CARDIOVASCULAR DISEASE; PRIORITIES AND OUTCOMES IN END STAGE KIDNEY DISEASE

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STATEMENT OF ORIGINALITY

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

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AUTHOR'S CONTRIBUTION

The work presented in this thesis has been carried out by the author under the supervision of Professor Angela Webster, School of Public Health, The University of Sydney and co-supervision of Professor Jonathan Craig, Flinders University, Adelaide.

The author planned the research, participated in the design of the studies, managed and analysed the data, interpreted results, wrote and revised the manuscripts for submission to peer-reviewed journals, and wrote and compiled this thesis.

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

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Professor Angela Webster

ETHICAL APPROVAL

The studies presented in chapters 2 and 7 did not require ethical approval. The study in Chapter 3 was approved by the Human Research Ethics Committee at the University of Sydney (Project no: 2015-228) and all participants gave written informed consent for participation in the survey and workshop (Chapters 3 and 4).

The Australia and New Zealand Dialysis and Transplant Registry approved the release and use of data for the analyses presented in chapters 5 and 6. The interpretation of these data is the responsibility of the author and should in no way be seen as an official policy or interpretation of the Australia and New Zealand Dialysis and Transplant Registry. The study in Chapter 5 was also approved by the New South Wales Population and Health Services Research Ethics Committee (Approval Number 2011/12/363) and by the University of Sydney ethics board (Project no: 2013/104). For the study in Chapter 6 ethics approval was granted by the University of Sydney (Project No.: 2014/917), AIHW (Reference No.: EO2015/3/181) and the New Zealand Ministry of Health (Reference No.: 14/NTB/171).

ABSTRACT

Introduction

End stage kidney disease (ESKD) accounts for 5-10 million deaths annually worldwide. The current treatment modalities for ESKD include dialysis, transplant and supportive care. The leading cause of death for people with ESKD is cardiovascular disease (CVD). CVD is a collective term for disease affecting the heart and blood vessels including coronary, cerebral and peripheral blood vessels. CVD causes significant morbidity and has a substantial impact on quality of life for people with ESKD. Improving cardiovascular outcomes for people living with ESKD is a priority.

The escalating incidence of chronic kidney disease, its progression to ESKD and the high burden of cardiovascular disease has generated an increasing amount of research in the ESKD population. The ESKD population have previously been under-represented in clinical trials and current trials in ESKD have infrequently and inconsistently reported CVD outcomes. It is important to standardise outcomes used in research. When outcome reporting is standardised it enables comparisons of findings across trials, populations and eras. It is important that the outcomes reflect patient priorities and are relevant to patients and clinicians for use in shared decision making.

The Standardised Outcomes in Nephrology Group (SONG) is an international initiative to establish a set of core outcomes and outcome measures across the spectrum of kidney disease for trials and other forms of research. The SONG-Haemodialysis (SONG - HD) initiative is developing a core outcome set for use in haemodialysis. As part of SONG-HD, CVD (as well as fatigue, vascular access and mortality) has been identified as

important to all stakeholders and included in the core outcome set for haemodialysis. This requires appropriate measures of CVD to be identified and used.

The first aim of this thesis was to achieve consensus on a CVD outcome measure for use in haemodialysis trials. In approaching this goal I first needed to ascertain the current use of cardiovascular outcomes (Chapter 2) and then determine which ones were important to all stakeholders (Chapter 3). Consensus over which is the most appropriate measure of CVD for use in trials in people on haemodialysis (Chapter 4) will allow improved standardisation of cardiovascular outcome reporting, reducing research wastage and will propel forward cardiovascular research to improve morbidity and mortality in this high risk population.

The second aim of this thesis was to further examine some of the prioritised outcomes and to review the patterns and risks of CVD in the ESKD population. The magnitude of risk for cardiac events and cardiac deaths in people with ESKD relative to the general population and the changes over time are not well described. I hypothesised that the magnitude of risk remained high in the ESKD population and that epidemiological improvements seen in CVD outcomes in the general population have not been mirrored in the ESKD population (Chapters 5 and 6). CVD and more specifically cerebrovascular disease can lead to significant cognitive impairment which has a substantial impact on the ability of ESKD patients to understand their disease, interpret education and be involved in shared decision making. The patterns of cognitive deficit in the ESKD population are not well understood and I hypothesised

that cognitive deficits in the ESKD population may be different to those found in the general population and may differ by modality of renal replacement therapy.

Standardising CVD outcomes, examining the epidemiology of CVD in ESKD and comparing the trends and patterns to the general population can drive hypotheses into potential causative mechanisms and new treatments. I present this thesis as a hybrid of published work, work currently under peer review for publication and work submitted for publication on the theme of priorities and outcomes in ESKD.

Cardiovascular outcomes reported in contemporary haemodialysis trials (Chapter 2)

There are currently no universally agreed cardiovascular outcomes for trials conducted specifically in the haemodialysis population. To ascertain current practice, as part of the SONG-HD initiative, I undertook a systematic search of published or in progress, randomised control trials in adults on haemodialysis, from 2011 to 2017, which reported at least one cardiovascular outcome. I identified and included 174 trials involving 148,730 participants. I found that trials reporting cardiovascular outcomes in haemodialysis patients are usually of short duration (median 3 to 6 months) and are small (59% of trials have <100 participants). I extracted 1743 definitions of outcomes and classified the outcomes into 236 measures (e.g. troponin) and then distilled these into 26 outcome groups (e.g. cardiac biomarker). Of the 26 outcome groups, 15 (58%) were clinical, 10 (38%) were surrogate outcomes and only one (4%), was a patient-reported outcome – pain. Nearly a third of trials (51[29%]) used a composite outcome and of those 51 trials there were 50 unique composite combinations illustrating the current difficulty in comparing composite outcomes across trials. Currently reported

cardiovascular outcomes are very heterogeneous and are often surrogates or composites which may not reflect outcomes that are meaningful to patients nor help clinicians in supporting decision making.

International survey to identify important cardiovascular outcomes (Chapter 3)

A critical component of developing a proposed outcome is that the outcome is deemed meaningful and relevant to all stakeholders. The aim of this study was to identify the priorities of patients/caregivers and health professionals for cardiovascular disease outcomes to be reported in all haemodialysis trials. I performed an international, online survey (available in English and Chinese languages). Participants were asked to rate the importance of ten cardiovascular outcomes (derived from the systematic review described in Chapter 2) on a 9-point Likert Scale, with a score of 7-9 being critically important. To determine relative importance participants also completed a best-worst scale. Likert means, medians and proportions and best-worst preference scores were calculated for each outcome. Participants included 127 (19%) patients/caregivers and 549 (81%) health professionals from 53 countries; of whom 530 (78%) completed the survey in English and 146 (22%) in Chinese. All but one CV outcome (*valve replacement*) was rated as critically important (Likert 7-9) by all participants. Patients/caregivers ranked *sudden cardiac death, heart attack, stroke* and *heart failure* as the most important outcomes with mean preference scores and 95% CI of 6.2 (4.8-7.5), 5.9 (4.6-7.2), 5.3 (4.0-6.6) and 4.9 (3.6-6.3). The same four outcomes were ranked most highly by health professionals. We identified five themes for prioritisation of outcomes: c*linical equipoise and potential for intervention, specific or attributable to haemodialysis, severity or impact on quality of life, strengthen*

knowledge and education, and *inextricably linked burden and risk.* Patients and health professionals believe that cardiovascular outcomes are of critical importance but consistently identify sudden cardiac death, myocardial infarction, heart failure and stroke as the most important outcomes to be measured in all haemodialysis trials.

Report of the international consensus workshop to establish core cardiovascular outcomes (Chapter 4)

Following the international survey and discussion with the SONG-HD Cardiovascular disease Expert Working Group two measures which had been consistently ranked as most important, were proposed as core outcome measures of CVD in trials in people on haemodialysis: myocardial infarction (MI) and sudden cardiac death (SCD). We convened a consensus workshop to discuss the potential use of these as core outcome measures. Seven patients/caregivers and 51 health-professionals from 15 countries discussed selection and implementation of the proposed core outcomes. Five main themes were identified. *Capturing specific relevance to the haemodialysis population,* acknowledging prevalence, risk, severity, unique symptomology and pathophysiology. *The dilemmas in using composite outcomes* were recognised. *Addressing challenges in outcome definitions,* establishing a common definition, and addressing uncertainty in the utility of biomarkers in haemodialysis. *Ensuring a meaningful metric for decision-making* to facilitate comparison across trials. *Enabling and incentivising implementation* by ensuring cardiologists are involved in development and integration of the outcome measure into registries, trial-design and reporting guidelines. Based on these themes, participants supported the use of *MI* and *SCD* as core outcome measures of CVD to be reported in all haemodialysis trials.

Incidence of ischaemic heart disease in men and women with ESKD (Chapter 5)

Ischaemic heart disease (IHD) is the most prevalent of the cardiovascular diseases in the ESKD population and myocardial infarction was specifically identified as a critically important outcome for research in people on haemodialysis. The incidence of IHD has fallen consistently in the general population; attributed to effective primary prevention strategies. Differences in incidence in the general population have been demonstrated by sex. Whether this fall in incidence and sex differences are mirrored in people with ESKD is unclear. I aimed to establish the relative risk of IHD events in the ESKD population. Using data linkage I performed a cohort study from 2000-2010 in people with ESKD in New South Wales. I calculated incidence rates, incidence rate ratios (IRR), and time-trends using indirect standardisation by IHD event. A total of 10,766 participants, contributed 44,149 years of observation time. Incidence rates were substantially higher than the general population for all IHD events (any IHD event: IRR 1.8, 95% confidence interval (CI) 1.7-1.9 for men, IRR 3.4, 95%CI 3.1-3.6 for women). Excess risk was higher in younger people (age 30-49 IRR 4.8, 95%CI 4.2-5.4), and in women with a three-fold increase risk overall and nearly a ten-fold increase in risk in young women (female age 30-49 years: IRR 9.8 95%CI 7.7-12.3), results were similar for angina and acute myocardial infarction. IHD rates showed some decline for men over time, (ratio of IRR 0.93, 95%CI 0.90-0.95) but were stable for women (ratio of IRR 0.97, 95%CI 0.94-1.01). People with ESKD have substantially higher rates of IHD than the general population, especially women, in whom no improvement appears evident over the past 10 years.

Cardiac mortality in people with ESKD (Chapter 6)

Having looked at IHD incidence I wanted to perform a similar study to look at mortality; I performed a population-based study across two countries to increase generalisability and the accuracy of the risk estimates. Although in general cardiovascular disease refers to pathologies involving the vasculature, heart disease including cardiac muscle, valvular pathologies and arrhythmias are also affected in ESKD and so we expanded this study to include cardiac disease outcomes. Cardiac disease affects over two-thirds of patients with ESKD and is the leading cause of death in this population. Cardiac death rates have fallen in the general population, but benefits from improved preventative therapies and treatment of cardiac events may not be generalisable to people with ESKD. I aimed to review absolute and relative rates for cardiac death in the ESKD population compared to the general population. Again using data linkage we performed a cohort study of incident people with ESKD in Australia and New Zealand from 1980-2013. We calculated mortality rates for cardiac disease as defined by ICD-10-AM codes and standardised mortality ratios (SMR) compared with the general population using indirect standardisation, adjusting for age, sex, calendar year, and country. We included 60,823 participants observed over 381,874 person-years, of whom 34,322 died. A primary cardiac death was recorded in 6847 participants (20%) and 27,475 (80%) participants died of other causes. Absolute cardiac death rates in the ESKD population were higher for men than women (men: 2002, 95%CI: 1945-2062; and women: 1502, 95%CI: 1444-1564/100,000 person-years) and both decreased over time. Relative to the general population, men and women with ESKD experienced more deaths (SMR in men: 5.6, 95%CI: 5.5-5.8; and women: 8.3, 95%CI: 8.0-8.6). Excess deaths were greatest in younger ESKD patients,

particularly women; aged 30-49 years women had 60 times (SMR 60.0, 95%CI: 51.8-69.0) whereas men had 18 times (SMR 17.7, 95%CI: 15.9-19.7) more deaths than expected. However, among people with ESKD, cardiac death rates improved over time more markedly than for the general population, especially in women. Cardiac deaths in the Australian and New Zealand ESKD population were higher than expected in the general population, particularly at younger ages and for women. Young women with ESKD have an excess relative risk of dying from cardiac causes, though there has been some improvement over time. Disaggregation of these data by sex identifies differences which need to be addressed in future research.

Cognition in people with end-stage kidney disease treated with haemodialysis (Chapter 7)

Cerebrovascular disease is prevalent in the ESKD population and associated with cognitive impairment which significantly affects quality of life and mortality. Cognitive impairment is under recognised in people with ESKD treated with haemodialysis and the severity and the specific patterns of cognitive deficits are poorly understood. I performed a systematic review and meta-analysis of randomised control trials and observational studies which used validated neuropsychological tests of cognition in adults on haemodialysis compared with the general population, people on peritoneal dialysis or people with chronic and ESKD. Cognitive test scores were aggregated by cognitive domain: orientation and attention, perception, memory, language, construction and motor performance, concept formation and reasoning, and executive functions. We found 42 studies including 3522 participants. Studies were mainly of high or uncertain risk of bias with high heterogeneity. We found that people treated

with haemodialysis had more impaired cognition than the general population, particularly in attention (standardised mean difference (SMD) -0.93, 95% confidence intervals (CI) -1.18, -0.68). Haemodialysis patients performed better than non-dialysed ESKD in attention (SMD 0.70, CI 0.45, 0.96) and memory (SMD 0.36 CI 0.08, 0.63) but had poorer memory than the general population (SMD -0.41 CI -0.91, 0.09) and people with CKD (SMD -0.40, CI -0.60, -0.21). There was insufficient data to show other differences between people on HD and people on PD or with CKD. People treated with haemodialysis have impaired cognitive function compared to the general population, particularly in the domains of orientation, attention and executive function. Cognitive deficits in specific domains should be further explored in this population and be considered when approaching education and chronic disease management.

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FIRST AUTHOR PUBLICATIONS ARISING FROM THIS THESIS

This thesis is presented for examination as a thesis containing published work. Chapters 2 and 7 have been published in international peer-reviewed journals, Chapter 4 has been accepted pending revision and Chapters 3, 5 and 7 have been submitted and are currently under peer review for publication in international peer-reviewed journals.

Chapter 2:

O'Lone E, Viecelli AK, Craig JC, Tong A, Sautenet B, Roy D, Herrington WG, Herzog C, Jafar T, Jardine M, Krane V, Levin A, Malyszko J, Rocco MJ, Strippoli G, Tonelli M, Wang AYM, Wanner C, Zannad F, Winkelmayer WC, Webster AC, Wheeler D. Cardiovascular Outcomes Reported in Haemodialysis Trials. **Journal of the American College of Cardiology. June 2018, 71 (24) 2802-2810.**

Chapter 3:

O'Lone E, Howell M**,** Viecelli AK, Craig JC, Tong A, Sautenet B, Herrington WG, Herzog C, Jafar T, Jardine M, Krane V, Levin A, Malyszko J, Rocco MJ, Strippoli G, Tonelli M, Wang AYM, Wanner C, Zannad F, Winkelmayer WC, Wheeler D on behalf of the SONG-HD Investigators. Identifying critically important cardiovascular outcomes for trials in hemodialysis: an international survey with patients, caregivers and health professionals. **Nephrology Dialysis Transplantatio. [published online ahead of print, 2020 Feb 10]Chapter 4:**

O'Lone E, Viecelli AK, Craig JC, Tong A, Sautenet B, Herrington WG, Herzog C, Jafar T, Jardine M, Krane V, Levin A, Malyszko J, Rocco MJ, Strippoli G, Tonelli M, Wang AYM, Wanner C, Zannad F, Winkelmayer WC, Wheeler D on behalf of the SONG-HD Investigators. Establishing core cardiovascular outcome measures for trials in haemodialysis: report of an international consensus workshop.

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Chapter 5:

O'Lone E, Kelly PJ, Masson P, Kotwal S, Gallagher M, Cass A, Craig JCC, Webster AC. Incidence of Ischemic Heart Disease in Men and Women with End-Stage Kidney disease: a Cohort Study**. Heart Lung Circulation. [Published online ahead of print, 2020 March 23]**

Chapter 6:

O'Lone E, De La Mata NL, Kelly PJ, Rosales B, Masson P, Webster AC. Cardiac mortality in people with end stage kidney disease; a two nation cohort study. **Submitted to Journal of the American College of Cardiology September 2019**

Chapter 7:

O'Lone E, Connors M, Masson P, Wu S, Kelly PJ, Gillespie D, Parker D, Whitely W, Strippoli G, Palmer S, Craig JC , Webster AC. Cognition in People With End-Stage Kidney Disease Treated With Haemodialysis: A Systematic Review and Meta-analysis. **American Journal of Kidney Diseases. 2016 Jun;67(6):925-35.**

LISTS OF FIGURES

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CHAPTER 1

INTRODUCTION

1.1. Introduction

The aim of this body of work is to expand our understanding of the interaction between cardiovascular disease (CVD) and end stage kidney disease (ESKD). The burden of ESKD is ever increasing and there is a need to prioritise research based on the greatest needs of the population, the absolute and relative size of the problem and its impact on the individual patient.

The first part of this thesis is concerned with the need to achieve consensus on an appropriate measure of CVD for use in trials in people on haemodialysis. My first hypothesis was that the current measures of CVD used in trials were not fit for purpose, supporting the need to develop core measures to reduce research waste and make outcome measures more relevant to patients and clinicians for use in shared decision making (Chapters 2-4). The second part of this thesis explores the risks and patterns of prioritised CVD outcomes. My hypothesis was that the epidemiological improvements and sex differences seen in cardiovascular disease outcomes in the general population are not mirrored in the ESKD population (Chapters 5 and 6). Having explored patterns of risk I also wanted to examine cerebrovascular aspects of cardiovascular disease. My final hypothesis was that cerebrovascular disease and specifically cognitive impairment seen in ESKD patients did not share the same pattern of deficits as that seen in the general population. Identifying patterns in cardiovascular incidence rates, mortality and pattern differences with the general population allows us to more accurately prioritise future directions of research.

The specific objectives are:

1. To describe the current use of cardiovascular outcomes in contemporary trials of people on haemodialysis (Chapter 2)
2. To report the results of an international survey conducted to elicit stakeholder opinions on the relative importance of individual cardiovascular outcomes to people on haemodialysis (Chapter 3)
3. To summarise the perspectives of patients on haemodialysis, caregivers and health professionals regarding the proposed core outcome measures for cardiovascular disease (Chapter 4)
4. To examine and describe the incidence rates of cardiac events in the end stage kidney disease population and compare them to the cardiac event rates in the general population (Chapter 5)
5. To examine and describe the cardiac mortality rates in the end stage kidney disease population and compare them to the cardiac mortality rates in the general population (Chapter 6)
6. To ascertain the impact of cerebrovascular disease in people on haemodialysis by describing the patterns of cognitive impairment (Chapter 7)

This chapter outlines the rationale for the importance of research into ESKD and the role that cardiovascular disease has to play. It summarises the weaknesses in current research focussing specifically on cardiovascular outcomes in trials in people with ESKD and the gaps in evidence for differences between these outcomes in the ESKD population and the general population.

1.2. End Stage Kidney Disease

Worldwide about 13% of the population are affected by chronic kidney disease (CKD)[1]. The incidence of CKD is increasing, in the main due to the increase in cardio-metabolic syndrome; driven by over-nutrition and inadequate physical activity, increasing weight and obesity. The risk of CKD progressing to ESKD is relatively small at between 3 and 8%[2] however, worldwide this equates to an estimated 5–10 million deaths annually from kidney disease [3]. For those persons who progress to ESKD treatment options are dialysis (haemodialysis and peritoneal dialysis), kidney transplantation or supportive care. ESKD leads to high morbidity and mortality and the numbers of people being treated for ESKD are projected to increase by about 7% per year[4,5]. The provision of renal replacement therapies (RRT) is expensive and has a substantial economic impact both to the individual patient and to society.

1.3. Cardiovascular disease

CVD is an umbrella term which incorporates diseases of the heart and blood vessels including the coronary, cerebral and peripheral vessels. Globally CVD is the leading cause of death. The World Health Organisation project that by 2030 almost 23.6 million people will die from CVD, and the major contributors are coronary heart disease (CHD) and cerebrovascular disease [6]. In the general population the prevalence of CVD is higher amongst men than women and increases with age. The Australian burden of disease study which measured the impact of living with illness and injury and dying prematurely, found that CHD was the leading individual disease and stroke ranked 9th[7]. As a result of heath expenditures and lost productivity from increased morbidity and mortality, CVD is a significant economic burden to individuals and society[8]. Most importantly CVD affects physical functioning as well as resulting in

neuropsychological sequelae such as depression and cognitive impairment all of which can contribute to reduced survival and quality of life.

1.4. ESKD and its relationship to cardiovascular disease

The Global Burden of Disease 2015 study estimated that 1.2 million deaths, 19 million disability-adjusted life-years (DALYs) and 18 million years of life lost from CVD were directly attributable to reduced glomerular filtration rates[9,10]. CVD is a risk factor for both progression of CKD to ESKD as well as an independent risk factor for morbidity and mortality in ESKD patients[11]. CVD is present in over 50% of people on haemodialysis and is the leading cause of death in patients with ESKD[12-14]. The high risk of CVD in ESKD is partially explained by the high prevalence of traditional risk factors for CVD in this population such as diabetes and hypertension[15]. Additional cardiovascular risk factors are also at play in ESKD including albuminuria, uraemic toxins, fluid and electrolyte imbalance, and renal replacement itself[16]. These risk factors collectively contribute to oxidative stress, inflammation, immune dysfunction and disorders of bone and mineral metabolism leading to increased vascular calcification and microvascular dysfunction [17-20].

Health related quality of life of patients is significantly lower if patients have CVD in addition to ESKD[21]. CVD is significantly associated with limitations in mobility and physical activity as well as depression, all of which are highly prevalent in people with co-existing ESKD and CVD[22,23]. There have been links to suggest that psychological factors, such as depression and stress are independent risk factors for developing CVD[23]. This is of particular importance as depression has been identified as the most

prevalent psychological illness in the ESKD population[24]. People with multiple chronic comorbid conditions such as ESKD and CVD are at far higher risk of limitation in their daily activities, poorer self-rated health and poorer quality of life.

Given the impact that cardiovascular disease has on the morbidity, mortality and quality of life of people with ESKD the inclusion of cardiovascular disease outcomes into all research in people with ESKD may help to deliver interventions which make a difference to patients' lives.

1.5. Cardiovascular outcomes in ESKD research

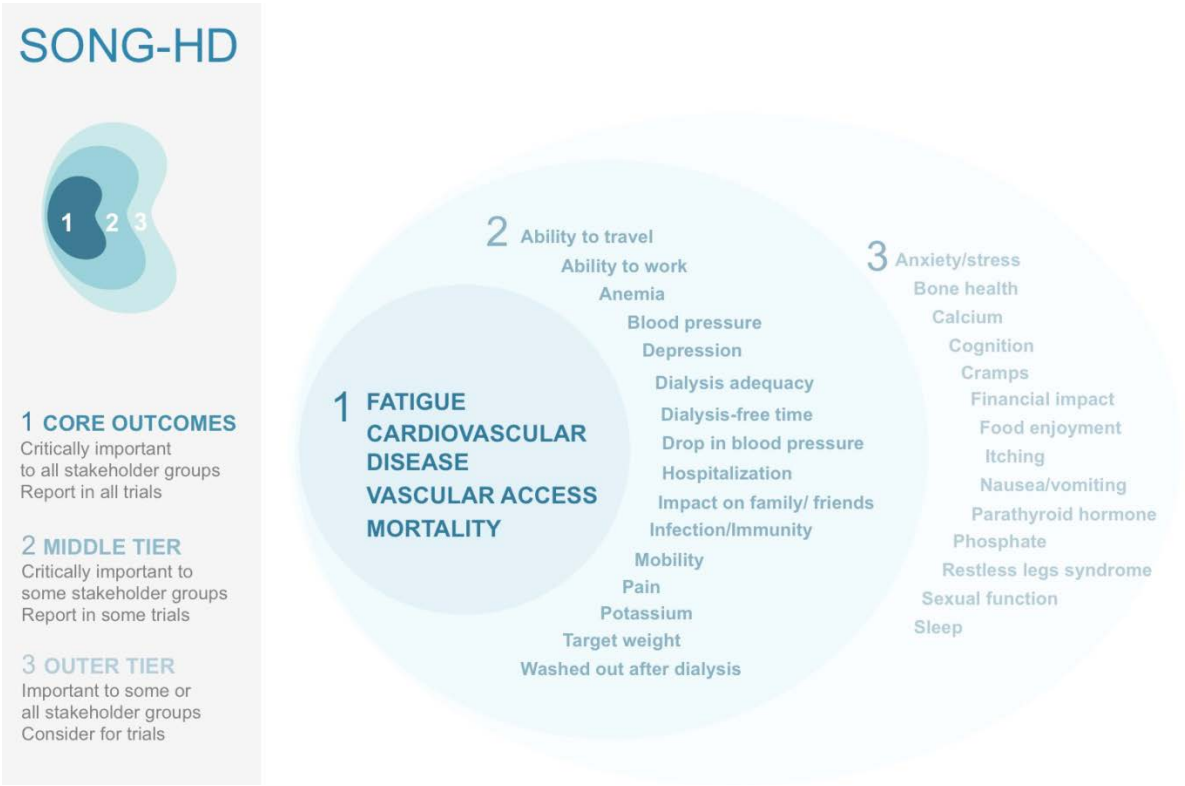
Cardiovascular disease outcomes

People with ESKD are frequently excluded from large scale cardiovascular trials[25]. Even when people with ESKD are included in trials a recent systematic review reported that cardiovascular outcomes are infrequently reported, found in only 12% of trials in people on haemodialysis [26]. Exclusion of people with ESKD from trials, infrequent reporting of CVD outcomes in trials and difficulties comparing CVD outcomes across trials has led to significant research wastage and inadequate improvements in cardiovascular morbidity and mortality in this high risk population. Identifying the problems with the current utilisation of cardiovascular outcomes in trials of people on haemodialysis and attempting to improve the standardisation of that reporting has the potential to improve cardiovascular morbidity and mortality for people with ESKD.

Core outcome sets and the SONG-HD Initiative

A core outcome set is an agreed, standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care[27]. The core outcomes should be based on the shared priorities of patients, caregivers, clinicians, researchers, policy makers, and relevant stakeholders. The aim of developing a core outcome set is to ensure evidence from trials is relevant and meaningful for patients and healthcare providers in supporting treatment decisions. The Standardised Outcomes in Nephrology (SONG) initiative was founded to establish a set of core outcomes and their outcome measures for use in trials and research across the spectrum of kidney disease. Using validated methodology a core outcome set for haemodialysis was developed: **Cardiovascular disease**, fatigue, vascular access and mortality (Figure 1.1) [26,28,29]. Chapters 2-4 of this thesis are embedded within the SONG-HD initiative; to develop core outcome measures for cardiovascular disease.

FIGURE 1.1 SONG-HD Core Outcome Set



1.1 Risks and patterns of CVD outcomes in end stage kidney disease.

Cardiac events

The most prevalent cardiac events in this population continue to be driven by coronary artery disease; The 2017 United States Renal Data System (USRDS) report stated that stable coronary artery disease was the most prevalent disease in ESKD[30]. The Haemodialysis (HEMO) study reported that 40% of dialysis patients had pre-existing CVD and that coronary artery disease was the leading cardiovascular cause of hospital admissions[31]. More recently the EVOLVE study also showed that myocardial infarction and heart failure were the most prevalent cardiac events in people on haemodialysis[32]. Cardiovascular morbidity and mortality rates in the general population have improved over time and this is largely due to the improvements in treatments and primary and secondary prevention[33]. Changes in the cardiac event and mortality rates in the ESKD population have not been so well described. I wanted to examine the differences in cardiac event rates and cardiac mortality rates between the ESKD population and the general population and review the changes over time. The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) is a clinical quality registry that collects data relating to treatment and outcomes from all renal units in Australia and New Zealand. This registry allows comprehensive reporting on incidence, prevalence and outcomes of dialysis and transplant treatment for patients with ESKD across Australia and New Zealand. I wanted to use linked data to be able to provide unbiased comparisons between this ESKD group and the general population..

Impact of cerebrovascular changes

Cerebrovascular disease is a leading cause of CVD in people with ESKD with the risk of stroke thirty times higher than in the general population[34]. Cognitive impairment is

also highly prevalent in the ESKD population with some studies describing prevalence rates of up to 70%[35]. The pathogenesis of cognitive impairment is likely to be multifactorial but may be similar to that responsible for cognitive decline associated with other CVD; atherosclerosis, clinical and silent stroke, oxidative stress, and white matter lesions[36]. There are however, additional uraemia related risk factors potentially contributing to the high prevalence of microvascular changes in ESKD which have been associated with cognitive impairment[37,38]. Furthermore, *haemodialysis treatment has been shown to affect cerebral blood flow correlating to intradialytic variations in cognitive function[39].*

Cognitive impairment can have a significant impact on quality of life and has been shown to affect mortality[40,41]. Cognitive impairment in people with ESKD is poorly understood, particularly which cognitive domains are affected and how the pattern of deficits compares to the general population. The majority of studies have only recruited small numbers and comparator groups have varied. I wanted to pool available data to identify the cognitive domains most affected in people on haemodialysis and compare this to the general population and other renal replacement therapies.

These following chapters attempt to distil the evidence, improve standardisation of CVD outcomes and describe the differences in cardiovascular disease between the ESKD population and the general population.

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CHAPTER 2

CARDIOVASCULAR OUTCOMES REPORTED IN HAEMODIALYSIS TRIALS

Publication details and contribution of authors

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EO: conceived and designed the study, identified trial reports for inclusion, extracted, prepared and analysed the data, interpreted the results and wrote and revised the manuscript

AV: identified trial reports for inclusion, extracted the data, and revised the manuscript

AT: contributed to the design of the study, advised on interpretation and presentation of the results, and revision of the manuscript

BS: contributed to the analysis of the data and revision of the manuscript

DR: contributed to the analysis of the data and revision of the manuscript

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2.1 Abstract

Patients on long-term haemodialysis are at very high risk for cardiovascular disease, but are usually excluded from clinical trials conducted in the general population or in at-risk populations. There are no universally agreed cardiovascular outcomes for trials conducted specifically in the haemodialysis population. In this review we highlight that trials reporting cardiovascular outcomes in haemodialysis patients are usually of short duration (median = 3 to 6 months) and are small (59% of trials have less than 100 participants). Overall, the cardiovascular outcomes are very heterogeneous and may not reflect outcomes that are meaningful to patients and clinicians in supporting decision making, as they are often surrogates of uncertain clinical importance. Composite outcomes used in different trials rarely share the same components. In a field where a single trial is often insufficiently powered to fully assess clinical and economic impact of interventions, differences in outcome reporting across trials makes the task of meta-analysis and interpretation of all the available evidence challenging. Core outcomes sets are now being established across many specialties in healthcare to prevent these problems. Through the global Standardised Outcomes in Nephrology - Haemodialysis (SONG-HD) initiative, cardiovascular disease was identified as a critically important core domain to be reported in all trials in haemodialysis. Informed by the current state of reporting of cardiovascular outcomes, a core outcome measure for cardiovascular disease is currently being established with involvement of patients, caregivers and health professionals. Consistent reporting of cardiovascular outcomes that are critically important to haemodialysis patients and clinicians will strengthen the evidence base to inform care in this very high-risk population.

2.2 Introduction

“When I use a word," Humpty Dumpty said, in rather a scornful tone, "it means just what I choose it to mean- neither more nor less." "The question is," said Alice, "whether you can make words mean so many different things." In writing *Through the Looking Glass* [1], Lewis Carrol could have been referring to cardiovascular outcomes reported in clinical trials, particularly among patients on haemodialysis.

2.3 Cardiovascular disease and haemodialysis

Worldwide, more than two million people have end stage kidney disease (ESKD), with this number increasing annually by 5-7% [2]. Patients with ESKD who are treated with dialysis require a disproportionately high use of health-care resources. The prevalence of cardiovascular disease (CVD) in people on haemodialysis exceeds 60% [3,4] and accounts for over 50% of deaths [4-6]. CVD mortality remains up to 30 times higher in people on dialysis than in the general population [6].

2.4 The importance of an outcome

Clinical trials of interventions designed to reduce CVD in people with ESKD have evaluated the use of medications [7-10], and the intensity and type of haemodialysis [11-13], but the results have generally not identified clear evidence of benefit. Such trials may have been less informative than possible because they were too small to identify modest but realistic treatment effects, and inconsistencies in how cardiovascular outcomes were measured and reported made it difficult to compare the effectiveness of interventions across different trials or to combine trial results in meta-analyses [14]. Reporting bias, both in terms of selective outcome reporting and publication bias, also has the potential to cause misinterpretation of evidence [15]. The value of trials to

inform decision-making among patients, clinicians, and policy makers may also be reduced if the outcomes are selected on the basis of feasibility rather than importance [16].

The importance of choosing the right outcomes for clinical trials to inform decision making is widely accepted, but appropriate measurement of cardiovascular outcomes in trials can be challenging. In particular, the major cardiovascular outcomes occur only in a relatively small fraction of participants meaning, unless trials are very large, follow-up periods may need to be long in order to capture a sufficient number of specific events. This has led to an increasing use of composite outcomes to increase the number of events captured and to reduce sample size requirements [17,18]. When using composite endpoints, it is difficult to estimate the true effect of an intervention on different components of the composite, particularly those that occur less frequently. Composites often combine outcomes with very different levels of importance to patients, making interpretation of the overall importance of the trial findings difficult [18,19]. Similarly, a compounding problem is that inclusion of surrogates diverts attention from outcomes of more importance to patients and clinicians [20]. Outcomes need to be relevant to all stakeholders, in particular the patients within the specific disease group[21].

The capacity to compare outcomes across trials and produce summary effect estimates through meta-analysis would help to improve confidence in the effects of interventions in the haemodialysis population, but would require that the outcomes are reported consistently.

2.5 The need for core outcome sets

A core outcome set is an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in the relevant areas of health or healthcare [22].

Recently, there has been a proliferation of discipline-specific and global initiatives to develop core outcome sets [23,24]. The Outcome Measures in Rheumatology (OMERACT) initiative was formed in 1992 and set the foundation for the development of core outcomes, specifically in rheumatology trials. With the involvement of patients, health care providers, and policy makers, OMERACT has improved the relevance of outcomes reported in rheumatology trials. More recently, the Core Outcome Measures in Effectiveness Trials (COMET) initiative was established to facilitate the development and collation of core outcome sets across all diseases internationally (23).

Among cardiovascular trialists, there have been concerted efforts to standardize cardiovascular outcome reporting [25-27]. Early attempts include the introduction of the term MACE, defined as 'major adverse cardiac events,' in the mid-1990s with its use theoretically restricted to in-hospital complications related to percutaneous coronary interventions [28]. However, the components of a “MACE” vary, even between trials of similar interventions. For example, a systematic review assessing the components of MACE used in studies comparing bare metal versus drug-eluting stents, found large-scale heterogeneity in the outcomes used[29]. The use of MACE has become widespread, but is often used outside its original context with large number of varied

outcome measures used to make up the composite endpoint [29]. More recently, a number of core outcome sets have been developed for cardiovascular diseases in specific populations including a set for the effectiveness of cardiac surgery [30], and a set for pregnant women with cardiovascular disease [31].

2.6 Current state of reporting of CVD outcomes in haemodialysis trials

A systematic search was conducted in MEDLINE, Embase, the Cochrane Kidney and Transplant Specialized Register, and ClinicalTrials.gov for randomised controlled trials conducted in adults on haemodialysis (both published or in progress, from 2011 to 2017), which reported at least one cardiovascular outcome. We extracted a number of trial characteristics as well as all cardiovascular outcome measures, including all levels of specification(if reported), and the specific metric (e.g. time to event, change from baseline), method of aggregation (e.g. mean, median, proportion) and time point of measurement [32].

We classified the outcomes into 236 measures (e.g. troponin) and then again into twenty-six outcome groups (e.g. cardiac biomarker). A schema of the categorization is provided in Appendix 1 Figure 1 with an example in Appendix 1 Table 2. Outcomes were further classified as surrogate, clinical or patient-reported. A surrogate outcome was defined as a biochemical, imaging, or other marker used as a substitute for a clinical outcome [33]. A clinical outcome was defined as a medical event or comorbidity (e.g. mortality, myocardial infarction, hospitalization) diagnosed by the clinician. Patient-reported outcomes were those reported directly by patients regarding how

they function or feel in relation to a health condition and its therapy, without interpretation by a healthcare professional or anyone else [34].

Trial characteristics

We identified and included 174 trials involving 148,730 participants (Figure 2.1). Trial characteristics are presented in Table 1. Fifty-six (32%) trials were unpublished. The published trials were conducted across 28 countries, most frequently in Japan (8%) and the USA (8%), and 12 (7%) trials were multinational. The median (interquartile range [IQR]) trial duration was 15.0 months (IQR 5.5 to 42.0 months) and the median sample size was 83 participants (IQR 32 to 200 participants). It is of note that relative to many cardiovascular trials in the general population, both the trial duration and the sample size is small. The most common type of intervention was pharmacological (103 [60%] trials). In 48 (27%) trials, the intervention was a dialysate, dialysis membrane or modality of haemodialysis (such as haemodiafiltration or haemodialysis).

Outcomes and outcome measures

The 1743 definitions (including different time points of measurement) were categorised into 236 measures (e.g. troponin), with a median of 3.5 outcome measures reported per trial (range 1 to 23). Across all trials, measures were assessed at 67 different time points with a range of one to six time points per trial. The number of measures was not associated with the sample size (Appendix 1 Table 3). These measures were further grouped into 26 outcomes (e.g. cardiac biomarkers), with a median of two outcomes reported per trial (range 1 to 16). Of the 26 outcomes, 15 (58%) were clinical, 10 (38%) were surrogates and one (4%), was a patient-reported

outcome – pain. (Figure 2.2) The top three most frequently reported outcomes were: *serum biomarker* (biomarkers excluding lipids and traditional cardiac biomarkers) (52 [30%] trials), *cardiovascular composite* (52 [30%] trials), and *serum lipid levels* (41 [23%] trials).

The number of measures for each outcome ranged from 1 to 61 (Figure 2.3). The *serum biomarker* outcome included 61 different biomarker measures; C-reactive protein was the most frequently reported biomarker (34 [20%] trials) followed by homocysteine (8[5%] trials). The outcome *cardiovascular composite* included 11 composite measures, the three most frequent being a "cardiovascular composite" measure (e.g. "the cumulate rate of non-fatal MI or acute coronary syndrome, hospitalization for heart failure, nonfatal stroke or CV death" (27 [16%] trials), a "cardiovascular event" (e.g. "rate of cardiovascular events" (24 [14%] trials) and "cardiovascular event non-fatal" (4 [2%] trials) (Figure 2.3). The outcome *serum lipid levels* had ten different measures, the three most frequently reported being "HDL" (26 trials [15%], "triglycerides" (26 [15%] trials and "total cholesterol" (21 [12%] trials. Across the clinical outcomes, there were 13 different metrics used to report the original definitions and these included: number of events, rate of event, event free survival and time to event. The methods of aggregation for the clinical outcomes included mean, median, proportion and proportional change.

Cardiovascular composite outcome

Each composite measure was deconstructed into its components and the number of trials using each component was analysed as shown in Figure 2.4. Fifty-one trials (29%)

used a cardiovascular composite measure and each trial used a range of one to six different composite combinations. Within these 51 trials there were 50 unique composite combinations (Figure 2.4). The proportion of trials reporting each measure within the cardiovascular composite outcome is shown in Appendix 1 Figure 2.

Mortality outcomes

A cardiovascular *mortality* outcome was reported in 25 (14%) trials. Included in the mortality outcome were eight individual events of which "sudden cardiac death" was the most frequently reported (seven [4%] trials) (Appendix 1 Figure 3). A composite mortality measure was assessed in 14 (8%) trials and 12 composite combinations were used (Figure 2.5). Within the *mortality* outcome, the most frequently reported composite outcome measure was *Cardiovascular death*, reported as a unique term in 16 (9%) trials and also used in five (42%) mortality composite combinations (Figure 2.5).

2.7 Time for more confidence in outcomes

In contemporary clinical trials conducted in patients on haemodialysis, a very large number of different cardiovascular outcomes have been reported. Over a third of these outcomes were classified as surrogates rather than outcomes that would be expected to be directly important to patients and clinicians (such as sudden cardiac death, myocardial infarction), and only one was patient-reported (pain). The use of surrogate outcomes is probably a function of the small sample size of most of the trials identified. Use of composite outcomes was common being used in a third of the trials, but each trial used different components to make up their composites and they were

often ill-defined, making comparisons across studies problematic. This echoes the findings in other populations regarding the complexity and discord within composite outcomes [18,29]. A review of composite outcomes within cardiovascular trials found that the components of composite endpoints varied widely in terms of their importance to patients and in the magnitude of their effect of the intervention. This can give rise to misleading interpretations regarding the impact of treatment [18].
The variety of measures used to assess each outcome was substantial, particularly among the surrogate outcomes; with over 60 different serum biomarkers measured and over 30 different ways to measure vascular function and anatomy. Heterogeneity was evident at multiple levels including definition of the measurement, the metric, the method of aggregation and the time point of measurement of the outcome measure. This heterogeneity is not unique to the haemodialysis population. In a review of outcomes in cardiac arrest trials, over 160 individual outcomes were reported, including 39 different measures of survival [35].

This review highlights the urgent need to develop a core outcome set in haemodialysis trials. Recently, the Standardized Outcomes in Nephrology (SONG) initiative was established, which has used validated consensus methodology to bring together patients and health care professionals to identify critically important outcomes in haemodialysis [36-38]. Cardiovascular disease was identified as a core outcome domain (along with vascular access, fatigue and mortality). The next phase of the SONG initiative aims to establish these core measures with consensus on their definition. Moving forward, this effort will facilitate improvement in the quality, transparency and value of cardiovascular trials in people on haemodialysis, and most importantly, has

the potential to improve interpretation of clinical trials data in the hope of reducing mortality and morbidity for people on haemodialysis.

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2.9 Figures and tables

FIGURE 2.1 SEARCH RESULTS

Comprehensive literature search of MEDLINE, Embase, the Cochrane Kidney and Transplant Specialized Register, and ClinicalTrials.gov from 2011 to 2017 resulted in 174 randomised trials in patients on haemodialysis reporting at least one cardiovascular outcome.

HD = Haemodialysis, CVD = cardiovascular disease

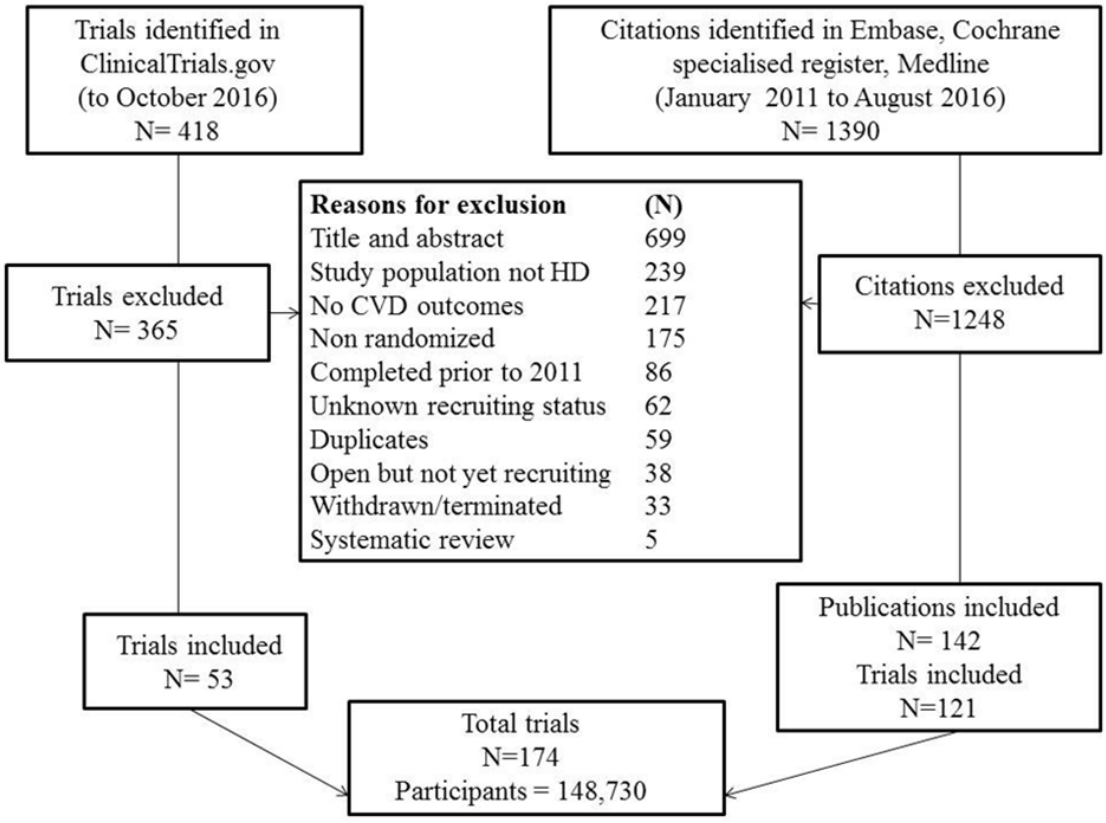


FIGURE 2.2 PROPORTION OF TRIALS REPORTING EACH OUTCOME (174 TRIALS, 26 OUTCOMES)

Chart to show the 26 outcome groups determined from the 174 trials and the proportion of trials which reported them. The most frequently reported outcomes were the surrogate outcome of *serum biomarker* and a *cardiovascular composite* outcome. Only one outcome was patient reported.

ACS - Acute coronary syndrome, ECG- Electrocardiogram

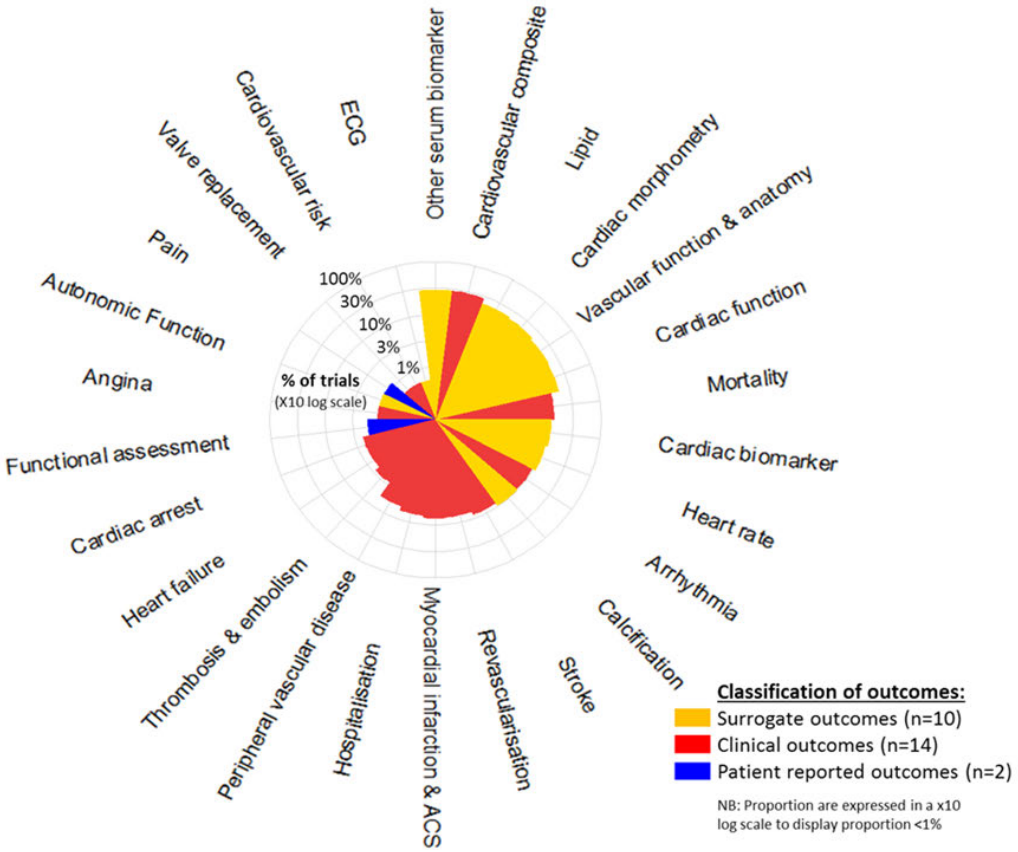


FIGURE 2.3 NUMBER OF UNIQUE MEASURES WITHIN EACH OUTCOME GROUP

Bar chart to show how the number of different measures that contributed to each outcome excluding time points. There were 61 different biomarkers measured in the outcome group *Other serum biomarkers,* and 32 different ways of measuring *Vascular function and anatomy.*

ACS – Acute coronary syndrome, CV – cardiovascular, ECG – electrocardiogram, MI – Myocardial infarction, PVD – Peripheral vascular disease

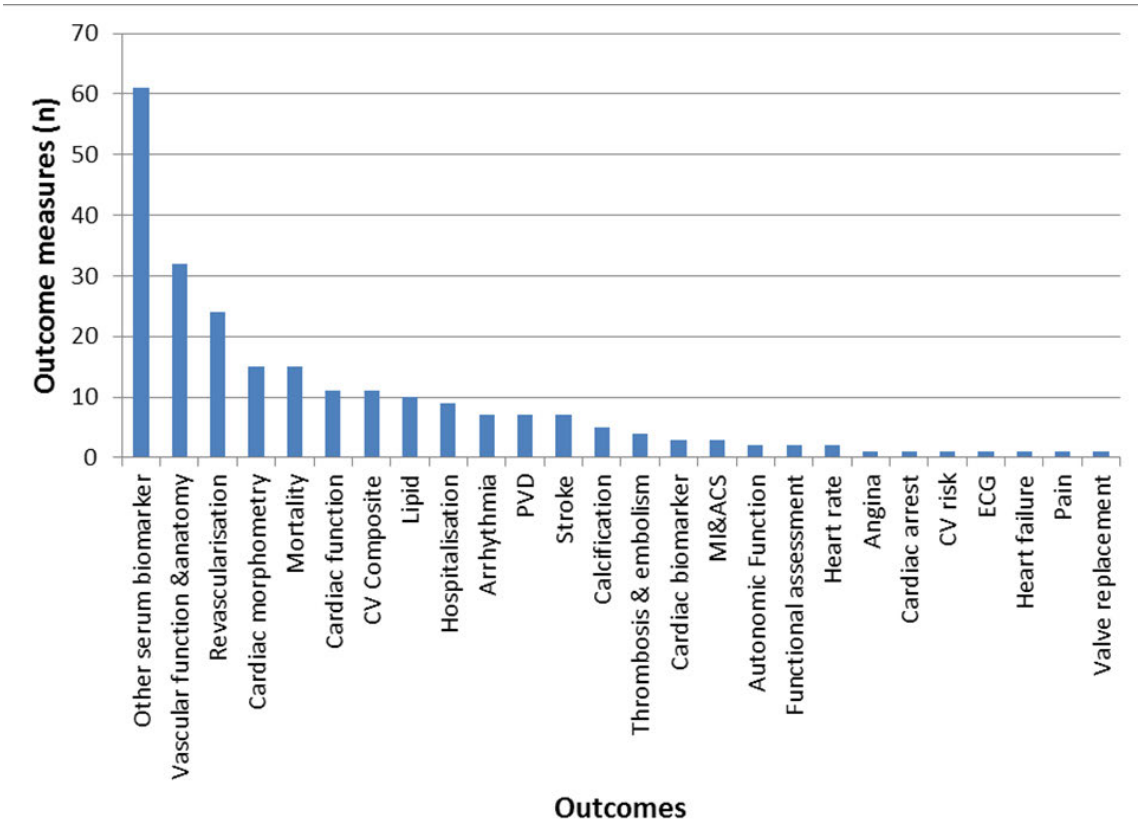
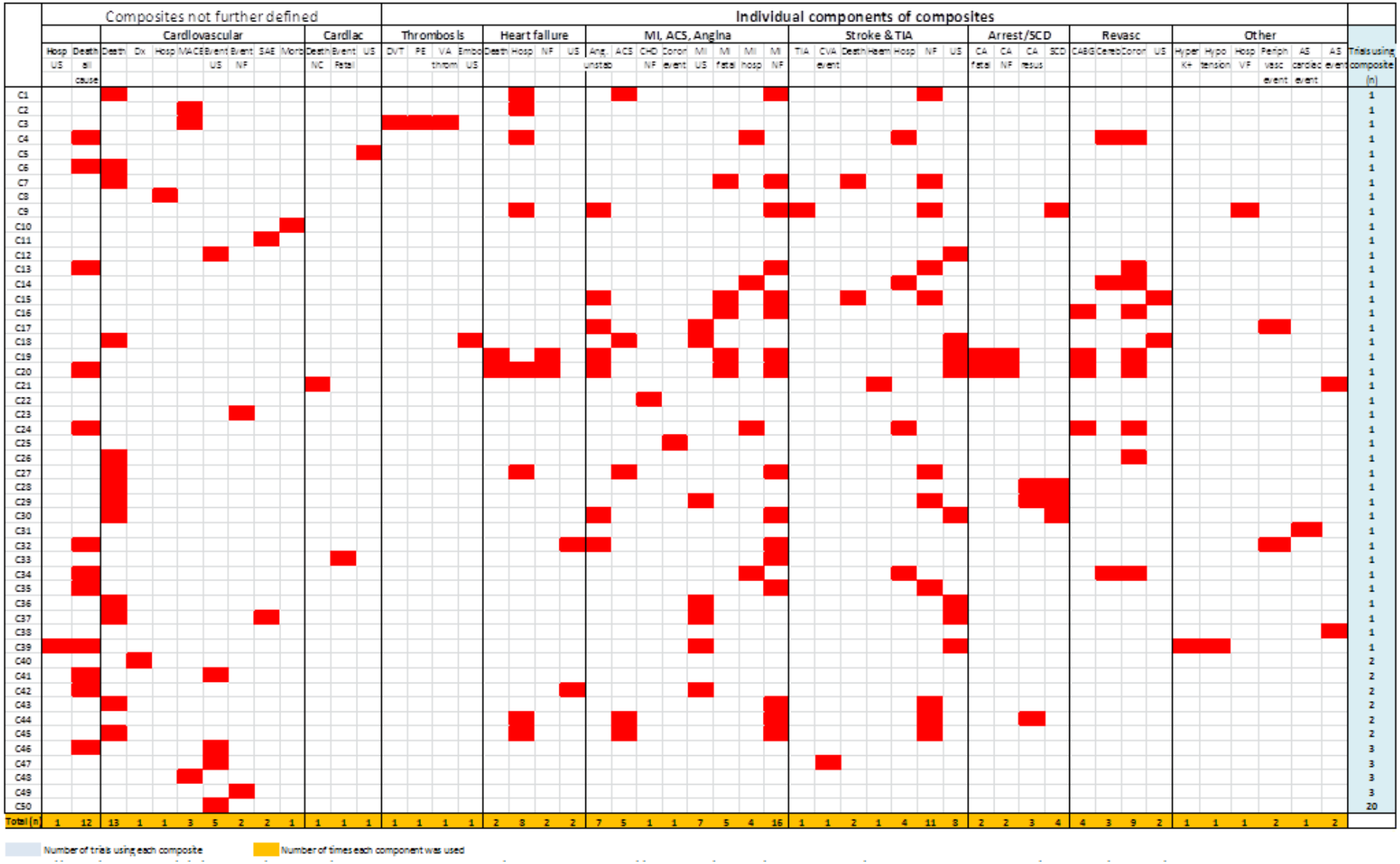


FIGURE 2.4 CARDIOVASCULAR COMPOSITE MATRIX.

Individual components of the 51 composite outcomes after deconstruction. The far right column tallies the number of trials that utilised each composite and the bottom row tallies the number of times each component was incorporated into a composite.



US= unspecified, Dx=disease, Hosp=hospitalisation, MACE=Major adverse cardiovascular event, NF= non fatal, SAE= Serious adverse event, Morb=morbidity, DVT=deep vein thrombosis, PE=pulmonary embolism, VA=vascular access, throm=thrombosis, Embol=embolism, Ang=angina, ACS=acute coronary syndrome, CHD=coronary heart disease, cor=coronary, MI=myocardial infarction, TIA=transient ischaemic attack, CVA=cerebrovascular, haem=hemorrhagic, CA=cardiac arrest, cereb=cerebrovascular, VF=cardiac arrhythmia, AS= Atherosclerotic, morb= morbidity

FIGURE 2.5 MORTALITY COMPOSITE MATRIX

Matrix to show the individual components of the 12 composites after deconstruction.

The far right column tallies the number of trials that utilised each composite and the bottom row tallies the number of times each component was incorporated into a composite. The composite *Cardiovascular death* was used in 16 trials but was not further defined.

		Composites not further defined					Individual components							
		Vascular death	CV Death	CHD death	Cardiac death	Cardiac arrest	SCD	Cardiac arrhythmia	Acute MI	Heart failure	Stroke US	Stroke ischaemic	Stroke haem	Trials using composite (n)
Composites	C1	■												2
	C2			■										2
	C3						■	■						2
	C4		■											16
	C5				■									4
	C6					■			■	■	■			1
	C7		■											1
	C8		■						■	■	■			1
	C9	■	■		■						■	■	■	1
	C10				■									1
	C11		■											1
	C12						■	■	■	■	■			1
Total (n)*		2	5	1	3	1	2	2	3	3	4	1	1	

Number of trials using each composite

*number of times each component is used

CV = cardiovascular, CHD=coronary heart disease, haem=hemorrhagic , MI=myocardial infarction, SCD=sudden cardiac death, US=unspecified

TABLE 2.1 CHARACTERISTICS OF INCLUDED TRIALS (TOTAL=174)

Characteristics		**Number of trials**	**%**
Participants (n)	0-49	64	38
	50-99	35	21
	100-499	49	29
	500-999	10	6
	1000-4999	9	5
	=>5000	2	1
	Not stated	5	3
Year of publication	2011-2012	50	29
	2013-2014	52	30
	2015-2016	16	9
	Not published	56	32
Region/Country	Not stated	64	37
	Europe	43	25
	Asia	23	13
	USA	13	7
	International	12	7
	Middle East	11	6
	South/Central America	4	2
	Australasia	4	2
Duration of trial (months)	1 to 3	8	7
	>3 to 6	24	20
	>6 to 12	11	9
	>12 to 24	28	23
	>24 to 48	23	19
	>48	27	22
	Not stated	53	30
Intervention type	Pharmacological/Supplement	104	60
	Dialysate	22	13
	Mode of haemodialysis	26	15
	Lifestyle	6	3
	Other	5	3
	Dialysis Machine	9	5
	Coronary intervention	3	2

CHAPTER 3

IDENTIFYING CRITICALLY IMPORTANT CARDIOVASCULAR OUTCOMES FOR TRIALS IN HAEMODIALYSIS: AN INTERNATIONAL SURVEY WITH PATIENTS, CAREGIVERS AND HEALTH PROFESSIONALS

Publication details and contribution of authors

O'Lone E, Howell M**,** Viecelli AK, Craig JC, Tong A, Sautenet B, Herrington WG, Herzog C, Jafar T, Jardine M, Krane V, Levin A, Malyszko J, Rocco MJ, Strippoli G, Tonelli M, Wang AYM, Wanner C, Zannad F, Winkelmayer WC, Wheeler D on behalf of the SONG-HD Investigators. Identifying critically important cardiovascular outcomes for trials in hemodialysis: an international survey with patients, caregivers and health professionals. **Nephrology Dialysis Transplantation [published online ahead of print, 2020 Feb 10]**

EO: conceived, designed and produced the workshop, helped prepare and analyse the data, interpreted the results and wrote and revised the manuscript

MH: helped prepare and analyse the data and revised the manuscript

AV: contributed to the design of the survey and revised the manuscript

AT: contributed to the design and production of the survey, advised on interpretation and presentation of the results, and revision of the manuscript

JCC: contributed to the design and production of the survey, advised on interpretation and presentation of the results, and revision of the manuscript

BS, WH, CH, VK, AL, MR, GS, MT, AW, CW, FZ, WW, TJ, MJ, JM, DW: contributed to the survey and revised the manuscript

3.1 Abstract

Background: Cardiovascular disease (CVD) is a major contributor to morbidity and mortality in people on haemodialysis. Cardiovascular outcomes are reported infrequently and inconsistently across trials in haemodialysis. This study aimed to identify the priorities of patients/caregivers and health professionals for CVD outcomes to be incorporated into a core outcome set reported in all haemodialysis trials.

Methods: In an international online survey, participants rated the absolute importance of ten cardiovascular outcomes (derived from a systematic review) on a 9-point Likert Scale, 7-9 being critically important. Relative importance was determined using a best-worst scale. Likert means, medians and proportions and best-worst preference scores were calculated for each outcome. Comments were thematically analysed.

Results: Participants included 127 (19%) patients/caregivers and 549 (81%) health professionals from 53 countries; of whom 530 (78%) completed the survey in English and 146 (22%) in Chinese. All but one CV outcome (*valve replacement*) was rated as critically important (Likert 7-9) by all participants. Patients/caregivers ranked *sudden cardiac death, heart attack, stroke* and *heart failure* as the most important outcomes with mean preference scores and 95% CI of 6.2 (4.8-7.5), 5.9 (4.6-7.2), 5.3 (4.0-6.6) and 4.9 (3.6-6.3). The same four outcomes were ranked most highly by health professionals. We identified five themes for the prioritisation of outcomes: c*linical equipoise and potential for intervention, specific or attributable to haemodialysis, severity or impact on quality of life, strengthen knowledge and education,* and *inextricably linked burden and risk.*

Conclusions: Patients and health professionals believe that all cardiovascular outcomes are of critical importance but consistently identify sudden cardiac death, myocardial infarction, heart failure and stroke as the most important outcomes to be measured in all haemodialysis trials.

3.2 Introduction

People on haemodialysis have a risk of cardiovascular death 20 times greater than that found in the general population [1]. Cardiovascular death accounts for nearly 50% of mortality in the haemodialysis population [1,2]. There is a high prevalence of cardiovascular risk factors in people on haemodialysis including hypertension and diabetes [3,4], as well as uremic toxins, fluid and electrolyte imbalance, metabolic bone disease and persistent inflammation [5,6]. Cardiovascular disease is a substantial contributor to morbidity and impaired quality of life in patients on haemodialysis.

Patients with kidney failure are often excluded from cardiovascular trials[7]. Unfortunately, the majority of interventions which have been studied in this population have not been found to improve cardiovascular mortality [8,9]. Cardiovascular outcomes are reported in only 12% of all trials in haemodialysis and have used over 47 different measures assessed at many different time points[10]. The relevance and importance of these outcomes to patients and clinicians remains unknown[11]. These limitations make decisions regarding the management of CVD in people on haemodialysis challenging and highlight the need for consistent reporting of outcomes across trials.

The Standardized Outcomes in Nephrology - Haemodialysis (SONG-HD) initiative has established cardiovascular disease as a core outcome domain for clinical trials in haemodialysis (as well as mortality, vascular access and fatigue)[10,12,13]. Standardised core outcome measures of cardiovascular disease need to be developed based on the shared priorities of patients, caregivers, clinicians, researchers, policy makers, and relevant stakeholders. The aim of this survey is to assess the absolute importance of cardiovascular

outcomes and their importance relative to each other outcome to determine the most important outcomes to be used as core measures of cardiovascular disease in trials.

3.3 Materials and Methods

Study Design

We conducted an international online survey to assess the absolute and relative importance of cardiovascular outcomes for use in all haemodialysis trials. The survey was administered online and available in English and Chinese languages.

Outcome inclusion

We identified cardiovascular outcomes based on a systematic review of cardiovascular outcomes reported in contemporary trials [11]. Composite outcomes were excluded from the survey but were deconstructed into respective components. Surrogate cardiovascular outcomes (e.g. left ventricular mass) and biomarkers (e.g. troponin) were not included as they are unlikely to be meaningful to patients, may not be validated in this population and may not automatically translate into health benefits[14]. The selection of outcomes was further informed by comments on CVD in haemodialysis from patients and caregivers in a previously published international Delphi survey[13] and discussion among the Expert Working Group. Ten outcomes were included in the survey and were accompanied by a plain language definition (Box 3.1).

Survey

The survey was translated into Chinese (Mandarin) by a professional translator and cross checked by a bilingual health professional to ensure the true meaning was interpreted. The

survey was piloted on 6 participants in each language and included patients, caregivers and healthcare professionals.

The absolute importance was assessed using a Likert scale, where each outcome was scored from 1-9. A score of 7-9 indicated that the outcome was of "critical importance", 4-6 indicated "important but not critical" and 1-3 indicated "limited importance". Participants were given an option to choose "uncertain" and could provide additional comments. To ascertain relative importance a Best-worse scale (BWS) survey was used. Each participant was presented with five choice sets each consisting of 5 of the 10 outcomes that were varied across the choice sets. For each choice set participants were asked to choose which was the most and which the least important outcome. The combination of outcomes across the choice sets was determined using a balanced incomplete block design[15]. The BWS scale is a preference elicitation method based on the theory underpinning discrete choice experiments but involves less cognitive burden and provides better discrimination between outcomes than the Likert scale and greater information retrieval[16-18]. The survey was completed using LimeSurvey from October 2016 to December 2018.

Participant recruitment

Adult patients aged over 18 years, caregivers/family members, nephrologists, cardiologists, allied health members, policy makers, researchers, and industry representatives with interest or experience in haemodialysis were eligible. To ensure broad representation multiple recruitment strategies were used. Patients and caregivers were invited via the SONG Initiative database and patient organizations worldwide using standardised invitation fliers; and via opt-in snowball sampling which included the use of social media. Health professionals were recruited via professional organizations via standardised email

invitations or newsletters to their membership list, investigator networks, and via the SONG database. Participants registered their email on the SONG website to receive an email invitation with a unique survey link. All participants provided informed consent. The study was approved by the ethics board of The University of Sydney (2015-228).

Data Analysis

For each CV outcome the absolute importance was assessed by calculating the mean, median, and the proportion of participants who rated the outcome as critically important (scores of 7-9 on the Likert Scale). Relative importance was determined using a multinomial logistic regression model and expressed as a mean relative importance score determined from the regression coefficients for each outcome. As the regression coefficients have the same underlying scale, preference scores can be adjusted to any convenient scale to aid interpretation. Absolute importance scores were calculated separately for patients/caregivers and health professionals while relative importance scores were calculated using interaction terms in the regression model. Mean differences in absolute (Likert) and relative (BWS) importance scores between stakeholder groups and respective 95% confidence intervals (CI) were calculated. The software packages Excel (Microsoft Corporation, Product version 16.0), Stata/SE version 14.0 (StataCorp. College Station, TX) and NLOGIT V6 (Econometric Software Inc.) were used to analyse the data.

All free text comments from the survey responses were extracted. Comments in Chinese were translated by two independent translators and all comments were imported into HyperRESEARCH (Version 3.7, Randolph, MA) software. Using thematic analysis, investigator EO conducted line-by-line coding of the text to inductively identify themes that reflected the reasons for their prioritization. The thematic analysis was cross checked by a second investigator (AT).

3.4 Results

In total, 676 participants completed the survey, 127 (19%) were patients/caregivers (112 patients and 15 caregivers) and 549 (81%) were healthcare professionals; the majority were nephrologists (63%). The majority of participants completed the survey in English (530 [78.4%]) with 146 (21.6%) completing the Chinese survey. The characteristics of patients/caregivers and health professionals are shown in Tables 3.1 and 3.2 respectively. Of the total cohort 315 (46.6%) were male. Participants were from 53 countries with the majority from China (26%), Europe (23%) and Australia/ New Zealand (19%). The majority (78%) of the patient/caregiver participants had experienced a cardiovascular event.

Absolute importance

All CV outcomes were considered critically important (7-9 on the Likert scale) by patients/caregivers and health professionals with mean scores greater than 7 with the exception of *valve replacement* for health professionals that had a mean absolute importance score of 6.8 (95% CI 6.7 to 7.0). Based on mean scores the top three highest rated outcomes by all participants were *heart attack* (8.34, 95% CI 8.24 to 8.43)*, sudden cardiac death* (8.34, 95% CI 8.29 to 8.40, and *heart failure* (8.24, 95% CI 8.15 to 8.33) (Figure 3.1). The three outcomes rated highest by patients/caregivers, based on mean scores, were *heart attack* (8.25, 95% CI 8.04 to 8.48), *stroke* (8.18, 95%CI 7.93 to 8.43) and *heart failure* (8.15, 95%CI 7.95 to 8.35) (Table 3.3). For health professionals, the top three outcomes were: *sudden cardiac death* (8.41, 95% CI 8.29 to 8.52), *myocardial infarction* (8.35, 95% CI 8.24 to 8.50) and *heart failure* (8.26, 95% CI 8.16 to 8.37) (Table 3.3).

Relative importance

Patients/caregivers ranked *sudden cardiac death, heart attack, stroke* and *heart failure* as the most important outcomes with mean preference scores and 95% CI of 6.2 (4.8-7.5), 5.9 (4.6-7.2), 5.3 (4.0-6.6) and 4.9 (3.6-6.3) respectively (Figure 3.2). The confidence limits for the top four outcomes overlapped suggesting little or no difference in relative importance. Health professionals ranked the same four outcomes as most important and again with similar relative importance with the exception of *sudden cardiac death* that was clearly ranked as the most important outcome with a mean importance score of 9.0 (8.7-9.3) (Table 3.3). The least important outcome to patients/caregivers was *Angina* with a mean preference score of 1 (95%CI -0.32 to 2.32) and for healthcare professionals it was the reference outcome *valve replacement* with a mean preference score of 1.53.

Subgroup analysis

The mean differences in absolute importance scores between patients/caregivers and health professionals for the four highest rated outcomes *sudden cardiac death, heart attack, stroke* and *heart failure* were similar ($P > 0.05$). There were too few Chinese patients/caregivers to enable us to perform subgroup analysis between the patient/caregiver groups by language. However, differences were evident between English and Chinese language health professionals (Figure 3.3). The top four most important outcomes for English language participants were *sudden cardiac death, heart attack, stroke* and *heart failure*, while the top four for Chinese language participants were *heart attack, heart failure, sudden cardiac death* and *clots*. Differences in absolute mean scores were evident for all outcomes ($P<0.05$) with the exception of *sudden cardiac death* and *peripheral vascular disease (PVD)* ($P>0.05$). The relative preferences for English and Chinese language participants were generally similar (Figure 3.3), with the exception of *stroke* and *PVD* both

of which were considered less important (P<0.05) by health professionals who completed the survey in Chinese.

Themes

From the free text comments we identified five themes for the prioritisation of outcomes: *clinical equipoise and potential for intervention, specific or attributable to haemodialysis, the severity or impact on quality of life, strengthen knowledge and education* and *inextricably linked burden and risk.* Selected comments for each theme are provided in Table 3.4.

Clinical equipoise and potential for intervention

Both professionals and patients believed that outcomes with potential for intervention were more important, "I've rated higher conditions where intervention could save a life or prevent serious incapacity" (health professional). Health professionals felt that outcomes with clinical equipoise should be prioritized for research, "I would have rated arrhythmia higher if I could, particularly atrial fibrillation, as this is a significant area of equipoise" (health professional). Patients considered the ability to control the outcome with lifestyle intervention – "the heart is a problem but with controlled food there is a better outcome that is more affordable" (patient).

Specific or attributable to haemodialysis

Outcomes specific to patients on haemodialysis were deemed to be particularly important, "I chose sudden cardiac death as I believe it is a particular problem in dialysis patients" (patient). Patients and health professionals noted that patients on dialysis and also the transplant waiting list were particularly vulnerable as a cardiovascular event may prevent access to transplantation: "outcomes that affect suitability for transplantation are of critical

importance" (health professional). This was also reinforced by patients/caregivers – "we are put on hold on the transplant list until the heart issues are fixed" (caregiver). Some indicated that cardiovascular outcomes may present differently in people on haemodialysis, "traditional cardiac vessel occlusion is not the issue in most cases" (health professional). Participants considered that outcomes directly attributable to haemodialysis were of critical importance and needed to be recognized, "I believe the heart damage and other side-effects of dialysis are not only preventable, but severely understated" (patient). They also considered the increased risk of CVD associated with medications prescribed for patients on dialysis – "for dialysis patients heart disease [because of medication] is something we have to deal with" (patient/caregiver).

Severity or impact on quality of life

Participants believed that outcomes which had a debilitating and broader impact on quality of life were important. One patient stated that their experience of multiple cardiovascular events continued to "greatly impact on my life with good kidney function". Some health professionals prioritized the outcomes based on the impact they observed or believed it had on the patients – "I used my sense as to how much patients tend to be impacted by each outcome and how frequently we see each outcome in patients on haemodialysis in prioritizing between outcomes."

Strengthen knowledge and education

Patients and health professionals prioritized outcomes based on consideration of knowledge and education about specific cardiovascular outcomes in haemodialysis – "cardiovascular pathology as a long term disease requires both patients and medical team continuous education" (HPR). Patients believed that some CVD outcomes were missed or overlooked,

"left ventricular hypertrophy is often forgotten by health professionals and leads to complications for patients in dialysis" (patient/caregiver). Patients wanted to highlight the need for education regarding cardiovascular disease so they could gain control and employ self-management, "it is important to educate the patients. If the patient knows what is going on with their body, they can manage to prevent unnecessary complications" (patient/caregiver).

Inextricably linked burden and risk,

Health professionals often prioritized outcomes that were highly prevalent in the haemodialysis population – "my view of importance was influenced in part by frequency" (health professionals). Participants agreed that cardiovascular outcomes were critical, "all are important and matter, both independently and as variables within the sphere of each other" (health professional) and that "in many cases they [outcomes] can not be arbitrarily separated' (health professional). Patients expressed similar concerns regarding the importance of all outcomes "[it is] very difficult to choose what is the most important and in need of the most study....It would seem that we need to know more about this cardiac problem so that we can find ways to prevent this devastating problem" (patient).

3.5 Discussion

All cardiovascular outcomes were seen as critically important to stakeholders. Prioritisation was given to *sudden cardiac death, heart attack, heart failure* and *stroke* by patients/caregivers and health professionals and these outcomes were consistently the most important across survey languages. Participants prioritized outcomes for many practical reasons, selecting outcomes because of their prevalence in haemodialysis or

perceived causation by haemodialysis. Participants also wanted to ensure that outcomes which had most impact on quality of life and highest likelihood of improvement from interventions were ranked most highly.

Sudden cardiac death and *myocardial infarction* were highly prioritised outcomes by all stakeholders. Other studies which have focussed on patient preference elicitation, albeit in the general population, have prioritized similar outcomes [19]. Interestingly, participants in this general population study added that when patients are involved in outcome selection and trial design, they are more likely to comply with the intervention [19]. *Sudden cardiac death* was ranked highest by all stakeholders which aligns with the disproportionately high rate of sudden cardiac death in the haemodialysis population [20-22]. There are a number of risk factors specific to people on haemodialysis which influences the high prevalence namely; large and regular shifts in fluid and electrolytes a high prevalence of left ventricular hypertrophy and vascular calcification[23]. The patterns of arrhythmias in haemodialysis patients differ from those in the general population and it is likely that the pathophysiology of sudden cardiac death is also different in haemodialysis[22]. It is possible that a number of participants had witnessed a sudden cardiac death or other acute CVD event on the dialysis unit. There is no research specific to the dialysis unit to determine what effect these experiences might have on patient or healthcare professionals' attitudes towards this outcome. Nonetheless, it is known that there are a number of psychological sequelae after witnessing an unsuccessful resuscitation attempt[24] and this is highly likely to affect prioritisation of outcomes.

Heart failure and myocardial infarction (MI) are similarly important to all stakeholders in this survey. Heart failure is an outcome which is clinically difficult to define in the dialysis

population as symptoms often overlap with excess fluid. The cause of heart failure can be multifactorial but is often secondary to ischaemic heart disease and survived myocardial infarction. Both heart failure and myocardial infarction have far reaching consequences on quality of life and survival [25]. All-cause mortality of dialysis patients with acute myocardial infarction (AMI) at 2 years is 58% and this is 20% lower than in people with ESKD with no AMI[26]. The incidence and mortality rate of myocardial infarction in the haemodialysis population exceeds that of the general population by over 20 times [27]. There is increasing evidence that prevention, diagnosis and treatment of MI in the haemodialysis population is inferior to that found in the general population resulting in poorer short term and long term prognosis[28-30]. Furthermore, haemodialysis patients are often excluded in large scale trials of primary and secondary preventative therapies for ischaemic heart disease [7,31].

This large international survey included respondents from 53 different countries and involved a broad spectrum of stakeholders including a large number of patients and caregivers. Using the Likert and BWS allowed us to determine absolute importance as well as prioritisation of the outcomes relative to each other. Prioritisation is necessary to ensure that the most important and relevant outcomes are incorporated into a core outcome set. We were only able to translate the survey into one language other than English due to resource limitations which may have led to ascertainment bias but the participants were from a large number of countries covering a broad geographic and socio-economic range. The survey was administered online to ensure efficient dissemination and to minimize data transfer errors, however we recognize this restricted participation to those with access to the internet and computer literacy.

The results of this survey will contribute to our initiative to develop core outcome measures for cardiovascular disease for use in trials of people on haemodialysis. Utilizing this survey will ensure that the core outcome set is representative of the shared priorities of patients, caregivers, clinicians, researchers, policy makers, and relevant stakeholders. After achieving consensus on the use of these core outcomes it will be necessary to develop definitions that are valid for the haemodialysis population to ensure that trialists are able to report the outcomes consistently following an agreed standardised approach.

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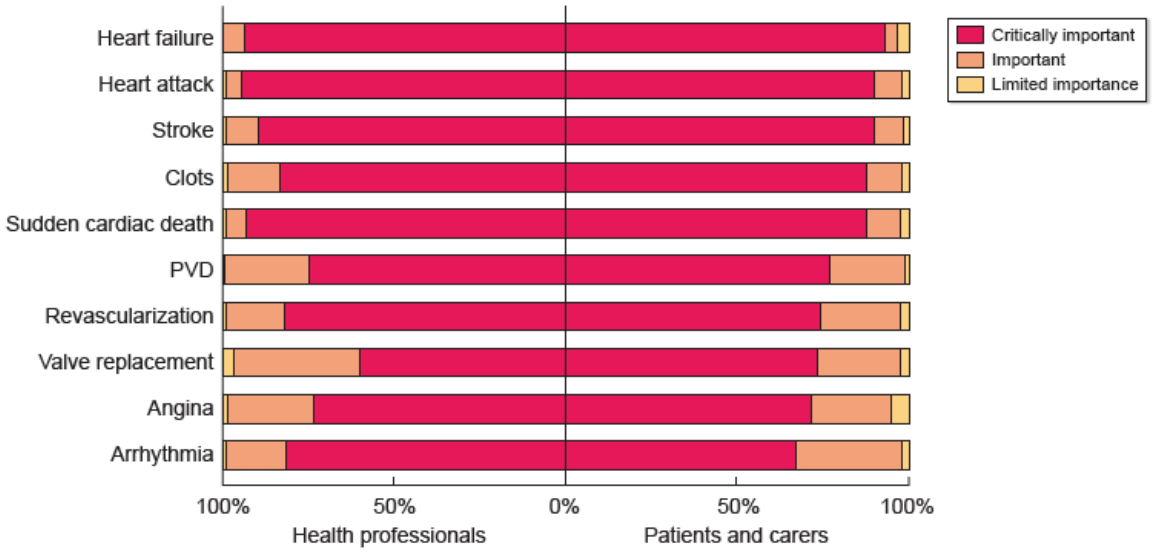
3.7 Figures and tables

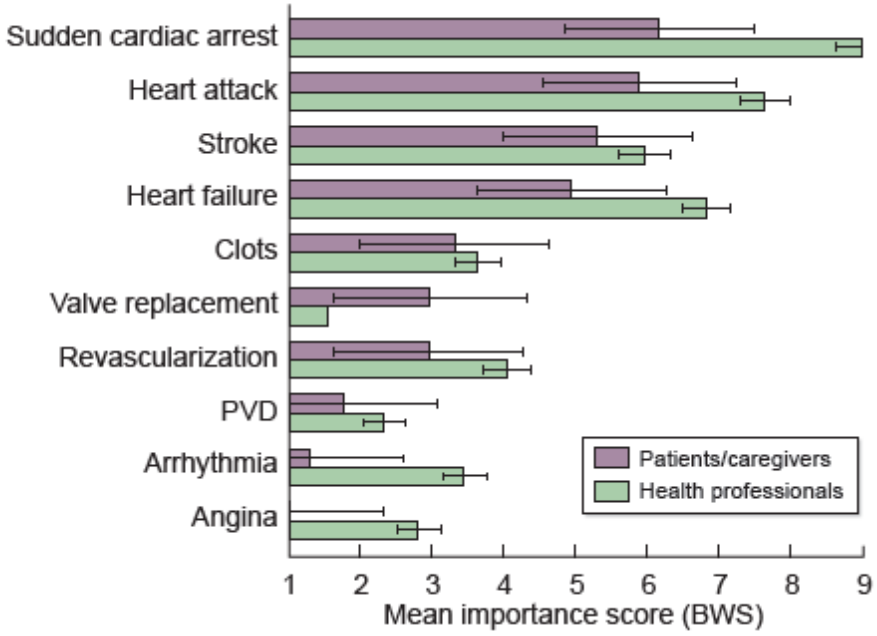
FIGURE 3.1 ABSOLUTE IMPORTANCE - PROPORTION OF PATIENTS/CAREGIVERS (RIGHT) AND HEALTH PROFESSIONALS (LEFT) CONSIDERING OUTCOMES AS CRITICALLY IMPORTANT, IMPORTANT OR OF LIMITED IMPORTANCE



Critically important (black): 7-9 points on Likert scale; important (dark gray): 4-6 points on Likert scale; limited importance (light gray): 1-3 points on Likert scale
PVD= Peripheral vascular disease

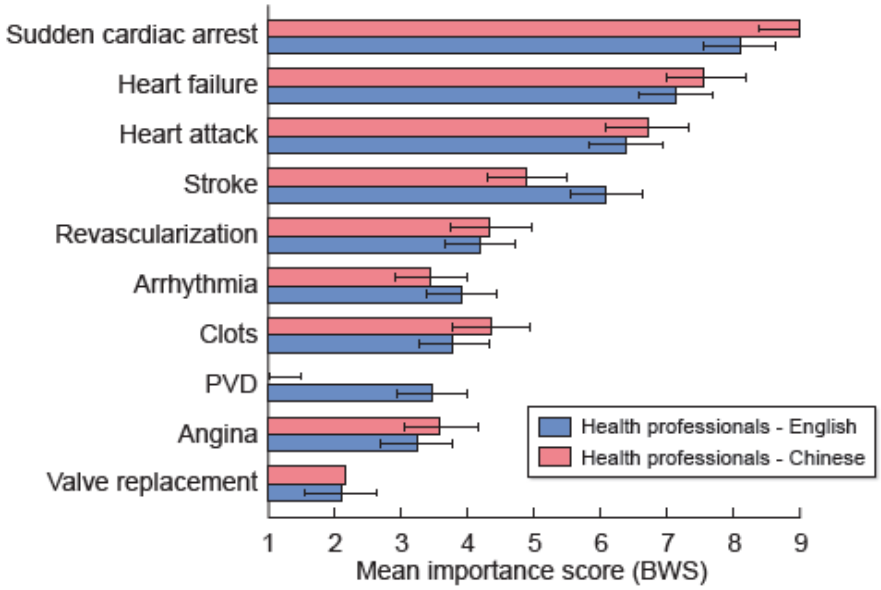
FIGURE 3.2 MEAN RELATIVE IMPORTANCE SCORES OF PATIENTS AND HEALTH PROFESSIONALS BASED ON THE BEST-WORST-SCALE.

Ordered by the mean preference scores of patients/caregivers (bars with 95% confidence intervals).



Bars represent mean preference score with 95% confidence intervals
BWS – Best-Worst-Scale, PVD = Peripheral vascular disease

FIGURE 3.3 MEAN RELATIVE IMPORTANCE SCORES OF HEALTH PROFESSIONALS BY SURVEY LANGUAGE BASED ON THE BEST-WORST-SCALE.



Bars represent mean preference score with 95% confidence intervals
PVD = Peripheral vascular disease

TABLE 3.1 CHARACTERISTICS OF PATIENTS AND CAREGIVERS

Patients/caregivers, n=127 (19%)					
Characteristics	**n**	**%**	**Characteristics**	**n**	**%**
Participant type and language survey			**Employment status***		
Patient			Full Time	22	19.3
English	105	82.7	Part time/casual	26	22.8
Chinese	7	5.5	Student	3	2.6
Caregiver/family member			Not employed	4	3.5
English	9	7.1	Retired	50	43.9
Chinese	6	4.7	Other	9	7.9
Gender*					
Male	58	45.7	**Education***		
Female	67	52.8	Did not complete high school	17	14.6
			High school graduate	14	12.1
Age group (years)*			Professional certificate/diploma	22	19.0
18-30	7	5.6	Undergraduate degree	39	33.6
31-40	16	12.8	Postgraduate degree	24	20.7
41-50	19	15.2			
51-60	26	20.8	**Experience of CVD****		
61-70	43	34.4	None	46	36.8
71-80	12	9.6	Abnormal heart rhythm	30	24.0
>80	2	1.6	Thrombosis	18	14.4
			Angina	17	13.6
Country*			Other	13	10.4
Australia	42	33.6	Heart bypass or stent	11	8.8
United Kingdom	22	17.6	Peripheral vascular disease	8	6.4
United States	22	17.6	Heart attack	7	5.6
China	13	10.4	Heart failure	5	4.0
Canada	9	7.2	Stroke	3	2.4
New Zealand	9	7.2	Heart valve replacement	3	2.4
Denmark	6	4.8	Cardiac arrest	1	0.8
India	1	0.8			
Spain	1	0.8			
Marital status*					
Single	14	13.2			
Married	67	63.2			
Living with partner/de facto	7	6.6			
Partner (not living with)	4	3.8			
Widowed	7	6.6			
Divorced	5	4.7			
Separated	2	1.9			

*Total numbers do not add up to total number of participants due to undisclosed responses (excluded). **>1 CVD event experienced by individual patients, 116 events experienced 99 patients/caregivers.

TABLE 3.2 CHARACTERISTICS OF HEALTH PROFESSIONALS

Health professionals, n=549 (81.2%)					
Characteristics	**n**	**%**	**Characteristics**	**n**	**%**
Language of survey			**Number of trials as investigator***		
English	416	75.8	0	232	43.0
Chinese	133	24.2	1-5	219	40.6
			6-10	50	9.3
Gender			11-15	11	2.0
Male	257	46.8	>15	27	5.0
Female	292	53.2			
			Participant type		
Age group (years)			Nephrologist	348	63.4
18-30	38	6.9	Nurse	105	19.1
31-40	130	23.7	Researcher	32	5.8
41-50	176	32.1	Physician (other eg. psychiatrist)	22	4.0
51-60	152	27.7	Nephrologist in training	16	2.9
61-70	43	7.8	Other	14	2.6
71-80	10	1.8	Surgeon	7	1.3
			Dietician	7	1.3
Country			Policy maker	7	1.3
China	164	29.9	Social worker	5	0.9
Australia	85	15.5	Pharmacist	5	0.9
Other European countries	71	12.9	Cardiologist	4	0.7
United Kingdom	44	8.0	Psychologist	4	0.7
United States	39	7.1	Industry/private sector	3	0.5
Canada	31	5.6	Radiologist	2	0.4
New Zealand	18	3.3			
South America	17	3.1	**Experience with HD (years)***		
Other Asian countries	17	3.1	≤10	194	35.3
India	16	2.9	11-20	187	34.1
Malaysia	16	2.9	21-30	97	17.7
Middle East and Russia	14	2.6	>30	61	11.1
Poland	12	2.2			
Africa	5	0.9	**Other roles***		
			Government, policy making	77	14.0
			Funding (government, charity)	63	11.5
			Clinical practice guidelines	1	0.2

*Total numbers do not add up to total number of participants due to undisclosed responses (excluded).

TABLE 3.3 SUMMARY OF IMPORTANCE SCORES FOR PATIENTS/CAREGIVERS AND HEALTH PROFESSIONALS.

Outcomes	Median Likert score		Mean Likert score		Mean difference Likert		Proportion (%) critically important (7-9)		Mean BWS score	
	Patients/Carers	HP	Patients/Carers	HP		P value	Patients/ Carers	HP	Patients/ Carers	HP
Sudden Cardiac Death	9	9	8.1	8.4	-0.3	0.03	87.9	93.1	6.2	9.0
Heart attack	9	9	8.3	8.4	-0.1	0.45	90.3	94.4	5.9	7.7
Stroke	9	9	8.2	8.1	0.1	0.64	89.9	89.6	5.3	6.0
Heart failure	9	9	8.1	8.3	-0.1	0.34	93.2	93.5	4.9	6.8
Thrombosis	8	8	7.9	7.7	0.2	0.13	88.4	83.4	3.3	3.6
Valve replacement	8	7	7.4	6.8	0.6	<0.001	73.5	59.8	3.0	1.5
Revascularization	8	8	7.6	7.6	0.0	0.99	74.0	81.3	3.0	4.0
PVD	8	8	7.5	7.3	0.1	0.34	76.9	74.5	1.8	2.3
Arrhythmia	7	8	7.2	7.6	-0.3	0.02	67.0	81.2	1.3	3.4
Angina	7	8	7.2	7.4	-0.2	0.2	72.1	73.4	1.0	2.8

HP – Health professionals PVD – Peripheral vascular disease

TABLE 3.4 QUALITATIVE ANALYSIS: THEMES WITH SELECTED ILLUSTRATIVE QUOTATIONS

Clinical equipoise and potential for intervention
I would have rated arrhythmia higher if I could, particularly atrial fibrillation, as this is a significant area (health professional).
I've rated higher conditions where intervention could save a life or prevent serious incapacity (health professional)
the heart is a problem but with controlled food there is a better outcome that is more affordable (patient/caregiver)
Specific or attributable to haemodialysis
I chose sudden cardiac death as I believe it is a particular problem in dialysis patients (patient/caregiver)
outcomes that affects suitability for transplantation are of critical importance (health professional)
we are put on hold on the transplant list until the heart issues are fixed(patient/caregiver)
As sudden cardiac death in dialysis patients can happen it is imperative to study this subject (health professional)
traditional cardiac vessel occlusion is not the issue in most cases (health professional)
For dialysis patients heart disease (because of medication) is something we have to deal with(patient/caregiver)" (patient/caregiver).
I believe the heart damage and other "side effects" of dialysis are not only preventable, but severely understated (patient/caregiver)
I have a heart murmur - 10 years plus and I have a calcified Aorta now 0.8 cm ID (patient/caregiver)
Severity or Impact on quality of life
[cardiovascular events] greatly impact my life with good kidney function (patient/caregiver)
I used my sense as to how much patients tend to be impacted by each outcome and how frequently we see each outcome in patients on haemodialysis in prioritizing between outcomes (health professional)
There are small strokes that may have less implication than valve replacement or NonSTEMI that may have little significance (health professional)
Sudden Cardiac arrest is least important because it is rare and may not be the worst way to die. Heart failure is most important because it is most common in dialysis, severely affects quality of life off dialysis and affects ability to dialyse and impacts on many of the other outcomes including transplantability (health professional)
In practice, as long as it causes patients the most suffering, the most threat to life, and/or the symptom causing the most impact on quality of life, then these are the most important problems we need to solve as clinicians/health professionals (health professional)
Strengthen knowledge and education
Cardiovascular pathology as a long term disease requires both patients and medical team continuous education (health professional).
left ventricular hypertrophy is often forgotten by health professionals, and leads to a complications for patients in dialysis (patient/caregiver).
it is important to educate the patients. If the patient knows what is going on with their body, they can manage to prevent unnecessary complications

(patient/caregiver)
Inextricably linked burden and risk
my view of importance was influenced in part by frequency (health professional).
all are important and matter, both independently and as variables within the sphere of each the others (health professional
it's very difficult to only choose one option of each, because maybe 2 or 3 are extremely important and none are "less important"(health professional).
The rankings asked for are rather artificial most of them are important and to place them as least important is not necessarily correct. In many cases they cannot be arbitrarily separated as the survey implies (health professional)
Very difficult to choose what is the most important and in need of the most study. As sudden cardiac death in dialysis patients can happen it is imperitave to study this subject. It would seem that we need to know more about this cardiac problem do that we can find ways to prevent this devastating problem. (patient)

BOX 3.1 OUTCOMES AND DEFINITIONS USED IN THE ONLINE SURVEY

Outcome	Definition
Heart attack (myocardial infarction)	A sudden blockage of a blood vessel that supplies blood to the heart, leading to death of heart muscle. It can cause immediate symptoms such as chest pain, long term problems such as shortness of breath and death.
Stroke	A sudden blockage or bleed of a blood vessel in the brain, leading to death of that part of the brain. A small stroke may lead to a temporary weakness or numbness of a limb and complete recovery. A big stroke may result in permanent weakness, numbness or paralysis, losing the ability to speak or death.
Clot or blockage (thrombosis and embolism)	A thrombus is a clot that forms in a blood vessel. An embolus is anything that travels through the blood vessels and can block them. These normally refer to a clot in a limb or in the lungs. If blood flow is stopped to a limb it can cause pain and swelling, if the clot is in the lung it can cause pain or shortness of breath and can affect the heart.
Heart failure	When the heart cannot pump enough blood to meet the needs of the body. This can cause symptoms such as dizziness, shortness of breath and swelling not related to dialysis and can lead to death.
Angina	The sensation of chest pain, pressure, or squeezing in the chest which comes from not enough blood reaching the heart. Often a warning sign for a heart attack.
Valve replacement	Heart valves control the flow of blood though the heart. If a valve becomes damaged it can become too stiff or leaky and stop the heart from pumping efficiently. If the valve is not replaced the heart can start to fail leading to pain, dizziness, shortness of breath, swelling and death.
Arrhythmia	A heart rhythm that is not normal and may lead to the heart not pumping enough blood for the body. The irregular rhythm may or may not cause problems such as palpitations, dizziness, chest pain or death.
Re-opening of a blocked blood vessel (revascularisation)	Arteries in the heart can become narrowed or blocked leading to poor blood supply to the heart muscle. This can lead to chest pain, a heart attack, heart failure or death. Revascularisation is the re-opening of a blocked blood vessel by a "stent" insertion or a "bypass" operation.
Disease of the vessels in the arms and legs (Peripheral vascular disease)	When the blood supply to areas like the arms and legs is damaged, this may result in pain, amputation or in a weakening of the vessel wall and ballooning of the vessel known as an aneurysm.
Sudden cardiac arrest/sudden cardiac death	The heart stops unexpectedly and suddenly, usually due to a harmful heart rhythm. If this happens, blood stops flowing to the brain and other vital organs and can cause death if it is not treated within minutes. In which case it is described as a "sudden cardiac death." If medical intervention restarts the heart there may be long lasting damage to the brain and other organs.

CHAPTER 4

ESTABLISHING CORE CARDIOVASCULAR OUTCOME MEASURES FOR TRIALS IN HAEMODIALYSIS: REPORT OF AN INTERNATIONAL CONSENSUS WORKSHOP

Publication details and contribution of authors

O'Lone E, Viecelli AK, Craig JC, Tong A, Sautenet B, Herrington WG, Herzog C, Jafar T, Jardine M, Krane V, Levin A, Malyszko J, Rocco MJ, Strippoli G, Tonelli M, Wang AYM, Wanner C, Zannad F, Winkelmayer WC, Wheeler D on behalf of the SONG-HD Investigators. Establishing core cardiovascular outcome measures for trials in haemodialysis: report of an international consensus workshop. **Accepted to American Journal of Kidney Diseases September 2019.**

EO: conceived, designed and produced the workshop, prepared and analysed the data, interpreted the results and wrote and revised the manuscript

AV: contributed to the workshop and revised the manuscript

AT: contributed to the design and production of the workshop, advised on interpretation and presentation of the results, and revision of the manuscript

BS: contributed to the workshop and revised the manuscript

JCC: contributed to the design and production of the workshop, advised on interpretation and presentation of the results, and revision of the manuscript

WH, CH, VK, AL, MR, GS, MT, AW, CW, FZ, WW : contributed to the workshop and revised the manuscript

TJ, MJ, JM: revised the manuscript

DW: chaired the workshop and revised the manuscript

4.1 Abstract

Cardiovascular disease (CVD) affects more than two-thirds of patients on haemodialysis, is the leading cause of death in this population and yet, CVD outcomes are infrequently and inconsistently reported in trials in patients receiving haemodialysis. As part of the Standardised Outcomes in Nephrology-Haemodialysis (SONG-HD) initiative, we convened a consensus workshop to discuss the potential use of myocardial infarction (MI) and sudden cardiac death (SCD) as core outcome measures for CVD for use in all trials in people on haemodialysis. Seven patients/caregivers and 51 health-professionals from 15 countries discussed selection and implementation of the proposed core outcomes. Five main themes were identified. *Capturing specific relevance to the haemodialysis population* acknowledging prevalence, risk, severity, unique symptomology and pathophysiology. *The dilemmas in using composite outcomes* were recognised. *Addressing challenges in outcome definitions,* establishing a common definition, and addressing uncertainty in the utility of biomarkers in haemodialysis. *Ensuring a meaningful metric for decision-making* to facilitate comparison across trials. *Enabling and incentivising* implementation by ensuring cardiologists are involved in development and integration of the outcome measure into registries, trial-design and reporting guidelines. Based on these themes, participants supported the use of *MI* and *SCD* as core outcomes of CVD to be reported in all haemodialysis trials.

4.2 Introduction

Cardiovascular disease (CVD) affects more than two thirds of people on haemodialysis and is the leading cause of death in this population[1,2]. CVD also increases their short and long-term morbidity in this population[2]. Traditional risk factors for CVD, including diabetes mellitus, hypertension and dyslipidaemia, are highly prevalent in the haemodialysis population[3] and may act synergistically with non-traditional risk factors including uraemic toxins, electrolyte and fluid imbalance, disordered bone and mineral metabolism and haemodialysis modality [4-8]. Optimal management of CVD in patients on haemodialysis remains uncertain. Evidence from trials to inform decisions is currently limited because patients on haemodialysis are often excluded from cardiovascular trials [9]. Furthermore, cardiovascular outcomes remain infrequently reported, appearing in only 12% of trials in haemodialysis [10].

There is considerable heterogeneity as well as extensive use of surrogate and composite cardiovascular outcomes across trials in haemodialysis [11]. In a recent systematic review of 175 trials in haemodialysis, over 230 measures were used for 26 cardiovascular outcomes such as myocardial infarction, stroke and cardiac arrest [12]. The three most frequently reported outcomes were serum biomarkers (excluding lipids and traditional cardiac biomarkers), cardiovascular composites, and serum lipids [11]. Composite outcomes were highly variable with more than 50 different composite combinations used, with most combinations used only in a single trial [11]. The differing degrees of clinical impact of the individual outcomes incorporated into a composite outcome as well as the difficulty in comparing composites across trials makes estimates of the comparative effectiveness of interventions highly uncertain. This in

turn, hinders progress towards improving cardiovascular morbidity and mortality in this high-risk population.

Surrogate markers of CVD, both biochemical (e.g. lipids) and anatomical (e.g. left ventricular mass index), are also frequently used in cardiovascular trials and yet they may not accurately predict the effect of an intervention on important clinical outcomes such as sudden cardiac death, myocardial infarction or stroke [13,14], nor are they meaningful to patients to support decision-making [15]. CVD has been prioritised by patients, caregivers and health professionals as a critically important outcome for use in all trials in haemodialysis [16]. Specifically, cardiovascular events such as myocardial infarction, sudden cardiac death and stroke, which have direct impact on patients in terms of symptoms and quality of life and survival, and yet these outcomes were reported in less than 10% of trials that report CVD outcomes in haemodialysis [11].

These problems with outcome reporting have driven efforts to develop core outcome sets, defined as an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care [17]. This is a two-step process requiring the identification of the domain, such as myocardial infarction, followed by determining the metric(s) that best defines that domain, such as ECG and cardiac enzyme. In cardiovascular medicine, core outcome sets are being developed in specific populations including pregnant women with CVD [18] and patients undergoing cardiac surgery [19]. In cardiac surgery the core outcome set consists of mortality, quality of life, hospitalisation and cerebrovascular complications [20]. The American Heart Association has developed key data elements and definitions for cardiovascular endpoint events in clinical trials, electrophysiological studies and

procedures reporting and a cardiovascular vocabulary for electronic health records [21-23]. Collectively, these efforts endeavour to improve consistency and relevance of cardiovascular events reported in the general population.

Recently, the Standardised Outcomes in Nephrology Haemodialysis (SONG-HD) initiative was launched to establish a set of core outcomes for trials in haemodialysis. Based on a consensus process involving more than 1200 patients, caregivers and health professionals from over 70 countries, CVD (together with vascular access, fatigue and mortality) was identified as a core outcome. As part of the SONG-HD Initiative to establish core outcome measures for CVD we administered an international survey to rank which CVD outcomes were the most important to all stakeholders[24]. We then convened a consensus workshop in New Orleans in November 2017 during the American Society of Nephrology Kidney Week Conference with patients, caregivers, and health professionals to discuss the identification and implementation of a core outcome measure for CVD to be reported in all trials in haemodialysis populations. This report provides a summary of the workshop discussion and outlines recommendations for establishing core CVD outcome measures in haemodialysis.

4.3 SONG-HD Cardiovascular Disease Consensus Workshop

Context and scope

The SONG-HD Cardiovascular Disease consensus workshop was held on November 1st, 2017 in New Orleans, USA in conjunction with the American Society of Nephrology Kidney Week Conference 2017. The workshop brought together stakeholders (patients, caregivers, and health professionals) to discuss the identification and

implementation of a core outcome specifically for CVD to be reported in all haemodialysis trials. Based on a systematic review [11] and interim results from an international survey on CVD outcomes completed by patients/caregivers and health professionals prior to the workshop, the two prioritised cardiovascular outcomes were myocardial infarction and sudden cardiac death. These potential core cardiovascular outcomes were presented to stakeholders for discussion.

Participants and contributors

Patients, caregivers and patient representatives with experience of haemodialysis, and health professionals (nephrologists, cardiologists, nursing and allied health professionals, researchers, trialists, regulators, funders, and policy makers) were invited to the workshop. Invitations were also extended to representatives of professional societies (e.g. American Society of Nephrology), regulatory agencies (e.g. Food and Drug and Administration [FDA], Centers for Medicare and Medicaid Services [CMS]), journal editors, registries, funding organisations (e.g. National Institutes for Health [NIH]), industry, and guideline organisations (e.g. Kidney Disease Improving Global Outcomes).

Workshop program and materials

The workshops materials were circulated to all investigators two weeks prior to the workshop. The materials included an overview of the SONG-HD process, results of the systematic review of cardiovascular outcomes in haemodialysis trials, and interim results of an international online survey with patients/caregivers and health professionals who ranked the importance of cardiovascular outcomes (e.g. myocardial infarction, sudden cardiac death) to be reported in trials in haemodialysis. We also

included definitions of myocardial infarction currently used including the Third Universal Definition [25] and the definitions used in a number of landmark cardiovascular trials in patients with end-stage kidney disease (ESKD) [26-29].

Participants were allocated to one of six break-out discussion groups with 7-10 members. Each group had at least one patient/caregiver. The groups were facilitated by EO, AKV, JCC, WW, AL and DW. The facilitator asked participants to discuss: the interim results of the survey (which is beyond the scope of the current report and will be published separately); the potential use of myocardial infarction and sudden cardiac death as core outcome measures including the definition, feasibility, validity and discrimination; how they should be reported, including metric, comprehensibility for patients; and implementation. In the plenary session, one member from each group presented the main points of their discussion. The Chair of the workshops (DCW) summarised the presentations across the groups. The group discussions and the plenary sessions were audio-taped and transcribed.

The transcripts were entered into HyperRESEARCH (ResearchWare Inc. United States; Version 3.0.) to facilitate coding and analysis of the data. The first author (EO) coded the transcript line-by-line and inductively identified concepts relating to the identification and implementation of a core outcome measure for CVD to be reported in trials in haemodialysis. All participants and contributors received a draft workshop report to provide feedback within a two-week timeframe to ensure that the findings reflected participants' perspectives. Additional comments were integrated into the final report.

In total, 51 healthcare professionals (nephrologists, cardiologists, nursing and allied health professionals, researchers [including trialists], journal editors, policy makers and industry representatives) and seven patients/caregivers attended the workshop. The participants were from 15 countries. Additional investigators who were unable to attend (n=58) contributed feedback on the workshop program and the draft workshop report by email.

4.4 Summary of the workshop discussion

We identified five main themes (Figure 4.1): capturing specific relevance to the haemodialysis population; dilemmas in using composite outcomes; addressing challenges in outcome definition; ensuring a meaningful metric for decision-making; and enabling and incentivising implementation. The respective subthemes are described below. Selected illustrative quotations for each theme are shown in Table 4.1. Recommendations from the workshop discussions are summarised in Figure 4.2.

Capturing specific relevance to the haemodialysis population

"It's a different conversation with somebody on dialysis, and I don't believe that that's always acknowledged, that dialysis patients are unique. Not just in their risk factors [for CVD], but in how they can and should be treated and take care of themselves."

(Health professional, Group 3)

Prevalence, risk and severity of the cardiovascular outcome: Participants considered whether the core CVD outcome should be based on prevalence in the haemodialysis population (i.e. myocardial infarction), its specificity to a haemodialysis population (i.e. sudden cardiac death) or the impact of the outcome to patients (i.e. heart failure or

stroke), "There is a difference between importance versus frequency" (Health professional, Group 1). The relevance of the CVD outcomes was argued to be fundamental to the decision – "I'm okay with the fact that it's [*myocardial infarction]* the most frequently measured, but I'm not okay with the fact that probably it's not really the most relevant" (Health professional, Group 1).

Complex symptomology and diagnosis: It was emphasised that CVD in a patient on haemodialysis did not often present in a classical way, and the ability to diagnose CVD in the haemodialysis population was particularly difficult. Heart failure could be misdiagnosed in a patient with fluid overload, a myocardial infarction could be missed in a patient without chest pain, and a sudden cardiac death could be misclassified as a myocardial infarction. The core outcome measure for CVD had to be carefully established for the specific population, "that sudden cardiac death in someone who is on dialysis, if you were to use the general population term, probably you would think this is a myocardial infarction death. When in actual fact you realise in the years that pass that actually a very large proportion may not be myocardial infarction" (Health professional, Group 3).

Considering consequences on quality of life: CVD could impact quality of life, which was a key consideration as patients "want to be able to survive and have some semblance of quality of life" (Health professional, Group 2). Stroke and heart failure were highlighted as having a potentially more severe and immediate impact on function and overall quality of life day-to-day. "Most of my patients put a stroke ahead of everything, ahead of sudden cardiac death, myocardial infarction, because it'll be the thing with the most obvious change in quality of life because it's immediate"

(Health professional, Group 2). However, silent or recurrent myocardial infarction was felt to contribute to long term poor outcomes and quality of life, “you were saying about quality of life and heart failure, it [*myocardial infarction*] is crucial in the development of heart failure and it does impact on functional cardiovascular reserve, so it is sensitive to have it in there because it will ultimately impact adversely on function.” (Health professional, Group 2)

Accounting for geographic variation: The variation in prevalence of CVD across countries was recognised – “Like in Japan, strokes are a lot more common *[than MI*]." (Health professional, Group 4). Treatment could vary depending on the healthcare context – “hospitalisation is region-dependent, because in some regions, patients are going to be hospitalised earlier than in other regions” (Health professional, Group 5). A core outcome for CVD in haemodialysis had to be feasible to measure internationally, for example “countries around the world where you cannot measure troponin” (Health professional, Group 6).

Having potential for intervention: There was some concern that establishing a core outcome in CVD may drive research in a futile direction, particularly if they expected there to be little potential for interventions to change the outcome – “MIs, heart attacks are clearly important. My concern is that by reporting them in every trial, they’re so poorly modifiable that it’s not going to get us where we want to go in terms of getting better, patients better at the end of the day” (Health professional, Group 5). It was speculated that sudden cardiac death and heart failure might be more modifiable than myocardial infarction. Participants realised that trialists may not want to include an outcome which is unlikely to be responsive to their particular

intervention but agreed that outcomes of critical importance to patients and clinicians' decision making should still be measured and reported, irrespective of whether they may respond to the intervention.

Dilemmas in using composite outcomes

Obfuscation and misinterpretation of findings: For a core CVD outcome, "having a composite outcome would be very complex" (Health professional, Group 4). The combination of outcomes used in composites (presented during the workshop) was extremely heterogenous, making comparisons across trials impossible – "it would be great if everybody used the same definition of MACE and MACE-plus.....even imperfect, at least we could compare results" (Health professional, Group 4). Issues discussed also included: the potential to "cherry pick" components for a composite cardiovascular disease outcome in the attempt to demonstrate a positive effect for an intervention, and combining outcomes of varying prevalence and importance to patients could dilute the relevance of the results, and be potentially misleading. For these reasons, it was "not actually appropriate to combine [*outcomes*], or it may not be smart to do so [*for a core outcome*]" (Health professional, Group 4). Reporting an individual specific CVD outcome would make results more transparent and thus preferable as a core outcome.

Benefits to trialists: It was acknowledged that "as much as we might not want to encourage the use of a composite endpoint, the reality is regulatory agencies, that's exactly what they demand" (Health professional, Group 5). The use of composite outcomes could reduce cost by reducing the required sample size – "you have to have a composite outcome in order to have statistical significance with a smaller sample

size" (Health professional, Group 5). Some thought it may be important to report more than one CVD outcome, and to "try and define what the composite outcome should be" (Health professional, Group 5).

Addressing challenges in symptomatology, definition and utility of outcomes

Consistency, applicability and specificity of definitions: Given the wide heterogeneity in definitions for cardiovascular outcomes in trials, establishing a consistent definition was thought to be paramount. There were conflicting views on the current definitions available: The Third Universal definition for myocardial infarction was suggested as a gold standard and whilst "there's a strength in a gold standard if you will, that is internationally accepted; rather than reinventing the wheel and defining this from scratch which may take decades" (Health professional, Group 6), some health professionals argued that the current definition had "to be adapted for the haemodialysis population" (Health professional, Group 3). This was on the basis of the different symptomatology and diagnostic criteria in haemodialysis: "they often don't have pain, so that's the first criteria. Their troponin's elevated anyway, that's the second criteria, troponin's up at baseline in many patients, no?" (Health professional, Group 2); and that "the type-2 MI is predominant, not the type-1" (Health professional, Group 4). The definition had to be practical, comprehensible to patients, and validated in the haemodialysis population, "it's good to be adapted, it's more important to be validated" (Health professional, Group 3).

Recognising variability in symptoms: In the haemodialysis population, the symptoms of MI and heart failure differed, "I didn't have a sharp pain, but I had difficulty breathing and stuff like that" (Patient, Group 3). A health professional further explained,

"because in our population, a lot of the heart attacks are actually silent, so actually it's quite different from the general heart attack that we see in the usual population. Most patients may manifest heart failure rather than classical heart attack symptoms or chest pain. That is one important consideration when you diagnose a heart attack in a classical way where you need to have the symptoms, chest pain" (Health professional, Group 4). It was also difficult to differentiate heart failure from fluid overload in haemodialysis.

Uncertainty in the clinical utility of biomarkers specific to haemodialysis: The limitations of biomarkers in haemodialysis were recognised – "biomarkers which are very useful in general population cannot be truly interpreted in renal patients" (Health professional, Group 6). Troponin levels were not standardised in a haemodialysis population and each assay and lab performs differently. The timing of a biomarker, whether it was before or after dialysis and what constituted a significant change in troponin levels was uncertain in the context of haemodialysis – "we don't know what a significant delta is, right?" (Health professional, Group 1).

Clarity for adjudication: The definition of the core CVD outcome in haemodialysis had to have potential for use not only by clinicians as a diagnostic tool but also by trialists and registries, "frankly the definition comes a bit too late. It's already been defined by the local doctor" (Health professional, Group 4). The ability to use the definition in the context of clinical care and in trials was suggested to align outcome ascertainment based upon clinical diagnosis and by trial outcome adjudicators, "It turns out only about two-thirds to three-quarters of what the investigators reporting as an MI is finally adjudicated positively as an MI … you're limited in your data that you get in a

clinical trial setting, because often times heart attacks are happening in the hospital. The investigator's not there, and you're limited by the data that you're getting" (Health professional, Group 4).

Selecting a meaningful metric for decision-making

Comprehensible and meaningful to patients: The core outcome for CVD had to be simple and readily understood by patients so that it could inform decision-making, "I wonder whether the definition of 'heart attack' to a patient is different as well, whether any condition involving the heart, including sudden cardiac death that we define differently, could mean heart attack for patients" (Health professional, Group 1). "The simpler you can make it for the average patient the better, because remember when you're giving them information; the vast majority of them are being overwhelmed by the process itself" (Health professional, Group 2). Patients and caregivers wanted to be told the specific risks of CVD, "I'd rather know the numbers and know the facts so that I can do my best to prevent that [*myocardial infarction]* from happening to me." (Patient, Group 2). Some suggested providing information in a visual format and to "use numbers, not percentages when describing anything" (Patient, Group 6) and "you should always be grounded in the absolute [*risk*]" (Patient, Group 6). Personalising cardiovascular risk was important to patients, "there's ways of putting it that you give that information, and yet you're actually personalising it as well" (Patient, Group 2).

Distinguishing severity and recurrence: The outcome measure for CVD needed to capture the severity of an event, mainly in terms of its clinical consequences and impact on quality of life, "you could have someone who has a very large MI and

develops heart failure and other complications, arrhythmias, and then you can have another patient who meets the criteria but just squeaks by and doesn't have a lot in terms of effects, in terms of quality of life, and in terms of function" (Health professional, Group 5). The outcome measure should capture severity by defining a clear threshold after which the event fulfils the definition. "If we want to assess severity at the same time, it has to have some sort of a consequence, either needing an intervention or needing hospitalisation" (Health professional, Group 5) and trialists may want to add this outcome to the core outcome. The recurrence of events also had to be considered – "it matters to people if they had one heart attack or three" (Group 6), though the same definition could be used by trialists to capture recurrence.

Comparability across trials: A single metric would facilitate ease of comparison across trials. Some particular metrics may lead to further inconsistencies. For example, CVD-related hospitalisation would lead to undue variability across trials because "hospitalisation is region-dependent; in some regions patients are going to be hospitalised earlier than in other regions" (Health professional, Group 5). Using a time-to-event metric may be simpler and would mean that "you could still infer your proportion of events. You could extract whatever other metric you want" (Health professional, Group 2), however this would miss subsequent events. Ultimately the metric should facilitate collection of a minimum dataset with minimal flexibility because "if we say leave it to trialists, we'll just get the same mess we've got now" (Health professional, Group 2).

Enabling and incentivising implementation

Integration into registries: Recognising the growing interest in conducting registry-based trials to increase efficiency and reduce the burden to trialists, the core outcome measure had to be applicable and feasibly integrated in registries across healthcare contexts - “to do more efficient trials....to build your outcome measures so they can be used across borders as in across different healthcare systems” (Health professional, Group 4).

Incorporating into clinical care: The definition for the core CVD outcome had to be readily embedded into routine clinical care, “definitions for MI which we could standardise in administrative data sets” (Health professional, Group 6) then “if this was adopted by regulators or registry trials, ...healthcare systems or registry systems could participate, and may actually have an incentive to be competitive and implement [*the definition]* into the clinical, everyday care setting” (Health professional, Group 6).

Seeking authoritative endorsement: Buy-in and endorsement by journals and guidelines would support implementation of the core outcome measure for CVD, incorporating them into trial reporting guidelines “just as journal editors now require a CONSORT diagram, perhaps we could convince the journal editors that using standard definitions is also going to be important to be published in that particular journal” (Health professional Group 5). It also requires uptake by those involved in trial design, “bring in some of the thought leaders that design these trials, you need to bring in the regulatory agencies. They all need to come together and hash it out, and comment on the feasibility of doing this and the appropriateness of doing this. If you don’t have the buy-in from those who are designing the trials, you don’t have the buy-in in the regulatory agencies, it’s not going to happen” (Health professional, Group 4). They

questioned, "how much is [*the core outcome measure to be used as*] a guideline, how much is it something we aspire to, and how much is going to be mandated?" (Health professional, Group 6), and some contended that the measure should be compulsory to ensure uptake, "prescriptive is usually the best vehicle towards implementing and making change happen" (Health professional, Group 6). They suggested to: "[*make*] it be part of the requirements for FDA approval, that trials have actually measured these core outcomes?"(Health Professional, Group 5). They thought it would be similar to implementing "mandatory trial registration, everybody was like, 'Ugh, this is horrible. It's so much extra work,' and now we don't think twice. We just do it." (Health professional, Group 6) Alternatively an "opt in" system could be considered, "maybe provide a checklist that investigators have to [*fill in*]" (Health professional, Group 5).

Requiring cardiology input and buy in: Cardiologists needed to be integrally involved in the development of the core outcome measure for CVD in haemodialysis to support implementation – "it's of great value to have an expert group of cardiologists look at these things (Health professional, Group 4) so the measure would be "accepted into the cardiology community" (Health professional, Group 1). The involvement of cardiologists would facilitate acceptance and ensure that both nephrology- and cardiology-led trials could be effectively compared and would be relevant to the haemodialysis population, "It would be very difficult to extrapolate anything if we don't have a common language with the cardiologists" (Health professional, Group 1).

4.5 Discussion

Core outcomes for CVD should reflect what is most important and relevant to patients on haemodialysis and their clinicians. Myocardial infarction and sudden cardiac death

were agreed upon as the most important CVD outcomes to report in haemodialysis trials. CVD outcomes such as heart failure and stroke were recognised as important but consensus was achieved for myocardial infarction and sudden cardiac death for a number of patient-centred, clinical and pragmatic reasons. They are of high importance to patients and health professionals, and there is an increased risk in and are of specific relevance to patients on haemodialysis. Myocardial infarctions were believed to contribute to heart failure and participants felt that heart failure (due to the difficult clinical distinction from fluid overload) and stroke (due to the extensive investigations required to accurately diagnose) would not be simple outcomes to adjudicate in people on haemodialysis. Myocardial infarction is particularly relevant because it is associated with high mortality, functioning, quality of life, and had long-term health and psychosocial consequences in patients on haemodialysis.

Composite outcomes are frequently used in cardiovascular trials, because they can minimise resources and increase power in a trial. However, they should not be used as core outcomes because of the challenges they pose for interpretation of the findings. Even the frequently used composite endpoint "Major adverse cardiovascular events (MACE)" demonstrates substantial heterogeneity in the study-specific individual outcomes used to define MACE, with substantially different results and conclusions across trials [30]. A recent systematic review found similar heterogeneity across other CVD composite endpoints used in trials in haemodialysis [12]. The CVD core outcomes should be simple and the data for the outcomes should be able to be collected in all trials in haemodialysis regardless of the intervention. Using well-defined individual CVD outcomes would therefore be preferable to a composite when selecting core outcomes for CVD in trials in haemodialysis.

As recognised by the workshop attendees, defining the core outcomes would be difficult given that current definitions for CVD outcomes in the general population could not be readily extrapolated and applied in patients on haemodialysis. This is because of the variability in clinical presentation of CVD, uncertainty in the clinical utility of CVD biomarkers, and problems with the interpretation of diagnostic tests in the haemodialysis population.

Myocardial infarction and sudden cardiac death are not only frequent events in HD, these outcomes have specific relevance to the haemodialysis population. Patients on dialysis are more likely to die during hospitalisation for acute MI than patients with normal kidney function [31] and one year mortality following acute myocardial infarction approaches 60% in patients with ESKD [32] compared to less than 10% in the general population [33,34]. Sudden cardiac death accounts for nearly 30% of all-cause mortality in prevalent haemodialysis patients and around 35% of all-cause mortality in patients initiating dialysis [2,35]. The annual risk of sudden cardiac death is almost three-fold higher in haemodialysis patients (5-7%) compared to the general population (1.5-2.7%) [36].

There are several challenges in defining myocardial infarction and sudden cardiac death for the haemodialysis population. The current components of the Fourth Universal definition of myocardial infarction includes symptoms, biomarker increments and ECG changes[37]. These may not always apply to people on haemodialysis because chest pain is not always present in patients on haemodialysis and troponin levels can be raised at baseline and altered by haemodialysis. A specialist group will be convened

to determine how the Fourth Universal definition can be used or adapted in the haemodialysis population. The heterogeneity in the events ascribed to sudden cardiac death, particularly in the haemodialysis population, also poses a major challenge. The recent Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on Chronic kidney disease and arrhythmias similarly highlighted the need to refine the definitions of sudden cardiac death in ESKD patients, emphasising the unexpected nature of sudden death to avoid misclassifications. This international group have proposed definitions of sudden death, sudden cardiac death, and aborted cardiac arrest pertinent for ESKD patients [36].

Both outcome measures require a meaningful and simple metric to allow comparability across trials. Implementation of core outcomes for CVD in haemodialysis trials would require input from cardiologists and support from registries, guidelines, journals; and should be feasibly implemented in routine clinical practice.
The consensus workshop was conducted in English and therefore potentially limited input from non-English speaking participants. However, representatives from 15 countries, both developed and developing, attended the workshop which we hope does make our work more generalisable.

Recommendations from the workshop are summarised in Figure 4.2. To address the challenges in the measurement of the core outcomes *myocardial infarction* and *sudden cardiac death*, an expert working group will be convened to derive universally agreed upon definitions for use in the haemodialysis population. These definitions will need to be globally feasible and of minimal burden to implement in trials. Making these definitions as pragmatic as possible will support implementation. These

measures will need to be assessed based upon the Core Outcome Measures in Effectiveness Trials (COMET) criteria including content and structural validity, responsiveness and measurement error [38] and then validated by using them as outcome measures in historical trials to ensure they are fit for purpose. The ability to accurately compare data across trials using core CVD outcomes will optimise shared decision making and likely contribute to improved cardiovascular morbidity and mortality in this very high risk population.

4.6 References

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4.7 Figures and Tables

FIGURE 4.1 SUMMARY OF THEMES DERIVED FROM THE CONSENSUS WORKSHOP

HD-haemodialysis, ESKD – end stage kidney disease

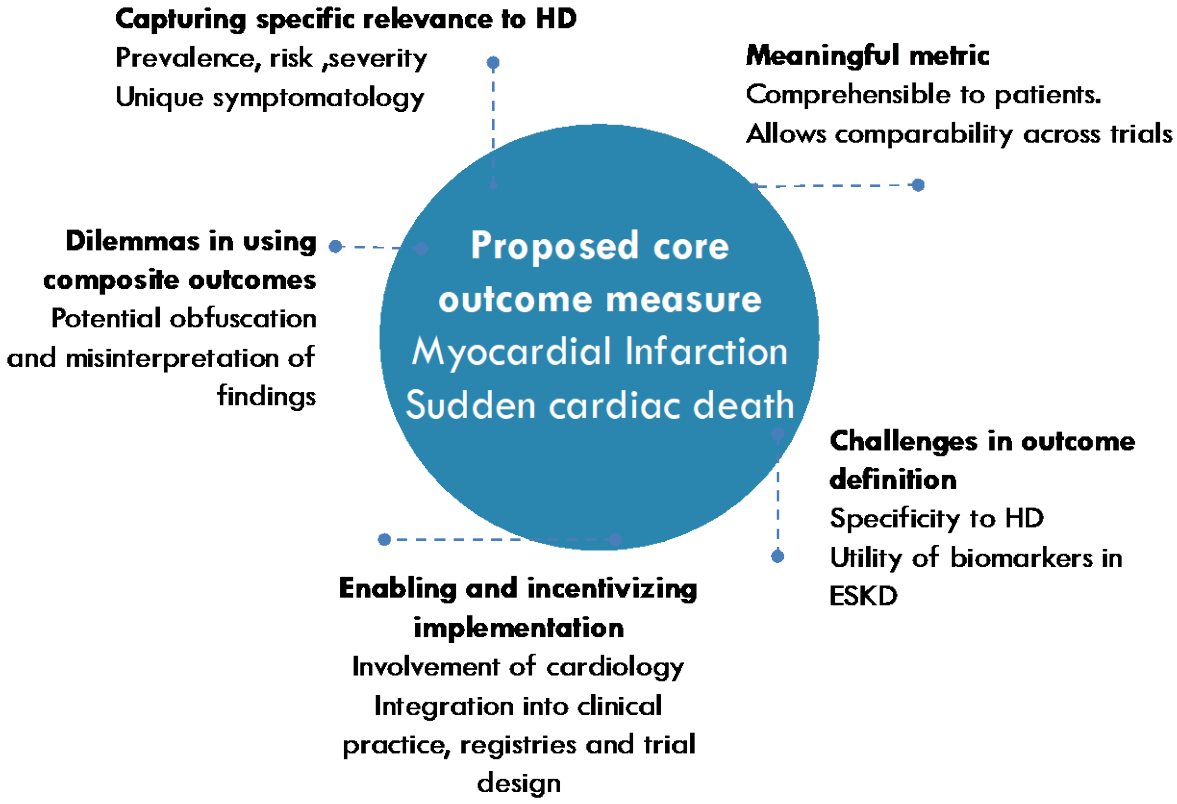

FIGURE 4.2 RECOMMENDATIONS FROM THE CONSENSUS WORKSHOP ON SELECTING, DEFINING AND IMPLEMENTING A CORE OUTCOME MEASURE FOR CARDIOVASCULAR DISEASE IN TRIALS IN HAEMODIALYSIS

Recommendations from the Consensus Workshop

Selecting a core CVD outcome

1. Myocardial infarction (MI) as the core outcome measure for cardiovascular **disease**
2. Sudden cardiac death (SCD) as the core outcome measure for cardiovascular **death**.

Reasons

- High prevalence in the haemodialysis population
- Direct consequences on quality of life, function and long term-outcomes
- Feasible to be measured across countries
- Potential to be modified by intervention
- Individual CVD outcome for transparency and accurate interpretation (not a composite outcome)

Developing a core outcome measure

- Requires consideration of the complex symptomology and diagnosis
- Establish a consistent, standardised definition (may need to be adapted for the haemodialysis population due to different symptomatology and diagnostic criteria)
- Consider variability in symptoms (e.g. myocardial infarctions may be "silent")
- Recognize limitations in the clinical utility of biomarkers specific to haemodialysis
- Definition to be used in the context of routine clinical care and trials
- Needs to be meaningful and comprehensible to patients

Implementation of a core outcome measure

- Integrate into registries and routine clinical care
- Obtain endorsement by journals, guidelines, regulatory agencies
- Ensure joint development with cardiologists

TABLE 4.1 ILLUSTRATIVE QUOTATIONS

Theme	Quotation
Capturing specific relevance to the haemodialysis population	
Prevalence, risk and severity of the cardiovascular outcome	I'm okay with the fact that it's the most frequently measured, but I'm not okay with the fact that probably it's not really the most relevant. (Group 1, health professional) There is a difference between importance versus frequency. Something that is most frequent may not be considered the most important. (Group 3, health professional) From a public health standpoint in dialysis patients, what's more prevalent or what's more disabling? (Group 4, health professional)
Complex symptomology and diagnosis	Sudden cardiac death in someone who is on dialysis, if you were to use the general population term, probably you would think this is a myocardial infarction death. When in actual fact you realise in the years that pass that actually a very large proportion may not be myocardial infarction. The nomenclature is very difficult. (Group 3, health professional) Heart failure is very difficult to define in the dialysis population. The question that many adjudication committees have is, is it patient heart failure, or is it simply that the patient is at the incorrect dry weight, or the patient has missed a dialysis treatment, and that's why their fluid overloaded (Group 5, health professional) I don't think a lot of patients do know what a heart attack is, because you… you get them in different ways and different forms. You can get them by chest pain, certain back pains, your arms, whatever. (Group 6, patient)
Considering consequences on quality of life	You have that longevity with stroke disability, with heart failure disability. It impacts every single aspect of life. I guess that's where I was coming from and I agree with you with the stroke. It's devastating, it's catastrophic. (Group 2, patient)
Accounting for geographic variation	Different cultures may present, say their symptoms differently. (Group 3, health professional) In Japan, strokes are a lot more common than in other parts. (Group 4, health professional) What you can also have is that the hospitalisation is region-dependent, because in some regions, patients are going to be hospitalised earlier than in other regions. (Group 5, health professional) Then they'll agree with the decision and be consistent across the world, worldwide. Nobody will argue the patient over in Germany had a bypass, had a heart attack, or in the United States, a bypass is a bypass. But just mild elevation in troponin, how much, one, two, three, which has high degree of heterogeneity in this population. (Group 5, health professional)
Having potential for intervention	Whatever we do, does it prevent or improve the outcome with MI? (Group 1, health professional) I find heart failure to be the outcome that is not only most applicable, but most potentially modifiable when we do interventional trials. (Group 5, health professional) MIs, heart attacks are clearly important. My concern is that by reporting them in every trial, they're so poorly modifiable that it's not going to get us where we want to go in terms of getting better, patients better at the end of the day. Heart failure to me is a better outcome measure. (Group 5, health professional)
Dilemmas in using composite outcomes	

Obfuscation and misinterpretation of findings	Having a composite outcome would be very complex. (Group 4, health professional) It would be great if everybody used the same definition of MACE and MACE-plus, so that as complicated as defining heart failure is, if we all used the same one, even imperfect, at least we could compare results. (Group 6, health professional) Lots of reasons why composite outcomes are potentially bad to put up there, but there's a whole series of reasons why they could be really important. (Group 4, health professional)
Benefits to trialists	Not only do you have a regulatory issue in terms of the need for composite, but also most dialysis trials other than some of the very large pharmaceutical trials are not powered to look at this, so you have to have a composite outcome in order to have statistical significance with a smaller sample size. (Group 5, health professional) Regulatory agency demanding a composite endpoint that includes death, all-cause death, MI, and stroke. As much as we might not want to encourage the use of a composite endpoint, the reality is regulatory agencies, that's exactly what they demand. (Group 5, health professional) Maybe SONG should consider acknowledging this composite is going to happen, and trying to put some sort of, maybe we all should use the same definitions for the composite. (Group 5, health professional)
Addressing challenges in outcome definitions	
Consistency, applicability and specificity of definitions	We have an issue of whether or not the definition needs to be modified in the dialysis patient, who may have a slightly elevated troponin level. To get to your point in terms of the biomarkers, one of the questions we'll need to discuss is whether or not the definition is cardiac biomarker as one of the choices, but not a required choice. (Group 5, health professional) There's a strength in a gold standard if you will, that is internationally accepted. Rather than reinventing the wheel and defining this from scratch which may take decades. (Group 6, health professional) The so-called validating, making sure that that universal definition, which was never developed in the dialysis patient, is actually applicable to it. Because the danger is, let's adopt it, and then find out that it actually doesn't work that way. (Group 6, health professional)
Recognising variability in symptoms	It's expected that men are more likely to have cardiac disease than women, and so symptoms are interpreted differently. (Group 3, health professional) Patients who do come in with MI who are on dialysis often don't have classical symptoms of angina. Chest pain, no numbness, all of the classical symptoms we see in non-dialysis patients are not there. (Group 1, health professional) Because in our population, a lot of the heart attacks are actually silent, so actually it's quite different from the general heart attack that we see in the usual population. Most patients may manifest heart failure rather than classical heart attack symptoms or chest pain. That is one important consideration when you diagnose a heart attack in a classical way where you need to have the symptoms, chest pain. (Group 4, health professional)
Uncertainty in the clinical utility of biomarkers specific to haemodialysis	In terms of this description, it says 'detect a rise of one' but maybe we're going to have to consider doing two, right. The delta is probably more important than the absolute level, right. (Group 1, health professional) We're trying to define thresholds based on level of kidney function in CKD and potentially dialysis, but the problem is that it's not measured in a lot of dialysis

	patients, but we are trying to come up with absolute thresholds. (Group 1, health professional) The problem with looking for change is that it involves time, but what we don't want is time to pass. You want patients with an MI to get to cardiology as quickly as possible. (Group 1, health professional)
Clarity for adjudication	It turns out you're limited in your data that you get in a clinical trial setting, because heart attacks are happening in the hospital. The investigator's not there, and you're limited by the data that you're getting. (Group 4, health professional) It turns out only about two-thirds to three-quarters of what the investigators reporting as an MI is finally adjudicated positively as an MI. I think it's important to bear that in mind, how we're adjudicating. (Group 4, health professional) Frankly the definition comes a bit too late. It's already been defined by the local doctor. (Group 4, health professional)
Selecting a meaningful metric for decision-making	
Comprehensible and meaningful to patients	There's ways of putting it that you give that information, and yet you're actually personalising it as well. (Group 2, patient) Typically on dialysis we expect five episodes per ten years, whatever it is, one episode per ten years. With the treatment we could reduce that to one every thirteen years or fourteen years, so you get an idea of the magnitude of the difference. (Group 2, health professional) Express it to me where, in my terms, where I can understand it. Don't come and tell me in doctors' terms. No, because I'm not a physician. Break it down and tell me. (Group 6, patient)
Distinguishing severity and recurrence	This is a difficult question because you could have someone who has a very large MI and develops heart failure and other complications, arrhythmias, and then you can have another patient who meets the criteria but just squeaks by and doesn't have a lot in terms of effects, in terms of quality of life, and in terms of function. (Group 5, health professional) If we want to assess severity at the same time, it has to have some sort of a consequence. Either needing an intervention or needing hospitalization (Group 5, health professional) It would be really challenging to incorporate a severity measure in standardised reporting. One option would be why not ask that they record both? (Group 5, health professional)
Comparability across trials	Wouldn't it be better to have something that we could compare? (Group 2, patient) We also want to be able to compare to other fields and it's important that we have consistency. (Group 4, health professional) We want to be able to pool trials together to really get more from the evidence than any single trial. I totally agree with that. (Group 6, health professional) If we say leave it (*choosing a metric)* to trialists, we'll just get the same mess we've got now. (Group 2, health professional)
Enabling and incentivising implementation	
Integration into registries	If you're requiring the full list of troponins and ECGs, that's a big burden and that would strike out a lot of trials, let's say registry-based trials, trials that are not in the position where they can get that level of detail. (Group 6, health professional) What's going to be considered acceptable as an outcome? How high do you have to set the bar for evidence to be acceptable at the FDA? (Group 4, health professional)
Incorporating	If for example this were adopted by regulators or registrational trials, although it

into clinical care	can never match in a registration trial being a registry trial, but still. Let's assume that they do so, then actually healthcare systems or registry systems participate, may actually have an incentive to be competitive to implement that in the clinical, everyday care setting. (Group 6, health professional) Definitions for MI we could standardize in administrative data sets, so it might be an opportunity for more of that. (Group 6, health professional)
Seeking authoritative endorsement	Should it be part of the requirements for FDA approval, that trials have actually measured these core outcomes? (Group 5, health professional) How much is it a guideline, how much is it something we aspire to, and how much is going to be mandated. That's an important issue. (Group 6, health professional) Being prescriptive is usually the best vehicle towards implementing and making change happen. An example that was mentioned earlier was mandatory trial registration at the time when clinical trials registration became mandatory, everybody was like, 'Ugh, this is horrible. It's so much extra work,' and now we don't think twice. We just do it. (Group 6, health professional)
Requiring cardiology input and buy in	We should bring all the stakeholders to the table. You need to bring the cardiologists to the table, you need to bring not only the MI, but the heart failure and whatever else is going to be in the composite. You need to bring in some of the thought leaders that design these trials, you need to bring in the regulatory agencies. They all need to come together and hash it out, and comment on the feasibility of doing this and the appropriateness of doing this. Because if you don't have the buy-in from those who are designing the trials, you don't have the buy-in in the regulatory agencies, it's not going to happen. (Group 5, health professional) Approach the cardiologists and maybe to become a stakeholder in the process [*of writing the next Universal Definition]*, and make sure that the kidney perspective gets heard and potentially implemented in future iterations of it. (Group 6, health professional) It's of great value to have an expert group of cardiologists look at these things, because even they tend to disagree sometimes, and at least what you have finally is a consensus opinion. (Group 4, health professional)

Abbreviations: CKD – chronic kidney disease; ECG – electrocardiogram; FDA – Food and

Drug Administration.

CHAPTER 5

INCIDENCE OF ISCHAEMIC HEART DISEASE IN MEN AND WOMEN WITH END-STAGE KIDNEY DISEASE: A COHORT STUDY

Publication details and contribution of authors

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EO: contributed to the design of the study, prepared and analysed the data, interpreted the results and wrote and revised the manuscript

PJK: contributed to the design of the study, advised on the preparation, analysis, interpretation and presentation of the results, and revised the manuscript

PM: contributed to the design and analysis of the study and revised the manuscript

SK: helped conceive the study and contributed to the design and revised the manuscript

MG: helped conceive the study and contributed to the design and revised the manuscript

AC: helped conceive the study and contributed to the design and revised the manuscript

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5.1 Abstract

Background: The incidence of ischaemic heart disease (IHD) has fallen consistently in the general population; attributed to effective primary prevention strategies. Differences in incidence have been demonstrated by sex. Whether this fall in incidence and sex differences is mirrored in people with end stage kidney disease (ESKD) is unclear. We aimed to establish the relative risk of IHD events in the ESKD population.

Methods: We performed a retrospective cohort study from 2000-2010 in people with ESKD in New South Wales. We performed data linkage of the Australia and New Zealand Dialysis and Transplant Registry and state-wide hospital admission and death registry data and compared this to general population data. We calculated incidence rates, incidence rate ratios (IRR), and time-trends using indirect standardisation by IHD event.

Results: 10,766 participants, contributed 44,149 years of observation time. Incidence rates were substantially higher than the general population for all IHD events (any IHD event: IRR 1.8, 95% confidence interval (CI) 1.7-1.9 for men, IRR 3.4, 95%CI 3.1-3.6 for women). Excess risk was higher in younger people (age 30-49 IRR 4.8, 95%CI 4.2-5.4), and in women with a three-fold increase risk overall and nearly a ten-fold increase in risk in young women (female age 30-49 years: IRR 9.8 95%CI 7.7-12.3), results were similar for angina and acute myocardial infarction. IHD rates showed some decline for men over time, (ratio of IRR 0.93, 95%CI 0.90-0.95) but were stable for women (ratio of IRR 0.97, 95%CI 0.94-1.01).

Conclusions: People with ESKD have substantially higher rates of IHD than the general population, especially women, in whom no improvement appears evident over the past 10 years.

5.2 Introduction

Ischaemic heart disease (IHD) is the most common of all cardiovascular diseases and globally is the leading cause of death[1,2]. The incidence and mortality from IHD in the general population in high income countries has steadily declined[3,4]. The decline in incidence has predominantly been ascribed to improvements in primary prevention strategies with reduced mortality due to improved medical management[5-9]. In people with end stage kidney disease (ESKD) there is an increased prevalence of IHD and outcomes are poorer[10,11]. People receiving haemodialysis for ESKD who present with acute myocardial infarction (AMI) have greater in-hospital, and post discharge mortality, as well as higher recurrence rates and more readmissions[12,13].

The aetiology of IHD in the ESKD population is multifactorial with a more complex pathogenisis than that found in the general population[14]. In ESKD the pathogenesis is driven in part by conventional risk factors including dyslipidaemia, diabetes and hypertension but supplemented with ESKD-specific risk factors[14,15]. These include uraemic toxins and dialysis therapy itself, which collectively contribute to oxidative stress, inflammation, immune dysfunction, together with disorders of bone and mineral metabolism leading to increased vascular calcification[14,16-18]. ESKD populations are often excluded from cardiovascular trials and there is paucity of evidence regarding the effectiveness of primary prevention strategies in the ESKD population[19-21].

In the general population, IHD is the largest contributor to cardiovascular mortality and morbidity for both men and women, however there are gender discrepancies. The most recent NHANES data suggest that the average annual rate of first cardiovascular event rises from 3 per 1000 men of 35 to 44 years of age to 74 per 1000 men of 85 to 94 years of age[22].

For women, comparable rates occur 10 years later in life though the gap narrows with advancing age[22]. Data from the Framingham Heart Study have shown that over the last two decades the prevalence of myocardial infarctions has declined in men in mid-life (35 to 54 years)[23]. Over the same time period the prevalence of myocardial infarction has increased in women in the same age group[23,24]. Women have higher cardiovascular mortality rates than men, a difference partially ascribed to gender bias in the management of coronary heart disease and stroke in women[25-28]. A number of initiatives in the general population to address this imbalance have seen the cardiovascular death rate in women fall by nearly half[29]. Whilst addressing the cardiovascular disease burden in the ESKD population became an international priority nearly 20 years ago it is unclear whether there has been improvement over time[30,31]. The aims of this study were to describe the trends in incidence of IHD in the ESKD population compared to the general population, and to identify any gender or age group differences.

5.3 Methods

Study design and setting

We performed a retrospective cohort study of all adults treated for ESKD in New South Wales (NSW), and compared them with the general population of Australia between July 1st 2000 and June 30th 2010. The study used data linkage, procedures for which have been reported previously[32]. NSW has a population of 7.4 million people, approximately one third of the total Australian population, and is demographically representative of the country.

Study populations

ESKD population: NSW ESKD patients were identified from The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), which collects demographic, clinical and

treatment data on all people requiring renal replacement therapy. ANZDATA records co-morbidities including diabetes, ischaemic heart disease, peripheral artery disease and cerebrovascular disease along with smoking history and cause of renal failure.

To identify hospitalisation and death events in the ESKD population we linked ANZDATA records with the NSW Admitted Patient Data Collection and the NSW Registry of Births Deaths and Marriages (Appendix 2 Figure 1). Admitted Patient Data Collection is a mandatory state-wide collection of all admitted patient services provided by public and private hospitals. Key clinical information (including the principal and secondary diagnoses made during admission, coded according to the International Classification of Diseases, 10th revision Australian modification (ICD-10-AM) and health service utilisation (referrals and procedures) are recorded for every hospital discharge, death, or transfer. By statute, a death certificate is completed by a doctor and returned to the Registry of Births, Deaths and Marriages for all deaths in NSW, and we obtained information on the date of death for cohort participants. Data linkage (Appendix 2 Figure 1) was undertaken independently by the NSW Centre for Health Record Linkage using ChoiceMaker software. ChoiceMaker uses probabilistic linkage and achieves a false positive rate of around 5/1,000 and a false negative rate of around 5/1,000[33]. The Centre for Health Record Linkage complies with best-practice in privacy-preserving record linkage[33]. Ethical approval was granted by the New South Wales Population and Health Services Research Ethics Committee (Approval Number 2011/12/363).

General population: Data on hospitalisation were not available at the state level, so Australian general population data were obtained from the Australian Institute of Health and Welfare (AIHW) which compiles annual statistics for every episode of care provided in public

and private hospitals in Australia. Data are coded using ICD-10-AM. To calculate rates of hospital admission, population numbers were obtained with age and sex-stratified estimates of the entire Australian population from the Australian Bureau of Statistics, 2000 to 2010.

Statistical methods

The primary outcome measure was hospitalisation with any IHD event. IHD event types were identified from hospitalisations with a principal admission diagnosis code of; "Angina" (ICD-10 AM code of I20), "Acute MI"(I21) and the composite "Any IHD" defined as I20, I21 as well as "Other acute IHD" (I22), "Subsequent MI" (I23), "Certain complications after acute MI" (I24) and "Chronic IHD" (I25)). We included both incident and prevalent ESKD patients; time at risk was measured from date of first treatment for ESKD, or July 1st 2000 if they already had started dialysis before July 1st 2000, until their first of each IHD event, death, or June 30th 2010, whichever came first. Incidence rate ratios (IRR with 95% confidence intervals CI) for comparison to the general Australian population were calculated using indirect standardization by age, sex and calendar year. Using only incident patients, we estimated cumulative incidence for any IHD event after starting treatment for ESKD using Kaplan Meier method. For both prevalent and incident patients we examined event rates, testing for trends over time using the Mantel-Haentszel method. For comparisons between people with ESKD who were admitted with IHD and those who were not, we performed t-tests to examine continuous data and Chi squared tests to examine categorical data.

5.4 Results

Participants

We included 10,766 participants, contributing 44,149 years of observation time. The characteristics of participants are described in Table 5.1. There were 6,271 (58.3%) men and

4,495 (41.7%) women at commencement, with 4,540 (42.2%) dying during follow up. Of those that died, 1,098 (24.2%) were documented as having had at least one admission with IHD. The majority of participants were white (N=8902, 82.5%) with glomerulonephritis and IgA nephropathy as the most common causes for ESKD (N=3,301, 30.9%). Haemodialysis (N=7,433, 69.0%) was the most frequently initiated treatment for ESKD. Over the duration of the study 1,961 (18.4%) people with ESKD experienced at least one ischaemic heart disease admission. Those with at least one admission with IHD were more likely to be older (mean difference 4.7 years older, $p<0.001$), men ($p<0.001$), smokers, both current and former ($p<0.001$), and had pre-existing coronary artery disease, peripheral vascular disease and diabetes ($p<0.001$). A total of 1, 910 (17.7%) participants received a kidney transplant and 10.4% of those transplanted were hospitalised for IHD at some point during the study.

IHD events

There were 1,961 participants admitted 4,133 times with an IHD event, (range 1-26 times) over the study period. The first IHD event resulting in hospitalisation was: angina in 37.1%, acute MI in 38.7% and chronic IHD in 23.6% (Appendix 2 Table 1). Cumulative incidence from starting treatment for ESKD of IHD for men at one year was 9.4% (95%CI 8.5 to 10.4%) at five years was 26.5% (95%CI 24.7 to 28.3%) and by eight years was 32.3% (95%CI 30.0 to 4.7%). For women, the cumulative incidence at one year was 6.6% (95%CI 5.7 to 7.6%), at five years 21.2% (95%CI 19.2 to 23.3%) and by eight years was 26.6% (95%CI 24.0 to 29.5%). The majority of events occurred over the first few years following the commencement of treatment for ESKD (Figure 5.1a). These patterns were similar for acute MI and angina. The overall incidence rate of admission for any IHD event was 4,442 per 100,000 person years (95% CI 4,249 to 4,643). For men the rate was 4,923 per 100,000 person-years (95% CI 4,657 to 5,203/100,000) and for women it was 3,789 per 100,000 person-years (95% CI

3,520 to 4,078/ 100,000). When compared to the general population, the relative rate in men with ESKD was over one and a half times that of the general population (IRR 1.8 95%CI 1.7 to 1.9). For women, the relative rate was substantially higher (IRR 3.4 95%CI 3.1 to 3.6). For both men and women, relative rates were highest in the younger age groups and steadily declined with increasing age (Figure 5.2, Table 5.2). Risk was particularly high for younger women; for women with ESKD aged 30-49 the rate was nearly ten times that of the general population (IRR 9.8 95%CI 7.7 to 12.3) (Figure 5.3, Table 5.2). Women with ESKD experienced higher event rates than women in the general population across all age groups but the difference diminished as age increased.

Acute MI: There were 1,532 (14.2%) people admitted with at least one acute MI (range 1-12 admissions per person). The overall event rate was 2,072 per 100,000 person years (95%CI 1,947 to 2,206). For men this rate was 2,289 (95%CI 2,117 to 2,474) and for women it was 1,772 (95%CI 1,598 to 1,968) per 100,000 person years. In both men and women this rate steadily increased with age, but the relative rates were much higher in the younger age groups, again particularly for women (Figure 5.3).

Angina: There were 1691 (15.7%) people admitted with at least one episode of angina (range 1-17 admissions). The incidence rate for hospitalisation with angina was 1,987 per 100,000 person years (95% CI 1,863 to 2,119 per 100,000 person-years). For men the rate was 2,142 (1,974 to 2,323/100,000) and for women it was 1,773 (1,596 to 1,970/100,000). Rates in men increased until the age of 70 and then started to fall; in women rates continued to increase with age (Figure 5.3). Both men and women with ESKD experienced higher event rates the general population (IRRs -men: 1.6, 95% CI 1.5 to 1.7 and women 2.9, 95%CI 2.6 to

3.2); again this rate steadily increased with age, but the relative rates were much higher in the younger age groups, again particularly for women (Figure 5.3, Table 5.2).

Progress over time:

Incidence rates over time, for any IHD event, differed between males and females (p=0.04). Rates were stable over the decade in the female ESKD population (RR 0.97 per year, 95%CI 0.94 to 1.01), while for men there was a decline (RR 0.93 per year, 95% CI 0.90 to 0.95) . Rates of angina fell for both men (RR 0.88 per year, 95%CI 0.84 to 0.92) and women (RR 0.93 per year, 95%CI 0.87 to 0.99), with no evidence of a difference between the sexes (p=0.17). For acute MI, rates were relatively stable; with no difference between the sexes (p=0.5): men (RR 1.01 per year 95%CI 0.97 to 1.05) and women (RR 1.04 per year 95%CI 0.98 to 1.10) (Figure 5.4).

5.5 Discussion

This large retrospective cohort study shows greatly elevated rates of ischaemic heart disease for people with ESKD compared to the general population. The majority of these events occurred within three years of starting haemodialysis. Compared to the general population, risk was much higher in the younger years, particularly for women. For women between 30 and 49 years the risk of an IHD event was nearly ten times that of the general population risk. Over the duration of the study, rates decreased for men but have remained unchanged for women.

For women with ESKD, the relative risk of cardiovascular disease compared to the general population is significantly higher than for men with ESKD. In the general population, cardiovascular risk may be under-recognised and undertreated particularly in women and it

may be that this effect is magnified in the ESKD population[34]. Under-recognition of IHD in women might be due to physicians perceiving a woman's cardiovascular risk is lower than that of a man[34]. It is also known that some preventative therapies such as aspirin and statins appear less effective in women than in men[35-38]. It is less clear how well primary prevention strategies are applied or are effective in the ESKD population. It is possible that the burden of cardiovascular risk is under recognised or perhaps under treated given the context of other life limiting disease. Patients with advanced CKD are routinely excluded from clinical trials testing cardiovascular disease interventions so evidence surrounding efficacy in the ESKD population is sparse, with even less information about efficacy by gender[21]. The sex difference could also arise because the protection usually experienced by women in the general population is diminished by ESKD, perhaps mediated by hormonal differences. In the general population, cardiovascular disease rates in women rise sharply following the menopause and this has led to a number of hypotheses suggesting the protective effect of oestrogen on lipid profiles and vascular remodelling. In women with ESKD there is altered gonadotrophin release and that cyclical variation in oestrogen levels is lost[39]. Menopause occurs at a younger age among women with chronic kidney disease; the median age of menopause is 50–51 years in normal women and 47 years among women with chronic kidney disease[40]. Reduced cycling and lower levels of oestrogen may result in reduced vascular protection in the younger age groups. Hormone replacement therapy has been used in the general population for the prevention of cardiovascular disease in post-menopausal women. However, a recent Cochrane Systematic review found no evidence that hormone therapy provided any protective effect against death from any cause including death specifically from cardiovascular disease. Rather, in post-menopausal women, hormone therapy increased the risk of stroke and venous thromboembolic events[41].

Our study highlights IHD risk at a younger age for people with ESKD. It is possible that preventative strategies are not instituted early enough in the course of CKD, given the accelerated vascular pathology experienced as early as chronic kidney disease stage three. Clinical practice guidelines do not encourage early therapy; KDIGO guidelines from 2013 recommended treatment with statin for adults of at least 50 years of age with an estimated glomerular filtration rate less than 60 mL/minute per 1.73 m^2 when not treated with chronic dialysis or kidney transplantation. It might also be that current preventative strategies are not efficacious. The different pathophysiology involved in cardiovascular disease in ESKD together with the routine exclusion of patients with advanced CKD from most clinical trials testing CVD preventative therapies creates an evidence gap.

Decrease in IHD over time for men suggests some progress preventing IHD in the ESKD population. However, that same trend is not apparent in women with ESKD; with the magnitude of this difference being much greater than in general population epidemiology. The Framingham heart study gave higher weighting to men when calculating cardiovascular risk and this score has been used for over 20 years. This has now led to better recognition of risk in men and over time a reduction in event rate. A decade on, these improvements are now being reflected in the ESKD population. Research collecting population-representative Australian data in 2008, documented gender disparities in the assessment and management of cardiovascular disease in primary care[34]. Education strategies regarding risk of cardiovascular disease in women in the general population have been employed more recently but whether with lag time this will be reflected in a reduction in event rate is yet to be seen.

This is a large cohort with a follow up duration sufficient to evaluate the outcomes of interest with reasonable precision. The ANZDATA registry is also population based, which increases the generalisability of our results. This study is consistent with cerebrovascular disease as the outcome of interest; people with ESKD had a substantially higher risk of stroke, again particularly in women and young people[42]. There are some potential limitations. Data linkage has inherent weaknesses, particularly when using administrative data not collected for research purposes. The Australian Institute of Health and Welfare undertook a validation study amongst the Australian general population and concluded that in the absence of an acute coronary heart disease event register, despite the limitations of using data linkage, it remains the best approach for estimating incidence rates[43]. We had only summary level data for the general population and in calculating rates, assumed that the point prevalence population of Australia was at risk of IHD for the entire year. This may have over-estimated actual time at risk and would bias estimates of IHD risk amongst the general population to being smaller than they actually are, though this is a limitation common to all studies using population data. Our study only standardised rates by age, sex and year. Data on rates by co-morbidities among the general population were not available to us, for example we did not have smoking status for the general population admissions and smoking is obviously a significant risk factor for IHD. Recent Australian data from 2011-12 showed that 53.5% of over 18 year olds in the general population had never smoked, which was similar to those treated for ESKD[44].

The findings from this study raise a number of important issues regarding the increased risk of cardiovascular disease in the ESKD population. This population has double the risk of IHD events irrespective of our current preventative strategies suggesting a need for revision of both evaluation and treatment strategies in this high risk population.

5.6 References

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5.7 Figures and tables

FIGURE 5.1 (A) CUMULATIVE INCIDENCE OF ANY ISCHAEMIC HEART DISEASE EVENT SINCE STARTING TREATMENT FOR ESKD AND (B) INCIDENCE RATE RATIO OF ANY IHD EVENT SINCE STARTING TREATMENT FOR ESKD COMPARED TO THE GENERAL POPULATION.

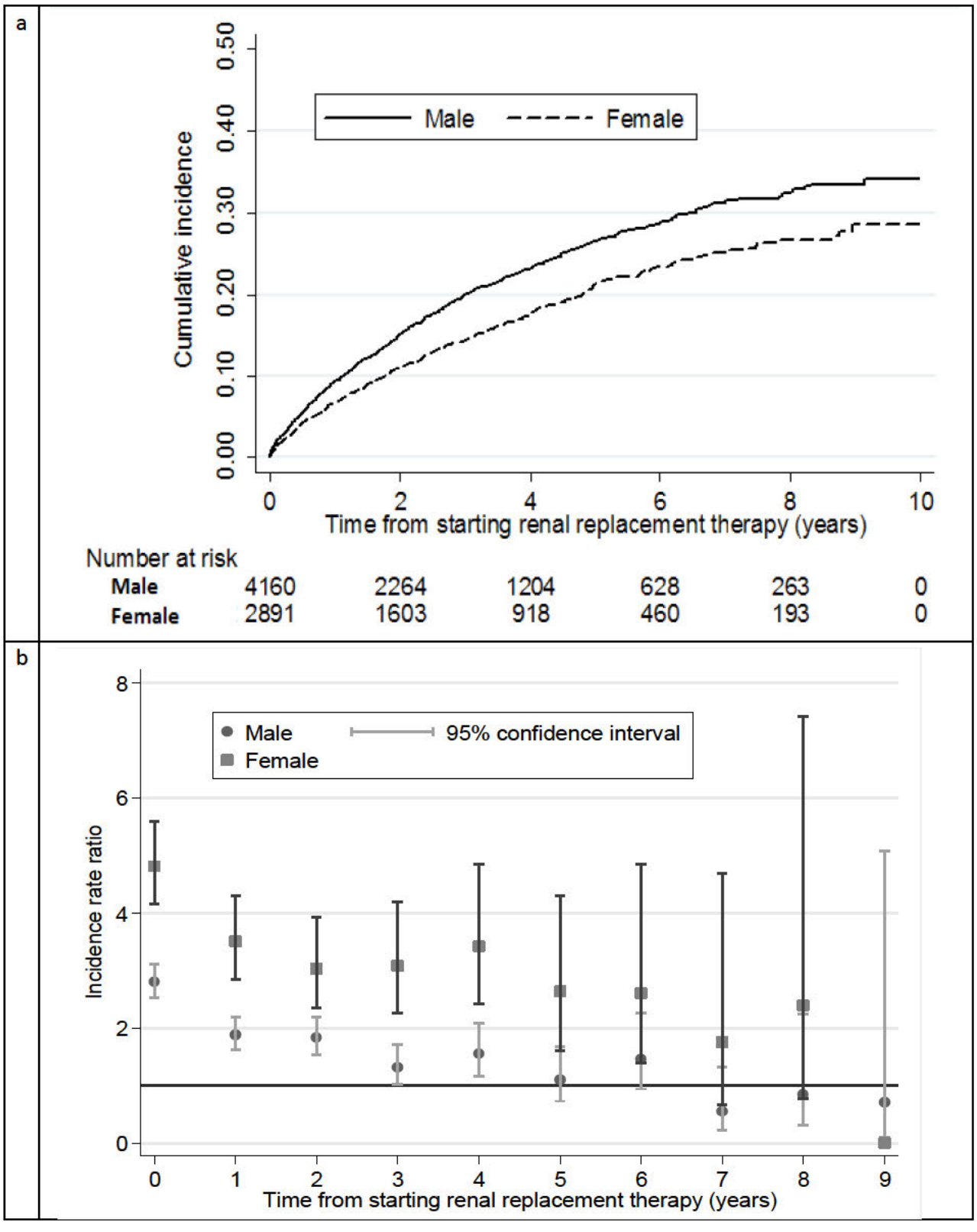
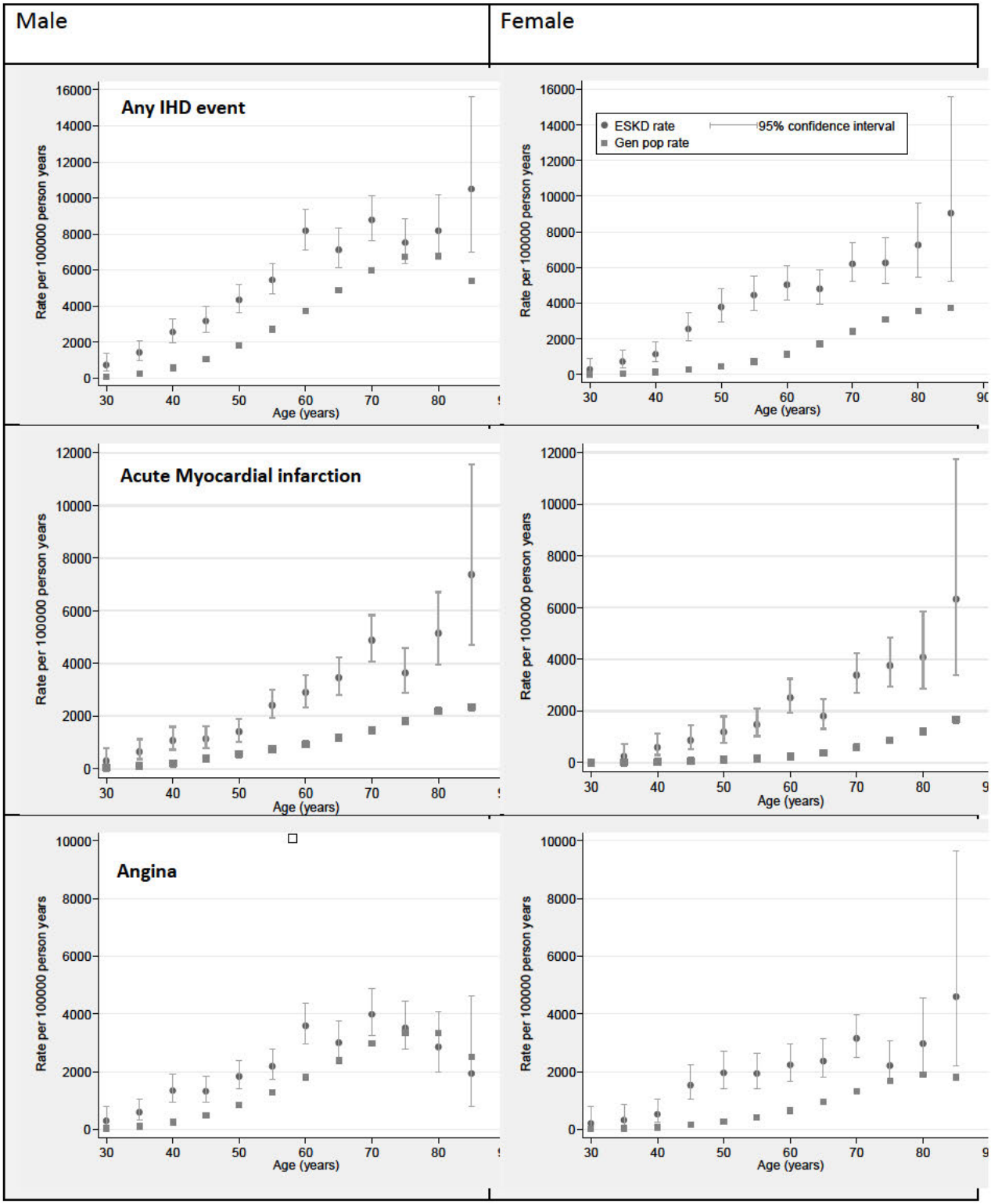
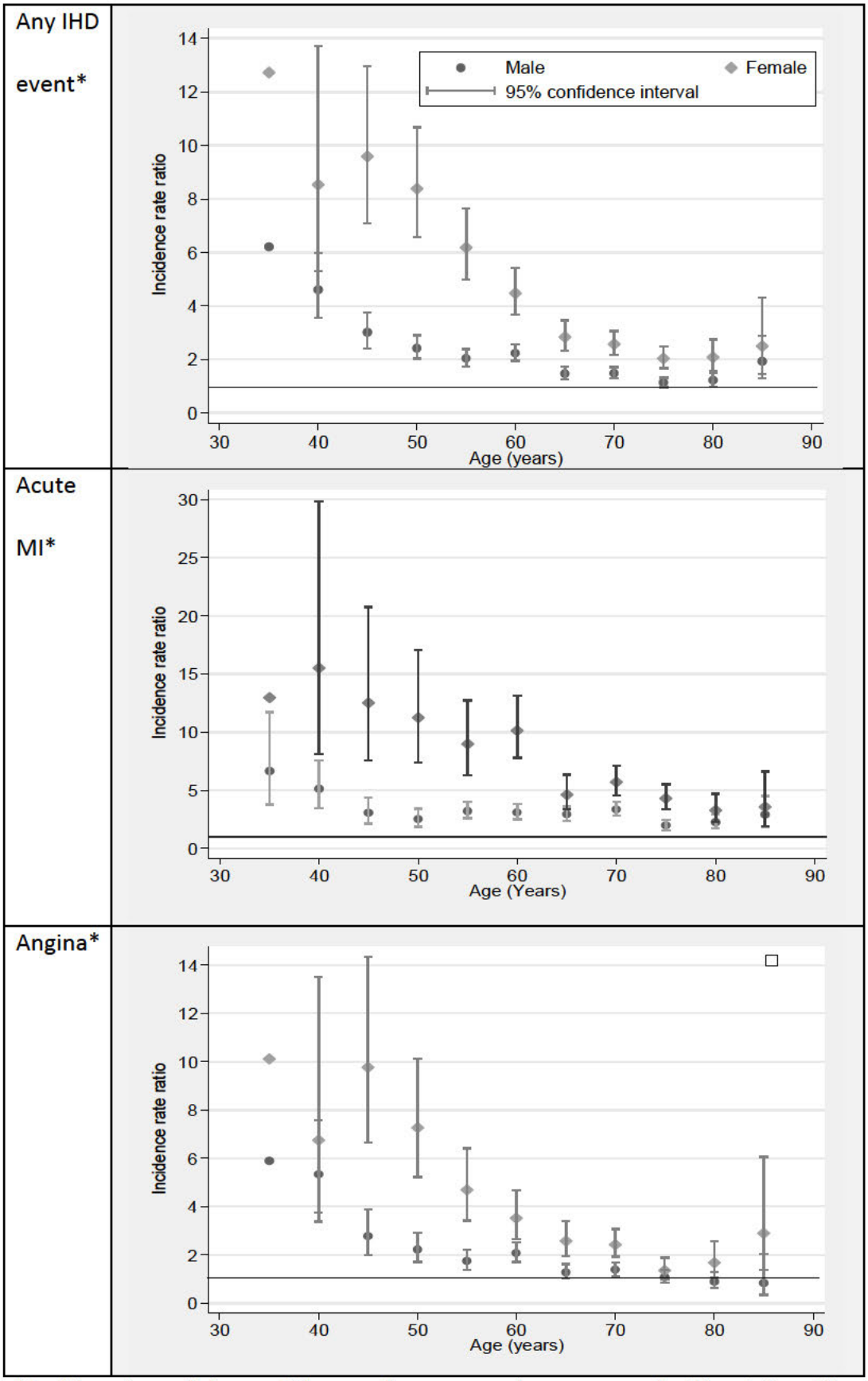


FIGURE 5.2 INCIDENCE RATES PER 100,000 PERSON YEARS BY SEX FOR ANY IHD EVENT, ACUTE MYOCARDIAL INFARCTION AND ANGINA IN ESKD POPULATION



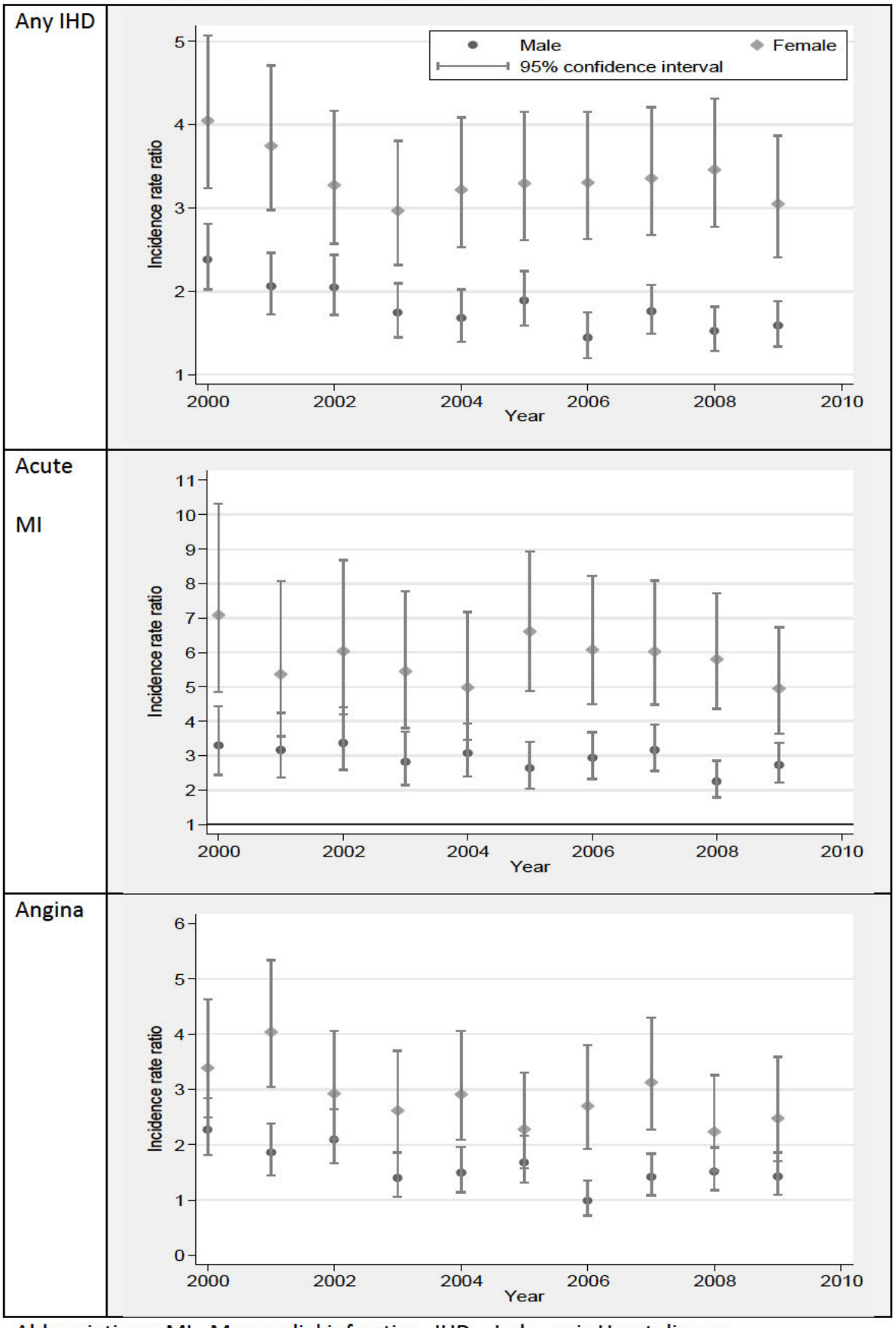
Abbreviations: IHD – Ischaemic Heart disease, ESKD – End stage kidney disease

FIGURE 5.3 INCIDENCE RATE RATIOS BY AGE FOR ANY IHD EVENT, ACUTE MYOCARDIAL INFARCTION AND ANGINA FOR ESKD POPULATION COMPARED TO GENERAL POPULATION



*Confidence intervals for age=35 have not been presented to preserve scale, Abbreviations: MI – Myocardial infarction, IHD – Ischaemic Heart disease,

FIGURE 5.4 INCIDENCE RATE RATIOS OVER TIME FOR ANY IHD EVENT, ACUTE MYOCARDIAL INFARCTION AND ANGINA FOR ESKD POPULATION COMPARED TO GENERAL POPULATION



Abbreviations: MI –Myocardial infarction, IHD – Ischaemic Heart disease

TABLE 5.1 CHARACTERISTICS OF PARTICIPANTS WITH END-STAGE KIDNEY DISEASE, STRATIFIED BY HOSPITALISATIONS FOR IHD

Characteristic	Admission with		No admission with		All
	N	%	N	%	N
Total, %	1961	18.2	8805	81.8	10766
Age at start of study (years)					
<40	92	4.7	1632	18.5	1724
40<50	250	12.7	1238	14.1	1488
50<60	482	24.6	1580	17.9	2062
60<70	539	27.5	1873	21.3	2412
70<80	504	25.7	1971	22.4	2475
≥80	94	4.8	511	5.8	605
Sex					
Male	1251	63.8	5020	57.0	6271
Female	710	36.2	3785	43.0	4495
Racial background					
White	1631	83.2	7271	82.6	8902
Asian	163	8.3	813	9.2	976
Other	186	9.5	702	8.0	888
Comorbidities at end-stage					
Cerebrovascular disease	386	19.7	1260	14.3	1646
Diabetes	790	40.3	2550	29.0	3340
Coronary artery disease	1031	52.6	2753	31.3	3784
Peripheral vascular disease	622	31.7	1899	21.6	2521
Smoking status at end-stage					
Never	906	46.2	4920	55.9	5826
Former or current	1055	53.8	3885	44.1	4940
Cause of kidney failure					
Diabetes	597	30.4	1869	21.2	2466
Hypertension/renal artery	305	15.6	1057	12.0	1362
Glomerulonephritis/IgA	507	25.9	2794	31.7	3301
Polycystic kidney disease	135	6.9	697	8.2	832
Other	436	22.2	2369	26.9	2805
First renal replacement					
Haemodialysis	1446	73.7	5987	68.0	7433
Peritoneal dialysis	523	26.7	2529	28.7	3052
Transplant	14	0.7	267	3.0	281
Transplanted during study	198	10.1	1712	19.4	1910
Died during study	1098	56.0	3442	39.1	4540

TABLE 5.2. STANDARDISED INCIDENCE RATE RATIOS FOR HOSPITALISATION WITH IHD EVENTS IN PEOPLE WITH END-STAGE KIDNEY DISEASE, BY AGE AND SEX

Age at event (years)	30-49			50-69			70-84			≥85		
	O*	E‡	IRR† (95%CI)	O*	E‡	IRR† (95%CI)	O*	E‡	IRR† (95%CI)	O*	E‡	IRR† (95%CI)
Male												
Any IHD event	171	43.5	3.9(3.4, 4.6)	642	326.8	2.0 (1.8, 2.1)	411	318.3	1.3 (1.2, 1.4)	24	12.4	1.9 (1.3, 2.9)
Angina	80	20.4	3.9(3.2, 4.9)	297	169.6	1.8 (1.6, 2.0)	195	166.0	1.2 (1.0, 1.4)	5	5.9	0.8 (0.4, 2.0)
Acute MI	71	17.1	4.2 (3.3, 5.3)	294	98.9	3.0 (2.7, 3.3)	248	97.2	2.6 (2.3, 2.9)	19	6.6	2.9 (1.8, 4.5)
Chronic IHD	73	7.9	9.2 (7.3, 11.6)	253	92.5	2.7 (2.4, 3.1)	109	82.8	1.3 (1.1, 1.6)	3	1.5	2.1 (0.7, 6.4)
Female												
Any IHD event	71	7.3	9.8 (7.7, 12.3)	349	78.4	4.5 (4.0, 4.9)	273	120.3	2.3 (2.0, 2.6)	13	5.2	2.5 (1.5, 4.3)
Angina	40	4.4	9.2 (6.8, 12.5)	172	46.2	3.7 (3.2, 4.3)	126	67.5	1.9 (1.6, 2.2)	7	2.4	2.9 (1.4, 6.1)
Acute MI	27	2.1	13.0 (8.9, 18.9)	148	19.4	7.6 (6.5, 9.0)	168	37.0	4.5 (3.9, 5.3)	10	2.8	3.6 (1.9, 6.6)
Chronic IHD	28	1.0	27.4 (18.9, 39.6)	123	17.7	6.9 (5.8, 8.3)	46	24.4	1.9 (1.4, 2.5)	0	0.4	-

*Observed, ‡ Expected, †Incidence rate ratio

CHAPTER 6

CARDIAC MORTALITY IN PEOPLE WITH END STAGE KIDNEY DISEASE; A TWO NATION COHORT STUDY

Publication details and contribution of authors

O'Lone E, De La Mata NL, Kelly PJ, Rosales B, Masson P, Webster AC. Cardiac mortality in people with end stage kidney disease; a two nation cohort study. **Submitted to Journal of the American College of Cardiology September 2019**

EO: contributed to the design of the study, prepared and analysed the data, interpreted the results and wrote and revised the manuscript

NDLM: contributed to preparation and analysis of the data and revised the manuscript

PJK: contributed to the design of the study, advised on the analysis and revised the manuscript

BR: advised on the presentation and revised the manuscript

PM: contributed to the design of the study and revised the manuscript

ACW: conceived the study and contributed to the design, helped with the analysis, interpretation and presentation of the results and revision of the manuscript

6.1 Abstract

Background: Cardiac disease affects over two-thirds of patients with end-stage kidney disease (ESKD) and is the leading cause of death in this population. Cardiac death rates have fallen in the general population, but benefits from improved preventative therapies and treatment of cardiac events may not be generalisable to people with ESKD. We aimed to review absolute and relative rates for cardiac death in the ESKD population compared to the general population.

Methods: Cohort study of incident people with ESKD in Australia and New Zealand, 1980-2013. Australian and New Zealand death registers were linked to Australian and New Zealand dialysis and transplant registry (ANZDATA) data to obtain date and cause of death. We calculated mortality rates for cardiac disease as defined by ICD-10-AM codes and standardised mortality ratios (SMR) compared with the general population using indirect standardisation, adjusting for age, sex, calendar year, and country.

Results: We included 60,823 participants observed over 381,874 person-years, of whom 34,322 died. A primary cardiac death was recorded in 6847 participants (20%) and 27,475 (80%) participants died of other causes. Absolute cardiac death rates in the ESKD population were higher for men than women (men: 2002, 95%CI: 1945-2062; and women:1502, 95%CI:1444-1564/100,000 person-years) and both decreased over time. Relative to the general population, men and women with ESKD experienced more deaths (SMR in men: 5.6, 95%CI:5.5-5.8; and women: 8.3, 95%CI:8.0-8.6). Excess deaths were greatest in younger ESKD patients, particularly women; aged 30-49 years women had 60 times (SMR 60.0, 95%CI:51.8-69.0) whereas men had 18 times (SMR 17.7, 95%CI:15.9-

19.7) more deaths than expected. However, among people with ESKD cardiac death rates improved over time more markedly than for the general population, especially in women.

Conclusions: Cardiac deaths in the Australian and New Zealand ESKD population are higher than expected in the general population, particularly at younger ages and women. Young women with ESKD have an excess relative risk of dying from cardiac causes, though there has been some improvement over time. Disaggregation of these data by sex identifies differences which need to be addressed in future research.

6.2 Introduction

Cardiac disease affects over two thirds of people with end stage kidney disease (ESKD)[1]. The most prevalent cardiac diseases in ESKD include acute myocardial infarction (AMI), coronary artery disease (CAD), heart failure (HF), and sudden death/cardiac arrhythmias[1]. Cardiac disease is also the leading cause of death in the ESKD population with arrhythmia and cardiac arrests comprising 40% of known causes of death among dialysis patients, and 17% of the known causes of death among transplant recipients [1].

In the general population, the age-standardised cardiac death rate has fallen over the past two decades with the largest decline occurring between 2000 and 2005 in both men and women[2]. Nearly half of this decrease has been attributed to improved application of treatments including primary and secondary preventative therapies[3]. Prevalence of risk factors has also changed, including decreases in smoking rates and increases in the treatment of hypertension[3].

The pathophysiology of cardiac disease is different in people with ESKD compared to the general population. Accepted risk factors such as diabetes and hypertension are more prevalent [4] and act synergistically with ESKD to increase the risk of cardiac disease[5]. Unique cardiovascular risk factors specifically associated with ESKD include albuminuria [6], uraemic toxins, fluid and electrolyte imbalance, and renal replacement itself. These risk factors collectively contribute to oxidative stress, inflammation, immune dysfunction and disorders of bone and mineral metabolism leading to increased vascular calcification [7-10]. Primary preventative strategies for cardiovascular

disease used in the general population have little evidence of efficacy in the ESKD population [11-13] and studies have also shown that patients with ESKD are potentially under-investigated and under-treated for cardiac presentations, despite their increased risk [14]. It remains unclear whether improvements in cardiac mortality seen in the general population have also been evident in the ESKD population.

Our study aimed to investigate comparative mortality over time, specifically cardiac mortality and sex differences, comparing people with ESKD to the Australian and New Zealand general population.

6.3 Methods

Study design and populations

We performed a two nation cohort study of all adults starting treatment for ESKD in Australia and New Zealand from 1980 to 2013.

We used the ANZDATA registry which has been described in detail elsewhere[15]. ANZDATA collects real time and annual survey data on all people undergoing treatment for ESKD from all centres in Australia and New Zealand. These data include patient demographics, comorbidities, cause of ESKD and treatment-related information as well as the event of death and underlying mode of death. Unlike international classification coding, the death is recorded by the treating nephrologist using 84 death codes, designed specifically for the registry to encompass common causes of death among people with ESKD excluding kidney disease and diabetes.

Both Australia and New Zealand operate mandatory death and cause of death reporting, with data aggregated in death registers, using internationally standardised coding to permit comparisons within and across populations. The Australian Institute for Health and Welfare (AIHW) collates death notifications and cause of death from the Registrars of Births, Deaths and Marriages in each state and territory. The AIHW records the causes of death using the *International Statistical Classification of Diseases and Related Health Problems tenth revision, Australian Modification (ICD-10-AM)*. The New Zealand Health Ministry uses data from The Mortality Collection (MORT) which classifies the underlying cause of death for all deaths registered in New Zealand also using the ICD-10-AMIn both countries, primary and contributory causes of death are recorded. The primary cause of death is determined as the condition or event that initiated the sequence of events that led to the death. Secondary or contributory causes of death are deemed to have contributed to death but did not initiate death. Data linkage of ANZDATA to these national death registers was undertaken to ascertain the date and cause of death in all people with ESKD in Australia and New Zealand. Linkage was performed for Australian participants by the AIHW using probabilistic linkage matching on identifiers including age, sex and name. The New Zealand Ministry of Health used deterministic linkage matching New Zealander participants on the National Health Index number. Best-practice privacy-preserving protocols were employed, where only de-identified data was made available to researchers after data linkage was performed. Ethics approval was granted by the University of Sydney (Project No.: 2014/917), AIHW (Reference No.: EO2015/3/181) and the New Zealand Ministry of Health (Reference No.: 14/NTB/171).

Data on deaths in the general population were obtained from the Australian Bureau of Statistics for Australia and from the New Zealand Ministry of Health for New Zealand. Cause-specific (as recorded by ICD-10-AM) summary-level data on the number of deaths by sex, age (5-year age band) and calendar year, were obtained for each country, along with census data for the total population in each of these groups. Death register data were only available in Australia during 1980-2013 and in New Zealand during 1988-2012. Hence, our data linkage was limited by availability of general population data.

Statistical methods

The primary outcome was cardiac death. Cardiac deaths were identified from the underlying cause of death including ICD-10-AM codes: I20-I25, I34-I37 and I42-I50, listed in full in the supplementary material (Appendix 3, Table 1). Subgroup analysis was performed for *a priori* groups of common cardiac diseases "Ischaemic heart disease (IHD) deaths" (I20-25), "valvular deaths" (I34-I37), "cardiomyopathy deaths" (I42), "arrhythmic deaths" (I44-49) and "heart failure deaths" (I50). In supplementary analyses, we examined contributing causes of death among people with ESKD whose underlying cause of death was attributed to kidney disease in the Death Register (including diabetes E10-E14, kidney failure N17-N19, hypertensive disease I10-I15, glomerular disease N00-N08, other kidney or ureter disorders N25-N29 and renal tubule-interstitial disease N10-N16).

Time at risk was measured from date of first treatment for ESKD, until death, or 31st December 2013 (AU) and 31st December 2012 (NZ), whichever came first. Mortality

rates were calculated by age, sex, calendar year, and country for the ESKD population for each cardiac event type. Using all-cause and cause-specific cardiac mortality rates in the Australia and New Zealand general population, we used indirect standardisation to calculate standardised mortality ratios (SMRs) adjusting for country, age, sex and calendar year. To investigate differences in those who died a cardiac death from those who died of other causes we used the rank-sum test for data not normally distributed and Chi-squared tests to examine categorical data. Linear regression was used on the log-transformed SMR to compare change over time.

6.4 Results

There were 60,823 participants included in the study contributing 381,874 person-years of observation during which 34,322 (56%) people died. Of those that died, 6847 participants (20%) suffered a cardiac death and 27,475 (80%) participants died of other causes. Participant characteristics are described in Table 6.1. In the full cohort, there were more men (59%) than women (41%), and the majority of participants were from Australia (85%). A greater proportion of men died from cardiac (65%) than from other causes (56%). The median age at starting treatment for ESKD was significantly higher in those with a cardiac death ($p<0.001$, median 64 years [IQR 55 to 72] compared to 63 years [IQR 53 to 72]). The age at death was also significantly higher in those with a cardiac death ($p\leq0.001$, median 69 years [IQR 61 to 76 years] compared to 68 years [IQR 53 to 72 years]). The majority of participants were white (81%). The most prevalent cause of ESKD in the whole cohort was diabetes (28%), and the proportion of diabetics was lower in those who died of cardiac causes (26%) compared to other causes (30%;). The proportion of participants diagnosed with coronary artery disease

and hypertension at commencement ESKD treatment was higher among those who died of cardiac causes. There were no important differences between countries so estimates are presented for both together.

The absolute cardiac death rate for women was 1502 (95% CI: 1444-1564)/100,000 person-years and for men was higher at 2002 (95% CI: 1945-2062)/100,000 person-years. As expected, the death rate increased as participants aged (Figure 6.1A).
In relative terms, women with ESKD had more deaths than expected in the general population (SMR 8.3, 95% CI: 8.0-8.6) and had a greater excess mortality compared to men with ESKD (SMR 5.6, 95% CI: 5.5-5.8) (Figure 6.1B). This difference was exaggerated in younger age groups but particularly in women. Among those aged 30-49 years, women had 60 times (SMR 60.0, 95% CI: 51.8-69.0) more deaths than expected, while deaths in men had nearly 18 times more deaths than expected (SMR 17.7, 95% CI: 15.9-19.7).

Subgroup analysis of cardiac deaths revealed that IHD deaths represented the largest proportion of all cardiac deaths and similarly, relative to the general population, women had greater mortality compared to men (SMR in women: 9.0, 95% CI: 8.6-9.4; and in men 5.8, 95% CI: 5.6-6.0) (Figure 6.2). This was substantially higher in the younger age group (30 to 49 years), nearing 70 times higher than the general population for women (SMR 68.5, 95%CI 58.7 to 79.9). There were fewer deaths in the other cardiac subgroups (Table 6.2), though SMRs remained high as ESKD patients still experienced an excess of cardiac deaths compared to the general population.

Cardiac death rates have been reducing over time and at a similar rate in both men and women (Figure 6.3). Over the study period the SMR of cardiac deaths for women has significantly decreased over time (p-value<0.001), with the SMR halving from 13.4 (95%CI 11.8 to 15.2) in 1980-1990 to 5.6 (95%CI 5.1 to 6.2) in 2010-2013. The reduction was much smaller in men and not statistically significant (P for trend 0.13), falling from 5.9 (95% CI 5.3 to 6.5) to 4.8 (95% CI 4.5 to 5.1) over the same period.

An additional 7,738 participants died with a cardiac cause listed in at least one of the additional contributory causes. Further breakdown of contributory causes revealed, ischaemic heart disease as a contributory cause of death in 6,090 participants; arrhythmia in 4187 participants and heart failure in 1866 participants. The most prevalent primary causes of death in those with a cardiac contributory cause were diabetes (28%) and kidney failure (22%) (Appendix 3, Table 2). Of these 7,738 participants, 4,431 (57%) had a primary cause of death related to their kidney disease.

6.5 Discussion

This large bi-national cohort study which examined the causes of death in people with ESKD over more than 30 years has three major novel findings. First, there is significant disparity between the relative rates of cardiac death between women and men with ESKD and the general population. Second, the burden of excess deaths in people with ESKD is most notable in the younger age groups. Third, over time there have been improvements in both the absolute and relative rates of cardiac deaths in the ESKD population and this improvement has been most notable in women with ESKD.

Our first major finding of sex disparity in the relative risk of cardiac death between men and women with ESKD may potentially be explained by differences in coronary microvascular dysfunction. Most women with acute coronary syndromes have coronary atherosclerosis, but there are differences in the symptoms, presentation, pathology and the pathophysiology of coronary artery disease by sex [16,17]. Studies have also shown that women in the general population have higher mortality than men post intervention for myocardial infarction, evident in studies following both primary coronary angioplasty and coronary artery bypass grafting [18-22]. One hypothesis is that in a high proportion of women, coronary microvascular dysfunction plays more of a role than coronary artery disease in the development of symptoms and cardiac mortality [23,24]. The sex disparity is particularly apparent in the younger age groups and coronary microvascular dysfunction is facilitated by the loss of protective oestrogen cycling which occurs early in CKD. Women on dialysis become menopausal significantly earlier than the general population and it is accepted that earlier age at menopause increases cardiovascular risk [25-27]. Ovarian dysfunction likely occurs early in CKD and progresses with CKD, largely through disruption of the normal hypothalamus–pituitary–gonadal axis[28]. Oestrogen mediates its cardioprotective effect by increasing angiogenesis and vasodilation and decreasing reactive oxygen species, oxidative stress, and fibrosis, thus limiting cardiac remodelling [29]. There is also some evidence to suggest that oestrogen may help to protect cardiac endothelium from the adverse effects of uraemic toxins which may explain why the absolute cardiac mortality rates in women are still lower than in men with ESKD [30]. Potentially female sex (mediated by hormonal differences) and uraemic toxins have an additive or

synergistic effect on the microcirculation resulting in the vastly increased SMR for women.

Our study describes the magnitude of excess cardiac deaths suffered by younger age groups with ESKD, as previously mentioned, most notable in young females. Reduced coronary flow reserve, a marker of coronary microvascular dysfunction is reduced in chronic kidney disease and may play a role in the pathogenesis of uremic cardiac disease [31]. The mechanisms of coronary microvascular dysfunction in CKD are not fully understood but it is likely that changes to the microvasculature begin early in CKD and are progressive causing ischaemia, fibrosis, remodelling and myocardial dysfunction[32]. These changes can occur independent of age and may explain the excess of deaths in the younger age groups. Interestingly, there is increasing evidence that SGLT2 inhibition can improve coronary microvascular dysfunction and this may be one of the drivers for the reduction in major cardiovascular events in the recent CREDENCE trial in patients with diabetes and CKD [33,34], though results were not stratified by sex.

Last, we found evidence of decreasing cardiac mortality over time, particularly among women with ESKD. Our previous work suggested that incidence rate ratios for cardiac events had improved over time for men but there had not been much improvement in women[35]. These new data suggest that despite potentially no improvement in the prevention of cardiac events there has been improvement in the treatment of those events resulting in reduced death rates over time. The high relative risk in young ESKD patients is of particular interest and adds to the findings of a recent study in the USA which found high cardiovascular mortality rates in children and young adults with

ESKD. However, as this study did not use linked data they were unable to make unbiased comparison to the general population [36]. Our study also shows that these high mortality rates found in children remain a problem into adulthood and the excess of deaths in adults with ESKD may not be solely explained by the differences in causes of ESKD and the higher rates of comorbidity.

The main strength of this study is that it is a large cohort encompassing the entire population of people with ESKD in Australia and New Zealand, which increases the generalisability of our results. The use of linked data allows the least biased comparison to the general population as deaths in both populations are ascertained in the same way. Further, it provides a long follow-up period and minimal to no biases due to loss to follow-up. There are some limitations inherent with the use of ICD coding including accuracy of the original diagnosis, medical record and the allocation of the code[37]. However, the ICD coding system is standardised internationally and therefore provides the least biased population comparisons. The reported SMRs may be an underestimation in view of the potential additional cardiac deaths suggested by the contributory causes of death. It is likely that significant ascertainment bias exists in the coding of deaths in the ESKD population. A large proportion of primary causes of death were recorded as kidney failure and not a specific mechanism of death.

This study highlights the excess risk of cardiac mortality within the ESKD population and in particular in young women. The US National Institutes of Health has prioritised sex as a biological variable within research and this study contributes to our understanding of the interaction between sex and ESKD as major contributors to

cardiovascular mortality. Improvements have been made over time and our future work will look at risk factors as well as the impact of transplant on these risks. There remains a significant excess of risk for people with ESKD and by understanding the gender and age disparities we can generate tailored research hypotheses to address these risks.

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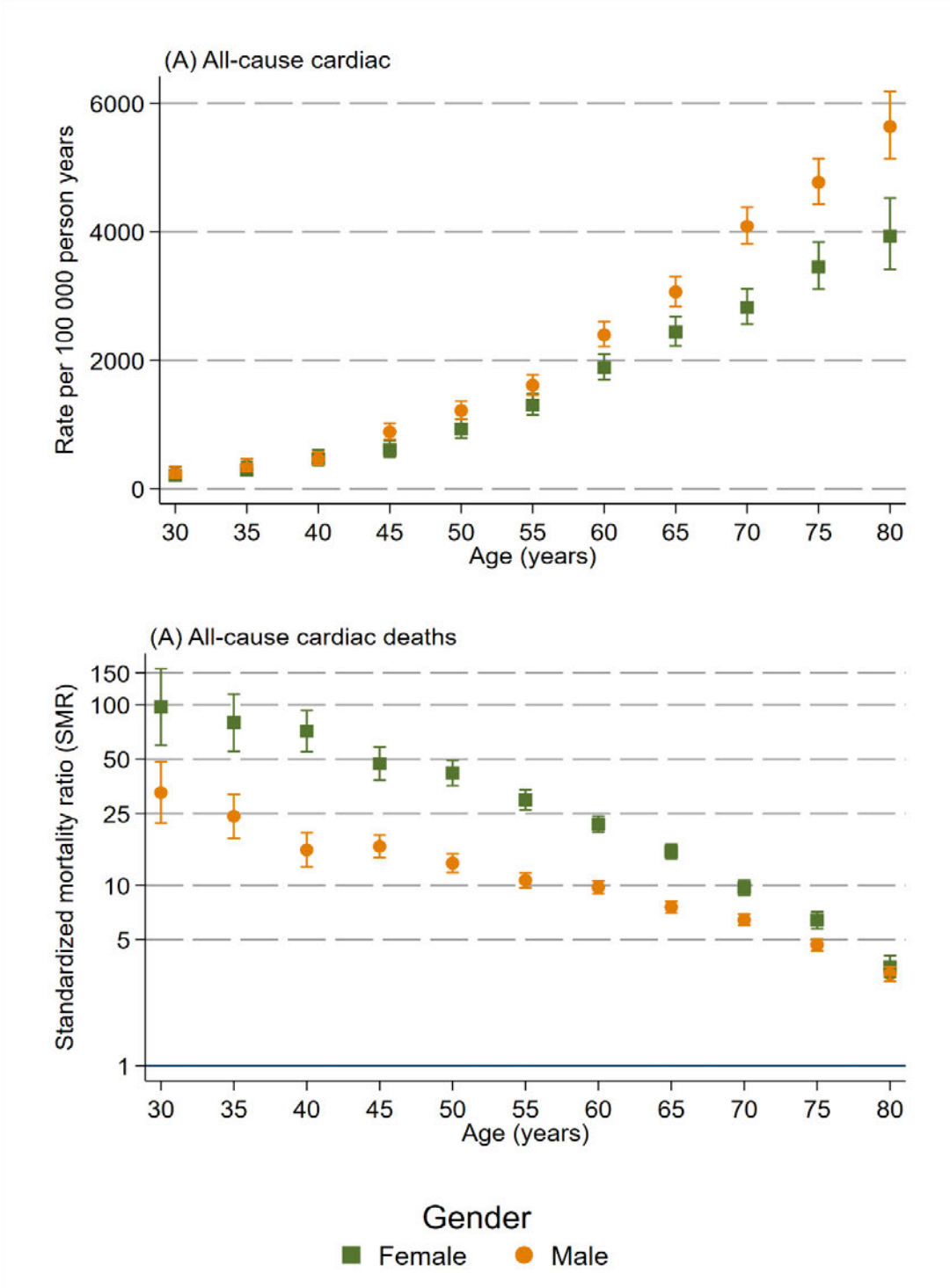
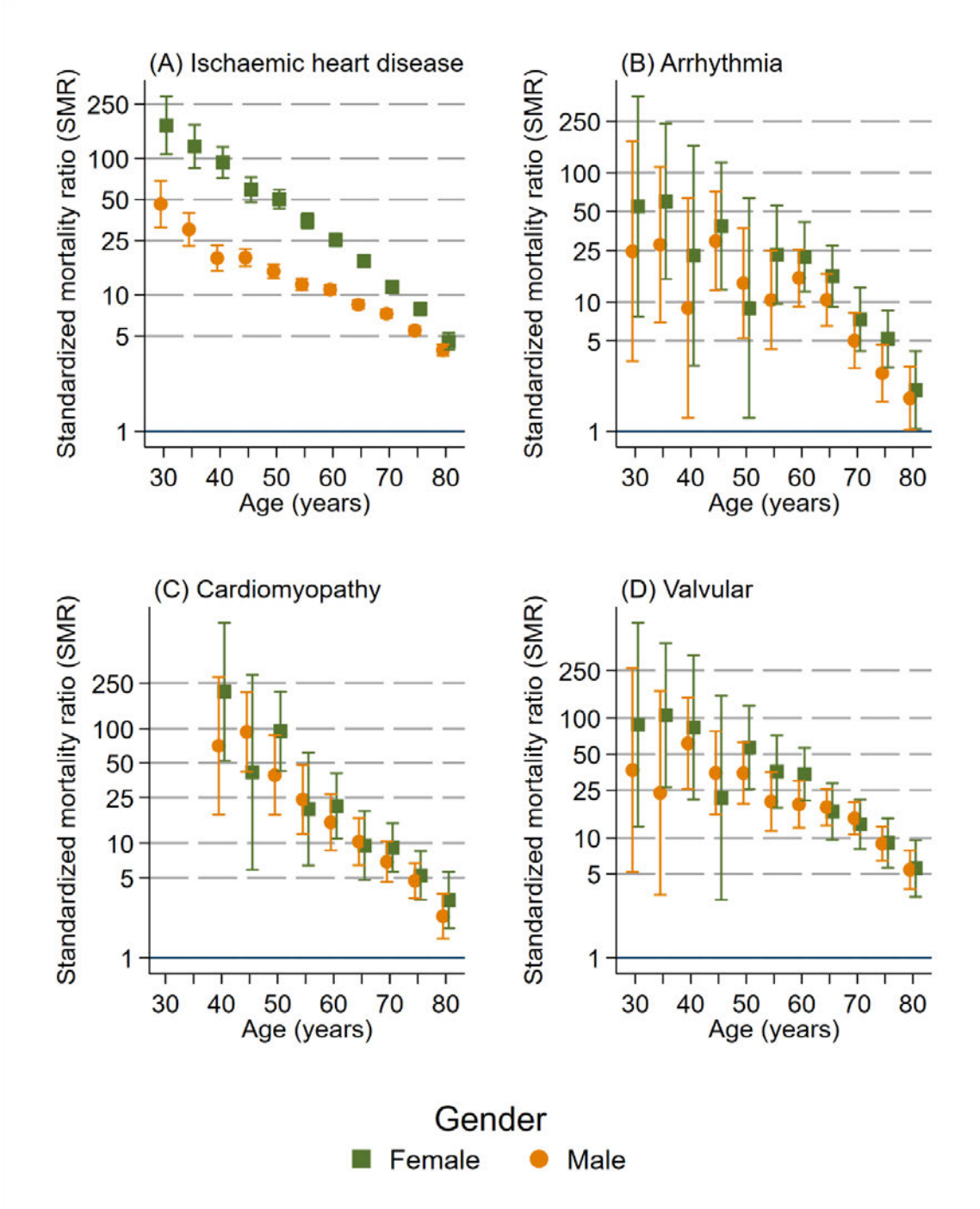
6.7 Figures and tables

FIGURE 6.1 (A)INCIDENCE RATES, AND (B) STANDARDISED MORTALITY RATIOS (SMR)* FOR ALL-CAUSE CARDIAC DEATHS IN THE AUSTRALIAN AND NEW ZEALAND ESKD POPULATION (1980-2013), BY AGE AND SEX.



*SMRs are presented on a log scale

FIGURE 6.2 STANDARDISED MORTALITY RATIOS (SMR)* FOR SUBTYPES OF CARDIAC DEATHS IN THE AUSTRALIAN AND NEW ZEALAND ESKD POPULATION (1980-2013), BY AGE AND SEX.



*SMRs are presented on a log scale

FIGURE 6.3 (A) INCIDENCE RATES AND (B) STANDARDISED MORTALITY RATIOS (SMR) FOR CARDIAC DEATH IN THE AUSTRALIAN AND NEW ZEALAND ESKD POPULATION, BY CALENDAR YEAR.

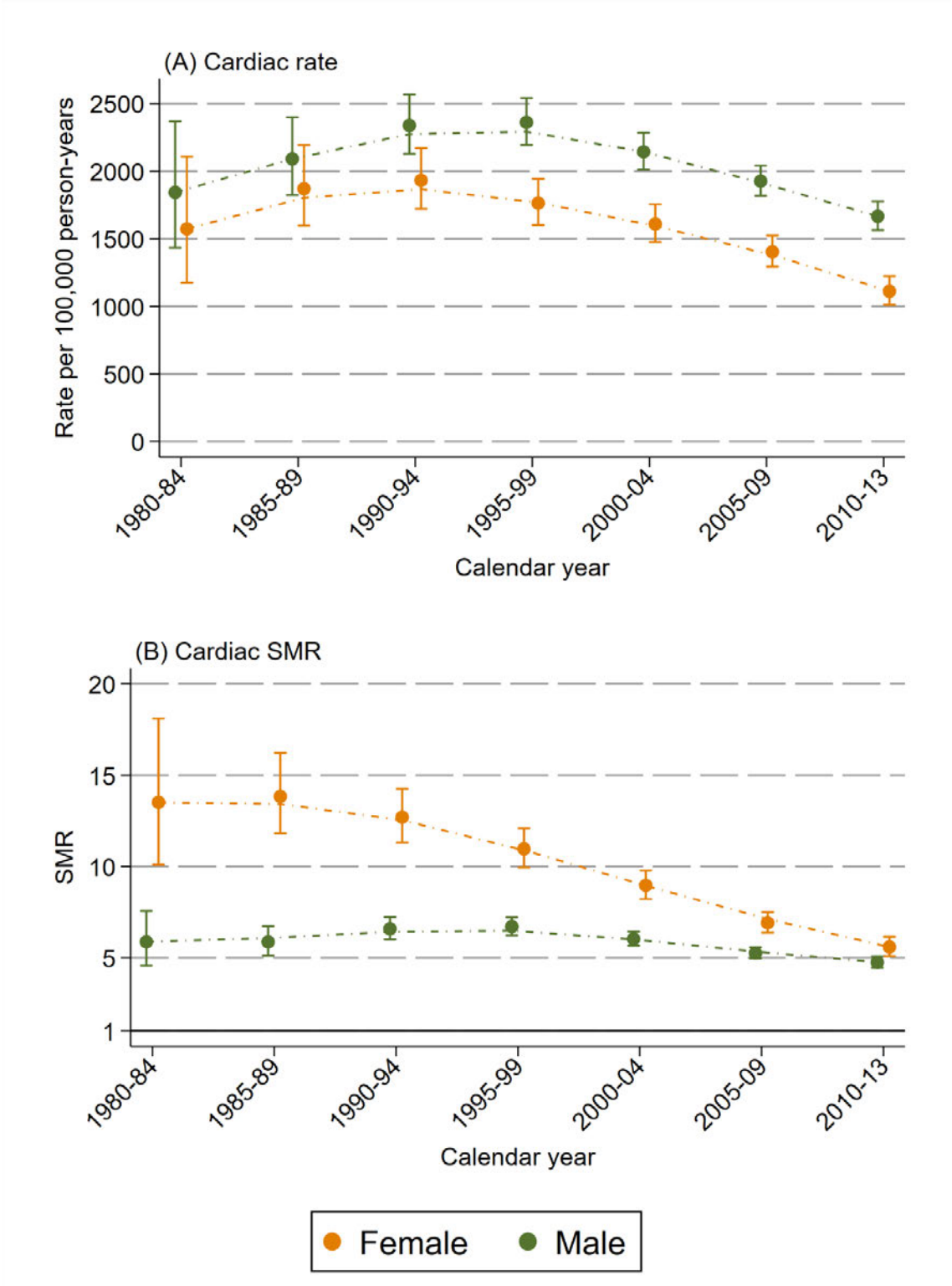


TABLE 6.1 CHARACTERISTICS OF ALL PATIENTS WITH END-STAGE KIDNEY DISEASE INCLUDED IN THE STUDY, STRATIFIED BY DEATH STATUS.

Characteristics	All cardiac deaths		Other deaths		Alive		Total	
	n	(%)	n	(%)[1]	n	(%)	n	(%)[1]
Total, (%)	6843	(11)[1]	27,475	(45)[2]	26,505	(43)[1]	60,823	(100)
Age at commencement of RRT (years)								
Median [IQR]	64	[55,72]	63	[53,72]	52	[38,64]	59	[46,70]
Age at death (years)								
Median [IQR]	69	[61, 76]	68	[58,76]				
Gender								
Female	2404	(35)	11,969	(44)	10,669	(40)	25,042	(41)
Male	4439	(65)	15,506	(56)	15,836	(60)	35,781	(59)
Year of commencing ESKD								
≤1990	1,413	(21)	5,065	(18)	1,770	(7)	8,248	(14)
1991-1999	2226	(33)	8,708	(32)	3,819	(14)	14,753	(24)
2000-2009	2876	(42)	12,067	(44)	11,401	(43)	26,344	(43)
2010-2013	328	(5)	1635	(6)	9,515	(36)	11,478	(19)
Country								
Australia	5795	(85)	23,197	(84)	22,459	(85)	51,451	(85)
New Zealand	1048	(15)	4278	(16)	4,046	(15)	9,372	(15)
Racial background								
Caucasian	5523	(81)	21,504	(78)	19,003	(72)	46,030	(76)
Asian	270	(4)	1307	(5)	2304	(9)	3881	(6)
Australian first nations*	402	(6)	1941	(7)	1905	(7)	4248	(7)
People of the PI & Maori	582	(9)	2412	(9)	2407	(9)	5401	(9)
Other	66	(1)	311	(1)	886	(3)	1263	(2)
Comorbidities at ESKD								
Cerebrovascular disease	1170	(17)	4469	(16)	2,037	(8)	7,676	(13)
Diabetes	2390	(35)	10,786	(39)	8,541	(32)	21,717	(36)
Coronary artery disease	3626	(53)	11,056	(40)	6,103	(23)	20,785	(34)
Hypertension	3454	(50)	13,273	(48)	7238	(27)	23,965	(39)
Previous malignancy	1447	(17)	8,468	(31)	5,873	(22)	15,788	(26)
Smoking status								
Current/Former	3429	(50)	13,065	(48)	11,895	(45)	28,389	(47)
Never	2163	(8)	10,137	(37)	13,561	(51)	25,861	(43)
Not recorded	1251	(<0.5)	4,273	(16)	1,049	(4)	6,573	(11)
Cause of renal failure								
Diabetes	1805	(26)	8357	(30)	6,735	(25)	16,909	(28)
Hypertension/RA disease	1460	(21)	3472	(13)	2,332	(9)	7,264	(12)

GN/IgA nephropathy	1547	(23)	6290	(23)	8,795	(33)	16,632	(27)
Polycystic kidney disease	314	(5)	1440	(5)	2,491	(9)	4,245	(7)
Analgesic nephropathy	528	(8)	1971	(7)	385	(1)	2884	(5)
Unknown diagnosis	539	(8)	1850	(7)	1223	(5)	3612	(6)
Other	646	(9)	4077	(15)	4441	(17)	9164	(15)
Transplanted at beginning of study	16	(<0.5)	139	(<0.5)	1,494	(0.1)	1,649	(3)
Transplanted during study	920	(13)	4,231	(15)	11,051	(42)	16,202	(27)

[12]Column percentage [3] Aboriginal and Torres Strait Islands, RRT = Renal replacement therapy, ESKD= end stage kidney disease, RA=renal artery , GN= glomerulonephritis,. PI=Pacific Islands

TABLE 6.2 STANDARDISED MORTALITY RATIOS BY SUBGROUP AND GENDER

		All cardiac deaths (n=6847)			IHD Deaths (n=5947)			Arrhythmia deaths (n=173)		
Sex	Age	Observe	Expected	SMR (95% CI)	Observe	Expected	SMR (95% CI)	Observe	Expected	SMR (95% CI)
Female	<30	16	0.1	156.6 (95.9 - 255.6)	7	0	226.4 (107.9 – 474.8)	1	0	45.5 (6.4 – 322.7)
	30-49	186	3.1	59.7 (51.8 - 69.0)	162	2.4	68.5 (58.7 – 79.9)	7	0.2	40.5 (19.3 – 84.9)
	50-64	744	27.9	26.7 (24.8 - 28.7)	658	23.9	27.5 (25.5 – 29.7)	16	0.8	20.7 (12.7 – 33.7)
	65-74	837	70	12.0 (11.2 - 12.8)	744	60	12.4 (11.5 – 13.3)	25	2.5	10.2 (6.9 – 15.1)
	75+	621	189.3	3.3 (3.0 - 3.6)	512	145	3.5 (3.2 – 3.9)	25	13.2	1.9 (1.3 – 2.8)
Male	<30	14	0.4	36.8 (21.8 - 62.1)	4	0.2	23.4 (8.8 – 62.2)	1	0.1	19.6 (2.8 – 139.4)
	30-49	337	19	17.7 (15.9 - 19.7)	282	16.2	17.4 (15.5 – 19.5)	9	0.4	22.9 (11.9 – 44.0)
	50-64	1288	121	10.6 (10.1 - 11.2)	1151	107.9	10.7 (10.1 – 11.3)	24	1.8	13.7 (9.2 – 20.5)
	65-74	1469	212.5	6.9 (6.6 - 7.3)	1292	188.7	6.8 (6.5 – 7.2)	34	4.9	6.9 (4.9 – 9.7)
	75+	1335	436.2	3.1 (2.9 – 3.2)	1135	354.2	3.2 (3.0 – 3.4)	31	20.7	1.5 (1.1 – 2.1)

		Valvular deaths (n=315)			Heart failure deaths (n=221)			Cardiomyopathy deaths (n=191)		
Sex	Age	Observe	Expected	SMR (95% CI)	Observe	Expected	SMR (95% CI)	Observe	Expected	SMR (95% CI)
Female	<30	2	0	230.5 (57.7 – 921.7)	1	0	212.0 (29.0 – 1504.8)	5	0	139.5 (58.0 – 335.0)
	30-49	6	0.1	59.6 (26.8 – 132.7)	3	0.1	45.6 (14.7 – 141.3)	8	0.4	19.6 (9.8 – 39.2)
	50-64	29	0.8	37.6 (26.1 – 54.1)	18	0.8	21.7 (13.7 – 34.4)	23	1.6	14.3 (9.5 – 21.5)
	65-74	30	2.1	14.3 (10.0 – 20.5)	24	3.2	7.5 (5.0 – 11.2)	14	2.3	6.2 (3.7 – 10.4)
	75+	38	7.7	4.9 (3.6 – 6.8)	34	20.4	1.7 (1.2 – 2.3)	12	2.9	4.1 (2.4 – 7.3)
Male	<30	1	0	57.7 (8.1 – 409.7)	1	0	120.5 (17.0 – 855.1)	6	0.1	45.1 (20.3 – 100.4)
	30-49	13	0.3	40.3 (23.4 – 69.4)	9	0.2	48.3 (25.1 – 92.7)	24	1.9	12.4 (8.3 – 18.6)
	50-64	42	1.9	22.0 (16.3 – 29.8)	26	1.7	15.0 (10.2 – 22.1)	45	7.7	5.8 (4.4 – 7.8)
	65-74	71	4.5	15.9 (12.6 – 20.0)	40	6.2	6.5 (4.8 – 8.8)	32	8.3	3.8 (2.7 – 5.4)
	75+	82	15.8	5.2 (4.2 – 6.4)	65	35.7	1.8 (1.4 – 2.3)	22	9.7	2.3 (1.5 – 3.4)

CHAPTER 7

COGNITION IN PEOPLE WITH END-STAGE KIDNEY DISEASE TREATED WITH HAEMODIALYSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Publication details and contribution of authors

O'Lone E, Connors M, Masson P, Wu S, Kelly PJ, Gillespie D, Parker D, Whitely W, Strippoli G, Palmer S, Craig JC , Webster AC. Cognition in People With End-Stage Kidney Disease Treated With Haemodialysis: A Systematic Review and Meta-analysis. **American Journal of Kidney Diseases. 2016 Jun;67(6):925-35.**

EO: conceived and designed the study, identified trial reports for inclusion, extracted, prepared and analysed the data, interpreted the results and wrote and revised the manuscript

MC: identified trials reports for inclusion, extracted the data, prepared the data and revised the manuscript

PM: revised the manuscript

SW: extracted data and helped revise the manuscript

PJK: advised on the analysis and interpretation of the results and revised the manuscript

DG: mapped neuropsychological tests to cognitive skills, interpreted the results and revised the manuscript

DP: mapped neuropsychological tests to cognitive skills, interpreted the results and revised the manuscript

WW: contributed to the design of the study, advised on interpretation and presentation of the results, and revision of the manuscript

SP: helped conceive the study, and revised the manuscript

GS: helped conceive the study, and revised the manuscript

JC: advised on presentation of results and revised the manuscript

ACW: conceived and designed the study, advised on the analysis, interpretation and presentation of the results and helped revise the manuscript

7.1 Abstract

Background: Cognitive impairment is associated with poorer quality of life, risk of hospitalisation and mortality. Cognitive impairment is common in people with end-stage kidney disease treated with haemodialysis, yet the severity and specific cognitive deficits uncertain.

Study Design: Systematic review and meta-analysis.

Setting & Population: Adults on haemodialysis compared with the general population, people on peritoneal dialysis or with chronic or nondialyzed chronic kidney failure.

Selection criteria for studies: Randomised control trials, cohort or cross sectional studies without language restriction.

Index tests: Validated neuropsychological tests of cognition

Outcomes: Cognitive test scores, aggregated by cognitive domain: orientation and attention, perception, memory, language, construction and motor performance, concept formation and reasoning, and executive functions.

Results: 42 studies of 3522 participants. Studies were of high or uncertain risk of bias, assessed by the Newcastle-Ottawa scale. People treated with haemodialysis had worse cognition than the general population, particularly in attention (N=22 standardised mean difference, SMD, -0.93, 95% CI -1.18, -0.68). Haemodialysis patients performed better than nondialyzed chronic kidney failure in attention (N=6 SMD 0.70, CI 0.45, 0.96) and memory (N=6 SMD 0.36 CI 0.08, 0.63) but had poorer memory than the general population (N=16 SMD -0.41 CI -0.91, 0.09) and people with CKD (N=5 SMD -0.40, CI -0.60, -0.21). There was insufficient data to show other differences among people on haemodialysis and people on PD or with CKD.

Limitations: Potentially biased studies, not wholly adjusted for education. High heterogeneity, mainly due to the large variety of tests used to assess cognition.

Conclusions: People treated with haemodialysis have impaired cognitive function compared to the general population, particularly in the domains of orientation and attention and executive function. Cognitive deficits in specific domains should be further explored in this population and be considered when approaching education and chronic disease management.

7.2 Introduction

Cognitive impairment is the deterioration in cognitive function beyond that which might be expected from normal ageing and is usually chronic and progressive[1,2]. Cognition describes several discrete skill domains and these may be differently affected by pathophysiological mechanisms. 'Normal' ageing is associated with decline in executive function and memory (episodic and working) [3, 4]. Dialysis patients have many of the known risk factors for cognitive impairment including; hypertension, diabetes and dyslipidaemia[5-7]. In addition, dialysis patients are exposed to hypoxaemia, large fluid and osmolar shifts, fluctuating titres of uraemic toxins and a pro-inflammatory state, all factors purported to affect cognitive function[8-10].

Chronic kidney disease (CKD) is associated with an increased risk of cognitive impairment[11]. Up to 70% of haemodialysis patients aged 55 years and older have moderate to severe cognitive impairment, which is up to three times higher than age-matched controls[12-14]. The specific domains of cognition most affected in people on dialysis remain unclear.
Cognitive impairment contributes significantly to the burden of disease and disability in the community and as such has been made a national health priority in several countries[15],[16]. Cognitive skills are needed to access health services, process, understand and recall written and spoken information and assimilate and express decisions about health care[17]. Impaired cognition has been linked to reduced health literacy, decreased medication adherence, impaired physical and mental health and a greater risk of death[18-22]. This is of particular relevance to dialysis patients as they access health services almost more than any other population[23,24].

Most studies of cognition in people treated with haemodialysis have been of relatively small size and few have sought to establish how cognition varies between people treated with haemodialysis compared to: people with no kidney disease (general population), CKD, people on peritoneal dialysis (PD), and people with nondialyzed chronic kidney failure (nondialyzed CKF).

7.3 Methods

Protocol

The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42014015226[25]). This work is reported according to Meta-analysis Of Observational Studies in Epidemiology (MOOSE) criteria.

Eligibility criteria and search strategies

We included all randomised controlled trials, cohort and cross-sectional studies reporting cognitive function among people with end-stage kidney disease treated with haemodialysis compared to other specified populations (general population, people with CKD, people on PD and people with nondialyzed CKF). There was no language restriction. Studies must have used a validated measure of cognitive function. We excluded studies in children (<18 years). We searched MEDLINE, EMBASE and CENTRAL (inception to 30th June 2015) using a sensitive search strategy developed by a specialist librarian (Appendix 4 Table 1).

Study selection, data collection and risk of bias appraisal

Two reviewers (of PM, SW, EO, MC) independently screened titles and abstracts of retrieved citations and where necessary, full text, to identify potentially eligible studies.

Two reviewers (EO, MC) independently abstracted pre-specified data including test scores from neuropsychological tests of cognition, using a standardised data extraction form. Disagreements were resolved on discussion with a third investigator (ACW). Where more than one publication of a study existed, reports were grouped and all relevant outcome data included. When repeated measures were collected on individuals within studies we prioritized the measure taken 24 hours following dialysis. Study and participant characteristics were collated.

We assessed study risk of bias using the Newcastle-Ottawa scale for cohort or cross-sectional study designs [26]. The Newcastle-Ottawa scale is a tool to assess potential bias in studies and each study is awarded stars for eight bias reducing measures: selection of the study groups (maximum four stars for cohort and five stars for cross-sectional studies); comparability of the groups (maximum two stars); ascertainment of outcome of interest for case-control or cohort studies (maximum 3 stars). The selection measures were awarded stars based on representative samples and sample size. We judged age, previous cerebrovascular disease and diabetes mellitus as the most important potential confounders and scored comparability as: one star awarded if age was adjusted for and two stars if age and either cerebrovascular disease or diabetes mellitus were adjusted for. For outcome assessment, we awarded two stars if outcome assessors were blinded to whether participants were on dialysis, and one further star for presentation of statistical data (p value or 95% CI).

Summary measures and synthesis of results

The many available tests of cognition vary in the particular domains they assess. To examine patterns of cognitive deficit across studies, two clinical psychologists with expertise in cognition (DG, DP) independently mapped each cognitive test to the cognitive skill it best measured. We classified cognitive domains using a commonly used neuropsychiatric framework: orientation and attention (primarily tests of attention, sustained attention, concentration, and processing speed), perception, memory, verbal functions and language, construction and motor performance, concept formation and reasoning, and executive functions [27]. Tests which could not be assigned to one primary cognitive domain (including IQ and general cognitive screening tests) were classified as assessing global cognition. Mapping agreement between the two psychologists was assessed using the kappa statistic.

In order to combine different tests and measurement scales within each domain, we used standardised mean differences (SMD and 95% confidence interval [CI]). We aligned scales by multiplying mean values from tests where a higher score indicated a poorer cognitive test score, by -1. Where studies administered several different tests assessing the same cognitive domain, we synthesized overall scores by domain by computing a combined effect size and variance of that mean using a correlation coefficient of 0.5. We undertook sensitivity analysis using correlation coefficients of 0.01, 0.1 and 0.9. [28]. Meta-analysis was performed, as per Cochrane methodology, using a random-effects model, with heterogeneity investigated using Chi^2 on N-1 degrees of freedom, with an alpha of 0.05 used to represent evidence of statistical significance. We analysed the data using the profile-likelihood random-effects method as a sensitivity analysis, no substantive differences were found (results available on request). We assumed I^2 test values from 0-40% represented

heterogeneity which might not be important, 30-60% represented moderate heterogeneity, 50-90% represented substantial heterogeneity and 75-100% represented considerable heterogeneity [29].

To demonstrate clinical applicability, we multiplied the summary SMD by the pooled standard deviation from the largest study, for the most frequent test within each domain. This allowed the summary effect to be re-expressed in terms of the original units of that instrument, to understand whether observed differences might be clinically important[24].

Subgroup and sensitivity analyses

We did pre-specified subgroup analyses and meta-regression to explore potential sources of heterogeneity. We examined whether differences in cognition were affected by study populations (differing definitions of CKD, nondialyzed CKF and selection of general population). We examined year the study was conducted, comparing studies published after 1995 versus before 1995, as around this time there was widespread reduction in the use of aluminium in dialysate, a contributor to aluminium-related dementia. To investigate the effect of potential bias we performed sensitivity analyses, using only data from studies that scored >4 out of a total of 9 stars in the Newcastle-Ottawa Scale.

7.4 Results

We identified 49 eligible studies involving 4964 participants (Figure 7.1). We were unable to include data from 7 studies (1442 participants) as cognitive data were not dis-aggregated by population or test (Appendix 4 Table 2). The remaining 42 studies consisted of 38 cross-sectional and four cohort studies, described in Table 7.1. Seventeen studies were

performed in the USA (40%), 14 studies in Europe (33%), six studies in Asia and the Middle East (14%), three studies in Central and South America (7%) and two studies in Africa (5%). Patient characteristics are described in Table 7.1. The median number of participants in the studies was 57, range 20-490. The mean age of all study participants was 51.4 years (SD 10.6, range 32.0–69.5) and in tests of interaction there were no statistical differences ($p>0.05$) between the age of the haemodialysis population and any other population. The mean proportion of men was 63.1% (range 0-100%). Race was only reported in 10 studies; on average 59.0% were white, 40.0% black, 20.5% Asian and 12.9% were reported as other.

Risk of bias

The four cohort studies achieved higher total scores (median 7 stars out of 9,range 5-9 stars) in the Newcastle-Ottawa scale than the 38 cross-sectional studies (median 4 stars out of 10, range 3-8 stars) (Figure 7.2). Within the *selection* category very few studies reported sampling strategy, justified the sample size or described the non-respondents; the median number of stars obtained was two for cross-sectional studies but 3.5 for cohort studies. In the *comparability* category; 38 (90.5%) studies adjusted for age though only 23 (54.8%) adjusted for education. Only five studies (12%) adjusted for age and either diabetes mellitus or cerebrovascular disease (Table 7.1). Sixteen studies excluded patients already diagnosed with dementia or those who had an MMSE <24. Thirteen studies excluded those with a previous history of stroke. In assessing *outcome* the assessor was only blinded to whether the patient was on haemodialysis in one study.

Cognitive Tests

Inter-rater agreement (DP, DG) of the primary cognitive domain that each test assessed was excellent, with a kappa statistic of 0.95.

Studies used multiple tests, often measuring the same domain numerous times. Fifty four different cognitive tests were employed over the 42 studies. Within each study, a median of 5 tests (range 1-41) were used. Overall, global cognition was measured in 27 (64.3%) studies. Orientation and attention was the most frequently measured in 33 (78.6%) studies and perception the least frequently measured in only four (9.5%) studies (Figure 7.3).
A large variety of tests were used to measure each cognitive domain, the most common test was the MMSE, used 25 times out of 49 measures of global cognition (53%). The most frequent test used in the other domains varied from being used 17-37% of the time (Figure 7.3).

People on haemodialysis compared to the general population.

The participants in the general population groups across the 32 studies were somewhat heterogeneous; they included healthy volunteers, people selected from outpatient clinics, relatives and friends of people on dialysis, living kidney donors and primary care patients. People on haemodialysis had significantly lower cognitive test scores than the general population in all domains apart from perception, where data were sparse and imprecise (Figure 7.4). The SMD, number of studies and participants across each cognitive domain is shown in Appendix 4 Table 4. People on haemodialysis performed most poorly compared to the general population in tests of orientation and attention (SMD -0.93, CIs -1.18, -0.68). It is worth noting that the majority of tests assessing the domain of orientation and attention

focussed on attention, processing speed and working memory (this is the case for all of the following results where the domain of orientation and attention is referred to.)
Global cognition was tested 23 times in 18 studies (583 haemodialysis and 562 general population participants), SMD -0.70 (CI -0.95 to -0.45). In absolute terms, this equates to 1.1 point lower MMSE score in adults treated with haemodialysis compared to the general population (Figure 7.5).

Orientation and attention was measured in 22 studies (969 haemodialysis and 722 people in the general population) SMD -0.93 (CI -1.18 to -0.68). For this domain the most frequently performed test was the Trail-Making Test A (TMT-A), measured in 470 people on haemodialysis and 285 general population. In absolute terms, this SMD suggested haemodialysis patients were 11.4 seconds slower than the general population in performing the TMT-A test (Figure 7.5).

Tests of interaction to investigate potential sources of heterogeneity did not reach statistical significance ($p>0.09$, details in Appendix 4 Table 3).We firstly restricted studies to those in which haemodialysis patients were compared with only healthy, age matched controls. All domains showed a small increase in difference, but I^2 did not change (Appendix 4 Table 4). Restricting to studies published since 1995, improved heterogeneity for memory (I^2 56% to 35%) and construction and motor skills (I^2 78% to 30%) (Appendix 4 Table 4). Including only studies with lower risk of bias (>4 stars out of 9 in the Newcastle-Ottawa scale) improved heterogeneity for memory (56% to 32% in 6 studies) and construction and motor (78% to 0% in 5 studies) (Appendix 4 Table 4).

People on haemodialysis compared to people with CKD.

The majority of studies defined CKD as between Stages 2 and 4, one study included some acute kidney injury patients and two studies had ambiguous definitions including "pre-dialysis".

People on haemodialysis had lower memory scores than people with CKD (Figure 7.4), tested nine times in five studies (221 haemodialysis and 201 CKD participants) SMD -0.40 (CI-0.60 to -0.21). In all other domains the differences were either not statistically significant or imprecise (Figure 7.4).

To investigate heterogeneity we excluded studies where the patients with acute kidney injury or undefined "predialysis" groups were included, this did not affect the I^2 value (Appendix 4 Table 5). Only one study was performed after 1995 and analysing only studies with low risk of bias did not explain heterogeneity (Appendix 4 Table 5).

People on haemodialysis compared to people on PD

People on haemodialysis performed more poorly in tests of executive function than people on PD (Figure 7.4), tested four times in two studies (464 haemodialysis and 65 PD participants, I^2 89%) SMD -0.98 (CI -1.91 to -0.05). Both studies adjusted for age, diabetes and stroke though only one adjusted for education. The results for language were based on one study (338 haemodialysis and 51 PD patients) where haemodialysis patients were poorer, SMD -0.31(CI -0.60 to -0.01). In all other domains the mean difference did not meet significance (Figure 7.4).

The analyses excluding studies published before 1995 and those with a high risk of bias did not explain the high heterogeneity (Appendix 4 Table 6). Other potential sources of between-study heterogeneity could not be explored due to insufficient observations.

People on haemodialysis compared to people with nondialyzed CKF.

The nondialyzed CKF comparator group included one study with conservative care patients, one "severe azotemia" population, two studies with people immediately prior to starting dialysis and three studies which quoted mean creatinine within the range of CKD stage 5. People on haemodialysis performed better than people with nondialyzed CKF in orientation and attention, measured 22 times in 6 studies, (128 haemodialysis and 73 nondialyzed CKF participants) SMD 0.70 (CI 0.45 to 0.96), and memory, measured 16 times in 6 studies (135 haemodialysis and 81 nondialysed CKF participants) SMD 0.36 (CI 0.08 to 0.63) (Figure 7.4).

In absolute terms nondialyzed CKF patients performed the TMT-A test, measuring orientation and attention, 12.3 seconds slower than people on haemodialysis (Figure 7.5). Removing studies which included conservative care patients and studies which only described the group as "severely azotemic" made little difference to either the magnitude of effect nor heterogeneity (Appendix 4 **Table 1**).

7.5 Discussion

We present a systematic summary of cognitive impairment in people on haemodialysis, and more specifically the patterns of cognitive domains most affected People on haemodialysis demonstrated more cognitive impairment than the general population in most cognitive domains. There were pronounced deficits in orientation and attention, memory and also

executive function. There is not sufficient evidence to find any major differences between people on haemodialysis compared with either PD or those with CKD apart from a small decline in memory compared to people with CKD. Finally, there is some limited evidence that people treated with haemodialysis may perform better in tests of attention and memory compared to those with nondialyzed CKF.

In the process of normal aging the most affected domains are memory and executive functions[3,30]. We found that in people on haemodialysis, memory and executive function are impaired but that the domain of orientation and attention is particularly compromised. This impairment was predominantly found in tests of attention, processing speed and working memory. Our findings, based on limited evidence, suggests that as people with nondialyzed CKF perform more poorly than people on dialysis in these tests, this deficit may be reversible to some degree. There appears to be a spectrum of declining cognitive function from people in the general population through haemodialysis to those with nondialyzed CKF.

This impairment in orientation and attention may have particular clinical implications. The LitCog study found a strong correlation between orientation and attention (measured as processing speed) and several literacy measures including the Test of Functional Health Literacy in Adults (r=0.68) [17],[31]. Deficits in orientation and attention greatly affect an individuals' ability to actively process information which has a significant association with poorer health literacy and poorer performance of common health tasks [17]. This is particularly important in a clinical setting because it is often peri-CKF and again whilst on

haemodialysis that people are counselled with regards to choice of renal replacement therapy, transplantation options and education in how that therapy is implemented.

The prominence in the deficit in orientation and attention also suggests the possibility that there is a different pathophysiological pathway causing the deficits in cognitive function for people on haemodialysis, neither accelerated aging nor early vascular dementia. In our own work, a systematic review looking at cognition in people with ESKD pre and post-transplant, we have shown that there is improvement, particularly in orientation and attention, memory, construction and motor performance after transplantation[32]. This would suggest that the cognitive deficits in people on haemodialysis may be at least partially reversible and potentially metabolic in origin. Whether any reversibility is dose dependent is not clear.

The main strength of our study is that we comprehensively synthesised data and analysed by cognitive domain. There is currently no gold standard cognitive test battery for CKD and we found multiple tests had been used both within and across studies. Our approach was to map every cognitive test reported, to the broad cognitive skill domain the test assessed (and achieved extremely close inter-rater agreement between two clinical psychologists based in different countries). We used a validated method for analysing correlated data to synthesize data from every cognitive test used on the same people within studies, thereby avoiding potential bias in selecting which data to include.

Our synthesis had several limitations. Many of the studies excluded people with MMSE <24 or diagnosed with dementia from both the control and intervention groups. This may introduce bias, and so underestimate the size of differences. The average age of

participants in our study was 52.9 years and this is somewhat younger than the contemporary age in many developed populations[33,34] but reflects practices worldwide. The majority of studies adjusted for age, but education was only adjusted for in about half of the studies, which may also introduce bias. The lack of an agreed standard tool for measuring cognition in CKD has led to a multitude of tests being used and leaves our study open to the potential of outcome reporting bias. Studies frequently presented crude (unadjusted) cognitive tests scores and did not report other potential confounders that might affect cognition in people on dialysis, for example; comorbid cardiovascular disease, stroke, and dialysis adequacy. Our analyses were also subject to assumptions about correlations among different cognitive tests used at the same time. We used conservative estimates of correlation from published reports but could not verify our assumptions without access to individual participant test score data or more detailed statistical reporting of study summary level data. Other potential explanations for the heterogeneity include: inherent difficulties analysing continuous scales using SMD where statistical heterogeneity is inevitable[35], the sparse data for many comparisons, the broad range of comparator groups and the high variability in the tests used to test each domain. The choice of the random-effects model acknowledged the *a priori* assumption of high heterogeneity. Many of the studies included in this meta-analysis performed poorly on the Newcastle-Ottawa scale, suggesting low quality evidence. It is difficult to ascertain how clinically relevant the demonstrated difference between measures of cognition in the haemodialysis population and the general population are.

A strength of our work is that to try and account for this we expressed SMD in absolute terms. The MMSE difference of 1.1 point lower was statistically significant (p=<0.03), but it

is unclear whether this difference is clinically important in such a blunt tool. Contrastingly, when we calculated absolute difference for orientation and attention, using the TMT-A test, the haemodialysis population were 11.4 seconds slower than the general population; we found that people on haemodialysis were classed as having extremely low performance relative to normative data for age 55-74 years. In our analysis set the general population were classified as low average (Figure 7.5); this was skewed by one study with exceptionally long test times, removal of this study resulted in the general population falling into the normative data "Average" category).[27] This information emphasises the clinical applicability of our work.

This study also highlights areas where improvements can be made in the design of future studies; principally reaching consensus on which cognitive tests should be used in the haemodialysis population to allow for meaningful comparison between studies and more detailed information on areas of impairment. A pragmatic way forward may be to incorporate testing for each cognitive domain into standardised reporting outcomes for haemodialysis.

Cognitive impairment on dialysis impacts the individual patient journey as well as the public health agenda. Understanding the specific domains affected in cognitive impairment on dialysis can help shape service delivery and patient self-management initiatives.

7.6 References

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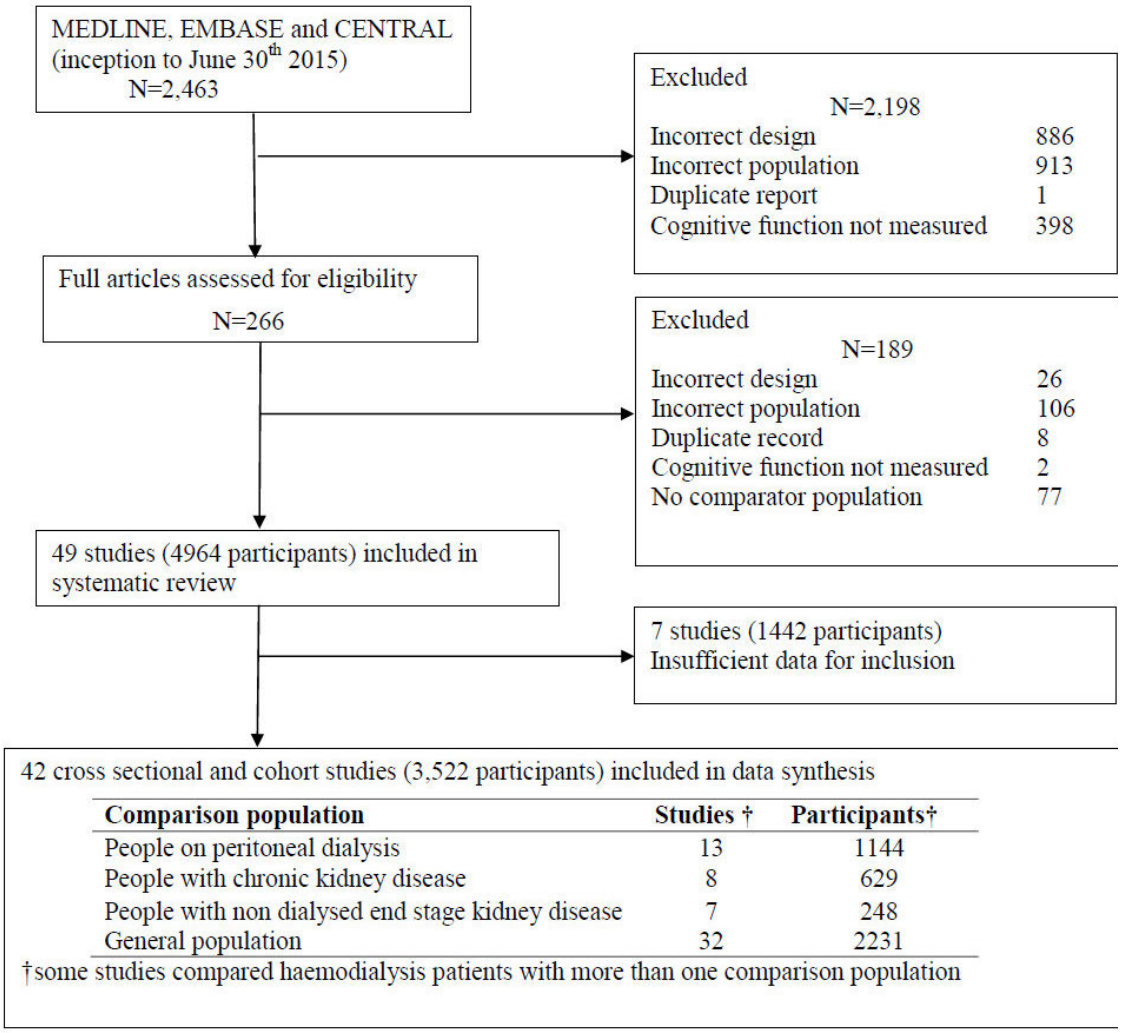
7.7 Figures and tables

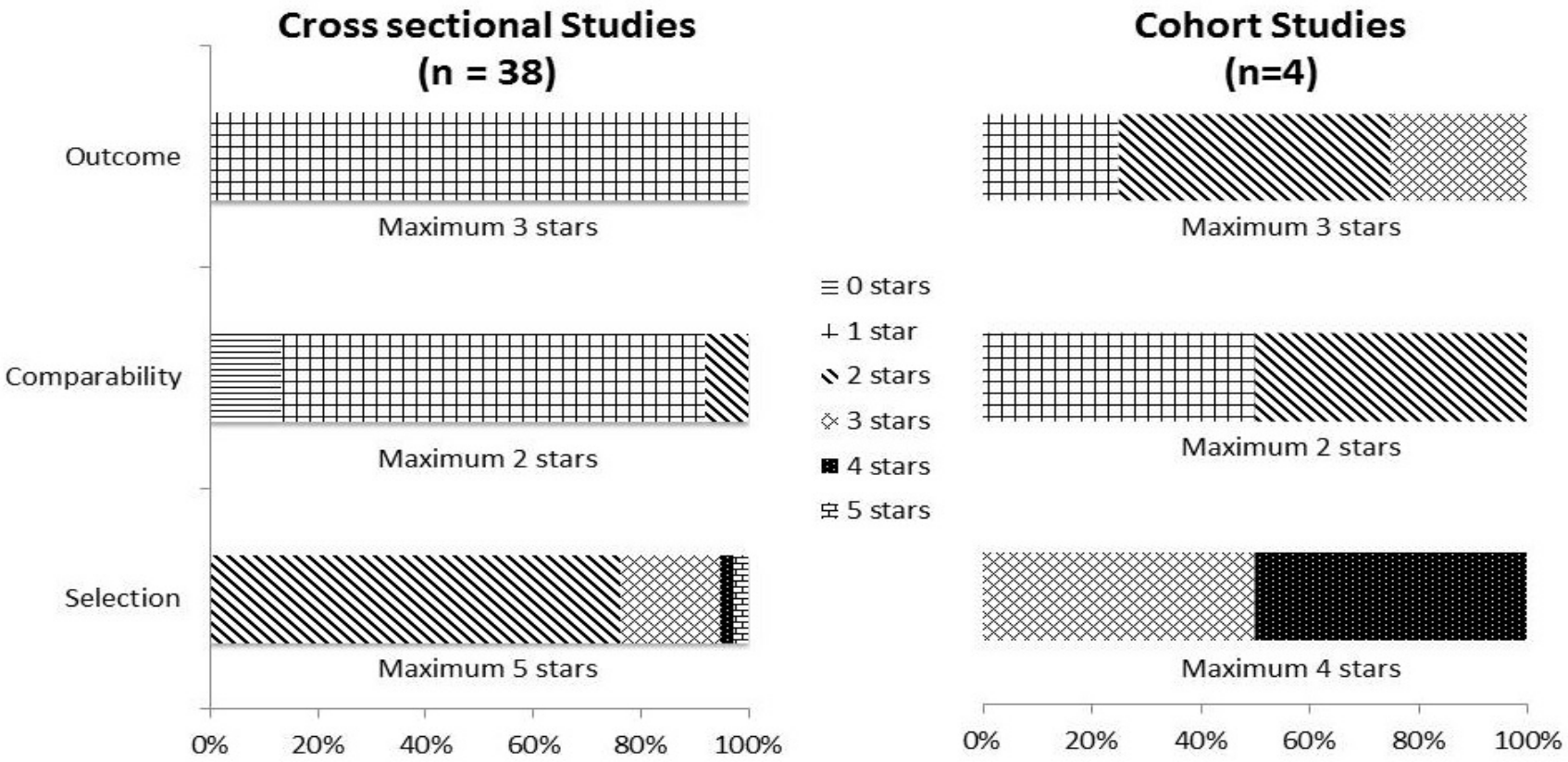
FIGURE 7.1 LITERATURE SEARCH



Comparison population	Studies †	Participants†
People on peritoneal dialysis	13	1144
People with chronic kidney disease	8	629
People with non dialysed end stage kidney disease	7	248
General population	32	2231

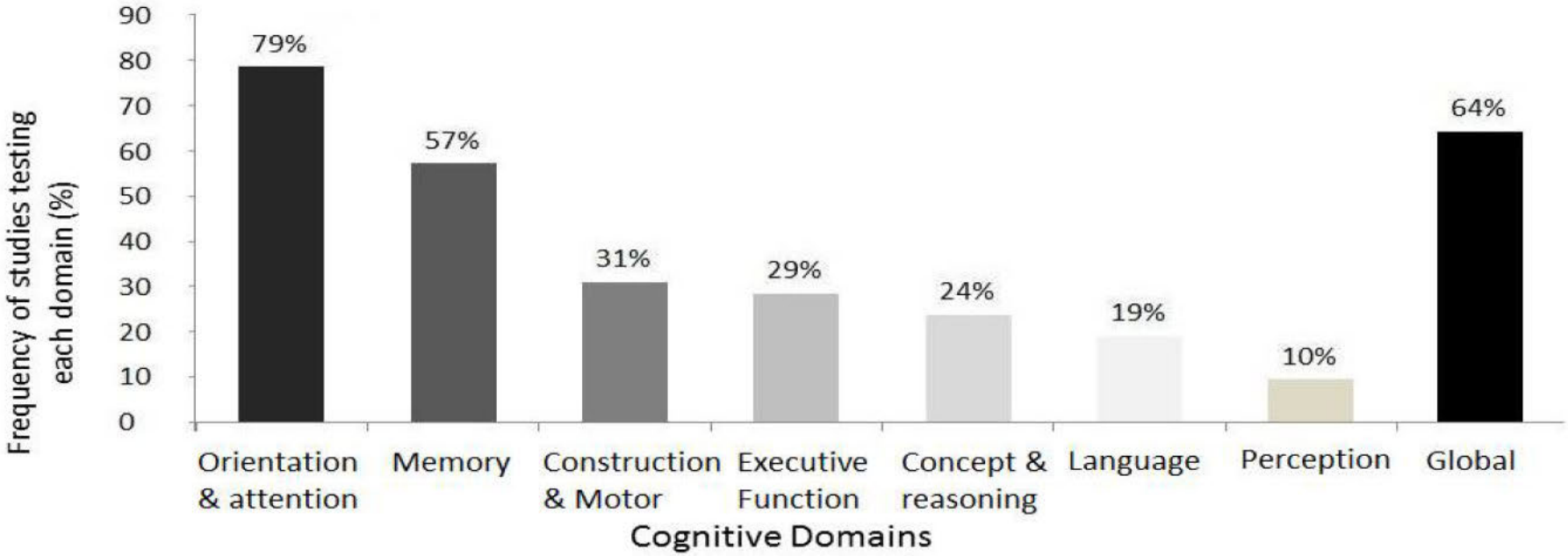
†some studies compared haemodialysis patients with more than one comparison population

FIGURE 7.2 RISK OF BIAS(NEWCASTLE OTTAWA SCALE)*



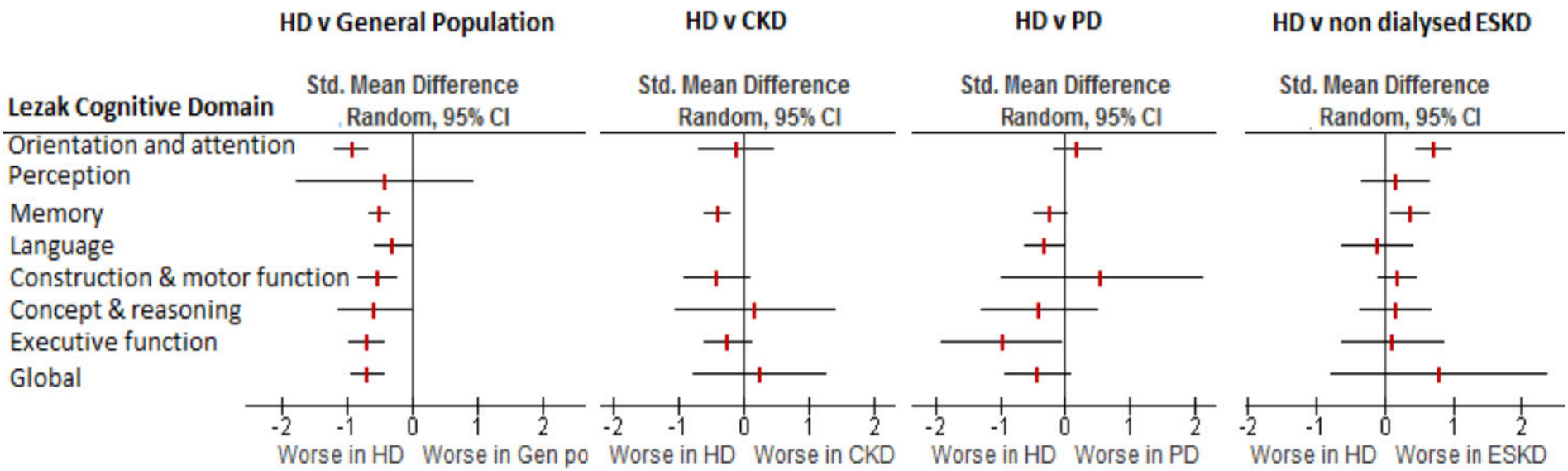
Guide to allocation of stars: Selection: Representation of sample: all subjects or random sampling or non random sampling, no description or selected users – no stars
Sample size: Justified and satisfied*, no justification or no description – no stars
Non-respondents: comparability established and response rate satisfactory*, unsatisfactory response rate or no description – no stars
Tool: validated** Comparability: Adjusted for age*, Adjusted for age **and** cerebrovascular disease OR diabetes**
Outcomes: Statistical test presented*,Outcome assessor blinded**

FIGURE 7.3 FREQUENCY OF COGNITIVE DOMAINS REPORTED IN STUDIES



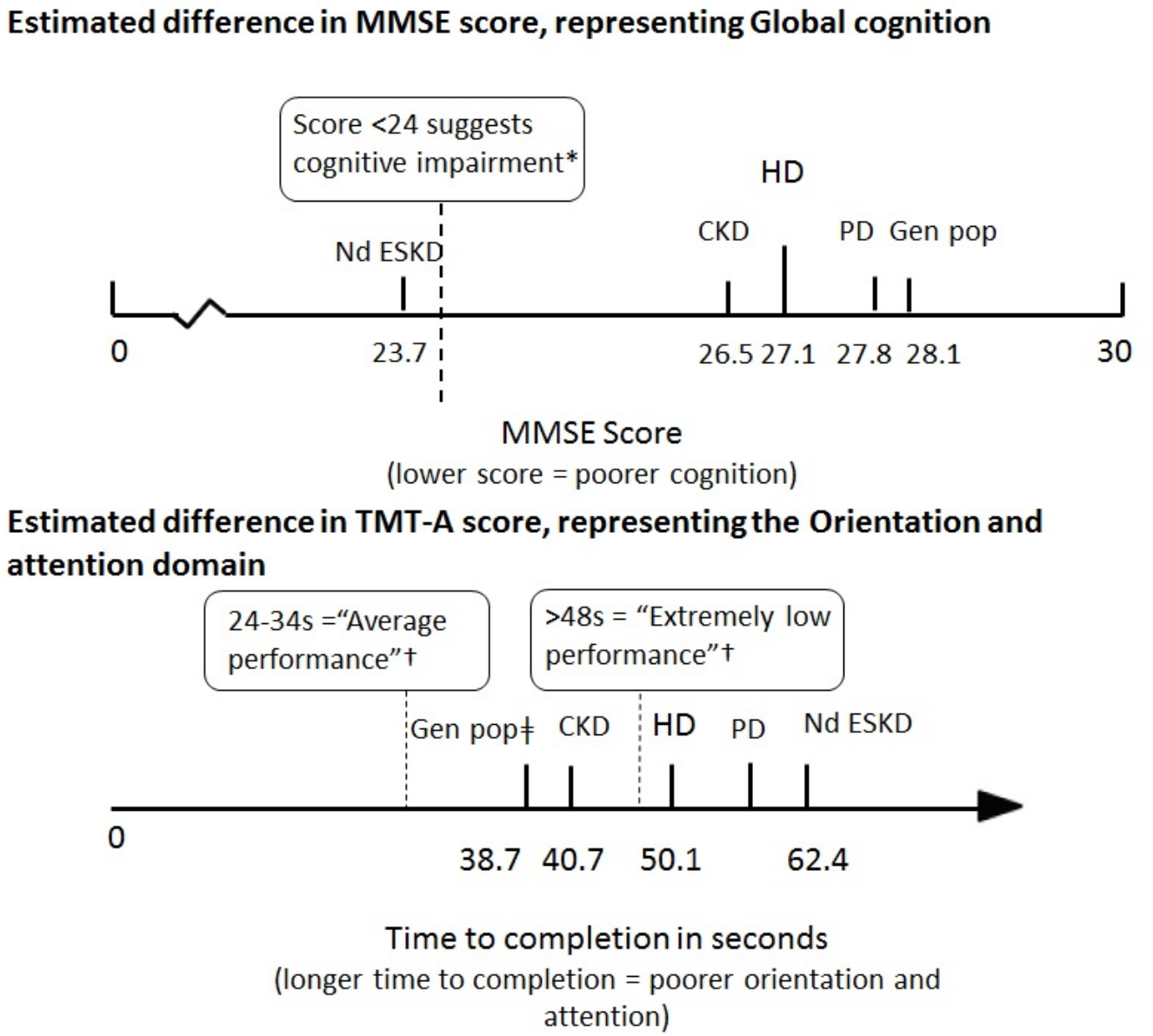
Trials (N)	33	24	13	12	10	8	4	27
Participants	3361	2922	1812	1554	376	1264	126	2458
Number of tests utilised to measure the domain	33	38	13	11	11	9	5	12
Most frequent test used	TMT A and B (17%)	WMS (25%)	Clock and GPB (17% each)	Stroop test (37%)	Progressive matrices (22%)	HVLT (20%)	Halstead Reitan (25%)	MMSE (53%)

FIGURE 7.4 COGNITIVE SCORES STRATIFIED BY COGNITIVE DOMAINS



HD = Haemodialysis, Gen pop = General population, PD = Peritoneal dialysis, ESKD = non dialysed end stage kidney disease

FIGURE 7.5 ESTIMATED DIFFERENCES IN COGNITIVE TESTS



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†Normative data for ages 55-74 Ashendorf L, Jefferson AL, O'Connor MK, Chaisson C, Green RC, Stern RA. Trail Making Test Errors in Normal Aging, Mild Cognitive Impairment, and Dementia. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists*. 2008;23(2):129-137.

‡ The mean time for our general population was skewed by one study and when this study was excluded the mean time fell into the "Average performance" category.

HD = Haemodialysis, Gen pop = General population, PD = Peritoneal dialysis, Nd ESKD = non dialysed end stage kidney disease

TABLE 7.1 CHARACTERISTICS OF STUDIES INCLUDED IN META-ANALYSIS, STRATIFIED BY COMPARATOR GROUP

Author	Country	Total (n)	% Men	Mean age (years)	Mean HD duration (years) (SD/range)	Risk of Bias		
						Selection Max 4stars	Comparison Max 2 stars	Outcome Max 3 stars
Haemodialysis versus General population								
Alexander 1980	USA	56	unknown	unknown		2	1	1
Bae 2008	South Korea	27	59.1	48.8	3.3(3.2)	2	1	1
Bossola 2011†	Italy	240	60.0	67.0	4.9(4.9)	2	1	1
Dahbour 2009†	Jordan	108	73.4	46.7	8.5(5.9)	4	2	3
Fazekas 1996	Austria	40	28.0	58.0	2.7	3	1	1
Figueiredo 2007	Brasil	57	19.1	37.9	2.8(2.0)	2	1	1
Grimm 1990	Austria	65	10.8	51.5	2.9(2.5)	2	0	1
Harciarek 2009†	Poland	50	66.0	46.4	4.7(4.0)	3	2	1
Harciarek 2010	Poland	91	69.6	48.3	5.3(6.2)	4	2	2
Kramer 1996†	Austria	60	21.9	44.0	unknown	3	1	2
Lux 2010	Germany	24	91.7	44.9	unknown	2	1	1
Madan 2007	India	30	0.0	32.0	unknown	2	1	1
Murray 2006	USA	202	50.5	69.5	3.0(3.5)	3	1	1
Pliskin 1996	USA	28	32.1	59.3	3.2(0.5-7.0)	2	1	1
Post 2012	USA	76	100.0	63.3	2.5(3.8)	3	1	1
Shin 2013	USA	28	67.9	49.3	4.3(3.0)	2	1	1
Umans 1998	USA	20	unknown	61.5	unknown	2	1	1
Haemodialysis versus chronic kidney disease								
Kurella 2004	USA	160	64.4	62.7	3(1.7-4.0)	5	2	1
Rabinowitz 1980	South Africa	34	unknown	unknown	unknown	2	0	1
Post 2010	USA	51	100.0	67.2	unknown	3	2	1

Haemodialysis versus peritoneal dialysis								
Buoncristiani 1993	Italy	37	unknown	59.6	unknown	2	1	1
Cukor 2013	USA	31	10.0	49.6	4.5(3.9)	2	1	1
Griva 2003	UK	145	64.8	50.1	4.4(4.6)	4	1	1
Radic 2011	Croatia	42	unknown	50.3	7.1(4.3)	2	1	1
Sithinamsuwan 2005	Thailand	90	36.7	54.3	5.7(2.8)	2	1	1
Williams 2004	USA	30	50.0	51.4	5.5(1.1)	2	0	1
Wolcott 1988	USA	35	63.1	50.2	5.8(4.2)	2	1	1
McKee 1982	USA	34	50.0	unknown	unknown	2	0	1
Takuma 1987	Japan	65	unknown	unknown	unknown	2	0	1
Haemodialysis versus multiple comparator groups								
Caltagirone 1987	Italy	28	unknown	45.4		2	1	1
Conde 2010	Brasil	119	50.1	58.5	4.7(0.8)	2	1	1
Garcia-Maldonado 1991	USA	56	100.0	53.5	3.4(0.6)	2	1	1
Hart 1983	USA	62	62.9	41.1	2.7(2.7)	2	1	1
Heidbreder 1979	Germany	98	49.0	45.0	unknown	2	1	1
Kaliroa 2011	USA	490	53.2	69.2	2.7(2.7)	2	1	1
Kato 2012	Japan	100	47.3	68.2	unknown	2	1	1
Nasser 2012	Egypt	120	53.6	43	unknown	3	1	1
Ryan 1981	USA	48	100.0	48.1	3.2(2.1)	2	1	1
Sanchez-Roman 2011	Mexico	161	unknown	36.6	unknown	3	1	1
Sujic 1997	Croatia	50	unknown	unknown	unknown	2	1	1
Teschan 1979	USA	167	unknown	53.6	unknown	2	1	1
Tilki 2004	Turkey	67	50.7	40.5	5.2	2	1	1

*7 additional studies did not provide data suitable for synthesis (Appendix 4 Table 2), †Cohort study HD = Haemodialysis, GP = general population, CKD = chronic kidney disease, PD = peritoneal dialysis, ESKD = non dialysed end stage kidney disease.

CHAPTER 8

DISCUSSION AND CONCLUDING REMARKS

The aims of this thesis were to examine CVD in the ESKD population by investigating priorities and outcomes. Firstly, to ascertain the priorities of patients and health professionals and to standardise them as outcome measures of CVD for use in trials in haemodialysis. Secondly to identify patterns in the epidemiology and impact of CVD in the ESKD population

I addressed my aims using both quantitative and qualitative methods. I performed systematic reviews to describe the contemporary use of cardiovascular outcomes (Chapter 2) and to meta-analyse smaller trials assessing cognition in people with ESKD (Chapter 7). I used two types of survey methods in terms of absolute (Likert scale) and relative (best-worst scaling) importance, which elicited stakeholder preferences about the most important measures of CVD to be used as core outcome measures (Chapter 3). I convened an international consensus workshop (Chapter 4), which provided considerations for establishing a CVD core outcome measure in terms of its relevance to haemodialysis, difficulties with defining outcomes and considerations for implementation. I also employed thematic analysis to reflect comments from the survey and contributions from participants at the consensus workshop.

I made efficient use of routinely collected clinical and administrative datasets and ensured minimal bias by using linked health data to make population-based comparisons. I used a wide range of epidemiological methods to describe patterns of CVD in ESKD, resulting in novel findings, such as discrepancies in outcomes for women

compared to men. To facilitate simple clinical application I expressed the findings in terms of absolute risk and risk relative to the general population (Chapters 5 and 6).

Implications of main findings

Cardiovascular outcomes in trials of people on haemodialysis

I have characterized the variety and lack of standardisation in cardiovascular outcome reporting in trials of people on haemodialysis. I have identified and achieved consensus on using myocardial infarction and sudden cardiac death as core measures of CVD important to all stakeholders. These are critical steps in the process of defining a CVD core outcome set for use in trials of people on haemodialysis.

Future Work

I will be conducting an Expert Working Group discussion at The American Society of Nephrology Kidney Week 2019 to produce a standardised definition of myocardial infarction for use in trials in people on haemodialysis. The Expert Working group consists of patients, nephrologists, cardiologists, regulatory bodies and biomarker specialists. Once the definition of myocardial infarction is standardised for this population we will aim to design and perform a study to validate this definition in the haemodialysis population. If appropriately validated, this definition of MI will be able to be used as a core measure of CVD in all trials in people on haemodialysis.

Epidemiology of cardiac disease in the ESKD population

Significantly higher rates of cardiovascular disease remain in the ESKD population compared to the general population and patterns in the epidemiology do not mirror the general population. The discrepancy between the improvements seen in the cardiac mortality rate in ESKD and the lack of improvements in cardiac event rate may be explained by the improvements in the treatment of these events. It also highlights potentially ineffective primary preventative strategies. Recognition of the sex discrepancies between the ESKD population and the general population generates hypotheses with regard to the pathophysiology of CVD in ESKD, the access to care and management of CVD in women with ESKD.

Future Work

I am continuing to explore the linked data to examine potential risk factors for cardiac mortality, the differences in cardiac mortality rates between different renal replacement therapy modalities and the impact of transplant on cardiac mortality rates. My work to date has highlighted the sex differences in the ESKD population and I intend to explore the reasons for the differences including access to treatment, provision of preventative and treatment strategies and the potential of excess harms in the use of current treatments.

Cognition in people with ESKD

I have identified specific patterns of cognitive deficits in people with ESKD, particularly in orientation and attention and in executive function. Much of the education provided to patients with ESKD is offered at or near the onset of ESKD when it is likely that these cognitive deficits are already apparent. Education is also often provided

through extended educational programs lasting a number of hours. This work should inform the design of future education programs for people on haemodialysis, potentially with a focus on shorter and more frequent education sessions to account for the attention deficits. These cognitive deficits are also critical for consideration by clinicians in shared clinical decision-making and promoting self-management of this chronic disease. The comparison of cognitive deficits in ESKD and the general population may inform hypotheses on the involvement of cerebrovascular disease in the development of cognitive impairment in ESKD.

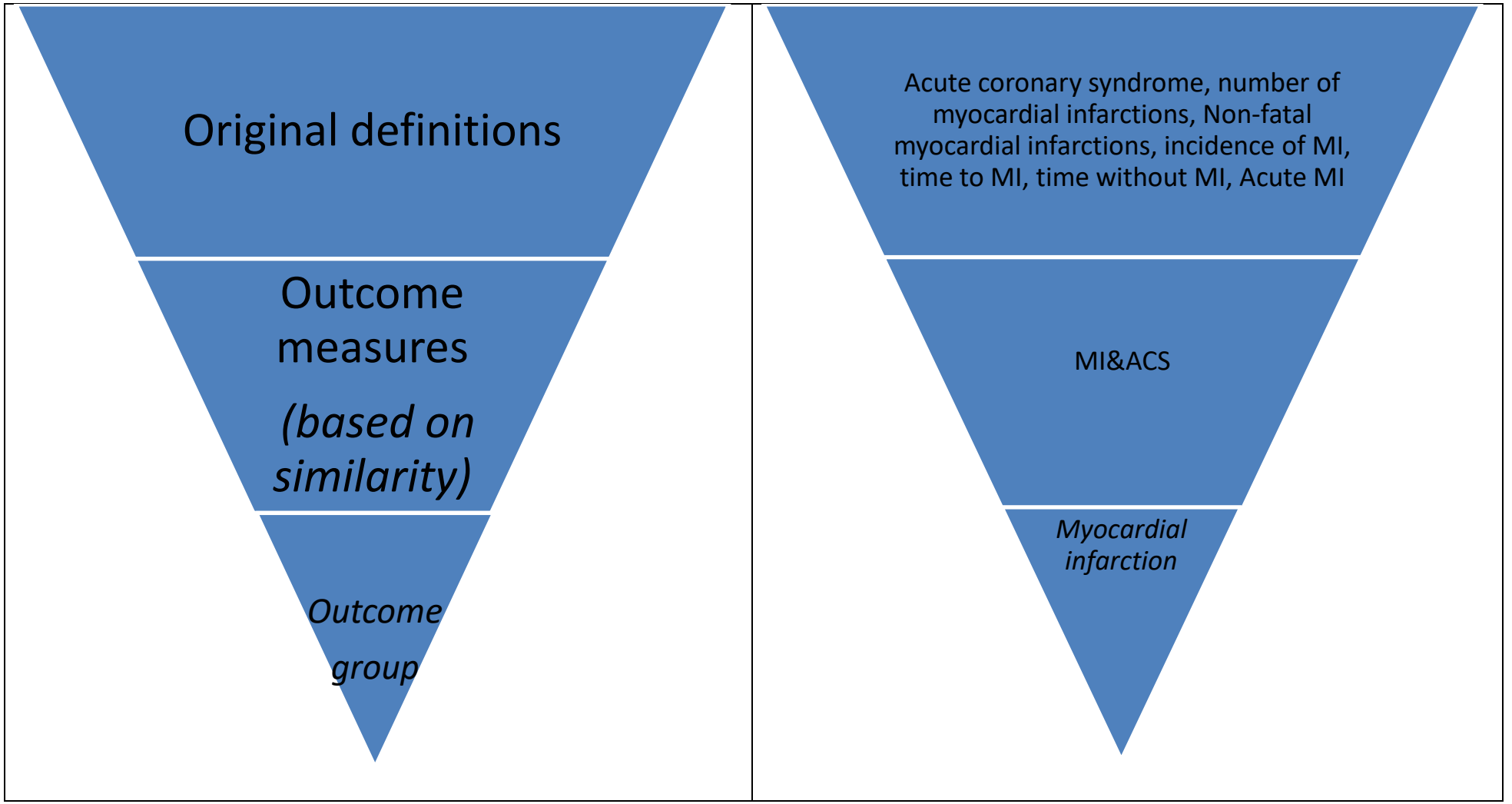
Future Work

One of the challenges presented in performing the meta-analysis of trials assessing cognition was the lack of standardisation in the use of cognitive tests to assess the individual cognitive domains. I am in the process of performing a similar meta-analysis focussing on the cognitive impairments in people on peritoneal dialysis. Using meta-analyses performed across the spectrum of kidney disease we intend to summarise, evaluate and rank the cognitive tests that are most suitable for use in the assessment of cognitive impairment in people with ESKD.

APPENDIX 1

SUPPLEMENTARY DATA FOR CHAPTER 2

Figure 1 Example schema for categorization of original definitions into the final outcome group



Abbreviations: ACS – acute coronary syndrome, MI – myocardial infarction

Figure 2 Measures and time points within the *cardiovascular composite outcome*.

Bar chart to show the proportion of trials reporting each measure within the *Cardiovascular composite* outcome, as well as the time points at which they are reported

Time points reported as dots and % trials reporting outcome measure in bars.

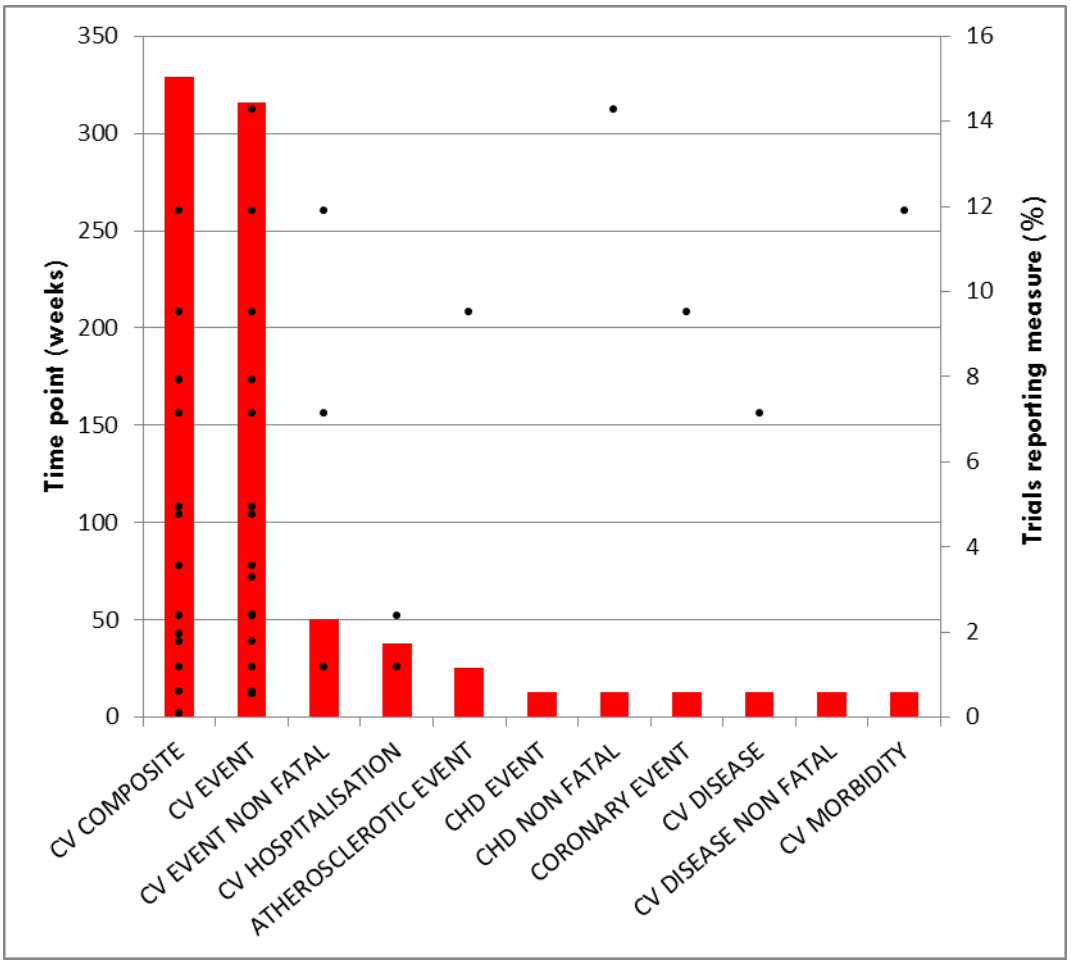


Figure 3 Proportion of trials reporting CVD *mortality* outcome

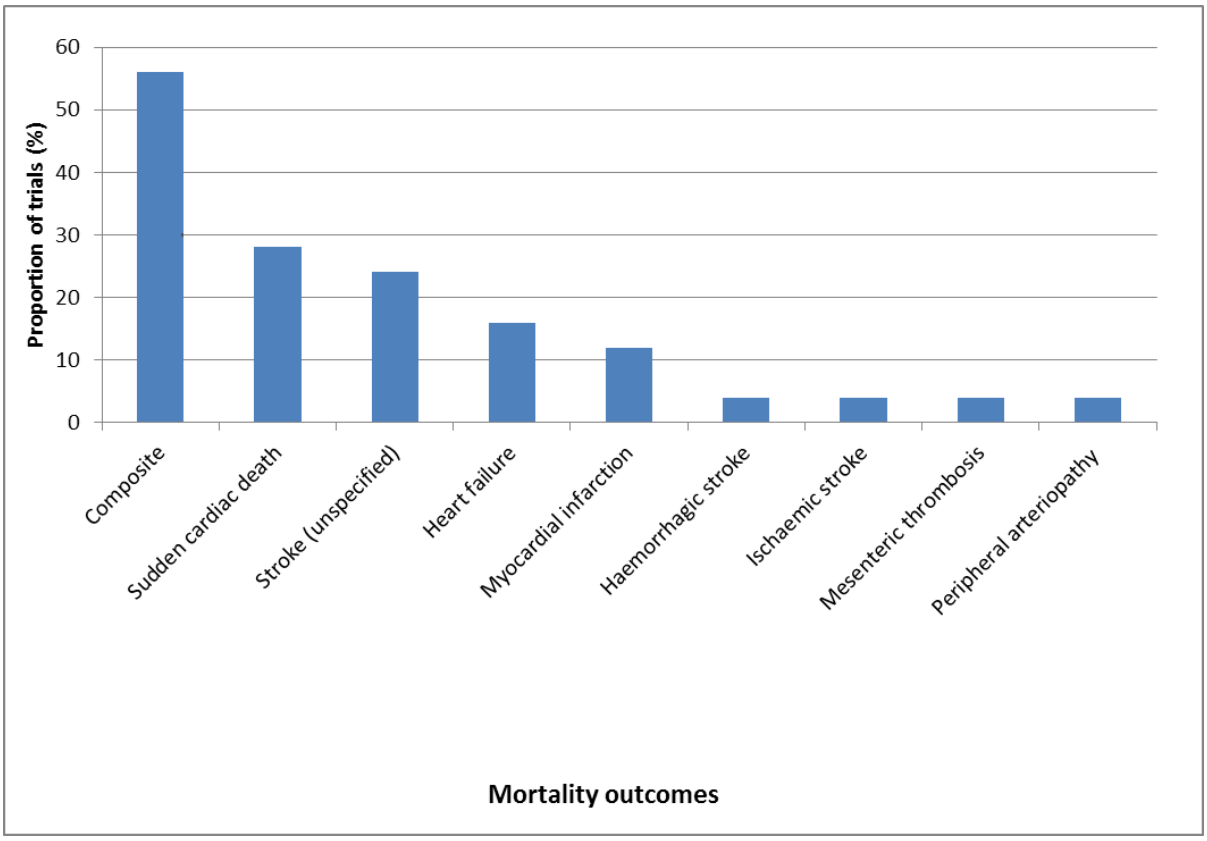


Table 1 Search strategy

Database	Number	Search term
Medline	1	Renal Replacement Therapy/
	2	Renal Dialysis/
	3	Hemodiafiltration/
	4	Haemodialysis, home/
	5	exp Hemofiltration/
	6	dialysis.tw.
	7	(haemodialysis or haemodialysis).tw.
	8	(hemofiltration or haemofiltration).tw.
	9	(hemodiafiltration or haemodiafiltration).tw.
	10	or/1-9
	11	randomized controlled trial.pt.
	12	10 and 11
	13	limit 12 to yr="2011 -Current"
	14	exp Cardiovascular Diseases/
	15	exp Cerebrovascular Circulation/ or exp Cerebrovascular Disorders/
	16	exp Myocardial Revascularization/ or exp Myocardial Ischemia/ or exp Myocardial Infarction/
	17	14 or 15 or 16
	18	13 and 17
	19	exp Coronary Disease/ or exp Atherosclerosis/
	20	exp Stroke/
	21	exp Vascular Diseases/
	22	14 or 15 or 16 or 19 or 20 or 21
	23	13 and 22
	24	exp Mortality/
	25	22 or 24
	26	13 and 25
	27	clinical trial.pt. or randomized.ab. or placebo.ab. or dt.fs. or randomly.ab. or trial.ab. or groups.ab.
	28	10 and 22
	29	10 and 25
	30	27 and 29
	31	limit 30 to yr="2011 -Current"

	32	limit 31 to ("all adult (19 plus years)" and humans)
Embase	1	haemodialysis/
	2	dialysis membrane/ or dialysis catheter/ or dialysis pump/ or home dialysis/ or dialysis/ or dialysis.mp. or extended daily dialysis/ or equilibrium dialysis/ or
	3	haemodialysis.mp. or haemodialysis/
	4	hemofiltration/ or continuous hemofiltration/ or hemofiltration.mp.
	5	hemodiafiltration/ or continuous hemodiafiltration/ or hemodiafiltration.mp.
	6	exp mortality/ or exp hemofiltration/ or exp haemodialysis/ or exp renal replacement therapy/
	7	1 or 2 or 3 or 4 or 5 or 6
	8	cardiovascular.mp. or interventional cardiovascular procedure/ or cardiovascular risk/ or cardiovascular equipment/ or cardiovascular system/ or
	9	exp cerebrovascular disease/ or exp occlusive cerebrovascular disease/ or exp cerebrovascular accident/ or exp cerebrovascular surgery/
	10	cardiac.mp.
	11	exp peripheral occlusive artery disease/ or exp peripheral circulation/ or exp peripheral vascular system/ or exp peripheral vascular disease/ or exp peripheral
	12	exp cardiovascular mortality/ or exp mortality/
	13	exp atherosclerosis/ or exp coronary artery atherosclerosis/ or exp aorta atherosclerosis/ or exp carotid atherosclerosis/ or exp brain atherosclerosis/
	14	exp heart/
	15	stroke.mp.
	16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
	17	7 and 16
	18	limit 17 to (randomized controlled trial and yr="2011")
	19	limit 18 to human
	20	limit 19 to adult <18 to 64 years>
	21	limit 19 to aged <65+ years>
	22	20 or 21
Clinicaltrials.gov	1	haemodialysis
	2	cardiovascular

Table 2 Original definitions and categorized outcome measures allocated to the *cardiovascular composite outcome*.

Trial	Original Outcome definition	Measure
7	Time to atherosclerotic cardiac event	Atherosclerotic Event
60	Total: any major atherosclerotic event	Atherosclerotic Event
12	Fatal and nonfatal CHD (MI, PTCA, CABG)	CHD Event
12	Non-fatal coronary heart disease	CHD Non Fatal
199	Coronary artery disease	Coronary Artery Disease
60	Any major coronary event	Coronary Event
3	Time to the occurrence of a combined end-point consisting of new onset of documented acute myocardial infarction,	CV Composite
3	Time to the occurrence of a combined end-point consisting of new onset of documented acute myocardial infarction,	CV Composite
6	The cumulate rate of non fatal MI or acute coronary syndrome, hospitalization for heart failure, nonfatal stroke or CV	CV Composite
6	The time of survival without a major CV event (non fatal MI, acute coronary syndrome, hospitalization for heart failure,	CV Composite
6	The time to onset of the first incident :non-fatal MI or acute coronary syndrome or hospitalization for heart failure or	CV Composite
6	The cumulate rate of non fatal MI or acute coronary syndrome, hospitalization for heart failure, nonfatal stroke or CV	CV Composite
7	Major adverse cardiac events (non fatal MI, non fatal stroke, death from cardiovasc cause)	CV Composite
7	Time to first cardiac event (combined endpoint of cardiac death and nonfatal myocardial infarction)	CV Composite
12	Fatal and nonfatal cardiovascular events	CV Composite
19	Time to death or the first nonfatal cardiovascular event (myocardial infarction, hospitalization for unstable angina,	CV Composite
22	Deaths and major cardiovascular events	CV Composite
26	Cumulative incidence of the composite outcome "death, myocardial infarction, heart failure".	CV Composite
31	Major cardiovascular event (fatal or non fatal cardiac event such as cardiac arrest, heart failure, myocardial infarction,	CV Composite
51	Composite of death, nonfatal stroke, nonfatal myocardial infarction and coronary revascularization	CV Composite
57	Composite of major cardiovascular events (hospitalised myocardial infarction, hospitalised stroke, coronary artery or	CV Composite
57	Major cardiovascular events (as above), all-cause death and hospitalized heart failure	CV Composite
60	Major vascular events (ie, major atherosclerotic events plus non-coronary, cardiac deaths and haemorrhagic strokes:	CV Composite
77	Major adverse cardiovascular events (Death, non-fatal myocardial infarction and stroke)	CV Composite
78	Death or hospitalisation from cardio- and cerebrovascular causes (CCV events included new occurrence or exacerbation	CV Composite
85	Symptom-driven coronary revascularization and death from cardiovascular cause	CV Composite
95	Fatal and non fatal CV events (MI, stroke, unstable angina, revasc)	CV Composite
98	Cardiovascular disease defined as a composite of the following outcomes: fatal and non-fatal myocardial infarction (MI),	CV Composite
155	Any CV event + CV death	CV Composite
155	Any CV event + death of any cause	CV Composite

156	MACE	CV Composite
156	Major adverse cardiovascular events: myocardial infarction, stroke, acute coronary syndrome,embolism, symptom-	CV Composite
167	The main outcome variable will be a combined end-point of cardiovascular death (including sudden death and cardiac	CV Composite
167	The main outcome variable will be a combined end-point of cardiovascular death (including sudden death and cardiac	CV Composite
171	All cause and cardiovascular mortality	CV Composite
174	The primary endpoint is composite of :1) cardiovascular death 2)sudden cardiac death 3)nonfatal myocardial infarction	CV Composite
182	Treatment-emergent events - combined incidence of death, myocardial infarction, stroke, hospitalizations, potassium	CV Composite
184	Cumulative incidence of the composite outcome "death, myocardial infarction, heart failure"	CV Composite
188	Composite outcome of all-cause mortality or major cardiovascular event rate	CV Composite
188	Rate for the composite outcome of all-cause mortality or hospitalization for ischemic stroke, myocardial infarction, or	CV Composite
192	Time to first occurrence of an event in the primary composite outcome composite of major cardiovascular events	CV Composite
192	|Time to first occurrence of an event in the secondary composite outcome major cardiovascular events (hospitalised	CV Composite
195	Time to first occurrence of adjudicated MACE	CV Composite
195	Time to the first occurrence of adjudicated major adverse cardiovascular event (MACE) (composite of all-cause	CV Composite
195	Time to first occurrence of adjudicated MACE or a hospitalization for heart failure (HF)	CV Composite
195	Time to first occurrence of adjudicated MACE or a thromboembolic event (vascular access thrombosis, deep vein	CV Composite
197	Cardiovascular event free survival time Cardiovascular event consisting of death due to cardiovascular diseases	CV Composite
198	Cardiovascular disease	CV Disease
12	Nonfatal cardiovascular disease (first event)	CV Disease Non Fatal
1	All cardiac events	CV Event
1	Combined cardiovascular events	CV Event
6	The time of survival without a major CV event (non fatal MI, acute coronary syndrome, hospitalization for heart failure,	CV Event
11	Composite cardiovascular events	CV Event
12	Cardio- and cerebrovascular events	CV Event
14	Cardiovascular event	CV Event
17	Cardiovascular events	CV Event
23	Cardiovascular events	CV Event
31	Cardiovascular event free survival	CV Event
38	Cardiovascular events (adv events)	CV Event
44	Major adverse cardiac events	CV Event
51	CVD	CV Event
53	Cardiovascular serious adverse events in each arm of treatment.	CV Event

54	Cardiovascular events	CV Event
68	Cardiovascular events	CV Event
71	The Occurrence of Cardiovascular Event	CV Event
76	Incidence of Composite Cardiovascular Events	CV Event
82	Cardio-cerebral event	CV Event
121	Cardiovascular/stroke	CV Event
146	Cardiovascular events	CV Event
165	Cardiovascular event rate: events per 1,000 access	CV Event
165	One cardiovascular event	CV Event
165	Cardiovascular event-free	CV Event
170	Rate of cardiovascular events	CV Event
171	Incidence of cardiovascular events	CV Event
172	Composite endpoints cardiovascular event	CV Event
173	Major CVD events	CV Event
12	Non fatal cardiovascular event	CV Event Non Fatal
51	Non-fatal non outcome CVD	CV Event Non Fatal
95	Non fatal CV event	CV Event Non Fatal
98	First cardiovascular event non fatal(myocardial infarction hospitalization for unstable angina heart failure or periph vasc	CV Event Non Fatal
24	Cardiovascular hospitalization (defined as hospitalization for ischemic heart disease, heart failure, arrhythmias, other	CV Hospitalisation
100	Cardiovascular disease hospitalisation	CV Hospitalisation
184	All-cause and cardiovascular hospitalization.	CV Hospitalisation
28	Cardiovascular morbidity	CV Morbidity

Table 3 Subgroup analysis: number of measures reported per trial by size of trial

		Number of measures		
No of Participants	No of trials	Median	IQR	Range
<=100	99	3	1.0-6.5	1-18
>100 to <=500	47	4	1.5-6.0	1-17
>500 to <=5000	19	5	1.5-10	1-23
>5000	2	6	6.0-6.0	6-6
Missing	7	1	1.0-6.0	1-6

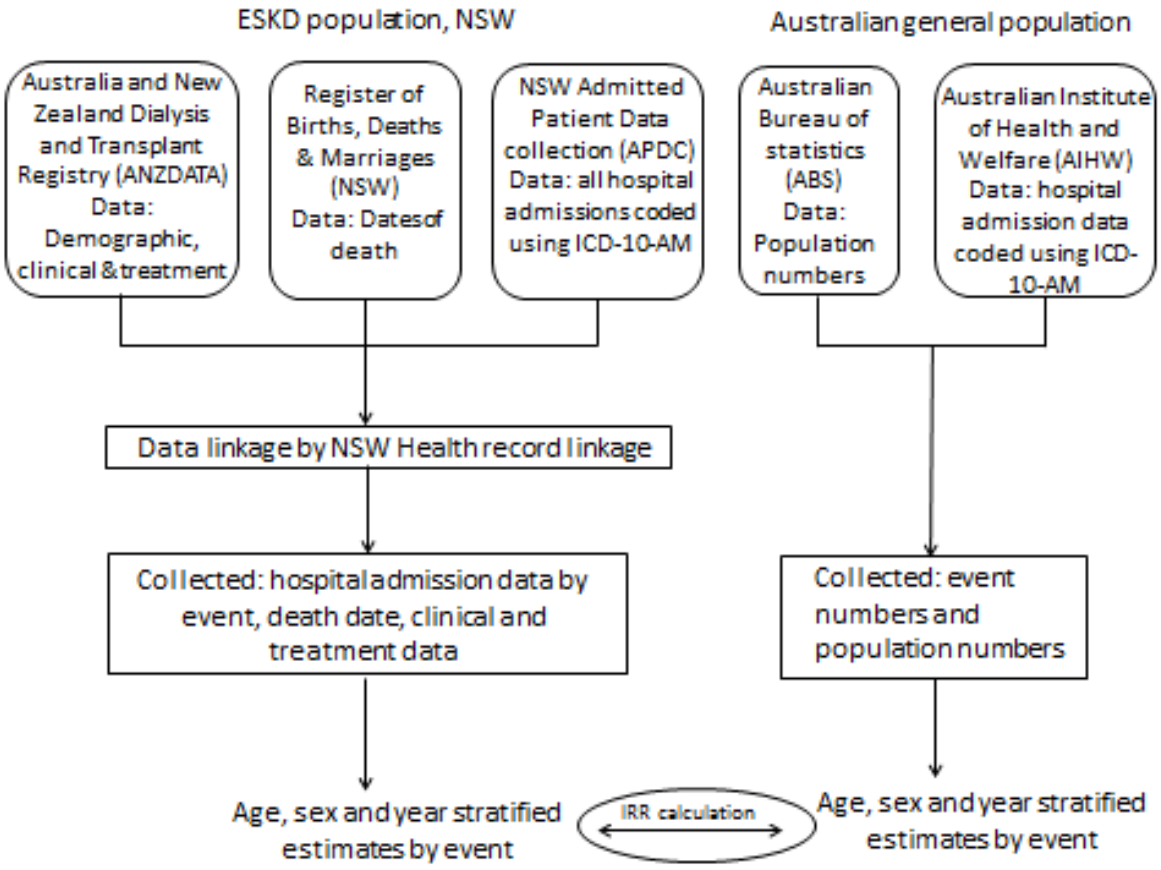
APPENDIX 2

SUPPLEMENTARY DATA FOR CHAPTER 5

Table 1 Composition of "Any IHD" category and frequency of each component

ICD Code	Diagnosis	n	%
I20	Angina	727	37·1
I21	Acute MI	759	38·7
I22	Subsequent MI	1	0·05
I23	Complications post acute MI	1	0·05
I24	Other acute IHD	10	0·51
I25	Chronic IHD	463	23·6
I20-I25	Any IHD	1961	100

Figure 1 Data linkage process



APPENDIX 3

SUPPLEMENTARY DATA FOR CHAPTER 6

Table 1 ICD Codes of interest*

ICD10	ICD 10 Class	ICD 10 Description	ICD9 Code	ICD 9 Description
Ischaemic heart disease				
I20	I20-I25 Ischaemic Heart Diseases	I20 Angina Pectoris	413	413 Angina Pectoris
I21	I20-I25 Ischaemic Heart Diseases	I21 Acute Myocardial Infarction	410	410 Acute Myocardial Infarction
I22	I20-I25 Ischaemic Heart Diseases	I22 Subsequent Myocardial Infarction		(Also 410)
I24	I20-I25 Ischaemic Heart Diseases	I24 Other Acute Ischaemic Heart Diseases	411	411 Other Acute & Subacute Forms Of Ihd
I25	I20-I25 Ischaemic Heart Diseases	I25 Chronic Ischaemic Heart Disease	414	414 Other Forms Of Chronic Ihd
Valve disease				
I34	I30-I52 Other Forms Of Heart Disease	I34 Nonrheumatic Mitral Valve Disorders	424	424 Other Diseases Of Endocardium
I35	I30-I52 Other Forms Of Heart Disease	I35 Nonrheumatic Aortic Valve Disorders		
I36	I30-I52 Other Forms Of Heart Disease	I36 Nonrheumatic Tricuspid Valve Disorders		
I37	I30-I52 Other Forms Of Heart Disease	I37 Nonrheumatic Pulmonary valve disorders		
Cardiomyopathy				
I42	I30-I52 Other Forms Of Heart Disease	I42 Cardiomyopathy	425	425 Cardiomyopathy
Arrhythmia				
I44	I30-I52 Other Forms Of Heart Disease	I44 Atrioventricular And Left Bundle-Branch Block	426	426 Conduction Disorders
I45	I30-I52 Other Forms Of Heart Disease	I45 Other Conduction Disorders		
I46	I30-I52 Other Forms Of Heart Disease	I46 Cardiac Arrest	427.5	(427.5 Cardiac Arrest)
I47	I30-I52 Other Forms Of Heart Disease	I47 Paroxysmal Tachycardia	427	427 Cardiac Dysrhythmias (Approximate)
I48	I30-I52 Other Forms Of Heart Disease	I48 Atrial Fibrillation And Flutter		(Also 427)
I49	I30-I52 Other Forms Of Heart Disease	I49 Other Cardiac Arrhythmias		(Also 427)
Heart Failure				
I50	I30-I52 Other Forms Of Heart Disease	I50 Heart Failure	428	428 Heart Failure

*https://www.who.int/classifications/icd/icdonlineversions/en/

Table 2 The top ten underlying causes of death (as grouped by the leading causes of death defined by the Australian Institute of Health and Welfare

Underlying cause of death		Frequency	Percent
1	Diabetes	2,140	27.66
2	Kidney failure	1,725	22.29
3	Hypertensive disease	266	3.44
4	Renal tubulo-interstitial disease	243	3.14
5	Glomerular disease	210	2.71
6	Septicaemia	208	2.69
7	Diseases of the musculoskeletal system and connective tissue	150	1.94
8	Other diseases of intestines excluding paralytic ileus and intestinal obstruction without hernia	142	1.84
9	Certain conditions originating in the perinatal period, congenital malformations, deformations and chromosomal abnormalities	141	1.82
10	Diseases of arteries, arterioles and capillaries excl. atherosclerosis, aortic aneurysm and dissection	131	1.69

APPENDIX 4

SUPPLEMENTARY DATA FOR CHAPTER 7

Table 1 Search Strategy

1. Cognition disorders/
2. Mild Cognitive Impairment/
3. Dementia/
4. exp Aphasia, Primary Progressive/
5. exp Dementia, Vascular/
6. Diffuse Neurofibrillary Tangles with Calcification/
7. exp Frontotemporal Lobar Degeneration/
8. (cognit* adj3 (impair* or disorder* or def*)).tw.
9. dement*.tw.
10. aphasi*.tw.
11. (fronto?temporal lob* or fronto?temporal dement*).tw.
12. diffuse neuro?fibrillary tangles with calcification.tw.
13. or/1-12
14. exp Renal Replacement Therapy/
15. h?emo?dialysis.tw.
16. h?emo?filtration.tw.
17. h?emo?diafiltration.tw.
18. dialysis.tw.
19. (CAPD or CCPD or APD).tw.
20. (kidney transplant* or renal transplant* or kidney graft* or renal graft*).tw.
21. Renal Insufficiency/
22. exp Renal Insufficiency, Chronic/
23. exp Kidney Diseases/
24. Uremia/
25. (kidney disease* or renal disease* or kidney failure or renal failure).tw.
26. (ESRF or ESKF or ESRD or ESKD).tw.
27. (CKF or CKD or CRF or CRD).tw.
28. (predialysis or pre-dialysis).tw.
29. ur?emi$.tw.
30. or/14-29
31. and/13,30
32. exp Neuropsychological Tests/
33. Language Tests/
34. mini mental state exam*.tw.
35. frontal assessment battery.tw.
36. (wechsler adj3 (intelligen* or memory)).tw.
37. (span adj2 (digit or spatial or symbol)).tw.
38. matrix reasoning.tw.
39. (clock drawing adj2 (test or task)).tw.
40. halstead reitan battery.tw.
41. trail making test.tw.
42. tactual performance test.tw.
43. block design test.tw.
44. letter number sequencing test.tw.
45. finger tapping test.tw.
46. (reitan adj4 (test or task or exam*)).tw.
47. token test.tw.
48. boston naming test.tw.
49. stroop test.tw.
50. (word adj2 (rec* or list or associat* or context) adj2 (test or task or exam*)).tw.
51. (picture adj2 (completion or recognition or presentation)).tw.
52. (fluency adj2 (verbal or design or animal or lexical) adj3 (test or task or exam*)).tw.
53. (memory adj3 (spatial or numeric or working) adj3 (test or task or exam*)).tw.
54. stockings of cambridge.tw.
55. rey osterrieth complex figure test.tw.
56. buschke selective reminding test.tw.
57. wisconsin card sorting test.tw.
58. progressive matri*.tw.
59. cognitive assessment screening.tw.
60. ((simple or choice) adj3 reaction adj3 (speed or time)).tw.
61. progressive matri*.tw.
62. hooper visual.tw.
63. "visual object and space perception battery".tw.
64. (neuropsychiatric adj (inventory or battery)).tw.
65. neuropsychological test*.tw.
66. (3MS or PASAT or WASI or WAIS).tw.

67. or/32-66
68. and/31,67
69. executive function/
70. memory/
71. language/
72. attention/
73. memory, long-term/
74. memory, short-term/
75. memory, episodic/
76. visual perception/
77. space perception/
78. psychomotor performance/
79. motor skills/
80. "task performance and analysis"/
81. global cognitive function*.tw.
82. executive function*.tw.
83. (memory adj3 (disorder* or function* or def*)).tw.
84. (language adj3 (function* or disorder* or def*)).tw.
85. ((attention or concentration) adj3 (def* or disorder* or function*)).tw.
86. ((visual or spatial or visualspatial or visuospatial) adj3 (function* or abilit* or awareness)).tw.
87. (mental adj3 (efficien* or automatation or fluency) adj3 (def* or disorder* or function*)).tw.
88. intelligence/
89. (intelligence adj3 (quotient or def* or abilit*)).tw.
90. ((motor or psychomotor) adj3 (abilit* or function* or def*)).tw.
91. or/69-90
92. and/30,91
93. or/31,68,92
94. remove duplicates from 93
95. limit 94 to humans
96. from 95 keep 1-1000
97. from 95 keep 1001-2000
98. from 95 keep 2001-2296

Table 2 Characteristics of studies meeting inclusion criteria, but without data that could contribute to meta-analysis

Author	Country	Total (n)	Study Design	% Men	Mean age (yrs) (SD/range)	Reason for not contributing
Brady 2009	USA	659	RCT	98.3	63.7(11.7)	Data for CKD and HD not presented separately
Groothoff 2002	Netherlands	162	Cohort	unknown	29.4(20.7-41.8)	Data for groups not presented separately
Kang 2012	America	169	Cross sectional	65.1	52.6(14.6)	Data for CKD and HD patients not presented separately
Morosanu 2011	Romania	92	Cross sectional	unknown	72.1(5.9)	Data presented not suitable for meta-analysis
Tryc 2011	Germany	101	Cross sectional	47.5	51.0(12.9)	Data presented not suitable for meta-analysis
Tiffin-Richards 2014	Germany	85	Cross sectional	52.9	58	Data presented not suitable for meta-analysis
Afsar 2014	Turkey	174	Cross sectional	45.4	52.2 (16.3)	Data for HD, CKD and gen pop not presented separately

Table 3: Subgroup analysis to explore heterogeneity and sensitivity analysis for the haemodialysis group compared to general population group.

		All studies	Post 1995 studies only	Pre 1995 studies only	Low risk of bias studies only	Only "healthy" controls
Orientation & attention	Studies	22	16	6	8	16
	Participants	1691	1379	312	684	1287
	SMD (95% CI)	-0.93 [-1.18, -0.68]	-0.81 [-1.04, -0.59]	-1.51 [-2.40, -0.61]	-0.90 [-1.25, -0.55]	-1.15 [-1.46, -0.84]
	I^2	86	80	94	84	87
Memory	Studies	16	12	3	6	10
	Participants	1394	1211	142	543	937
	SMD (95% CI)	-0.52 [-0.67, -0.36]	-0.58 [-0.72, -0.44]	-0.48 [-1.03, 0.07]	-0.64 [-0.83, -0.46]	-0.66 [-0.87, -0.45]
	I^2	56	35	75	32	54
Construction & motor	Studies	11	7	4	4	5
	Participants	988	843	145	320	572
	SMD (95% CI)	-0.54 [-0.84, -0.24]	-0.41 [-0.60, -0.22]	-0.90 [-1.94, 0.13]	-0.34 [-0.56, -0.12]	-0.71 [-1.43, 0.02]
	I^2	78	30	91	10	89
Executive function	Studies	10	9	1	4	6
	Participants	946	905	41	368	646
	SMD (95% CI)	-0.70 [-0.97, -0.44]	-0.79 [-1.02, -0.56]	0.34 [-0.32, 1.00]	-0.85 [-1.22, -0.49]	-0.86 [-1.24, -0.47]
	I^2	77	69	n/a	73	77
Concept & reasoning	Studies	6	4	2	2	3
	Participants	215	142	73	90	105
	SMD (95% CI)	-0.59 [-1.15, -0.03]	-0.84 [-1.65, -0.03]	-0.12 [-0.60, 0.36]	-1.03 [-1.65, -0.42]	-0.96 [-1.99, 0.06]

	I^2	77	84	0	46	82
Language	Studies	7	5	2	2	4
	Participants	815	742	73	252	705
	SMD (95% CI)	-0.30 [-0.59, -0.02]	-0.38 [-0.71, -0.04]	-0.02 [-0.50, 0.45]	-0.36 [-0.59, -0.12]	-0.49 [-0.82, -0.16]
	I^2	65	73	0	0	61
Perception	Studies	3	2	1	none	2
	Participants	94	62	32		62
	SMD (95% CI)	-0.43 [-1.79, 0.92]	-0.70 [-3.29, 1.89]	0.04 [-0.45, 0.54]		-0.70 [-3.29, 1.89]
	I^2	93	96	n/a		96
Global	Studies	18	16	2	6	14
	Participants	1145	1056	89	528	1005
	SMD (95% CI)	-0.70 [-0.95, -0.45]	-0.75 [-1.02, -0.49]	-0.27 [-0.69, 0.14]	-0.83 [-1.22, -0.43]	-0.82 [-1.08, -0.55]
	I^2	70	71	0	73	69

Table 4: Subgroup analysis to explore heterogeneity and sensitivity analysis for the haemodialysis group compared to the chronic kidney disease group.

		All studies	Post 1995 studies	Pre 1995 studies	Low risk of bias	Remove AKI
Orientation & attention	Studies	6	1	5	4	4
	Participants	509	57	452	390	347
	SMD (95% CI)	-0.12 [-0.70, 0.45]	0.11 [-0.38, 0.60]	-0.17 [-0.84, 0.51]	-0.07 [-0.87, 0.72]	-0.30 [-0.68, 0.07]
	I^2	92	n/a	94	95	71
Memory	Studies	5	1	4	2	4
	Participants	422	69	353	291	360
	SMD (95% CI)	-0.40 [-0.60, -0.21]	-0.55 [-1.07, -0.04]	-0.39 [-0.62, -0.16]	-0.35 [-0.64, -0.07]	-0.38 [-0.61, -0.16]
	I^2	20	n/a	35	50	34
Construction & motor	Studies	1	none		none	None
	Participants	70				
	SMD (95% CI)	0.17 [-1.06, 1.39]				
	I^2	n/a				
Executive function	Studies	1	none		1	1
	Participants	51			51	51
	SMD (95% CI)	-0.25 [-0.61, 0.11]			-0.25 [-0.61, 0.11]	-0.25 [-0.61, 0.11]
	I^2	n/a			n/a	n/a
Concept & reasoning	Studies	2	1	1	1	1
	Participants	70	25	45	45	45
	SMD (95% CI)	0.17 [-1.06, 1.39]	0.84 [-0.04, 1.71]	-0.42 [-1.02, 0.18]	-0.42 [-1.02, 0.18]	-0.42 [-1.02, 0.18]
	I^2	81	n/a	n/a	n/a	n/a
Global	Studies	4	none	4	3	3
	Participants	394		394	311	294
	SMD (95% CI)	0.23 [-0.77, 1.24]		0.23 [-0.77, 1.24]	0.09 [-1.24, 1.43]	-0.16 [-0.98, 0.65]
	I^2	95		95	97	90

Table 5: Subgroup analysis to explore heterogeneity and sensitivity analysis for the haemodialysis group compared to the peritoneal dialysis group.

		All	Post 1995 studies only	Pre 1995 studies only	Low risk of bias studies only
Orientation & attention	Studies	10	7	3	3
	Participants	992	882	110	363
	SMD (95% CI)	0.20 [-0.17, 0.56]	0.03 [-0.25, 0.32]	0.92 [-0.89, 2.73]	0.23 [-0.24, 0.69]
	I^2	87	75	95	80
Memory	Studies	7	6	1	3
	Participants	890	856	34	368
	SMD (95% CI)	-0.22 [-0.46, 0.01]	-0.21 [-0.48, 0.07]	-0.32 [-0.75, 0.11]	-0.23 [-0.57, 0.10]
	I^2	63	68	n/a	61
Construction & motor	Studies	4	3	1	1
	Participants	640	591	37	145
	SMD (95% CI)	0.55 [-1.01, 2.12]	0.69 [-1.27, 2.64]	0.14 [-0.51, 0.80]	-0.13 [-0.39, 0.12]
	I^2	98	99	n/a	n/a
Executive function	Studies	2	2	none	1
	Participants	529	529		140
	SMD (95% CI)	-0.98 [-1.91, -0.05]	-0.98 [-1.91, -0.05]		-0.47 [-1.03, 0.08]
	I^2	89	89		n/a
Concept & reasoning	Studies	1	1	none	none
	Participants	32	32		
	SMD (95% CI)	-0.40 [-1.30, 0.49]	-0.40 [-1.30, 0.49]		

	I^2	n/a	n/a		
Language	Studies	1	1	none	none
	Participants	389	389		
	SMD (95% CI)	-0.31 [-0.60, -0.01]	-0.31 [-0.60, -0.01]		
	I^2	n/a	n/a		
Perception	Studies	n/a	n/a		n/a
	Participants				
	SMD (95% CI)				
	I^2				
Global	Studies	8	7	1	2
	Participants	843	806	37	224
	SMD (95% CI)	-0.43 [-0.94, 0.09]	-0.52 [-1.08, 0.04]	0.20 [-0.45, 0.86]	-0.34 [-0.69, 0.00]
	I^2	86	87	n/a	0

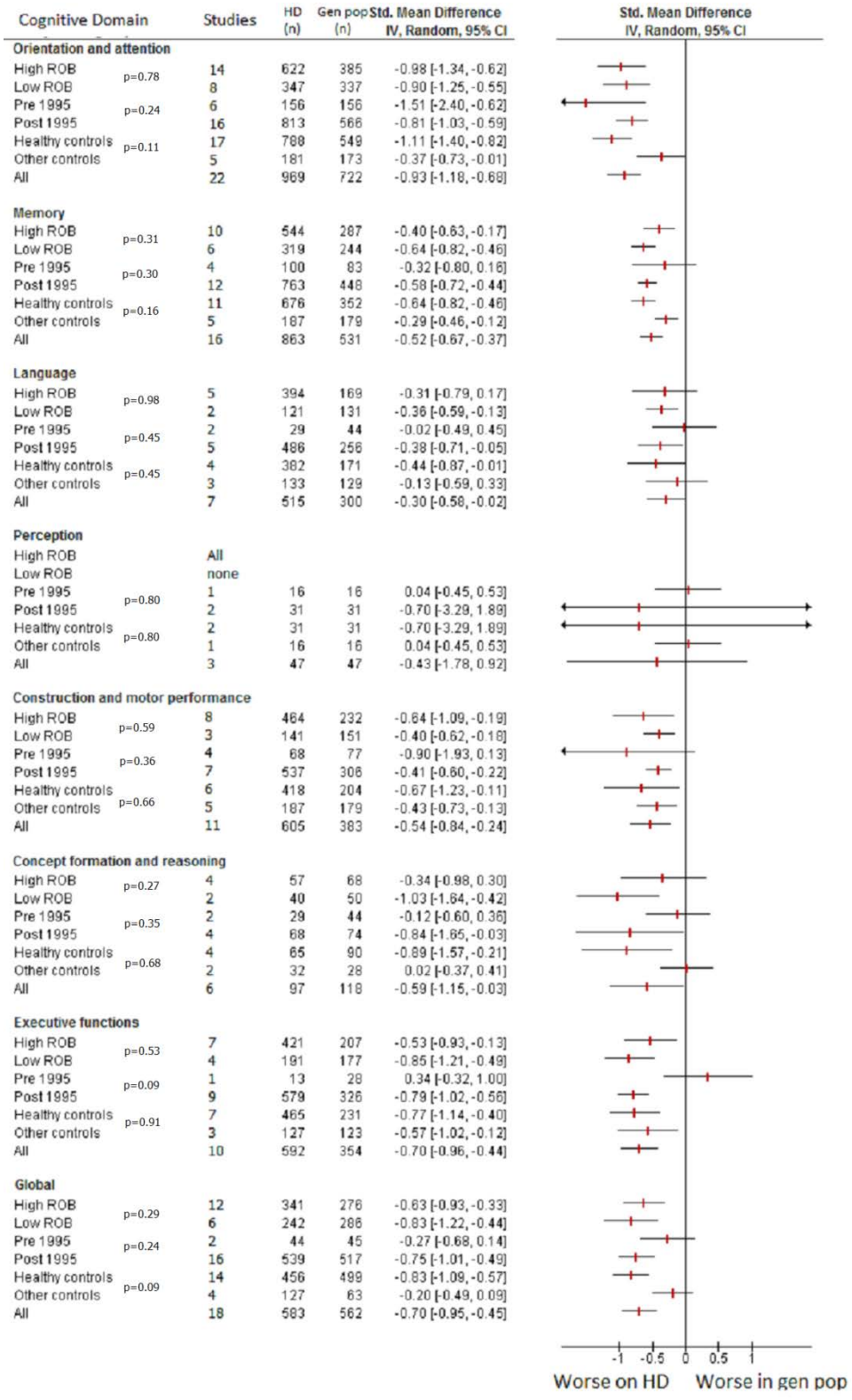
Table 6: Subgroup analysis to explore heterogeneity and sensitivity analysis for the haemodialysis group compared to the non-dialysed end stage kidney group.

		All	Post 1995 studies	Pre 1995 studies	Low risk of bias	Remove conservative
Orientation & attention	Studies	6	5	1	none	5
	Participants	201	171	30	0	159
	SMD (95% CI)	0.70 [0.45, 0.96]	0.60 [0.36, 0.84]	1.12 [0.57, 1.66]		0.77 [0.45, 1.10]
	I^2	23	0	n/a	none	29
Memory	Studies	6	5	1	none	4
	Participants	216	186	30		146
	SMD (95% CI)	0.36 [0.08, 0.63]	0.27 [0.04, 0.50]	0.43 [-0.25, 1.11]		0.41 [-0.06, 0.88]
	I^2	31	0	n/a		56
Construction & motor	Studies	4	4	none	none	2
	Participants	134	134			64
	SMD (95% CI)	0.18 [-0.10, 0.46]	0.18 [-0.10, 0.46]			0.24 [-0.15, 0.63]
	I^2	0	0			10
Executive function	Studies	1	1	none	none	none
	Participants					
	SMD (95% CI)	0.11 [-0.63, 0.85]	0.11 [-0.63, 0.85]			
	I^2	n/a	n/a			
Concept & reasoning	Studies	2	2	none	none	1
	Participants	60	60	0	0	32
	SMD (95% CI)	0.14 [-0.37, 0.65]	0.14 [-0.37, 0.65]			-0.02 [-0.72, 0.67]

	I^2	0	0			n/a
Language	Studies	2	2	none	none	1
	Participants	60	60			32
	SMD (95% CI)	-0.12 [-0.63, 0.39]	-0.12 [-0.63, 0.39]			-0.10 [-0.79, 0.59]
	I^2	0	0			n/a
Perception	Studies	1	1	none	none	1
	Participants	32	32			32
	SMD (95% CI)	0.14 [-0.35, 0.63]	0.14 [-0.35, 0.63]			0.14 [-0.35, 0.63]
	I^2	n/a	n/a			n/a
Global	Studies	2	1	1	none	2
	Participants	62	32	30		62
	SMD (95% CI)	0.79 [-0.79, 2.38]	0.02 [-0.53, 0.57]	1.64 [0.76, 2.52]		0.79 [-0.79, 2.38]
	I^2	89	n/a	n/a		89

Figure 1 Sources of heterogeneity.

P values for interaction are for high versus low risk of bias (ROB), pre and post 1995, controls classified as healthy and other (which included controls taken from other primary care clinics).



APPENDIX 5

PUBLISHED MANUSCRIPTS ARISING DURING THE COURSE OF MY PHD BUT NOT INCLUDED IN THE MAIN THESIS.

First author publications during the course of the PhD but not included in the thesis:

1. Barriers to the Professional Advancement of Women in Nephrology. O'Lone E, Webster AC. Clin J Am Soc Nephrol. 2019 Sep 6;14(9):1399-1401. PMID: 31350274
2. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. O'Lone EL, Hodson EM, Nistor I, Bolignano D, Webster AC, Craig JC. Cochrane Database Syst Rev. 2019 Feb 21;2 PMID: 30790278
3. In Reply to 'Abnormality in FGF-23-α-Klotho Axis: A Possible Mechanism Underlying Haemodialysis-Related Cognitive Dysfunction?' O'Lone E, Webster AC. Am J Kidney Dis. 2016 Nov;68(5):818.

Papers related to the SONG-HD Initiative and my involvement:

1. Identifying critically important vascular access outcomes for trials in haemodialysis: an international survey with patients, caregivers and health professionals. Viecelli AK, Howell M, Tong A, Teixeira-Pinto A, **O'Lone E**, Ju A, Craig JC, Hooi LS, Lee T, Lok CE, Polkinghorne KR, Quinn RR, Vachharajani TJ, Vanholder R, Zuo L, Tordoir J, Pecoits-Filho R, Yuo T, Kopperschmidt P, Smith R, Irish AB, Mori TA, Pascoe EM, Johnson DW, Hawley CM. Nephrol Dial Transplant. 2019 Aug 1. pii: gfz148. [Epub ahead of print] PMID: 31369099

   I was involved in the design of the survey and the revision of the manuscript.

2. Identifying dimensions of fatigue in haemodialysis important to patients, caregivers and health professionals: An international survey. Ju A, Unruh M, Davison SN, Dapueto J, Dew MA, Fluck R, Germain M, Jassal SV, Obrador G, O'Donoghue D, Howell M, **O'Lone E**, Shen JI, Craig JC, Tong A; SONG-HD Initiative. Nephrology (Carlton). 2019 Jul 25. [Epub ahead of print] PMID: 31347227

   I was involved in the design of the survey and the revision of the manuscript.

3. Implementing core outcomes in kidney disease: report of the Standardized Outcomes in Nephrology (SONG) implementation workshop. Tong A, Manns B, Wang AYM, Hemmelgarn B, Wheeler DC, Gill J, Tugwell P, Pecoits-Filho R, Crowe S, Harris T, Van Biesen W, Winkelmayer WC, Levin A, Thompson A, Perkovic V, Ju A, Gutman T, Bernier-Jean A, Viecelli AK, **O'Lone E**, Shen J, Josephson MA, Cho Y, Johnson DW, Sautenet B, Tonelli M, Craig JC; SONG Implementation Workshop Investigators. Kidney Int. 2018 Dec;94(6):1053-1068.

   I was involved in the design of the study, the workshop and in the revision of the manuscript.

4. Establishing a Core Outcome Measure for Fatigue in Patients on Haemodialysis: A Standardized Outcomes in Nephrology-Haemodialysis (SONG-HD) Consensus Workshop Report. Ju A, Unruh M, Davison S, Dapueto J, Dew MA, Fluck R, Germain M, Jassal SV, Obrador G, O'Donoghue D, Josephson MA, Craig JC, Viecelli A, **O'Lone E**, Hanson CS, Manns B, Sautenet B, Howell M, Reddy B, Wilkie C, Rutherford C, Tong A; SONG-HD Fatigue Workshop Collaborators. Am J Kidney Dis. 2018 Jul;72(1):104-112. PMID: 29551585

I was involved in the design of the study and the revision of the manuscript.

5. Clinicians' and researchers' perspectives on establishing and implementing core outcomes in haemodialysis: semistructured interview study. Tong A, Crowe S, Gill JS, Harris T, Hemmelgarn BR, Manns B, Pecoits-Filho R, Tugwell P, van Biesen W, Wang AYM, Wheeler DC, Winkelmayer WC, Gutman T, Ju A, **O'Lone E**, Sautenet B, Viecelli A, Craig JC. BMJ Open. 2018 Apr 20;8(4):e021198. PMID: 29678992

I was involved in the design of the study and the revision of the manuscript.

6. Vascular Access Outcomes Reported in Maintenance Haemodialysis Trials: A Systematic Review. Viecelli AK, O'Lone E, Sautenet B, Craig JC, Tong A, Chemla E, Hooi LS, Lee T, Lok C, Polkinghorne KR, Quinn RR, Vachharajani T, Vanholder R, Zuo L, Irish AB, Mori TA, Pascoe EM, Johnson DW, Hawley CM. Am J Kidney Dis. 2018 Mar;71(3):382-391. PMID: 29203125

I was involved in the design of the study, the data collection, data analysis and revision of manuscript.

7. Nephrologists' Perspectives on Defining and Applying Patient-Centered Outcomes in Haemodialysis. Tong A, Winkelmayer WC, Wheeler DC, van Biesen W, Tugwell P, Manns B, Hemmelgarn B, Harris T, Crowe S, Ju A, O'Lone E, Evangelidis N, Craig JC; SONG-HD Initiative. Clin J Am Soc Nephrol. 2017 Mar 7;12(3):454-466. PMID: 28223290

I was involved in the design of the study and the revision of the manuscript.