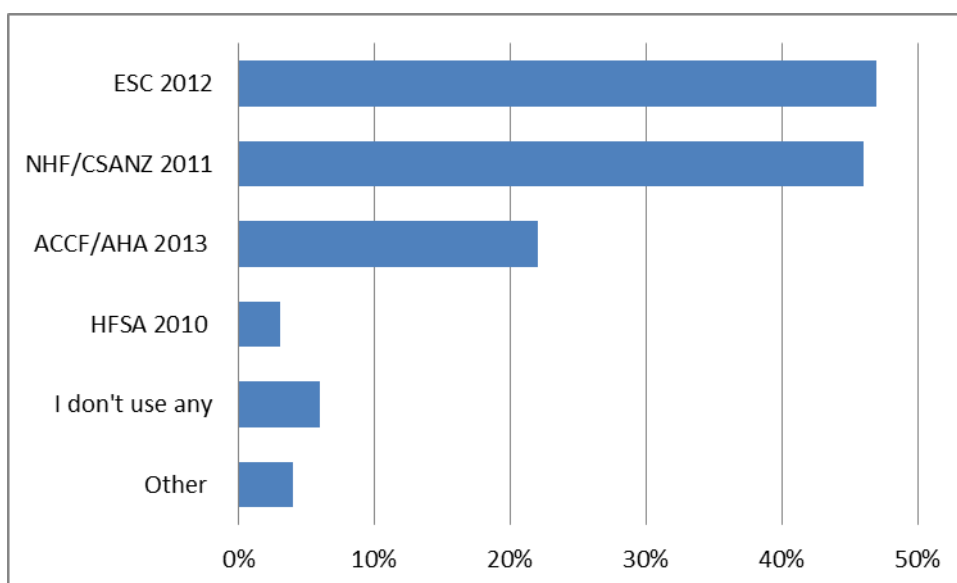
A total of 74 responses were received. The response rate at the Alfred HF symposium was 25/32 (78%). A response rate from the CSANZ newsletter and email could not be ascertained. The majority of respondents were cardiologists (51, 69%), with 14 nurse practitioners and 9 general physicians. Respondents had mostly over ten years’ experience treating HF (47, 64%). Polypharmacy was considered by respondents to be highly prevalent. Only 10 respondents considered that polypharmacy was present in fewer than 50% of their patients. The remainder (86%) estimated that polypharmacy was present in over half of patients, with 28% of respondents nominating 90-100% of patients as having polypharmacy.

#### **5.4.2.1 Prescribing practice**

Respondents were asked questions about their prescribing practice and asked to rate their agreement with the statements on a Likert scale, from which a mean value (from 0 to 5) was then calculated, with a higher number indicating greater agreement with the statement. Respondents agreed that their HF practice was driven by both experience (mean 4.33) and guidelines (4.22), and that polypharmacy was inevitable when treating HF patients (3.60). There was a preference to commence multiple medications at low doses (3.67) rather than titrating to a maximum dosage of one medication before starting another (2.73).

Prescribing clinicians appeared to value the concept of reducing medications, agreeing that they reviewed medications with a view to stopping them if possible (3.22), more than they agreed that they were reluctant to stop prescribed medications (2.79). They agreed that attempting to reduce patients' intake of medications was worthwhile (3.48), and that patients could benefit from reducing the number of their medications (3.40), more than they agreed that stopping a prescribed medication exposed the patient to unnecessary risk (2.88). However, stopping medication was the issue considered least frequently (2.36) in clinical consultations compared with other issues including signs of HF (3.88), symptoms of HF (3.80), up-titrating medication doses (3.62), test results (3.46), need for devices (3.07), adding more medications (2.92), down-titrating medication dosage (2.66).

The guidelines that respondents followed most closely included the ESC [18] (47%) and the National Heart Foundation (NHF)/CSANZ guidelines [93] (46%), followed by the ACCF/AHA Guidelines [7] (23%) (Figure 5.2). Only two respondents followed the HFSA guidelines [225], four respondents did not use any guidelines, and two stated they followed "the NZ guidelines", with one respondent electing to consult a cardiologist for direction on treatment of their HF patients. More than one guideline was nominated by many respondents.



**Figure 5.2 – HF guidelines followed most closely by prescribing clinicians**

Respondents were asked to rate their level of comfort or discomfort withdrawing medications in a number of scenarios, none of which are explicitly covered by any of the HF guidelines. Respondents were most comfortable ceasing digoxin in patients in SR, including both in low EF, NYHA class I-II patients successfully titrated to maximal beta-blocker dosage (4.01), and in stable HF after recovery of EF to over 40% (4.01). They were also comfortable ceasing statin (3.93) and aspirin (3.74) in patients with idiopathic HF, and also ceasing spironolactone after recovery to normal EF after previous low EF and in NYHA class I for 12 months (3.47). Respondents were clearly very uncomfortable ceasing a statin (1.73) or aspirin (1.85) in patients with ischaemic HF. They were also uncomfortable with ceasing ACE inhibitor (2.15) or beta-blocker (2.45) after recovery to normal EF from low EF if NYHA class I for 12 months.

#### **5.4.2.2 Prescribing priorities**

Patients and prescribing clinicians were asked to rate the importance of a number of issues related to medication usage (Table 5.1). Both groups rated symptomatic treatment of HF as the highest priority. There was general agreement that prolonging survival, and slowing or stopping progression of the disease were important. Patients were more concerned for their kidney function than were the prescribing clinicians. Both groups rated the number of medications and the costs of medications as the least important two issues of those listed in prescribing.

**Table 5.1 – Patient and prescribing clinician rating of importance of prescribing issues**

PATIENTS	Mean	Mean	PRESCRIBERS
2. Making you feel better	4.81	4.95	2. Reducing symptoms of heart failure
8. Stopping the progress of the disease	4.80	4.46	1. Prolonging survival
7. Protecting the function of your kidneys	4.74	4.45	8. Beneficially affecting underlying disease process
1. Making you live longer	4.65	4.27	4. Minimising drug side effects
4. Avoiding side effects of medications	4.38	4.23	6. Avoiding symptomatic hypotension
6. Avoiding dizziness	4.38	4.08	7. Preserving renal function
3. Taking the least number of medications possible	3.77	3.55	5. Costs of drugs to the patient
5. How expensive medications are	3.49	3.50	3. Reducing the number of medications

## 5.5 Discussion

This survey explored the attitudes of patients and prescribing clinicians to the issue of polypharmacy in HF and potential deprescribing with reduction in the number of medications taken. The sample of patients was taking a large number of medications, but there was general satisfaction with the number of medications taken. Prescribing clinicians were well aware of the presence of polypharmacy in their patients, and agreed that reducing medications was a good idea. However in their clinical practice they addressed this rarely. There was high concordance between patients and prescribing clinicians with regards to priorities when using medications in HF, and the number of medications and their cost were the least important issues.

The low level of dissatisfaction (16%) with the number of medications taken was unexpected in this patient group. It was lower than that seen in a study of general medical outpatients, which found 30% disagreed that they were comfortable with the number of medications they were taking [249], and also lower than among patients with hypertension [259] or amongst elderly patients taking a statin [260]. This may be one of the many benefits of a multidisciplinary HF clinic [261,262] in which education of patients is a high priority. It may also reflect the patient population referred to a tertiary HF clinic, which may have more severe HF initially than in other institutions, and thus altered expectations of what their treatment entails [263]. We were not able to collect information on respondents' initial presentation to confirm this due to constraints related to anonymity. Our sample of patients had experienced HF for many years, which may have allowed them time to accept taking multiple medications. Additionally they were quite young, with a mean age of 62, and medication burden may be a more important issue as age increases and prognosis declines. Our study found that only 42% would reduce the number of medications they took if they could, contrasting with another study in which 66% of general medical patients would have liked to reduce the number of medications they were taking [249]. That patient group was older, with a median age of 72 years, and may reflect that elderly patients are more likely to be prescribed medications inappropriately [264,265] than the younger HF patients recruited to our study.



Prescribing clinicians were clearly aware of the presence of polypharmacy in their HF patients, and the high concordance between physicians and patients with regards to their priorities in prescribing was reassuring for both groups. This has not been explored previously. Both groups rated the number of medications and the cost of medications as the least important issues. This contrasts with other studies which suggest that cost can be an issue when polypharmacy is present [138]. We did not explore our patients' socioeconomic status. The Pharmaceutical Benefits Scheme in Australia help support the cost of obtaining medications [266], ensuring that is not a major barrier to accessing appropriate therapies for HF.

There was general support amongst prescribing clinicians for reducing medications if possible, however this was rarely actually considered during consultations. This would be expected, given the complexity of HF patients generally and the many competing priorities during a consultation. Similarly to prescribing drugs, cessation of drugs can result in harm as well as benefit [267] and should be undertaken as an ordered process [268]. It may be appropriate for a pharmacist to lead a comprehensive medication review as part of a multidisciplinary clinic [269] in order to best achieve this.

There was a high consensus of opinion amongst prescribing clinicians with regards to which medications could be ceased in stable HF patients. In all of these scenarios, guidelines are uninformative [7,18,93], and the evidence base to inform these decisions is either absent or controversial. It is not unexpected that clinicians' practice differs from that recommended by guidelines. A review of studies of clinicians' attitudes to clinical practice guidelines found that a third of clinicians thought them impractical, too rigid, and that they oversimplified medicine [270]. Future guidelines should seek to address scenarios in which the evidence base is limited, including those presented here, even if only as expert opinion.

There are many limitations to the generalisability of these results. We cannot confirm whether the sample who agreed to the surveys was representative of the larger population of HF patients. Sicker patients presenting to the HF clinic more frequently would have been more likely to have been surveyed. Theoretically there may have been a respondent bias in the sample of patients who were agreeable to answering the survey. However the high response rate would

suggest otherwise. The clinic's HF nurses were consulted before contact with patients was made, and patients particularly unhappy with their treatment in general may have been excluded from this sample. Although the HF research nurse was trained not to lead the respondents in answering questions, respondents may have altered their responses in light of her presence. However, it is equally possible that respondents seized the opportunity to talk about their negative feelings regarding their medications to an interested researcher. Prescribing clinicians were likely to be a highly selected sample with a high level of knowledge in the area, attending a HF symposium and responding to an online questionnaire.

## **5.6 Conclusion**

HF patients in whom polypharmacy is present are largely not dissatisfied with the number of medications they take. There is high concordance between patients and prescribing clinicians about priorities in prescribing, with symptomatic treatment and prolonging survival being the most important issues, and the cost and number of medications being the least important issues. Although prescribing clinicians regard reducing medications as valuable in HF patients, they rarely address it in clinical consultation but have clear views on which medications could be reduced and which should not.

*Appendix 1– Survey questionnaires*

## Chapter 6: Conclusions and future directions

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This thesis set out to explore the issue of polypharmacy in patients with HF and examined whether polypharmacy could be safely reduced. This issue is of increasing importance in our society, as HF therapeutics becomes more complex, and population ageing contributes further to age-related comorbidities in HF patients. The existing literature was utilised to identify medications that could, or should not, be withdrawn. However the evidence was inconclusive on several medications in which a mortality benefit has not been identified in HF patients. RCTs were performed to address whether three of these medications, digoxin, HMG-CoA reductase inhibitors (statins) or aspirin could be safely withdrawn in stable chronic HF patients. In addition, the attitudes of HF patients and prescribing clinicians to medication withdrawal were explored.

The clinical and biochemical deterioration seen on withdrawal of digoxin, without significant associated deterioration in sub-maximal exercise capacity or QoL measures, highlights the fact that the role of digoxin in contemporaneous HF therapeutics remains poorly characterised. This challenges the perception of prescribing clinicians that digoxin is a drug which could be safely ceased with optimised background neurohormonal blockade. Ziff and colleagues recently published a review of all observational and randomised studies of digoxin between 1960 and 2014 [271]. They found profound differences in baseline characteristics of digoxin and control groups in observational studies, and used meta-regression methods to expose their impact on mortality. The authors concluded that regardless of the statistical method used, prescription bias limit the utility of observational studies. An editorial accompanying this paper with the entertaining title “Trials are best, ignore the rest: safety and efficacy of digoxin” called for RCTs, not observational studies, to further investigate the role of digoxin in HF [272].

Digoxin’s likely role is in more severe HF patients with lower EF, which is the group that deteriorated most markedly during the digoxin withdrawal trial. As digoxin does not confer a mortality benefit, it would be essential to incorporate QoL endpoints in a RCT examining digoxin

in HF, as was performed in our research. Obtaining sponsorship from a pharmaceutical company for a RCT in HFREF is unlikely due to the absence of patent potential, and public funding would be necessary. A potentially lower cost and novel alternative may be to embed a clinical trial of digoxin within an existing HF registry [273], in which the issue of recruitment can be minimised by having patients already familiar with research, regularly in contact with the registry staff, and follow up pre-determined in the registry protocol. The clinical picture constructed from such prospective RCTs would help to address how digoxin can be most effectively employed in patients with HF in SR with background neurohormonal blockade.

The investigations into whether statins and aspirin were able to be withdrawn demonstrated no short-term concerns with regards to deterioration in HF clinical status, but the issue of long-term safety remains to be addressed. The interpretation of the major statin trials continues to be debated [241,274,275]. Given the neutral effect on mortality, it is unlikely that we will see further trials of statins in HF that would expand the available dataset. Recruitment for large trials of statin withdrawal would be difficult, especially given that the statin trials demonstrated safety in HF [113,116]. The WARCEF trial, comparing aspirin and warfarin in HFREF patients in SR, was published during the course of this research and found no excess of HF hospitalisations with aspirin use [215]. While equipoise remains on the influence of aspirin on HF, this evidence allays previous concerns about excess hospitalisation with aspirin use, and thus eliminates the need for a large scale trial of aspirin withdrawal. Additionally, the views of prescribing clinicians surveyed on this matter are clear: they are comfortable withdrawing aspirin and statins in non-ischaemic HF but not in ischaemic HF.

Further information on the safety of withdrawal of statin and aspirin may be obtainable through administrative claims databases. Linked datasets bringing together claims from the claims for pharmaceuticals and investigations, hospitalisations, emergency presentations, disease registries and the death register have been established within Australia [276], and have been used to monitor side effects of therapy [277]. Such datasets could be interrogated for outcomes after commencement or cessation of statins or aspirin (although less easily the latter as this product is

often obtained without a prescription, thus not appearing on databases of filled prescriptions). Administrative claims databases can be a powerful tool for pharmacovigilance [278], but they are observational in nature, and therefore liable to significant confounding. Thus the findings should usually be considered to be hypothesis-generating and not definitive.

While the finding that patients were not dissatisfied with the number of medications they were taking was reassuring, it does not lessen the need to address the issue of polypharmacy. The patients surveyed did not rate the cost of drugs highly on a list of issues related to prescribing, but that does not mean we should stop striving for affordable drugs. Equally these patients did not rate the issue of the number of drugs they took as highly important to them, but we should still strive to minimise polypharmacy where possible. The concept of the fixed-dose combination pill for preventing CV disease, or “polypill” has been investigated in both primary [279] and secondary prevention settings [280,281] and has been shown to increase medication adherence. There may be a role in the future for a HF polypill comprising an ACE inhibitor, beta-blocker, MRA and perhaps a diuretic to attenuate risk of hyperkalaemia [282]. HF patients tend to be less homogenous and more unwell than patients with hypertension and CV risk factors, and the need for more individualised titration of medication doses to maximise benefits while minimising side effects may thus impede its development. However given the burgeoning number of HF patients and the fact that all of these medications are off-patent, a HF polypill may be a very reasonable financial proposition for a pharmaceutical company, and potentially improve the rates of attaining treatment targets of all three medications.

Finally, beyond the scope of HF to the more general population there is a need to more formally approach the issue of polypharmacy through “deprescribing”, the process of reducing or tapering drugs to improve patient outcomes [268]. This term has cemented itself in medical parlance since the commencement of this thesis [152,283]. There is increasing interest in deprescribing in a number of other fields, particularly in older adults, but also related to specific drug classes [245,260,284,285]. Of particular interest was a recent state-of-the-art paper by Rossello and colleagues examining cessation of long-term use of aspirin, statins, beta-blockers and

ACE inhibitors after MI [286]. The role for a polypharmacy clinic, comprising a multi-disciplinary team including medical practitioners, nurses, and pharmacists, to systematically review the medication list and deprescribe in a supervised manner, should be further explored. Such clinics already exist [287,288] but improvements in mortality and reductions in hospitalisations such as those seen in multi-disciplinary HF clinics [261,262], as well as cost-effectiveness, need to be demonstrated in order to establish them as a reasonable proposition.

Polypharmacy will continue to challenge patients and physicians into the future. Based on the research presented in this thesis, some of the prescribed medications that patients with HF are currently taking can be safely reduced or withdrawn. Prescribing is a dynamic process and the effects of cessation should be closely monitored in order for this to occur in a safe and effective manner, and multi-disciplinary collaborations should be further explored as a means to achieve this.

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# Appendices

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## Appendix 1

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The following pages contain the surveys for patients and prescribing clinicians for the study described in Chapter 5 titled “Attitudes of patients and prescribing clinicians to polypharmacy and medications withdrawal in heart failure.”

# Heart Failure Patients and Medications

Questionnaire for patients

Centre of Cardiovascular Research and Education in Therapeutics  
School of Public Health and Preventive Medicine  
Monash University



MONASH University



AlfredHealth

You are invited to participate in this study. The aim of this study is to learn more about how patients with heart failure feel about their medications. Your time and cooperation in completing this questionnaire are greatly appreciated.

Your answers to this questionnaire will be combined with those of other patients with heart failure and reported as group data only. Your individual answers will not be identifiable so please do not write your name anywhere on the questionnaire. All information you give will be completely confidential. Your doctor is happy for his/her patients to complete this survey, however they will not be told whether or not you participated in this survey. If you have any questions as a result of the issues raised in the survey, then please feel comfortable asking your doctor.

The research is being conducted by researchers at the Monash Centre of Cardiovascular Research and Education in Therapeutics, at the School of Public Health and Preventive Medicine, Monash University. It forms part of Dr Ingrid Hopper's doctoral thesis, with supervision by Professor Henry Krum. The research has been approved by the Alfred Health Human Ethics Committee.

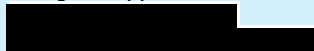
### How to answer the survey

We know that patients have a wide variety of views on their medications. There are no right and wrong answers to the questions. We are simply interested in your experiences, thoughts and opinions. If you are unsure about how to answer a question, mark the response which corresponds most closely to how you feel. The questionnaire will take approximately 10 minutes to complete. To answer the questions, please place a mark inside the appropriate circle or write in the space provided.

### For further information

If you would like any further information concerning the project, or if you have any problems which may be related to your involvement in the project, then you can contact the principal researchers as follows:

**Dr Ingrid Hopper**



**Professor Henry Krum**



If you have any complaints about any aspect of the project or the way it is being conducted, or any questions about being a research participant in general, then you may contact:

Ms Emily Bingle, Office of Ethics and Research Governance, Alfred Hospital

Email: [research@alfred.org.au](mailto:research@alfred.org.au)



# Heart Failure Patients and Medications

## Questionnaire for patients

1. What was your age at your last birthday in years?

2. What is your sex?

☐

Male

☐

Female

3. Heart failure means that your heart muscle is weaker than normal and unable to pump blood around the body as well as it should. What was the year that your heart failure was first diagnosed?

4. Please list all of the medications that you take, and tick when you take them?

Medication	Morning	Mid morning	Lunchtime	Mid afternoon	Dinnertime	Bedtime
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	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
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	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

PAGE 1

5. Please rate how satisfied you are with the **number** of prescription medications you are taking, that are listed in question 4.

Very unsatisfied	Unsatisfied	Neutral	Satisfied	Very satisfied	Don't Know
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

6. Could you please comment on any thoughts you may have about the **number** of medications you take.

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7. Regarding the medications you are currently taking for heart failure, how important are the following concerns for you? Please read through all options before completing the question.

	Not at all important	Not important	Neutral	Important	Highly important	Don't know
Making you live longer	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Making you feel better	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Taking the least number of medications possible	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Avoiding side effects of medications	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
How expensive medications are	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Avoiding dizziness	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Protecting the function of your kidneys	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Stopping the progress of the disease	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**8. Is there a medication you would stop if you could?**

☐ YES – please go to question 9

☐ NO – please go to question 12

**9. Which medication would you stop if you could and why?**

	Reason
<input type="radio"/>	The price is too high
<input type="radio"/>	This medication gives me side effects
<input type="radio"/>	I am taking too many medications
<input type="radio"/>	The directions for taking this medication are difficult to follow
<input type="radio"/>	Other (please state) _____

**10. Is there a second medication you would stop if you could?**

☐ YES – please go to question 11

☐ NO – please go to question 12

**11. Is there a second medication you would stop if you could?**

	Reason
<input type="radio"/>	The price is too high
<input type="radio"/>	This medication gives me side effects
<input type="radio"/>	I am taking too many medications
<input type="radio"/>	The directions for taking this medication are difficult to follow
<input type="radio"/>	Other (please state) _____

[illegible]

If you did not get time to complete the survey, you can take a reply-paid envelope to send it to:

PAGE 4

*Thank you*

very much for taking the time  
to complete this survey.

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# Heart Failure Patients and Medications

Questionnaire for  
prescribing doctors



MONASH University



CCRE  
THERAPEUTICS

AlfredHealth

You are invited to participate in this study. The purpose of this research is to understand more about doctors' prescribing habits in heart failure. There is also a companion survey of patients looking at similar issues. Your time is greatly appreciated.

Your participation is voluntary. Completing and returning the survey will be taken as confirmation of consent to participate. The survey is anonymous and your answers will be completely confidential. When you have completed the survey, please leave it in the box labelled "Surveys" by the doors.

This research is being conducted by researchers at the Monash Centre of Cardiovascular Research and Education in Therapeutics, at the School of Public Health and Preventive Medicine, Monash University. It forms part of Dr Ingrid Hopper's doctoral thesis, with supervision by Professor Henry Krum. The research has been approved by the Alfred Hospital Ethics Committee.

#### **For further information**

If you would like any further information concerning the project, or if you have any problems which may be related to your involvement in the project, then you can contact the principal researchers as follows:

**Dr Ingrid Hopper**

[Redacted contact information for Dr Ingrid Hopper]

**Professor Henry Krum**

[Redacted contact information for Professor Henry Krum]

If you have any complaints about any aspect of the project or the way it is being conducted, or any questions about being a research participant in general, then you may contact:

Ms Emily Bingle, Office of Ethics and Research Governance, Alfred Hospital

[Redacted contact information for Ms Emily Bingle]



# Heart Failure Patients and Medications

## Questionnaire for prescribing doctors

### 1. Which of the following best describes your clinical role?

- |  |                                    |
|--|------------------------------------|
| <input type="radio"/> Cardiologist               | <input type="radio"/> Geriatrician |
| <input type="radio"/> General physician          | <input type="radio"/> Intensivist  |
| <input type="radio"/> Other – please state _____ |                                    |

### 2. For how many years have you treated patients with heart failure?

- |   |                                     |  |
|---|-------------------------------------|--|
| <input type="radio"/> Less than 5 years | <input type="radio"/> 5 to 10 years | <input type="radio"/> More than 10 years |
|---|-------------------------------------|--|

### 3. In which setting is your highest patient load seeing patients with heart failure?

- ☐ General cardiology wards
- ☐ General medical wards
- ☐ Cardiology outpatient clinics
- ☐ General medical outpatient clinics
- ☐ Heart transplant clinics
- ☐ Other – please state \_\_\_\_\_

### 4. Please estimate the average number of patients with heart failure you see per month?

- |                                    |                                    |
|------------------------------------|------------------------------------|
| <input type="radio"/> Less than 10 | <input type="radio"/> 21-40        |
| <input type="radio"/> 10-20        | <input type="radio"/> More than 40 |

### 5. Please estimate the number of patients per month that you see with a recent (last 6 months) diagnosis of heart failure?

- |                                   |                                    |
|-----------------------------------|------------------------------------|
| <input type="radio"/> Less than 5 | <input type="radio"/> 11-20        |
| <input type="radio"/> 5-10        | <input type="radio"/> More than 20 |

### 6. What proportion of your heart failure patients are taking four or more cardiovascular medications (exclude non-cardiovascular medications)?

%
---

### 7. Which heart failure guidelines do you follow most closely?

- ☐ NHF/CSANZ Guidelines for the prevention, detection and management of chronic heart failure in Australia, updated July 2011
- ☐ 2013 ACCF/AHA Guideline for the Management of Heart Failure
- ☐ ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012
- ☐ HFSA 2010 Comprehensive Heart Failure Practice Guideline
- ☐ I don't use any guidelines
- ☐ Other – please state \_\_\_\_\_

### 8. How important do you consider the following issues when prescribing medications in heart failure?

	Not at all important	Not important	Neutral	Important	Highly important
Prolonging survival	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Reducing symptoms of heart failure	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Reducing the number of medications	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Minimising drug side effects	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Costs of drugs to the patient	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Avoiding symptomatic hypotension	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Preserving renal function	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Beneficially affecting underlying disease process	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**9. In clinical consultations, how often do you consider the following issues with heart failure specific medications other than diuretics?**

	Never	Occasionally	Often	Always
Symptoms of stability of heart failure	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Signs of heart failure	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Test results	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Adding more medication	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Uptitrating existing medication dosage	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Downtitrating existing medication dosage	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Stopping medication	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Need for devices	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**10. To what extent do you agree with the following statements?**

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
My heart failure practice is driven by guidelines	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
My heart failure practice is driven by experience	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I prefer to start multiple medications at low doses	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I prefer to titrate to maximum dosage of one medication before I start another	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I am reluctant to stop prescribed medications	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
I review prescribed medications with a view to reducing them if possible	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Stopping a prescription medication exposes the patient to unnecessary risk	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Patients can benefit from reducing the number of their medications	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Attempting to reduce patients' intake of prescription medications is worthwhile	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Polypharmacy (use of 4 or more different classes of medication) is inevitable in the heart failure population	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**11. Please rate your level of comfort or discomfort with doing the following:**

EF = ejection fraction, HF = heart failure, NYHA = New York Heart Association

	Very uncomfortable	Uncomfortable	Neutral	Comfortable	Very comfortable
Ceasing beta-blocker after recovery to normal EF from low EF if NYHA class I for 12 months	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ceasing ACEi after recovery to normal EF from low EF if NYHA class I for 12 months	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ceasing spironolactone after recovery to normal EF after low EF if NYHA class I for 12 months	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ceasing statin in idiopathic HF	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ceasing statin in ischaemic HF	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ceasing digoxin in a low EF, NYHA class I-II patient successfully titrated to maximal beta-blocker dosage in sinus rhythm	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ceasing digoxin in stable HF after recovery of EF to >40% in sinus rhythm	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ceasing aspirin in idiopathic HF with EF <40%	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ceasing aspirin in ischaemic HF with EF <40%	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Please add any extra comments you would like to make.

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Thank you very much for completing this survey. Please leave it in one of the boxes labelled "surveys" by the doors.

**Dr Ingrid Hopper**

Clinical Pharmacology and Therapeutics Department  
 Alfred Hospital  
 Commercial Road  
 Melbourne VIC 3004

*Thank you*

very much for completing  
this survey.

Please leave it in one of the boxes labelled  
“surveys” by the doors.

**Dr Ingrid Hopper**

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## Appendix 2

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The following pages contain publications directly arising from the studies described in this thesis.

They include:

1. **Hopper I**, Samuel R, Hayward C, Tonkin A, Krum H. Can medications be safely withdrawn in patients with stable chronic heart failure? Systematic review and meta-analysis. *Journal of Cardiac Failure*. 2014; 20(7):522-532
2. Supplemental material – manuscripts assessed and excluded for **Hopper I**, Samuel R, Hayward C, Tonkin A, Krum H. Can medications be safely withdrawn in patients with stable chronic heart failure? Systematic review and meta-analysis. *Journal of Cardiac Failure*. 2014; 20(7):522-532
3. **Hopper I**, Skiba M, von Lueder TG, Watanabe M, Funston R, Tonkin A, Krum H. Digoxin withdrawal worsens clinical status in stable heart failure patients receiving optimal contemporaneous therapy – a randomized controlled trial. *Journal of Cardiac Failure*. 2015; 21:779-81.
4. **Hopper I**, Skiba M, Windebank E, Brack J, Tonkin A, Krum H. Polypharmacy in heart failure – is reducing medication safe? *International Journal of Cardiology*. 2015. In press.

## Appendix 2.1

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**Hopper I**, Samuel R, Hayward C, Tonkin A, Krum H. Can medications be safely withdrawn in patients with stable chronic heart failure? Systematic review and meta-analysis. *Journal of Cardiac Failure*. 2014; 20(7):522-532



## Review Articles

# Can Medications be Safely Withdrawn in Patients With Stable Chronic Heart Failure? Systematic Review and Meta-analysis

INGRID HOPPER, FRACP,<sup>1,2</sup> ROHIT SAMUEL, MBBS,<sup>1</sup> CHRISTOPHER HAYWARD, FRACP, FCSANZ,<sup>3</sup>  
ANDREW TONKIN, MD, FRACP,<sup>1</sup> AND HENRY KRUM, PhD, FESC<sup>1,2</sup>

Melbourne and Sydney, Australia

### ABSTRACT

**Background:** Heart failure (HF) therapy involves use of multiple medications. There is little guidance on the safety and impact on clinical outcomes of stopping HF medications.

**Methods and Results:** A comprehensive systematic search for studies of drug therapy withdrawal in HF was performed. Meta-analysis of the risk ratio (RR) was performed with the use of the Mantel-Haenszel random effects model for all-cause mortality and cardiovascular outcomes. Twenty-six studies met the inclusion criteria. Studies on withdrawal of renin-angiotensin-aldosterone system (RAAS) inhibitors and beta-blockers in HF are scarce and small, yet show relatively convincingly that such withdrawals have untoward effects on cardiac structure, symptoms, and major outcomes. Meta-analysis of 7 studies of digoxin withdrawal (2,987 participants) without background beta-blocker showed increased HF hospitalizations (RR 1.30, 95% confidence interval [CI] 1.16–1.46;  $P < .0001$ ), but no impact on all-cause mortality (RR 1.00, 95% CI 0.90–1.12;  $P = .06$ ) nor reduction in all-cause hospitalization (RR 1.03, 95% CI 0.98–1.09;  $P = .27$ ). Diuretic withdrawal trials demonstrated an ongoing need for these agents in chronic HF. Studies in peripartum cardiomyopathy showed that medications could be successfully withdrawn after recovery.

**Conclusion:** Current evidence discourages any attempt to discontinue RAAS inhibitors or beta-blockers in patients with stable HF, regardless of clinical and/or echocardiographic status. Formal withdrawal trials of other classes are needed. (*J Cardiac Fail* 2014;20:522–532)

**Key Words:** Medication discontinuation, polypharmacy, peripartum cardiomyopathy, digoxin.

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Reprint requests: Ingrid Hopper, FRACP, Centre of Cardiovascular Research and Education in Therapeutics, Department of Epidemiology and Preventive Medicine, Alfred Centre, Monash University, Melbourne, Vic 3004 Australia.

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See page 530 for disclosure information.

1071-9164/\$ - see front matter

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<http://dx.doi.org/10.1016/j.cardfail.2014.04.013>

Chronic heart failure (HF) patients generally require life-long pharmacologic therapy involving multiple medications. Studies have shown a median of 6–11 prescription medications taken daily by patients with HF.<sup>1–3</sup> Polypharmacy, defined as the use of  $\geq 5$  medications,<sup>4</sup> is also becoming more common,<sup>5,6</sup> with associated increased risk of drug-drug interactions<sup>7</sup> and reduced medication adherence, often for reasons of cost to the patient.<sup>2</sup> However, when considering a reduction in use of multiple agents, there is a paucity of literature available on the effects of actually withdrawing HF medications and little guidance regarding evidence-based decisions on their reduction.

There are a number of clinical scenarios in which medication withdrawal may be considered. First, HF with recovered left ventricular ejection fraction (LVEF) is becoming increasingly common.<sup>8,9</sup> Such patients are generally younger and healthier than the usual HF population and,

following therapeutic response to angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, may request cessation of their medications. Peripartum cardiomyopathy also is associated with a return of normal ventricular function in more than one-half of patients, for whom also withdrawal of medications is a consideration.<sup>10</sup> Furthermore, as the population ages and comorbidities increase, it is useful to review individual HF drug regimens for possibly unnecessary agents.

We therefore performed a systematic review and, where possible, meta-analysis of studies of withdrawal of drug therapies in HF. These data might also inform which withdrawal trials are feasible in light of these preliminary experiences and ethical considerations.

## Methods

The study was performed according to recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statements.<sup>11</sup>

### Trial Design

We searched for any study in which a drug for HF was withdrawn in which the population was adult and patients had HF with recovered ejection fraction or stable systolic HF. Chronic HF was defined as a clinical syndrome in which patients have typical symptoms, such as breathlessness, ankle swelling, and fatigue, and signs, such as elevated jugular venous pressure, pulmonary crackles, and displaced apex beat resulting from an abnormality of cardiac structure or function.<sup>12</sup> Study designs included double-blind randomized controlled trials (RCTs), crossover trials, open-label prospective trials, observational studies, retrospective case series, and case reports.

### Agents Investigated

Interventions included therapies with proven mortality benefit, including blockers of the renin-angiotensin-aldosterone system (RAAS), beta-blockers, and the combination of hydralazine/nitrates. Withdrawal trials involving diuretics also were investigated. Guideline-recommended medications for coexisting conditions in HF also were evaluated, including digoxin, HMG-CoA reductase inhibitors (statins), aspirin, and nitrates.

### Outcomes Evaluated

Where possible, outcomes including all-cause mortality, HF hospitalization, and all-cause hospitalization were examined. We also aimed to assess the effect of drug withdrawal on clinical status, New York Heart Association (NYHA) functional class, hemodynamic measures, echocardiographic parameters, exercise capacity and quality-of-life measures, hormones, and hemodynamic parameters assessed by right heart catheterization.

### Search Methodology

Searches took place up to January 2014. We searched Medline (1966–January 2014), Embase (1980–January 2014), the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled trials, as well as [ClinicalTrials.gov](http://ClinicalTrials.gov) and abstracts from major international cardiology meetings from 2007 to

2013. The search strategy combined key words and MeSH terms related to removing medications (de-prescribing, withdraw\*, cessation, cease\*, discontinue\*, stop\*, interrupt\*), with terms related to HF (HF, cardiomyopathies, dilated cardiomyopathy, left ventricular dysfunction, myocarditis, peripartum cardiomyopathy, cardiovascular pregnancy complications) and cross-linked with classes of drugs as well as individual drug names. Extensive manual reference checking was also undertaken. Studies were limited to those reported in English.

Initially studies were limited to RCTs, but owing to the low number of studies identified, the search criteria were broadened to include studies published or unpublished, full articles, abstracts, and letters. All abstracts and letters identified through our searches were assessed to determine relevant full-text articles for retrieval. Studies were excluded from the final analysis if they reported on medications that were no longer available or no longer used in the treatment of HF. Abstracts or letters without an accompanying peer-reviewed article, case studies, and case series were not included in the final analysis but are listed in the [Supplemental Appendix](#). Studies were reviewed by 2 authors (I.H. and R.S.).

### Statistical Methods

The statistical analysis was performed with the use of Review Manager (Revman) version 5.2.5.<sup>13</sup> Meta-analysis was performed if  $\geq 3$  papers examined the same prespecified end point. Mantel-Haenszel random effects models were used for data analysis, given the clinical heterogeneity of the studies found. The significance of risk ratios was assessed with the use of the Z test with a statistical significance of .05. Risk ratio (RR) with 95% confidence interval (CI) was derived for each study as well as for overall outcome. Weighting was calculated for each study in accordance with the number of events that occurred in that study to enable derivation of an average overall outcome statistic and 95% CI. To examine potential publication bias, symmetry of individual study estimates around the overall estimate was assessed with funnel plots in which standard errors of log RRs were plotted against their corresponding RRs.<sup>14</sup>

## Results

The literature search identified 1,230 relevant titles from databases and hand searches: 867 were excluded at the title level, and 273 at the abstract level ([Fig. 1](#)). Full-text articles were retrieved for 90. A total of 64 full-text articles were excluded (see [Supplemental Material](#) for list of excluded studies). Twenty-six drug withdrawal studies were identified ([Table 1](#)): 11 were RCTs, 4 were crossover trials, and 11 were observational trials. One observational trial instituted several medication changes sequentially, and each was dealt with separately.<sup>15</sup> There were no studies of withdrawal of aldosterone antagonists or statins from patients with HF.

### Renin-Angiotensin-Aldosterone System Inhibitors

Data on the withdrawal of RAAS inhibitors are scarce. However, the small studies reported are relatively convincing in showing that such withdrawals are likely to have untoward effects on cardiac structure and patients' symptoms and outcomes. Two studies of RAAS inhibitor

withdrawal were identified. Withdrawal of captopril was associated with a sharp increase in RAAS activity within 1 day.<sup>16,17</sup> Marked increases in angiotensin II and aldosterone, a decrease in plasma renin activity, and increases in plasma and urinary cortisol excretion were observed, together with increases in heart rate and arterial blood pressure. However, no worsening in clinical status was observed in this short time frame. Pflugfelder et al<sup>18</sup> found higher rates of worsening HF in the quinapril withdrawal group compared with the continuation group (33% vs 19%;  $P = .003$ ) in 224 participants with stable chronic HF. Exercise tolerance, NYHA functional class, quality of life, and clinical status of HF deteriorated, which occurred gradually over a 4–6-week period.

Dose reduction however appears to be tolerated in the setting of renal dysfunction at least. De Silva<sup>15</sup> studied 68 patients with HF and renal dysfunction (serum creatinine [SCr]  $> 130 \mu\text{mol/L}$  [ $1.5 \text{ mg/dL}$ ] and estimated glomerular filtration rate  $< 60 \text{ mL/min}$ ). ACE inhibitors or angiotensin II receptor blockers (ARBs) were taken by this group at 75% of maximum recommended dose. No increase in symptoms of HF was seen after the dose was halved (or stopped in 4 patients on low doses). Mean blood pressure was unchanged, although blood pressure rose by  $> 10 \text{ mm Hg}$  in 22 (32%) patients. Mean SCr also fell from  $170 (\pm 55) \mu\text{mol/L}$  to  $164 (\pm 46) \mu\text{mol/L}$ .

Cessation of ACE inhibitor and use of beta-blocker in its place may also be safe. The Carvedilol and ACE-Inhibitor Remodeling Mild Heart Failure Evaluation Trial (CAR-MEN) study<sup>19</sup> compared enalapril, carvedilol, and enalapril/carvedilol combination in mild HF. Participants randomized to the carvedilol group ( $n = 191$ ) had their ACE inhibitor ceased before the trial (62% were taking an ACE inhibitor). Compared with the enalapril group, the carvedilol group showed a nonsignificant reduction in left ventricular end systolic volume index determined by transthoracic echo and an improvement in LVEF at 6 and 12 months, which, however, was not present at 18 months. The enalapril-carvedilol combination was superior to either alone.

#### Beta-Blockers

Beta-blockers were withdrawn in 3 small uncontrolled open-label observational trials in idiopathic dilated cardiomyopathy (IDCM) with stable HF, with all trials observing deterioration in clinical signs of HF and reduction in LVEF. Swedberg et al<sup>20</sup> withdrew beta-blockers from 15 patients whose HF had improved after 6–50 months of beta-blocker use, with continuation of background digitalis and diuretics. Clinical features of HF recurred in 9 of the 15, with 1 sudden death. Echocardiography demonstrated an overall reduction in LVEF from  $46 \pm 3\%$  to  $35 \pm 3\%$  ( $P < .01$ ) after a mean of 72 (range 7–119) days following beta-blocker withdrawal. Waagstein et al<sup>21</sup> withdrew metoprolol in 24 patients, with 16 deteriorating (4 of whom died) after an average of 5.8 (range 1–12) months. Mean

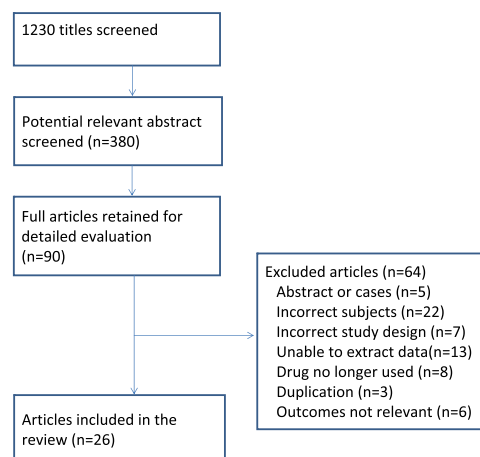


Fig. 1. Study flow diagram.

LVEF on echocardiography before withdrawal was  $41 \pm 12\%$ , decreasing to  $32 \pm 13\%$  after withdrawal ( $P < .01$ ). The remaining 8 patients remained stable for a follow-up period ranging from 2.5 to 6.5 years. Morimoto et al<sup>22</sup> withdrew metoprolol (mean dose of  $61.5 \pm 34.1 \text{ mg/d}$  for  $46.8 \pm 9.8 \text{ mo}$ ) in a stepwise fashion over a period of 14 weeks in 13 patients, 10 of whom were in NYHA functional class I. Seven patients deteriorated (2 sudden deaths and 2 deaths from worsening HF) during the 4-month follow-up period. Six patients remained stable. Overall, LVEF fell from  $38.3 \pm 14\%$  to  $33.9 \pm 14\%$  ( $P < .05$ ).

Medication cessation was the only identified predictor of recurrence of HF in a retrospective study by Moon et al<sup>23</sup> of 42 patients with IDCM and recovered LVEF. All patients were receiving ACE inhibitors and about one-half receiving beta-blockers. Recovery was considered to be LVEF  $\geq 40\%$  and a net increase in LVEF of  $\geq 10\%$ . Of the 42 patients, 8 experienced recurrence of HF, defined as left ventricular systolic dysfunction with LVEF  $< 40\%$ . Of the 8 with recurrence, 5 had ceased “anti-heart failure medications.” The odds ratio for recurrence of HF with cessation of anti-HF medications was 26.7 (95% CI 3.5–201.5;  $P < .007$ ) and was the only significant predictor of recurrence. The investigators also described 2 patients who ceased medications who did not experience a recurrence of HF at 9 and 72 months.

Amos et al<sup>24</sup> retrospectively studied the outcomes of 55 patients with peripartum cardiomyopathy, 22 (45%) of whom had recovery of normal LVEF during a mean follow-up of  $38 \pm 28$  months. Baseline LVEF was  $23 \pm 10\%$  at initial presentation, and improved to 43% (no SD available) by 2 months. The authors stated that this group of 22 patients thereafter normalized their LVEF (considered to be LVEF  $> 50\%$ ; actual values not available). Fifteen patients then had further

**Table 1.** Characteristics of Included Studies

Study	Year	Drug Withdrawn	Population	No. of Patients	Follow-Up (wk)	Background Therapy	Study Design	Random Allocation	Control Group
de Silva et al <sup>15</sup>	2007	ACE	HFRD, ICM (81%)	68	4	ACE/ARB, BB	OB	N	Y
de Silva et al <sup>15</sup>	2007	DIU	HFRD, ICM (81%)	68	4	ACE/ARB, BB	OB	N	Y
de Silva et al <sup>15</sup>	2007	ASP	HFRD, ICM (81%)	32	4	ACE/ARB, BB	OB	N	Y
Nicholls et al <sup>16</sup>	1982	ACE	ICM	5	0.5	DIG DIU	OB	N	N
Maslowski et al <sup>17</sup>	1981	ACE	ICM	5	0.5	DIG DIU	OB	N	N
Pflugfelder et al <sup>18</sup>	1993	ACE	ICM (63%)	224	16	DIG	RCT	Y	Y
Remme et al <sup>19</sup>	2004	ACE	ICM (67%)	572	78	ACE DIG DIU	RCT	Y	Y
Swedberg et al <sup>20</sup>	1980	BB	NICM	15	16	DIG	OB	N	N
Waagstein et al <sup>21</sup>	1989	BB	NICM	24	52	NS	OB	N	N
Morimoto et al <sup>22</sup>	1999	BB	NICM	13	16	NS	OB	N	N
Moon et al <sup>23</sup>	2009	ACE/ARB ± BB	NICM	7	192	ACE/ARB, BB	RET OB	N	N
Amos et al <sup>24</sup>	2006	ACE, BB	PPCM	11	116	ACE, BB	RET OB	N	N
PROVED <sup>26</sup>	1993	DIG	ICM (60%)	88	12	DIU	RCT	Y	Y
RADIANCE <sup>27</sup>	1993	DIG	ICM (60%)	178	12	DIU, ACE	RCT	Y	Y
DIG trial <sup>30</sup>	1997	DIG	ICM (68%)	3365	160	ACE	RCT	Y	Y
Fleg et al <sup>32</sup>	1982	DIG	ICM (63%)	30	12	DIU	XO	Y	X
Guyatt et al <sup>33</sup>	1988	DIG	ICM (85%)	20	7	DIU	XO	Y	X
Lee et al <sup>34</sup>	1982	DIG	ICM (60%)	25	9	DIU	XO	Y	X
Taggart et al <sup>35</sup>	1983	DIG	ICM (77%)	22	12	DIU	XO	Y	X
Shammas et al <sup>36</sup>	2001	DIG	NICM	8	68	ACE, BB	OB	N	N
Khand et al <sup>37</sup>	2003	DIG	ICM + AF	47	24	BB	RCT	Y	Y
Richardson et al <sup>43</sup>	1987	DIU	ICM (53%)	14	8	ACE, DIG	RCT	Y	X
Grinstead et al <sup>44</sup>	1994	DIU	ICM (75%)	41	12	DIG NIT	OB	N	N
Magnani et al <sup>45</sup>	1988	DIU	ICM (44%)	64	52	DIG	RCT	N	N
Walma et al <sup>46</sup>	1997	DIU	NS	84	26	NS	RCT	Y	Y
Galve et al <sup>47</sup>	2005	FRU	ICM (52%)	26	12	ACE, DIG	OB	N	N
Braunschweig et al <sup>48</sup>	2002	FRU	ICM (75%)	4	2	ACE, BB, DIG	OB	N	N
Wieshammer et al <sup>49</sup>	1993	NIT	ICM	29	6	ACE, DIG	RCT	Y	Y
WASH <sup>51</sup>	2004	ASP	ICM (64%)	279	108	ACE, DIG, DIU	RCT	Y	Y

ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASP, aspirin; BB, beta-blocker; DIG, digoxin; DIU, diuretics; FRU, frusemide; ICM, ischemic cardiomyopathy; NICM, nonischemic cardiomyopathy; NIT, nitrates; NS, not stated; OB, observational trial; PPCM, peripartum cardiomyopathy; RCT, randomized controlled trial; HFRD, heart failure with renal dysfunction; RET, retrospective; XO, cross-over trial.

echocardiography, and of them, 11 had ceased either ACE inhibitor or beta-blocker and 5 had ceased both. No deterioration in LVEF was observed an average of 29 (range 5–63) months after recovery.

### Digoxin

Use of digoxin in HF preceded formal RCTs. Studies of digoxin withdrawal were commenced in the 1960s, and were heterogeneous in nature, with diverse patient selection, including patients with atrial arrhythmias, and mostly uncontrolled and poorly designed. Those early trials have been reviewed,<sup>25</sup> with the conclusion that responses to digoxin and its withdrawal were highly variable.

Two larger-scale RCTs of withdrawal demonstrated the importance of digoxin in patients with HF with reduced LVEF and sinus rhythm in the pre-beta-blocker era. The Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED)<sup>26</sup> and Randomized Assessment of the Effect of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE) Study<sup>27</sup> were both 12-week double-blind RCTs of digoxin withdrawal. In PROVED, patients received background diuretics without ACE inhibitors, and in RADIANCE patients received diuretics and ACE inhibitors.

In PROVED, a total of 88 patients with baseline LVEF of  $28 \pm 1\%$  were randomized to digoxin continuation or withdrawal. Three of the 4 primary end points worsened on digoxin withdrawal. Maximal exercise performance deteriorated ( $P = .003$ ), “treatment failures” (defined as increased diuretic requirement, need for addition of new medications for HF, emergency visit/hospitalization, or HF-related death) were higher (39% vs 19%;  $P = .039$ ) and time to treatment failure was less when digoxin was withdrawn ( $P = .037$ ). No difference was observed in submaximal (6-minute walk) exercise test. RADIANCE randomized 178 patients with baseline LVEF of  $27 \pm 0.01\%$  to digoxin continuation or withdrawal. The RR of withdrawal from the study due to worsening HF in the digoxin withdrawal group was 5.9 (95% CI 2.1–17.2;  $P < .001$ ) compared with continued use. Significant deterioration in maximal treadmill exercise tolerance and exercise endurance was also observed after digoxin withdrawal ( $P = .033$ ).

Statistically significant small reductions in LVEF in the digoxin withdrawal groups (4% in PROVED, 3% in RADIANCE;  $P < .05$ ) were observed compared with the digoxin continuation groups. Meta-analysis demonstrated that even patients with clinically mild HF with few or no symptoms and signs of HF at randomization deteriorated after digoxin withdrawal.<sup>28</sup> Multivariate analysis found that participants who were not receiving an ACE inhibitor at randomization were more likely to deteriorate after digoxin withdrawal.<sup>29</sup>

A subgroup analysis of the much larger Digitalis Investigation Group (DIG) study examined participants taking digoxin at enrollment, who then had it randomly withdrawn or continued with background ACE inhibitors and diuretics ( $n = 3,365$ ).<sup>30</sup> Mean LVEF overall was  $31 \pm 12\%$ , with

10% having an LVEF  $> 45\%$ . Compared with continuing digoxin ( $n = 1,666$ ), its cessation ( $n = 1,699$ ) resulted in significant increases in hospitalization, both all-cause hospitalization (adjusted hazard ratio [AHR] 1.18, 95% CI 1.09–1.28;  $P < .0001$ ) and hospitalization related to HF (AHR 1.35, 95% CI 1.20–1.51;  $P < .0001$ ). However all-cause mortality was not significantly different over a median 39.7 months of follow-up (AHR 1.06, 95% CI 0.95–1.19;  $P = .272$ ).

We performed meta-analysis of all available (7) RCTs of digoxin withdrawal in sinus rhythm,<sup>26,27,31–35</sup> including a total of 2,987 participants (Table 2). On withdrawal of digoxin, there was an increase in HF hospitalizations (RR 1.30, 95% CI 1.16–1.46;  $P < .0001$ ; Fig. 2), but no change in all-cause mortality (RR 1.00, 95% CI 0.90–1.12;  $P = .95$ ) nor any change in all-cause hospitalization (RR 1.03, 95% CI 0.98–1.09;  $P = .27$ ). These results were dominated by the DIG trial, which accounted for 95% of the weighting. Sensitivity analysis excluding the DIG trial did not alter the results. A significant rise in heart rate was seen after withdrawal of digoxin (reported in 5 studies [ $n = 416$ ], mean difference 6.57 (95% CI 3.74–9.41) beats/min;  $P < .00001$ ; Fig. 3) as well as a fall in systolic blood pressure (BP; mean difference  $-5.13$  (95% CI  $-9.83$  to  $-0.42$ ) mm Hg;  $P = .03$ ). No significant mean differences were seen in LVEF, left ventricular end-diastolic diameter, body weight, cardiothoracic ratio, or diastolic BP (Table 2). No publication bias was evident on visual inspection of the funnel plot (Fig. 4).

Shammas et al<sup>36</sup> examined digoxin withdrawal with background ACE inhibitors and beta-blockers in a single-arm observational trial with 8 patients with IDCM and normalized EF  $> 50\%$ . Mean baseline LVEF measured with isotope ventriculography at initial presentation was  $28.5 \pm 8.3\%$ , and it improved to  $56.1 \pm 4.7\%$  over  $17.3 \pm 5.4$  months. Digoxin was withdrawn, and LVEF fell to  $51.0 \pm 7.35\%$  ( $P = .05$ ) at a mean follow-up of  $7.0 \pm 4.3$  months, although this remained in the normal range. No comment was made on the clinical status of the patients.

The Carvedilol in Atrial Fibrillation Evaluation (CAFÉ) trial enrolled 47 participants with atrial fibrillation and HF taking background ACE inhibitors.<sup>37</sup> When digoxin was withdrawn and carvedilol continued, a significant increase of 22 beats/min in mean heart rate (from  $65.2 \pm 15$  bpm to  $88.8 \pm 18.7$  beats/min) and a 9% decline in LVEF (from  $30.6 \pm 9.6\%$  to  $21.6 \pm 11\%$ ) were seen. Participants in the digoxin withdrawal-carvedilol continuation arm rated their symptoms better than the digoxin arm, although 3 subjects withdrew from the study after digoxin withdrawal because of worsening symptoms associated with HF owing to increased heart rate. Greater control of ventricular response with digoxin was considered to be beneficial, but this has recently been challenged.<sup>38,39</sup>

### Diuretics

Diuretics cause contraction of intravascular volume, leading to short-term relief from symptoms of congestion,

**Table 2.** Digoxin Withdrawal Trials: Meta-analysis Results

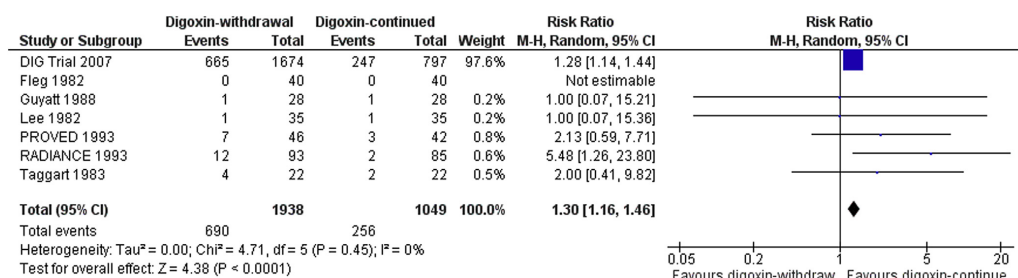
Outcome or Subgroup	Studies	Participants	Effect Estimate (95% CI)
1.1 Hospitalization—heart failure	7	2,987	1.30 (1.16–1.46)
1.2 Mortality	7	2,987	1.00 (0.90–1.12)
1.3 Hospitalization—all causes	4	2,677	1.03 (0.98–1.09)
1.4 Left ventricular ejection fraction	3	316	0.01 (–0.05–0.06)
1.5 Left ventricular end-diastolic dimension	4	308	0.23 (–1.95–2.41)
1.6 Heart rate	5	416	6.57 (3.74–9.41)
1.7 Body weight	5	420	4.24 (–0.24–8.72)
1.8 Cardiothoracic ratio	5	326	0.00 (–0.02–0.02)
1.9 Systolic blood pressure	3	282	–5.13 (–9.83 to –0.42)
1.10 Diastolic blood pressure	3	282	1.74 (–0.52–4.01)
1.11 Hospitalization—heart failure (without DIG trial)	7	516	2.41 (1.13–5.14)
1.12 Mortality (without DIG trial)	7	516	0.68 (0.19–2.43)
1.13 Hospitalization—all causes (without DIG trial)	3	206	1.11 (0.20–6.25)

but have been shown to stimulate the RAAS<sup>40,41</sup> and worsen renal function in the short term. The safety of diuretics has not been established.<sup>42</sup> We identified 7 studies of diuretic withdrawal. Deterioration was more frequent in the diuretic withdrawal group throughout, indicating an ongoing need for this class of drug in stable chronic HF.

Three trials withdrew diuretics, commencing ACE inhibitors concomitantly in subjects with euvoletic HF, in an attempt to determine whether ACE inhibitors could replace diuretics in subjects with mild to moderate HF. Richardson et al<sup>43</sup> performed a 16-week double-blind crossover trial. Four of 14 participants (29%) developed pulmonary edema when diuretics were withdrawn and captopril started, compared with none in the diuretic (frusemide with amiloride) continuation arm. Grinstead et al<sup>44</sup> found that 29 of 41 participants (71%) required diuretic after a median 15 (range 2–42) days after withdrawal of diuretic and randomization to lisinopril or placebo. Independent predictors of the need to restart diuretics included a history of hypertension, baseline daily frusemide dose > 40 mg, and LVEF < 27%. Magnani et al<sup>45</sup> withdrew diuretics from 64 participants who were then randomized to captopril or placebo in a 12-month trial in mild to moderate heart failure (NYHA functional class II or III). Background medication was digoxin. That study found that 34% required diuretics to be restarted and that captopril was associated with reduced need for diuretics.

Significant failure rates were seen on withdrawal of diuretics in heart failure. Walma et al<sup>46</sup> performed a 6-month double-blind randomized trial withdrawing or continuing diuretics in 202 subjects with various indications aged > 65 years recruited from general practice. Of the subjects with HF, diuretic withdrawal was poorly tolerated, with 30 of the 46 subjects (65%) in the withdrawal group requiring diuretics to be restarted, whereas only 4 of the 38 subjects (11%) randomized to diuretic continuation required further diuretics during the trial. The risk difference was 57% (95% CI 36%–78%). De Silva<sup>15</sup> halved the doses of diuretic in 50 patients with HF and renal dysfunction, with doses of frusemide ranging from 40 mg to 160 mg daily, and 36% were unable to tolerate such a reduction. Diuretics were ceased in 18 patients on a 20 mg dose, and 39% were unable to tolerate cessation of even this small dose. Reasons for recommencement of diuretics included shortness of breath, ankle swelling, and weight gain. Of the 42 participants who could tolerate cessation, modest improvements in SCr were seen. Higher baseline SCr was associated with worse tolerance of diuretic withdrawal and less marked improvements in SCr.

Two trials investigated the neurohormonal effects of diuretic withdrawal. Galve et al<sup>47</sup> withdrew diuretics from 26 subjects with stable HF (mean LVEF 34%) on background ACE inhibitor. At 3 months, 9 (35%) required diuretics to be restarted (median time to reinitiation

**Fig. 2.** Heart failure hospitalizations: digoxin withdrawal versus digoxin continuation.



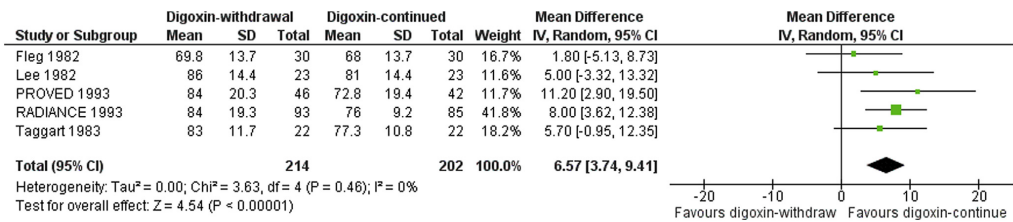


Fig. 3. Heart rate: digoxin withdrawal versus digoxin continuation.

33 days, range 2–83), and 17 (65%) tolerated withdrawal successfully with no deterioration in exercise tolerance or NYHA functional class (15 of whom remained off diuretics without deterioration out to 12 months). Importantly, diuretic withdrawal was associated with improvement in renal function parameters and glucose metabolism, with no change in heart rate or systolic BP and a rise in diastolic BP observed. A decrease in plasma renin activity was noted, but no change in aldosterone, arginine-vasopressin, endothelin-1, and norepinephrine was seen. A-type natriuretic peptide levels increased. Braunschweig et al<sup>48</sup> withdrew furosemide from 4 patients with stable severe HF, with LVEF ranging from 21% to 33%, receiving both ACE inhibitors and beta-blockers, using implantable hemodynamic monitoring devices to allow continuous hemodynamic monitoring. Right ventricular systolic and diastolic pressures and estimated pulmonary arterial pressures increased over the 2-week study period in all 4 patients, in parallel with increasing symptoms of HF, reduction in exercise tolerance, and increase in B-type natriuretic peptide levels, demonstrating the rapidity of fluid accumulation on diuretic cessation.

#### Vasodilators

Withdrawal of isosorbide dinitrate alone was compared with withdrawal of a placebo in HF patients.<sup>49</sup> At rest, withdrawal of nitrates had no effect on left ventricular

chamber size, but during exercise, nitrate withdrawal was associated with a reduction in LVEF (mean change +0.8% vs -2.7%;  $P < .02$ ). No studies were identified that tested the withdrawal of combination hydralazine and nitrates.

#### Ancillary Agents Used in HF

**Aspirin.** Aspirin's use in both ischemic and nonischemic HF to reduce thrombotic risk is mired by evidence of worsening of HF status with this drug.<sup>50</sup> The Warfarin/Aspirin Study in Heart Failure (WASH) study included 279 participants randomized to no antithrombotic (ATT), aspirin, or warfarin in HF in sinus rhythm.<sup>51</sup> Baseline aspirin was withdrawn in the no-ATT (46% of the group) and warfarin (56% of the group) arms. Overall, there were no significant differences in the primary outcomes of death, nonfatal myocardial infarction, and nonfatal stroke across the 3 groups. However, a prespecified secondary analysis found that aspirin was associated with a significantly increased risk of cardiovascular hospitalization, mainly for worsening heart failure, suggesting that aspirin may exacerbate HF and that its withdrawal may reduce HF occurrence.

Withdrawal of aspirin may also improve renal function. De Silva's study<sup>15</sup> of participants with HF and renal dysfunction also withdrew aspirin and substituted clopidogrel in 32 participants, with a resulting fall in SCr by 8 (SD 19)  $\mu\text{mol/L}$  ( $P = .05$  within the group). No comment on symptoms of HF was made.

**HMG-CoA Reductase Inhibitors.** RCTs of statins have shown no mortality benefit in HF.<sup>52,53</sup> However, there have been no trials investigating the effects of statin withdrawal in the HF setting when they are not considered otherwise indicated.

#### Discussion

In patients with chronic stable HF, the studies reviewed here indicate that continuation of RAAS inhibitors and beta-blockers is mandatory, given the deterioration in clinical status seen on withdrawal of these medications as well as their known survival benefit. This assessment also likely extends to aldosterone antagonists and combination hydralazine/nitrates, despite the absence of withdrawal trials. The

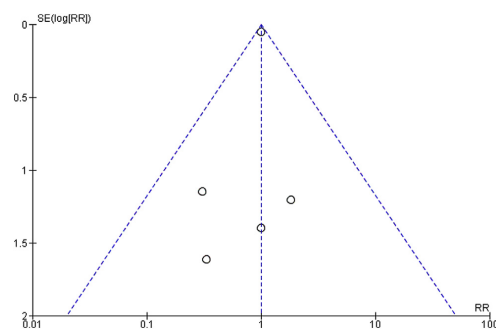


Fig. 4. Funnel plot of digoxin withdrawal versus digoxin continuation for mortality, demonstrating no publication bias.

limited data reviewed show that patients with HF with normalized LVEF increase their risk of recurrent HF if neurohormonal blockade is withdrawn. This can occur many years later, suggesting that the underlying pathology continues despite normalization of LVEF. Indeed, recurrence has been well documented in subsequent pregnancies in patients with peripartum cardiomyopathy.<sup>54</sup>

This methodical and comprehensive review of the literature has demonstrated the scarcity of robust evidence to guide withdrawal of medications in HF. The majority were observational or crossover trials, and only a minority were RCTs. Follow-up in most studies was <1 year. The studies reflect a different era of HF therapeutics, with most trials performed with digoxin as background therapy. The relative absence of high-quality data has precluded meta-analysis, other than of digoxin withdrawal, and even there, no contributing trials involved patients receiving background beta-blockers. Pragmatic reasons also contribute to the inadequacy of the available data. Objections from physicians and Ethics Committees, poor recruitment, and difficulty in obtaining funding all may have resulted in RCTs too small to adequately answer the question they were designed to address. In effect, new medications developed for patients with HF have been added to existing therapies, because it has been considered to be unethical to remove older medications with possible benefit.

Withdrawal trials can be difficult to interpret. There may be weaknesses inherent in their design, and interpretation can be ambiguous. Withdrawal trials may introduce bias in favor of the drug, because participants who cannot tolerate the drug are not included in the trial and therefore participants represent a group who benefit from, or at least tolerate, the drug, consequently deteriorating on its withdrawal. The effect of medication withdrawal is also complex and may be influenced by a number of factors that cannot be addressed in this review, such as the etiology, duration, and severity of HF symptoms, degree of systolic dysfunction, patient age, and method of withdrawal (abrupt or stepped). Withdrawal of drugs without manipulation of other medications may not be a fair test of a therapeutic strategy.<sup>55</sup> Crossover designs assume that there will not be a “carryover” effect from the intervention from the 1st to the 2nd phase of the trial. The long-term benefits of neurohormonal antagonists may occur far from their time of initiation, and it is reasonable to expect that the effects of withdrawal also may be delayed. Additionally, the rationale for withdrawing medications varies between trials, with confounding by indication problematic, especially in observational trials.

In light of these caveats, which trials of medication withdrawal would be important to inform clinicians considering reducing HF therapies in patients? A prospective trial of withdrawal of neurohormonal blockade in patients with HF with recovered LVEF would be difficult to justify because of the evidence presented here, and it is possible that such a trial would not have sufficient follow-up to capture late deterioration. However, there may be a role for

trials of dose reduction in this population, and in such a trial, an important element would be to investigate possible markers that could predict recurrence of HF. Furthermore, trials of medication withdrawal after normalization of LVEF in patients with peripartum cardiomyopathy would be a relatively safe clinical situation in which to consider such trials.

There are questions relating to both efficacy and safety of digoxin such that its role in HF remains unresolved. It has been suggested that the benefits of modern HF therapies, including ACE inhibitors, beta-blockers, and aldosterone antagonists, may overwhelm any benefit seen with the use of digoxin.<sup>56</sup> Although the DIG trial, which was performed before beta-blockers were established as standard of care in HF, did not show an overall mortality benefit with digoxin compared with placebo,<sup>31</sup> statistically significant reductions in HF hospitalizations were observed, and post hoc analysis suggested a potential mortality benefit at low serum concentrations.<sup>57</sup> Recent retrospective studies failed to show any benefit with digoxin, but issues with confounding by indication and patients receiving digoxin having more severe HF made interpretation difficult.<sup>58,59</sup> Higher-quality data come from a post hoc analysis of the Valsartan Heart Failure Trial (Val-HeFT) trial, which demonstrated no benefit from the addition of digoxin to ACE inhibitors, beta-blockers, and diuretics and suggested a possible detrimental interaction between digoxin and beta-blockers; however, participants were not randomized to digoxin.<sup>60</sup> Further safety issues arise from digoxin's modest positive inotropic effects, because drugs with such effects have been associated with poorer outcomes and increased risk of sudden death in HF.<sup>61</sup> However, digoxin continues to be used in clinical practice, albeit with calls for further trials.<sup>56,62,63</sup> An important question to address is whether there continues to be a role for digoxin in such patients on optimal background HF pharmacotherapy, and a randomized digoxin withdrawal trial could inform this.

The overall quality of the diuretic withdrawal trials identified was poor, with three studies introducing an ACE inhibitor at the same time as withdrawing diuretic, the type of diuretic (whether potassium sparing or not) poorly specified, and background therapies not optimized according to current guideline recommendations. A key question is whether diuretics confer benefit or risk in the setting of chronic euvolemic HF in patients prescribed optimal neurohormonal blockade. A diuretic withdrawal study could be designed to compare continuation of higher or withdrawal to lower doses as well as complete cessation of diuretic, and an important element would be to attempt to identify accurate predictors of sustained clinical stability following diuretic withdrawal.

Despite statins failing to confer a survival benefit in large RCTs in patients with HF,<sup>53,64</sup> they are still commonly prescribed. Reasons to continue statins include their purported beneficial pleiotropic properties, including antiinflammatory effects and improvement in endothelial function,<sup>64</sup> other potential benefits which may be important in patients



with ischemic cardiomyopathy, including reduced risk of coronary heart disease events, primary and secondary stroke,<sup>65</sup> and, in those with peripheral arterial disease, improvement in symptoms and reduced progression of disease.<sup>66,67</sup> Although the proportion of patients with side effects from statin usage is low, the number of patients taking them means that side effects are commonly encountered in practice.<sup>68</sup> Statins are the class of drug that HF patients themselves identify as causing the greatest frequency of side effects.<sup>69</sup> Coenzyme Q10 depletion potentially exacerbates poor myocardial contractility<sup>70</sup> and impairs the ability of cholesterol-rich lipoproteins to detoxify bacterial lipopolysaccharides.<sup>71</sup> Statins have not been abandoned in HF, despite evidence lacking for their efficacy. A trial of statin withdrawal in patients with ischaemic HF would inform clinicians on the safety of doing so.

Aspirin is commonly used in patients with HF as an antithrombotic, although there is no evidence for a reduction in myocardial infarction or stroke or of a mortality benefit in this context.<sup>51,72,73</sup> The antiprostaglandin effects of aspirin result in sodium and water retention, and indeed, early trial evidence suggested a worsening of HF status with aspirin,<sup>51,72</sup> though recent evidence in mild HF found otherwise.<sup>73</sup> There is also potential for interaction with ACE inhibitors that might negate their mortality benefit.<sup>74,75</sup> An aspirin withdrawal trial in patients with ischemic cardiomyopathy is warranted.

In summary, the database regarding drug withdrawal is incomplete, though it does demonstrate specific risks with withdrawal of neurohormonal blocking agents. Medication cessation in patients with HF and recovered LVEF increases risk of late recurrence of HF. Based on the above, there clearly is a need for high-quality RCTs examining the discontinuation of medications without proven mortality benefit in HF, specifically digoxin, statins, and aspirin.

### Disclosures

None.

### Supplementary Data

Supplemental data related to this article can be found at <http://dx.doi.org/10.1016/j.cardfail.2014.04.013>

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## Appendix 2.2

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Supplemental material – manuscripts assessed and excluded for:

**Hopper I**, Samuel R, Hayward C, Tonkin A, Krum H. Can medications be safely withdrawn in patients with stable chronic heart failure? Systematic review and meta-analysis. *Journal of Cardiac Failure*. 2014; 20:522-532

Full manuscripts for the following were assessed and excluded for the following reasons:

Abstracts without peer review[1-3], case studies or case series[4, 5], studies were in the incorrect group of patients[6-23] including patients with acutely decompensated heart failure[24-28], inappropriate study design[29-35], unable to extract data[36-48], drugs no longer used in heart failure[49-56], data already presented in another paper[57-59], outcomes not relevant[60-65].

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## Appendix 2.3

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**Hopper I**, Skiba M, von Lueder TG, Watanabe M, Funston R, Tonkin A, Krum H. Digoxin withdrawal worsens clinical status in stable heart failure patients receiving optimal contemporaneous therapy – a randomized controlled trial. *Journal of Cardiac Failure*. 2015; 21:779-81.

## Research Letter

### Digoxin Withdrawal Worsens Clinical Status in Stable Patients With Heart Failure Receiving Optimal Contemporaneous Therapy—A Randomized Controlled Trial

To the Editor:

The current role of digoxin in heart failure (HF) patients with reduced ejection fraction (EF) in sinus rhythm (SR) is unclear.<sup>1</sup> We therefore sought to investigate the effect of digoxin withdrawal in such patients, currently receiving a stable dose (> 3 mo) of digoxin with optimal contemporaneous therapy.

We performed a prospective, randomized, single-blind, placebo-controlled, 2-arm crossover trial (NCT01398371). Participants were randomized to digoxin continuation ("dig-on") or unmatched placebo ("dig-off") for 3 months and then crossed over. Standard HF clinical status and quality of life (QoL) end points were evaluated. Results were compared across dig-on versus dig-off groups with the use of Student's paired *t* test. Institutional ethics approval was obtained, and written informed consent of study subjects. The research conformed to principles of the Declaration of Helsinki.

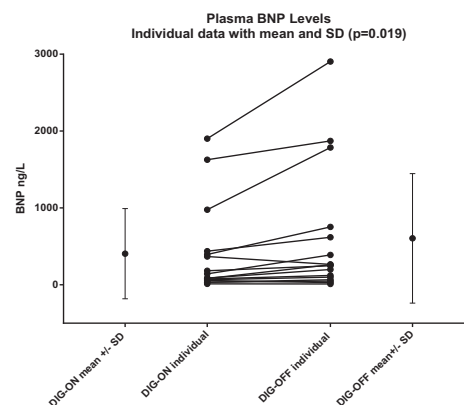
The 16 study participants had a mean age of  $61.3 \pm 11.0$  years, 81% were male, mean duration of HF was  $5.6 \pm 3.3$  years, and mean EF was  $33 \pm 10\%$ . HF etiology was ischemic in 7 and nonischemic in 9. All participants were on optimal doses of angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) and beta-blockers. Other therapies included mineralocorticoid receptor antagonists (MRAs) in 9, implantable cardiac defibrillator (ICD) in 11, and cardiac resynchronization therapy (CRT) in 2.

All participants completed the dig-on arm. Two participants were withdrawn from the dig-off arm early owing to deteriorating HF symptoms, with end-of-period assessments performed early and included in the analysis. The mean plasma digoxin level during the active phase was  $0.5 \pm 0.2$  ng/mL. During the dig-off arm, 4 participants required an increase in diuretic compared with 1 participant in the dig-on arm.

Compared with taking digoxin, withdrawal of digoxin resulted in a 50% rise in plasma B-type natriuretic peptide (BNP; dig-on  $405 \pm 587$  ng/L vs dig-off  $604 \pm 843$  ng/L;  $P = .019$  [95% confidence interval [CI] 39–361];

Figure 1). There was a clinically insignificant reduction in 6 minute walk distance (dig-on  $474 \pm 69$  m vs dig-off  $455 \pm 64$  m;  $P = .015$  [95% CI 4–34]) and no deterioration in QoL measures, including Cardiac Depression Scale (dig-on  $82 \pm 20$  on vs dig-off  $72 \pm 22$ ;  $P = .005$  [95% CI 4–17]), Minnesota Living With Heart Failure Questionnaire (dig-on  $29 \pm 19$  vs dig-off  $25 \pm 16$ ;  $P = .105$  [95% CI –1 to 9]) and Short-Form (36) Health Survey (dig-on  $98 \pm 15$  vs dig-off  $97 \pm 14$ ;  $P = .714$  [95% CI –5 to 7]). Minor changes were seen in body weight (dig-on  $87.3 \pm 13.2$  kg vs dig-off  $88.2 \pm 13.1$  kg;  $P = .064$  [95% CI 0.1–1.8]), heart rate (dig-on  $66 \pm 8$  beats/min vs dig-off  $69 \pm 9$  beats/min;  $P = .060$  [95% CI 0–6]), systolic blood pressure (dig-on  $115 \pm 15$  mm Hg vs dig-off  $115 \pm 17$  mm Hg;  $P = .896$  [95% CI –7 to 7]), serum creatinine (dig-on  $105 \pm 37$   $\mu$ mol/L vs dig-off  $108 \pm 40$   $\mu$ mol/L;  $P = .350$  [95% CI –8 to 3]) and estimated glomerular filtration rate (dig-on  $65 \pm 20$  mL min<sup>–1</sup> 1.73 m<sup>–2</sup> vs dig-off  $64 \pm 19$  mL min<sup>–1</sup> 1.73 m<sup>–2</sup>;  $P = .716$  [95% CI –3 to 5]). No significant differences for any echocardiographic parameters could be discerned (Table 1), although there was a noteworthy nonsignificant trend toward increased left ventricular (LV) end-diastolic and end-systolic volumes by Simpson's method. There was no evidence of a treatment order effect ( $P = .6$ ).

This is the first prospective randomized clinical trial of the effects of digoxin withdrawal in the context of currently recommended plasma digoxin levels in stable HF patients in SR, performed with mandatory background ACE



**Fig. 1.** Plasma B-type natriuretic peptide (BNP) levels: individual data as well as group means and SDs ( $P = .019$ ). DIG, digoxin.

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**Table 1.** Cardiac Dimensions and Function According to Echocardiography

Variable	Dig-on	Dig-off	P Value
Left atrial area (cm <sup>2</sup> )	31 ± 11	32 ± 12	.154
EF, biplane (%)	36 ± 8	36 ± 8	.740
LVEDV (mL)	175 ± 42	195 ± 42	.092
LVESV (mL)	111 ± 37	126 ± 35	.093
FS (%)	17.4 ± 4.1	17.5 ± 5.3	.932
IVSd (mm)	9.5 ± 2.0	8.9 ± 1.4	.061
RWT	0.27 ± 0.1	0.26 ± 0.0	.239
Heart rate (beats/min)	64 ± 9	68 ± 10	.642
MV E vel (m/s)	0.66 ± 0.23	0.65 ± 0.20	.712
MV A vel (m/s)	0.54 ± 0.25	0.52 ± 0.22	.969
MV dec T (ms)	141 ± 35	133 ± 49	.602
MV E/A ratio	1.8 ± 1.0	1.4 ± 0.76	.340
E/e'	16.4 ± 7.9	14.6 ± 7.1	.176
Tei index	0.5 ± 0.2	0.5 ± 0.2	.941
MV S' (cm/s)	4.8 ± 1.1	4.5 ± 1.4	.916
TR max PG	29.8 ± 11.3	31.0 ± 15.6	.755
TAPSE (mm)	19 ± 4	12 ± 7	.209

Dig, digoxin; EF, ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; FS, fractional shortening; IVSd, end-diastolic interventricular septum thickness; RWT, relative wall thickness; HR, heart rate; MV E vel, peak transmitral E-wave velocity; MV A vel, peak transmitral A-wave velocity; TR max PG, tricuspid regurgitation maximum pressure gradient; TAPSE, tricuspid annular plane systolic excursion; e', early diastolic septal myocardial velocity; S', peak systolic septal myocardial velocity.

Values are presented as mean ± SD.

inhibitors/ARBs and beta-blockers, as well as high utilization of MRAs and ICD/CRT. The results echo the RADIANCE trial<sup>2</sup> and suggest that digoxin may provide benefits (at least in those stabilized on it) and that although some participants can be safely withdrawn from digoxin, deterioration in HF status as well as measures of adverse LV remodeling and LV filling pressures may occur despite modern HF therapy.

Although digoxin has weak positive inotropic action<sup>3</sup> and beneficial autonomic effects,<sup>4,5</sup> the pharmacologic and clinical effects of digoxin in SR are thought to be overwhelmed by modern therapies, rendering it redundant in the contemporary era.<sup>6</sup> Recent studies have demonstrated that digoxin was associated with worse outcomes in various settings,<sup>7–9</sup> although other studies suggest that digoxin may have add-on benefits in HF in synergy with other proven drugs.<sup>10,11</sup> Of note, use of digoxin in these studies was not randomized, and therefore digoxin's role remains unclear.

Withdrawal trials have important limitations, including that selection of other HF treatments is made concomitantly with digoxin use, and therefore withdrawal trials may overstate its efficacy by selecting stable patients benefitting from its use and therefore more likely to deteriorate on its removal. The strength of this study is the crossover design, in which each patient acted as his or her own control, reducing variation and potential for type II error. An obvious limitation is the single-blind design, but evaluation of the primary end point of plasma BNP and all other end points were performed blinded to the investigators. A larger double-blind study is needed to further evaluate the safety and impact of digoxin withdrawal in the modern era.

## Disclosures

None.

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## Appendix 2.4

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**Hopper I**, Skiba M, Windebank E, Brack J, Tonkin A, Krum H. Polypharmacy in heart failure – is reducing medication safe? International Journal of Cardiology. 2015. In press.



Letter to the editor

**Title: Polypharmacy in heart failure – is reducing medication safe?**

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Sir,

Polypharmacy is increasing in heart failure (HF) patients, due in part to the widespread adoption of medications recommended in guidelines for HF [1], and the multiple comorbidities that accompany aging [2]. However there is scant evidence to guide physicians when considering reduction of medications for HF. A recent review of studies in which medications were withdrawn in HF demonstrated that cessation of ACE inhibitors and beta-blockers, and to a lesser extent diuretics, was associated with worsening of HF clinical status [3]. Other classes of medications which have been shown to lack benefit in HF could be withdrawn.

Two such classes include aspirin and HMG CoA reductase inhibitors (statins). Aspirin has been shown to reduce neither mortality nor cardiovascular events in HF [4], and has been associated with increases in plasma brain natriuretic peptide (BNP) in HF patients [5], presumably by inhibiting the synthesis of prostaglandins, and increased HF hospitalisations have been observed in some studies [6]. Statins have been shown to have a neutral effect on mortality in HF, in both ischaemic [7] and mixed cohorts [8]. Therefore we performed pilot studies investigating the safety of withdrawing aspirin and statins in stable HF patients while maintaining optimal doses of proven HF medications. We hypothesised that withdrawal of these medications would not affect HF clinical status.

These studies were prospective, randomised, placebo-controlled, single-blind cross-over trials, in which participants were randomised to either aspirin (asp-on) or placebo (asp-off), or statin (statin-on) or placebo (statin-off) with cross-over after three months. Stable optimised doses of ACE inhibitor / angiotensin receptor blocker and beta-blockers were required. Standard HF clinical status and quality of life (QoL) endpoints were evaluated, including the Cardiac Depression Scale (CDS), Minnesota Living with Heart Failure Questionnaire (MLHFQ) and Short Form (36) Health Survey (SF-36). Groups were compared using two-tailed paired t-test. Institutional ethics approval was obtained, each patient provided informed consent, and the studies conformed to the ethical guidelines of the Declaration of Helsinki. Registration numbers NCT01534026 and NCT01554592.

Aspirin was withdrawn from participants with documented non-ischaemic cardiomyopathy in sinus rhythm at randomisation, with left ventricular ejection fraction (LVEF)  $\leq 45\%$ . Participants were excluded if they were at high risk or had a previous history of thromboembolism. The 12 study participants had mean age  $58 \pm 10$  years, 75% were male, duration of HF was  $5.9 \pm 4.8$  years, and mean LVEF  $37.3 \pm 9.5\%$ . Two participants withdrew, one due to transient ischaemic attack (TIA) with visual symptoms on placebo (not included in the analysis) and one due to onset of atrial fibrillation (results included). Compared with taking 100mg aspirin, withdrawal of aspirin resulted in no change in plasma BNP (asp-on:  $110 \pm 82$  vs asp-off:  $97 \pm 102$  ng/L,  $p=0.526$ , 95% CI -66-36) (Figure 1) or 6 minute walk distance (asp-on:  $562 \pm 94$  vs asp-off:  $563 \pm 104$  m,  $p=0.532$ , -25-14). QoL measures were unchanged, including MLHFQ (asp-on:  $28 \pm 21$  vs asp-off:  $26 \pm 21$ ,  $p=0.284$ , -2-7), CDS (asp-on:  $71 \pm 20$  vs asp-off:  $70 \pm 19$ ,  $p=0.373$ , -3-7) and SF-36 (asp-on:  $99 \pm 11$  vs asp-off:  $102 \pm 11$ ,  $p=0.396$ , -3-6). There were no changes in serum creatinine (asp-on:  $98 \pm 31$  vs asp-off:  $114 \pm 74$   $\mu$ mol/L,  $p=0.255$ , -14-46), eGFR (asp-on:  $68 \pm 19$  vs asp-off:  $65 \pm 24$  ml/min/1.73m<sup>2</sup>,  $p=0.323$ , -9-3), heart rate (asp-on:  $69 \pm 9$  vs asp-off:  $73 \pm 13$  bpm,  $p=0.458$ , -6-12), systolic blood pressure (asp-on:  $122 \pm 17$  vs asp-off:  $115 \pm 23$  mmHg,  $p=0.512$ , -25-13) or weight (asp-on:  $90 \pm 24$  vs asp-off:  $91 \pm 24$  kg,  $p=0.602$ , -2-3). Results were unchanged in a sensitivity analysis in which the participant with TIA was assigned the worst score. This patient was withdrawn from the study and commenced on clopidogrel, and a further TIA occurred eight months later.

Statin was withdrawn from participants with idiopathic (12) or ischaemic (1) HF with LVEF  $\leq 40\%$ . Exclusion criteria included treatment with statins primarily for hypercholesterolaemia or unstable ischaemic heart disease. The trial statin was that prescribed by their treating physician. The 13 study participants had a mean age of  $64 \pm 11$  years, 62% were male, duration of HF was  $7.7 \pm 5.7$  years, and mean ejection fraction was  $38.1 \pm 10.4\%$ . Compared with taking statin, withdrawal of statin resulted in significant rises in LDL cholesterol (stat-on:  $2.4 \pm 0.7$  vs stat-off:  $4.4 \pm 1.4$  mmol/L,  $p < 0.0001$ , 1.3 to 2.7) and non-significant changes in HDL cholesterol (stat-on:  $1.2 \pm 0.5$  vs stat-off:  $1.2 \pm 0.4$  mmol/L,  $p=0.265$ , -0.2 to 0.1) and triglycerides (stat-on:  $1.3 \pm 0.6$  to stat-off:  $1.7 \pm 0.7$  mmol/L,  $p=0.079$ , 0.0 to 0.7). There were no significant changes in BNP (stat-on:  $130 \pm 175$  vs stat-off:  $129 \pm 180$  ng/L,  $p=0.924$ , -23 to 21) (Figure 2), 6 minute walk distance (stat-on:

455±172 vs stat-off: 450±182m,  $p=0.802$ , -19 to 23) or QoL measures, including MLHFQ (stat-on: 32±26 vs stat-off: 31±30,  $p=0.406$ , -17 to 8), CDS (stat-on: 77±20 vs stat-off: 81±22,  $p=0.445$ , -4 to 8) and SF-36 (stat-on: 93±18 vs stat-off: 94±19,  $p=0.248$ , -2 to 7). Serum Uric acid (stat-on: 0.41±0.1 vs stat-off: 0.40±0.1mmol/L,  $p=0.789$ , -0.03 to 0.03), serum glucose (stat-on: 5.0±0.6 vs stat-off: 4.9±0.5mmol/L,  $p=0.465$ , -0.5 to 0.2) or HbA1c (stat-on: 5.6±0.3 vs stat-off: 5.6±0.4%,  $p=0.488$ , -0.1 to 0.2) were also unchanged.

These pilot studies demonstrate that withdrawal of aspirin or statins did not result in change to the HF clinical status, as expected. Whether statins and aspirin have a role in the management of HF continues to be debated. HF guidelines do not recommend their use [9], yet physicians are reluctant to discontinue them, as reflected in a recent large scale clinical trial in systolic HF involving 3846 patients in which 50% were on aspirin and 39% were on statins [10]. Physician reluctance to cease medications may relate to concern about the risk of an outcome which could possibly be related to cessation, such as the TIA seen in a patient in this study, which recurred when the same patient was later taking clopidogrel, suggesting that it was unrelated to medication use. Physicians may also be reluctant to cease medications commenced by someone else, or have inadequate time to thoroughly review the medication list during consultations. Reducing medications may not be considered a priority compared with reaching target doses of medications with mortality benefits. However as polypharmacy continue to rise in the HF population, there is increased potential for drug interactions, and the incidence of hospital admissions caused by adverse drug events will likely rise. Proper randomised, adequately powered trials of withdrawal of medications for which mortality benefit has not been demonstrated are needed to inform consideration of the risks and benefits of reducing polypharmacy.

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*Conflict of interest* – The authors report no relationships that could be construed as a conflict of interest.

Figure 1

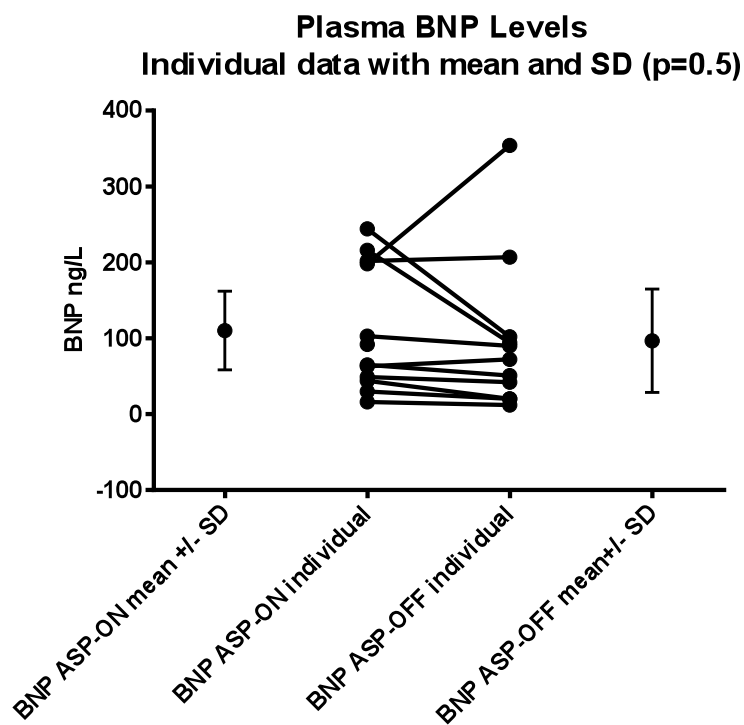
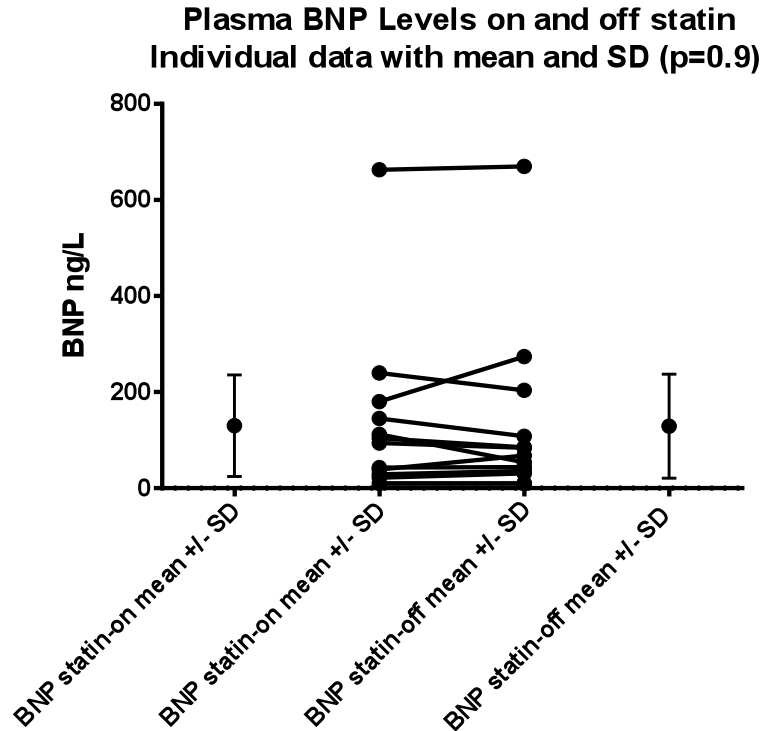


Figure 2



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## Appendix 3

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The following pages contain other manuscripts completed during the period of candidature. They include:

### *Systematic reviews and meta-analysis*

**Hopper I**, Skiba M, Krum H. Updated meta-analysis on anti-thrombotic therapy in patients with heart failure and sinus rhythm. *European Journal of Heart Failure*. 2013; 15: 69-78.

**Hopper I**, Billah B, Skiba M, Krum H. Prevention of Diabetes and Reduction in Major Cardiovascular Events in Studies of Subjects with Impaired Glucose Tolerance: Meta-Analysis of Randomized Controlled Clinical Trials. *European Journal of Cardiovascular Prevention and Rehabilitation* 2011; 18: 813-23.

Clark H, Krum H, **Hopper I**. Worsening renal function during RAAS inhibitor initiation and long term outcomes in patients with left ventricular systolic dysfunction. *European Journal of Heart Failure*. 2014; 16: 41-48

Peck KY, Lim YZ, **Hopper I**, Krum H. Medical therapy versus implantable cardioverter-defibrillator in preventing sudden cardiac death in patients with left ventricular systolic dysfunction and heart failure: A meta-analysis of > 35,000 patients. *International Journal of Cardiology*. 2014; 173: 197-203.

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### *Original research papers*

**Hopper I**, Kemp W, Porapakkham P, Sata Y, Condon E, Skiba M, Farber L, Porapakkham P, Williams TJ, Menahem S, Roberts S, Krum H. Impact of Heart Failure and Changes to Volume

Status on Liver Stiffness: Non-Invasive Assessment using Transient Elastography. European Journal of Heart Failure 2012; 14: 621-7.

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### ***Research letter***

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### ***Editorial***

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### ***Invited review***

**Hopper I**, Kotecha D, Chin KL, Mentz RJ, von Lueder TG. Comorbidities in heart failure: are there gender differences? Current Heart Failure Reports. Submitted manuscript.

### ***Letters to the editor***

Krum H, **Hopper I**. Statins in congestive heart failure. Letter to the editor. Heart, Lung and Circulation. 2014; 23: 988.

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***Case report***

Power A, Graudins LV, McLean C, **Hopper I**. Probable fenofibrate-induced acute generalized exanthematous pustulosis. American Journal of Health Systems Pharmacy. 2015. In press.

## Appendix 3.1

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### *Systematic review and meta-analysis*

**Hopper I, Skiba M, Krum H.** Updated meta-analysis on anti-thrombotic therapy in patients with heart failure and sinus rhythm. *European Journal of Heart Failure*. 2013; 15:69-78.



# Updated meta-analysis on antithrombotic therapy in patients with heart failure and sinus rhythm

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<b>Aim</b>	Heart failure (HF) is a prothrombotic state, but current evidence does not support the routine use of aspirin, antiplatelet agents, or anticoagulation in these patients in sinus rhythm (SR). We conducted an updated meta-analysis comparing these medications on outcomes in HF.
<b>Methods and results</b>	All randomized trials in patients with chronic HF and reduced ejection fraction (HFrEF) in sinus rhythm (SR; $n > 100$ ), in which the effect of aspirin, antiplatelet agents, or anticoagulants was determined, were prospectively evaluated. Four trials met the entry criteria. Intervention time was 28 months. No difference in all-cause mortality was seen when aspirin was compared with warfarin [ $n = 3701$ , relative risk (RR) 1.00, 95% confidence interval (CI) 0.88–1.13, $P = 0.94$ ]. Compared with aspirin, significantly fewer strokes were seen with warfarin ( $n = 3701$ , RR 0.59, 95% CI 0.41–0.85, $P = 0.004$ ), and fewer fatal and non-fatal ischaemic strokes ( $n = 3368$ , RR 0.48, 95% CI 0.32–0.73, $P = 0.0006$ ). Warfarin doubled the risk of major haemorrhage compared with aspirin ( $n = 3701$ , RR 2.02, 95% CI 1.45–2.80, $P < 0.0001$ ); however, intracranial haemorrhage was rare. There was no significant difference in HF hospitalizations with aspirin vs. warfarin ( $n = 3701$ , RR 1.16, 95% CI 0.79–1.71, $P = 0.45$ ).
<b>Conclusion</b>	With warfarin compared with aspirin in HFrEF in SR, significant reductions in stroke risk were observed but no mortality benefit was seen. Major haemorrhage doubled but intracranial haemorrhage was rare. These findings suggest that overall the benefit of warfarin in HFrEF in SR outweighs the risk. Aspirin use did not increase HF hospitalization as has been previously suggested.
<b>Keywords</b>	Heart failure • Anticoagulation • Mortality • Stroke • Myocardial infarction • Heart failure hospitalization

## Introduction

Heart failure (HF) is a prothrombotic state, with increased risk of deep venous thrombosis, pulmonary embolism, stroke, and myocardial infarction (MI). The pathophysiology of HF contributes to the hypercoagulable state.<sup>1</sup> Benefit has been shown with the use of warfarin compared with aspirin in atrial fibrillation, with a significant reduction in stroke risk in the primary prevention setting,<sup>2</sup> and use of warfarin is supported by Class 1 evidence and recommended by guideline authorities.<sup>3</sup> In contrast, it is not entirely clear whether there is net benefit of

anticoagulation in patients with HF in sinus rhythm (SR).<sup>4</sup> With the release of the WARCEF trial,<sup>5</sup> the largest trial of antithrombotic strategies to date, we have re-examined the totality of clinical trial evidence to see if more definitive outcomes can be elucidated.

Accordingly, we conducted a meta-analysis of all relevant trials to determine the effect of antiplatelet agents (specifically aspirin) compared with anticoagulants (specifically warfarin) and antithrombotics (clopidogrel) on deaths and major thrombotic events in patients with heart failure with reduced ejection fraction (HFrEF) in SR.

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## Methods

### Search strategy and selection criteria

We searched for prospective randomized controlled trials in Medline (source PubMed, 1966 to May 2012) and EMBASE (1974 to May 2012). Searches included the keywords and corresponding MeSH terms for anticoagulants and antithrombotics including aspirin, warfarin, and clopidogrel, heart failure, sinus rhythm, and randomized controlled trial. The bibliographies of all retrieved articles were also manually checked. Prospective randomized controlled trials conducted in adults that were published in English were considered. We looked at all trials in which > 100 people were included. Any follow-up time was considered acceptable.

### Data extraction and quality assessment

Independent assessment of the trials was performed by two authors (I.H. and M.S.). Data were extracted on all stroke, fatal and non-fatal ischaemic stroke, non-fatal MI, all-cause mortality, major haemorrhage, intracranial haemorrhage, and HF hospitalizations. All data were reported in intention-to-treat analysis. Bias was assessed by looking at randomization, blinding, and losses to follow-up. Unpublished data were not sought.

### Statistical analysis

Statistical analysis was performed using Review Manager (RevMan) Version 5.1. The results were pooled using Mantel-Haenszel fixed or random effects models, depending on the heterogeneity of the data extracted from individual studies. Heterogeneity between studies was analysed by  $\chi^2$  test and the significance of relative risks

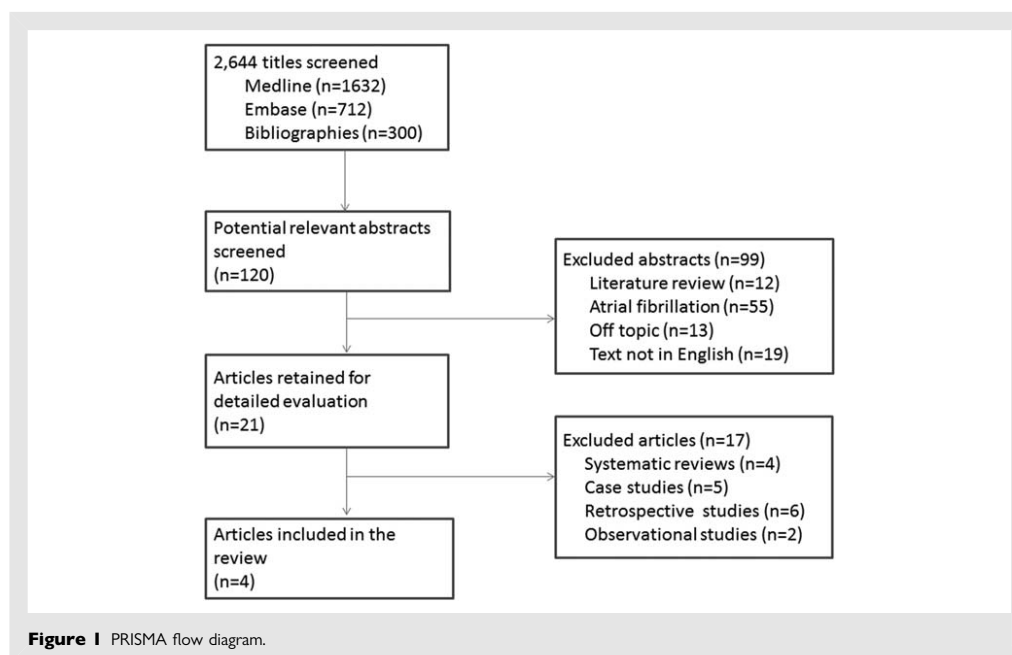
(RRs) was performed using the Z-test. RRs with 95% confidence intervals (CIs) were derived from each individual study and determined for overall outcome. A weighting was calculated based on the number of events that occurred in each study. Potential publication bias was assessed by funnel plot symmetry.

## Meta-analysis

### Characteristics of included studies

A total of 2644 titles were screened, with 120 abstracts reviewed further. Of these, 99 were excluded as most were studies of patients with atrial fibrillation or reviewed the relevant literature. Twenty-one articles were evaluated further, 17 of which were excluded because they were not prospective trials. Four studies met the inclusion criteria—WASH<sup>6</sup>, HELAS<sup>7</sup>, WATCH<sup>8</sup>, and WARCEF<sup>5</sup> trials (Figure 1).

Table 1 summarizes the characteristics of the included trials. The number of subjects included in the meta-analysis was 4368 (range 197–2305). No trial reached its target recruitment. The trial populations were similar, with average age being 61.8 years (range 59–63), and 85% were male. The WARCEF trial had a smaller proportion of ischaemic cardiomyopathy than the other three trials. Background HF medications were predominantly angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) and digoxin in WASH and HELAS, with ACE inhibitors/ARBs, beta-blockers, and spironolactone in WATCH and WARCEF. The intervention time overall was 28 months, ranging from 19 to 42 months. Inclusion criteria included an ejection fraction (EF) of  $\leq 35\%$  in all trials, and SR at randomization. Atrial fibrillation developed in a small number of participants, and resulted in exclusion from the results in only the HELAS trial. All data were presented in the intention-to-treat format, and



**Table 1** Characteristics of included studies

Trial	Study design	No. of participants	Target sample size	Follow-up (mean)	Primary outcome	Background HF therapies	Therapies evaluated	Achieved INR	Time in Rx range	Study drug discontinued	Ischaemic HF (%)	LVEF (%)	AF (%)	Age (years)	Male (%)	Outcomes
WASH (2004)	Prospective randomized, open-label, blinded endpoints	279	NS	27 ± 1 months	Composite of: death; non-fatal MI; non-fatal stroke	ACEi/ARB 91% BB 11% Digoxin 36% Aldo blocker NS	No antithrombotic			21%	60	≤35	6.5	63	74	No difference in primary outcome
							Aspirin 300 mg			12%						HF hospitalization higher with aspirin
							Warfarin INR 2.5	2.3	NS	25% (at 12 months)						
HELAS (2006)	Double-blind randomized controlled trial	197	6000	19.5 months	Composite of: non-fatal stroke; peripheral/pulmonary emboli; MI; rehospitalization; exacerbation of HF; death from any cause	ACEi/ARB 61% BB 12% Digoxin 44% Aldo blocker NS	No therapy (DCM only)				58	28 ± 6	0 <sup>a</sup>	59	85	No difference in primary outcome
							Aspirin 325 mg (IHD only)			NS						Overall increase in EF, most in warfarin group
							Warfarin INR 2–3 (IHD and DCM)	NS	NS	NS						
WATCH (2009)	Prospective randomized trial, partially blinded	1587	4500	1.9 years	Composite of: all-cause mortality; non-fatal MI; non-fatal stroke	ACEi/ARB 97% BB 70% Digoxin 51% Aldo blocker 28%	Aspirin 162 mg			19%	73	25 ± 6	10	63	85	No difference in primary outcome
							Warfarin INR 2.5–3	2.6 ± 0.9	70%	20%						HF hospitalization higher in aspirin
							Clopidogrel 75 mg			19%						Fewer strokes with warfarin

*Continued*

Table Continued

Trial	Study design	No. of participants	Target sample size	Follow-up (mean)	Primary outcome	Background HF therapies	Therapies evaluated	Achieved INR	Time in Rx range	Study drug discontinued	Ischaemic HF (%)	LVEF (%)	AF (%)	Age (years)	Male (%)	Outcomes
WARCEF (2012)	Double-blind randomized controlled trial	2305	2860	3.5 ± 1.8 years	Time to first event in composite of: ischaemic stroke; intracerebral haemorrhage; death from any cause	ACEi/ARB 98% BB 90% Digoxin NS Aldo blocker 60%	Aspirin 325 mg			32%	43	25 ± 7.5	3.7	61	80	More haemorrhages with warfarin No difference in primary outcome Fewer ischaemic strokes with warfarin No difference in HF hospitalization More major haemorrhage with warfarin
							Warfarin INR 2.75	2.5 ± 1.0	63%	34% (of total follow-up time)						

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; Aldo, aldosterone; BB, beta-blockers; DCM, dilated cardiomyopathy; HF, heart failure; IHD, ischaemic heart disease; INR, international normalized ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NS, not stated; Rx, therapeutic.

<sup>a</sup>Three participants developed AF and were subsequently excluded.



the number of participants with the relevant outcome used, rather than the number of events recorded.

Randomization was adequate in all studies. However, blinding was more variable. The WASH trial compared open-label aspirin, warfarin, and no antithrombotic therapy, with blinded endpoints. WATCH compared open-label warfarin with clopidogrel and aspirin in a double-blind manner. The HELAS trial stratified treatment groups according to aetiology, trialling no antithrombotic therapy only with dilated cardiomyopathy, aspirin in ischaemic cardiomyopathy (as the risk of no antithrombotic therapy in ischaemic HF was thought to be too high), and warfarin in both aetiologies. WARCEF compared aspirin and warfarin in a double-blind, double-dummy design. Study drug continuation was similar across all groups, with the exception of aspirin in the WASH trial, which had a lower drop-out rate than other groups in this trial.

Composite primary endpoints were assessed in all studies, which included death, MI, and stroke for the WASH and WATCH trial; the HELAS trial added other cardiovascular endpoints to the primary composite outcome. WARCEF had a primary outcome of death and ischaemic or haemorrhagic stroke, and used time to first event analysis. Only one trial evaluated clopidogrel (WATCH), so this arm of the trial was not included in the meta-analysis.

Aspirin was dosed at 162–325 mg daily. The international normalized ratio (INR) achieved with warfarin was slightly less than the target INR in all trials, at  $\sim 2.5$ . Time in therapeutic range was recorded for WATCH and WARCEF, and was approximately two-thirds. Study drug discontinuation occurred overall in  $\sim 20\%$  of participants, with the WARCEF trial giving the data in time off study drug, which was  $\sim 33\%$ .

## Results

### All-cause mortality outcomes

There was no difference in all-cause mortality when aspirin was compared with warfarin ( $n = 3701$ , RR 1.00, 95% CI 0.88–1.13,  $P = 0.94$ ; Figure 2), with all four trials contributing to this outcome. When compared with no antithrombotic therapy, there was a non-significant increase in mortality with the use of aspirin ( $n = 295$ , RR 1.33, 95% CI 0.84–2.11,  $P = 0.22$ ) and also with warfarin ( $n = 324$ , RR 1.21, 95% CI 0.76–1.93,  $P = 0.41$ ) (data not shown). Only two trials contributed data to this outcome, the HELAS and WASH trials. There was no evidence of significant publication bias when investigated via funnel plot (Figure 3).

### Stroke

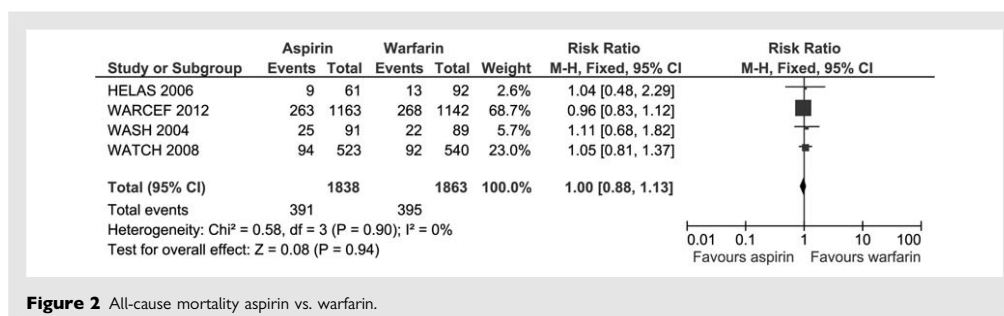
A significant reduction in all stroke (fatal and non-fatal ischaemic and haemorrhagic stroke) was seen with warfarin compared with aspirin ( $n = 3701$ , RR = 0.59, 95% CI 0.41–0.85,  $P = 0.004$ ; Figure 4). All four trials contributed to this outcome. A significant reduction in fatal and non-fatal ischaemic stroke was seen with the use of warfarin compared with aspirin ( $n = 3368$ , RR 0.48, 95% CI 0.32–0.73,  $P = 0.0006$ ; Figure 5). Only the WATCH and WARCEF trials provided data in which ischaemic stroke was clearly defined. The number needed to treat with warfarin to prevent one all stroke is 58, and to prevent one ischaemic stroke is 49.

### Non-fatal myocardial infarction

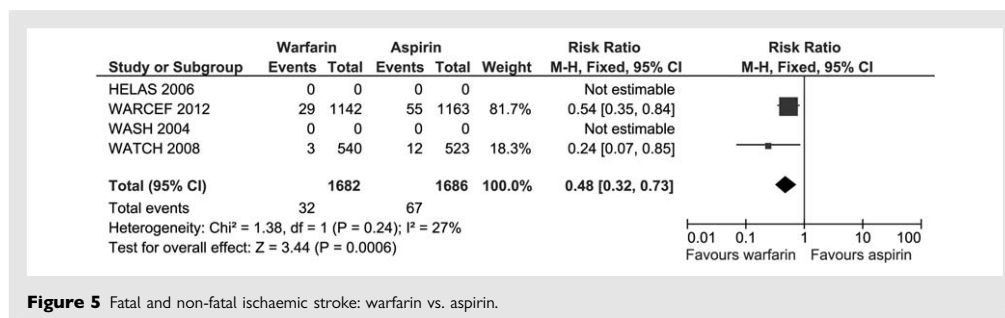
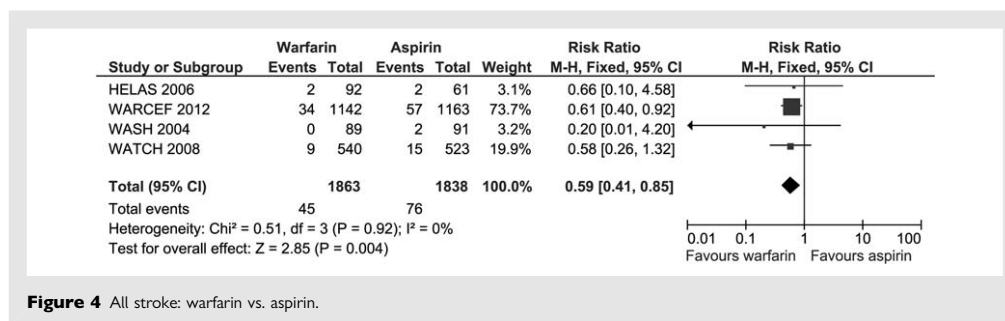
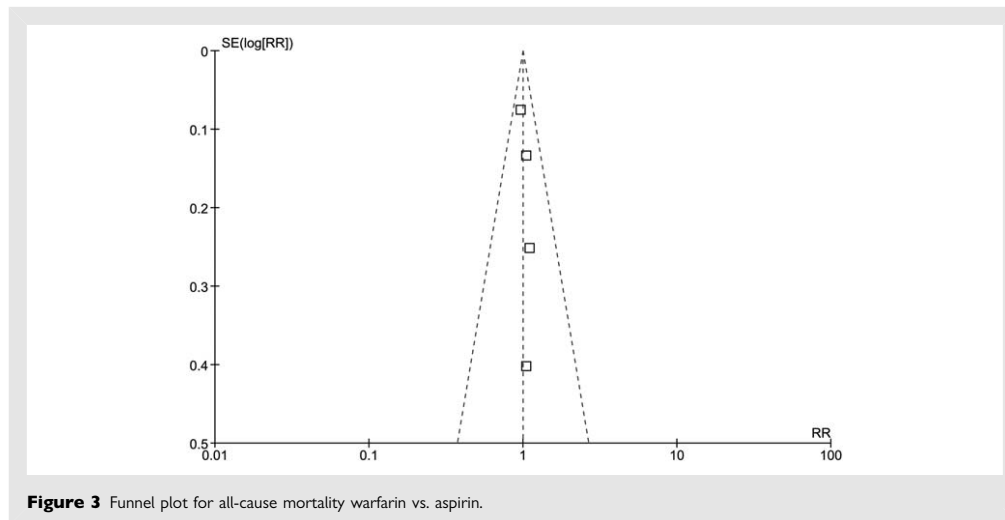
Overall, there was no significant difference in non-fatal MI with aspirin vs. warfarin ( $n = 3701$ , RR 0.87, 95% CI 0.63–1.21,  $P = 0.40$ ; Figure 6). All four trials contributed to this outcome. The WASH trial did not distinguish between fatal and non-fatal MI, but all data were included. The data from WARCEF were obtained from the secondary outcome of time to first event analysis, and it was assumed that MI was non-fatal, as deaths are listed separately. As this was time to first event, it is possible that further non-fatal MIs occurred but were not included in the results. The HELAS trial had 'myocardial reinfarction' as part of its primary endpoint, and this was presumed to be non-fatal.

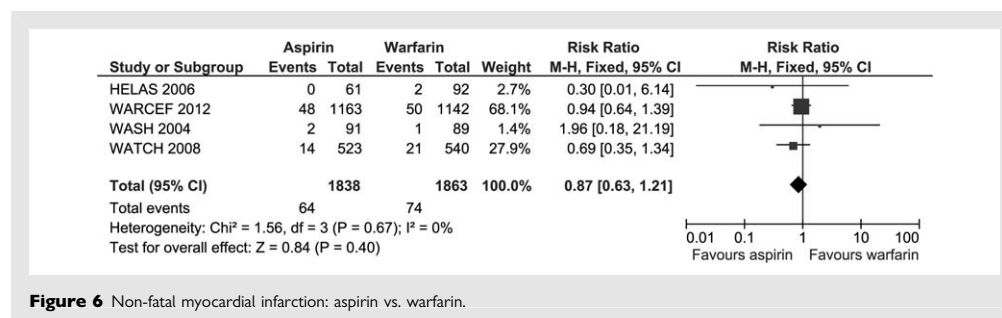
### Heart failure hospitalization

Compared with the use of aspirin, there was a non-significant increase in hospitalization with warfarin ( $n = 3701$ , RR 1.16, 95% CI 0.79–1.71,  $P = 0.45$ ; Figure 7). All four trials contributed to this outcome. A random effects model was used for this data, as heterogeneity was present. Two trials (WASH and WATCH) found an increase in HF hospitalizations with aspirin use, compared with warfarin, clopidogrel, or no antithrombotic therapy, while the largest and most recent trial (WARCEF) found the opposite result, a decrease in HF hospitalizations with aspirin compared with warfarin. Compared with no antithrombotic therapy, there was no significant increase in the rate of HF hospitalization with aspirin ( $n = 295$ , RR 1.20, 95% CI 0.40–3.60,  $P = 0.75$ ) or warfarin ( $n = 324$ , RR 0.96, 95% CI 0.57–1.62,  $P = 0.87$ ; data not shown).

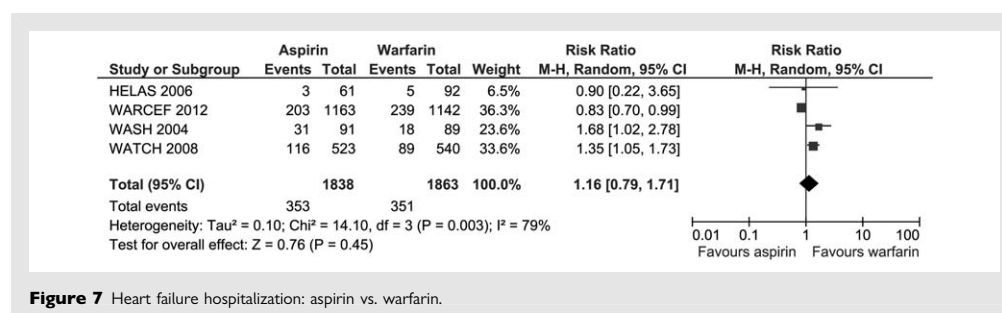


**Figure 2** All-cause mortality aspirin vs. warfarin.





**Figure 6** Non-fatal myocardial infarction: aspirin vs. warfarin.



**Figure 7** Heart failure hospitalization: aspirin vs. warfarin.

with only data from the WASH and HELAS trials contributing to this outcome.

### Major haemorrhage

There was a significant increase in major haemorrhage seen in the warfarin group compared with all other therapies. Compared with aspirin, warfarin use was associated with a doubling in the risk of major haemorrhage ( $n = 3701$ , RR 2.02, 95% 1.45–2.80,  $P < 0.0001$ ; Figure 8). The definition of major haemorrhage varied between trials. The WASH trial used the definition of any haemorrhage requiring blood transfusion, while the WATCH and WARCEF trials also included bleeds which led to death or disability. Of the 167 patients with major haemorrhage recorded across the four trials (including 11 in the clopidogrel arm of the WATCH trial), the majority were gastrointestinal. Thirty-five patients need to be treated with warfarin to result in one major haemorrhage.

### Intracranial and central nervous system haemorrhage

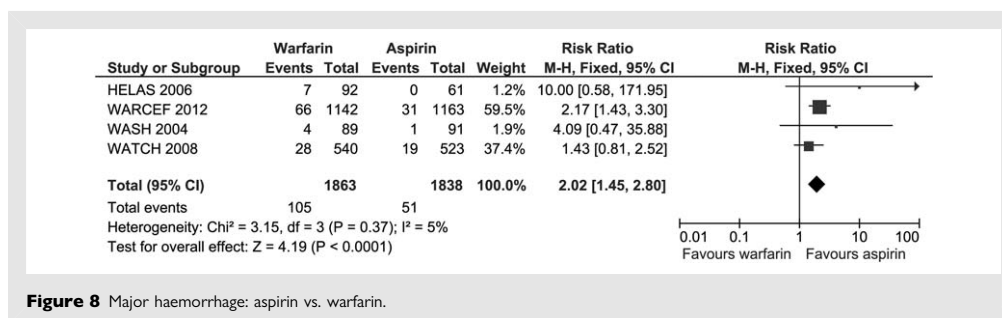
Seventeen bleeds defined as either intracranial or to the central nervous system were recorded across the four trials. The number of bleeds in the warfarin group was double that of the aspirin group (11 vs. 5); however, overall, the event rate was low, 0.62% for the warfarin group and 0.28% for the aspirin group. The

number needed to treat with warfarin to harm one patient with an intracranial or central nervous system haemorrhage is 294.

## Discussion

This meta-analysis has demonstrated that in patients with HFREF and SR, there is a statistically significant 41% relative risk reduction (RRR) in all stroke with the use of warfarin compared with aspirin, and a 52% RRR in ischaemic stroke. There was also a non-significant reduction in MI with warfarin compared with aspirin. Despite this, an overall neutral effect on mortality was seen, with no benefit with the use of one particular antithrombotic strategy over another, including no antithrombotic therapy at all. In contrast, a doubling in major haemorrhage was associated with warfarin compared with aspirin, which was predominantly gastrointestinal with a low rate of intracranial or central nervous system bleeds. The use of aspirin was not associated with a significant increase in HF hospitalizations compared with warfarin.

A 41% RRR in all stroke with warfarin compared with aspirin is similar to that seen with primary prevention in non-valvular atrial fibrillation with warfarin compared with aspirin [odds ratio (OR) 0.68, 95% CI 0.54–0.85].<sup>2</sup> Similar to this meta-analysis, no mortality benefit was seen in atrial fibrillation with the use of warfarin compared with aspirin without prior stroke or transient ischaemic



**Figure 8** Major haemorrhage: aspirin vs. warfarin.

attack (OR 0.99, 95% CI 0.83–1.18).<sup>2</sup> The background risk of stroke in the general population is ~0.5%. The risk of stroke in patients with atrial fibrillation and with no therapy ranges from 1% per year in low-risk groups to 6% per year in high-risk groups.<sup>9</sup> The risk of stroke in HFREF in SR has been difficult to ascertain, but has been estimated at 1% per annum in mild to moderate HF, and up to 4% in severe HF,<sup>10</sup> although the latter studies include patients in atrial fibrillation, which occurs more frequently in advanced HF.

Identifying risk factors for stroke in the setting of HFREF has proven difficult. Reduced EF is a known risk factor for stroke. The SAVE study demonstrated an 18% increase in risk of stroke with every 5% reduction in EF, and the risk of stroke doubled when the EF dropped below 28%.<sup>11</sup> An analysis of the SCD-HeFT trial in moderately symptomatic HFREF found an increase in thrombo-embolic events with reductions in EF, with the annual rate if the EF was <20% of 1.2%, compared with 0.9% at higher EFs.<sup>12</sup> The time after diagnosis of incident HF is important. Two cohort studies demonstrated a markedly increased risk of stroke in the first month after incident HF, and elevated risk extending 6 months after diagnosis, with rates attenuating thereafter.<sup>13,14</sup> Additionally, prior thrombo-embolic events and possibly the presence of a pedunculated thrombus can also predict further events, but other risk factors have been difficult to elucidate clearly.<sup>4</sup> Development of tools that can better predict the likelihood of stroke in HFREF in SR would aid in this decision-making process.

Another important finding of this meta-analysis is the complication rate from warfarin therapy, with a doubling of major haemorrhage, predominantly gastrointestinal. The overall rate of intracranial haemorrhage and central nervous system bleeds was extremely low, with 294 patients needing to be treated with warfarin to see one intracranial bleed, compared with 58 patients treated with warfarin to prevent one stroke, thus appearing to favour anticoagulation in this setting. It has been noted that patients value stroke reduction more than they fear gastrointestinal bleeds;<sup>15</sup> however, the absolute benefit of anticoagulant therapy in HF rests on both stroke and bleeding risk, and it is difficult to compare them directly.

Studies in atrial fibrillation can offer some guidance when assessing bleeding risk with warfarin use. The CHADS<sub>2</sub> and HAS-BLED

scores have been developed to allow swift calculation of the risks of stroke and bleeding to guide decisions on starting or withholding anticoagulants,<sup>16</sup> although this schema has not been validated in HF. The highest risk of bleeding is in the first month after initiation of anticoagulant therapy, due to factors associated with incident atrial fibrillation,<sup>17</sup> and time in therapeutic range has been shown to be an important factor in determining both major haemorrhage and thrombo-embolism.<sup>18,19</sup> These factors are likely to be important in HF too.

The neutral effect on HF hospitalization was an important finding, in contrast to earlier reports of increased risk with aspirin. A biologically feasible mechanism for increased HF hospitalization with aspirin use exists, namely inhibition of vascular wall cyclo-oxygenase and thus prostacyclin synthesis as well as potentiation of endothelin-induced vasoconstriction leading to salt and water retention. The WASH and WATCH trials both found that aspirin was associated with increases in HF hospitalization; however, as post-hoc analyses these were considered hypothesis generating only. Further studies demonstrated an increase in natriuretic peptides with aspirin use against clopidogrel as a comparator.<sup>20,21</sup> The WARCEF trial found a directionally opposite result, that of an increase in HF hospitalizations with warfarin compared with aspirin, resulting in an overall neutral result when all studies were meta-analysed. The mechanism behind this finding is not clear. Participants were similar across all studies, so patient selection is unlikely to play a role. The HELAS trial noted an increase in EF across all groups, most notably the warfarin group, so a change in EF is unlikely to explain this finding. The overall findings of this meta-analysis can reassure clinicians that use of aspirin is unlikely to be harming their patient.

Further research is obviously needed. Studies to determine more precisely predictors of stroke in HFREF in SR would enhance appropriate patient selection. A trial of approaches to anticoagulation during the first 6 months following diagnosis of HF would target higher risk groups and potentially show greater benefit. Furthermore, investigation of the role of the new anticoagulants, e.g. dabigatran and rivaroxaban, in this setting is yet to be determined. Finally, in the lower risk groups, determining whether there may be a role for no antithrombotic therapy, given that the results of this meta-analysis show a trend towards worse outcomes with any therapy compared with no therapy, albeit with

low numbers. This finding was also demonstrated in a recent Cochrane review.<sup>22</sup>

Even with the benefit of meta-analysis, we cannot overcome the limitations of the individual studies. These studies universally had difficulty recruiting participants and are underpowered. The prevailing view in the HF community of the necessity for some form of anticoagulation, despite the lack of evidence in support of this, led to these recruitment difficulties. Recently published European Society of Cardiology (ESC) HF guidelines have been non-prescriptive with its guidance to practitioners on this issue,<sup>23</sup> although a recent consensus statement by the ESC has more clearly come out against using warfarin routinely for patients with HF in SR.<sup>24</sup> While this meta-analysis does not overcome the limitations of individual trials, it is the largest body of evidence existing in this setting.

An important limitation of this meta-analysis is that studies were from different eras of HF pharmacotherapy, with HELAS and WASH having much lower use of beta-blockers, and none of aldosterone blockers. This may have resulted in poorer outcomes than seen in the later trials; however, these were the smallest of the four trials, and the impact of this would be limited. There was a lack of consistency between the trials on the outcome of HF hospitalization, making overall interpretation difficult. Potential for bias exists, resulting from partial blinding, a potential weakening of effect from the substantial period of time in which patients were not taking their assigned medication and/or had subtherapeutic INR, and from survivor bias, in which patients who manage to remain on warfarin for longer periods having a lower risk profile.<sup>17</sup> However, these all probably reflect the real-world situation. Finally, the use of time to first event analysis in the WARCEF trial meant that the total number of each event was not made clear. However, these results are probably non-discriminatory in that any such bias would be present across all groups in the trial and is unlikely to affect the overall outcome.

## Conclusion

This meta-analysis suggests that anticoagulation with warfarin vs. aspirin can significantly lower the risk of stroke in HFREF in SR; however, determining who is at increased risk of stroke in this setting is difficult. No mortality benefit was demonstrated with the use of warfarin compared with aspirin, and an increase in major bleeds was seen, although intracranial and central nervous system bleeds were rare. Clinicians can be reassured that the use of aspirin is not associated with an increase in hospitalizations for HF.

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## Appendix 3.2

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### *Systematic review and meta-analysis*

**Hopper I**, Billah B, Skiba M, Krum H. Prevention of Diabetes and Reduction in Major Cardiovascular Events in Studies of Subjects with Impaired Glucose Tolerance: Meta-Analysis of Randomized Controlled Clinical Trials. *European Journal of Cardiovascular Prevention and Rehabilitation* 2011; 18: 813-23.

# Prevention of diabetes and reduction in major cardiovascular events in studies of subjects with prediabetes: meta-analysis of randomised controlled clinical trials

Ingrid Hopper<sup>1,2</sup>, Baki Billah<sup>2</sup>, Marina Skiba<sup>1,2</sup> and Henry Krum<sup>1,2</sup>

## Abstract

**Background:** Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are pre-diabetic states, treatment of which may prevent or delay the onset of overt diabetes and thus potentially reduce major cardiovascular (CV) events. We therefore sought to determine whether interventions (including diet, exercise and pharmacological therapy), altered all-cause and cardiovascular related mortality in such subjects.

**Methods:** We performed a meta-analysis of prospective, randomised controlled trials (RCTs) that were identified in the medical literature and databases. Trials were eligible for inclusion if they reported all-cause mortality rates (at a minimum), recruited approximately 100 patients and had a minimum follow-up of one year. Interventions were divided into pharmacological and non-pharmacological.

**Results:** Ten RCTs that enrolled 23,152 patients met the above entry criteria. Trials ran for an average of 3.75 years. Diabetes was delayed or prevented by these interventions vs control (risk ratio 0.83, 95%CI 0.80–0.86). Non-drug approaches ( $n = 3495$ ) were superior to drug-based approaches ( $n = 20,872$ ) in diabetes prevention (0.52, 0.46–0.58 vs 0.70, 0.58–0.85,  $P < 0.05$ ). There was no difference in risk of all-cause mortality in the intervention versus control group (0.96, 0.84–1.10) and no difference in CV death (1.04, 0.61–1.78). There was a non-significant trend towards reduction in fatal and non-fatal myocardial infarction (0.59, 0.23–1.50). Fatal and non-fatal stroke was borderline reduced (0.76, 0.58–0.99) with intervention versus control.

**Conclusions:** Despite interventions being mostly successful in retarding progression to overt diabetes, this did not result in reductions in all-cause or cardiovascular mortality, or myocardial infarction, with the possible exception of stroke.

## Keywords

Prediabetes, myocardial infarction, stroke, meta-analysis

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## Introduction

Prediabetes includes impaired glucose tolerance (IGT), defined as fasting plasma glucose less than 7.0 mmol/l (126 mg/dl) and 2-h plasma glucose on the 75 g oral glucose tolerance test between 7.8 and 11.0 mmol/l (140 mg/dl and 199 mg/dl),<sup>1,2</sup> and impaired fasting

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glucose (IFG), defined as plasma glucose concentration of between 6.1 and 6.9 mmol/l (110 to <126 mg/dl).<sup>1</sup> These are intermediate states of abnormal glucose regulation, between normal glucose homeostasis and diabetes mellitus.<sup>3</sup> Almost 7% of adults have either IGT or IFG and prevalence of these states is greater than that of type 2 diabetes.<sup>4</sup> IGT and IFG are risk factors for both diabetes and cardiovascular disease.<sup>5</sup> They are associated with increased mortality, predominantly due to cardiovascular causes, compared with age- and gender-matched populations who have normal glucose tolerance.<sup>6</sup>

Preventing diabetes therefore has the potential to reduce cardiovascular disease. Interventions in pre-diabetes with lifestyle or pharmacological interventions have been shown to reduce the rate of progression to diabetes.<sup>7</sup> However, tight blood glucose control in type 2 diabetes had no significant effect on CV complications although it reduced microvascular complications.<sup>8</sup>

By intervening earlier in the course of diabetes, when glucose homeostasis is abnormal but not yet diabetic, macrovascular events could potentially be reduced. We therefore sought to determine through meta-analysis of available trials, whether interventions directed towards prevention of diabetes in people with IGT and IFG alter macrovascular outcomes, including all-cause and cardiovascular mortality, as well as the incidence of major cardiovascular events. Secondary analyses included whether the interventions assessed in this setting delayed the progression of diabetes, whether lifestyle or drug treatment was the more effective intervention, and the effect of rosiglitazone on these outcomes.

## Methods

### Search strategy and selection criteria

Randomised controlled trials were identified via MEDLINE (source PubMed, 1966 to March 2010) and EMBASE (1974 to March 2010). All searches included the keywords and corresponding MeSH terms for diabetes mellitus type 2, glucose intolerance and randomised controlled trial. Manual reference checking of the bibliographies of all retrieved articles was also conducted.

Studies were assessed for data quality and validity by consensus between two investigators (IH and MS). Prospective randomised controlled trials conducted in adults that were published in English were considered for inclusion in this meta-analysis. Development of diabetes was a required outcome measure. The definition of IGT and IFG contemporaneous with the reported study was taken for inclusion.

Studies were included if they assessed the effects of a lifestyle intervention (diet, exercise or diet with exercise) or pharmacological intervention in participants with IGT and IFG.

Studies with fewer than 100 participants and follow-up of less than one year were the chosen exclusion criteria, and studies in which relevant data could not be extracted were not included in the meta-analysis.

### Data extraction and quality assessment

Trials were assessed independently by two reviewers (IH and MS). Data were extracted on all-cause mortality, cardiovascular death, fatal and non-fatal myocardial infarction and fatal and non-fatal stroke. For adjudicated trials, the data were extracted from the tables. Some trials had mortality reported in the serious adverse events section of the text, and if unavailable elsewhere, these data were used.

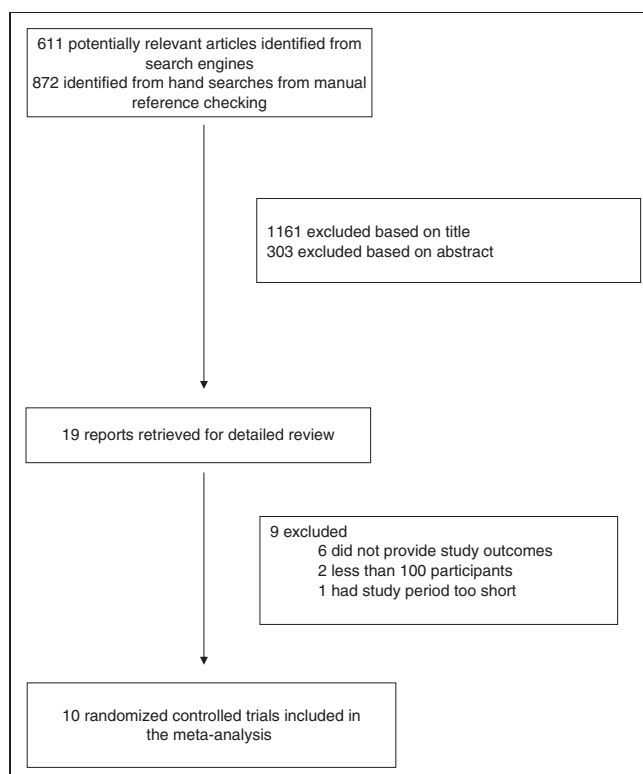
### Statistical analysis

Statistical analyses were performed using statistical package STATA, version 11. The Mantel-Haenszel fixed or random effects models were used for data analysis, based on the heterogeneity of the data extracted from individual studies. Heterogeneity between studies was analysed by chi-square test and significance of risk ratios (RRs) was performed using Z-test with a statistical significance of 0.05 for both tests. The fixed effect model was used if the *p* value was greater than 0.05 indicating homogeneity of the studies, and the random effect model was used if the *p* value was less than 0.05 indicating heterogeneity of the studies. RRs with 95% confidence interval (CI) were derived from every study and also for overall outcome. A weighting was calculated for every study in accordance with the number of events that occurred in every study to form an average overall outcome statistic and 95%CI. To examine potential publication bias, symmetry of individual study estimates around the overall estimate was assessed with funnel plots in which standard error of log RRs were plotted against their corresponding RR.

## Results

### Search results

The search (Figure 1) identified 611 articles with a further 872 identified from manual reference checking. A total of 1161 were excluded after review of the title, and a further 303 were excluded after review of the abstract. Full manuscripts were received for 19 trials, six of which were excluded because they did not provide study outcomes,<sup>9-14</sup> two had fewer than 100



**Figure 1.** QUORUM flow diagram.

participants<sup>15,16</sup> and one covered too short a time period.<sup>17</sup> Included in the meta-analysis were ten trials involving 23,152 participants. The trials included were the US DPP (Diabetes Prevention Program),<sup>18,19</sup> the Finnish DPS (Diabetes Prevention Study),<sup>20,21</sup> the Da Qing (Da Qing IGT and Diabetes Study),<sup>22,23</sup> the IDPP 1 and 2 (Indian Diabetes Prevention Program 1 and 2),<sup>24, 25</sup> STOP-NIDDM (Acarbose for prevention of type 2 diabetes),<sup>26,27</sup> Kawamori et al.,<sup>28</sup> DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone study),<sup>29,30</sup> NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research)<sup>31,32</sup> and the CANOE trial.<sup>33</sup>

Table 1 summarises the characteristics of these trials and the participants. The number of subjects in each study ranged from 207 to 9306. All studies were conducted on subjects with IGT and four included IFG (US DPP, STOP NIDDM, DREAM and NAVIGATOR). Definitions of IGT and IFG were revised downwards over time (Table 1).

Duration of follow-up ranged from 2.8 to 6 years for the intervention arms, with mean intervention time of 3.75 years. Most trials had follow-up only for the time of the intervention, but three studies reported extended follow-ups of 10.6, 20 and 6.5 years (Finnish DPS, Da Qing and NAVIGATOR respectively). Reporting of outcomes differed between the trials. Mortality data were obtained from adjudicated end-points, or extracted from death records or hospital records.

The trials differed in terms of populations studied. Trials included participants with established cardiovascular disease, one or more cardiac risk factors, risk factors for diabetes, or elevated body mass index as entry criteria.

The average age was 52 years, range 45–64 years, and overall 47% of participants were male.

Interventions were divided into pharmacological and non-pharmacological. Diet and exercise interventions differed between the trials. The lifestyle interventions in the non-drug trials achieved greater weight loss

Table 1. Characteristics of included studies

Source	No. of patients			Average age	Time <sup>a</sup>	Long follow-up	% male	Population	Intervention	Control
	ND	Drug	Control							
DPS (Finland) <sup>20,21</sup> 2003	257		248	55	4	10.6	33	IGT <sup>e</sup> , middle-aged, overweight	Tailored, detailed advice on diet, weight reduction and exercise	Limited advice on diet and exercise
Da Qing <sup>22,23</sup> 2008	438 <sup>b</sup>		138	45.6	6.0	(20 <sup>c</sup> )	53	IGT <sup>e</sup> , age ≥ 25	Individual and group counselling sessions: Diet - education and if BMI > 25 encouraged to lose weight Exercise group – taught to exercise Diet and exercise received both as above	Routine advice with no formal counselling
US DPP <sup>19,19</sup> 2002	1079	1073	1082	50.6	2.8	2.8	32	IGT <sup>e</sup> and IFG <sup>h</sup> , age ≥ 25	Standard LSM plus metformin (850 mg twice daily)	Standard LSM plus placebo
IDPP-1 <sup>24</sup> 2006	120	249 <sup>d</sup>	133	45.8	2.5	2.5	79	Min BMI 24 (22 in Asians) IGT <sup>e</sup> , age 35–55	Intensive LSM programme LSM Metformin (500 mg then 250 mg at day 40) Combination of LSM and metformin	Standard health care advice
IDPP-2 <sup>25</sup> 2009	204	203	203	45.3	3	3	87	IGT <sup>e</sup> , age 35–55	LSM with pioglitazone	LSM with placebo
STOP NIDDM <sup>26,27</sup> 2002	682	686	686	54.4	3.3	3.3	50	IGT <sup>e</sup> and IFG <sup>h</sup> , age 40–70, BMI 25–40	100 mg acarbose three times/day	Placebo
Kawamori et al <sup>28</sup> 2009	897	881	881	55.7	4	4	60	IGT <sup>e</sup> , age 30–70 and at least one CVRF	LSM plus voglibose	LSM with placebo
DREAM (2006) <sup>29,30</sup>				55.5	3	3	41	IFG <sup>f</sup> , IGT <sup>e</sup> or both, no CVD	2x2 factorial design	
Rosiglitazone + placebo	1325							Age > 30	LSM with either rosiglitazone and placebo, ramipril and placebo, rosiglitazone and ramipril	Placebo + placebo
Ramipril + placebo	1313									
Rosiglitazone + ramipril	1310									
Placebo + placebo	1321									
NAVIGATOR (2010) <sup>31,32,34</sup>	63.7	5	6.5	49				IGT <sup>h</sup> and IFG <sup>j</sup> with CVD (if age > 50)	2x2 factorial design	

(continued)

Table 1. Continued

Source	No. of patients		Average age	Time <sup>a</sup>	Long follow-up	% male	Population or one/more CVRF (if age >55)	Intervention	Control
	ND	Drug							
Nateglinide + placebo	2329								Placebo + placebo
Valsartan + placebo	2315							LSM with either valsartan and placebo, nateglinide and placebo, valsartan and nateglinide	
Nateglinide + valsartan	2316								
Placebo + placebo	2346								
CANOE (2010) <sup>33</sup>	103	104	52.5	3.9	3.9	33	IGT <sup>a</sup> 30–75, one risk factor for DM <sup>b</sup>	LSM with metformin plus rosiglitazone	LSM + placebo

<sup>a</sup>Years of intervention (extended follow-up period after intervention complete); ND, non-drug; <sup>b</sup>three groups – diet, exercise, diet and exercise; <sup>c</sup>530 analysed, figures from 20 year follow-up; CVD, cardiovascular disease; LSM, lifestyle modification; <sup>d</sup>two groups – metformin alone, and metformin with lifestyle; CVRF, cardiovascular risk factor; BMI, body mass index; <sup>e</sup>WHO 1985 IGT (FPG < 7.8 or 2 h PG 7.8–11.1 mmol/l) and diabetes (FPG ≥ 7.8 or 2 h PG ≥ 11.1 mmol/l); <sup>f</sup>ADA 1997 IFG (FPG ≥ 6.1 and < 7.0 mmol/l) and < 7.0 mmol/l) IGT (not stated) and diabetes (FPG ≥ 7.0 mmol/l or 2 h ≥ 11.1 mmol/l); <sup>g</sup>WHO 1999 IFG (FPG ≥ 6.1 and < 7.0 and 2 h PG < 7.8 mmol/l) IGT (FPG < 7.0 and 2 h value ≥ 7.8 and < 11.1 mmol/l) and diabetes (fasting ≥ 7.0 and/or 2 h ≥ 11.1 mmol/l); <sup>h</sup>FPG 5.3–6.9 mmol/l; <sup>i</sup>FPG 5.5–7.8 mmol/l; <sup>j</sup>ADA 2003 IFG (FPG ≥ 5.6 and < 7.0 mmol/l) IGT (not stated) and diabetes FPG ≥ 7.0 mmol/l; values are expressed as venous plasma glucose. 2h PG = two hour post-load plasma glucose; <sup>k</sup>overweight, family history type 2 diabetes, self-reported high blood pressure, history of gestational diabetes or birth of macrosomic infant.

than those in the drug trials. The US DPP and IDPP-1 had a lifestyle arm, a drug arm and a placebo control group. The lifestyle and drug arms were analysed separately but compared to the same control group. IDPP-2 had arms with drug only and drug with lifestyle, and these were grouped together in the drug approaches section. Pharmacological agents included metformin, acarbose, voglibose, rosiglitazone, pioglitazone, nateglinide, ramipril and valsartan.

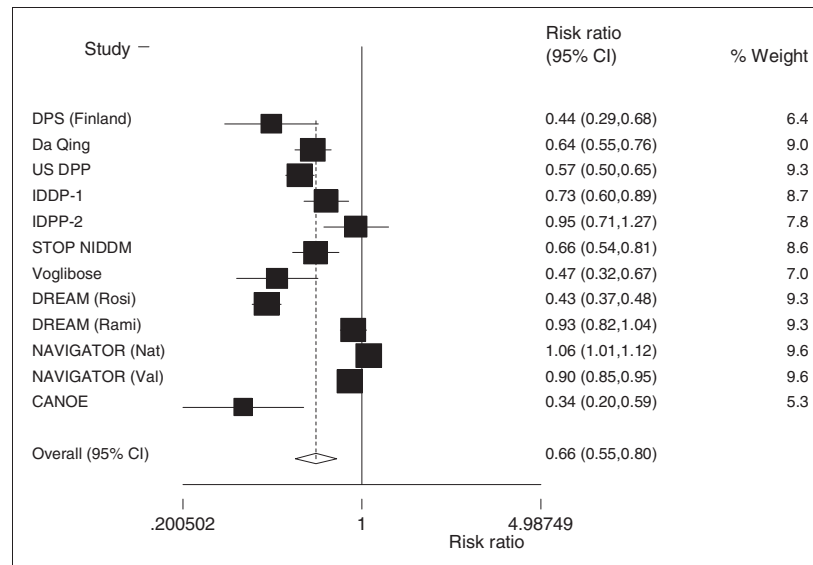
The DREAM and NAVIGATOR studies<sup>29–32</sup> had a factorial design so that it was not possible to evaluate a direct comparison of each drug against placebo. A further report<sup>34</sup> from the DREAM investigators provided data from the individual treatment groups for CV death, MI and stroke. When these data were available, the drug intervention outcomes data were grouped together and compared against the placebo group. Data from the individual treatment groups from NAVIGATOR were obtained from the supplementary appendix with further information provided by the investigators. There was no supplementary information available about diabetes prevention.

### Diabetes prevention

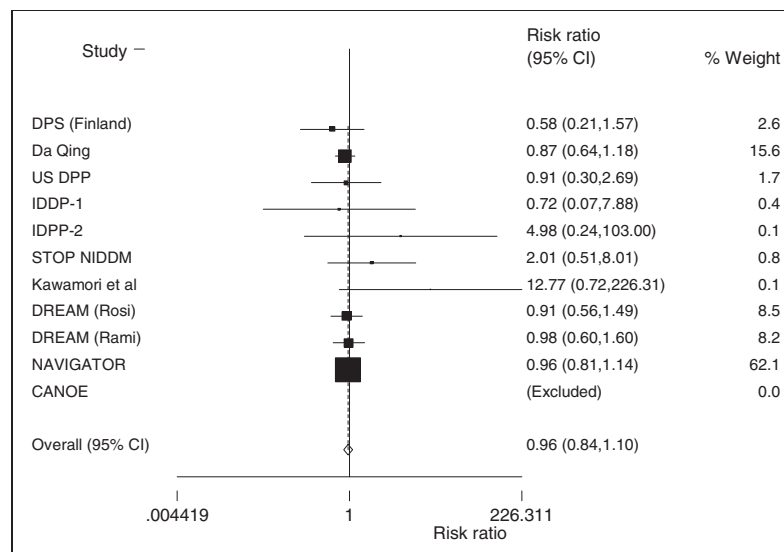
Diabetes was delayed or prevented overall (RR 0.66, 0.55–0.80) by intervention versus control (Figure 2), with a heterogeneity  $\chi^2$  of 267.3 ( $p < 0.001$ ). Both non-drug and drug-based approaches reduced progression to overt diabetes. Non-drug approaches ( $n = 3495$ , 0.52 95%CI 0.46–0.58) were superior ( $p < 0.05$ ) to drug-based approaches ( $n = 20,872$ , 0.70, 0.58–0.85). Diabetes was not prevented in three trials, which included the pioglitazone arm of IDPP-2, the ramipril arm of DREAM and the nateglinide arm of NAVIGATOR (Figure 2).

### All-cause mortality outcomes

There was no difference in all-cause mortality with an intervention in prediabetes versus control group (0.96, 0.84–1.10, Figure 3). There was no significant heterogeneity between the trials (heterogeneity  $\chi^2$  of 6.86,  $p = 0.651$ ). This result was dominated by the NAVIGATOR trial with 62.1% of the weight. There was no difference ( $p = \text{NS}$ ) between non-drug (0.81, 0.61–1.09) and drug approaches (0.99, 0.85–1.15). Sub-group analysis that looked only at trials that prevented diabetes did not alter this result (0.93, 0.80–1.07), and removal of rosiglitazone did not alter the result (0.96, 0.84–1.09). NAVIGATOR was analysed with the three intervention arms (valsartan, nateglinide, both) against placebo. There was no evidence of significant publication bias when investigated with Egger's



**Figure 2.** Diabetes incidence. Interventions that reduce events vs control are to the left of line of unity; interventions that increase events vs control are to the right of line of unity.



**Figure 3.** All-cause mortality combined: drug-based and non-drug approaches.

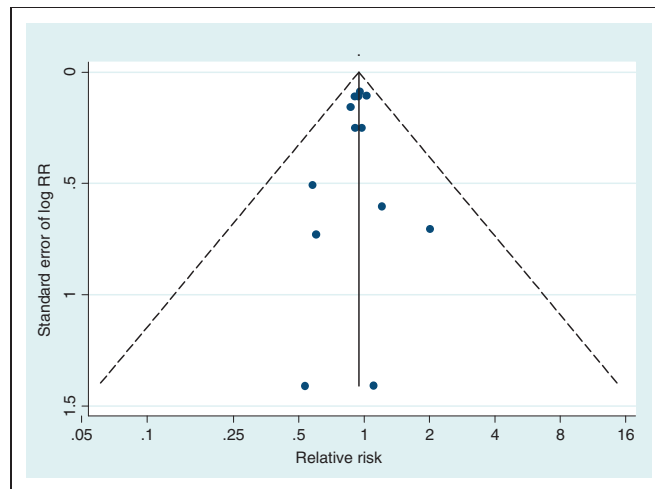


Figure 4. Funnel plot for cardiovascular mortality.

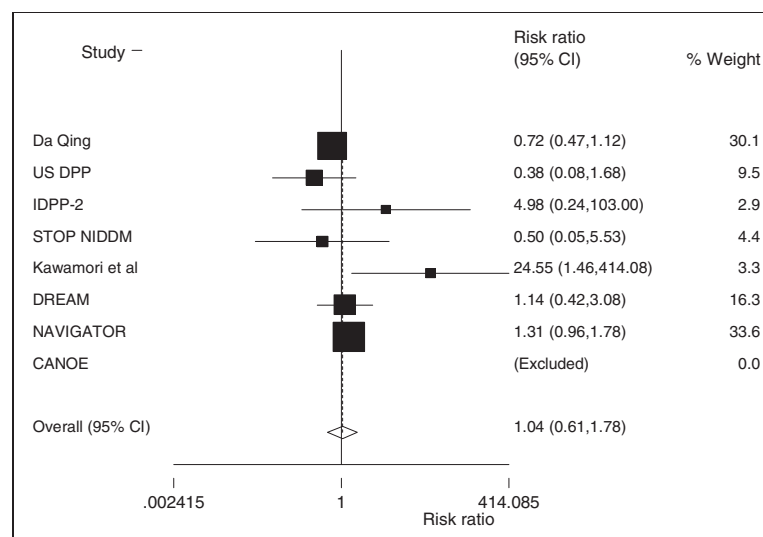


Figure 5. Cardiovascular death: drug-based and non-drug approaches.

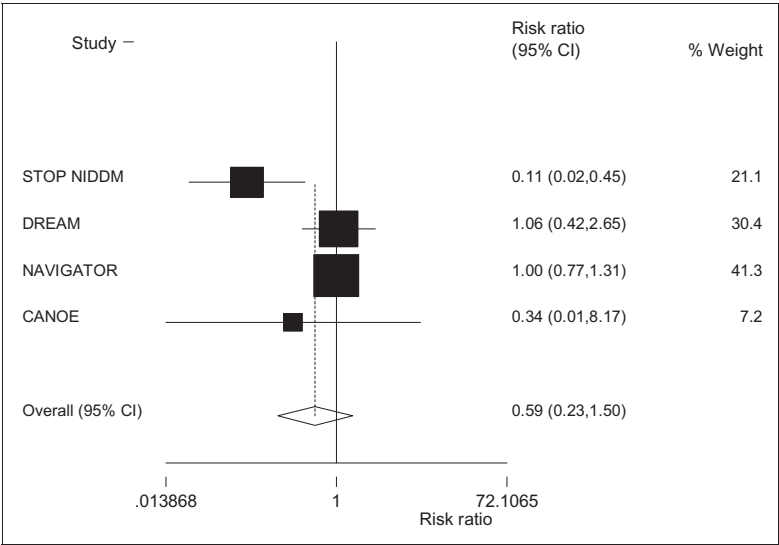


Figure 6. Fatal and non-fatal myocardial infarction: drug-based approaches.

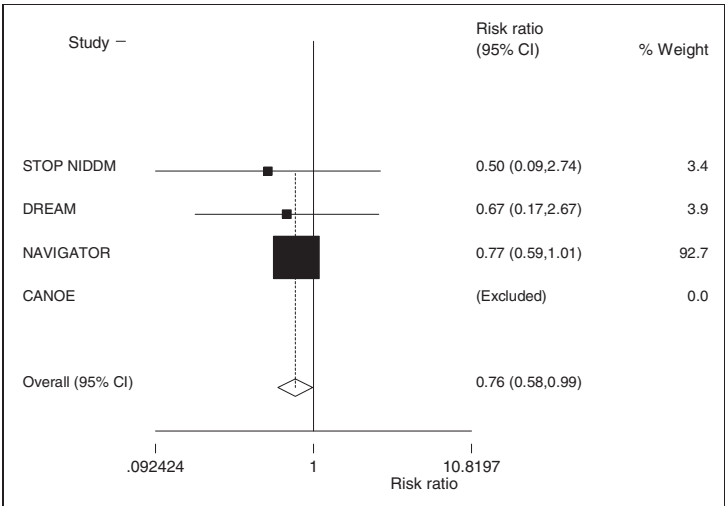


Figure 7. Fatal and non-fatal stroke: drug-based approaches.

tests ( $p=0.5$ ) and confirmed by minimal funnel plot asymmetry (Figure 4).

### Cardiovascular death outcomes

Two trials of non-drug approaches<sup>18,19,22,23</sup> and all the pharmacological interventions recorded cardiovascular death. There was no overall difference in risk of cardiovascular death in the intervention vs the control group (1.04, 0.61–1.78  $p=NS$ , Figure 5) with a heterogeneity  $\chi^2$  of 13.30 ( $p=0.038$ ). There was a non-significant trend towards increased cardiovascular death when the drug sub-group alone was considered (1.27, 0.96–1.68,  $p=NS$ ), and a non-significant trend towards reduction in cardiovascular death when the non-drug sub-group (0.70, 0.46–1.07  $p=NS$ ) was assessed. This result did not change when only trials that prevented diabetes were examined (1.06, 0.83–1.36) or with the removal of rosiglitazone (1.10, 0.87–1.40).

### Myocardial infarction and stroke outcomes

Only four drug trials contributed data to this endpoint. There was a 41% relative risk reduction in fatal and non-fatal myocardial infarctions; however, this result failed to reach statistical significance (RR 0.59, 0.23–1.50  $p=NS$ , Figure 6) with a heterogeneity  $\chi^2$  of 9.64,  $p=0.022$ . This result changed little with the removal of trials that did not prevent diabetes (0.51, 0.18–1.48), or when rosiglitazone was removed from the analysis (0.43, 0.11–1.65).

A 24% relative risk reduction in fatal and non-fatal strokes was of borderline statistical significance (0.76, 0.58–0.99, Figure 7), with no significant heterogeneity between the trials (heterogeneity  $\chi^2$  0.27,  $p=0.872$ ). However, this result lost statistical significance when only the trials that prevented diabetes were examined (0.76, 0.57–1.01). Removal of rosiglitazone did not alter the result (0.75, 0.58–0.98). Four trials recorded this outcome but CANOE contributed no events and the NAVIGATOR trial provided 92.7% of the data.

## Discussion

The present meta-analysis found overall that with interventions targeting prediabetes for an average 3.75 years, there was no reduction in all-cause or cardiovascular mortality. A non-significant trend towards reduced risk of fatal and non-fatal myocardial infarction was observed, and fatal and non-fatal stroke was borderline reduced. A clear reduction in progression to type 2 diabetes occurred with these interventions, with intensive lifestyle therapy being superior to drug

treatments, although with smaller numbers of subjects evaluated.

Studies evaluated were individually underpowered to examine mortality and cardiovascular outcomes, with generally low cardiovascular risk in patients with prediabetes combined with a relatively short follow-up time. When examined together in this meta-analysis, the confidence intervals around the point estimates are wide.

The reasons for the absence of a significant beneficial effect on macrovascular outcomes, despite success in diabetes prevention, could be explained by the interventions and follow-up periods applied in these studies being of too brief duration to influence all-cause and cardiovascular mortality, or indeed numbers are insufficient to show an effect despite meta-analysis. It may be that non-glycaemic cardiovascular risk factors, including hypertension, dyslipidaemia, hypercoagulability and obesity, have greater impact than glycaemic control on these outcomes. Additionally, the protective effect of preventing diabetes may be masked by 'off-target' cardiovascular effects of the therapies themselves. For example, rosiglitazone may increase the incidence of MI<sup>35</sup>, and nateglinide – one of two drugs used in the largest trial (NAVIGATOR) – elevates glucose levels after a glucose challenge.<sup>31</sup>

The trend towards reduction in non-fatal and fatal myocardial infarction and stroke is noteworthy. Further studies contributing greater numbers may strengthen the robustness of these conclusions. The Diabetes Prevention Program Outcome Study will be completed in 2014, and will look at long-term cardiovascular outcomes with diet and lifestyle changes. The Acarbose Cardiovascular Evaluation (ACE) trial will recruit 6500 patients with IGT and specifically examine cardiovascular outcomes with acarbose, and Actos Now for the Prevention of Diabetes (ACT NOW) will study pioglitazone in 600 participants.

Based on this analysis in prediabetes, together with trials in patients with overt type 2 diabetes mellitus, the role of glucose lowering in the prevention of cardiovascular events remains unclear. The UKPDS showed a non-significant reduction in macrovascular events when reductions in HbA1c were seen in type 2 diabetes.<sup>8</sup> Our meta-analysis had the same finding with a non-significant trend towards reduction in MI and stroke in prediabetes. In contrast, the ACCORD trial<sup>36</sup> found that tighter blood glucose control resulted in an excess of deaths. More studies are needed to answer this question.

Our meta-analysis has several limitations. Some trials included subjects with cardiovascular risk factors, others with previous cardiovascular events, so there is marked variation in risk between the trials. Also, prediabetes was not addressed in isolation, with other risk



factors optimised according to guidelines. When identified, elevated blood pressure and dyslipidaemia were referred back to the local doctor for treatment. These results were secondary outcomes pooled from trials looking at development of diabetes in pre-diabetic subjects, not necessarily cardiovascular outcomes. Although the larger trials predefined cardiovascular endpoints that were adjudicated, other studies relied on reporting from national agencies or hospital records. Thus, the reliability of these reports compared with adjudicated reports is questionable. Additionally, we did not have access to the original source data.

A further limitation of this specific study is the revising downwards of the definition of IGT and IFG over time, meaning that in earlier studies, some participants would have been enrolled in the study with what would later be considered diabetes; however given the size of the changes in the definition, we expect this effect to be minimal.

All studies were in English so trials in other languages were not identified. Additionally, a number of important studies were excluded because cardiovascular outcomes were not specifically reported,<sup>10,12,14</sup> and studies that examined IGT as a secondary outcome were also excluded.

In conclusion, despite interventions in prediabetes being mostly successful in retarding the progression to overt diabetes, this did not result in reduced all-cause mortality or cardiovascular mortality. This may relate to size of the sample in our study, the low cardiovascular risk of the groups studied, or it may indicate that risk factors other than IGT are more important. A non-significant trend in reduction in fatal and non-fatal myocardial infarction, and a borderline statistically significant reduction in fatal and non-fatal stroke was observed. Further studies examining this outcome are needed.

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#### Conflicts of interest

None declared.

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## Appendix 3.3

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### *Systematic review and meta-analysis*

Clark H, Krum H, **Hopper I**. Worsening renal function during RAAS inhibitor initiation and long term outcomes in patients with left ventricular systolic dysfunction. *European Journal of Heart Failure*. 2014; 16: 41-48

# Worsening renal function during renin–angiotensin–aldosterone system inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction

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<b>Aims</b>	Impaired renal function is associated with worse clinical outcomes in patients with LV systolic dysfunction (LVSD) and heart failure. Renin–angiotensin–aldosterone system (RAAS) inhibitors provide clinical benefit in these settings and often worsen renal function. It is not clear whether worsening renal function (WRF) in patients exposed to these agents predicts a worse prognosis or merely reflects the pharmacological action of the drug on the kidney.
<b>Methods and results</b>	We performed a meta-analysis of all RAAS inhibitor LVSD trials reporting on outcomes according to WRF (as per individual study definition) in both active intervention and placebo groups. Five major studies (SOLVD, SAVE, RALES, Val-HeFT and EPHEsus) contributed, with 20 573 patients. Compared with placebo, RAAS inhibitors reduced all-cause mortality overall [ $n = 20\,573$ , relative risk ratio (RR) 0.91, 95% confidence interval (CI) 0.86–0.95, $P = 0.0003$ ], in the group with no WRF ( $n = 18\,209$ , RR 0.91, 95% CI 0.83–0.99, $P = 0.04$ ), and in the WRF group ( $n = 2364$ , RR 0.72, 95% CI 0.62–0.84, $P < 0.0001$ ). Compared with no WRF, WRF was associated with increased all-cause mortality; however, this was less in the RAAS inhibitor group ( $n = 8905$ , RR 1.22, 95% CI 1.10–1.36, $P = 0.0003$ ) than in the placebo group ( $n = 9304$ , RR 1.52, 95% CI 1.37–1.69, $P < 0.00001$ ).
<b>Conclusions</b>	WRF shortly after randomization is associated with worsened outcomes compared with no WRF; however, the reduction in all-cause mortality associated with the use of RAAS inhibitors was significantly greater in the presence of WRF than in the no WRF group. Clinicians should not be deterred from using RAAS inhibitors in the setting of WRF.
<b>Keywords</b>	Heart failure • Worsening renal function • Renal impairment • RAAS inhibitors • Mineralocorticoid receptor antagonists • Angiotensin receptor blocker

## Introduction

Baseline renal impairment is well accepted as being associated with worse long-term outcomes, in both the post-myocardial infarction (MI) LV dysfunction<sup>1</sup> and systolic heart failure (HF) settings.<sup>2-7</sup> Less well studied has been the impact of change in renal function

on major clinical outcomes. Worsening renal function (WRF) has been associated with increased mortality in both HF inpatients and outpatients,<sup>8–10</sup> however, the majority of studies investigating WRF have focused on the acute decompensated setting.<sup>9–12</sup> The pathophysiology underlying WRF and its prognostic implications may differ considerably in the acute and chronic HF settings, given

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differences in clinical presentation and treatment.<sup>13</sup> Furthermore, changes in renal function in response to specific pharmacological and other interventions have not been well studied.

Worsening renal function is particularly relevant to inhibitors of the renin–angiotensin–aldosterone system (RAAS) as these agents may reduce the glomerular filtration rate (GFR) and thus may worsen measures of renal function, at least initially, but provide long-term major clinical outcome benefits in these settings. WRF may lead practitioners to discontinue beneficial therapies such as RAAS inhibitors, in the belief that WRF may adversely impact outcomes long term. However, it is unclear whether this WRF is a reflection of structural damage to the kidney itself or of HF-related changes in haemodynamic status. It therefore remains uncertain whether WRF negates the benefits of RAAS inhibitor treatment when given to patients with LV systolic dysfunction (LVSD).

A number of randomized controlled studies have recently investigated the interaction between WRF secondary to use of RAAS inhibitors on initiation of treatment as well as the impact this has on long-term prognosis in patients with LVSD post-MI and in established HF.<sup>14–18</sup>

Therefore, the aim of the present meta-analysis was to determine the impact of WRF in the setting of pharmacological intervention with RAAS inhibitors in patients with LVSD on prognosis and other long-term major clinical outcomes.

## Methods

### Search strategy and selection criteria

Eligible studies were identified using MEDLINE (source OVID 1966 to July 2013). All searches included the keywords and corresponding MeSH terms describing LV dysfunction, currently advised HF treatment drug classes, and WRF. Additionally, bibliographies of retrieved articles were manually searched, as well as those of review articles. Previous systematic reviews and meta-analyses were used as sources for relevant articles.<sup>8,9,19</sup>

Only English-language, full-text, peer-reviewed articles were considered. Titles and abstracts on initial screening were evaluated and excluded if they did not define WRF, did not investigate the interaction between a treatment class, WRF, and prognosis as the primary aim, had a follow up <12 months, were based on acutely decompensated HF, or did not provide measures of renal function both at baseline and after treatment initiation. There was no minimum number of patients. Study authors were contacted for further information. A Quality of Reporting of Meta-analyses flow diagram illustrates the study selection process (Figure 1).

### Data extraction

Trials were assessed by all authors. We aimed to extract data on all-cause mortality, cardiovascular (CV) mortality, HF hospitalization, MI, and sudden cardiac death. All data were reported in intention-to-treat analysis. Numbers were extrapolated from figures when unavailable. Unpublished data were sought.

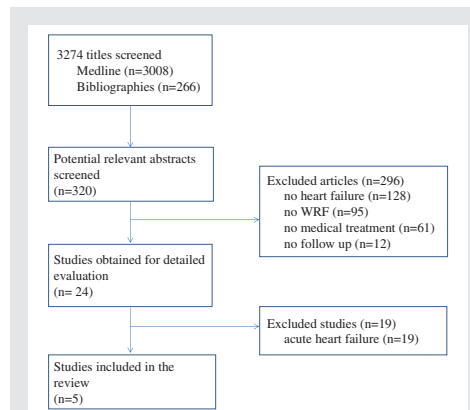


Figure 1 QUORUM flow diagram.

### Assessment of risk of bias

We used criteria described in the *Cochrane Handbook of Systematic Reviews 5.0*,<sup>20</sup> to describe the quality of the included trials. To assess the risk of bias, we focused on the following criteria: adequate sequence generation (such as computer-generated random numbers), adequate allocation concealment (concealment was considered adequate when randomization was centralized or pharmacy controlled), adequate blinding (of participants or outcome assessors), completeness of outcome data (considered adequate if intention-to-treat analysis was performed for each outcome), and free of selective reporting (considered adequate if all stated outcomes were reported on and presented).

### Statistical analysis

Statistical analysis was performed using Review Manager (RevMan) Version 5.2.5.<sup>21</sup> The results were pooled using random effects model because of the clinical heterogeneity of the studies. Relative risk ratios (RRs) with 95% confidence intervals (CIs) were derived from each individual study and determined for overall outcome using the Mantel–Haenszel method and the Z-test for significance of RRs. A weighting was calculated based on the number of events that occurred in each study. A test for interaction examining the difference between two estimates was performed.<sup>22</sup> Potential publication bias was assessed by funnel plot symmetry.

### Meta-analysis

#### Characteristics of included studies

A total of 3274 titles were screened, with 320 abstracts reviewed further. Of these, 296 were excluded, and 24 studies were obtained for detailed evaluation. Five studies met the inclusion criteria (Figure 1). All were post-hoc analyses of major randomized controlled trials investigating HF treatments with RAAS

inhibitors. Included analyses were based on SOLVD, Studies of Left Ventricular Dysfunction<sup>15</sup> SAVE, Survival and Ventricular Enlargement Trial;<sup>16</sup> RALES, the Randomized Aldactone Evaluation Study;<sup>14</sup> Val-HeFT, Valsartan Heart Failure Trial;<sup>18</sup> and EPHEUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study.<sup>17</sup>

Table 1 summarizes the characteristics of the included trials. Overall the number of participants included in the meta-analysis was 20 573. The number of participants in the individual trials ranged from 1663 to 6377. The SAVE and EPHEUS trials enrolled participants within 2 weeks of an MI with EF < 40%. SOLVD, RALES and Val-HeFT enrolled participants with clinically stable HF with reduced EF. RALES enrolled participants with severe HF. Average follow-up ranged from 16 to 41 months. The average age of participants was 61.9 years, with 79% male and approx a quarter were diabetic. Average EF was 28.8% overall.

All studies trialled inhibitors of the RAAS against a matched placebo. Two studies used the ACE inhibitors enalapril (SOLVD) and captopril (SAVE), one used the ARB valsartan (Val-HeFT), and two studied mineralocorticoid receptor antagonists spironolactone (RALES) and eplerenone (EPHEUS). SOLVD and SAVE were conducted in the early era of neurohormonal blockade, and trialled only an ACE inhibitor with little in the way of neurohormonal blockade. RALES, Val-HeFT, and EPHEUS reflect a more modern paradigm of HF treatment, with high rates of ACE inhibitor/ARB usage, but only EPHEUS also had a high rate of use of beta-blockers.

The estimated GFR (eGFR) was calculated in all studies using the Modification of Diet in Renal Disease (MDRD) study equation. All studies excluded participants with serum creatinine >220 µmol/L (2.5 mg/dL). Definitions of WRF varied between studies (Table 2). Three studies used a decrease in eGFR of 20%, one of 30%, and one used an increase in creatinine of 27 µmol/L (>0.3 mg/dL) from baseline. Time points from randomization used by different studies included 2 weeks, 4 weeks, and 12 weeks. All studies investigated worsening from baseline renal function after randomization. Data were divided into two groups: one receiving placebo and the other receiving a drug intervention with a RAAS inhibitor. Within those groups, participants who had WRF were compared with those with no WRF (see Table 3 for baseline characteristics of these groups). WRF was considered to be the intervention, and no WRF the control state.

Risk of bias in included studies was assessed as being generally low, despite all trials being sponsored by industry (Table 1). All trials were randomized, with two noting computer randomization, and three not describing the method. Allocation concealment was adequate in two trials, and not described in three. All trials used double-blinding to reduce bias. Intention-to-treat analysis was used in all studies. All studies were free from selective reporting.

Data were able to be extracted on all-cause mortality, CV mortality, HF hospitalization, and a composite of CV death and HF hospitalization. All were post-hoc analyses of their respective prospective randomized controlled trials. All studies included all-cause mortality. Other outcomes investigated included CV death<sup>16,17</sup> and a composite of death, stroke, recurrent MI, and hospitalization for congestive HF;<sup>16</sup> the combined endpoint of death

Table 1 Included studies

Study and publication date	n	Study design	Participants	Intervention	Comparison	Outcomes	Follow-up (months)	Risk of bias
Tessani et al. <sup>15</sup>	6377	Secondary analysis of RCT SOLVD (1991, 1992)	Symptomatic and asymptomatic LVD LVEF ≤33% Post-MI (3–16 days) LVEF ≤40% No overt HF	Enalapril	Placebo	Death	41	Low
Jose et al. <sup>16</sup>	1813	Secondary analysis of RCT SAVE (1992)		Captopril	Placebo	Death CVD MI CHF	37 95% CI 36.2–37.5	Low
Vardeny et al. <sup>14</sup>	1663	Secondary analysis of RCT RALES (1999)	HF NYHA III–IV LVEF <35% Clinically stable HF	Spironolactone	Placebo	Comp: all above Death Death or HF hospitalization	24	Low
Lesogor et al. <sup>18</sup>	4928	Secondary analysis of RCT Val-HeFT (2001)	NYHA II–IV LVEF <40% Post-MI HF (3–14 days) LVEF ≤40% If DM no HF	Valsartan	Placebo	Death Comp: CVD HF hospitalization	'Up to 36'	Low
Rossignol et al. <sup>17</sup>	5792	Secondary analysis RCT EPHEUS (2003)		Eplerenone	Placebo	Death CVD Death/hospitalization HF hospitalization CVD/hospitalization SCD	16 (range 0–33)	Low

Comp, composite; Cr, creatinine; CVD, cardiovascular death; DM, diabetes mellitus; HF, heart failure; LVD, left ventricular dysfunction; MI, myocardial infarction; RCT, randomized controlled trial; SCD, sudden cardiac death.

**Table 2** Definitions of worsening renal function according to study

Study	Definition of WRF
Testani et al. <sup>15</sup>	20% decrease in eGFR at 14 days after randomization
Jose et al. <sup>16</sup>	Increase in creatinine >0.3 mg/dL from baseline at week 2
Vardeny et al. <sup>14</sup>	Reduction in GFR >30% from baseline any time during the titration phase to week 12
Lesogor et al. <sup>18</sup>	Reduction in eGFR >20% from baseline within 1 month of randomization
Rossignol et al. <sup>17</sup>	Reduction in eGFR >20% from baseline at 1 month

eGFR, estimated glomerular filtration rate; WRF, worsening renal function.

or HF hospitalization;<sup>14,17</sup> and hospitalization for HF, CV death or CV hospitalization, and sudden cardiac death.<sup>17</sup>

## Results

### All-cause mortality

All five trials contributed data to this outcome. Including all participants, there was an overall reduction in all-cause mortality with the use of RAAS inhibitors compared with placebo ( $n=20\,573$ , RR 0.89, 95% CI 0.81–0.98,  $P=0.02$ ). Use of RAAS inhibitors compared with placebo was associated with a reduction in all-cause mortality in the no WRF group ( $n=18\,209$ , RR 0.91, 95% CI 0.83–0.99,  $P=0.04$ ), and also in the WRF group ( $n=2\,364$ , RR 0.72, 95% CI 0.62–0.84,  $P<0.0001$ ) (Figure 2). The estimated interaction effect was significant ( $P=0.009$ ), demonstrating that RAAS inhibitors confer greater benefit in participants with WRF than in participants with no WRF.

More participants developed WRF in the RAAS inhibitor group than in the placebo group. In the placebo group, WRF ( $n=990$ ) was associated with an increase in all-cause mortality when compared with no WRF ( $n=9\,304$ , RR 1.52, 95% CI 1.37–1.69,  $P<0.00001$ ). In the RAAS inhibitor group, WRF ( $n=1\,374$ ) was associated with an increase in all-cause mortality compared with no WRF ( $n=8\,905$ , RR 1.22, 95% CI 1.10–1.36,  $P=0.0003$ ) (Figure 3). The estimated interaction effect was significant ( $P=0.004$ ), indicating that the use of RAAS inhibitors in the setting of WRF reduces all-cause mortality. There was no evidence of significant publication bias when investigated via funnel plot (Figure 4).

When only modern trials with background ACE inhibitor or ARB were included (i.e. EPHEsus, RALES, and Val-HeFT), there was no overall mortality benefit (RR 0.90, 95% CI 0.76–1.06,  $P=0.21$ ). There was no mortality benefit in the group with no WRF (RR 0.90, 95% CI 0.78–1.06,  $P=0.21$ ), and there was a borderline statistically significant mortality benefit in the WRF group (RR 0.74, 95% CI 0.55–1.00,  $P=0.04$ ). The test for interaction was not significant ( $P=0.2$ ), indicating that there is no evidence to support a treatment difference between the WRF and no WRF groups.

### Cardiovascular mortality

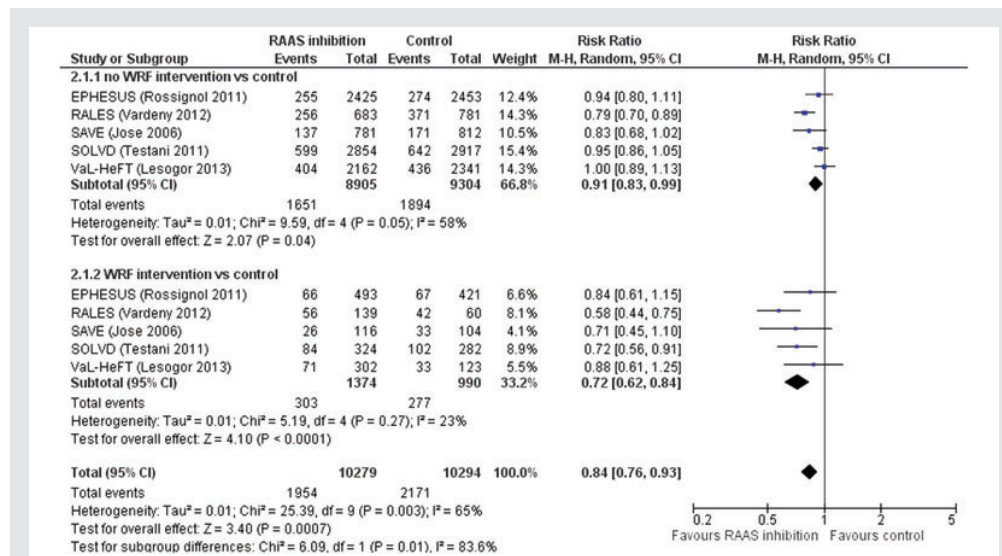
Including all participants, there was overall no reduction in CV mortality (0.89, 95% CI 0.78–1.01,  $P=0.07$ ). There was no reduction

**Table 3** Baseline characteristics of included studies

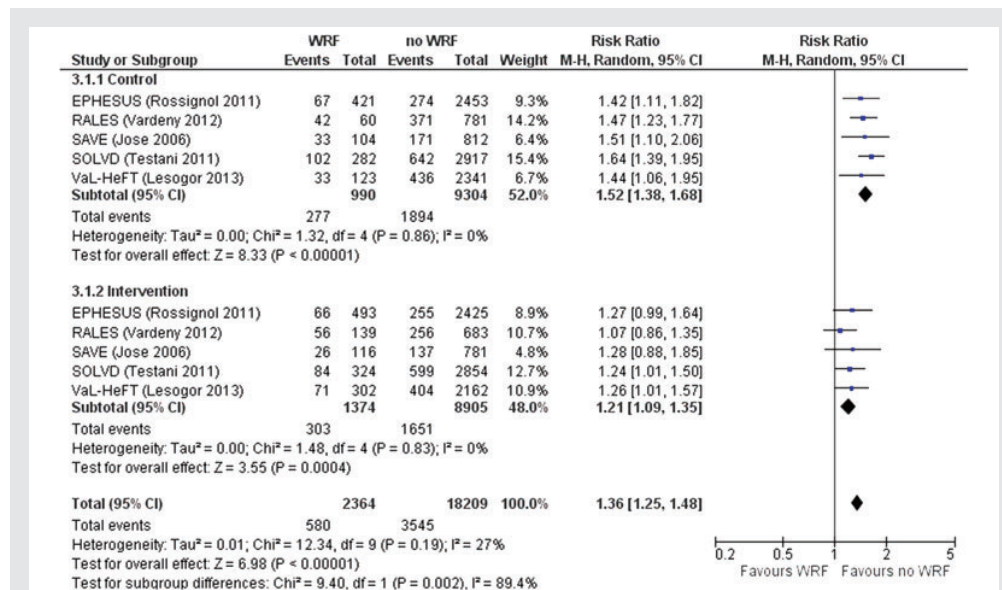
Study	Renal function	n	Age (SD)	Males (%)	DM (%)	HTN (%)	MI (%)	EF (SD)	SCr $\mu\text{mol/L}$ Mean (SD)	eGFR Mean (SD)	Background medications (%)			
											ACE/ARB	BB	AA	Digoxin
Testani et al. <sup>15</sup>	No WRF	5771	59.3 $\pm$ 10.2	86	19	38	75	27.1 $\pm$ 6.2	106 $\pm$ 27	64.1 $\pm$ 17.3	49.5	18.3	—	32.5
Jose et al. <sup>16</sup>	WRF	606	59.8 $\pm$ 10.1	82	22	41	74	26.4 $\pm$ 6.4	88 $\pm$ 27	79.5 $\pm$ 28	53.5	14.5	—	37.1
	No WRF	1631	58.8 $\pm$ 10.6	84	20	42	38	31.1 $\pm$ 6.6	106 $\pm$ 27	—	50.2	—	—	—
	WRF	223	60.7 $\pm$ 10.8	76	28	46	29	30.7 $\pm$ 6.4	97 $\pm$ 31	—	53.4	—	—	—
Vardeny et al. <sup>14</sup>	No WRF	1464	65.2 $\pm$ 11.8	74	22	24	29	25.3 $\pm$ 6.7	115 $\pm$ 35	64 $\pm$ 21.8	95.3	10.5	—	72.3
	WRF	199	66.7 $\pm$ 12.3	63	25	19	27	25.6 $\pm$ 7.0	106 $\pm$ 35	71.3 $\pm$ 29.7	97.5	8.5	—	78.9
Lesogor et al. <sup>18</sup>	No WRF	4503	62.6	80	25	7	—	26.9	—	61.3	92.7	35.2	4.8	—
	WRF	425	63.3	75	28	6	—	25.3	—	63.0	92.7	33.2	6.4	—
Rossignol et al. <sup>17</sup>	eGFR $\geq 60$ mL/min <sup>a</sup>	4878	61.2 $\pm$ 12	78	29	56	24	34 $\pm$ 6.0	—	81.7 $\pm$ 17	87	78	—	—
	eGFR <60 mL/min <sup>a</sup>	914	70 $\pm$ 11	57	37	70	33	33 $\pm$ 6.0	—	48 $\pm$ 9	87	71	—	—

AA, aldosterone antagonist; ACE, ACE inhibitor; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate (mL/min/1.73 m<sup>2</sup>); HTN, hypertension; MI, myocardial infarction; SCr, serum creatinine; SD, standard deviation; WRF, worsening renal function.<sup>a</sup> Only baseline renal status was available; no data according to WRF for no WRF.



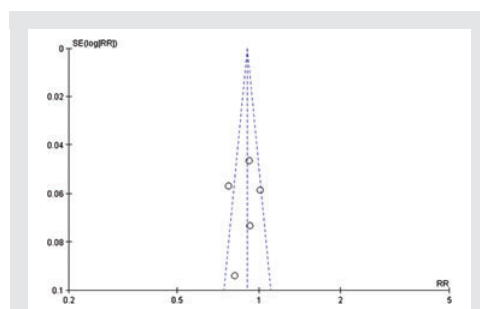


**Figure 2** Forest plot of comparison. All-cause mortality, outcome: no WRF intervention vs. control and WRF intervention vs. control. CI, confidence interval; RAAS, renin-angiotensin-aldosterone system; WRF, worsening renal function.



**Figure 3** Forest plot of comparison. All-cause mortality, outcome: WRF vs. no WRF control and intervention. CI, confidence interval; RAAS, renin-angiotensin-aldosterone system; WRF, worsening renal function.





**Figure 4** Funnel plot of comparison. All-cause mortality, outcome: all. RR, relative risk ratio; SE, standard error.

in CV mortality with RAAS inhibitors compared with placebo in participants with no WRF ( $n=6471$ , RR 0.89, 95% CI 0.78–1.03,  $P=0.11$ ), or in the group with WRF ( $n=1134$ , RR 0.84, 95% CI 0.64–1.12,  $P=0.24$ ). In the placebo group, WRF ( $n=525$ ) compared with no WRF ( $n=3265$ ) was associated with an increase in CV mortality (RR 1.42, 95% CI 1.14–1.76,  $P=0.002$ ). In the RAAS inhibitor group, WRF ( $n=609$ ) compared with no WRF ( $n=3206$ ) was also associated with an increase in CV mortality (RR 1.33, 95% CI 1.06–1.67,  $P=0.01$ ). The estimated interaction effect was not significant ( $P=0.6$ ), indicating that RAAS inhibitors did not confer a CV mortality benefit in the WRF group compared with the no WRF group. Only two studies contributed data to this outcome (SAVE and EPHEUS).

### Heart failure hospitalization

Including all participants, there was overall a reduction in HF hospitalization ( $n=7605$ , RR 0.79, 95% CI 0.66–0.95,  $P=0.01$ ). In participants with no WRF, there was a borderline reduction in HF hospitalization with RAAS inhibitors compared with placebo ( $n=6471$ , RR 0.82, 95% CI 0.67–1.00,  $P=0.05$ ). In participants with WRF, there was no reduction in HF hospitalization with RAAS inhibitors compared with placebo ( $n=1134$ , RR 0.70, 95% CI 0.45–1.09,  $P=0.02$ ). In the placebo group, WRF ( $n=525$ ) compared with no WRF ( $n=3265$ ) was associated with an increase in HF hospitalization (RR 1.43, 95% CI 1.04–1.98,  $P=0.02$ ). In the RAAS inhibitor group, WRF ( $n=609$ ) compared with no WRF ( $n=3206$ ), no statistically significant increase in HF hospitalization was observed (RR 1.23, 95% CI 0.85–1.78,  $P=0.27$ ). Two studies contributed data to this outcome (SAVE and EPHEUS).

### Cardiovascular death/heart failure hospitalization

Including all participants, there was overall a reduction in CV death/HF hospitalization ( $n=12533$ , RR 0.87, 95% CI 0.83–0.92,  $P<0.00001$ ). In participants with no WRF, there was a reduction in

CV death/HF hospitalization with RAAS inhibitors compared with placebo ( $n=10974$ , RR 0.86, 95% CI 0.81–0.92,  $P<0.00001$ ). In participants with WRF, there was also a reduction in CV death/HF hospitalization with RAAS inhibitors compared with placebo ( $n=1134$ , RR 0.84, 95% CI 0.74–0.97,  $P=0.01$ ). The test for interaction was not significant ( $P=0.7$ ). In the placebo group, WRF ( $n=648$ ) compared with no WRF ( $n=5606$ ) was associated with an increase in CV death/HF hospitalization (RR 1.31, 95% CI 1.18–1.46,  $P<0.00001$ ). In the RAAS inhibitor group, WRF ( $n=911$ ) compared with no WRF ( $n=5368$ ) was associated with an increase in the combined endpoint of CV death/HF hospitalization (RR 1.27, 95% CI 1.15–1.40,  $P<0.00001$ ). Three studies contributed to this outcome (SAVE, EPHEUS, and Val-HeFT).

## Discussion

This meta-analysis sought to quantify the risk associated with WRF compared with no WRF on commencement of RAAS inhibitors compared with placebo in LVSD post-MI and established HF settings. It is important to note that WRF occurred frequently in the placebo group, meaning that the group of participants under study had a high background rate of WRF independent of use of RAAS inhibitors. While the rate of WRF was higher in the RAAS inhibitor group than in the placebo group, it is impossible to determine which participants had RAAS inhibitor-induced WRF and which had spontaneous WRF. As such, this analysis cannot directly address the risk associated with RAAS inhibitor-induced WRF; only the risk of WRF (some RAAS inhibitor induced, some not) in the setting of a RAAS inhibitor.

There are two important findings from this meta-analysis. First is that the benefit of the RAAS inhibitor is not negated or diminished by WRF. Indeed, the benefit of these medications in WRF is greater than in the no WRF group. This stands to reason, as it has been observed that there is greater stimulation of the RAAS in the presence of reduced renal function,<sup>23,24</sup> and this can confer greater potential for improvement when the RAAS is adequately blocked. This is illustrated in HF which is the only CV condition where the clinical outcome benefits of multiple RAAS blockade generally outweigh the side effects.<sup>25–28</sup> The results of this meta-analysis therefore strongly support continued use of RAAS blockade especially in the presence of WRF. This is in line with HF guidelines from the European Society of Cardiology (ESC),<sup>29</sup> which recommend continuing to use ACE inhibitors/ARBs despite small increases in creatinine, and, indeed, a rise in creatinine up to 50% of baseline can be considered acceptable. Of note, these guidelines also caution that an immediate and large fall in eGFR raises suspicion of renal artery stenosis, and should be investigated accordingly.

The second finding of note is that WRF is associated with a poorer prognosis than no WRF. This is not surprising, as it is well established that impaired renal function in HF is associated with a worse prognosis,<sup>3,6,30</sup> but it is now also clear that a short-term WRF also portends a poorer prognosis. WRF in HF represents a heterogeneous group of disorders with a variety of causes.<sup>31</sup> WRF

can occur spontaneously with tubular damage (with or without persistent hypotension) as part of the ongoing HF disease process.<sup>18</sup> The vasodilator effects and reductions in efferent arteriolar tone in the kidney with RAAS inhibitors are also common causes of WRF,<sup>32</sup> and indeed a greater number of participants developed WRF in the RAAS inhibitor group than was observed in the placebo group. The pathophysiology of WRF under these differing circumstances is vastly different. Unfortunately we did not have access to individual baseline patient data, and as randomizing to WRF is not possible we were unable to account for residual risk. The results of this meta-analysis, however, suggest that different causes of WRF may be associated with different outcomes. Despite the above considerations, RAAS blockade clearly improves clinical outcomes regardless of WRF presence compared with placebo.

The trials included in this meta-analysis were derived from somewhat different eras in heart failure therapy; thus the magnitude of the changes in renal function and indeed the outcomes seen may be different if they were evaluated today. If these trials had uniformly included beta-blockade, then a lower incidence of WRF may have been expected, as beta-blockers act to reduce renal sympathetic tone<sup>33</sup> as well as improving all outcomes. Additionally the participants in each trial differed, including participants who were post-MI as well as those on the continuum from asymptomatic to severe HF, and it is not clear whether these results are applicable across the full continuum of HF severity. As RAAS inhibitors may differ in underlying pharmacology and receptor affinities, it is also not known whether the effects of WRF among placebo and RAAS inhibitor groups observed in these analyses apply to other agents in the drug class.

The strengths of this meta-analysis are that the data were derived from high-quality, randomized, controlled trials with participants numbering over 20 000. Despite that, there were significant limitations. The data were all obtained from post-hoc analyses which were not pre-specified. Thus, they should be considered hypothesis-generating only. Although participants were randomized to treatment or placebo, they were not randomized according to their change in renal function. A potential bias may have been introduced as a result of study physicians making different treatment decisions according to knowledge of participants' renal function status. The trials all used different definitions of WRF, being measured at different time points (between 2 and 12 weeks), and having a 20–30% drop in eGFR. We also do not have longer-term measures of renal function to ascertain whether the WRF was acute and reversible, or ongoing. Additionally, severe renal dysfunction at baseline was excluded in all trials, so the results cannot be extrapolated to this group of patients. We were also largely limited to information available in the public domain, and thus were unable to characterize completely participants who developed WRF.

In summary, in the setting of pharmacological intervention with RAAS inhibition for HF, WRF measured shortly after randomization is associated with worsened outcomes compared with no WRF; however, the reduction in all-cause mortality associated with the use of RAAS inhibitors was significantly greater in the presence of WRF than in the no WRF group. Clinicians should continue to use RAAS inhibitors despite a modest drop in renal function.

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## Appendix 3.4

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### *Systematic review and meta-analysis*

Peck KY, Lim YZ, **Hopper I**, Krum H. Medical therapy versus implantable cardioverter-defibrillator in preventing sudden cardiac death in patients with left ventricular systolic dysfunction and heart failure: A meta-analysis of > 35,000 patients. *International Journal of Cardiology*. 2014; 173: 197-203.



## Medical therapy versus implantable cardioverter-defibrillator in preventing sudden cardiac death in patients with left ventricular systolic dysfunction and heart failure: A meta-analysis of > 35,000 patients



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### ABSTRACT

**Background:** Patients with left ventricular systolic dysfunction (LVSD) are at high risk of sudden cardiac death (SCD). Implantable cardioverter defibrillators (ICDs) have an important role in preventing SCD in selected patients with LVSD and chronic heart failure (CHF). Drug therapies for LVSD and CHF also appear to also be useful in reducing SCD. However, the magnitude of benefit of these approaches on SCD is uncertain. We therefore conducted a meta-analysis comparing the effect on SCD achieved by ICDs versus medical therapies, additional to standard background medical therapies including ACE inhibitors and/or beta-blockers (BBs).

**Methods:** Our meta-analysis included trials of >100 patients with reduced left ventricular ejection fraction (LVEF), i.e., <40%. Fourteen randomized controlled trials met the criteria for meta-analysis, 10 involving medical therapies (angiotensin receptor blockers [ARBs], mineralocorticoid receptor antagonists [MRAs], ivabradine, n3-polyunsaturated fatty acid [PUFA], ferric carboxymaltose and aliskiren) and four involving ICDs. Results were pooled using the Mantel-Haenszel random effects method.

**Results:** Drug therapy ( $n = 36,172$ ) reduced the risk of SCD overall (risk ratio (RR) = 0.89, 95% confidence interval (CI) = 0.82–0.98,  $p = 0.02$ ) when compared to placebo. MRAs alone were most effective in reducing SCD ( $n = 11,032$ , RR = 0.79 [0.68–0.91],  $p = 0.001$ ). ICD insertion greatly reduced SCD ( $n = 4,269$ , RR = 0.39 [0.30–0.51],  $p < 0.00001$ ) compared with placebo. The difference in treatment effect between the ICD and drug therapy was significant ( $p < 0.002$ ), and between ICD and MRAs ( $p < 0.002$ ).

**Conclusions:** Drug therapies when added to a standard background regimen comprising ACE inhibitor and/or BB reduced SCD overall and MRAs alone were most effective in this regard. ICDs were more effective than drugs in SCD abrogation. However, the added procedural morbidity and the cost of ICD need to be considered in decision-making re-approach to SCD reduction in the individual patient.

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### 1. Introduction

Heart failure is a common clinical syndrome resulting in high levels of morbidity and mortality despite best current management strategies for the condition [1]. Effective pharmacological therapies for patients with systolic heart failure include ACE inhibitors and beta-blockers (BB) [1]. It has been proven to be relatively difficult to demonstrate morbidity and mortality benefits in addition to these background agents in improving outcomes in this setting. This is particularly true of sudden cardiac death (SCD), a mode of

death that affects approximately 50% of all systolic heart failure patients [2]. The recent use of implantable cardioverter defibrillators (ICDs) has provided substantial benefit in this regard. As SCD is often, but not always, related to a ventricular tachyarrhythmia, ICDs are particularly effective at circumventing this problem [3–5]. What is unclear is whether more recently studied pharmacological therapies may also have beneficial effects on SCD and how this may compare to the implantation of ICDs. In contrast to drug therapies, ICDs have expensive up-front cost and come with their own morbidity related to insertion as well as potential for long-term complications of having hardware reside within the body [6,7].

The purpose of this study was therefore to meta-analyze the impact of medical therapies in addition to background ACE inhibitor and/or BB on SCD and all-cause mortality in participants with left ventricular systolic dysfunction (LVSD) and to compare these with the beneficial effects of ICDs in this regard.

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## 2. Methods

### 2.1. Search strategy

A comprehensive search of English-language publications was conducted in Medline (1946 to May 2013) and Embase (1974 to May 2013). The following keywords were used: systolic heart failure, cardiomyopathy, angiotensin inhibitors, beta-blockers, aldosterone antagonist, defibrillator, sudden cardiac death, and mortality. Manual reference checking of the bibliographies of all retrieved articles was also conducted.

### 2.2. Selection criteria

Studies were eligible if they were randomized placebo-controlled trials examining the effects of medical therapy (in addition to background ACE inhibitors and/or BB) or ICD on SCD in patients with left ventricular ejection fraction (LVEF) of less than 40%. Studies had to have minimum of 100 patients, and there was no minimum duration of time for the trial. Only studies published in English were considered.

### 2.3. Data extraction

Two independent reviewers (KYP and YL) assessed and selected the studies. We aimed to extract data on sudden death and all-cause mortality. All data were reported on intention-to-treat analysis. Unpublished data were not sought.

### 2.4. Assessment of the risk of bias

The assessment of the risk of bias was performed in accordance with the Cochrane Collaboration's handbook [8]. We assessed three aspects of trial quality relevant to this analysis: random sequence generation, degree of blinding, and losses to follow-up. Studies with high or unclear risk of bias for any of the three criteria were considered to be low quality.

### 2.5. Statistical analysis

Statistical analysis was performed using Review Manager (RevMan) Version 5.2.5 (Cochrane Collaboration) and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [9,10]. The results were pooled using Mantel-Haenszel random effects model given the clinical heterogeneity of the studies included. Risk Ratio (RRs) with 95% confidence interval (CI) were derived from each individual study and determined for overall outcome, and the significance of risk ratio (RR) was performed using Z-test. A weighting was calculated based on the number of events that occurred in each study. Sensitivity analyses were performed excluding post-myocardial infarction (MI) studies to determine whether there was a differential effect versus non-ischemic heart failure and heart failure remote from an MI. A further sensitivity analysis was performed excluding trials of low quality. A test for interaction was used to estimate differences between the subgroups [11]. Potential publication bias was estimated visually by funnel plots which plot the trials' effect estimates against sample size [12]. Precision in estimating the underlying treatment effect increases as the sample size of individual studies increases, with small studies scattering widely at the bottom and larger studies with greater precision scattering more narrowly at the top. The plot will take on the appearance of a symmetrical inverted funnel with all studies falling within the triangle (2 standard deviations of the effect estimate) if bias is not present. An Egger regression asymmetry test was applied [12].

## 3. Results

### 3.1. Search results

The search (Fig. 1) revealed 753 potentially relevant articles through the search engine. In addition, 5 articles were found from hand searches

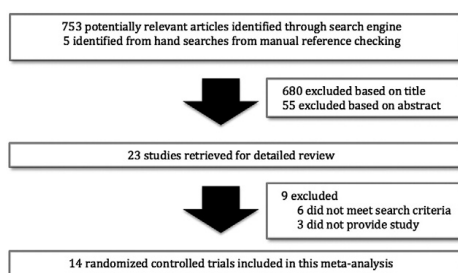


Fig. 1. Flow chart showing the search strategy and exclusion of articles.

following manual reference checking. Six hundred and eighty of these articles were excluded based on title, and a further 55 were excluded based on abstract. Twenty-three studies remained for detailed review. Of these, six were excluded because they did not meet the search criteria with two of these including active comparators. In addition, three studies were excluded because they did not provide data on SCD. Thus, a total of 14 randomized controlled trials were included in this meta-analysis. Ten studies involved drug therapies developed since the introduction of ACE inhibitors and BB as standard of care. These include angiotensin receptor blockers (ARBs) [13–15], mineralocorticoid receptor antagonists (MRAs) [16–18], ivabradine [19], n3-PUFA [20], ferric carboxymaltose [21], and aliskiren [22]. Four studies trialled ICDs [3–5,23]. The characteristics of the participants involved in these trials are summarized in Table 1.

The risk of bias was assessed as low overall. Of the 14 trials, 12 reported adequate randomization except for the RALES and Val-HeFT trial; hence, these two trials were deemed as low quality. All trials involving medications were adequately blinded, and the ICD trials were unblinded. However, this was considered not likely to have influenced outcomes. Losses to follow-up were low and generally equal across all trials.

### 3.2. Sudden cardiac death (SCD)

Overall, there was a statistically significant reduction in SCD with drug therapies when compared with placebo ( $n = 36,172$ ,  $RR = 0.89$  [0.82–0.98],  $p = 0.02$ ) (Fig. 2). This result was unchanged when studies of low quality were excluded ( $n = 29,499$ ,  $RR = 0.89$  [0.80–0.98],  $p = 0.02$ ). When post-MI studies were excluded, there was a borderline statistically significant reduction in the risk of SCD compared with placebo ( $n = 29,540$ ,  $RR = 0.91$  [0.82–1.00],  $p = 0.05$ ) (Fig. 3). MRAs alone compared with placebo were most effective in reducing SCD by 21% ( $n = 11,032$ ,  $RR = 0.79$  [0.68–0.91],  $p = 0.001$ ) (Fig. 4). ICD insertion greatly reduced SCD by 61% ( $n = 4,269$ ,  $RR = 0.39$  [0.30–0.51],  $p < 0.00001$ ) compared with placebo (Fig. 5). The test of interaction indicated that the difference in treatment effect between the ICD and the drug therapy was significant ( $p < 0.002$ ), and between ICD and MRAs also significant ( $p < 0.002$ ).

### 3.3. All-cause mortality

Drug therapies in addition to background ACE inhibitors and/or BB significantly reduced the risk of all-cause mortality compared to placebo by 10% overall ( $n = 36,172$ ,  $RR = 0.90$  [0.85–0.95],  $p = 0.0002$ ) (Fig. 6). This result was unchanged when studies of low quality were excluded ( $n = 29,499$ ,  $RR = 0.91$  [0.87–0.95],  $p < 0.0001$ ). ICD insertion reduced all-cause mortality by 26% ( $n = 4,269$ ,  $RR = 0.74$  [0.65–0.83],  $p < 0.00001$ ) (Fig. 7).

### 3.4. Assessment of potential publication bias

No evidence of publication bias was suggested by visual inspection of the funnel plots (Fig. 8) and the Egger regression asymmetry test ( $p = 0.13248$ ).

## 4. Discussion

Sudden cardiac death generally refers to an unexpected death from a cardiovascular cause in a person with or without pre-existing heart disease [24]. SCD ranges from 50 to 100 per 100,000 in the general population [24]. It has been known that ACE inhibitors and beta-blockers do offer protection against SCD [25,26]. However, it is unclear whether more recently studied pharmacological therapies when added to ACE inhibitors and/or beta-blockers may also have beneficial effects on SCD and how this may compare to SCD reduction observed with the implantation of ICDs.

**Table 1**  
Characteristics of the trials included in the meta-analysis.

Trial	Trial design	No. of patients	Follow-up time	Intervention	Control	Background medical therapy for both intervention and control group	Inclusion criteria	Age	NYHA	Primary causes of HF	Quality of study
RALES 1999 (16)	RCT PC DB	1663	24.0 months	Spironolactone 25 mg daily	Placebo	ACEi: 95% BB: 11% Diuretic: 100%	LVEF $\leq$ 35%	65.0 $\pm$ 12.0	III–IV	Ischemic: 54% Non-ischemic: 46%	Low
Val-HeFT 2001 (13)	RCT PC DB	5010	23.0 months	Valsartan 160 mg BD	Placebo	ACEi: 92.6% BB: 34.5% Diuretic: 85.8%	LVEF < 40%	63.0 $\pm$ 10.8	II–IV	Ischemic: 54.8% Non-ischemic: 45.2%	Low
EPHESUS 2003 (17)	RCT PC DB	6632	16.0 months	Eplerenone 50 mg daily	Placebo	ACEi/ARB: 86% BB: 75% Diuretic: 60%	3–14 days post-MI LVEF $\leq$ 40%	64.0 $\pm$ 11.0	Not stated	Not stated	High
CHARM-Added 2003 (15)	RCT PC DB	2548	41.0 months	Candesartan 32 mg daily	Placebo	ACEi: 100% BB: 55% MRA: 17% Diuretic: 90%	LVEF $\leq$ 40%	64.0	II–IV	Ischemic: 62.2% Non-ischemic: 37.8%	High
CHARM-Alternative 2003 (14)	RCT PC DB	2028	33.7 months	Candesartan 32 mg daily	Placebo	No ACEi BB: 54.6% MRA: 24.7% Diuretic: 85.3%	LVEF $\leq$ 40% Intolerance to ACEi	66.3	II–IV	Ischemic: 69.7% Non-ischemic: 30.3%	High
GISSI-HF 2008 (20)	RCT PC DB	6975	46.8 months	n-3 PUFA 1 g daily	Placebo	ACEi: 77.2% ARB: 19.3% BB: 65.1% MRA: 38.6% Diuretic: 89.5%	Any LVEF (average LVEF 33%)	67.0	II–IV	Ischemic: 49.1% Non-ischemic: 50.9%	High
FAIR-HF 2009 (21)	RCT PC Single blinded	459	6.0 months	Ferric carboxymaltose 200 mg IV	Placebo (saline)	ACEi/ARB: 92.4% BB: 86.2% Diuretic: 92.1%	LVEF $\leq$ 40% (NYHA II) or $\leq$ 45% (NYHA III) Iron deficiency (ferritin <100 $\mu$ g/L or transferrin saturation <20%) Anemia: Hb 95–135	67.8 $\pm$ 10.3	II–III	Ischemic: 80.6% Non-ischemic: 19.4%	High
SHIFT 2010 (19)		6505	22.9 months		Placebo			60.7	II–IV		High

(continued on next page)

Table 1 (continued)

Trial	Trial design	No. of patients	Follow-up time	Intervention	Control	Background medical therapy for both intervention and control group	Inclusion criteria	Age	NYHA	Primary causes of HF	Quality of study
	RCT PC DB			Ivabradine 7.5 mg BD		ACEi: 79% ARB: 14% BB: 89% Diuretic: 84% MRA: 81%	LVEF $\leq$ 35% Sinus rhythm Hospitalization within the last 12 months Symptomatic heart failure			Ischemic: 68% Non-ischemic: 32%	
EMPHASIS HF 2011 (18)	RCT PC DB	2737	21.0 months	Eplerenone 50 mg daily	Placebo	ACEi: 78.3% ARB: 19.1% BB: 86.6% Diuretic: 84.3%	LVEF $\leq$ 30%	68.0 $\pm$ 7.0	II	Ischemic: 69.7% Non-ischemic: 30.3%	High
ASTRONAUT 2013 (22)	RCT	1617	11.3 months	Aliskiren 150 mg, up to 300 mg daily if tolerated	Placebo	ACEi/ARB: 84.9% BB: 81.7% Diuretic: 95.9% MRA: 39.5%	LVEF $\leq$ 40%	64.6	I–IV	Ischemic: 63% Non-ischemic: 37%	High
MADIT-II 2002 (5)	RCT	1232	20.0 months	ICD	Standard medical therapy	ACEi: 68% BB: 70% Diuretic: 72%	LVEF $\leq$ 30%	64.0 $\pm$ 10.0	I–IV	Not stated	High
DEFINITE 2004 (23)	RCT	458	29.0 $\pm$ 14.4 months	ICD	Standard medical therapy	ACEi: 83.8% ARB: 13.5% BB: 85.6% Diuretic: 87.3%	LVEF $\leq$ 35% Non-ischemic cardiomyopathy	58.4	I–III	Non-ischemic: 100%	High
COMPANION 2005 (4)	RCT	903	15.7 months	CRT + ICD	Standard medical therapy	ACEi/ARB: 90% BB: 68% Diuretic: 97% MRA: 55%	QRS $\geq$ 120 msec LVEF $\leq$ 35% PR interval >150 msec	67.0	III–IV	Ischemic: 55% Non-ischemic: 45%	High
SCD-HEFT 2005 (3)	RCT	1676	45.5 months	ICD * not using amiodarone arm	Placebo drug	ACEi: 83% ARB: 14% BB: 69% Diuretic: 82% MRA: 20%	Sinus rhythm LVEF $\leq$ 35%	60.1	II–III	Not stated	High

ACEi: angiotensin converting enzyme inhibitors; AML: acute myocardial infarction; ARB: angiotensin receptor blocker; BB: beta blockers; CHF: chronic heart failure; DB: double-blind; MRA: mineralocorticoid receptor antagonist; OR: odds ratio; PC: placebo controlled; RCT: randomized controlled trial;  $\downarrow$ : decreased



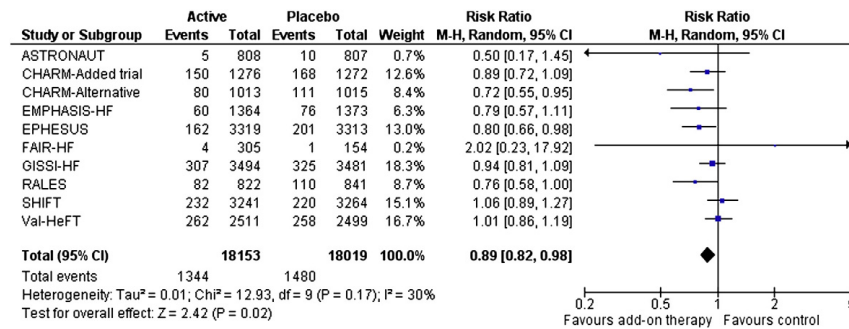


Fig. 2. Effect of drug therapies (when added to background ACE inhibitors and/or beta-blockers) on sudden cardiac death.

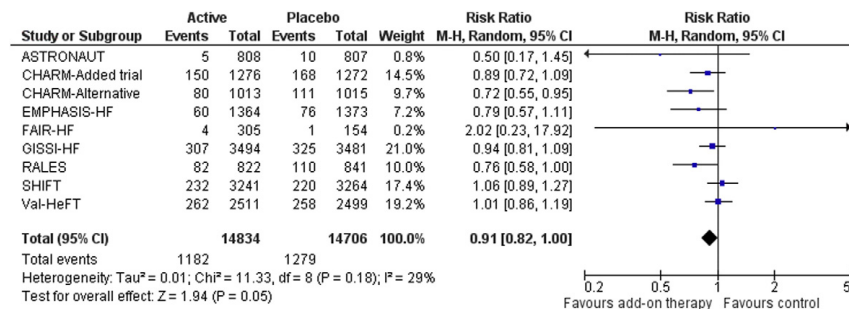


Fig. 3. Effect of drug therapies (when added to background ACE inhibitors and/or beta-blockers) without post myocardial infarction studies on sudden cardiac death.

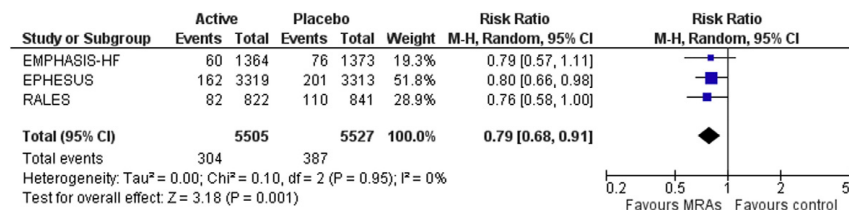


Fig. 4. Effect of mineralocorticoid receptor antagonists on sudden cardiac death.

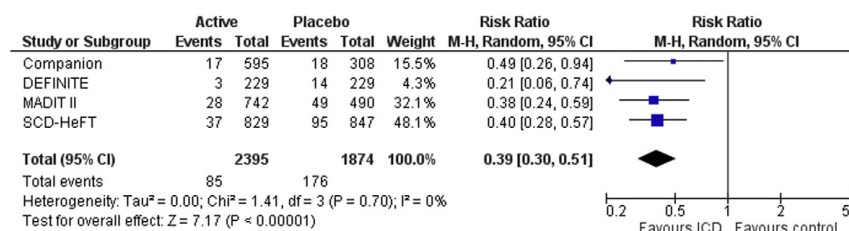


Fig. 5. Effect of implantable cardioverter defibrillators on sudden cardiac death.

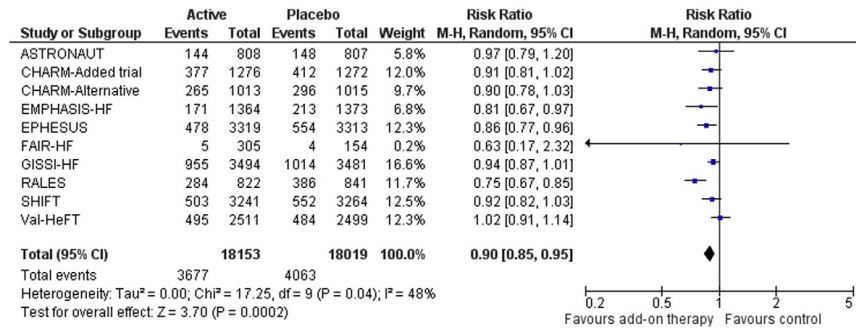


Fig. 6. Effect of drug therapies (when added to background ACE inhibitors and/or beta-blockers) on all-cause mortality.

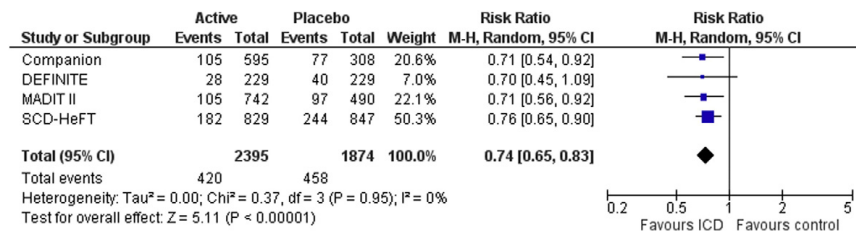


Fig. 7. Effect of implantable cardioverter defibrillators on all-cause mortality.

The present meta-analysis has found that drug therapies added to background ACE inhibitor and beta-blocker significantly reduced the incidence of SCD in major clinical trials. This was particularly driven by the effect of MRAs. When MRAs alone were analyzed, a consistent and overall significant benefit on SCD was observed. This is consistent with the putative mechanism of action of MRAs. In addition to conferring electrical stability within the myocardium due to antifibrotic and other effects, these agents lessen the risk of hypokalemia, a frequent trigger for ventricular tachyarrhythmia and sudden death [27–29].

Nevertheless, despite these benefits, reductions in SCD observed with add-on drug therapies pale in comparison to those of ICDs. Overall,

ICDs more than halved the risk of SCD. However, they do come as mentioned with high up-front financial costs as well as the peri-procedural and long-term risks of having hardware implanted in the patient [6,7].

Careful economic analysis is required of both of these therapeutic modalities to determine the most cost-effective way of reducing SCD in patients with systolic LV dysfunction and heart failure. Furthermore, based on the present analysis, the combination of MRAs and ICD would appear to offer the best defence against SCD in the systolic heart failure LV dysfunction patient. However, trials to formally assess the combination of these approaches have not as yet been conducted [30].

With regard to outcomes on all-cause mortality, drug therapies added to background ACE inhibitor and/or beta-blocker reduce the risk of all-cause mortality significantly compared to placebo. Notably, the positive effects on all-cause mortality came predominantly from trials of MRAs [16–18]. ICDs were associated with a greater absolute reduction in all-cause mortality compared to placebo. This is primarily driven by the reduction in SCD with ICDs. In addition, the relative reduction in all-cause mortality was of lesser magnitude than its benefit on SCD. This may indicate that although ICDs come with significant sudden death benefits, there may be associated offsetting peri-procedural risks. The greater benefit of ICD on SCD compared to all-cause mortality can also be due to greater detection of SCD and immediate intervention with ICD.

There were some limitations in our study. We only included trials with data on SCD. We had to rely on published data rather than individual patient data. In addition, we excluded non-English trials and so could have missed some relevant trials. There is also a different duration of follow-up across studies, with some studies having shorter (<24 months) follow-up times, and it may be that longer follow-up time may be required for medical therapy to achieve significant benefit.

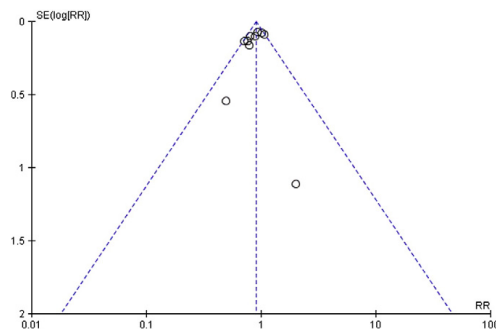


Fig. 8. Funnel plot for add-on therapies, demonstrating no publication bias.

The strengths of this meta-analysis is the inclusion of a large number of randomized controlled trials with varied therapies, which may reflect the mix of pharmacotherapy used by heart failure patients in the real-world setting rather than in the controlled settings of clinical trials assessing singular therapies. It is difficult to construct scientifically rigorous studies in which a number of different medications are evaluated, and meta-analysis may therefore be the best tool for assessing the overall effect of a number of discrete interventions. There is no significant detectable publication bias in this report, confirmed by minimal funnel plot asymmetry and Egger's test (Fig. 8). This and the consistency of the results when trials at high risk of bias were excluded indicate that our results are likely to be robust.

In conclusion, the present analysis has found that drug therapies when added to background ACE inhibitors and/or BB do overall confer a statistically significant benefit in reducing SCD in patients with systolic HF, primarily driven by MRAs providing consistent reductions in SCD across trials. In contrast, SCD was reduced by >50% in ICD trials.

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None.

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None.

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## Appendix 3.5

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### *Systematic review and meta-analysis*

Wu S, **Hopper I**, Skiba M, Krum H. Dipeptidyl peptidase-4 inhibitors and cardiovascular outcomes: Meta-analysis of randomized clinical trials with 55,141 participants. *Cardiovascular Therapeutics*. 2014; 32:147-58.

## Dipeptidyl Peptidase-4 Inhibitors and Cardiovascular Outcomes: Meta-Analysis of Randomized Clinical Trials with 55,141 Participants

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### Keywords

DPP-4 inhibitors; Heart failure hospitalization; Meta-analysis; Myocardial infarction; Stroke; Type 2 diabetes.

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### ABSTRACT

**Aims:** The association between glucose lowering in diabetes mellitus and major cardiovascular (CV) outcomes is weak; indeed, some oral hypoglycemic agents are associated with increased CV events. Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) are a new class of oral hypoglycemic agent that may have beneficial CV effects. We undertook a systematic review and meta-analysis to appraise the CV safety and efficacy of DPP-4 inhibitors.

**Methods:** Comprehensive search for prospective trials involving DPP-4 inhibitors. Trials included reported at least one of the outcomes examined, recruited minimum 100 patients and minimum follow-up 24 weeks. The risk ratio (RR) was calculated using the Mantel–Haenszel random-effects model for mortality and major cardiovascular (CV) outcomes.

**Results:** Fifty trials enrolling 55,141 participants were included. Mean follow-up 45.3 weeks. DPP-4 inhibitors compared with all comparators (placebo and active) showed no difference in all-cause mortality ( $n = 50,982$ ,  $RR = 1.01$ , 95% CI 0.91–1.13,  $P = 0.83$ ), CV mortality ( $n = 48,151$ ,  $RR = 0.97$ , 95% CI 0.85–1.11,  $P = 0.70$ ), acute coronary syndrome (ACS) ( $n = 53,034$ ,  $RR = 0.97$ , 95% CI 0.87–1.08,  $P = 0.59$ ), or stroke ( $n = 42,737$ ,  $RR = 0.98$ , 95% CI 0.81–1.18,  $P = 0.80$ ), and a statistically significant increase in heart failure outcomes ( $n = 39,953$ ,  $RR = 1.16$ , 95% CI 1.01–1.33,  $P = 0.04$ ). **Discussion:** Treatment with DPP-4 inhibitors compared with placebo shows no increase in risk with regards to all-cause mortality, CV mortality, ACS, or stroke, but a statistically significant trend toward increased risk of HF outcomes. **Conclusion:** These findings suggest no cardiovascular harm (or benefit) with DPP-4 inhibitors; further large-scale CV outcome studies will resolve the issue of excess HF risk.

### Introduction

Diabetes mellitus is a major public health problem. It is projected that, by 2025, there will be 380 million people with type 2 diabetes and 418 million people with impaired glucose tolerance [1]. It is associated with considerable morbidity and mortality, particularly involving cardiovascular (CV) complications. Such complications include accelerated atherosclerosis, myocardial infarction and stroke, as well as increased rates of heart failure [2].

In addition to insulin, a number of oral glucose-lowering drug classes have been developed, which have proven extremely effective at improving glycemic control in diabetics, whether as monotherapy or in combination. However, it has been somewhat difficult to demonstrate that improved glycemic control with these agents has translated into reductions in major CV outcomes [3]. Furthermore, some hypoglycemic agents, for example, the thiazolidinediones, have been associated with increased CV

adverse effects such as myocardial infarction [4] and fluid retention/heart failure [5]. Subsequent to these and other observations, the FDA mandated long-term CV outcome studies for all diabetes drugs [6].

The dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of oral hypoglycemic agent possessing pharmacological actions that would suggest potentially beneficial effects on CV outcomes [7]. They are effective as blood glucose-lowering agents, with less risk of hypoglycemia and a more favorable weight profile than sulfonylureas [8]. Meta-analyses of earlier trials have suggested that DPP-4 inhibitors confer considerable CV benefit [9,10]; however, lack of long-term CV outcome trial data has been a major shortcoming. Such data on the long-term safety and efficacy of this class in Phase 3 trials are only just now emerging. We therefore undertook a systematic review of all available data to appraise the effect of DPP-4 inhibitors on major CV outcomes.

## Methods

### Data Sources and Searches

Studies were identified via MEDLINE (source PubMed, 2005 to February 2014) and EMBASE (2005 to February 2014). All searches included the keywords and corresponding MeSH terms for diabetes mellitus type 2, randomized controlled trial, and dipeptidyl peptidase-4 inhibitors ("gliptins"). Manual reference checking was performed on the bibliographies of all retrieved articles. Unpublished data were sought by interrogating the largest clinical trials registry site, clinicaltrials.gov, using the search terms "sitagliptin," "saxagliptin," "vildagliptin," "linagliptin," and "alogliptin". Study authors were also contacted for further information.

### Study Selection

Prospective randomized controlled trials conducted in adults assessing the effects of DPP-4 inhibitors in participants with type 2 diabetes mellitus and published in English were considered. Studies were excluded if they had fewer than 100 participants, follow-up of less than 24 weeks, relevant data could not be extracted or studies were open label (Figure 1). Independent assessment of the trials was performed by two authors (SW and MS). Disagreements were resolved by consensus in discussion with other authors (IH and HK).

### Data Extraction and Quality Assessment

We sought to extract data on outcomes including all-cause mortality, CV mortality, acute coronary syndrome (ACS), stroke, and heart failure (HF) outcomes. For adjudicated trials, the data were extracted from tables included in the trial reports preferentially or in the Serious Adverse Events section on clinicaltrials.gov. Some trials had mortality reported in the safety or adverse events section of the text, and if unavailable elsewhere, these data were used. If mortality was not reported

in either the manuscript reporting on the trial or available in the Serious Adverse Events section on the clinicaltrials.gov website, then these data were not included, rather than assuming a result of zero. ACS was considered to be fatal or nonfatal MI and unstable angina. Stroke was considered to be stroke, cerebrovascular accident, cerebral infarction, ischemic stroke, cerebral ischemia, thalamic infarction, cerebellar infarction, hemorrhagic stroke, cerebral hemorrhage, and cerebellar hemorrhage. Transient ischemic attack was not included. Heart failure outcomes included clinically significant HF episodes and HF hospitalization.

When trials had multiple treatment arms, if a gliptin was present in any of the treatment groups, it was assigned to the gliptin group, and any treatment group that did not include a gliptin was assigned to either the placebo or comparator groups, as appropriate. Placebo and comparator were grouped together in the "all" analysis, and split for the "placebo" and "comparator" groups, and compared to the gliptin intervention group. If the trial had variable doses of gliptins, these were grouped together. Data from extension trials were used in preference to the shorter initial trial if the participants remained blinded; however, open-label extension trials were excluded.

Various sensitivity analyses were performed, as indicated.

The Cochrane Collaboration risk of bias tool was used [11]. Criteria used for quality assessment included random sequence generation, allocation concealment, blinding of participants and personnel, outcome assessment, and incomplete outcome data. Studies with high or unclear risk of bias for any of the first three criteria were considered to be low quality. A sensitivity analysis was performed for each outcome, excluding reports at high overall risk of bias.

### Data Synthesis and Analysis

The statistical analysis was performed in line with recommendations from the Cochrane Collaboration using Review Manager (RevMan), version 5.2 [12] and was reported according to the PRISMA guidelines [13]. The results were pooled using Mantel-Haenszel random-effects model, given the clinical heterogeneity of the studies selected. Risk ratios (RRs) with 95% confidence intervals (CIs) were derived from each individual study and determined for overall outcome, and the significance of RRs was tested with the Z-test. A weighting was calculated based on the number of events that occurred in each study. Potential publication bias was assessed by funnel plot symmetry.

### Role of the Funding Source

The funding sources had no role in the collection, analysis, and interpretation of the data or in the decision to submit the manuscript for publication.

## Results

### Search Results

The search of the literature identified 1244 titles (Figure 1). Full manuscripts were received for 265 trials, of which 50 were

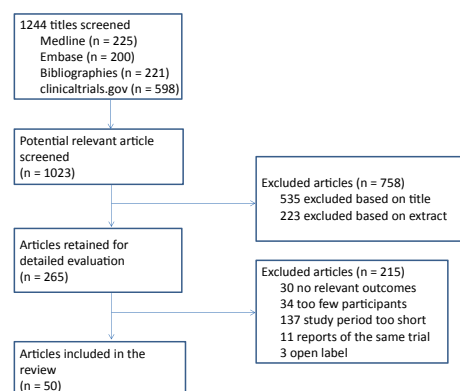


Figure 1 PRISMA search strategy

**Table 1** Characteristics of included studies

Trial	NCT	n	Participants	Intervention	Comparator	Outcomes	Duration (weeks)
Arechavaleta <i>et al.</i> (2011) <sup>14</sup>	NCT00701090	1035	TN/IC	SITA	SULF	HbA1c	30
Aschner <i>et al.</i> (2010) <sup>15</sup>	NCT00449930	1050	TN	SITA	MET	HbA1c	24
Barnett <i>et al.</i> (2012) (1) <sup>16</sup>	NCT00740051	227	IGC	LINA	PBO/SULF	HbA1c	52
Barnett <i>et al.</i> (2012) (2) <sup>17</sup>	NCT00757588	455	IGC	SAXA	PBO	HbA1c	24
Bergental (2010) <sup>18</sup>	NCT00637273	491	Stable	SITA	Exenatide/PIO	HbA1c	26
Bolli <i>et al.</i> (2009) <sup>19</sup>	NCT00237237	576	IGC	VILDA	PIO	HbA1c	52
Bosi <i>et al.</i> (2007) <sup>20</sup>	NCT00099892	544	IGC	VILDA	PBO	HbA1c	24
Bosi <i>et al.</i> (2009) <sup>21</sup>	NCT00468039	1179	TN	VILDA	MET	HbA1c	24
Bosi <i>et al.</i> (2011) <sup>22</sup>	NCT00432276	803	IGC	ALOG	PIO	HbA1c	52
Chacra <i>et al.</i> (2011) <sup>23</sup>	NCT00313313	768	IGC	SAXA	PBO	HbA1c	24
Charbonnel <i>et al.</i> (2006) <sup>24</sup>	NCT00086515	701	IGC	SITA	PBO	HbA1c	24
DeFronzo <i>et al.</i> (2008) <sup>25</sup>	NCT00286455	328	TN	ALOG	PBO	HbA1c	26
DeFronzo <i>et al.</i> (2009) <sup>26</sup>	NCT00121667	743	IGC	SAXA	PBO	HbA1c	206
Ferrannini <i>et al.</i> (2009) <sup>27</sup>	NCT00106340	2789	IGC	VILDA	SULF	HbA1c	52
Fonseca <i>et al.</i> (2007) <sup>28</sup>	NCT00099931	296	IGC	VILDA	PBO	HbA1c	24
Frederich <i>et al.</i> (2012) <sup>29</sup>	NCT00316082	365	TN	SAXA	PBO	HbA1c	24
Gallwitz <i>et al.</i> (2012) <sup>30</sup>	NCT00622284	1551	Stable	LINA	SULF	HbA1c	104
Goke <i>et al.</i> (2008) <sup>31</sup>	NCT00138567	462	TN	VILDA	MET	HbA1c	104
Goke <i>et al.</i> (2010) <sup>32</sup>	NCT00575588	858	TN	SAXA	SULF	HbA1c	52
Gomis <i>et al.</i> (2011) <sup>33</sup>	NCT00641043	389	TN/IC	LINA	PBO	HbA1c	24
Haak <i>et al.</i> (2012) <sup>34</sup>	NCT00798161	857	TN/IC	LINA	PBO/MET	HbA1c	24
Hermans <i>et al.</i> (2012) <sup>35</sup>	NCT01006590	286	IGC	SAXA	MET	HbA1c	24
Hermansen <i>et al.</i> (2007) <sup>36</sup>	NCT00106704	441	IGC	SITA	PBO	HbA1c	24
Hollander <i>et al.</i> (2011) <sup>37</sup>	NCT00295633	565	IGC	SAXA	PBO	HbA1c	24
Jadzinsky <i>et al.</i> (2009) <sup>38</sup>	NCT00327015	1306	TN	SAXA	MET	HbA1c	24
Kawamori <i>et al.</i> (2012) <sup>39</sup>	NCT00654381	481	TN/IC	LINA	Voglibose	HbA1c	26
McMurray <i>et al.</i> (2013) <sup>40</sup>	NCT00894868	253	NYHA I-III HF	VILDA	PBO	LVF	52
Nauck <i>et al.</i> (2009) <sup>41</sup>	NCT00286442	527	IC	ALOG	PBO	HbA1c	26
NCT00509262 <sup>42</sup>	NCT00509262	422	RI	SITA	SULF	HbA1c	54
NCT00722371 <sup>43</sup>	NCT00722371	1615	NR	SITA	PIO	HbA1c	54
Nowicki <i>et al.</i> (2011) <sup>44</sup>	NCT00614939	170	RI	SAXA	PBO	HbA1c	52
Owens <i>et al.</i> (2011) <sup>45</sup>	NCT00602472	1055	IGC	LINA	PBO	HbA1c	24
Pan <i>et al.</i> (2012) <sup>46</sup>	NCT00698932	568	TN	SAXA	PBO	HbA1c	24
Perez-Monteverde <i>et al.</i> (2011) <sup>47</sup>	NCT00541450	492	TN	SITA	PIO	HbA1c	40
Plutzner <i>et al.</i> (2011) <sup>48</sup>	NCT00327015	1306	TN	SAXA	MET	HbA1c	76
Pratley <i>et al.</i> (2009) (1) <sup>49</sup>	NCT00286494	493	IGC	ALOG	PBO	HbA1c	26
Pratley <i>et al.</i> (2009) (2) <sup>50</sup>	NCT00286468	500	IGC	ALOG	PBO	HbA1c	26
Raz <i>et al.</i> (2008) <sup>51</sup>	NCT00337610	190	Stable	SITA	PBO	HbA1c	30
Rosenstock <i>et al.</i> (2009) (1) <sup>52</sup>	NCT00121641	401	IGC	SAXA	PBO	HbA1c	24
Rosenstock <i>et al.</i> (2009) (2) <sup>53</sup>	NCT00286429	389	TN	ALOG	PBO	HbA1c	26
Scherbaum <i>et al.</i> (2008) <sup>54</sup>	NCT00300287	306	TN	VILDA	PBO	HbA1c	52
Schweizer <i>et al.</i> (2007) <sup>55</sup>	NCT00099866	780	TN	VILDA	MET	HbA1c	52
Schweizer <i>et al.</i> (2009) <sup>56</sup>	NCT00383578	335	TN elderly	VILDA	MET	HbA1c	24
Scirica <i>et al.</i> (2013) <sup>57</sup>	NCT01107886	16,492	CVD or RF	SAXA	PBO	Comp: CV death, MI, stroke	101
Seck <i>et al.</i> (2010) <sup>58</sup>	NCT00094770	1172	Stable	SITA	SULF	HbA1c	104
Taskinen <i>et al.</i> (2011) <sup>59</sup>	NCT00601250	700	IGC	LINA	PBO	HbA1c	24
Vilsboll <i>et al.</i> (2010) <sup>60</sup>	NCT00395343	641	IGC	SITA	PBO	HbA1c	24
White <i>et al.</i> (2013) <sup>61</sup>	NCT00968708	5380	Recent ACS	ALOG	PBO	Comp: CV death, MI, stroke	72
Williams-Herman <i>et al.</i> (2010) <sup>62</sup>	NCT00103857	1091	IGC	SITA	MET	HbA1c	104
Yoon <i>et al.</i> (2012) <sup>63</sup>	NCT01028391	317	TN	SITA	PBO	HbA1c	54

ACS, Acute coronary syndrome; ALOG, alogliptin; Comp, Composite; CVD or RF, cardiovascular disease or risk factors; HbA1c, Hemoglobin A1c; HF, heart failure; IGC, inadequate glycaemic control; LINA, linagliptin; MET, metformin; MI, myocardial infarction; NCT National Clinical Trial number; NR, not recorded; NYHA, New York Heart Association class; PBO, placebo; PIO, pioglitazone; RI, renal impairment; TN, treatment naïve; SAXA, saxagliptin; SITA, sitagliptin; SULF, sulphonylurea; VILDA, vildagliptin.

**Table 2** Baseline characteristics of participants in included studies

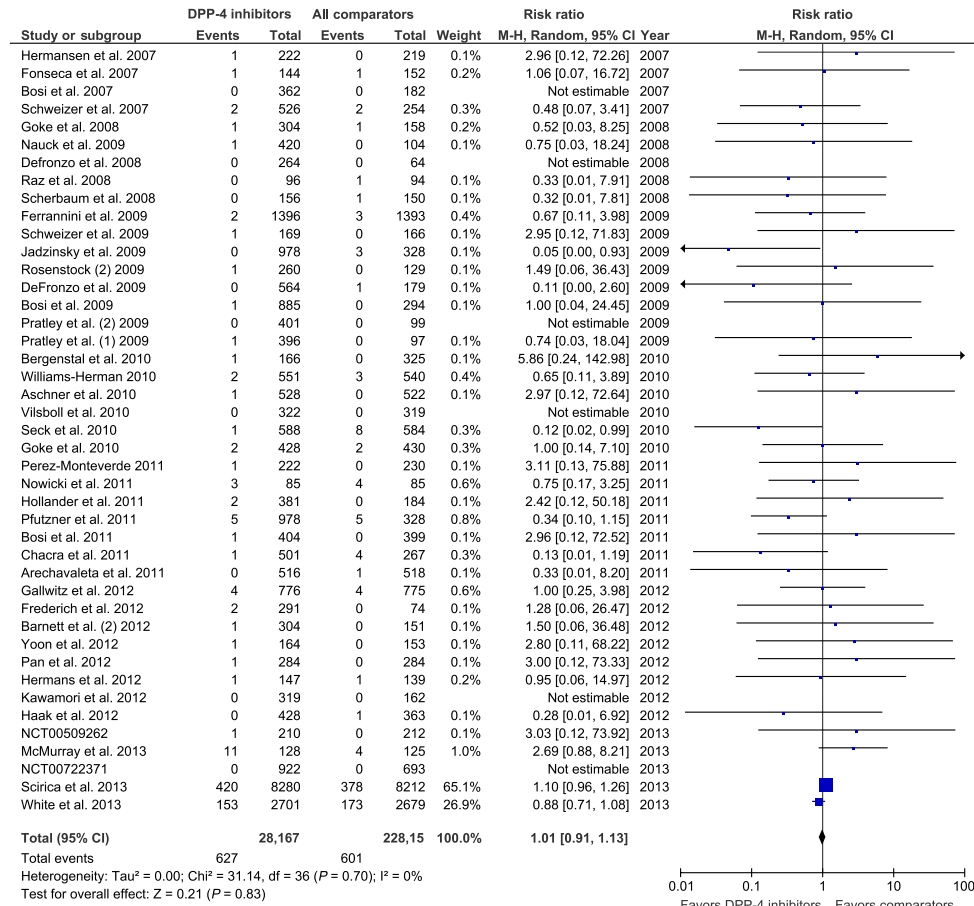
Trial	Age (years)	Males (%)	HbA1c (%)	Mean duration of DM (years)	Bodyweight (kg)	BMI (kg/m <sup>2</sup> )
Arechavaleta <i>et al.</i> (2011) <sup>14</sup>	56	54.4	7.5	6.7	81	30
Aschner <i>et al.</i> (2010) <sup>15</sup>	56	46.1	7.3	2.4	84.7	30.8
Barnett <i>et al.</i> (2012) (1) <sup>16</sup>	56	38.8	8.1	3	78	29.5
Barnett <i>et al.</i> (2012) (2) <sup>17</sup>	57	41.3	8.7	11.9	86.7	32.1
Bergental (2010) <sup>18</sup>	53	51.7	8.5	5.7	87	32
Bolli <i>et al.</i> (2009) <sup>19</sup>	57	62.8	8.4	6.4	91.6	32.2
Bosi <i>et al.</i> (2007) <sup>20</sup>	54	46	8.4	6.2	NR	32.9
Bosi <i>et al.</i> (2009) <sup>21</sup>	53	58	8.6	24.3	88.3	31.3
Bosi <i>et al.</i> (2011) <sup>22</sup>	55	51.6	8.2	7.2	88.1	31.5
Chacra <i>et al.</i> (2011) <sup>23</sup>	55	45.1	8.4	6.9	NR	29.1
Charbonnel <i>et al.</i> (2006) <sup>24</sup>	55	57.1	8	4.6	NR	31
DeFronzo <i>et al.</i> (2008) <sup>25</sup>	53	53.2	7.9	NR	NR	NR
DeFronzo <i>et al.</i> (2009) <sup>26</sup>	55	50.7	8.1	6.5	87	31.4
Ferrannini <i>et al.</i> (2009) <sup>27</sup>	57	53.4	7.3	5.7	NR	31.8
Fonseca <i>et al.</i> (2007) <sup>28</sup>	59	51.4	8.4	14.7	NR	33.1
Frederich <i>et al.</i> (2012) <sup>29</sup>	55	46	7.9	1.7	85	30.5
Gallwitz <i>et al.</i> (2012) <sup>30</sup>	60	60.2	7.7	5	86.5	35.3
Goke <i>et al.</i> (2008) <sup>31</sup>	54	NR	8.6	2.4	94.4	32.7
Goke <i>et al.</i> (2010) <sup>32</sup>	58	51.7	7.7	5.5	88.6	31.4
Gomis <i>et al.</i> (2011) <sup>33</sup>	58	60.9	8.6	NR	79.8	29
Haak <i>et al.</i> (2012) <sup>34</sup>	55	50.6	8.7	2.5	78.5	29.1
Hermans <i>et al.</i> (2012) <sup>35</sup>	59	57.3	7.8	6.5	NR	31.7
Hermansen <i>et al.</i> (2007) <sup>36</sup>	56	53.1	8.3	8.8	86.2	31
Hollander <i>et al.</i> (2011) <sup>37</sup>	54	49.6	8.3	5.2	80.9	30
Jadzinsky <i>et al.</i> (2009) <sup>38</sup>	52	49.2	9.5	1.7	82.7	30.2
Kawamori <i>et al.</i> (2012) <sup>39</sup>	60	66.8	8	5	NR	24.8
McMurray <i>et al.</i> (2013) <sup>40</sup>	63	76	7.8	NR	NR	29.4
Nauck <i>et al.</i> (2009) <sup>41</sup>	55	50.3	7.9	6	NR	32
NCT00509262 <sup>42</sup>	64	67.1	7.8	NR	NR	NR
NCT00722371 <sup>43</sup>	57	56.5	NR	NR	NR	NR
Nowicki <i>et al.</i> (2011) <sup>44</sup>	67	42.9	8.3	NR	NR	NR
Owens <i>et al.</i> (2011) <sup>45</sup>	58	47.2	8.1	NR	76.7	28.3
Pan <i>et al.</i> (2012) <sup>46</sup>	51	55.5	8.1	1	69.2	25.9
Perez-Monteverde <i>et al.</i> (2011) <sup>47</sup>	51	61	NR	3.2	82.8	29.8
Pfutzner <i>et al.</i> (2011) <sup>48</sup>	52	49.2	9.5	1.7	NR	30.2
Pratley <i>et al.</i> (2009) (1) <sup>49</sup>	55	58.2	8	7.6	NR	32.8
Pratley <i>et al.</i> (2009) (2) <sup>50</sup>	57	52.2	8.1	7.7	NR	30
Raz <i>et al.</i> (2008) <sup>51</sup>	55	46.3	9.2	7.9	81.4	30.2
Rosenstock <i>et al.</i> (2009) (1) <sup>52</sup>	53	50.9	7.9	2.6	90.9	31.9
Rosenstock <i>et al.</i> (2009) (2) <sup>53</sup>	56	41.3	9.3	12.6	88	32.4
Scherbaum <i>et al.</i> (2008) <sup>54</sup>	63	59.5	6.7	2.6	NR	30.2
Schweizer <i>et al.</i> (2007) <sup>55</sup>	53	54.4	8.7	1.04	NR	32.4
Schweizer <i>et al.</i> (2009) <sup>56</sup>	71	48.7	7.7	2.9	NR	29.6
Scirica <i>et al.</i> (2013) <sup>57</sup>	65	67	8	10.3	87.9	31.1
Seck <i>et al.</i> (2010) <sup>58</sup>	57	59.2	7.6	5.7	88.9	31.1
Taskinen <i>et al.</i> (2011) <sup>59</sup>	56	54.1	8.1	5	82.5	29.9
Vilsboll <i>et al.</i> (2010) <sup>60</sup>	58	50.9	8.7	12.5	86.9	31
White <i>et al.</i> (2013) <sup>61</sup>	61	68	8	6.6	NR	31.3
Williams-Herman <i>et al.</i> (2010) <sup>62</sup>	53	50.2	8.7	4	NR	37.9
Yoon <i>et al.</i> (2012) <sup>63</sup>	52	54.2	9.4	2.1	81.7	29.8

DM, diabetes mellitus; NR, not recorded.

included in the meta-analysis, involving 55,141 participants [14–63]. Characteristics of the trials are detailed in Table 1. The number of subjects in each study ranged from 170 to 16,492.

Mean intervention time was 45.3 weeks. All participants had a diagnosis of type 2 diabetes mellitus and were either treatment naïve when enrolled, not achieving adequate control of blood





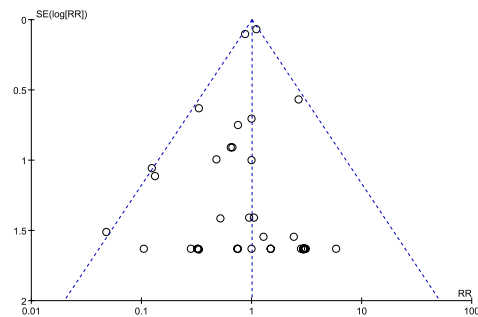
**Figure 2** Forest plot of comparison: 1 DPP-4 inhibitors versus all comparators, outcome: 1.1 all-cause mortality.

sugars on current medications, or had renal impairment, high CV risk, or HF. Twenty-seven trials were placebo-controlled and 21 used an active comparator, while two trials included both placebo and active comparator arms. DPP-4 inhibitors that were trialed included sitagliptin, saxagliptin, vildagliptin, linagliptin, and alogliptin. Active comparators included metformin, sulfonylureas, or thiazolidinediones. Trials with insulin were excluded due to lack of blinding. The primary outcome for most trials was a change in HbA1c over the period of the study, and other measures related to diabetes control, safety, and tolerability. The SAVOR-TIMI-53 [57] and EXAMINE [64] trials had a composite primary outcome of CV death, nonfatal MI, and nonfatal stroke. HF hospitalization was an adjudicated secondary outcome for SAVOR-TIMI-53 and was adjudicated as a component of a secondary endpoint in

EXAMINE. VIVID [40] enrolled subjects with HF and had change in LVEF as its primary outcome, with HF signs and symptoms a secondary outcome.

Baseline characteristics of participants are included in Table 2. The average age was 56.7 years, range 51–71 years, and overall 53.6% of participants were male. Average duration of diabetes was 6.2 years. Background CV medications were only available for EXAMINE, which had 31.4% on ACEi/ARB, 17.5% on beta-blockers, and 48.1% on mineralocorticoid receptor antagonists. Previous cardiac history was only available for SAVOR-TIMI-53, with 37.8% having a previous ACS.

Of the 50 trials included in the meta-analysis, 24 reported adequate random sequence generation, 32 reported adequate allocation concealment and all adequate masking of participants, staff, and



**Figure 3** Funnel plot of comparison: 1 DPP-4 inhibitors versus all comparators, outcome: 1.1 all-cause mortality.

outcome assessors. On the basis of this quality assessment, 20 were deemed to be at low risk of bias and the remainder at high risk.

Data were able to be extracted on outcomes including all-cause mortality, CV mortality, ACS, stroke, and HF outcomes.

## Meta-Analysis

### All-Cause Mortality Outcomes

All-cause mortality was reported in 43 trials with 50,982 participants. Against all comparators (placebo and active), there was no difference in all-cause mortality (RR = 1.01, 95% CI 0.91–1.13,  $P = 0.83$ ) (Figure 2). Two trials (EXAMINE and SAVOR-TIMI 53) contributed 92.0% of the weighting. This result was similar with placebo comparator ( $n = 31,228$ , RR = 1.04, 95% CI 0.93–1.16,  $P = 0.54$ ) and active comparator ( $n = 20,182$ , RR = 0.65, 95% CI 0.39–1.09,  $P = 0.10$ ). Sensitivity analysis including only trials at low risk of bias was similar ( $n = 35,829$ , RR = 0.95, 95% CI 0.74–1.20,  $P = 0.65$ ). Funnel plot symmetry indicated no publication bias (Figure 3).

### CV Mortality Outcomes

CV mortality was reported in 40 trials with 48,151 participants. When DPP-4 inhibitors were compared with all comparators, there was no difference in CV mortality (RR = 0.97, 95% CI 0.85–1.11,  $P = 0.70$ ) (Figure 4). There was no difference with placebo comparator only ( $n = 30,485$ , RR = 0.97, 95% CI 0.85–1.12,  $P = 0.70$ ), nor with active comparator only ( $n = 18,094$ , RR = 0.98, 95% CI 0.44–2.17,  $P = 0.95$ ). Sensitivity analysis including only trials with low risk of bias was similar ( $n = 33,463$ , RR = 0.97, 95% CI 0.85–1.11,  $P = 0.69$ ).

### ACS Outcomes

This was reported in 44 trials with 53,034 participants. There was no difference in ACS against all comparators (RR = 0.97, 95% CI 0.87–1.08,  $P = 0.59$ ) (Figure 5) and against placebo ( $n = 33,227$ , RR = 1.00, 95% CI 0.89–1.12,  $P = 0.98$ ). There was a statistically significant reduction in ACS when DPP-4 inhibitors were

compared with active comparators ( $n = 20,235$ , RR = 0.63, 95% CI 0.41–0.96,  $P = 0.03$ ). Sensitivity analysis including only trials with low risk of bias was similar ( $n = 36,088$ , RR = 1.00, 95% CI 0.88–1.13,  $P = 0.02$ ).

### Stroke Outcomes

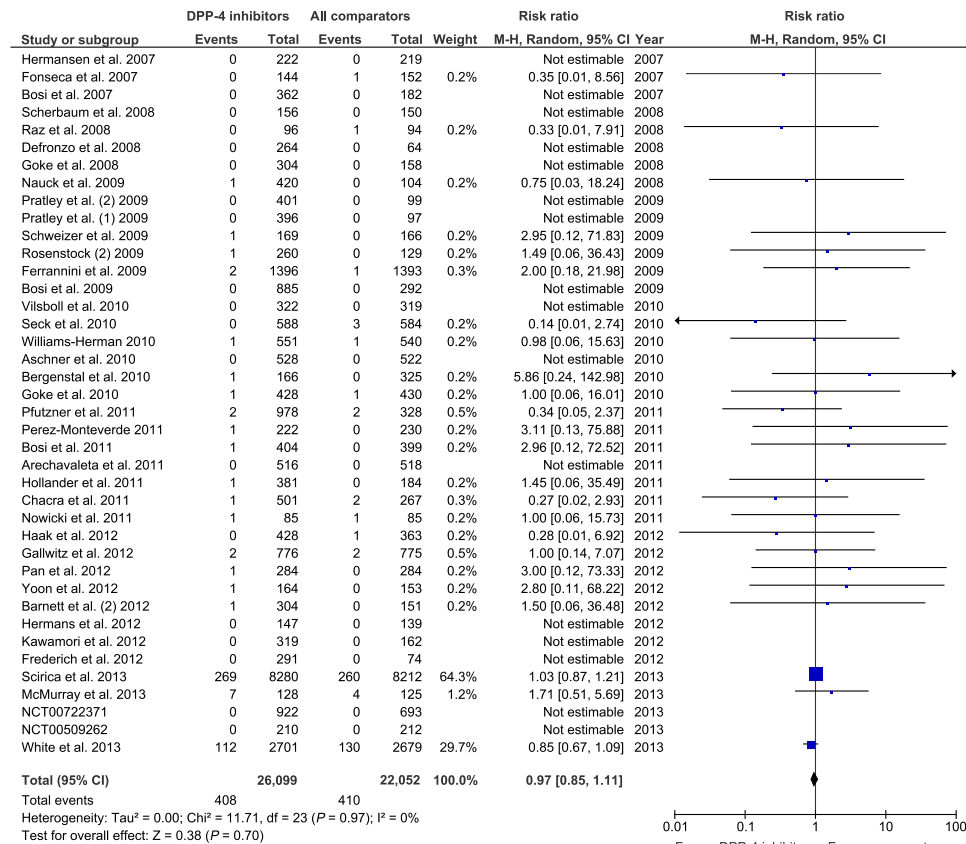
This outcome was reported in 29 trials with 42,737 participants. There was no difference in stroke when DPP-4 inhibitors were compared with all comparators (RR = 0.98, 95% CI 0.81–1.18,  $P = 0.80$ ) (Figure 6) and against placebo comparators ( $n = 28,187$ , RR = 1.05, 95% CI 0.86–1.28,  $P = 0.64$ ). There was a nominally statistically significant reduction in stroke against active comparator ( $n = 14,550$ , RR = 0.48, 95% CI 0.26–0.89,  $P = 0.02$ ). When only trials with low risk of bias were included, there was a similar result ( $n = 32,208$ , RR = 1.00, 95% CI 0.82–1.21,  $P = 0.98$ ).

### Heart Failure Outcomes (Clinically Significant HF/HF Hospitalizations)

This was reported in 24 trials with 39,953 participants. Only the SAVOR-TIMI 53 trial [57] and EXAMINE [64] reported HF hospitalization as an outcome. The data for the other 22 were reports of HF obtained from the published reports or Serious Adverse Events section on the clinical trials registry data. Against all comparators, there was a statistically significant increase in HF outcomes ( $n = 39,953$ , RR = 1.16, 95% CI 1.01–1.33,  $P = 0.04$ ) (Figure 7). This result was dominated by the SAVOR-TIMI-53 trial [57], contributing 66.2% of the weight in the analysis, EXAMINE [64] 21.3%, and the VIVID [40] trial 6.9%. The results were similar when compared to placebo comparator ( $n = 27,818$ , RR = 1.17, 95% CI 1.01–1.34,  $P = 0.03$ ) and were not significant when compared to active comparator ( $n = 12,563$ , RR = 0.80, 95% CI 0.35–1.81,  $P = 0.59$ ). Sensitivity analysis removing the VIVID trial [40] which enrolled only participants with systolic HF and left ventricular ejection fraction (LVEF) < 40% did not alter the result ( $n = 39,700$ , RR = 1.17, 95% CI 1.01–1.35,  $P = 0.03$ ). When only the HF hospitalizations were included (SAVOR-TIMI-53 and EXAMINE), the outcome was again similar ( $n = 21,872$ , RR = 1.21, 95% CI 1.04–1.40,  $P = 0.01$ ). The result lost statistical significance when only trials with low risk of bias were included ( $n = 30,429$ , RR = 1.15, 95% CI 0.98–1.34,  $P = 0.09$ ).

## Discussion

Given the widespread use of oral hypoglycemic agents in the management of diabetes mellitus, there is understandable interest in their overall clinical safety with long-term use. Because of earlier experiences with other drug classes in diabetes management, for example, thiazolidinediones [4,5] and PPAR $\alpha/\gamma$  inhibitors [65], much of this focus has been on CV adverse effects. The DPP-4 inhibitors possess a number of pharmacological attributes that would suggest cardiovascular safety. Additional to glucose lowering, they are weight neutral (or even induce modest weight loss), lower blood pressure, improve postprandial lipemia, reduce inflammatory markers, diminish oxidative stress, and improve

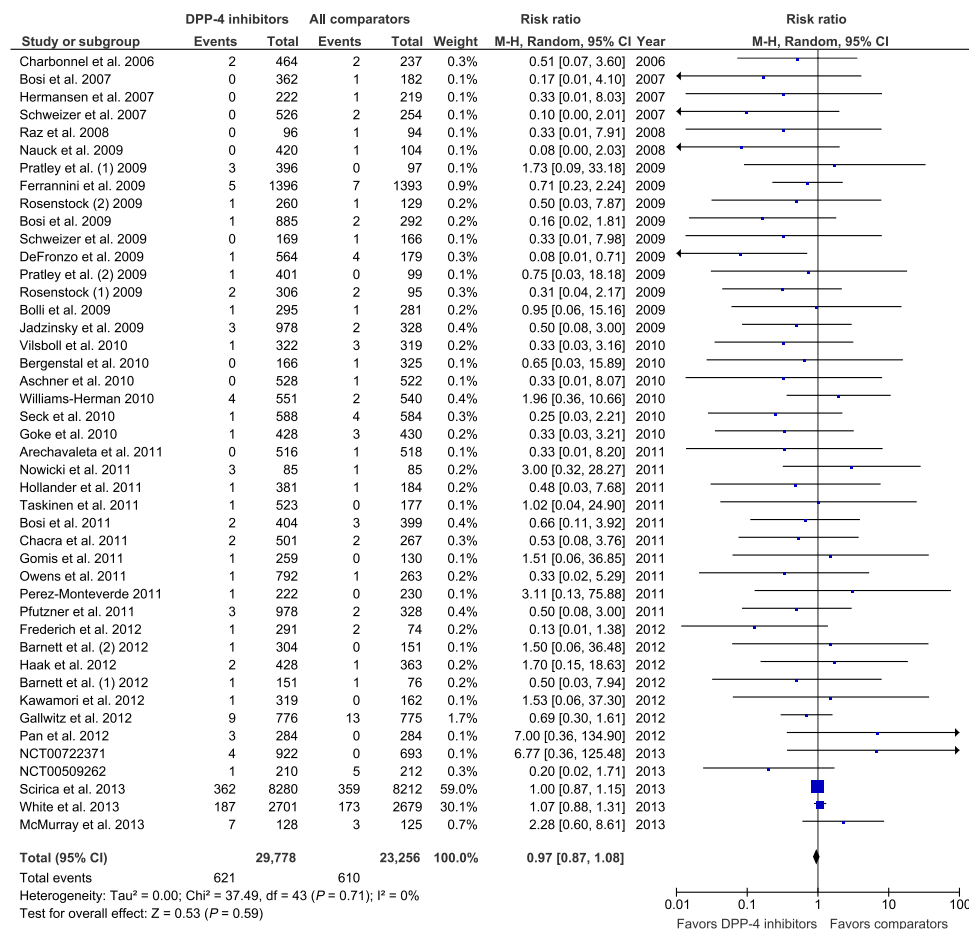


**Figure 4** Forest plot of comparison: 1 DPP-4 inhibitors versus all comparators, outcome: 1.2 CV mortality.

endothelial function [7]. Indeed, the hope with their introduction was that major CV outcomes would be improved by their use. For this reason (and a US Food & Drug Administration (FDA), regulatory mandate requiring evidence of cardiovascular safety with hypoglycemic agents after the thiazolidinediones and PPAR $\alpha/\gamma$  inhibitor experience), a number of large-scale cardiac outcome trials have been conducted with DPP-4 inhibitors with others ongoing, including TECOS [66] and CAROLINA [67].

The present analysis of available data strongly suggests that the DPP-4 inhibitors have a neutral effect on both all-cause and CV mortality. Indeed, the two main outcome trials contributing to analysis of these outcomes (SAVOR-TIMI 53 with saxagliptin [57] and EXAMINE with alogliptin [61]) both reported stand-alone neutral outcomes, meeting the formal FDA definition of noninferiority for hypoglycemic agents in diabetes trials. Nevertheless, this result would be considered disappointing by those who had hoped that the epidemiological relationship of

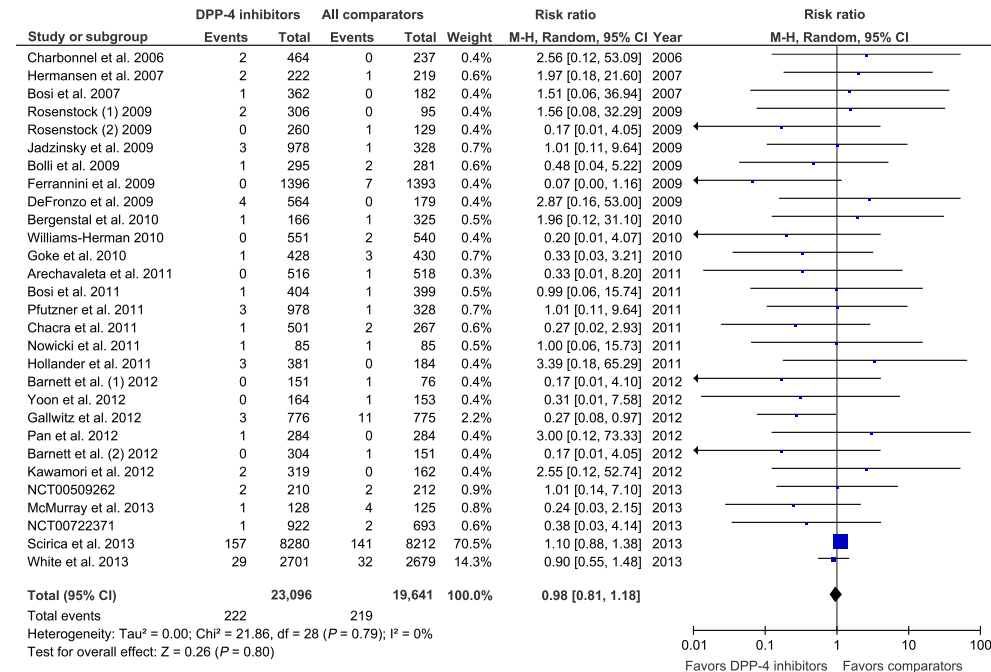
plasma glucose (or glycosylated hemoglobin) levels to mortality would translate to better prognostic outcomes with the improved glycemic control (as well as other putative beneficial cardiovascular effects) afforded by these agents. Furthermore, there was no overall increase (nor decrease) in ACS or stroke events with these agents, consistent with the neutral effect observed on all-cause and CV mortality. This differs markedly from findings from previous meta-analyses [9,10], which suggested that DPP-4 inhibitors afforded significant CV risk reduction, particularly in MI. The inclusion of EXAMINE, SAVORTIMI 53, and also VIVID has significantly increased the size of this meta-analysis compared with previous, as well as contributing patients at higher risk of CV outcomes. This has increased the overall robustness of these findings. Although a significant proportion of these trials were at high risk of bias, the consistency in the sensitivity analysis when only trials with low risk of bias were included lends weight to this robustness.



**Figure 5** Forest plot of comparison: 1 DPP-4 inhibitors versus all comparators, outcome: 1.3 ACS.

A novel finding of this meta-analysis was the statistically significant excess of heart failure hospitalizations with the DPP-4 inhibitors in comparison with placebo or other hypoglycemic agents. This was mainly driven by the excess in such hospitalizations observed in SAVOR-TIMI 53 where it was a formal adjudicated secondary endpoint, as well as the EXAMINE study. However, significance was lost with sensitivity analysis looking only at trials at low risk of bias, so these findings should be interpreted with caution. In addition, there are no specific mechanistic reasons to attribute an increase in heart failure outcomes to the pharmacological properties of the DPP-4 inhibitors [68]. Indeed, among their many actions, these agents tend to augment circulating levels of glucagon-like peptide-1, which in

itself has been shown to improve cardiac contractile function in the setting of systolic chronic heart failure [69]. Furthermore, DPP-4 inhibitors may enhance circulating levels of stromal derived factor (SDF)-alpha, which should theoretically have favorable effects on cardiac functional status [70]. However, as with all glucose-lowering agents, this class may cause hypoglycemia (particularly in combination with other hypoglycemic agents) which is associated with sympathetic activation, albeit short-term. Whether repeated episodes of hypoglycemia may contribute to deterioration in cardiac function and/or clinical heart failure is uncertain [68]. Moreover, an important component of the popularity of the DPP-4 inhibitors is the relatively low rates of hypoglycemia induced by their use. The lack of



**Figure 6** Forest plot of comparison: 1 DPP-4 inhibitors versus all comparators, outcome: 1.4 stroke.

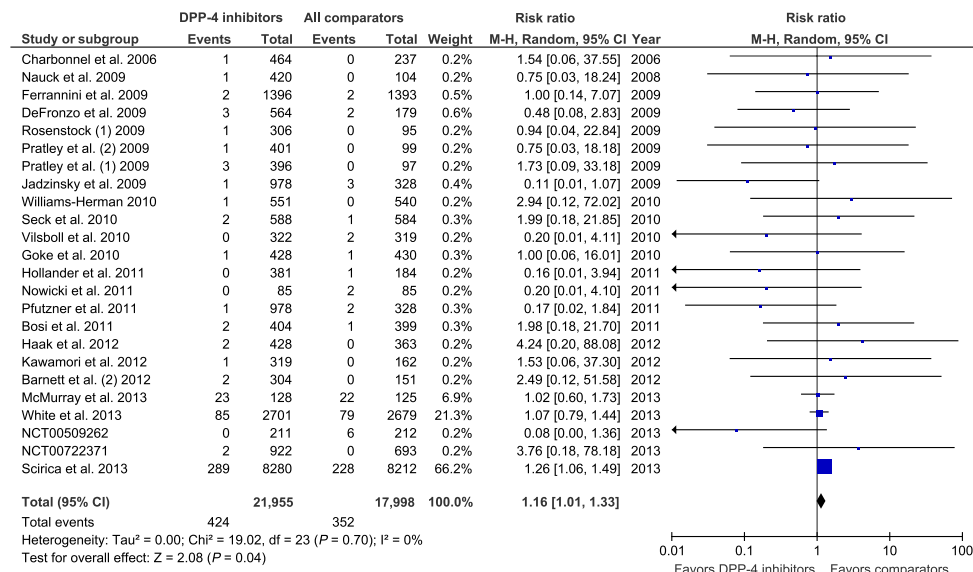
definitive data on this issue with earlier agents, for example, sulfonylureas is largely due to these agents never having been comprehensively evaluated in large-scale trials.

Use of DPP-4 inhibitors has also been noted to be associated with small increases in resting heart rate when used in conjunction with ACE inhibitors [71]. This may be secondary to the blood pressure-lowering achieved with these agents but may also denote chronic (as opposed to acute, hypoglycemia-induced) activation of potentially adverse neurohormonal systems such as the sympathetic nervous system (SNS) [71]. Chronic SNS activation is a well-established contributor to the pathogenesis and progression of heart failure in susceptible subjects.

It is important to note that the vast majority of the studies conducted with DPP-4 inhibitors thus far have excluded diabetic patients with advanced heart failure. However, one study, VIVID with vildagliptin [40], specifically recruited such patients, to primarily examine safety of DPP-4 inhibitors in this setting. There was no difference between vildagliptin and placebo in the primary endpoint of the study (left ventricular ejection fraction at 12 months) and interestingly no excess of heart failure hospitalizations with vildagliptin. However, despite a significant fall in plasma levels of brain natriuretic peptide (which would generally indicate improved overall heart failure status), both systolic and diastolic left ventricular dimensions were increased, and there was a numeric (although not statistical) excess of all-cause and cardiovascular deaths with vildagliptin.

There are a number of important caveats to be acknowledged with regard to the present meta-analysis. Specifically, short-term and small-scale studies have been included and pooled in this analysis with large-scale, long-term evaluation of these agents. These data are derived from secondary outcomes, many of which were unadjudicated. There is variation between trials with regard to definitions of outcomes, particularly HF, with many studies not providing a definition, and included episodes varying from "HF signs and symptoms" in the VIVID trial, to adjudicated HF hospitalizations in the SAVOR-TIMI-53. There is also considerable variability in the background therapies and time since diagnosis of diabetes. However, pooling is inherent in the meta-analytic process, and the need for greater certainty with regard to outcomes observed is why such analyses are performed. The possibility of publication bias exists with all meta-analyses. However, the funnel plot analysis would suggest this is not a major issue in the present evaluation.

In conclusion, the present meta-analysis of 55,141 diabetic participants receiving DPP-4 inhibitors would suggest a neutral effect on all-cause and cardiovascular mortality as well as ACS and stroke with these agents. However, a significant excess of heart failure hospitalizations was observed, requiring further evaluation as to the consistency and potential mechanisms underlying this finding. As mentioned, further large-scale cardiovascular outcome studies are ongoing with the DPP-4 inhibitors, which should help address this issue.



**Figure 7** Forest plot of comparison: 1 DPP-4 inhibitors versus all comparators, outcome: 1.5 HF outcomes.

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## Conflict of Interest

The authors declare no conflict of interest.

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## Appendix 3.6

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### *Original research paper*

**Hopper I**, Kemp W, Porapakkham P, Sata Y, Condon E, Skiba M, Farber L, Porapakkham P, Williams TJ, Menahem S, Roberts S, Krum H. Impact of Heart Failure and Changes to Volume Status on Liver Stiffness: Non-Invasive Assessment using Transient Elastography. *European Journal of Heart Failure* 2012; 14:621-7.

# Impact of heart failure and changes to volume status on liver stiffness: non-invasive assessment using transient elastography

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<b>Aim</b>	The impact of cardiac dysfunction on the liver is known as cardiac hepatopathy. In certain instances this can result in significant hepatic fibrosis or cirrhosis. The validity of non-invasive tools to assess hepatic fibrosis, such as FibroScan <sup>®</sup> which measures liver stiffness (LSM), has not been established in this setting. We examined the impact of cardiac dysfunction on LSM using FibroScan <sup>®</sup> and the influence of volume changes on LSM.
<b>Methods and results</b>	A prospective, cross-sectional study examined the use of FibroScan <sup>®</sup> in subjects with left-sided heart failure (LHF, $n = 32$ ), right-sided heart failure (RHF, $n = 9$ ), and acute decompensated heart failure (ADHF, $n = 8$ ). The impact of volume changes upon LSM was further examined in the ADHF group (pre- and post-diuresis) and in a haemodialysis group (HD, $n = 12$ ), pre- and post-ultrafiltration on dialysis. Compared with healthy controls [ $n = 55$ , LSM = median 4.4 (25th percentile 3.6, 75th percentile 5.1) kPa], LSM was increased in all the cardiac dysfunction subgroups [LHF, 4.7 (4.0, 8.7) kPa, $P = 0.04$ ; RHF, 9.7 (5.0, 10.8) kPa, $P < 0.001$ ; ADHF, 11.2 (6.7, 14.3) kPa, $P < 0.001$ ]. Alteration in volume status via diuresis did not change the baseline LSM in ADHF [11.2 (6.7, 14.3) to 9.5 (7.3, 21.6) kPa, $P > 0.05$ ] with mean diuresis $5051 \pm 1585$ mL, or ultrafiltration in HD [6.0 (3.6, 5.1) vs. 5.7 (4.8, 7.0) kPa, $P > 0.05$ ] with mean diuresis $1962 \pm 233$ mL.
<b>Conclusion</b>	Our findings support the concept of increased LSM in the cardiac failure population. LSM was not altered to a statistically significant level with acute volume changes.
<b>Keywords</b>	Transient elastography • Cardiac hepatopathy • Diuresis • Heart failure • Haemodialysis

## Introduction

The impact of cardiac dysfunction upon the liver has long been recognized.<sup>1–4</sup> The resulting hepatic dysfunction is frequently referred to as cardiac hepatopathy. Such liver function test abnormalities are usually small in magnitude and generally not associated with clinically apparent hepatic disease.<sup>5</sup> Recent observations, however, suggest that chronic heart failure may result in irreversible liver injury and cirrhosis.<sup>6</sup> Hepatic fibrosis, the precursor to

cirrhosis, is relatively common in the setting of advanced heart failure, but is rarely evaluated clinically in such patients.<sup>7</sup>

Liver biopsy is considered the gold standard in diagnosing liver fibrosis. It is an invasive and expensive procedure which carries a small but definite risk of bleeding, pneumothorax, haemothorax, or puncture of adjacent organs. More recently, rapid, highly reproducible, non-invasive assessments have been developed comprising two different but complementary approaches: a 'biological' approach based on the level of serum biomarkers, for which

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FibroTest (Biopredictive, Paris, France) has been the pioneer; and a 'physical' approach based on measurement of liver stiffness using transient elastography (TE), FibroScan® (Echosens, Paris, France).<sup>8–10</sup> TE has been validated in a variety of hepatological conditions including chronic viral hepatitis, and TE and biomarkers have been recently recommended by the EASL Clinical Practice Guidelines for the first-line assessment of liver fibrosis in patients with hepatitis C.<sup>11</sup> It is now being used on a routine basis in some centres to screen patients for the presence of significant hepatic fibrosis. In this setting hepatic fibrosis is known to be the predominant cause of increased liver stiffness; however, confounders for liver stiffness measurement (LSM) include inflammation,<sup>12,13</sup> extra-hepatic cholestasis,<sup>14</sup> and, more recently, hepatic congestion.<sup>15</sup>

The impact of cardiac dysfunction and cardiac hepatopathy on liver stiffness remains largely unexplored.<sup>16,17</sup> This lack of information may have implications for the widespread use of TE in patients with known cardiac disease. Furthermore, it is unknown whether changes in the liver stiffness may be utilized in the assessment of cardiac function and volume status of patients with established cardiac dysfunction.

The aim of the present study was to evaluate whether TE could detect differences in liver stiffness in patients with heart failure (both left and right) in comparison with normal subjects. We additionally measured the effect of volume changes on liver stiffness parameters by evaluating the responses to diuretic therapy in overloaded, acutely decompensated heart failure patients. Similarly we measured the change in liver stiffness in patients with renal failure before and after a single haemodialysis (HD) session.

## Methods

We performed a single-centre, prospective, diagnostic, cross-sectional study. From April 2009 to September 2010, four groups of patients were enrolled: Group 1, stable left-sided heart failure (LHF) with echographic evidence of systolic or diastolic heart failure or congestive heart failure patients ( $n = 32$ ); Group 2, right-sided heart failure (RHF), which was secondary to pulmonary artery hypertension from various aetiologies, including idiopathic, autoimmune, repaired congenital heart disease, or chronic thrombotic disease, and without evidence of LHF on clinical assessment ( $n = 9$ ); Group 3, acute decompensated left-sided HF (ADHF) with volume overload presenting to the emergency department for treatment ( $n = 8$ ); and Group 4, patients with end-stage renal disease on HD ( $n = 12$ ). A control group with no known history of heart or liver disease was also recruited ( $n = 55$ ).

Exclusion criteria for all groups included a history of alcohol consumption of  $\geq 30$  g/day for males or  $\geq 20$  g/day for females, known chronic liver disease of aetiology other than heart failure, obesity with body mass index (BMI)  $> 35$  kg/m<sup>2</sup>, and presence of an active implantable device such as a pacemaker or defibrillator.

The investigation conforms to the principles outlined in the Declaration of Helsinki. The Alfred Hospital Ethics Committee approved the research protocol (approval number 318/08). Informed consent was obtained from all subjects.

## Transient tissue elastography

Transient elastography was performed by two physicians experienced in the use of TE ( $> 500$  assessments). All LSMs were obtained according to

a standardized protocol.<sup>9</sup> To facilitate LSM, hepatic ultrasound was performed immediately prior to FibroScan® to identify the optimal position for LSM from the right lobe of the liver with the patient in the supine position and right arm fully abducted. A successful FibroScan® examination was defined as  $\geq 10$  successful readings with  $\geq 60\%$  success rate and an interquartile range (IQR) to median ratio  $\leq 0.30$ . The LSMs are expressed as median  $\pm$  IQR kPa. Ranges for TE (kPa) are 2.5–7.5 for absent or mild fibrosis, 7.5–9.5 for significant fibrosis, 9.5–13.0 for severe fibrosis, and  $> 13.0$  for cirrhosis. The LSMs were obtained from patients with LHF and RHF as outpatients, while ADHF patients were scanned initially (within 24 h of admission), then just prior to discharge when euvoemia, as assessed clinically, had been approached or achieved. Patients on HD were scanned twice, once prior to dialysis and once following dialysis. Laboratory tests were performed on site, and included routine tests and biomarkers including N-terminal pro brain natriuretic peptide (NT-proBNP) sampled on the same day as the scan. The TEs were obtained from the hospital record and data were used if the scan was performed within the previous 12 months. Echocardiograms were performed using Simpson's rule for left ventricular ejection fraction (LVEF) estimation.

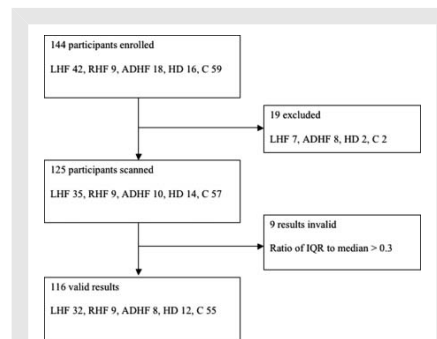
## Statistics

Analysis was performed using the statistical package SPSS 15.0 (SPSS Inc., 1989–2004, Chicago, IL, USA). All data are expressed as mean  $\pm$  standard deviation (SD) or median (IQR) as appropriate. For continuous data, comparisons between groups were assessed using the Wilcoxon rank sum test/Mann–Whitney U-test or Kruskal–Wallis tests, as appropriate. Categorical variables were compared by  $\chi^2$  test or Fisher's exact test. A two-sided  $P$ -value of  $\leq 0.05$  was considered to be statistically significant.

## Results

### Study population and disposition

In all, 144 subjects (42 with LHF, 9 with RHF, 18 with ADHF, 16 on HD, and 59 controls) were enrolled for this study. Nineteen patients were withdrawn prior to completion of scanning, for



**Figure 1** Trial profile. ADHF, acute decompensated left-sided heart failure; C, controls; HD, haemodialysis; LHF, left-sided heart failure; RHF, right-sided heart failure.

reasons including body habitus or presence of ascites precluding scanning, withdrawal of consent, failure to attend the second scan, insertion of a ventricular assist device, and death. A further nine were removed from the analysis due to invalid scans (ratio of IQR to median >0.3) (see Figure 1).

### Baseline characteristics

The LHF and ADHF groups had mixed aetiology, while the RHF group all had pulmonary arterial hypertension from various causes (see Table 1). The baseline characteristics of the 116 subjects included are shown in Table 2 and the TE results in Table 3.

**Table 1** Details of heart failure

Group	Aetiology of heart failure	Duration of heart failure [median (IQR) years]	Mean ejection fraction	Medications
LHF	Ischaemic 9 Idiopathic 15 Other 8	5 (6.5)	42 ± 10	RAASB 28 BB 24 AA 9 Diuretics 14
RHF	All had PAH Idiopathic 3 Autoimmune 2 Thrombo-embolic 2 Congenital heart disease 2	Not available	68 ± 6	Not available
ADHF	Ischaemic 3 Idiopathic 2 Other 3	5.5 (17)	40 ± 27	RAASB 7 BB 6 AA 2 Diuretics 8

AA, aldosterone antagonist; ADHF, acute left-sided decompensated heart failure; BB, beta-blocker; HD, haemodialysis; IQR, interquartile range; LHF, left-sided heart failure; PAH, pulmonary artery hypertension; RAASB, renin–angiotensin–aldosterone system blockade; RHF, right-sided heart failure.

**Table 2** Baseline characteristics for all participants

	Stable LHF (n = 32)	Stable RHF (n = 9)	ADHF (n = 8)	HD (n = 12)	C (n = 55)
Age (years)	63 ± 15	52 ± 18	70 ± 13	57 ± 16	48 ± 12
Male [number (%)]	21 (65)	3 (33)	6 (60)	8 (66)	23 (42)
BMI	27.6 ± 3.9	24.3 ± 4.5	28.0 ± 7.4	27.0 ± 7.0	24.5 ± 3.3
Waist circumference (cm)	98 ± 17	88 ± 12	103 ± 13	N/A	84 ± 13
Systolic BP (mmHg)	123 ± 17	122 ± 12	119 ± 17	118 ± 17	123 ± 14
Diastolic BP (mmHg)	74 ± 12	76 ± 7	71 ± 14	73 ± 10	74 ± 11
HR (b.p.m.)	66 ± 15	80 ± 6	91 ± 26	78 ± 10	69 ± 10
Haemoglobin (g/L)	142 ± 16	148 ± 19	130 ± 22	116 ± 13	143 ± 12
Platelet count (10 <sup>9</sup> )	239 ± 35	217 ± 121	270 ± 79	188 ± 60	242 ± 60
Prothrombin time (s)	18.5 ± 8.6	20.8 ± 6.9	22.1 ± 6.8	13.9 ± 0.8	13.1 ± 0.6
Glucose (mmol/L)	6.3 ± 2.2	5.1 ± 0.4	8.4 ± 3.5	5.7 ± 1.7	4.9 ± 0.5
ALT (U/L)	31 ± 29	28 ± 18	25 ± 11	16 ± 8	23 ± 12
Albumin (g/L)	42 ± 4	40 ± 4	35 ± 4	30 ± 5	44 ± 7
Total bilirubin (μmol/L)	15 ± 10	10 ± 3	17 ± 9	8 ± 3	12 ± 6
GGT (U/L)	53 ± 44	91 ± 81	289 ± 178	39 ± 37	34 ± 44
ALP (U/L)	83 ± 25	115 ± 72	159 ± 87	93 ± 39	70 ± 22
Triglycerides (mmol/L)	1.5 ± 0.7	1.3 ± 0.3	2.3 ± 1.1	1.9 ± 0.8	1.2 ± 0.6
Total cholesterol (mmol/L)	4.5 ± 0.1	5.1 ± 1.0	4.1 ± 0.6	4.0 ± 1.0	5.7 ± 1.7
HDL-cholesterol (mmol/L)	1.3 ± 0.3	1.4 ± 0.3	1.0 ± 0.2	1.0 ± 0.3	1.9 ± 0.9
LDL-cholesterol (mmol/L)	2.4 ± 0.8	3.3 ± 0.6	2.0 ± 0.6	2.2 ± 1.1	3.0 ± 1.0
HbA <sub>1c</sub> (%)	5.8 ± 1.0	5.6 ± 0.5	6.6 ± 1.1	5.4 ± 0.5	5.2 ± 0.9
eGFR (mL/min/1.73 m <sup>2</sup> )	69 ± 20	77 ± 15	40 ± 17	N/A	75 ± 18
NT-proBNP (ng/L)	1200 ± 1530	1138 ± 2025	4596 ± 4237	6748 ± 8086	60 ± 4

ADHF, acute decompensated left-sided heart failure; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BMI, body mass index; BP, blood pressure; C, controls; eGFR, estimated glomerular filtration rate; GGT, γ-glutamyltransferase; HD, haemodialysis; HR, heart rate; HbA<sub>1c</sub>, glycated haemoglobin; LHF, left-sided heart failure; N/A, not applicable; NT-proBNP N-terminal pro brain natriuretic peptide; RHF, right-sided heart failure.

The groups with LHF, ADHF, and HD had more males, while the RHF group and controls had more females. BMI was significantly higher in the LHF group than in controls. There were also significant differences in the baseline liver function between controls and the other groups and in baseline kidney function vs. all groups except RHF. Patients with ADHF had the lowest mean LVEF ( $40 \pm 27$ ), followed by patients with stable LHF ( $42 \pm 10$ ) and HD ( $50 \pm 14$ ), and the RHF patients had near normal LVEF ( $68 \pm 6$ ) (Table 2).

Compared with controls, patients with LHF were significantly older, with higher BMI, worse renal function, higher glucose and glycated haemoglobin ( $Hb_{A1c}$ ), and higher  $\gamma$ -glutamyltransferase (GGT), alkaline phosphatase (ALP), NT-proBNP, and lipids. Patients with RHF were of a similar age to controls with similar BMI, but had higher heart rate, GGT, ALP, NT-proBNP, and  $Hb_{A1c}$ . Patients with ADHF were significantly older than controls, had a higher heart rate, more impaired renal function and liver function, more elevated NT-proBNP, glucose, and  $Hb_{A1c}$ , and a higher lipid profile. Patients on HD were significantly older than controls, had a higher heart rate, potassium, NT-proBNP, albumin, bilirubin, haemoglobin, and platelets, and worse lipid profile (data not shown).

Transient elastography results

Successful measurements were obtained in 116/125 (93%) of participants. Measurements are reported as median (25th percentile, 75th percentile) (Table 4) and the distribution is shown (Figure 2).

Left heart failure vs. controls

Although liver stiffness was significantly higher for LHF patients than controls [4.7 (4.0, 8.7) vs. 4.4 (3.6, 5.1) kPa;  $P = 0.04$ ], the result was within the normal range. Patients with New York Heart Association (NYHA) class III symptoms ( $n = 3$ ) had higher values than those in NYHA I–II ( $n = 29$ ) [11.6 (7.5, 36.6) vs. 4.7 (4.0, 8.4) kPa;  $P = 0.07$ ], but this failed to reach significance as numbers were small in the NYHA class III group.

Right heart failure vs. controls

Liver stiffness measurement was significantly higher for the RHF group than controls [9.7 (5.0, 10.8) vs. 4.4 (3.6, 5.1) kPa;  $P < 0.001$ ].

Acute decompensated heart failure pre- and post-diuresis

Liver stiffness measurement was increased in patients with ADHF compared with controls [11.2 (6.7, 14.3) vs. 4.4 (3.6, 5.1) kPa;  $P < 0.001$ ], and was also higher than in patients with stable chronic LHF

Table 3 Transthoracic echocardiogram results

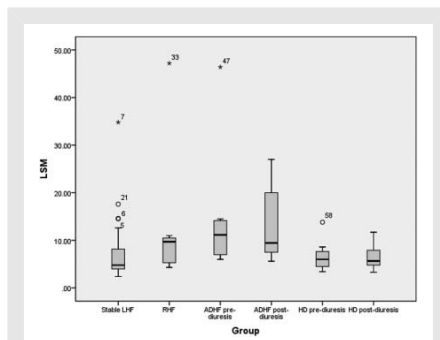
Group number		LVDd	LVDs	FS	EF	TR grade	PR grade	TMF E/A	TMF E/E'	RA pressure	RV systolic pressure
LHF	Mean	60	47	23	42	0.4	0.1	1.2	16.4	10	40
$n = 29$	SD	7	11	10	10	0.7	0.3	1.1	12.0	3	16
RHF	Mean	46	27	44	68	1.0	0.0	1.3	12.5	14	76
$n = 8$	SD	5	7	10	6	1.1	0.0	0.7	6.0	6	28
ADHF	Mean	60	47	26	40	1.8	0.6	2.0	34.1	13	6
$n = 8$	SD	18	21	16	27	1.2	0.5	1.5	26.5	5	10
HD	Mean	50	34	32	50	0.3	0.1	1.1	11.0	10	39
$n = 9$	SD	8	10	12	14	0.5	0.3	0.6	2.4	0	5

ADHF, acute decompensated left-sided heart failure; EF, ejection fraction; FS, fractional shortening; HD, haemodialysis group; LHF, left-sided heart failure; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; PR grade, pulmonary regurgitation grade (1 = mild, 2 = moderate, 3 = severe); RA, right atrial; RHF, right-sided heart failure; RV, right ventricular; TMF, transmittal flow; TR grade, tricuspid regurgitation grade.

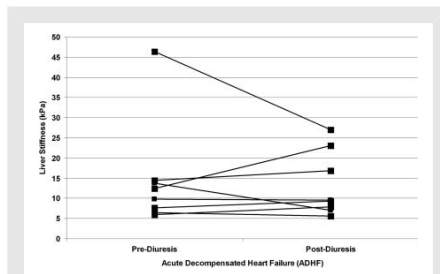
Table 4 Liver stiffness measurement values expressed as median (25th percentile, 75th percentile)

Group	LSM	IQR	IQR:LSM	LSM post-diuresis	IQR	IQR:LSM
Stable LHF	4.7 (4.0, 8.7)	1.0	0.20			
Stable RHF	9.7 (5.0, 10.8)	1.6	0.16			
ADHF	11.2 (6.7, 14.3)	1.4	0.19	9.5 (7.3, 21.6)	1.7	0.16
HD	6.0 (4.4, 7.2)	0.8	0.13	5.7 (4.8, 7.0)	0.8	0.11
Control	4.4 (3.6, 5.1)	0.8	0.17			

ADHF, acute decompensated left-sided heart failure; HD, haemodialysis group; IQR, interquartile range; LHF, left-sided heart failure; LSM, liver stiffness measurement; RHF, right-sided heart failure.



**Figure 2** Liver stiffness measurement (LSM) distribution between different groups. ADHF, acute decompensated left-sided heart failure; HD, haemodialysis; LHF, left-sided heart failure; RHF, right-sided heart failure.



**Figure 3** Median liver stiffness measurements in the acute decompensated heart failure subjects before and after diuresis.

[11.2 (6.7, 14.3) vs. 4.7 (4.0, 8.7) kPa;  $P = 0.01$ ]. LSM was performed again at a median of 5 (3.75, 11.75) days after admission, and did not significantly decrease following diuresis [11.2 (6.7, 14.3) to 9.5 (7.3, 21.6),  $P > 0.09$ ] with a mean diuresis of  $5051 \pm 1585$  mL and return to euvoemia in ADHF (Figure 3).

#### Pre- and post-dialysis

Liver stiffness measurement was only modestly but significantly increased in HD patients pre-dialysis compared with controls [6.0 (4.4, 7.2) vs. 4.4 (3.6, 5.1) kPa;  $P < 0.01$ ], and did not alter significantly [6.0 (4.4, 7.2) vs. 5.7 (4.8, 7.0) kPa;  $P > 0.69$ ] following a mean ultrafiltration volume of  $1962 \pm 233$  mL.

#### Correlations of liver stiffness with heart failure parameters

Median LSM was correlated significantly with NT-proBNP ( $r = 0.24$ ,  $P = 0.001$ ), right atrial pressure ( $r = 0.66$ ,  $P < 0.001$ )

and right ventricular pressure ( $r = 0.47$ ,  $P < 0.001$ ). There was no significant correlation between LSM and LVEF, tricuspid regurgitation, or estimated glomerular filtration rate.

## Discussion

In this study we demonstrated significant increases in LSM in association with cardiac dysfunction in a population of subjects not known to have pre-existing liver disease. The increased LSM was observed in both the LHF and RHF subpopulations. Notably, the magnitude of the LSM elevation was higher in the RHF group and the ADHF group when compared to a statistically significant level. Within the stable LHF population, a higher NYHA class was associated with higher LSM, although these differences were not statistically significant due to small numbers. Furthermore, we observed that acute reductions in total body volume status, induced by diuresis of ADHF or by ultrafiltration in HD patients, did not alter liver stiffness values to a statistically significant level. We do not have long-term follow-up data from the ADHF group, to track their liver stiffness status as they recover from the acute volume overload.

These data highlight the impact of chronic cardiac disease upon the liver. Cardiac hepatopathy is thought to be related to hepatic venous congestion and arterial ischaemia, and in our study increased liver stiffness was positively correlated with increased bilirubin, GGT, and ALP. This cholestatic picture has been seen previously in studies of cardiac hepatopathy.<sup>18</sup> Histological examination of liver biopsies from patients with cardiac hepatopathy has shown the incidence of fibrosis to be relatively low at 19%, with cirrhosis rarely present.<sup>7</sup>

Another finding of this study is the robustness of the liver stiffness parameters in the setting of acute shifts in volume status. FibroScan<sup>®</sup>-derived values did not alter significantly with large changes in volume status. As mentioned, this has been demonstrated in the present study for both acute heart failure patients with a low median reduction of 1.7 kPa (a 15% change), and patients undergoing HD, with a minimal median reduction of 0.3 kPa. The findings in ADHF are similar to the observations of Colli *et al.*<sup>19</sup> who demonstrated a reduction in LSM with diuresis from 8.8 to 7.2 kPa ( $P = 0.03$ ) in 27 patients, with a median reduction of 1.2 kPa, similar to our study. With only eight patients included in the final analysis, our study is underpowered to demonstrate a statistically significant change in LSM following diuresis. However, our results contrast with those of the study by Milonig *et al.*<sup>15</sup> who found a much larger decrease in LSM of 15.3 kPa after cardiac recompensation in 10 patients with ADHF scanned after an interval of 7.2 days (range 5–11). This study also elegantly demonstrated in an animal model that the central venous pressure directly and reversibly controls liver stiffness.

The explanation for the relatively small change in LSM in ADHF pre- and post-diuresis is not clear, and the significance of the finding of elevated LSM in patients without liver disease is unknown. It may be that the observed small reduction in LSM with diuresis is mediated by a reduction in hepatic congestion, as suggested by the Milonig study,<sup>15</sup> and the elevated LSM following attainment of euvoemia may be due to the presence of

underlying hepatic fibrosis. Variables implicated in determining LSM include hepatocyte oedema, cholestasis, and fibrosis.<sup>20</sup> Our results may support the hypothesis that a loss of hepatocyte oedema with diuresis results in the small reduction in LSM in the short time frame of hospital admission with a small but statistically insignificant change following diuresis in ADHF (diuresis 5051 mL), virtually no change after a small diuresis with HD (1962 mL), and statistically significant elevations in LSM in the stable euvoalaemic LHF group and HD group compared with controls. This reflects that changes in total body water *per se* are insufficient to influence liver stiffness substantially. It is however evident that there is individual patient variability, as demonstrated by the substantial LSM reduction observed in one of the ADHF subjects ( $46.4 \pm 12.3$  to  $27.0 \pm 7.1$ ) post-diuresis. Larger studies focusing on this patient subgroup are required to validate LSM as an assessment of hepatic fibrosis in this population.

Our findings may suggest that TE can measure underlying liver stiffness, independent of acute changes in fluid status, although we are unable to comment on whether the increased liver stiffness indicates underlying fibrosis or ongoing liver congestion. If we were to compare our findings with ranges established in liver disease, LSM was in the fibrotic range in the RHF and ADHF groups but not in the LHF group, and measurements in the cirrhotic range were rare. Due to concerns related to the poor cardiac status of the patients, we did not collect liver biopsy information to validate or refute these associations.

Transient elastography is a rapid and non-invasive means of assessing liver stiffness and can be readily incorporated into the overall clinical evaluation of the patient with heart failure to assist with prognostication. Two recent trials have demonstrated that elevated TE is correlated with mortality in the absence of liver disease. Lindvig et al. demonstrated that increased liver stiffness on admission to hospital in a general medical unit was an independent risk factor for 30-day mortality.<sup>21</sup> Transient elastography was evaluated in a cohort of intensive care patients, demonstrating that those with liver stiffness values in the upper quartile had increased short-term mortality in the intensive care unit.<sup>22</sup>

The main limitation to the use of TE in clinical practice is its applicability. The largest series of TE examinations to date, numbering > 13000, demonstrated that TE was not applicable in ~20% of patients.<sup>23</sup> Overall, 6% of results were not valid in our study, but 20% in the ADHF group mainly related to the need for paired scans. BMI has also been shown to be a confounding factor for LSM, either increasing LSM<sup>24</sup> or resulting in decreased applicability.<sup>23</sup> BMI was not corrected for in this analysis, except that a BMI > 35 kg/m<sup>2</sup> was an exclusion criterion. Furthermore, BMIs were generally similar across trial groups.

There are several limitations to the present study. This was a cross-sectional rather than a longitudinal study with no repeat measures at differing time points to determine stability and/or reproducibility of the liver stiffness findings. Furthermore, as liver biopsies were not performed in these high-risk populations, we were unable to correlate LSM with the underlying histological severity of liver fibrosis. It is therefore possible that the increased LSM observed in both the LHF and RHF groups indicates the true presence of hepatic fibrosis rather than hepatic

congestion *per se*. Also the high drop-out rate in the ADHF group compounded by the invalidity of 20% of the scans has resulted in a small sample size, from which it is difficult to draw firm conclusions.

## Conclusion

In summary, we observed elevated measures of liver stiffness in patients with left- and right-sided heart failure, consistent with a subclinical cardiac hepatopathy in this group of patients with heart failure. There were small changes in liver stiffness parameters following short-term changes in volume status, and the significance of these changes is not known. These findings highlight the frequently overlooked but clinically relevant issue of cardiac hepatopathy and underpin a greater appreciation of the presence of underlying liver disease in this patient population. Furthermore, with an increasing use of FibroScan® as part of the clinical assessment of liver disease, our results serve to highlight the potential relevance of cardiac dysfunction as a cause for increased liver stiffness.

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**Conflict of interest:** none declared.

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## Appendix 3.7

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### *Original research paper*

Graudins LV, **Hopper I**, Treseder RJ, Lord JAV, Dooley MJ. Adverse drug reactions during hospital stay: evaluation of a model for informing patients and caregivers. *Journal of Pharmacy Practice and Research* 2012; 42(2):95-9.

# Adverse Drug Reactions during Hospital Stay: Evaluation of a Model for Informing Patients

Linda V Graudins, Ingrid Hopper, Rowena J Treseder, Julie AV Lord, Michael J Dooley

## ABSTRACT

**Background:** Informing patients about their adverse drug reactions (ADRs) and involving them in their medication management should decrease repeat ADRs. An innovative model for informing patients about their ADRs has been in place at an Australian health network. The health network's ADR Review Committee reviews the ADR reports, assigns causality and makes recommendations. Patients are sent a letter about their ADR along with an alert card.

**Aim:** To evaluate the existing ADR model.

**Method:** Over a 6-month period, patients who had an ADR report reviewed by the ADR Review Committee were contacted by telephone within 4 weeks of the review and asked questions about the ADR information sent to them. Patients' discharge summaries were concurrently reviewed for ADR information. Feedback about the model was also sought from the hospital's consumer groups.

**Results:** Of the 89 ADR reports reviewed, 76 patients were eligible, and 55 (72%) patients consented to participate in the survey. 50 (91%) patients recalled the name of the causative drug, 53 (96%) recalled the reaction, 48 (87%) recalled the ADR Review Committee's recommendation, 28 (50%) had an alert card in their wallet, and 29 (52%) had shown or were intending to show the letter to their doctor, but only 3 to their pharmacist. 95% of respondents would recommend this model to other hospitals. 35 (63%) patients wanted the letter sent directly to their doctor. Of the 54 discharge summaries reviewed, the ADR was documented in 43 (80%), details of the reaction in 43 (80%) and specific management advice in 10 (19%). Feedback from the hospital's consumer groups (n = 15) was positive and informed improvements to the model.

**Conclusion:** The ADR model was well received by patients, who retained the information sent. Patient feedback was used to improve the format and content of the ADR information sent. This model could be adapted by other acute and ambulatory settings to facilitate communication between health professionals and patients to avoid repeat ADRs.

**J Pharm Pract Res 2012; 42: 95-9.**

## INTRODUCTION

Adverse drug reactions (ADRs) are prevalent and the direct cause of up to 6% of hospital admissions.<sup>1,2</sup> Fatal ADRs are the fifth leading cause of death in hospitalised patients.<sup>3</sup> Although many ADRs are unavoidable, an

estimated 60% are preventable and these tend to be severe and result in hospitalisation.<sup>4,5</sup> A systematic literature review reported that 3.7% (range 1.4% to 15%) of hospital admissions were due to preventable drug-related causes.<sup>6</sup> ADRs increase the length and cost of hospitalisation.<sup>7,8</sup> A common cause of preventable ADRs is administering a medication despite documented allergy to the medication or similar medications.<sup>5,7</sup> Therefore, communicating information to patients about ADRs is a vital step in error and harm prevention. Studies describing such communication is scant and best-practice models have not been evaluated.<sup>9,10</sup>

A model for informing patients about the ADRs associated with their hospital admission has been in place for several years at the study health network. Reporting ADRs is voluntary with paper reports completed by doctors, pharmacists and nurses. After collation and review by the medication safety pharmacist, reports are reviewed by the ADR Review Committee every 2 weeks. This formal review occurs from several days to weeks after ADR occurrence, depending on when the reports are sent to the Committee by clinicians. The Committee reviews the ADR reports, assigns causality and makes recommendations, such as use with caution, consider desensitisation or avoid the medication or class of medications. Referral to the drug allergy clinic is made when appropriate.

A double-sided alert card, with patient and hospital information on one side and the name of the causative drug, date of reaction and recommendation on the reverse side, is sent to the patient's home. The accompanying letter requests that the patient forward the information to their general practitioner (GP), pharmacist and carer and to keep the alert card in their purse or wallet. Also included is the medication safety pharmacist's contact telephone number for any inquiries about the ADR. The Committee's review is entered into the patient's medical record, the pharmacy dispensing system and the Committee's database. The de-identified ADR report is tabled at relevant hospital committees and sent via e-mail to the Therapeutics Goods Administration for inclusion in the national database. Independent of the Committee, at the time of discharge, the treating team writes a discharge summary for the patient's GP.

This model assesses each ADR report with an expert committee, in light of information available from the admission. The letter and alert card aim to improve communication between patients, their doctors and carers, and to improve patient's knowledge about their ADR, so that reactions can be avoided in the future. This study aimed to evaluate the existing ADR model.

## METHOD

The study was conducted at a university-affiliated hospital group with around 450 acute overnight beds at the tertiary referral campus and a further 450 general

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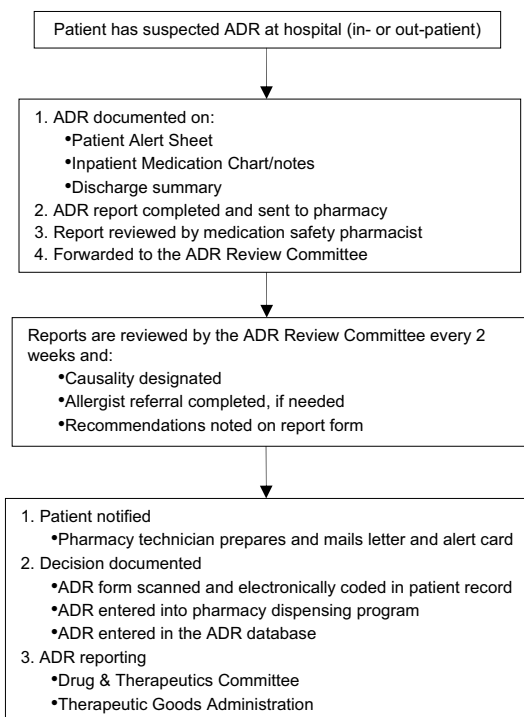


Figure 1. Flowchart of the ADR Review Committee process.

medical, surgical and rehabilitation beds at the other two campus hospitals. The multidisciplinary Committee comprises medical representatives from clinical pharmacology, allergy, infectious diseases, dermatology, and pharmacists from medicines information, medication safety and clinical specialties. The Committee reviews on average 170 ADR reports per year (Figure 1). As terminology used to describe medication-associated patient harm can cause confusion, we defined an adverse drug event as an untoward reaction causing harm that presents during treatment with a medication, but is not necessarily caused by the medication. The Committee reviews ADRs, including allergies and adverse effects (a subset of adverse drug event), and causality is established between a medication and the adverse event.<sup>11</sup>

The severity rating used by the Committee is: 'mild' for no treatment or oral/topical treatment alone; 'moderate' if intravenous treatment, emergency department stay and monitoring is required; 'severe' if the result is admission or increased length of stay; 'life-threatening' which would be fatal if not treated in time; and 'fatal' if the medication was the direct cause or contributed to death. Causality assignment is based on the Uppsala<sup>12</sup> monitoring and Naranjo<sup>13</sup> algorithm methods and decided by consensus. The following factors are considered: information from the literature; timeliness; previous exposure; re- and de-challenge and objective findings, including laboratory results.

The study was approved by the campus ethics committee as a low-risk application.

#### Patient Selection and Interviews

The three components of this observational cohort study included:

- telephone survey of eligible patients within 4 weeks of the Committee's review;

- review of discharge summaries provided to the GP by the hospital treating team; and
- feedback from the hospital's consumer groups.

Patients were identified from ADR reports reviewed by the Committee from February to July 2010. Patients were eligible for the telephone survey, if a medication was the cause of the incident, they were no longer an inpatient, and were able to be contacted by telephone. Patients were excluded if they were deceased, had no fixed address, were an inpatient, did not answer their telephone after three attempts, did not give consent, were unable to communicate via the telephone or if the reported incident was not related to a medication.

As there were no published surveys on ADR communication in the literature, we developed a survey by including questions that needed to be addressed, as well as giving patients the opportunity to comment. The survey was piloted on pharmacy staff and a relation of one of the researchers. The surveys were administered by telephone 2 to 4 weeks after the Committee's review, to enable hospital discharge, delivery of the letter and patient to visit their GP and pharmacy. The surveys were administered by trained pharmacy interns or study coauthors. Consent for the survey was obtained at the time of the telephone call. Patients were asked questions about their ADR, usefulness of the ADR letter and alert card, and suggestions were invited for improvement of the communication process.

#### Discharge Summaries

The Committee does not directly communicate with the GPs. Feedback from previous years was that GPs were burdened by paperwork from the hospital and they assumed that the discharge summary from the treating team would include all relevant information. As this had not been verified, we reviewed discharge summaries by accessing the scanned electronic copy for patients reviewed by the Committee from February to July 2010. The following were noted: suspected medication, ADR and recommendations from the admitting team about monitoring and/or for future avoidance or treatment.

#### Feedback

As this ADR model interfaces with patients, we also sought feedback from the community. The letter and alert card were e-mailed to 9 members of the hospital's Community Advisory Committee and to 36 members of the hospital's consumer register (database of consumers, carers and community members who have expressed an interest in participating in hospital matters). They were asked to comment via e-mail, whether they understood the information, whether they would like more or less information and if the alert card and letter were useful.

#### Statistical Analysis

Quantitative and qualitative data were collected on a standardised form. Descriptive statistics of patients in the study were tabulated. Surveyed and non-surveyed patients' characteristics were compared using the Wilcoxon rank sum and Fisher's exact tests to ensure the surveyed cohort was representative of all patients with reported ADRs.

#### RESULTS

Of the 89 ADR reports reviewed, 76 patients were eligible, and 55 patients (72%) consented to participate in the survey (Figure 2).

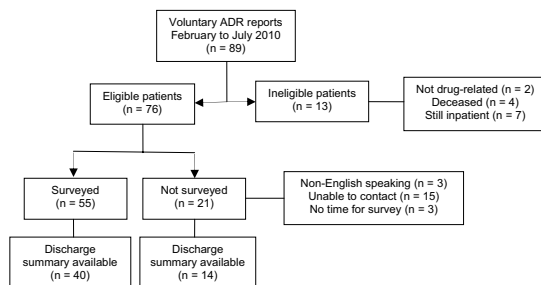


Figure 2. Patient recruitment flowchart.

Forty-four (60%) ADRs were rated as probable or definite and 17 (23%) were severe or life-threatening. Eighteen (25%) ADRs were implicated as the reason for hospital admission. Patients' median age was 52 years and 46 (61%) were male. Age and severity of ADRs were not significantly different in the surveyed and non-surveyed patients (Table 1).

Table 1. Characteristics of patients surveyed and not surveyed

Patient characteristics	All patients (n = 76)	Patients surveyed (n = 55)	Patients not surveyed (n = 21)	P-value
Male gender	46 (61%)	34 (62%)	12 (57%)	0.8*
Median age (range, years)	52 (17-85)	52 (17-85)	56 (25-83)	0.4†
Causality				0.1*
Definite	4 (5%)	4 (7%)	0	
Probable	42 (55%)	31 (56%)	11 (53%)	
Possible	26 (34%)	18 (35%)	7 (33%)	
Unlikely	4 (5%)	2 (2%)	3 (14%)	
Severity				0.9*
Mild	27 (36%)	20 (36%)	7 (33%)	
Moderate	32 (42%)	23 (42%)	9 (43%)	
Severe	12 (16%)	9 (16%)	3 (14%)	
Life-threatening	5 (7%)	3 (5%)	2 (10%)	

\*Fisher's exact test. †Wilcoxon rank sum test.

The results of the survey are presented in Table 2. Six (11%) patients did not receive or could not recall receiving the letter from the Committee (letter and card were resent). Of those in receipt of the letter, the level of knowledge was high. Fifty (91%) patients recalled the name of the causative drug, 53 (96%) recalled the reaction, and 48 (87%) could recall the recommendation. Forty-five (91%) patients were aware of the ADR at the time it occurred or learned of it from a health practitioner. Four (7%) patients first learned of the ADR when they received the letter. Two of these patients were disappointed that there was no discussion at the time of the ADR: *Would be good if someone notified me of the reaction while in hospital. Disappointed that the information did not come from the anaesthetist.* Four patients were concerned when they received the letter because the rash was still present or they did not understand the terminology.

The alert card was found to be more useful than the letter (80% vs 62%). Twenty-eight (50%) patients had the alert card in their wallet and 29 (52%) had shown or were

Table 2. Results of the survey (quantitative)

Questions	No. of patients
Did you receive a letter with the ADR alert card from the Alfred Hospital?	49 (89%)
Do you know the:	
Drug name	50 (91%)
Reaction	53 (96%)
Advice given	48 (87%)
When did you find out about the reaction?	
Hospital	40 (73%)
Home before admission	9 (16%)
Letter from ADR Committee	4 (7%)
GP admitted me to hospital	2 (4%)
How did you first find out about the reaction?	
Doctor	19 (35%)
Self	14 (26%)
Nurse	10 (6%)
ADR letter	4 (7%)
Pharmacist	2 (4%)
Did the letter cause concern? (Yes)	4 (7%)
What have you done with the letter? (May be more than one reply.)	
In wallet	0
Intend/have shown to GP	29 (52%)
Filed in documents	12 (22%)
Shown to carer	9 (16%)
Shown to pharmacist	2 (4%)
Thrown away	3 (5%)
What have you done with the card? (May be more than one reply.)	
In wallet	28 (50%)
Intend/have shown to GP	8 (15%)
Filed in documents	6 (11%)
Shown to carer	6 (11%)
Show to pharmacist	1 (2%)
Thrown away	1 (2%)
Was the card/letter useful?	
Yes, the card was useful	44 (80%)
Yes, the letter was useful	34 (62%)
What do you think the card was for? (May be more than one reply.)	
Show when admitted next time to hospital	29 (53%)
Show to other health professionals	21 (38%)
Show GP	15 (27%)
Alert me that ADR had occurred	14 (25%)
Keep in wallet/purse	14 (25%)
Don't know	1 (2%)
Hospital should send a copy of the letter directly to the GP.	35 (64%)
I would recommend this notification system to other hospitals.	52 (95%)

intending to show the letter to their GP, but only 3 to their pharmacist. Thirty-five (64%) patients would like the letter sent directly to their GP. Those not wanting the letter sent (n = 20) did not have a GP, attended hospital clinics, or preferred to take the letter to their GP themselves.

Thirty-one patients made either positive: *Made me more aware of ADR. I photocopied the card for pre-admission clinic and gave to nurse and anaesthetist.* or negative comments: *Writing on card is too small. Card was not useful because it only had one reaction on it.*

Features considered important were the generic drug name and instructions for future use. Weaknesses highlighted were jargon used, disappointment that their treating team did not supply a letter, difficulty in reading the handwriting, and insufficient information. Other suggestions included: e-mailing ADR information, providing space on the card to include previous and new reactions, and decreasing handwritten information.

### Discharge Summaries

Of the 76 patients, 10 (13%) were outpatients and did not have discharge summaries. Of the remaining 66 patients, 54 discharge summaries (81%) were available. Of these, the medication involved in the ADR was documented in 43 (80%) discharge summaries, details of the reaction in 43 (80%) and specific management advice in 10 (19%).

### Feedback

Feedback was received from 15 consumers – 10 members of the hospital's consumer register and 5 Community Advisory Committee members. All of them believed that the letter and alert card were useful and provided sufficient information. They made the following suggestions: include the option of obtaining an alert device; list all ADRs on the card; emphasise the importance of avoiding future ADRs by notifying the GP and pharmacist; and changing the tone of the letter to be more patient-friendly.

As a result of this feedback, the letter was changed to emphasise sharing of information with GPs, pharmacists and carers and is now fully typed and filed electronically. A fold out double-sided card with space for more information was adapted from the card developed by the Paediatric Therapeutics Program, University of NSW and Sydney Children's Hospital (Figure 3).<sup>24</sup>

### DISCUSSION

This study evaluated a model for follow-up of reported ADRs that included review by specialists, assessment

of causality and recommendations for future use, sent to patients after discharge. The telephone survey indicated a high level of knowledge of the ADR in patients who had received the letter. Patients perceived the written information was useful. Feedback from patients and consumer groups resulted in adjustments to the existing model, e.g. information is typed and acronyms are avoided. The alert card has been redesigned so that clinicians can list additional ADRs. To improve medication safety, the letter now emphasises the importance of sharing information with health professionals and gives clear advice for future use of the causative drug. Although the drug name and reaction was reported to GPs in the majority of discharge summaries, less than 20% contained instructions for future use or treatment, indicating a gap in information. This gap was filled by the ADR Committee communication model, which we propose as best practice for assessment and communication of ADRs in hospital practice.

Management of ADR information is of global concern.<sup>14</sup> Extensive collaborative pharmacovigilance systems operate worldwide to collate data.<sup>15</sup> The Advisory Committee for Safety of Medicine advises on the safety aspects of medicine regulation to the Australian Therapeutic Goods Administration, the national body responsible for collating and managing voluntary ADR reports.<sup>16</sup> Although such reporting schemes are valuable, assessment of individual cases, and communicating details to patients and health professionals is an important step in ensuring patients do not inadvertently risk an ADR through lack of awareness of prior reactions. Our model addresses these issues by evaluating each ADR report in a standardised fashion, assigning causality, sending written advice and following up with allergy consultation when necessary. It also provides direction to health professionals outside the hospital, which may not be possible at discharge. This model of care may also reduce the likelihood of patients being inappropriately treated. For example, a patient may be labelled allergic to penicillin, when the reaction was dose-related or mild, and may be treated with less appropriate antibiotics and potential adverse outcomes.

**Level of verification**

**P:** Patient/ carer report only

**C:** Noted by Clinician eg. GP, pharmacist

**A:** Confirmed by ADR Committee

**S:** Confirmed by Specialist in ADR. eg. allergist, dermatologist

## ADVERSE DRUG REACTION ALERT

Ensure that all health care providers are made aware of this information

AlfredHealth

Patient Details

*Example*

Medicine	ADR	Date	Verification
Penicillin	Anaphylaxis	Feb 09	S (skin test)

VCS: G10659 Dec 2010

Medicine	Adverse Drug Reaction (ADR)	Date of ADR	Verification (see back of card)	Recommendation <small>eg. use with caution; avoid use</small>

Clinician (Sign, Print Name)
Alfred Pharmacy tel: 9076 2061

**Figure 3.** New ADR alert card (adapted from the Sydney Children's Hospital's Medicine Alert Card<sup>24</sup>) (top half is the outside and the bottom half is the inside of the card, which is folded in the middle).



Involvement of patients in managing their ADRs is best practice according to the Australian Pharmaceutical Advisory Council, which emphasises educating patients about their medicines and communicating medicines management between hospital and community practitioners.<sup>17</sup> The *Indicators for QUM in Australian Hospitals* states that provision of written ADR information (percentage of patients with a new ADR who are given written ADR information and a copy communicated to the primary care physician) is an evidence-based indicator to assess the effectiveness of medicines management after discharge.<sup>18</sup> Despite these publications, we are unaware of papers evaluating existing communication to patients about ADRs or suggesting a gold standard.

The study had some limitations. Patients from non-English speaking backgrounds or those unable to use the telephone were not included. Arguably, these patients would benefit most from our model of care. Surveyed patients were not randomised, which may have introduced bias. However, surveyed patients were not statistically different with respect to age and ADR severity to non-surveyed patients. We rely on voluntary ADR reports, with the known risk of under-reporting. A study at our institution found that during a 1-year period, 613 ADRs were identified during the episode of care via ICD-10-AM codes.<sup>19</sup> In the same year, only 200 ADRs were reported to the Committee. Nevertheless, the hospital's reporting rate is well above the national average. For the first half of 2010, the number of ADRs reported were 0.7 per 100 separations (defined as when an admitted patient completes an episode of care, by being discharged, dying, transferring to another hospital or changing type of care), compared with a national average of 0.2% for the 52 hospitals submitting data.<sup>20</sup>

Although the majority of discharge summaries noted the drug and adverse reaction, recommendations to GPs were not always specified. GPs report dissatisfaction with the discharge summary as a means of communicating ADRs, and strongly support patients being provided with ADR alert cards.<sup>9</sup> Currently, there is no state or national standard for sharing health information between secondary and primary care. Computerised medical records and direct electronic entry of ADRs with decision support for prescribing may improve communication and prevent ADRs. However, evidence suggests that high rates of ADEs continue unabated in highly computerised hospitals.<sup>21</sup> Over the last decade, electronic health records have been considered and an Australian national e-health strategy has been published.<sup>22</sup> The Australian Government is investing \$466.7 million in a national Personally Controlled Electronic Health Record system for all Australians from 2012-13.<sup>23</sup> However, until this system is widely accepted, tested and proven, there remains a need to refine existing methods of communication.

In conclusion, the ADR model was well received by patients, who retained the information sent. Patient feedback was used to improve the format and content of the ADR information sent. This model could be adapted by other acute and ambulatory settings to facilitate communication between health professionals and patients to avoid repeat ADRs.

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**Competing interests:** None declared

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## Appendix 3.8

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### *Research letter*

Bodey F, **Hopper I**, Krum H. Neprilysin inhibitors preserve renal function in heart failure. International Journal of Cardiology. 2015; 179: 329-30.



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Letter to the Editor

## Neprilysin inhibitors preserve renal function in heart failure

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Recently the superiority of the angiotensin receptor neprilysin (NEP) inhibitor (ARNi) LCZ696 over the angiotensin converting enzyme inhibitor, enalapril, has been demonstrated [1]. Therapy for heart failure may be limited by deterioration of renal function secondary to pharmacological agents used in the management of the condition. NEP inhibition may have direct or indirect beneficial renal effects that contribute to this superiority.

We sought to determine the renal effects of NEP–renin–angiotensin–aldosterone system (RAAS) inhibition by conducting a meta-analysis of randomized controlled trials of either NEP–ACEi or ARNi reporting on renal function. Eligible studies were identified using MEDLINE. All searches included the keywords and corresponding MeSH term describing neprilysin inhibitor, LCZ696, omapatrilat, heart failure and hypertension. Additionally bibliographies of retrieved articles and recent reviews in the area were also searched. Only English-language, full-text, peer-reviewed papers were considered. Studies were excluded if they did not have a measure of renal function both at baseline and after treatment initiation or were based on acutely decompensated heart failure. There was no minimum number of patients or minimum follow-up time. Statistical analysis was performed using Review Manager [2]. The results were pooled using random effects model because of the clinical heterogeneity of the studies. Risk ratios (RRs) with 95% confidence intervals (CIs) were derived from each individual study and determined for overall outcome using the Mantel–Haenszel method and the Z test for significance of RRs (Fig. 1).

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A total of 499 titles were reviewed, with 104 abstracts. Of these 11 studies were obtained for detailed evaluation. Four studies met the inclusion criteria. All were major RCTs investigating NEP–RAAS inhibition in heart failure. No studies in hypertension met the inclusion criteria. Included studies were IMPRESS and OVERTURE, which looked at omapatrilat versus lisinopril or enalapril, respectively, and PARAMOUNT and PARADIGM-HF which looked at LCZ696 versus valsartan or enalapril, respectively. Overall the number of participants included in the trials was 15,043, and the number of participants in the individual trials ranged from 301 to 8399. Mean follow up time was 51 weeks, and ranged from 12 to 127 weeks. PARAMOUNT enrolled participants with heart failure and preserved left ventricular ejection fraction (EF 45% or greater), while the other trials enrolled patients with heart failure and reduced EF (40% or less). Average age of participants was 65.6 years with 73% male, 60% had an ischaemic cardiomyopathy and 95% were New York Heart Association class II or III (average Class II) (Table 1).

Data were able to be extracted on decline in renal function only. The definition of decline in renal function varied between studies. IMPRESS described the number of participants with “significantly elevated” creatinine without further definition, OVERTURE described the number of participants with “impaired renal function” as part of the adverse events, PARAMOUNT described “renal dysfunction” as an adverse event. PARADIGM-HF provided the number of participants with serum creatinine  $\geq 2.5$  mg/dL. Overall, compared with ACEi or ARB alone, combined NEP–RAAS inhibition resulted in a reduction in risk of decline in renal function (risk ratio 0.68, 95% confidence interval 0.51–0.92,  $p = 0.01$ ).

This meta-analysis of the renal effects of NEP–RAAS inhibition demonstrates that these agents preserve renal function in heart failure compared to ACEi or ARB alone, with a 32% relative risk reduction in decline in renal function. Cardiac and renal dysfunction may worsen each other through multiple mechanisms such as fluid overload and increased venous pressures, hypo-perfusion, neurohormonal and inflammatory activation and concomitant treatment [3]. Renal function frequently deteriorates in the treatment of patients hospitalized for heart failure, with creatinine increases of  $>0.1$  mg/dL demonstrated in approximately 70% of such patients [4]. In a study of 1906 patients GFR was a stronger predictor of mortality in patients with chronic heart failure than impaired cardiac function, with those in the lowest quartile of glomerular filtration rate (GFR) values having almost a three times relative risk of increased mortality [5]. Worsening renal function has become a major barrier to the use of treatments known to prolong survival including ACE inhibition, ARBs and aldosterone blockers [4].

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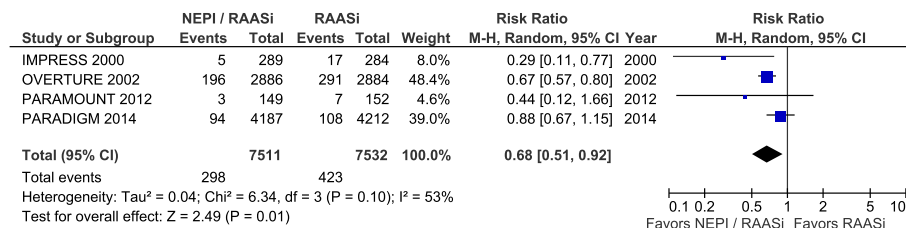


Fig. 1. Risk of decline in renal function.

Table 1  
Included studies.

Trial name	Agent	Number of participants	Follow-up (months)	Definition of decline in renal function	Inclusion criteria	Age (years)	Males	Ischaemic cardiomyopathy	Baseline serum Cr (μmol/L)	Baseline eGFR (mL/min per 1.73 m²)
Rouleau 2000 (IMPRESS)	Omapatrilat (ACE/NEP) vs lisinopril	573	6	'Elevated serum creatinine'	NYHA II–IV, LVEF ≤ 40%, on ACEi	64.3 ± 10.7	451 (79%)	377 (66%)	102.5	–
Packer 2002 (OVERTURE)	Omapatrilat (ACE/NEP) vs enalapril	5770	14.5	'Decline in renal function'	NYHA II–IV, LVEF ≤ 30% and hospitalized in last 12 months	63.4 ± 11.6	4559 (79%)	3202 (55%)	–	–
Solomon 2012 (PARAMOUNT)	LCZ696 (ARB/NEP) vs valsartan	301	3	>50% ↓GFR	NYHA II–III, HFPEF, EF ≥ 45%	70.9 ± 9.4	152 (57%)	–	–	66
McMurray 2014 (PARADIGM-HF)	LCZ696 (ARB/NEP) vs enalapril	8442	27	>50% ↓GFR	NYHA II–III, EF ≤ 40%	63.8 ± 11.5	6567 (78%)	5036 (60%)	113	–

Omapatrilat – ACE and neprilysin inhibitor, LCZ696 – ARB and neprilysin inhibitor AHU377, NYHA – New York Heart Association, HFPEF – Heart Failure with Preserved Ejection Fraction, EF – ejection fraction, GFR – glomerular filtration rate, Cr – creatinine, eGFR – estimated GFR.

The effect of NEP–RAAS inhibition has been examined in animal models of heart failure. Studies in dogs with pacing induced heart failure have previously demonstrated an increase in GFR and urinary sodium excretion with preservation of renal function [6]. By delaying the onset of sodium retention, this can prolong the compensated stage of chronic heart failure [7]. Another canine study showed that omapatrilat, with and without diuretic, resulted in more favorable cardiorenal and humoral responses than did ACEi and diuretic. Renal vasodilation was observed in association with maintenance of GFR and diuretic response [8]. Another study in subtotally nephrectomized rats showed omapatrilat reduced proteinuria and retarded glomerulosclerosis and tubulointerstitial fibrosis in progressive renal injury. This was associated with preservation of renal function [9]. Studies have shown that ANP dilates the afferent and constricts the efferent glomerular arteriole, thus increasing glomerular hydrostatic pressure and acting to preserve GFR despite reduced cardiac output [8]. This could explain the effect seen in PARADIGM-HF where no clinically important increase in serum creatinine was seen despite lower blood pressure and more clinical hypotension observed in the LCZ696 group [1].

There are a number of limitations to our meta-analysis. Firstly, only four randomized controlled trials of NEP/ARB (LCZ696) and NEP/ACEi (omapatrilat) met the inclusion criteria of reporting on renal outcomes. However, a strength is the large number of participants providing data on 15,043 patients, mostly from PARADIGM-HF which included 8442 patients. An attempt to strengthen data with trials involving NEP–RAASI for hypertension was not possible due to lack of published renal outcomes. The included trials were conducted between 1997 and 2014, during which time guidelines for background therapy for heart failure have changed [10]. Each trial reported on renal function in a different manner. We were also limited to the information available in the published literature.

Despite these limitations, our analysis demonstrates favorable renal effects of NEP–RAAS inhibition and offers promise for treatment of heart

failure and potentially the cardiorenal syndrome with these agents. These renal effects may also offer greater potential for dose-titration of other heart failure therapies which have additional mortality benefits.

#### Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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## Appendix 3.9

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### *Editorial*

Krum H, **Hopper I**. The ongoing evolution of optimal endpoints for heart failure trials. Journal of the American Collee of Cardiology: Heart Failure. 2015; 3: 615-7.

EDITORIAL COMMENT

## The Ongoing Evolution of Optimal Clinical Endpoints for Heart Failure Trials\*



Henry Krum, MBBS, PhD, Ingrid Hopper, MBBS

Advances in heart failure (HF) drug and device therapies over the past 3 decades have made major inroads into the lethality of this disease. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), as well as device-based approaches including cardiac resynchronization therapy and implantable cardioverter defibrillator therapy, have resulted in substantial mortality, morbidity and quality of life (QoL) benefits to such patients, particularly those with HF and reduced ejection fraction (HFrEF).

Beta-blockers are arguably the most potent therapy in reducing mortality in HF. Mortality reductions in mild to moderate as well as advanced HFrEF in the pivotal trials additional to background ACE inhibitors and diuretics were consistently of the order of 30% (1-3). This was accompanied by improvements in cardiac remodeling parameters, HF symptoms, and QoL measures.

SEE PAGE 603

In this issue of *JACC: Heart Failure*, Rush et al. (4) have reviewed the totality of HF randomized controlled trials in the past 3 decades, evaluating cardiovascular (CV) mortality according to beta-blocker usage in the trials. The authors have been meticulous in including all of the major, predominantly HFrEF, randomized control trials over this period. The analysis included 66 trials, including 136,182 participants and 32,140 deaths, with participants mostly with New York Heart Association (NYHA) functional class II and

III symptoms and a weighted average left ventricular ejection fraction of 27%. The trials were divided into 3 groups according to the proportion of patients treated with a beta-blocker. The proportion of CV deaths decreased from 87% with low beta-blocker use to 80% with high beta-blocker use. Non-CV deaths rose from 11.4% to 19.1% with high beta-blocker therapy, representing a proportional increase of two-thirds in non-CV deaths. The reduction in CV mortality was associated with a rise in non-CV deaths, which was due mostly to malignancy.

This analysis confirms what we have known for some time, which is that mortality rates are falling with modern HF treatment; these data allow us to go some way in quantifying the major therapeutic advances that have been made in this field. This analysis examines background beta-blocker use within these trials, and as the authors acknowledge, concomitant with increased beta-blocker use over recent years has been increased use of ACE inhibitor/ARB, rapid uptake of MRAs following the RALES study (Randomized Aldactone Evaluation Study) (5) and the EMPHASIS-HF study (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) (6) as well as the advent of devices, and it is therefore impossible to attribute improved CV mortality (and accompanying relative increase in non-CV mortality) entirely to beta-blocker therapy alone. However, a sensitivity analysis adjusting for ACE inhibitor/ARB use and adjusting for MRA use, and also using a meta-analytic approach, demonstrated that beta-blockers contributed most to the reduction in CV deaths.

This analysis includes the individual study outcomes of the placebo group and the intervention group. Many of these interventions are of novel agents that turned out to result in neutral or even adverse clinical outcomes. Examples include the BEST The Beta-Blocker Evaluation of Survival Trial study (7), in which bucindolol failed to improve

\*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

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survival in NYHA functional class III and IV HF, and the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico study) (8), in which rosuvastatin failed to improve survival in NYHA functional class II to IV HF. By definition, none of these interventions constitute standard therapy and thus their inclusion in the analysis may potentially skew the results. An analysis examining just the placebo group would be informative.

The falls in CV mortality have had consequences for the design of HF clinical trials. As the authors note, all-cause mortality has become an increasingly insensitive endpoint in HF clinical trials. Although this is an easily definable and confirmable endpoint, it has the obvious weakness that causes of death such as trauma and malignancy that are unrelated to HF (or its treatment) are included. More recent trials have required a more refined approach to capturing outcomes of most interest and over the past 15 years, HF trials have used CV mortality rather than all-cause mortality as at least a component of the primary endpoint. All-cause mortality should not be abandoned as an outcomes measure, because no reduction in all-cause mortality in the presence of a reduction in CV mortality may be a safety signal that the treatment is shifting the cause of death. This was seen in The Digitalis Investigation Group trial (9), in which symptomatic HF decreased with reduced HF hospitalizations, but no reduction in mortality was seen due to a presumed rise in arrhythmic deaths.

CV mortality allows greater precision with regard to evaluation of the benefits or otherwise of a HF therapeutic agent, but practically, it is expensive because independent adjudication committees are required to review the medical records and determine cause of death. There is also residual uncertainty about the cause of death in the absence of post-mortems and when the study participant is found deceased at home with an unwitnessed death. There is uncertainty about whether these deaths should be included as CV mortality or excluded from the analysis, but as the authors found, this accounted for only 5.7% of all deaths.

The inclusion of HF hospitalizations in outcomes has received increasing interest. One of the advantages of this outcome is that it reflects costs of HF treatment, which are rapidly increasing. Multiple admissions for HF reflects poor prognosis, and this outcome can capture that aspect, and the costs

associated with admissions are meaningful for health care payers. Again there are major issues with this as a clinical outcome. HF hospitalization may reflect regional practices and preferences, with significant regional variation in bed days and need for admission. Some centers use short-stay units or give outpatient intravenous diuretics in an effort to avoid "formal" admissions, which further blurs the definition of a HF hospitalization. It can also be difficult to determine the relative contribution of HF to an admission when multiple organ dysfunction exists; for example, with primary pneumonia resulting in HF decompensation.

All of these outcomes do not necessarily reflect what is important to the patient. This has been termed the "patient journey." QoL measures have traditionally been viewed as soft science, because they are somewhat subjective and often have not been particularly well-correlated with harder mortality outcomes (10). However, for the patient, these measures may be far more meaningful than the blunt instruments described previously. Alternatives to describe the patient journey have been suggested in the literature (11-13); however, these have not been widely accepted nor stringently validated, and regulators are somewhat uncertain of their clinical utility.

HF mortality is laudably falling due in large part to the addition of beta-blockers to our clinical armamentarium. However, these major gains cannot be seen in isolation from the contribution of other therapies to improvements in HF mortality. Beta-blockers continue to be underprescribed in HF, and this continues to be a major challenge going forward. Additionally, this analysis demonstrates that improvements in HF mortality forecast increasing difficulty demonstrating improved outcomes in future trials, and work is needed to develop appropriate clinical endpoints in contemporaneous HF trials. This endpoint evaluation work is urgently needed to optimize evaluation of new treatments to reduce the still unacceptably high mortality and morbidity associated with the condition.

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- KEY WORDS** beta-blockers, clinical trials, endpoints, mortality

## Appendix 3.10

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### *Editorial*

Krum H, Skiba M, Wu S, **Hopper I**. Heart failure and dipeptidyl peptidase-4 inhibitors. European Journal of Heart Failure. 2014; 16: 603-7.

# Heart failure and dipeptidyl peptidase-4 inhibitors

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## Background

Heart failure is a major co-morbid association of diabetes mellitus. The incidence of heart failure in diabetic vs. control subjects is 2- to 3-fold greater in every decade of life.<sup>1</sup> Similar data on prevalence have also been observed in the Framingham study.<sup>2</sup> Conversely, diabetes represents a major co-morbidity in patients with heart failure. In both clinical trials and registries of heart failure patients, between 24% and 44% have known diabetes mellitus.<sup>3</sup>

A key epidemiological issue in the context of discussion of therapies for diabetes and the associated risk of heart failure is the impact of glycaemic control on heart failure risk. Both UKPDS<sup>4</sup> and a large cohort investigated by Iribarren *et al.*<sup>5</sup> have demonstrated a close positive linear relationship between haemoglobin A<sub>1c</sub> levels and rate of heart failure development. Specifically, poorest glycaemic control was associated with greatest risk of heart failure. However, studies such as UKPDS demonstrated that more intensive glycaemic control was not associated with reduced development of heart failure.<sup>6</sup> More contemporaneous meta-analyses have supported this observation,<sup>7</sup> albeit potentially driven by drug treatments such as thiazolidinediones which may contribute to heart failure development.

## Cardiovascular actions of dipeptidyl peptidase-4 inhibitors

Based on pre-clinical and early clinical work, dipeptidyl peptidase-4 (DPP-4) inhibitors should, in theory, have beneficial rather than adverse effects on progression of LV remodelling and therefore delay development of symptomatic heart failure<sup>8</sup> (Figure 1).

Dipeptidyl peptidase-4 is involved in the enzymatic breakdown of glucagon-like peptide (GLP)-1; thus, DPP-4 inhibition augments circulating GLP-1 levels, which appears to have beneficial effects upon the heart in animal models as well as in the post-myocardial infarction and established heart failure settings in man.<sup>9</sup> DPP-4 stimulates activation of proinflammatory cytokines,<sup>9</sup> independent

drivers of progression of LV systolic dysfunction due to their prohypertrophic and profibrotic effects.<sup>10</sup>

Inhibition of DPP-4 augments circulating levels of soluble-derived factor (SDF)-1  $\alpha$ ,<sup>9</sup> a stimulant of bone marrow production of erythroid precursor cells, which should contribute to improved vascular and myocardial function. Finally, DPP-4 inhibition should direct BNP metabolism towards an increase in active BNP rather than biologically inactive BNP precursor fragments.<sup>9</sup>

Pre-clinical studies with DPP-4 inhibitors in animal models of LV systolic dysfunction<sup>11</sup> support a beneficial effect on LV remodelling and survival in comparison with controls.

## Major outcome trials with dipeptidyl peptidase-4 inhibitors

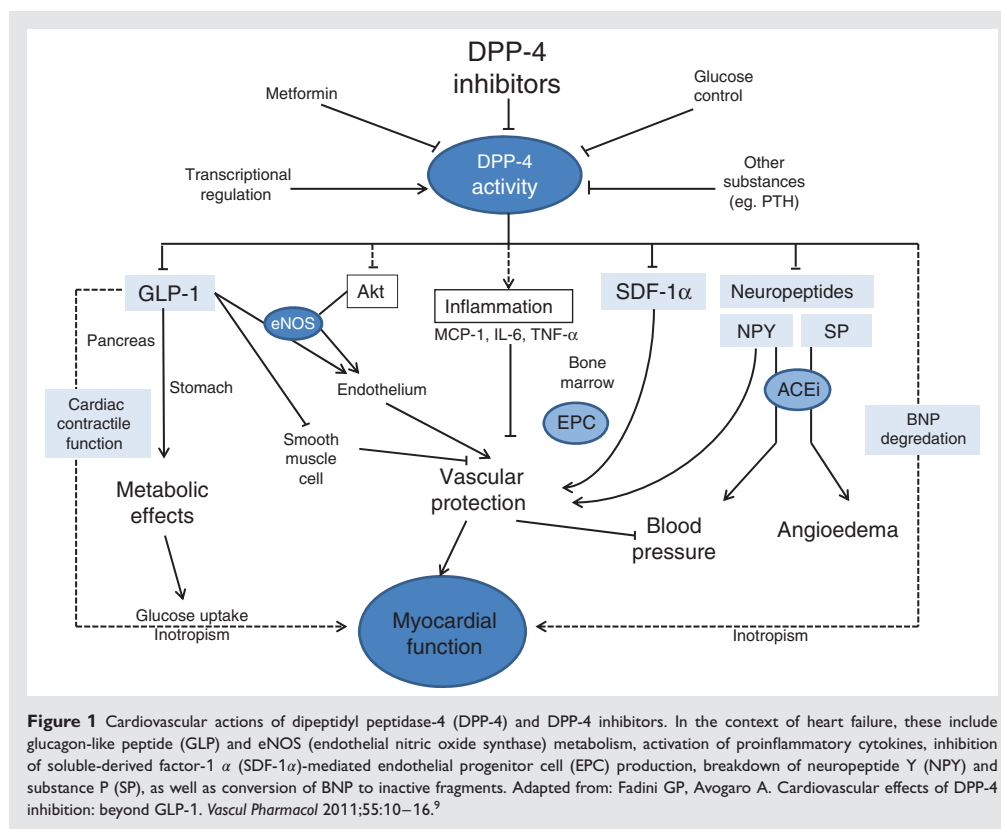
Published and ongoing major cardiovascular outcome trials with DPP-4 inhibitors are summarized in Table 1. Three major DPP-4 inhibitor trials have recently reported, all with implications for heart failure, and these are examined in greater detail below.

### SAVOR-TIMI 53

The SAVOR-TIMI 53 trial compared the DPP-4 inhibitor, saxagliptin, with placebo in the setting of patients with a history of, or who are at risk of, cardiovascular events.<sup>12</sup> There was no overall effect of saxagliptin vs. placebo on the primary endpoint of time to first event of cardiovascular death, myocardial infarction, or ischaemic stroke. However, patients in the saxagliptin group were more likely to be hospitalized for heart failure than those in the placebo group [3.5 vs. 2.8%, hazard ratio (HR) 1.27, 95% confidence interval (CI) 1.07–1.51,  $P=0.007$ ]. A Kaplan–Meier plot of accrual of heart failure hospitalizations over time showed an early divergence of the curves which continued to diverge slightly beyond the first 180 days of treatment.<sup>13</sup>

A Forrest plot of key baseline variables that may influence risk of heart failure hospitalization according to treatment did not

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demonstrate any heterogeneity, with all pre-defined subgroups trending towards an excess of primary endpoint events with saxagliptin vs. placebo. One exception may be baseline plasma NT-proBNP levels. In those patients within the highest BNP quartile (333–46627 pg/mL), 10.9% of saxagliptin and 8.9% of placebo patients had a hospitalization for heart failure ( $P=0.024$ ).

## EXAMINE

The EXAMINE study assessed the DPP-4 inhibitor, alogliptin, in patients who had recently had an acute coronary syndrome.<sup>14</sup> As with saxagliptin in SAVOR, there was no significant effect of this class on the primary endpoint (death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke). In EXAMINE, 3.9% of alogliptin-treated and 3.3% of placebo-treated patients had a hospitalization for heart failure (HR 1.19, 95% CI 0.89–1.58,  $P=NS$ ).<sup>15</sup> This was a pre-defined exploratory endpoint that was independently adjudicated.

In EXAMINE, 28% of patients had a history of congestive heart failure at baseline. The primary EXAMINE endpoint was

reduced with alogliptin vs. placebo, HR 0.82,  $P=0.20$ <sup>15</sup>, in these patients. Data on recurrent heart failure hospitalizations within this subgroup have not as yet been reported.

## VIVID

The Vildagliptin In Ventricular Dysfunction Diabetes (VIVID) trial has been presented<sup>16</sup> but not yet published. All patients in VIVID had evidence of symptomatic systolic heart failure with an LVEF <35% as well as diabetes requiring glucose-lowering therapy. There was no difference in adjudicated heart failure events between vildagliptin ( $n=128$ , 18%) and placebo ( $n=125$ , 17.6%) patients over the 52 weeks of the study.

The primary endpoint of the VIVID study was change in LVEF, with no difference observed between treatment groups (+0.54, 95% CI –1.97 to 3.06,  $P=0.67$ ). Interestingly, plasma BNP levels were reduced in both groups: vildagliptin, ratio of 0.72 vs. baseline; placebo, 0.86 vs. baseline. Somewhat surprisingly, LV diastolic and systolic volumes were both increased with vildagliptin compared with placebo.



**Table 1 Recent and ongoing major placebo-controlled dipeptidyl peptidase-4 inhibitor cardiovascular trials**

Trial	DPP-4 inhibitor	Patient population	Primary CV efficacy endpoint	Key findings	HF effects
SAVOR-TIMI 53 <sup>12</sup>	Saxagliptin	T2DM, established CVD, or multiple CV risk factors (n = 16 492)	CV death, MI, or ischaemic stroke	Not superior, HR 1.00 (0.89–1.12) Met non-inferiority criteria	↑HF hospitalization with saxagliptin (3.5% vs. 2.8%)
EXAMINE <sup>14</sup>	Alogliptin	T2DM, AMI, or UAP requiring hospitalization in previous 15–90 days (n = 5380)	CV death, non-fatal MI, non-fatal stroke	Not superior, HR 0.96 (–1.16) Met non-inferiority criteria	↑HF hospitalization with alogliptin (3.9% vs. 3.3%)
VIVID <sup>16</sup>	Vildagliptin	T2DM, systolic chronic HF (n = 254)	Change in LVEF	No change in LVEF (non-inferior) Non-significant ↓BNP, ↑LV volume with vildagliptin vs. PBO	No ↑ in adjudicated worsening HF with vildagliptin (18% vs. 17.6%)
TECOS	Sitagliptin	T2DM, >50 years, documented CVD (n = 14 000)	CV death, non-fatal MI, non-fatal stroke, hospitalization for UAP	Study ongoing	Study ongoing
CARMELINA	Linagliptin	T2DM, previous CV complications, albuminuria, CKD (n = 8000)	CV death; non-fatal MI, CVA, hospitalization for UAP (+ renal co-primary endpoint)	Study ongoing	Study ongoing

AMI, acute myocardial infarction; CKD, chronic kidney disease; CV, cardiovascular; CVA, cerebrovascular accident; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; PBO, placebo; T2DM, type 2 diabetes mellitus; UAP, unstable angina pectoris.

## Dipeptidyl peptidase-4 inhibitor meta-analysis

Our group recently performed a meta-analysis of heart failure outcomes with DPP-4 inhibitors, including the above studies. Forest plots of these data, comparing DPP-4 inhibitor with placebo and an active comparator, are shown in Figure 2. A sensitivity analysis was also undertaken, with thiazolidinediones included and excluded as comparator. With thiazolidinediones included, the risk ratio for heart failure with DPP-4 inhibitors was 0.80, 95% CI 0.35–1.81,  $P = 0.59$ . With thiazolidinediones removed as comparator, the risk ratio for heart failure was 1.15, 95% CI 1.00–1.33,  $P = 0.04$ .

## Mechanisms underlying dipeptidyl peptidase-4 inhibitor-related increases in heart failure

It is not entirely certain whether DPP-4 inhibitors directly or even indirectly cause heart failure, but if one accepts the premise that this is the case, then a number of potential explanations need to be considered.

### Play of chance

It is entirely plausible that the increase in heart failure events observed, particularly in SAVOR,<sup>12</sup> represents the play of chance. There is a long history of 'play of chance' influencing cardiovascular trials. This is particularly true of subgroup analysis, but would equally apply to analysis of 'off-target' effects of drugs.<sup>17</sup> Nevertheless, there are hints with DPP-4 inhibitors that this may not be the case, especially given the numerical increase in events

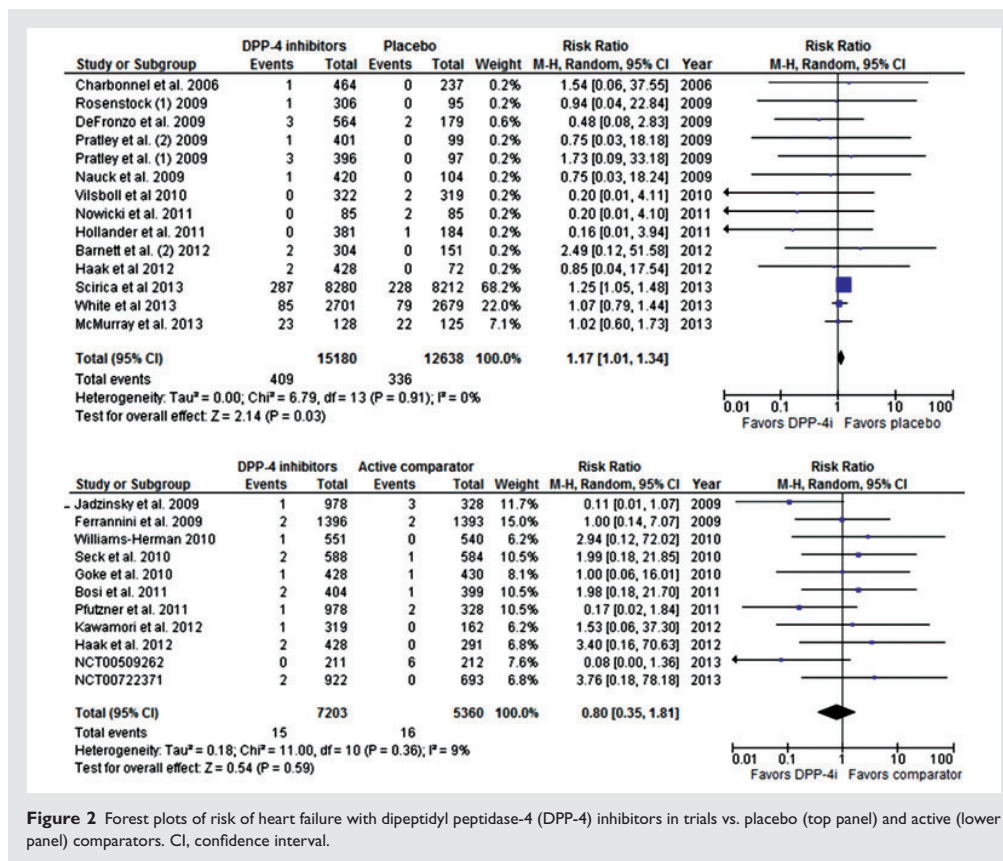
in EXAMINE<sup>14</sup> and the odd remodelling effects of vildagliptin in VIVID.<sup>16</sup> Furthermore, there was an excess (not significant) of all-cause mortality events with vildagliptin amongst patients in VIVID.<sup>24</sup>

### Imbalance between groups

Although SAVOR and EXAMINE were large trials and baseline characteristics appear to be well balanced, it is certainly possible that there were imbalances at baseline between groups, which may have led to an increase in risk of heart failure hospitalization with the DPP-4 inhibitor. Specifically, there may be imbalances in background medications that are known to retard heart failure progression, such as ACE inhibitors. It would certainly be prudent to look at the patients who did have a heart failure hospitalization to see if there are baseline imbalances within this specific subgroup.

### Excess hypoglycaemia with dipeptidyl peptidase-4 inhibitors

Hypoglycaemia stimulates the sympathetic and renin–angiotensin–aldosterone systems and, thus, with chronic stimulation, may have adverse consequences including progression to symptomatic heart failure. However, the increase in rates of hypoglycaemia in both SAVOR and EXAMINE were very modest compared with the placebo group. An increase in relative risk for hypoglycaemia with saxagliptin in SAVOR was noted in patients on background sulfonylureas.<sup>12</sup> However, when this subgroup was examined, there was no increase in risk of heart failure hospitalization with saxagliptin.<sup>13</sup> Similarly, in EXAMINE, differences in hypoglycaemia were very minor between the alogliptin and placebo groups.<sup>14</sup>



**Figure 2** Forest plots of risk of heart failure with dipeptidyl peptidase-4 (DPP-4) inhibitors in trials vs. placebo (top panel) and active (lower panel) comparators. CI, confidence interval.

### Interaction with angiotensin-converting enzyme inhibitors/vasoconstrictor effects

Marney et al.<sup>18</sup> suggested that sitagliptin interacted with high-dose enalapril to increase rather than decrease blood pressure levels in metabolic syndrome patients. This was associated with an increase in heart rate and plasma norepinephrine levels that was significant at the highest dose of enalapril. The mechanisms underlying this interaction are unclear but may relate to blockade of the peptides substance P and/or neuropeptide Y with DPP-4 inhibitors, leading to sympathetically mediated vasoconstriction. Similarly, Jackson et al.<sup>19</sup> demonstrated that, in a renal perfusion model, enhancement of angiotensin II-mediated constrictor responses due to increasing neuropeptide Y administration could be exacerbated by sitagliptin and blocked if sitagliptin is given with a neuropeptide Y inhibitor.

If the above are correct, then attention to heart rate and blood pressure responses in the major DPP-4 outcome trials would be of considerable interest. However, an analysis of earlier, much smaller

saxagliptin studies<sup>20</sup> suggested that (either as monotherapy or in combination) there was little impact on blood pressure with the DPP-4 inhibitor in comparison with placebo or metformin.

### Discussion

The recent major DPP-4 inhibitor outcome studies have raised the hypothesis that heart failure may be precipitated and/or exacerbated with the use of these agents in the management of patients with diabetes. This is surprising given that preceding DPP-4 inhibitor data suggested potential for theoretical benefit with regard to HF, on the basis of the mechanisms outlined above.<sup>8,9</sup> This may represent play of chance and/or imbalances across study groups, but, if real, mechanisms urgently need to be elucidated.

Until more data are available, guideline recommendations should be followed, but undoubtedly greater vigilance should be applied to recognizing the development of clinically significant HF in DPP-4 inhibitor-treated patients, including careful clinical assessment of

heart failure symptoms and signs, together with (as required) ancillary objective assessments of heart failure status including measurement of plasma BNP levels and echocardiography.

Two large-scale, placebo-controlled outcome trials, TECOS (with sitagliptin) and CARMELINA (with linagliptin), are due to report in the next few years, which should provide important data to support or refute the above hypothesis. In the meantime, a mechanistic explanation for this potential link should be further explored.

**Conflict of interest:** none declared.

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## Appendix 3.11

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### *Editorial*

Wang I, **Hopper I**. Celiac disease and drug absorption: Implications for cardiovascular therapeutics. *Cardiovascular Therapeutics*. 2014; 36: 253-6.

## Celiac Disease and Drug Absorption: Implications for Cardiovascular Therapeutics

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### Introduction

Current prevalence of celiac disease is estimated to be around 1% in the general population of Europe [1] and the United States [2]. Cardiovascular disease has an even higher prevalence and is the leading cause of death in these regions, causing 46% of all deaths in the European Union [3] and 32% in the United States [4]. Given that many cardiovascular drugs are orally administered, absorption of these drugs may be significantly altered in celiac disease.

### Cardiovascular Disease in Patients with Celiac Disease

Large population studies have found celiac disease to be associated with significant increases in cardiovascular disease compared with the general population [5–7], although in other studies, no elevation in risk has been observed [8,9]. Celiac disease has been associated with 19% higher risk of incident ischemic heart disease [5] and with 43% higher all-cause mortality 1 year post-myocardial infarction compared with the general population [10]. Despite this, a more favorable risk factor profile has been seen in celiac individuals than that seen in the general population with ischemic heart disease, including less smoking, lower body mass index, lower serum cholesterol, and less extensive coronary disease at angiography [11]. The proportion of patients with celiac disease using different classes of cardiovascular drugs has been found to be similar or higher than that of comparator groups [7]; however, one study in patients with celiac disease following myocardial

infarction found lower prescription rates of statins and aspirin, and higher prescription rates of warfarin [11].

The reasons for the apparent increase in cardiovascular risk in the presence of favorable risk factors are not clear. Chronic inflammatory states are associated with atherosclerosis and cardiovascular disease [12,13], and elevated cardiovascular risk has been observed in other auto-immune conditions [14,15]. The presence of gluten in the bowel and resultant chronic inflammation causes increased expression of interferon- $\gamma$  and other cytokines in celiac disease, which are known to promote progression of atherosclerosis [16]. Reduction of inflammation with a gluten-free diet improves inflammatory markers and also markers of vascular impairment [17]. A further contributor may be hyperhomocysteinemia secondary to malabsorption of folic acid and vitamin B<sub>12</sub>, which is a recognized cardiovascular risk factor and associated with thrombosis [18].

### Pathophysiology of Celiac Disease

Patients with celiac disease have an intolerance to gliadin, an alcohol-soluble fraction of gluten, present in wheat, barley, and rye [19]. Gluten ingestion results in an immunologically mediated inflammatory response which damages the mucosa of the small bowel, predominantly the jejunum, resulting in maldigestion and malabsorption. This damage occurs when gliadin is presented by human leukocyte antigen (HLA) molecules to T helper cells which then mediate the inflammatory response. The resulting villous atrophy and destruction of the absorptive surface may alter absorption of orally administered medication.

## How Celiac Disease Affects Pharmacokinetics

Celiac disease has a significant effect on drug absorption [20]. Due to its vast surface area compared with the stomach, most drug absorption occurs in the small intestine and in celiac disease, the surface area available for absorption is substantially reduced due to villous atrophy. The rate of gastric emptying is increased, delivering drug to the small intestine which can result in earlier absorption [21]. The majority of drugs are absorbed by passive diffusion. Nonionized molecules have greater lipid solubility and diffuse readily, while ionized molecules are less lipid soluble and cross membranes less effectively [22]. In celiac disease, the intraluminal pH of the small bowel is more alkaline [23], and this alters the ionization of the drug, which is determined by the drug's acid dissociation constant ( $pK_a$ )—the pH at which half the drug exists in the ionized form. Drugs with a high  $pK_a$  are more nonionized in alkaline environments, favoring their absorption. Changes to the intraluminal pH also alter the gradient across the intestinal membrane which can affect passive diffusion. Villous atrophy can also result in the loss of cytochrome p450 enzymes located in the tips of the villi and reduce first-pass metabolism [24].

## Evidence of Drugs Affected

A small number of pharmacokinetic studies in celiac disease looking at cardiovascular drugs have been performed. Most were performed some decades ago. Drug absorption can be increased, delayed, reduced, or normal in celiac disease [25]. Drugs with increased absorption include propranolol [23,26,27], aspirin [28], methyldopa [29], and simvastatin [30]. Reduced absorption is seen with digoxin [31].

Beta-blockers are used in hypertension and atrial fibrillation for their blood pressure and heart rate lowering properties, and have been shown to improve mortality in patients with heart failure and acute myocardial infarction. There is wide variation in the pharmacology of beta blockers and lipid solubility in particular, with most beta-blockers having lower lipid solubility than propranolol [22]. Three studies found increased propranolol levels in patients with celiac disease compared with normal subjects. Parsons et al. [26] compared two beta-blockers with differing absorptive properties. Propranolol, which is highly lipid soluble, was compared with practolol, which is a water-soluble beta-blocker that does not undergo hepatic metabolism. Fourteen patients with celiac disease in remission on gluten-free diet were compared with ten normal subjects. The plasma concentration and area under the curve (AUC) for propranolol was significantly higher in celiac subjects when compared to normal subjects. This was attributed to an increased rate of diffusion across the abnormal jejunal mucosa of the lipid soluble drug (with earlier peak levels) and also reduced hepatic clearance through saturation of first-pass hepatic metabolism. The plasma practolol concentration was slightly reduced compared to normal subjects, which the authors interpreted as indicating impaired diffusion of water-soluble drugs in celiac disease. However, another potential factor which can alter drug absorption is that some water-soluble drugs, including beta-blockers in current use, are absorbed via transporters in the intestine [32]. Practolol has since been removed from the market due to

severe side effects including conjunctival scarring, fibrosis, and metaplasia [33]. A follow-on study by Schneider et al. [27] found similar results, with increased plasma propranolol levels in the first four hours, but AUC was not increased. The authors questioned whether first-pass metabolism was saturated by the increased rate of absorption. Another study found that higher jejunal surface pH correlated with increased propranolol absorption and impaired folate absorption in celiac subjects compared with healthy controls [22]. Propranolol has been largely superseded in cardiovascular disease by beta-blockers with more targeted beta-receptor affinity and once daily dosing.

Acetylsalicylic acid, or aspirin, is a lipid-soluble, acidic platelet inhibitor. Absorption occurs in the stomach and in the small intestine. Low-dose aspirin (75–150 mg) is used for secondary prevention of myocardial infarction and also to reduce thrombophilic risk in heart failure. Low-dose aspirin has not been specifically examined in celiac disease; however, one study investigated aspirin at analgesic doses (600 mg) [28]. Absorption of aspirin occurred earlier in the patients with celiac disease than in the healthy controls, but overall the amount absorbed was the same in both groups, and by 45 min, the salicylate concentrations were the same in both groups. This finding is counter-intuitive, as absorption of acidic substances is impaired in a high pH environment, and suggests that factors other than the  $pK_a$  of lipid-soluble drugs may play a more prominent role in affecting absorption. The authors explain the earlier absorption by faster gastric emptying time delivering the aspirin to the small intestine earlier. It is difficult to say whether these altered pharmacokinetics have any clinical relevance with low-dose aspirin.

Methyldopa is an alpha-adrenergic agonist used mostly in pregnancy-induced hypertension. It is predominantly absorbed from the gut with high first-pass metabolism by sulfate conjugation which is most likely to occur in the intestinal wall. Renwick et al. [29] showed elevated blood levels of methyldopa, with a near doubling of the peak plasma concentration and the AUC in patients with celiac disease compared with healthy controls. Urinary methyldopa was collected and surprisingly, showed no increase in the amount of drug absorbed in the patients with celiac disease. The authors' explanation for this was a decrease in the distribution from plasma to tissues in celiac disease, which was consistent with the observation of no increase in pharmacological response to the drug in the celiac group.

Simvastatin is an HMG-CoA reductase inhibitor which lowers cholesterol by blocking conversion of HMG-CoA to mevalonate, an early, rate-limiting step in cholesterol synthesis. Statins are absorbed from the intestine with extensive first-pass hepatic metabolism. They are used in primary and secondary prevention of myocardial infarction. An interesting study examined whether simvastatin absorption could be used as a surrogate marker to assess disease activity in celiac disease [30]. After a single 20 mg dose, mean serum simvastatin levels were significantly elevated in 18 untreated patients with celiac disease compared with 11 healthy controls ( $46 \pm 24$  nM versus  $19 \pm 11$  nM,  $P < 0.005$ ), while in 25 treated patients with celiac disease on a gluten-free diet, the mean simvastatin level was closer to normal ( $21 \pm 16$  nM). A cut-off value of 24 nM for diagnosis of inadequately treated celiac disease was suggested. The authors proposed that the increase in serum simvastatin levels was explained

by reduced first-pass metabolism with the loss of intestinal CYP3A4.

Digoxin is a cardiac glycoside and is absorbed passively mostly in the duodenum and jejunum. Digoxin has a steroid structure similar to fat soluble vitamins, which are also poorly absorbed in patients with celiac disease. When used in atrial fibrillation, digoxin lowers ventricular rate at rest, and in heart failure, it modulates autonomic tone and is a positive inotrope. A study of participants with compensated congestive cardiac failure compared four patients with celiac disease with ten controls without celiac disease [31]. Steady state digoxin levels on a dose of 250 mcg daily were significantly reduced ( $P < 0.001$ ) in the patients with celiac disease (mean 0.4 ng/mL) compared to controls (mean 1.3 ng/mL). Decreased intestinal absorption was the likely explanation, as similar capacity for renal excretion was found in both groups.

Various blockers of the renin-angiotensin-aldosterone system including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists, used in hypertension, ischemic heart disease, and heart failure, have not been studied. Nor have calcium channel blockers which are commonly used in cardiovascular disease. Additionally, new oral anticoagulants (NOACs) including dabigatran, rivaroxaban, and apixaban which are used to reduce stroke risk in nonvalvular atrial fibrillation, and various fixed dose anti-platelet agents including dipyridamole, clopidogrel, ticlopidine, prasugrel, and ticagrelor also have not been studied in celiac disease.

## Implications for Cardiovascular Drugs

Cardiovascular drugs are used commonly in patients with celiac disease and pharmacokinetic studies of cardiovascular drugs in

celiac disease are sparse, particularly for the more recently developed drugs. For some drugs, the altered pharmacokinetics may have no clinical relevance, such as that seen with aspirin and methyldopa whereas for other drugs, including beta-blockers and other anti-hypertensive agents, plasma levels of drugs may be increased or decreased. The ability to measure blood pressure or heart rate allows a convenient way to confirm that the drug is working, although increased vigilance may be appropriate to ensure the drug is working over the full dosing period. There may be altered synergism between the agents with combination anti-hypertensive products as a result of altered absorption of individual components in celiac disease. Increased plasma levels of some drugs may increase the risk of side effects, for example with statins, and these should be enquired about carefully. When available, therapeutic drug monitoring should be used, such as with digoxin, and this should be pursued during remission as well as during flares. Anticoagulation in celiac disease deserves particular attention. Warfarin hypersensitivity can occur secondary to malabsorption of vitamin K [34]. No studies have investigated the pharmacokinetics of the NOACs in celiac disease, and monitoring of plasma drug levels, especially during initiation and flares, should be considered [35].

In summary, clinicians should be aware that the pharmacology of drugs may be altered in celiac disease, during both active and remission periods. The etiology of changes to pharmacokinetics is multifactorial and can be unpredictable. There is a need for a more significant evidence base to inform clinical practice in this particular patient group, as the clinical consequences of altered absorption may be significant.

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## Unsolicited Editorial

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## Appendix 3.12

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### *Invited review*

**Hopper I**, Kotecha D, Chin KL, Mentz RJ, von Lueder TG. Comorbidities in heart failure: are there gender differences? Current Heart Failure Reports. Submitted manuscript.

# Comorbidities in Heart Failure: Are There Gender Differences?

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## **Abstract**

Compared to men, women with heart failure (HF) are often older, smoke less, and have more preserved ejection fraction (EF), and hypertensive HF rather than HF of ischemic etiology. Gender-stratified outcome on comorbidities data in HF are scarce. Women have traditionally been under-represented in HF trials. Although data suggest that overall prognosis may be better in women, they experience lower quality of life with greater functional impairment from HF compared to men. Gender-differences have been reported for comorbid diabetes, chronic obstructive pulmonary disease, renal dysfunction, anemia and depression, and may explain gender disparity in outcomes. However, possible confounding of comorbidities with known prognostic determinants in HF (such as EF) as well as gender-differences in the utilization of medical therapies obscures interpretation.

In this review, we will explore the evidence for gender differences in non-cardiovascular comorbidities in HF. Our findings may guide clinicians to individualize HF care, according to best-practice, in the hope of improving prognosis for this chronic and debilitating condition.

## Introduction

The prevalence of heart failure (HF) is projected to increase substantially due to the ageing of populations and increased longevity<sup>1</sup>. The majority of HF patients suffer from comorbidities, defined as cardiovascular and non-cardiovascular chronic conditions that co-exist with the primary illness of HF<sup>2-5</sup>. Comorbidities put an additional burden on patients, healthcare utilization and expenditure for HF, and are associated with worse outcome<sup>4, 6, 7</sup>. Moreover, comorbidities may constitute risk factors for HF, trigger episodes of exacerbation, and have been proposed to drive the underlying disease process<sup>3, 8</sup>. A recent study providing longitudinal follow-up data of community-dwelling HF patients suggests that the percentage of HF patients with 4 or more comorbidities has increased substantially in recent years<sup>9</sup>. Another contemporary report showed that non-cardiovascular comorbidities constitute a greater hazard for hospitalizations and death than cardiovascular diseases in this population<sup>10</sup>.

There is a paucity of gender-specific data on comorbidities in HF. Despite the fact that more than half of the patients with HF in routine care are women, randomized clinical trials (RCT) supporting current HF management guidelines have recruited predominantly male subjects with a lack of prospective gender-specific analyses. Some evidence, largely from registries, demonstrates important gender-differences in HF etiology, risk factors, and clinical presentation: Women, compared to men, tend to be older; with higher blood pressure and non-ischemic HF etiology, as well as more comorbidities such diabetes, renal disease and arthritis<sup>11, 12</sup>.

Accumulating evidence suggests better overall prognosis for women with HF compared to men, although it is not possible to entirely separate the impact of these differences according to comorbidity burden<sup>13-23</sup>.

The Meta-Analysis Global Group In Chronic Heart Failure (MAGGIC), comprising individual patient data from 31 prospective observational and randomized studies in almost 42,000 patients with a mean follow-up of three years is currently the largest database containing gender-specific data in HF. MAGGIC demonstrated better survival for women irrespective of ejection fraction (EF) and age, although the gender-specific survival benefit was attenuated in subjects with ischemic etiology and those with comorbid diabetes<sup>9, 24</sup>. Also, the Registry to Improve the Use of

Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) in HF outpatients with reduced ejection fraction showed that women were more likely to have advanced CKD<sup>25</sup>. In contrast, the multicenter Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry involving 48,612 patients with HF showed a similar burden of comorbidity and outcomes for both genders<sup>17</sup>.

The evidence on gender-specific outcomes appears to be different between acute and chronic stable HF phenotypes. The Acute Decompensated Heart Failure National Registry (ADHERE) database and the American Heart Association Get With The Guidelines-Heart Failure (GWTG-HF) registry each comprising data from approximately 100,000 hospitalizations reported important gender differences for patient characteristics for the majority of comorbidities, but similar clinical outcomes for both genders<sup>26, 27</sup>. Likewise, the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) Trial in 4,133 patients hospitalized for HF and EF of  $\leq 40\%$  reported similar rates for all-cause mortality and CV death or HF hospitalizations for women and men<sup>23</sup>.

Comorbidities burden in HF increase with age, may exacerbate the progression and clinical severity of HF, and possibly be of prognostic importance<sup>28, 29</sup>. Several important differences between HF with reduced EF (HFrEF) compared to preserved EF (HFpEF; commonly defined as EF  $\geq 40\%$ , 45% or 50%) exist where diabetes, anemia, chronic obstructive pulmonary disease and obesity were more commonly observed in patients with HFpEF<sup>4, 26, 30, 31</sup>. In general, in women HFpEF is more predominant than HFrEF<sup>4, 10, 26, 27, 29, 32-34</sup>. Comorbidities exacerbate morbidity and mortality in HF although close relationships with other well-established prognostic determinants such as EF likely contribute.

This manuscript discusses the available evidence from registries, administrative data from healthcare providers and clinical trials on gender-specific differences in major non-cardiovascular chronic conditions comorbid to HF.

## Diabetes

Diabetes mellitus is not only a common and important comorbidity to HF, but also exerts maladaptive cardiovascular effects such as promoting coronary atherosclerosis, adverse myocardial remodelling, endothelial dysfunction, autonomic neuropathy, renal failure<sup>35</sup>. Diabetes is typically defined by clinical history, although some studies have distinguished between diabetes subtypes and/or insulin dependency. The reported prevalence of diabetes in clinical trials in HF ranges between 11% and 50% (Table)<sup>4, 5, 23, 34, 36</sup>[289,290]. Data from large registries such as OPTIMIZE-HF, ADHERE and GWTG-HF suggest a higher prevalence of diabetes of 30% to 44% in real-world patients with HF<sup>17, 26, 31, 37</sup>. The Framingham study reported a prevalence of 26% and 14% of women and men with HF, respectively<sup>5, 38</sup>.

The overall prevalence of diabetes (i.e., including both type 1 and type 2) among the 2,400 women and 5,199 men randomized in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program was similar in women (30%) and in men (28%). No significant gender differences were found for type 2 diabetes (18% in women vs 20% in men; OR 0.95 (95% CI 0.84 to 1.08)) but significantly more women suffered from type 1 diabetes (12% vs men 8%; OR 1.52 (95% CI 1.29 to 1.79);  $P<0.001$ )<sup>22</sup>.

Gender-stratified analysis of the Cardiac Insufficiency Bisoprolol Study (CIBIS-II) reported a fairly low prevalence of diabetes with no significant differences according to gender (women 14% versus men 11%,  $P=0.117$ ). Overall, women exhibited substantially lower rates of all-cause and cardiovascular mortality than men<sup>39</sup>.

Among 5,491 patients hospitalized with new or worsening HF in relation to the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) study, diabetes was present in 900 subjects (16%) of whom 370 were women and 530 men<sup>33</sup>. The investigators showed that diabetes was independently associated with increased mortality in patients hospitalized with HF (RR: 1.5; 95% CI 1.4 to 1.6;  $p<0.0001$ ). Of note, diabetes was associated with a larger increase in mortality in women than in men (RR 1.7 (95% CI 1.4 to 1.9) vs RR 1.4 (1.3 to 1.6),  $p<0.0001$ ).

In HF with preserved EF in the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) study, a trial with approximately 60% of patients being women, diabetes

prevalence was similar in men (27%) and women (28%). On multivariable analysis, no significant gender differences were found for the association between diabetes and clinical events<sup>40</sup>.

In the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2), a prospective observational study of HF in Japan (preserved EF in 75.1% of women vs in 65.8% of men,  $P<0.001$ ), diabetes was less prevalent in women (31.7%) vs men (36.4%;  $P=0.002$ ). Overall survival was similar. Analysis of predictors for all-cause mortality between genders showed significant interaction for diabetes although no detailed hazard ratios were reported<sup>41</sup>. These data are contrasted by a pooled analysis of prospective and observational studies from Spain. The multicentre Andalusian Heart Failure Registry (RAIC) examined 795 patients with a primary diagnosis of HF<sup>42</sup>. The relative prevalence of diabetes compared to men was higher in women (50.7% versus 41.2% in men,  $p<0.007$ ). The authors did not report gender-related differences in in-hospital mortality (5.2%) or short-term morbidity (19.2%), and the relative importance of diabetes to these outcomes was not presented.

In the MAGGIC database, diabetes was found in 25.4% of women vs 22.8% of men;  $p<0.001$ )<sup>24</sup>. The survival benefit in women was attenuated with comorbid diabetes: the hazard ratio (95% CI) of death for men vs. women without diabetes was 1.37 (1.30-1.45), but in the presence of diabetes only 1.11 (1.03-1.20);  $P<0.0001$  for interaction)<sup>24</sup>.

As with most other comorbidities in HF, diabetes is more frequently reported in registries compared to prospective randomized trials. There are important differences in epidemiology related to clinical HF status, with diabetes being more prevalent in hospitalized patients than outpatients<sup>35</sup>. The current HF literature does not support a consistent gender differences with regards to comorbid diabetes. Given the generally adverse association between diabetes and clinical outcomes, gender-differences in its prevalence are likely of clinical relevance. Some reports have demonstrated that concomitant DM attenuates the female gender benefit in outcomes compared to men. Thus, the negative impact of diabetes on prognosis might be enhanced in women, highlighting an urgent need for gender-specific management strategies and for prospective gender-stratified analysis in future studies in HF.

**Table 1. Comorbidities and demographics at baseline according to gender in important HF studies**

Paper	Author	Year	Country	Study type	HF phenotype	n		Age		EF		Diabetes		CKD		Anemia		Hb		COPD		Smoking		Depression		Thyroid		PVD		Obesity																										
						All	M	W	M	W	M	W	M	W	M	W	M	W	M	W	M	W	M	W	M	W	M	W	M	W	M	W	M	W																						
META-ANALYSIS																																																								
MAGGIC	Martinez-Sellés et al	2012	International	Individual patient meta-analysis	Stable HF	41949	28052	13897	65.6±11.6	70.5±12.1	33 (25-44)	42 (30-57)	22.8	25.4																																										
RANDOMISED CONTROLLED TRIALS																																																								
CIBIS II	Simon et al	2001	International	RCT	Chronic HF	2647	2132	515	60±11	65±9	27±6	28±6*	11	14*																			70	28																						
DIG	Rathore et al	2002	International	RCT	Chronic HF	6800	5281	1519	64	66	28	30	26.9	33.6																							27	26																		
I-PRESERVE	Lam et al	2012	International	RCT	HFpEF (EF>45%)	4128	1637	2491	71±7	72±7	58±9	61±9	27	28*	26	34	16	11	14.5±1.9	13.5±1.8	13	8	32	9											35	46																				
CHARM (included in MAGGIC)	O'Meara et al	2007	International	RCT	Chronic HF	7599	5199	2400	64.4±0.2	67.8±0.2	36.9±0.2	43.3±0.3	27.7	30																			73	42											28	29										
PROTECT	Meyer et al	2013	International	RCT	HFH impaired renal function	2033	1364	669	69±12	73±11	30±12	37±14	43	50																			21	16	27	9	6	9*					12	8												
REGISTRIES / SURVEY																																																								
ADHERE	Galvao et al	2006	USA	Registry	ADHF	105,388	50,713	54,674	70.1±14	74.5±14	32.9±15.8	42.2±17.3	44	44*	33	27	56	51	12.8±2.7	12.1±2.5											17	10					11	24																		
RAIC	Jiménez-Navarro et al	2008	Spain	Registry	ADHF	795	430	365	69.4±11	73.4±10	EF<45=57%	EF<45=36%	41.2	50.7																																										
EHFS II	Nieminen et al	2008	Europe	Prospective observational survey Cross-sectional survey	ADHF	3580	2196	1384	67.8±12.4	73.1±12.0	35.1±14.0	43.7±15.8	31.4	35	18.7	13.8	12.4	18.5											22.1	15	19.8	6.9					4.4	11.1	14.8	8.1	27	27*														
Baumhakel	Baumhakel et al	2009	Germany		Chronic HF	1857	977	880	66.5±9.8	69.9±11.1	48.5±11.9	49.2±13.4*	33.1	33.1*																																										
OPTIMIZE-HF	Fonarow et al	2009	USA	Registry and care improvement program	ADHF	48,612	23,537	25,075	70.8±13.9	75.4±13.6	34.2±16.2	43.7±17.8	41.5	41.5	22.5	16.8	15.2	19.8	12.5±2.1	11.8±1.9	28.8	26.4	20.8	12.4	8.8	12.3	9.2	20.5	15.1	12.3																										
BADAPIC registry	Jiménez-Navarro et al	2010	Spain	Registry	Chronic HF	4720	3351	1369	64±12	70±12	38±17	47±24	29	39																																										
GWTH-HF	Klein et al	2011	USA	Registry and care improvement program	ADHF	99,841	50,616	49,225	69±14	74±14	30(20-47)	45(30-60)	41	42*	23	18	15	20	12.4	11.7	29	29*	21	12	.	.	.	.	13	10																										
HFSIS	Klempfner et al	2014	Israel	Prospective cohort survey	ADHF	2212	1214	998	73.5±11	77±10	EF<50=62%	EF<50=39%	42	46*																			42	13											19	29										
CHART-2	Sakata et al	2014	Japan	Registry	Chronic HF (Stage C/D)	4736	3234	1502	67.7±12.1	71.5±12.3	55.5±15.2	60±15.4	36.4	31.7*																			13.6±2	12.3±2.2											23.4	6.6										
RICA	Conde-Martel et al	2015	Spain	Registry	ADHF	1772	836	936	76.6±9.3	79.3±7.8	45.7±16.4	54.1±14.3	44.3	46.0*	53	64.6	61.5	54.2*											43.2	12.8											22.2	4.7	30	43												
THESUS-HF	Ogah et al	2015	Sub-Saharan Africa	Registry	ADHF	931	494	437	54±16.9	54.6±18.3	37.5±15.7	43.4±16.1	11.8	11.9*																			17.3	2.8	3	4.1*					1.8	0.7														

Data are expressed in %

\*Difference is NOT statistically significant

Abbreviation: ADHF: Acute decompensated heart failure; BMI: Body mass index; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; EF: Ejection fraction; Hb: Hemoglobin; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; RCT: Randomised controlled trial; MAGGIC: Meta-Analysis Global Group in Chronic Heart Failure; CIBIS II: Cardiac Insufficiency Bisoprolol Study II; DIG: Digitalis Investigation Group; I-PRESERVE: Irbesartan in Heart Failure and PRESERVED Ejection fraction; CHARM: Candesartan in Heart Failure of the Selective A1 Adenosine Receptor Antagonist Assessment of Mortality and Morbidity; PROTECT: Placebo-controlled Randomized Study of Eplerenone for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function; ADHERE: Acute Decompensated Heart Failure National Registry; RAIC: Andalusian Heart Failure Registry; EHFS II: Euro Heart Failure Survey II; OPTIMIZE-HF: Treatment in Hospitalized Patients with HF; BADAPIC: base de datos de pacientes con IC; GWTH-HF: Get With The Guidelines-HF; HFSIS: Heart Failure Survey in Israel; CHART-2: Chronic Heart Failure Analysis and Registry in the Tohoku District-2; RICA: Registro de Insuficiencia Cardíaca; THESUS-HF: Sub-Saharan Africa Survey of HF.



## Chronic kidney disease

Chronic kidney disease (CKD) is another adverse prognostic indicator in HF subjects<sup>4, 5, 7, 36, 43-47</sup>. In previous analyses, CKD has usually been defined by past medical history, or determined from an estimated glomerular filtration rate (eGFR; for example  $<60$  ml/min/1.73 m<sup>2</sup>). The prevalence of concomitant CKD therefore differs widely between 14% up to 90% in various HF cohorts (e.g., acute vs. chronic; preserved vs. reduced EF) and definition used (see table)<sup>17, 26, 37, 48-51</sup>. Registries and population-based surveys reported higher prevalence figures than prospective trials which is likely due to the presence of exclusion criteria related to renal dysfunction in most HF trials.

In a retrospective cohort study of 18,322 age- and gender-matched Medicare beneficiaries with HF (59.1% women), the relative mortality risk of comorbid CKD was higher than for comorbid diabetes or colorectal cancer, and only second to lung cancer<sup>7</sup>.

With respect to gender, CKD has been reported more frequently in women with HF, while other authors reported male predominance or no gender-differences<sup>11, 23, 34, 37</sup>. A recent epidemiological study assessing healthcare utilization and outcomes in Olmsted county, Minnesota, US reported a lower prevalence of CKD in women with both preserved EF (15% compared to men 23%) and reduced EF (14% versus 17%)<sup>29</sup>.

Of note, eGFR has usually been computed using the Modification of Diet in Renal Disease equation (MDRD) formula which is based on serum creatinine, gender, age, and ethnicity, thereby potentially introducing some gender bias<sup>52</sup>. In the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) the proportion of women increased with declining eGFR<sup>25, 53</sup>. In contrast, in the large multicenter GWTG-HF registry (n=89,127), the prevalence for CKD was higher in men both with reduced and preserved EF, and CKD was strongly associated with increased mortality for both genders<sup>37</sup>. There was no gender-difference in in-hospital mortality.

In HF with preserved EF in the I-PRESERVE study, CKD was more prevalent in women than in men (34 vs 26%,  $p<0.001$ ). Despite better overall survival in female patients, the presence

of an eGFR <60 ml/min/1.73 m<sup>2</sup> attenuated the survival advantage in women compared with men<sup>40</sup>.

The National HF Registry under the Spanish Society of Internal Medicine (RICA) included 1,772 patients (836 men [47.2%] and 936 women [52.8%]) with HF and mean EF of 50%. CKD was seen more often in women than men (59.1% vs 53.0%,  $p < 0.001$ ) but was not associated with survival<sup>16</sup>.

CKD is highly prevalent and an important determinant of adverse outcome in HF. Registry data likely reflect the burden of comorbid CKD in HF more accurately than prospective trials from which HF patients with significant CKD traditionally have been excluded. The fact that more women with HF have hypertension, a predisposing condition for CKD, would provide a plausible explanation for female predominance in the prevalence of CKD. Yet, comorbid CKD in HF does not seem to exhibit a consistent gender distribution pattern, rather, its prevalence varies according to HF phenotype and clinical status. Even more important, differences in study type, methodology, investigated cohorts and employed definitions for CKD likely account for most inconsistencies. Based on the negative prognostic association of comorbid CKD in HF and the finding by some authors of gender-specific differences in its prevalence, gender-specific evaluation of CKD comorbid to HF should be the subject of prospective studies. With CKD and worsening renal function also frequently being the cause of discontinuation of medical therapies for HF, future studies should assess whether CKD requires tailored, gender-specific management in order to optimize outcomes in women and men with HF.

### **Anemia and iron deficiency**

Anemia and iron deficiency are common in HF and are associated with worse symptoms and outcomes in HF patients<sup>54-57</sup>. Commonly anemia has been defined as hemoglobin levels of <12 g/dl (7.5 mmol/l) in women and <13 g/dl (<8.1 mmol/l) in men<sup>36</sup>. Dilutional anemia can occur in decompensated congestive HF and together with non-uniform cut-off definitions for anemia, may explain some discrepancies between HF cohorts. The reported prevalence of anemia in HF

according to the above criteria ranges from 20-40%<sup>27, 57-61</sup>. In many HF cohorts, lower hemoglobin levels have been associated with higher morbidity and mortality<sup>4, 37, 58-60, 62</sup>.

Anemia seems to be more frequent in women with HF compared with men<sup>63-65</sup>. In the Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure (COACH) biomarker analysis (n=567; mean age 71 years; 38% women), anemia was more than twice as common in women (56% vs men 26%,  $p<0.001$ ).

It is important to note that anemia in heart failure is closely related to renal dysfunction, with complex and interacting pathophysiological mechanisms (cardio-renal-anemia syndrome)<sup>66</sup>. This notion is supported by data from the Norwegian HF Registry of outpatients with advanced HF in which baseline anemia was predictive of all-cause mortality but not in the subset of patients with renal failure or advanced HF functional class<sup>67</sup>.

The prevalence of iron deficiency in HF is at least twice that of clinically overt anemia<sup>55, 68</sup>. Iron plays a key role in erythropoiesis, and normal iron metabolism is crucial for normal function of cardiac cells<sup>69</sup>. Iron deficiency is associated with worse outcomes in HF<sup>70</sup>. In prospective observational study of 546 predominantly male HF patients, female gender was an independent predictor of iron deficiency<sup>69</sup>.

Anemia is associated with older age, higher mortality both in-hospital and long-term, and with reduced quality of life in patients with HF. Several reports suggest a marked female predominance in the prevalence of anemia and iron deficiency in HF. Apart from gender-specific epidemiological data, little is known on putative gender differences in the pathophysiology, clinical course and response to therapy of anemia and iron deficiency in HF. Ongoing studies evaluating the role of iron repletion strategies in anemia or iron deficiency comorbid to HF will provide further insights into putative gender-specific differences of these highly prevalent conditions and clarify a possible need for targeted therapies according to gender.

## Frailty and arthritis

Frailty is often circumscribed as the presence of general muscle weakness, fatigue, limited mobility, unintentional weight loss and reduced physical reserve<sup>71-74</sup>. Frailty increases with age and progressive HF symptoms, and predicts death and morbidity. Given the vague definition and inability to distinguish physiologic frailty of aging from that of HF and comorbid diseases, the prevalence estimates are wide and range between 10% in HF outpatients and up to 74% in hospitalized HF patients<sup>74-76</sup>. No robust data exist on the gender distribution of frailty in HF.

Osteoarthritis and rheumatoid arthritis are common in HF, especially in the elderly, and may share pathogenetic links with HF<sup>3, 5, 77-82</sup>. In particular, pro-inflammatory mechanisms have been proposed. The reported prevalence of chronic knee pain and radiographic osteoarthritis according to gender in the general population has differed substantially, due to differences in study design definitions used<sup>79, 83, 84</sup>.

As with osteoarthritis, the prevalence of rheumatoid arthritis in the general population, increases with age, with the presence of HF, and shows a more consistent female predominance<sup>85-87</sup>. Conversely, the prevalence of HF is higher in patients with arthritis<sup>85</sup>. In an analysis of 34,701 patients with arthritis, gender did not confer increased risk for HF, although the incidence of HF in that cohort was too low to make definitive conclusions<sup>88</sup>. Importantly, rheumatoid arthritis as a comorbidity to HF is associated with worse prognosis<sup>89</sup>.

Yet, most previous HF cohort have not systematically reported comorbid arthritis. A recent study in community-dwelling HF found arthritis (of any kind) to be more prevalent in women than men, in particular in women with HF preserved EF<sup>29</sup>.

Together, frailty and arthritis are very common comorbidities to HF, increase with age and carry prognostic importance. There is a striking scarcity of gender-specific data on the role these comorbidities in HF. Moreover, common arthritis therapies such as corticosteroids and non-steroidal anti-inflammatory drugs potentially exacerbate HF<sup>90</sup>. With polypharmacy being an

increasing concern in HF patients, particularly in the elderly, more gender-specific evidence is also needed for medication use for arthritis in HF.

### **Chronic obstructive pulmonary disease**

Chronic obstructive pulmonary disease (COPD) predicts mortality in HF<sup>91</sup>. COPD has been reported to be more common in male compared with female HF patients<sup>33, 92</sup>. Registries and RCTs show substantially higher rates of smoking in men, however gender differences in rates of COPD differences are less marked or absent (table)<sup>16, 19, 27, 34, 40, 91</sup>. The GWTG-HF registry found smoking rates of 21% in males and 12% in females, however the prevalence of COPD was 29% in both males and females. The OPTIMIZE-HF registry had similar rates of smoking according to gender (21% males, 12 % females) with a slightly lower prevalence of COPD in females (29% vs 26%). The EuroHeart Failure Survey II (EHFS II) demonstrated higher rates of smoking in males (20%) vs females (7%) and higher rates of COPD (22% vs 15% in females).

The prevalence of COPD has decreased much more in men than in women in recent decades, a finding which has been attributed to trends in smoking patterns but is also thought to reflect women's greater susceptibility to the effects of smoking<sup>93</sup>. Exact mechanisms for this are not understood, and hypotheses include that women have smaller airways leading to greater per cigarette exposure, differential metabolism of tobacco products and potentially also that a decrease in oestrogen in women smokers may exacerbate pulmonary disease<sup>94</sup>. There also may be under-diagnosis of COPD in women due in part to a distinct clinical presentation compared with men. Women are less likely to present with phlegm and more likely to present with dyspnoea<sup>93</sup>. One study surveying physicians found that they were less likely to give a diagnosis of COPD to a hypothetical female than male patient with the same presenting symptoms<sup>95</sup>. Diagnosing COPD in the HF population may be particularly complex given the overlap of symptoms and risk factors. This is especially true in decompensated HF as pulmonary venous congestion affects pulmonary function tests. In addition, the diagnosis of COPD is often particularly difficult in HF with

preserved EF, a HF phenotype which is more common in women. A recent report assessing comorbidities in COPD showed a higher prevalence of HF in women<sup>96</sup>.

Although COPD is a common comorbidity to HF, it is not always assessed and evaluated by pulmonary function tests. COPD negatively impacts on HF prognosis. The current literature points to male predominance in the prevalence of COPD comorbid to HF. A clinical challenge is the overlap in symptoms from HF and COPD, and further, the fact that pulmonary function tests are often unreliable in patients with decompensated HF. Drug interactions are another clinical problem: beta-blockers in HF have the potential to increase airway obstruction; in particular non-selective ones<sup>97</sup>. Despite proven efficacy, HF patients with COPD are therefore less likely to be prescribed beta-blockers. Conversely, beta-adrenergic agents and corticosteroids for COPD may lead to tachyarrhythmia and fluid retention<sup>98</sup>. Whether gender differences exist for the occurrence and severity of these important drug interactions should be the subject of future research.

## **Depression**

Depression is a common comorbid condition, and often under-recognised in the HF population as symptoms can overlap with those of HF<sup>34, 99-105</sup>. Depression is an independent predictor of poor outcomes in HF patients, including death and HF hospitalisation<sup>99-102</sup>. It is also recognised as an independent risk factor for CAD with the same weight as smoking, hypertension and hyperlipidaemia<sup>106</sup>, and depression and HF share several biological mechanisms, including neurohormonal activation and increased inflammatory markers<sup>107</sup>.

As with women in the general population, women with HF have a higher burden of depression than men<sup>108</sup>. A meta-analysis examining depression in HF found 16 studies in which gender differences were recorded, and demonstrated that the prevalence in women was 32.7% compared with 26.1% in men, which was 2-3 times the rate of the general population<sup>99</sup>. Prevalence estimates varied widely in this study, from 11-67% in women, and 7-63% in men depending on how depression was defined and which investigative tool used<sup>99</sup>. Depressive symptoms may not be routinely assessed in HF patients, and registries and RCTs have only infrequently included details on comorbid depression (see table)<sup>17, 31, 34</sup>. In the OPTIMIZE-HF registry of over 48,000 patients

with ADHF, only 12.3% of women and 8.8% of men had depression. A recent study examined the gender differences in comorbid conditions in HF in Olmsted County, Minnesota, using a records linkage system which allowed virtually complete capture of health care utilisation and outcomes in residents<sup>29</sup>. This study found higher rates of depression in women than men, and in both men and women, higher rates in HFpEF than HFrEF.

Overall, depression is a common condition in HF and exhibits a higher prevalence in women than men in most studies. Depression is a predictor of poor outcome in HF; moreover, depression severely and directly affects physical, mental and emotional wellbeing. In HF subjects, depression could potentially increase non-adherence to medication and other aspects of HF management<sup>109</sup>. In light of the gender disparity in prevalence, comorbid depression overall may exert greater detrimental effects in women with HF than men. Therefore, the lack of systematic gender-specific assessment of depression and the paucity of published gender-specific analyses is striking and calls for dedicated assessment in future work.

### **Other non-cardiac comorbidities**

Thyroid disease is common in HF, and both abnormally low and abnormally high thyroid function may increase HF event rates<sup>110-113</sup>. Thyroid hormone has fundamental effects on CV homeostasis<sup>114, 115</sup>. The reported prevalence of abnormal thyroid function in women is at least twice that of men with HF. In women, abnormal thyroid function was reported at around 20% and 11% in OPTIMIZE-HF and EHFS II respectively, contrary to less than 10% in men in both studies (table 1)<sup>17, 19, 32</sup>. Different definitions of comorbid thyroid disease may explain differences in the overall prevalence between studies.

Peripheral artery disease has been shown to predict adverse outcome in acute myocardial infarction complicated with HF, reduced EF or both<sup>116</sup>. In HF, peripheral artery disease is another highly prevalent comorbidity, and exhibits male preponderance which may be due to the markedly higher percentage of male smokers within the same studies (table 1)<sup>16, 17, 19, 27, 34</sup>.

The literature on gender differences of liver disease, obesity, hyperlipidemia, cognitive impairment, malignancies, mental disorders and others comorbid to HF is limited and these comorbidities are not further discussed here.



## Summary and conclusion

Despite some reported gender-differences in the prevalence of non-cardiovascular comorbidities in HF, our understanding of non-cardiovascular comorbidities in HF remains incomplete. Women with HF are older and more likely than men to have comorbid hypertension, diabetes, renal failure, obesity, depression and more severe symptoms, but appear to have better overall survival. Men with HF are more often smokers and tend to have more ischemic heart disease, COPD and HF with reduced EF compared with women.

In HF clinical trials, women have traditionally been underrepresented, and interpretation of comorbidities is frequently obscured by non-uniform definitions, lack of pre-specified gender-stratification, and lack of long-term follow-up. Registries and administrative data from healthcare providers generally report higher prevalence values for comorbidities, and contrast with prospective randomized studies in the gender-specific distribution of comorbidities and their association with outcome.

There is uncertainty as to whether gender-differences exist in adherence to guideline-directed pharmacological treatment of HF as well as that of comorbidities, and whether such differences are of prognostic relevance.

Temporal changes in epidemiology suggest an increasing incidence of HFpEF compared to HFrEF, higher comorbidity burden and female predominance with the aging of HF cohorts<sup>4, 10, 29, 117</sup>.

Combined efforts from regulators, trialists, health authorities and registry administrators are required to adequately fill our knowledge gap on gender-specific differences in epidemiology, pathogenesis, therapeutic management and prognostic significance of comorbidities in HF. There is an unmet need and a great opportunity for clinicians to assess whether gender-related differences in comorbidities of HF require specific management strategies.

**Conflicts of interest**

RJM receives research support from the NIH, Amgen, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Novartis, Otsuka, and ResMed; honoraria from HeartWare, Janssen, Luitpold Pharmaceuticals, Novartis, ResMed, and Thoratec; and has served on an advisory board for Luitpold Pharmaceuticals, Inc. TGVV has received research support from the South-Eastern Norwegian Health Authority, honoraria from Novartis and has served on advisory boards for Vifor and Novartis. IH, DK and KLC report no conflicts of interest.

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## Appendix 3.13

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### *Letter to the editor*

Krum H, **Hopper I**. Statins in congestive heart failure. Letter to the editor. Heart, Lung and Circulation. 2014; 23:988.

## Statins in CHF



Dear Sir

We read with interest the article of Wang et al [1] regarding their meta-analysis of major clinical outcomes according to statin use in patients with chronic heart failure (CHF).

We are concerned that, in this meta-analysis, non-randomised, observational studies of CHF patient cohorts were accorded equal if not greater weighting than adequately-powered, prospective, randomised, placebo-controlled trials of statin use, such as CORONA [2] and GISSI-HF [3]. As the authors are aware, both of these studies demonstrated neutral outcomes on their primary and secondary endpoints providing definitive evidence for lack of benefit of statins when added to standard therapy in CHF patients. It is therefore regrettable that these clear-cut results are distorted by the non-prospective, non-randomised studies in the meta-analysis of Wang et al<sup>1</sup>, with all of the attendant patient selection and other biases inherent in such studies.

We therefore believe the conclusion of the article that “there is a prevailing practice of insufficient statin therapy in CHF patients” to be unsupported by current clinical trial evidence. We also would argue that additional randomised control trials are not needed as both large-scale,

adequately-powered studies (CORONA [2], GISSI-HF [3]) came to an identical (neutral) conclusion regarding the clinical utility of addition of statins in patients with CHF.

Yours sincerely,

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## Appendix 3.14

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### *Letter to the editor*

Graudins L, Chen F, **Hopper I**. Warfarin Brands. Letter to the editor. Australian Prescriber. 2015; 38: 150-1.

## Letters to the Editor

### Warfarin and beetroot

I was interested to read your article 'How to manage warfarin therapy' (Aust Prescr 2015;38:44-8). In the article and subsequent online quiz, it mentions beetroot as being one of the foods that can affect INR, which I found rather unusual. After having worked as a senior pharmacist on a cardiothoracic ward for a number of years, I have counselled countless patients on warfarin and factors that can influence INR and I have never heard of beetroot being one of them. After doing some of my own research, I came across the vitamin K contents of beetroot, which was listed to be approximately 0.3 micrograms per 100 g in comparison with spinach 540 micrograms per 100 g.


Consequently, I believe that consuming beetroot while taking warfarin would have an insignificant effect on INR compared to other foods. I also noted in the quiz that vitamin C was listed as not affecting INR and, although there is limited evidence, there are a number of case reports of vitamin C at high doses affecting INR. Vitamin C is also listed in the Western Australian Department of Health's Living with Warfarin: Information for Patients,<sup>1</sup> so I believe that it is worth mentioning as something that could possibly affect INR.

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*Philip A Tideman, Rosy Tirimacco, Andrew St John and Gregory W Roberts, authors of the article, comment:*

 Louise Vanpraag rightly points out that the beetroot bulb is a negligible source of vitamin K. It was our oversight in not explicitly naming the beetroot leaves as the rich source of vitamin K rather than the bulb.

While there have been two separate case reports of a possible interaction between high doses of vitamin C and warfarin causing an elevated INR, three separate crossover trials using daily vitamin C doses of 1-10 g for periods of one week to six months have failed to reveal an interaction.

### Warfarin brands

Although a comprehensive guide to managing warfarin, the article in the April 2015 issue (Aust Prescr 2015;38:44-8) did not mention the problem of brand confusion with warfarin. Transition of care, such as hospital admission, is a time when warfarin management may be compromised. In Australia we have two brands – Coumadin and Marevan. Both are manufactured by Aspen Pharmaceuticals, and are available in different strengths and tablet colours. Recently reported incidents involving warfarin brand confusion at our hospital resulted in dose omissions due to Marevan not being available on the ward and inadvertent switching from Marevan to Coumadin. Although no patient harm resulted, time was spent in sourcing the 'right' brand and managing the incidents.

The Pharmaceutical Benefits Scheme notes that the brands have not been shown to be bioequivalent and should not be interchanged.<sup>1</sup> However, a systematic review comparing the bioequivalence of six international warfarin brands found that switching brands was relatively safe.<sup>2</sup> In 44 years of reporting adverse drug reactions in Australia, only three reports, all from 1977, implicate brand switching.<sup>3</sup>

The manufacturer has previously been approached to phase out one brand, with a recommendation that Coumadin be primarily used.<sup>4</sup> We call for either bioequivalence testing of Coumadin and Marevan by the manufacturer or, in the interests of medication safety, for only one brand of warfarin to be available.

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The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.



*Philip A Tideman, Rosy Tirimacco, Andrew St John and Gregory W Roberts, authors of the article, comment:*

 We agree that brand continuity for warfarin is preferred. While it seems unlikely there would be clinically significant differences in the two brands, which vary by a single excipient, there has been no formal bioequivalence testing. The availability of a single brand in Australia would simplify warfarin management and remove any confusion about brand swapping for both patients and clinicians.

#### **Naltrexone and liver disease**


In the good review on long-term drug treatment of patients with alcohol dependence (Aust Prescr 2015;38:41-3), the important issue of underuse of pharmacotherapy for alcohol dependence is identified and an outline of treatment is given. However, the article states that naltrexone is contraindicated in acute hepatitis or liver failure. In my clinical practice, varying degrees of chronic liver disease are commonly encountered when treating an alcohol-dependent population. Continued heavy drinking is much more likely to pose a greater risk to liver function than naltrexone. Arguably, the risk-benefit assessment likely favours naltrexone treatment. Naltrexone can be prescribed in patients with stable or compensated cirrhosis but is not recommended in acute liver failure. It carries a low risk of hepatotoxicity. However, in my experience, many potentially suitable patients are not given the drug because of concerns about hepatotoxicity.

**Mike McDonough**  
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*Philip Crowley, the author of the article, comments:*

 Precautions listed in naltrexone's product information include saying it may cause hepatocellular injury when given in excessive doses,

and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects. The product information also states that naltrexone is contraindicated in acute hepatitis or liver failure. This is based on a study in which 300 mg/day naltrexone was administered to obese patients. Five of 26 naltrexone recipients, and none of the placebo group, developed elevated serum transaminases after 3–8 weeks of treatment.<sup>1</sup>

Data on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) have been used as an indicator of hepatotoxicity, with concentrations indicating both the effects of medication on hepatotoxicity, and reduced hepatotoxicity due to reduced alcohol consumption. Twelve of 1383 participants (0.9%) in the COMBINE study<sup>2</sup> had elevated liver enzymes greater than five times the upper levels of normal. (Most cases were in the naltrexone group.) These effects resolved following discontinuation of the drug. This is the one study large enough to detect an adverse effect at this low level of incidence.

The study that Dr Mike McDonough refers to supports other smaller studies<sup>3,4</sup> indicating that naltrexone was not hepatotoxic at the recommended dose in a trial of 74 participants.

I agree that often patients do better in a risk-benefit assessment when taking naltrexone compared to not taking it (because of concerns about minor liver enzyme changes).

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## Appendix 3.15

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### *Case report*

Power A, Graudins LV, McLean C, **Hopper I**. Probable fenofibrate-induced acute generalized exanthematous pustulosis. American Journal of Health Systems Pharmacy. 2015. In press.

## **Probable fenofibrate-induced acute generalized exanthematous pustulosis**

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There is no conflict of interest for any authors.

## **Abstract**

**Purpose:** To describe a severe idiosyncratic reaction of acute generalized exanthematous pustulosis (AGEP) after a single 145mg dose of fenofibrate. **Summary:** A 58-year-old woman with Type 1 diabetes was commenced on fenofibrate for treatment of retinal cholesterol deposits. Four hours after her first dose, she became unwell with fever and vomiting. She presented to the emergency department 48 hours later and was admitted to the intensive care unit hypotensive and tachycardic with an extensive pustular exanthematous rash. She required vasopressor support and was treated with broad-spectrum antibiotics and a course of immunoglobulin until histopathology confirmed a diagnosis of acute generalized exanthematous pustulosis. Antibiotics were ceased and she was treated with topical steroids and discharged on day 7. Her condition was associated with neutrophilia, impaired renal function and deranged liver enzymes. According to the Naranjo scale of determining causality, fenofibrate-induced AGEP returned a score of 5; indicating probable causality. AGEP is predominantly a drug-induced condition and is associated with several causative agents, but is not typically associated with fenofibrate. The cutaneous eruptions in AGEP are often accompanied, as in this case, by systemic symptoms of fever and leukocytosis, and it can also be associated with impaired creatinine clearance and elevated aminotransaminases. **Conclusion:** Fenofibrate therapy should be added as a possible causative agent of AGEP.

## Introduction

Fenofibrate is a lipid-lowering drug indicated for use in hypertriglyceridaemia, hypercholesterolaemia, dyslipidaemia in type 2 diabetes and in the reduction of progression of diabetic retinopathy. The evidence for the use of fenofibrate in diabetic retinopathy in type 1 diabetes is limited. Its mode of action is to activate peroxisome proliferator-activated nuclear receptors and modulate lipoprotein synthesis and catabolism. The approved dose for adults is 145mg once daily. Common adverse reactions include gastrointestinal disturbances and increased aminotransferases, and although uncommon, severe idiosyncratic cutaneous reactions have been recorded.<sup>1</sup> Acute Generalised Exanthematous Pustulosis (AGEP) is a predominantly drug-induced severe cutaneous adverse reaction, characterised by oedematous erythema with eruptions of numerous non-follicular pustules.<sup>2</sup>

We report a case of AGEP after a single dose of fenofibrate.

## Case Report

A 58-year-old female with a 34 year history of type 1 diabetes mellitus, hypothyroidism and hypercholesterolaemia presented to the emergency department with a painless pustular exanthematous rash on her trunk, buttocks and proximal flexural surfaces, but no mucosal involvement. Recent ophthalmological review had resulted in the addition of fenofibrate 145mg, to treat retinal cholesterol deposits. Four hours after taking the first dose of fenofibrate, the patient became unwell with fever and vomiting. She spent the next twenty-four hours in bed with no food and no insulin and presented to the emergency department approximately 48 hours post-dose, with a blistering rash, which was initially thought to be a burn from her electric blanket. Upon presentation, the patient was febrile (39C), hypotensive (BP recorded at 99/35 on noradrenaline) and tachycardic (HR 124), with elevated blood glucose (13.5, normal 5-10 mmol/L) and normal lactate (1.3, normal 0.6-2.2 mmol/L ). The patient's medications on admission were; Insulin aspart (10 units mane, 7 units midday, 5 units nocte with meals), insulin detemir (15 units mane, 17 units nocte), thyroxine (100 mcg mane, many years), calcium (600mg daily , many years), vitamin D

(7,000 units weekly for many years) and fenofibrate 145mg (commenced two days prior to presentation). Initially, atorvastatin (*Lipitor*®) was thought to be the newly initiated therapy.

However, on medication reconciliation, it was found to be fenofibrate (*Lipidil*®). Her only previous adverse drug reaction was codeine-induced hallucinations.

Fenofibrate was ceased. Broad-spectrum antibiotics including lincomycin, vancomycin, meropenem and flucloxacillin were initially prescribed in standard doses. Anti-infective treatment was ceased on day three, as blood cultures were negative. Viral serology was not performed. She was admitted to Intensive Care for haemodynamic support, requiring noradrenaline (45mcg/min, titrated to mean arterial pressure >70), as well as intravenous immunoglobulin (2g/kg) until vasopressor support weaned, for suspected toxic shock syndrome. Insulin aspart and 25 % glucose infusion infusions (0 -10 units) were titrated to blood glucose levels). Intravenous compound sodium lactate and sodium chloride 0.9% infusions were infused to maintain hydration over two days. Infectious Diseases and Dermatology teams were consulted. Laboratory results on admission revealed a neutrophilia (8.51; normal  $1.9-8.0 \times 10^9/L$ ), raised C-reactive protein (180; normal <5mg/L), decreased eGFR (44; normal >90mL/min/1.73m<sup>2</sup>), and normal liver enzymes. Alanine aminotransferase (ALT) peaked on day 3 (164; normal 7-55U/L) and gamma glutamyl transpeptidase (GGT) (187; normal <38U/L) and alkaline phosphatase (ALP) (162; normal <106U/L) on day 6. Histopathology results from skin biopsies taken on day three showed intracorneal clustered neutrophils, associated with oedema and subepidermal oedema associated with a mixed inflammatory cell infiltrate in the dermis with a perivascular lymphocytic cuffing and scattered eosinophils; features consistent with AGEP.

As the patient's condition improved, she was transferred to the ward. Management with topical triamcinolone and salicylic acid for scalp scaling resulted in further clinical improvement. Oral steroids were not prescribed, due to instability of blood glucose levels. The patient was discharged on day 7. Dermatology follow-up a week later noted peeling skin and hyperpigmentation consistent with resolving AGEP.

## Discussion

The term Acute Generalized Exanthematous Pustulosis (AGEP), as distinct from pustular psoriasis, was first introduced in 1980<sup>3</sup>, to describe a predominantly drug-induced severe cutaneous eruption with specific clinical and histopathological features. The clinical presentation of AGEP is characterised by an oedematous erythema with the formation of non-follicular pustular skin lesions, typically with a flexural distribution and uncommonly mucosal involvement. Systemic symptoms such as fever and leukocytosis are common and it can also be associated with decreased creatinine clearance and elevated aminotransaminases.<sup>4</sup>

The pathogenesis of AGEP is cytotoxic T-cell mediated keratinocyte apoptosis and Fas ligation resulting in subcorneal blister formation and CD4 mediated release of CXCL8 and GM-CSF and migration of neutrophils into the epidermis transforming subcorneal blisters into sterile pustules.<sup>5</sup> Consequently, AGEP is histologically identified by subcorneal or intradermal pustules, oedema of the papillary dermis, perivascular infiltrates with neutrophils and occasionally eosinophils.<sup>2</sup>

The estimated incidence rate of AGEP is 1 to 5 patients per million per year with at least 90% of cases caused by drugs.<sup>2, 4</sup> EuroSCAR, a multinational case-control study found that the highest risk causative agents were: pristinamycin, aminopenicillins, quinolones, hydroxychloroquine, antibacterial sulphonamides, terbinafine and diltiazem. Other drugs found to be associated with AGEP were corticosteroids, macrolides, oxicam NSAIDs and antiepileptic drugs.<sup>2</sup> Infectious agents have also been implicated as causative in the absence of an identifiable pharmacological trigger, as have spider bites, and there have also been cases with no obvious precipitating factor.<sup>5</sup>

The onset of AGEP is typically rapid, and can develop within hours of exposure to the causative drug, but can develop up to 3 weeks after exposure.<sup>2, 4</sup> With the removal of the causative agent, AGEP is a self-limiting condition, usually resolving within 15 days of drug cessation.<sup>6</sup> Treatment predominantly consists of supportive measures and symptom relief. Dressings and disinfecting solutions aid in the prevention of concomitant superinfections during the pustular stage, while emollients during the post-pustular desquamation stage will preserve skin integrity. Topical



corticosteroids can be used for symptomatic relief and systemic corticosteroids can be used in patients with more disseminated disease and or internal organ involvement.<sup>5</sup>

Fenofibrate is not typically associated with AGEP, but is known to precipitate systemic complications, including renal dysfunction, impaired creatinine clearance and elevate transaminases.<sup>1</sup> Rare but severe adverse reactions include pancreatitis, hepatocellular, chronic active and cholestatic hepatitis. Fenofibrate may also cause elevations in creatinine phosphokinase, myositis, myopathy and rarely, rhabdomyolysis, with these risks being increased if taken in conjunction with HMG-CoA reductase inhibitors or other fibrates.<sup>1</sup> Cutaneous adverse reactions are uncommon and include rashes, pruritis, urticaria and photosensitivity reactions. Very rarely, photosensitivity reactions are associated with erythema, vesiculation or nodulation and some severe idiosyncratic cutaneous reactions include erythema multiforme, Steven-Johnsons syndrome and toxic epidermal necrolysis. The use of fenofibrate in Type 1 Diabetes has not been studied extensively. Chen et al.<sup>7</sup> demonstrated therapeutic effects of fenofibrate on diabetic retinopathy in type 1 diabetic rodent models, with amelioration of vascular leakage, leukostasis and neurovascularization. There have been no randomized controlled trials in human studies to support these animal model trials.

Two published case reports of fenofibrate-induced AGEP were found in the literature. Morais et al<sup>8</sup> described clinical manifestations including rash, fever, malaise and asthenia, associated with neutrophilia and raised C-reactive protein appearing in a 68-year old woman, after seven days of treatment. The patient recovered after a week of oral and topical steroid treatment. The second report was in a 68 year old male presenting with a pustulitic rash, fever and neutrophilia 15 days after starting fenofibrate. He recovered after 4 days of oral and topical steroid treatment.<sup>9</sup> Liver function was not noted in either case. Between January 1971 and October 2013 there were 76 skin and subcutaneous adverse reactions to fenofibrate reported to the Australian Therapeutic Goods Administration (TGA), of which 66 were cases where fenofibrate was the single suspected causative medication. Three reports were of similar cutaneous adverse reactions to our case, with possible or probable causality linked to fenofibrate. There have been 48 reported hepatic adverse

reactions of which 32 cases had fenofibrate as the single suspected causative medication.<sup>10</sup> According to the Naranjo scale for determining causality, fenofibrate-induced AGEF in this patient returned a score of 5, indicating a probable causality.<sup>11</sup>

This case is particularly unusual because of the rapid onset and severity of the reaction to the causative agent, and the association with significant haemodynamic compromise. Our patient had not previously experienced this reaction to any other medications, fibric acid derivatives or otherwise.

It is of utmost importance to elucidate an accurate medication history, in order to have an accurate description of medications and timing of dosing. In our patient, sound-alike brand names (Lipitor®/ Lipidil®) could have led to incorrect medication being thought of as the causative agent, leading to inappropriate changes in the patient's cholesterol treatments.

## **Conclusion**

We describe a probable adverse drug reaction to a single dose of fenofibrate, seen as the development of acute generalized exanthematous pustulosis associated with haemodynamic instability and hepatotoxicity. Consideration of an adverse drug reaction early in the presentation facilitated the diagnosis and shortened the length of antibiotic treatment. This idiosyncratic adverse reaction has not been commonly associated with fenofibrate, nor has the condition been reported in association with haemodynamic compromise. Fenofibrate therapy should be added as a possible causative agent of AGEF.

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