Adaptive Clinical Trials of Sodium Lowering in Chronic Kidney Disease and Dialysis: Analytic and Methodologic Challenges

Presented by:

Conor Stephen Judge

BMBS BEng MRCPI

To:

College of Medicine,

National University of Ireland, Galway

in fulfilment of the requirements for the degree of

Doctor of Philosophy.

Supervised by:

Martin O'Donnell and Martin O'Halloran

September 1st 2021

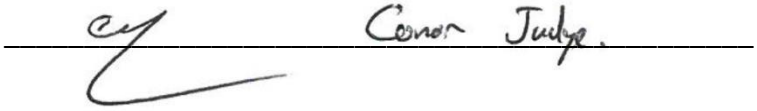
Contents

Declaration of Originality

I, the Candidate, Conor Stephen Judge, certify that the thesis entitled “Adaptive Clinical Trials of Sodium Lowering in Chronic Kidney Disease and Dialysis: Analytic and Methodologic Challenges":

- is all my own work
- has not been previously submitted for any degree or qualification at this University or any other institution
- and where any work in this thesis was conducted in collaboration, appropriate reference to published work by my collaborators has been made and the nature and extent of my contribution has been clearly stated.

Name:



Conor Stephen Judge

Abstract

The incidence and prevalence of kidney failure requiring dialysis is rising. Patients receiving dialysis are at increased cardiovascular risk, compared to the general population. Hypertension due to sodium and volume excess plays a key role in the underlying mechanism. Adaptive clinical trials in dialysis are urgently needed to investigate sodium lowering techniques in dialysis. In this thesis, I investigated: 1. The current use of adaptive design methods in dialysis trials, 2. Dietary sodium lowering on blood pressure outcomes and renal outcomes in a chronic kidney disease (CKD) and non-CKD population in two phase IIb randomised clinical trials (STICK and COSIP), 3. The association of dietary sodium intake and stroke in an international case control study and whether the association is modified by CKD (INTERSTROKE), 4. The association of reducing or stopping antihypertensive medications in a phase III randomised clinical trial and how this is modified by CKD (SPRINT), 5. The association of run-in periods in cardiovascular prevention trials and treatment estimates of efficacy, and, using these collective information, developed: 6. A protocol for a phase IIb, dose-finding, randomised crossover, exploratory response adaptive randomised intervention, double-blinded, multi-centre, controlled trial investigating dialysate sodium lowering in a kidney failure requiring dialysis population.

Acknowledgements

A special thanks goes to my amazing wife Suzanne, my two daughters Susanna and Emeline, and my parents Padraic and Antoinette for their patience, and support before, during, and now after my PhD. Your sacrifice has not gone unnoticed, and I will make it up to you.

I would like to thank Martin and Martin for being stellar supervisors. Charlie Mackesy summarised the PhD supervisor's role very succinctly: "Sometimes I think you believe in me more than I do", said the boy. "You'll catch up", said the horse. Thank you both for believing in me, supporting me, and for giving me the opportunity to work with two fantastic research groups. These groups included, Dr Maria Costello, Dr Robert Murphy, Dr Christine McCarthy, Dr Catriona Reddin, Dr Elaine Loughlin, Prof Andrew Smyth, Dr Eoghan Dunne, Dr Barry McDermott, Dr Marggie Jones, Dr Laura Farina, Dr John Ferguson, Dr Alberto Alvarez-Iglesias, and Dr Michelle Canavan. Throughout the PhD journey they have given me support both technically and personally, which I hope I have reciprocated in some way.

Thank you to the nephrology department in Galway University hospital especially Prof Donal Reddan, Prof David Lappin, Prof Matthew Griffin, Prof Andrew Smyth and Dr Sarah Cormican for supporting me both clinically and academically. Also thank you to Dr Paul O'Hara for always screening my crazy ideas and our friendship since our first days in medical school.

Finally, I would like to thank the Irish Clinical Academic Training Programme supported by the Wellcome Trust and Health Research Board Ireland especially the executive director Dr Conall Dennedy, the programme manager Dr Karen Misstear and all the other ICAT fellows.

List of Figures

List of Tables

Acronyms

AKI	Acute Kidney Injury
AHEI	Alternative Healthy Eating Index
ABPM	Ambulatory Blood Pressure Monitoring
BP	Blood Pressure
BUN	Blood Urea Nitrogen
BMI	Body Mass Index
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRIC	Chronic Renal Insufficiency Cohort Study
COSIP	Clarifying Optimal Sodium Intake in Populations
CT	Computed Tomography
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CNN	Convolutional Neural Networks
eGFR	Estimated Glomerular Filtration Rate
ECW	Extracellular Water
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GSD	Group Sequential Design
HR	Hazard Ratio
KDIGO	Kidney Disease: Improving Global Outcomes
ICW	Intracellular Water
ICH	Intracerebral Haemorrhage
ICC	Intra-class Correlation Coefficient
KRT	Kidney Replacement Therapy
MRI	Magnetic Resonance Imaging
MAMS	Multi-Arm Multi-Stage
NCDS	National Cooperative Dialysis Study
OR	Odds Ratio
PICO	Population, Intervention, Comparison, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines
PREVEND	Prevention of Renal and Vascular End stage Disease
PROSPERO	Prospective Register of Systematic Reviews
PURE	Prospective Urban and Rural Epidemiological
RESOLVE	Randomised Evaluation of Sodium Dialysate Levels on Vascular Events
RCT	Randomised Clinical Trial
RRR	Ratio of Relative Risk
RR	Relative Risk
RIS	Research Information Systems
STICK	Sodium InTake In Chronic Kidney Disease
SoLID	Sodium Lowering in Dialysate
SVM	Support Vector Machines
TOHP-II	The Trials of Hypertension Prevention, Phase II
TBW	Total Body Water
TONE	Trials of Nonpharmacologic Intervention in the Elderly
WHO	World Health Organisation

Chapter 1 Introduction

1.1 Burden of Chronic Kidney Disease and Kidney Failure Requiring Dialysis

In 2017, the Global Burden of Disease recorded 697.5 million cases of all-stage Chronic Kidney Disease (CKD) in the world, giving a global prevalence of 9.1% (1). The two main causes of CKD are diabetes and hypertension. In the last 30 years, the prevalence of CKD has increased by 29.3% and mortality due to CKD has increased by 43.1% (2). CKD is currently the 12th leading cause of death globally. Kidney failure, formerly known as end-stage kidney disease, is the final stage of chronic kidney disease (3). Data from a global survey reports a median prevalence of 759 per million population for kidney failure requiring dialysis (4); this figure includes 2,292 people living with kidney failure requiring dialysis in Ireland (5). The main treatments for kidney failure are kidney transplant and dialysis. Dialysis comes in two main forms: haemodialysis and peritoneal dialysis. Haemodialysis is removal of waste products from the blood stream through diffusion of molecules across a semipermeable membrane along an electrochemical concentration gradient (6). Peritoneal dialysis is removal of waste products by exposing blood vessels in the abdomen to a solution (dialysate) and allowing waste molecules to move down the concentration gradient into the solution and removed though a tube inserted into the abdomen (7).

Patients with CKD and patients receiving dialysis are at increased cardiovascular risk, with mortality due to cardiovascular disease 20 times higher in patients receiving dialysis compared to the general population (8). This increased mortality is due to both cardiovascular and non-cardiovascular causes (9), with hypertension playing a controversial role in the underlying mechanism (10), displaying a U-shaped association with mortality (11). The most prominent cause of hypertension in dialysis is sodium and volume excess (12). Non-pharmacological interventions such as lowering dietary sodium and lowering dialysate sodium are potential strategies for reducing hypertension but might not be feasible (12,13). There are two parallel topics in this thesis. The clinical focus of this PhD thesis is sodium modification in chronic kidney disease and kidney failure requiring haemodialysis, hereafter referred to as dialysis. Several chapters in this thesis focus on patients with CKD but lessons learned and insights gained can equally be applied to patients

with kidney failure requiring dialysis. The methodological focus is adaptive clinical trials in kidney failure requiring dialysis.

1.2 Importance of Efficient Dialysis

In this section, the factors that affect dialysis efficiency are introduced, including clearance, hypertension, volume, and their relationship with each other.

1.2.1 Clearance

The benefit of a higher dialysis dose on morbidity was established by the National Cooperative Dialysis Study (NCDS), where the lower blood urea nitrogen (BUN) arm had reduced hospital admissions compared to the higher BUN arm (14). Kt/V is the clearance (K) per time (t) of a molecule divided by the volume of distribution (V). For urea, the volume of distribution is equal to the total body water. “Single-pool Kt/V” refers to a simplified one compartment model that urea is removed from during dialysis. The HEMO study did not show a benefit on mortality for high dose (single-pool Kt/V 1.71+/-0.11) compared to standard dose (single-pool Kt/V 1.32+/-0.09), with an Odds Ratio of 0.96 (95% CI, 0.84 to 1.10) for mortality. Many guidelines agencies recommend a target single pool Kt/V of 1.4 with minimum delivered spKt/V of 1.2 (15).

1.2.2 Hypertension

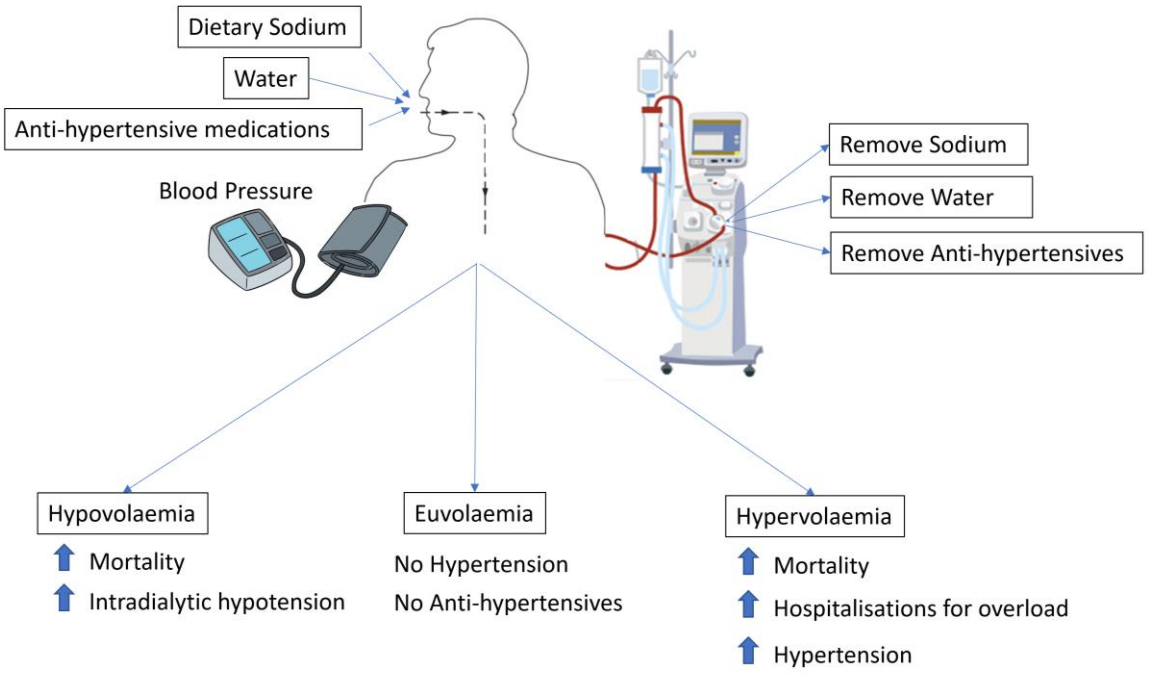
Hypertension is common in dialysis patients with some studies reporting prevalence of over 80% in patients on dialysis (16). Elevated blood pressure measured outside the dialysis unit is associated with increased mortality (17). Blood Pressure measured with 44-hour interdialytic Ambulatory Blood Pressure Monitoring (ABPM) is an independent predictor of cardiovascular death in dialysis patients (18). Excess sodium and volume are potent drivers of hypertension in dialysis and reduction in dietary sodium; reduction in dialysate sodium and gradual dry-weight reduction are key non-pharmaceutical interventions widely recommended (12,13).

1.2.3 Volume

There is no gold-standard measurement of volume excess in dialysis patients (19). In clinical practice, the aim is to optimise the patient’s dry weight. Dry weight is sometimes defined as “the lowest tolerated post-dialysis weight achieved with minimal signs or symptoms of

hypo- or hypervolemia" (20). The dry weight is the sweet spot, where there are no or minimal symptoms of intradialytic hypotension during dialysis and the patient is normotensive in the interdialytic period. A prospective cohort of 39,566 haemodialysis patients in the Fresenius Medical Care network, who had volume status measured using whole-body bioimpedance spectroscopy, found that 46% of patients were fluid overloaded (above the upper limit of normal range) (21). In both unadjusted (hazard ratio [HR], 1.62; 95% confidence interval, 1.54 to 1.70) and adjusted (HR, 1.26; 95% CI, 1.19 to 1.33) survival analysis, the overhydrated group compared to the non-overhydrated group, had an excess risk for all-cause mortality (21). There is a complex interplay between sodium intake, water intake, ultrafiltration, diffusion and antihypertensives with volume status and hypertension (Figure 1-1).

Figure 1-1 Relationship of Sodium, Water, and Dialysis with Hypertension and Volume Status



1.3 Importance of Safe Dialysis

In this section, the factors that affect dialysis safety are introduced, including intradialytic hypotension.

1.3.1 Intradialytic Hypotension

There are many complications of dialysis (22). An important blood pressure-related complication of dialysis is intradialytic hypotension, of which there are many definitions (Table 1-1).

Table 1-1 Definitions of Intradialytic Hypotension

Definition or Guideline (Year)	**Intradialytic hypotension definition**
Nadir 90	Minimum intradialytic systolic BP<90 mmHg
Nadir 100	Minimum intradialytic systolic BP<100 mmHg
Fall 20	(Pre-HD systolic BP − minimum intradialytic systolic BP) ≥20 mmHg
Fall 30	(Pre-HD systolic BP − minimum intradialytic systolic BP) ≥30 mmHg
Fall 20, Nadir 90	(Pre-HD systolic BP − minimum intradialytic systolic BP) ≥20 mmHg and minimum intradialytic systolic BP<90 mmHg
Fall 30, Nadir 90	(Pre-HD systolic BP − minimum intradialytic systolic BP) ≥30 mmHg and minimum intradialytic systolic BP<90 mmHg
K/DOQI Clinical Practice Guidelines (2002) (23)	A decrease in systolic BP ≥20 mmHg or a decrease in MAP ≥10 mmHg associated with symptoms that include abdominal discomfort; yawning; sighing; nausea; vomiting; muscle cramps; restlessness; dizziness or fainting; and anxiety
European Best Practice Guidelines (2007) (24)	A decrease in systolic BP ≥20 mmHg or a decrease in MAP ≥10 mmHg associated with clinical events and need for nursing interventions
UK Renal Association Guidelines (2019) (25)	An acute symptomatic fall in systolic BP during dialysis requiring immediate intervention to prevent syncope
Japanese Society for Dialysis Therapy Guidelines (2012) (26)	Symptomatic sudden drop systolic BP ≥30 mmHg during dialysis or a decrease in the mean BP by ≥10 mmHg

A post-hoc analysis of the HEMO trial evaluated the association of several different definitions of intradialytic hypotension and mortality (27). An absolute nadir systolic blood pressure <90 mmHg was most strongly associated with mortality (OR 1.56, 95% CI, 1.05-2.31) (27). Intradialytic hypotension is also extremely distressing for a patient with increased morbidity including symptoms of nausea, vomiting, pre-syncope and syncope (28). Intradialytic hypotension is caused by an inadequate cardiovascular response to the reduction in blood volume that occurs when water is removed by ultrafiltration over a short period of time. Many strategies have been employed to reduce intradialytic hypotension including increasing dialysate sodium concentration (>140 mmol/L). This is an effective

strategy for reducing intradialytic hypotension but also causes increased thirst, increased fluid gain between dialysis and an increase in interdialytic hypertension (28). Of note, there has never been a trial of increased dietary sodium intake for prevention of intradialytic hypotension.

1.4 Patient Reported outcomes in CKD and kidney failure requiring dialysis

Patients with CKD and kidney failure requiring dialysis have a large burden of morbidity. Health-related Quality of Life (HRQOL) measured using patient-reported outcome measures (PROMs) has increasingly been used in clinical trials studying kidney disease and can easily be delivered during dialysis treatments. A recent Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference recommended that PROMs be incorporated into clinical trials and that they are essential for patient-centred kidney care (29).

1.5 Uncertainty about Peri-Dialysis Sodium Environment

In this section, the uncertainty in guidelines related to sodium in dialysis are discussed, including guidelines for dietary sodium restriction, dialysate sodium concentration, and antihypertensive medication use in dialysis.

1.5.1 Guidelines for Dietary Sodium Restriction

KDOQI Clinical Practice Guideline for Haemodialysis Adequacy gives a 1B recommendation to reducing dietary sodium intake in patients on dialysis: “We recommend both reducing dietary sodium intake as well as adequate sodium/water removal with haemodialysis to manage hypertension, hypervolemia, and left ventricular hypertrophy. (1B)” (15). The guideline authors comment that there is a paucity of randomised controlled trials for both dietary sodium intake and individualised dialysis sodium prescription. This recommendation is based on a low number of small uncontrolled studies (n=8-27) (30,31). In one study, eight hypertensive haemodialysis patients had gradual lowering of dialysate sodium from 140 mmol/L to 135 mmol/L at a rate of 1 mmol/L every 3-4 weeks combined with a moderate dietary restriction of <6g NaCl per day through a no added salt diet and avoidance of canned and salty food. There was a trend for lower blood pressure (systolic BP 147±9.3 vs 136±17 mmHg) and four out of the eight patients completely stopped antihypertensive medications. There was also a slight increase in muscle cramps during haemodialysis (30).

1.5.2 Guidelines for Dialysate Sodium Concentration

The UK Renal Association's 2019 clinical practice guidelines on haemodialysis state that "there is insufficient consistency in the literature for a clear recommendation on concentration of dialysate sodium" (25). Observational studies have shown a positive association between lower dialysate sodium and lower blood pressure, lower interdialytic weight gain and lower antihypertensive medication use (32). However, the Sodium Lowering in Dialysate (SoLID) study conducted in New Zealand, randomised participants to dialysate sodium of 135 mmol/L compared to 140 mmol/L. There was no difference in their primary outcome of left ventricular mass index (g/m^2) at 12 months (Difference: −3.94 g/m^2, 95% CI, −10.52 to 2.63) despite differences in interdialytic weight gain (Difference: −0.57 kg, 95% CI, −0.86 to −0.27) and B-type natriuretic peptide ratio of intervention to control (0.49, 95% CI, 0.27 to 0.90) at 12 months. There was no difference in dialysis thirst index at 12 months (Difference: 0.70, 95% CI, −2.15 to 4.68) or Kidney Disease Quality of Life (KDQOL) at 12 months (Difference: 1.77, 95% CI, −1.66 to 5.20). Participants randomised to 135 mmol/L of sodium had increased intradialytic hypotension at 6 months but not at 12 months (OR, 7.5; 95% CI, 1.1 to 49.8 at 6 months and OR, 3.6; 95% CI, 0.5 to 28.8 at 12 months) (33). Potential explanations for lower dialysate sodium not resulting in a reduction in LV mass are: 1) The degree of LV hypertrophy in patient on home or self-care dialysis was insufficient to show an effect from the intervention, and 2) longer follow-up is needed to show a significant effect of lower dialysate sodium on LV mass. A related study is the Randomised Evaluation of Sodium Dialysate Levels on Vascular Events (RESOLVE) trial. RESOLVE is a pragmatic, cluster-randomised, open-label trial designed to evaluate, in real-world conditions, the comparative effectiveness of two fixed dialysate sodium concentrations (137 mmol/L versus 140 mmol/L). The primary outcome measure of the RESOLVE trial is a composite of major cardiovascular events (hospitalised acute myocardial infarction, hospitalised stroke) and all-cause death. RESOLVE has an estimated enrolment of 51,520 participants and an estimated completion date of December 2023 (34). RESOLVE and SoLID are evaluating fixed dialysate sodium concentrations rather than patient specific flexible dialysate sodium concentrations based on the patient's serum sodium concentration, which may have stronger physiologic rationale (32).

1.5.3 Guidelines for Antihypertensive Medications in Dialysis

Antihypertensive medications are often withheld on the day of dialysis to reduce the risk of intradialytic adverse advents such as intradialytic hypotension (35). This practice is often undocumented and therefore difficult to study in large administrative dialysis databases. There is also insufficient evidence to provide strong recommendations about blood pressure targets in dialysis patients, especially during the peri-dialysis period (36). For example, the KDOQI 2015 Guideline Update removed the previous blood pressure targets of pre-dialysis BP < 140/90 mmHg and post-dialysis blood pressure < 130/80 mmHg and have not given a target for pre-dialysis blood pressure, post-dialysis blood pressure or ambulatory blood pressure for haemodialysis patients, citing a paucity of clinical trial data (15).

1.6 Opportunity to Advance Methodology/Design of Trials in Dialysis

Large amounts of data are collected on a very frequent basis from individuals with kidney failure requiring dialysis (37). These data offer an opportunity to conduct pragmatic randomised clinical trials at low cost (38). The International Society of Nephrology CKD roadmap describes an action plan for optimising the design of trials in CKD. It states that nephrology lags behind other medical specialities in terms of number, size and quality of clinical trials (39). Two recommendations from the roadmap were increased use of adaptive design methods and run-in periods in nephrology clinical trials. This recommendation was echoed in the KDIGO controversies conference: Challenges in conducting clinical trials in nephrology, which stated that “run-in periods may be particularly beneficial in trials of dialysis patients, a complex group for which maintaining adherence to generally well-tolerated medications can be difficult” (40).

1.6.1 Measurement Issues (Sodium Intake)

Multiple 24-hour urine collections are the reference standard for estimation of dietary intake of sodium in individuals with normal kidney function (41). Individuals with kidney failure requiring dialysis are often anuric (no urine output) or oliguric (reduced urine output), and therefore 24-hour urine collection is not suitable for estimating dietary sodium intake. Food frequency questionnaires have been used to estimate dietary sodium intake in haemodialysis patients and are associated with higher extracellular water (ECW) to intracellular water (ICW) ratios pre-dialysis, as measured by bioimpedance. However, they

have not been shown to be associated with mean arterial blood pressure or interdialytic weight gain (42).

1.7 Overall Objective

Given the increasing prevalence of kidney failure and the high proportion of hypertension and volume overload in patients with kidney failure requiring dialysis, there is a need to identify the optimal peri-dialytic sodium, volume, and blood pressure environment that is associated with lowest morbidity and mortality. Sodium lowering, either through dietary sodium lowering or dialysate sodium lowering, is a potential intervention to reduce hypervolemia, hypertension and potentially, the mortality and morbidity associated with these conditions. Feasibility of a dietary sodium lowering intervention, the association of abrupt antihypertensive discontinuation and association of sodium intake and stroke will be examined in CKD populations.

1.7.1 Specific Objectives

1. To explore the current utility of adaptive design methods and trends in use in dialysis randomised clinical trials, by performing a systematic review of adaptive design methods in dialysis trials (Chapter 2).
2. To determine if a dietary counselling intervention (versus control) to lower sodium intake would be effective in hemodialysis patients by first examining the effect on renal and 24-hour ambulatory blood pressure outcomes over 2 years follow-up, in two phase IIb, randomised controlled trials of patients with CKD (STICK trial), and without CKD (COSIP trial) (Chapter 3).
3. To determine if low sodium intake has increased risk for hemodialysis patients by first examining whether CKD modifies the association of sodium intake and stroke risk, in a large international epidemiologic study (INTERSTROKE) (Chapter 4).
4. To determine whether stopping antihypertensive therapy is safe in hemodialysis patients by first examining the association with increased cardiovascular risk in a non-dialysis population, and whether CKD modifies this association in an observational analysis of the SPRINT trial (Chapter 5).
5. To determine whether use of a run-in period in cardiovascular prevention clinical trials is associated with biased treatment estimates of efficacy (versus clinical trials

not using a run-in period), employing a nested case-control meta-analysis (Chapter 6).

6. To develop a protocol for a randomised controlled trial (RCT), based on the results of the previous objectives, to evaluate the effect of lowering sodium in patients with kidney failure requiring dialysis (Chapter 7).

1.8 Journal Publications

The work presented in this thesis has resulted in six peer-reviewed publications and three conference presentations, with two as senior author.

1. **Judge C**, Murphy RP, Cormican S, Smyth A, O'Halloran M, O'Donnell M. Adaptive design methods in dialysis clinical trials: a systematic review protocol. BMJ open. 2020 Aug 1;10(8):e036755. http://dx.doi.org/10.1136/bmjopen-2019-036755
2. **Judge C**, Murphy R, Reddin C, Cormican S, Smyth A, O'Halloran M, O'Donnell MJ. Trends in Adaptive Design Methods in Dialysis Clinical Trials: A Systematic Review. Kidney Medicine. 2021 Aug 20. https://doi.org/10.1016/j.xkme.2021.08.001
3. Murphy R, McGrath E, Nolan A, Smyth A, Canavan M, O'Donnell M, **Judge C**. The impact of a run-in period on treatment effects in cardiovascular prevention randomised control trials: A protocol for a comprehensive review and meta-analysis. HRB Open Research. 2020 Nov 11;3(82):82. https://doi.org/10.12688/hrbopenres.13122.1
4. Murphy R, O'Donnell MJ, Nolan A, McGrath E, O'Conghaile A, Ferguson J, Alvarez-Iglesias A, Costello M, Loughlin E, Reddin C, Ruttledge S, Gorey S, Hughes D, Smyth A, Canavan M, **Judge C**. The Effect of a Run-In Period on Estimated Treatment Effects in Cardiovascular Randomized Clinical Trials: A Meta-analytic Review (Article in press with the Journal of the American Heart Association, August 2021)
5. **Conor Judge**, Martin J O'Donnell, Graeme J Hankey, Sumathy Rangarajan, Siu Lim Chin, Purnima Rao-Melacini, John Ferguson, Andrew Smyth, Denis Xavier, Liu Lisheng, Hongye Zhang, Patricio Lopez-Jaramillo, Albertino Damasceno, Peter Langhorne, Annika Rosengren, Antonio L Dans, Ahmed Elsayed, Alvaro Avezum, Charles Mondo, Danuta Ryglewicz, Anna Czlonkowska, Nana Pogosova, Christian Weimar, Rafael Diaz, Khalid Yusoff, Afzalhussein Yusufali, Aytekin Oguz, Xingyu Wang, Fernando Lanas, Okechukwu S Ogah, Adesola Ogunniyi, Helle K Iversen, German Malaga, Zvonko Rumboldt, Shahram Oveisgharan, Fawaz Al Hussain, Salim Yusuf, on behalf of the INTERSTROKE investigators, Urinary Sodium and Potassium, and Risk of Ischaemic and Haemorrhagic Stroke (INTERSTROKE): A Case–Control Study, American Journal of Hypertension, Volume 34, Issue 4, April 2021, Pages 414–425, https://doi.org/10.1093/ajh/hpaa176

6. **Judge, Conor**; Narula, Sukrit; Mente, Andrew; Smyth, Andrew; Yusuf, Salim; O'Donnell, Martin J. Measuring sodium intake, Journal of Hypertension: August 20, 2021 - Volume - Issue - https://doi.org/10.1097/HJH.0000000000002951

1.9 Conference Publications

Judge, Conor S., Alvarez-Iglesias, Alberto, Ferguson, John P., Costello, Maria, Smyth, Andrew, O'Donnell, Martin. Did Non-Standard Withdrawal of Antihypertensive Agents Exaggerate Treatment Effect in SPRINT? Kidney week, American Society of Nephrology. November 03, 2017, Morial Convention Center, New Orleans.

Conor S. Judge, Andrew Smyth, Martin O'Donnell. Renal Impairment Modifies the Association Between Sodium Intake and Risk of Stroke – An Analysis of INTERSTROKE. Kidney Week, American Society of Nephrology. October 25, 2018, San Diego Convention Center.

Conor Judge, Robert Murphy, Catriona Reddin, Sarah Cormican, Andrew Smyth, Martin O'Halloran, Martin O'Donnell, ADAPTIVE DESIGN METHODS IN DIALYSIS CLINICAL TRIALS – A SYSTEMATIC REVIEW, Nephrology Dialysis Transplantation, Volume 36, Issue Supplement_1, May 2021, gfab098.0032

1.10 Other Related Publications During PhD

7. Loughlin, E. A., **Judge, C**. S., Gorey, S. E., Costello, M. M., Murphy, R. P., Waters, R. F., Hughes, D. S., Kenny, R. A., O'Donnell, M. J., & Canavan, M. D. (2020). Increased Salt Intake for Orthostatic Intolerance Syndromes: A Systematic Review and Meta-Analysis. The American journal of medicine, 133(12), 1471–1478.e4. https://doi.org/10.1016/j.amjmed.2020.05.028
8. **Judge, C**.,* Hughes, D.,* Murphy, R., Loughlin, E., Costello, M., Whiteley, W., Bosch, J., O'Donnell, M. J., & Canavan, M. (2020). Association of Blood Pressure Lowering With Incident Dementia or Cognitive Impairment: A Systematic Review and Meta-analysis. JAMA, 323(19), 1934–1944. https://doi.org/10.1001/jama.2020.4249 (*Joint First)
9. **Judge, C**., O'Donnell, M. (2021). Low sodium intake increases plasma renin activity. EClinicalMedicine, 33, 100803. https://doi.org/10.1016/j.eclinm.2021.100803

Chapter 2 Trends in adaptive design methods in dialysis clinical trials – a systematic review

Conor Judge, Robert Murphy, Catriona Reddin, Sarah Cormican, Andrew Smyth, Martin O'Halloran, Martin O'Donnell, Adaptive Design Methods in Dialysis Clinical Trials – A Systematic Review, Nephrology Dialysis Transplantation, Volume 36, Issue Supplement_1, May 2021, gfab098.0032 (Conference Poster)

Judge C, Murphy RP, Cormican S, Smyth A, O'Halloran M, O'Donnell M. Adaptive design methods in dialysis clinical trials: a systematic review protocol. BMJ open. 2020 Aug 1;10(8):e036755.

Judge C, Murphy R, Reddin C, Cormican S, Smyth A, O'Halloran M, O'Donnell MJ. Trends in Adaptive Design Methods in Dialysis Clinical Trials: A Systematic Review. Kidney Medicine. 2021 Aug 20.

2.1 Introduction

2.1.1 Background

Randomised clinical trials are the gold standard for evaluating efficacy, futility or harm of new therapies (43). Compared to similar medical specialties, nephrology has traditionally had a low number of randomised clinical trials, particularly evident for patients with kidney failure requiring dialysis (44). The comparatively low number of trials in nephrology is postulated to be due to difficulty in recruitment, previous history of underpowered trials in nephrology and a lack of funding (40,45). Although the number of trials are increasing, nephrology continues to lag behind other specialities such as cardiology, haematology, oncology and gastroenterology (46,47).

Adaptive clinical trials use interim data analyses to modify the trial design or duration in a predefined way (48), without undermining the integrity or validity of the trial, thereby preserving the type I error (false positive) rate. The most common type of adaptive design is the Group Sequential Design (GSD), where planned interim analyses permit stopping of trials for efficacy or futility. Other designs include sample size re-estimation, multi-arm multi-stage trials, adaptive randomisation, biomarker adaptive and seamless phase II/III trials (49) (Table 2-1).

Table 2-1 Adaptive Design Descriptions

Adaptive Design	Description of adaptive design
Seamless phase II/III design	A design that combines a traditional phase II with a phase III trial. Referred to as the "learning" phase and "confirmatory" phase. This design can reduce sample size and time to market for a positive treatment.
Sample-size re-estimation design	A design that allows for sample-size adjustment or re-estimation based on the results of interim analyses. Particularly useful if there is uncertainty about the treatment effect and variability, and where inaccurate estimates could lead to overpowered or underpowered trials.
Group sequential design	A design that allows a trial to stop early based on the results of interim analysis. GSD is the most common type of adaptive design. GSD can take three forms: early efficacy stopping, early futility stopping and early efficacy or futility stopping design.
Multi-arm multi-stage (MAMS)	A multistage design with several treatment arms. At interim analysis, inferior treatment arms are dropped based on prespecified criteria. Ultimately, the best arms and the control group are retained. Some examples are pick-the-winners or drop-the-loser designs.
Biomarker-adaptive design	A design that allows for adaptations using information obtained from biomarkers. Often used in drug trials to target very selective populations for whom the drug is likely to work well. The biomarker response at interim analysis can be used to determine the target population.
Adaptive dose-escalation design	A design where the dose level used to treat the next patient is based on the toxicity of the previous patients and escalation rules.

Adaptive clinical trials appear particularly suitable for the evaluation of novel interventions in dialysis, by reducing resource requirements, decreasing time to study completion and increasing the likelihood of study success i.e. power to answer the hypothesis (50). Previous trials in dialysis have relied on observational data to inform trial design, including assumptions of expected effect size and variance (51), rather than estimates from early phase clinical trials. If these assumptions are incorrect, trials may be underpowered with an insufficient sample size to answer the underlying research question (51). Adaptive sample size re-estimation is a potential solution, as commonly used in cardiology trials (52), such as planned blinded sample size re-estimation, which identifies inaccurate assumptions, thereby triggering altered recruitment targets mid-trial to ensure adequate power.

Adaptive design may also be relevant to the evaluation of more established interventions. For example, 4D trial (53) reported that atorvastatin 20mg per day did not reduce cardiovascular events in kidney failure requiring dialysis despite evidence of a 20-30% reduction in other populations (54). This trial included a single dose of statin; it is hypothesised that alternative or multiple doses may have been more beneficial in a dialysis population given the significantly altered pharmacokinetics and pharmacodynamics (51,55). An adaptive multi-arm multi-stage (MAMS) trial design may have been more appropriate with one interim analysis at the end of stage I to identify an optimum dose to take forward into stage II. For example, the Telmisartan and Insulin Resistance in HIV (TAILoR) trial used a MAMS design with one interim analysis to identify the most appropriate dose among three telmisartan doses (20, 40 and 80mg daily). All three doses were tested in stage I and telmisartan 80mg was taken forward into stage II (56).

This systematic review aims to: (i) summarise the use of adaptive design methodology in randomised clinical trials in dialysis populations and populations at risk of requiring dialysis; (ii) describe the characteristics of the trials that use adaptive designs including dialysis modality, funding, and geographical location; (iii) describe the characteristics of adaptive trial designs in dialysis trials; (iv) estimate the percentage of adaptive clinical trials in dialysis among all dialysis RCTs; and (v) outline temporal trends in all the above.

2.2 Methods

We performed a systematic review, reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) (57). The protocol was registered with PROSPERO (CRD42020163946) and published separately (58). There were no age or English language restrictions. After testing our pre-defined search strategy (58), we found a small number (n=16) of dialysis RCTs that reported an adaptive design method. We discovered that the adaptive design methods are often not reported in the title and abstract of papers and would not be detected in a traditional systematic search. To overcome this, we developed a novel "full text systematic review" protocol and to our knowledge, this is the first use of this methodology.

2.2.1 Search Method for the Identification of Trials

2.2.1.1 Electronic Search – Dialysis Studies

We performed an electronic search of MEDLINE (PubMed) and clinicaltrials.gov from database inception until 01 June 2020. Zotero was used as our reference manager. The dialysis search terms were adapted from Beaubien-Souligny et al. 2019 (59) and included dialysis, peritoneal dialysis, haemodialysis, haemodiafiltration, hemodiafiltration, hemofiltration, haemofiltration, extracorporeal blood cleansing, haemodialysis, renal dialysis, renal replacement, end stage kidney, end stage renal, stage 5 kidney and stage 5 renal (Table 2-2). The output was stored in the Research Information Systems (RIS) file format for PubMed and XML files for clinicaltrials.gov.

Table 2-2 Search Strategy for Medline (PubMed) and Clinicaltrials.gov

dialysis[tiab] OR peritoneal dialysis[tiab] OR hemodialysis[tiab] OR hemodiafiltration[tiab] OR hemodiafiltration[tiab] OR hemofiltration[tiab] OR Hemofiltration[tiab] OR extracorporeal blood cleansing[tiab] OR haemodialysis[tiab] OR renal Dialysis[mh] OR renal replacement[tiab] OR end stage kidney[tiab] OR end stage renal[tiab] OR stage 5 kidney[tiab] OR stage 5 renal[tiab]

2.2.3.1 *Machine Learning Classifier – Randomised Clinical Trials*

We used the high sensitivity machine learning classifier (RobotSearch) to identify RCTs from the PubMed dialysis search output (60). RobotSearch is a machine learning classification algorithm combining an ensemble of Support Vector Machines (SVM) and Convolutional Neural Networks (CNN) with a reported Area Under the Curve of 0.987 (95% CI, 0.984 to 0.989) for RCT classification. RobotSearch was trained and optimised on titles and abstracts of the Cochrane Crowd RCT set (60). We adjusted the parameters of RobotSearch to perform a sensitive search to increase the proportion of RCTs that are correctly identified (60). Studies classified as likely to be randomised clinical trials were sourced for the full text systematic review.

2.2.3.2 *Full Text Systematic Review – Adaptive Design Methods*

We used Recoll for Windows to perform a full text systematic review on our dialysis randomised clinical trial search results from PubMed and clinicaltrials.gov. Recoll is based on the Xapian search engine library and provides a powerful text extraction layer and a graphical interface. The adaptive design search terms were adapted from Bothwell et al., 2018 (61) and included phase II/III, treatment switching, biomarker adaptive, biomarker adaptive design, biomarker adjusted, adaptive hypothesis, adaptive dose-finding, pick-the-winner, drop-the-loser, sample size re-estimation, re-estimations, adaptive randomization, group sequential, adaptive seamless, adaptive design, interim monitoring, Bayesian adaptive, flexible design, adaptive trial, play-the-winner, adaptive method, adaptive AND dose AND adjusting, response adaptive, adaptive allocation, adaptive signature design, treatment adaptive, covariate adaptive and sample size adjustment (Table 2-3).

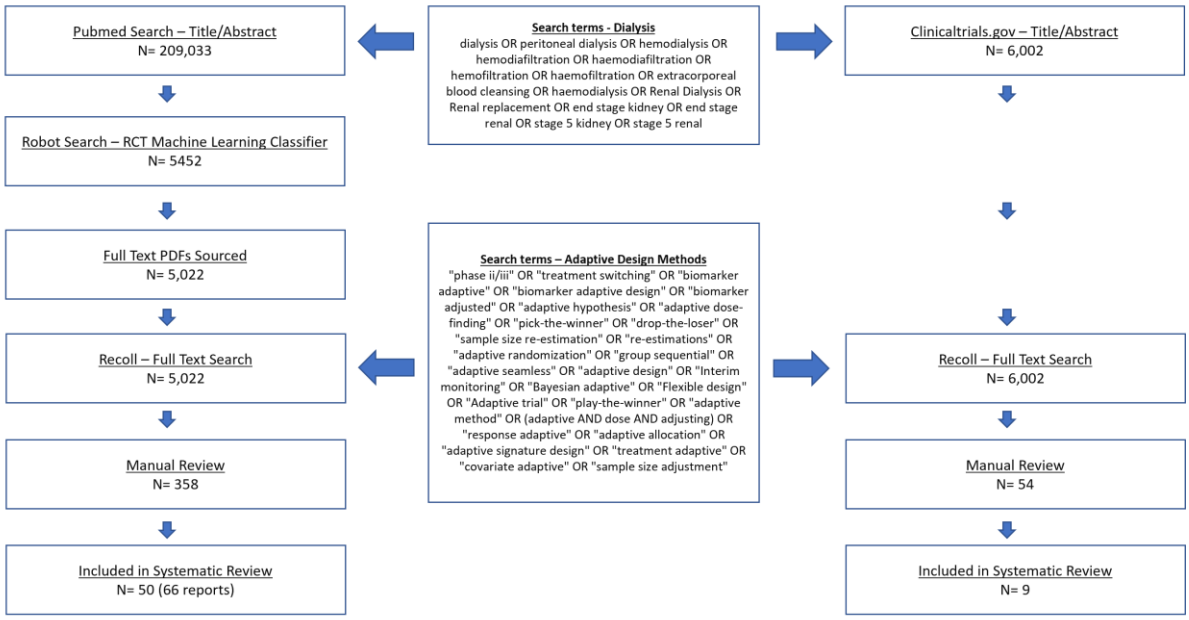
Table 2-3 Search Strategy for Recoll (Full Text Search)

phase ii/iii[tiab] OR treatment switching[tiab] OR biomarker adaptive[tiab] OR biomarker adaptive design[tiab] OR biomarker adjusted[tiab] OR adaptive hypothesis[tiab] OR adaptive dose-finding[tiab] OR pick-the winner[tiab] OR drop-the-loser[tiab] OR sample size re-estimation[tiab] OR re-estimations[tiab] OR adaptive randomization[tiab] OR group sequential[tiab] OR adaptive seamless[tiab] OR adaptive design[tiab] OR Interim monitoring[tiab] OR Bayesian adaptive[tiab] OR Flexible design[tiab] OR Adaptive trial[tiab] OR play-the-winner[tiab] OR adaptive method[tiab] OR (adaptive[All Fields] AND dose[All Fields] AND adjusting[All Fields]) OR response adaptive[All Fields] OR adaptive allocation[All Fields] OR adaptive signature design[tiab] OR treatment adaptive[tiab] OR covariate adaptive[tiab] OR sample size adjustment[tiab].

2.2.3.3 *Manual Full Text Review*

We then performed manual full text review to confirm studies that were included in the final systematic review. This process is summarised in a PRISMA flowchart (Figure 2-1). Full text review was performed by CJ, RM and CR. Disagreements were resolved by consensus and where a resolution was not reached by discussion, a consensus was reached through a third reviewer (MOD).

Figure 2-1 PRISMA Flow Diagram



2.2.4 Inclusion/Exclusion Criteria for the Selection of Studies

2.2.4.1 *Type of Study Design and Participants*

Randomised clinical trials of interventions in patients with kidney failure requiring dialysis, acute kidney injury undergoing kidney replacement therapy (KRT) including haemodialysis, peritoneal dialysis, haemodiafiltration and haemofiltration were included. We did not limit our population to any specific disease. Additionally, we included studies that included dialysis as either a primary or secondary outcome.

2.2.4.2 *Type of Intervention and Outcome*

We did not place a restriction on the intervention type and included trials that studied medications during dialysis, medical devices, dialysis parameters and dialysis modality. A dialysis parameter is any specification of the dialysis treatment that can be changed at each

session e.g., duration, ultrafiltration rate, and sodium profiling. We included all outcomes including surrogate markers, patient-centred outcomes, and hard clinical outcomes.

2.2.5 Selection and Analysis of Trials

CJ, RM and CR extracted the study characteristics independently and in parallel. Data collected included the type of the adaptive design, stopping rule, impact of adaptive design (i.e., stopping for futility or efficacy, sample size changes, etc.), trial population, intervention, dialysis modality, the country of the lead investigator and the funder of the study (adapted from Hatfield et al., 2016 (62))(Table 2-4).

Table 2-4 Characteristics of the Trials

Study Characteristic	**Categories**	**Description**
Nature of adaptive design	GSD/SSR/DS/DE/Seamless/Interim Analysis	The type of adaptive design used in the trial.
Stopping rule	Futility/Efficacy/Two sided/ N/A	If a stopping rule was used, what the nature of the stopping rule was.
Year of study completion	None	The year of study completion.
Population under study	None	A description of the population studied e.g., patients with diabetes.
Chronicity of KRT	Acute Kidney Injury (AKI) / Kidney failure requiring dialysis	A category for the chronicity of Kidney Replacement Therapy (KRT), either Acute Kidney Injury (AKI) or kidney failure requiring dialysis.
Intervention	None	A free text description of the intervention.
Nature of the intervention	Medication/Medical Device/Dialysis Parameter	A category for the nature of the intervention.
Primary outcome	None	A description of the primary outcome of the trial.
Type of primary outcome	Continuous or dichotomous	A categorial variable for the type of primary outcome variable.
Nature of primary outcome	Surrogate, patient-centred or hard clinical	A categorial variable for the nature of primary outcome variable- either surrogate, patient-centred or hard clinical.
Dialysis modality	Haemodialysis, peritoneal dialysis, haemodiafiltration or haemofiltration	A categorial variable for the dialysis modality.
Sample size of study	None	The number of participants in the study.
The country of the lead investigator	None	The country of the lead investigator.
The funder of the study	Public/Private	A categorial variable for source of funding for the study.
Study phase	Phase II/Phase III/Combined Phase II/III	A categorial variable for study phase.

2.3.1 Assessment of the Quality of the Studies: Risk Of Bias

We used the Cochrane Risk-of-Bias 2 Tool (63) to assess the methodological quality of eligible trials including random sequence generation, allocation concealment, blinding of participants and health care personnel, blinded outcome assessment, completeness of outcome data, evidence of selective reporting and other biases. Risk of bias assessments were performed independently (CJ, RM, CR, SC), and disagreements were resolved by consensus. If one or more domains were rated as high, the study was considered at high risk of bias. We summarised our findings in a risk-of-bias table using the Revised Cochrane risk-of-bias tool for randomised trials (64) (Table 2-5).

Table 2-5 Risk-of-Bias Assessment

Trial Name	Author	Intervention	Comparison	Randomisation	Deviations from intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
FENO HSR (65)	Bove et al	Fenoldopam infusion	Placebo (saline)	Low	Low	Low	Low	Low	Low
DAC (66)	Dember et al	Clopidogrel	Placebo	Low	Low	Low	Low	Low	Low
FAVOURED (67,68)	Irish et al, Viecelli et al	Fish Oil Supplementation and Aspirin Use	Placebo	Low	Low	Low	Low	Low	Low
Kwiatkowski et al (69)	Kwiatkowski et al	Peritoneal Dialysis	Furosemide	Low	Low	Low	Low	Low	Low
IVOIRE (70)	Joannes-Boyau et al	High-volume Haemofiltration	Standard-volume Haemofiltration	Some concerns	Some concerns	Low	Low	Low	Some concerns
CULPRIT-SHOCK (71,72)	Thiele et al	Culprit-lesion-only PCI	Immediate multivessel PCI	Low	High	Low	Low	Low	High
COACT (73,74)	Lemkes et al	Immediate coronary angiography	Delayed coronary angiography	Low	High	Low	Low	Low	High
LEVO-CTS (75,76)	Mehta et al	Levosimendan	Placebo	Low	Low	Low	Low	Low	Low
FRESH (77)	Douglas et al	Fluid Response Evaluation	Usual Care	Low	High	High	Low	Low	High
ATN (78,79)	Sharma et al	Intensive RRT	Less Intensive RRT	Low	High	Low	Low	Some concerns	High
IDPN-Trial (80)	Marsen et al	Intradialytic parenteral nutrition	Standardised nutritional counselling	Low	Low	Low	Low	High	High
Chapman et al (81)	Chapman et al	Topical Recombinant Human Thrombin	Bovine Thrombin	Low	Low	Low	Low	Some concerns	Some concerns
Ejaz et al (82)	Ejaz et al	Nesiritide	Placebo	Low	Some concerns	Low	Low	Some concerns	Some concerns
Hemodiafe (83)	Vinsonneau	Continuous venovenous haemodiafiltration	Intermittent Haemodialysis	Low	High	Low	Low	Some concerns	High
ACCORD (84)	Ismail-Beigi et al	Intensive glycaemic therapy with a target HbA1c of <6.0%	Standard therapy with a target of 7-7.9%	Low	Low	Low	Low	Low	Low
HONEYPOT (85,86)	Johnson et al	Antibacterial honey	Standard exit-site care	Low	High	Low	Some concerns	Low	High
Acker et al (87)	Acker et al	Thyroxine	Placebo	Some concerns	Low	Low	Low	Some concerns	Some concerns
Besarab et al (88)	Besarab et al	Normal Hematocrit Values	Low Hematocrit Values	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
DAC (89)	Dixon et al	Dipyridamole plus aspirin	Placebo	Low	Low	Low	Low	Low	Low
HALT-PKD (90)	Torres et al	Angiotensin Blockade	Placebo	Low	Low	Low	Low	Low	High

AKIKI (91,92)	Gaudry et al, Weisbord et al	Early phase RRT	Delayed phase RRT	Low	Low	Low	Low	Low	Low
PRESERVE (93)	Weisbord et al	Sodium bicarbonate	Normal saline and acetylcysteine	Low	Low	Low	Low	Low	Low
CREDENCE (94)	Perkovic et al	Canagliflozin	Placebo	Low	Low	Low	Low	Low	Low
DECLARE "TIMI 58 (95)	Wiviott et al	Dapagliflozin	Placebo	Low	Low	Low	Low	Low	Low
KALM-1 (96)	Fishbane	Difelikefalin	Placebo	Low	Low	Low	Low	Low	Low
Knoll et al (97,98)	Knoll et al	Ramipril	Placebo	Some concerns	Low	Low	Low	Low	Some concerns
Schanz et al (99)	Schanz et al	Renal consult	Usual care	Low	Low	Low	Low	Low	Low
CHART (100,101)	Kammerer et al	Hydroxyethyl starch	5% albumin	Low	Some concerns	Some concerns	Low	Low	Some concerns
STOP-AKI (102,103)	Pickkers et al, Peters et al	Recombinant alkaline phosphatase 0.4mg/kg	Recombinant alkaline phosphatase 1.6mg/kg or placebo	Low	Low	Low	Low	Low	Low
RICH (104,105)	Zarbock et al, Meersch et al	Regional citrate anticoagulation	Systemic heparin	Low	Some concerns	Low	Low	Low	Some concerns
CONTRAST (106,107)	Grooteman et al, The contrast group et al	Online haemodiafiltration	Low flux Haemofiltration	Low	Low	Low	Low	Low	Low
ELAIN-Trial (108,109)	Zarbock et al	Early RRT	Delayed RRT	Some concerns	Low	Low	Low	Low	Some concerns
SCD (110)	Tumlin et al	Selective cytopheretic device and CVVHD	CVVHD	Low	Low	High	Low	Low	High
Kratochwill et al (111)	Kratochwill et al	Alagn	Glucose based peritoneal dialysis fluid	Low	Low	Low	Low	Low	Low
Himmelfarb et al (112)	Himmelfarb et al	THR 184	Placebo	Some concerns	Low	Low	Low	Low	Some concerns
OPPORTUNITY (113,114)	Kopple et al	Recombinant hGH	Placebo	Some concerns	Low	Low	Low	Low	Some concerns
PREDICT (115,116)	Hayashi et al, Imai et al	High-hemoglobin	Low-hemoglobin	Low	Low	Low	High	Low	High
Riley et al (117)	Riley et al.	Continue CPD	Discontinue CPD	Some concerns	Low	Low	Some concerns	Low	Some concerns
AURORA (118,119)	Fellström et al	Rosuvastatin	Placebo	Some concerns	Low	Low	Low	Low	Some concerns
HEROICS (120)	Combes et al	Early high-volume Haemofiltration	Standard care	Some concerns	Low	Low	Low	Low	Low

2.5.1 Data Synthesis

A descriptive synthesis of the data was performed. We reported overall outcomes and outcomes by (i) frequency and type of adaptive design; (ii) adaptive designs as a proportion of studies classified as dialysis RCTs by RobotSearch (iii) Population, Intervention and Outcome including dialysis modality (haemodialysis, peritoneal dialysis, haemodiafiltration and haemofiltration); (iv) publication in high impact journals; (v) geographic location and funding; (vi) reporting of adaptive design methods in title and abstract; and (vii) a risk-of-bias assessment.

2.6 Results

The systematic search of articles on MEDLINE (PubMed) with dialysis keywords published before 01 June 2020, identified 209,033 results. 5,452 articles were classified as probable RCTs by the machine learning classifier RobotSearch (15). Full text articles were sourced (n=5,022) and we performed a full text systematic review using adaptive design keywords which identified 358 studies for manual screening. 50 studies, available as 66 articles, were included after full text review (Figure 2-1). The systematic search of clinicaltrials.gov with dialysis keywords published before 01 June 2020, identified 6,002 registered studies. A systematic search of clinicaltrials.gov summary files using adaptive design keywords identified 54 studies for full review and 9 studies were included. In total, 57 studies, available as 68 articles and 7 clinicaltrials.gov summaries, were included in the final analysis. 31 studies were conducted in dialysis populations and 26 studies included dialysis as a primary or secondary outcome.

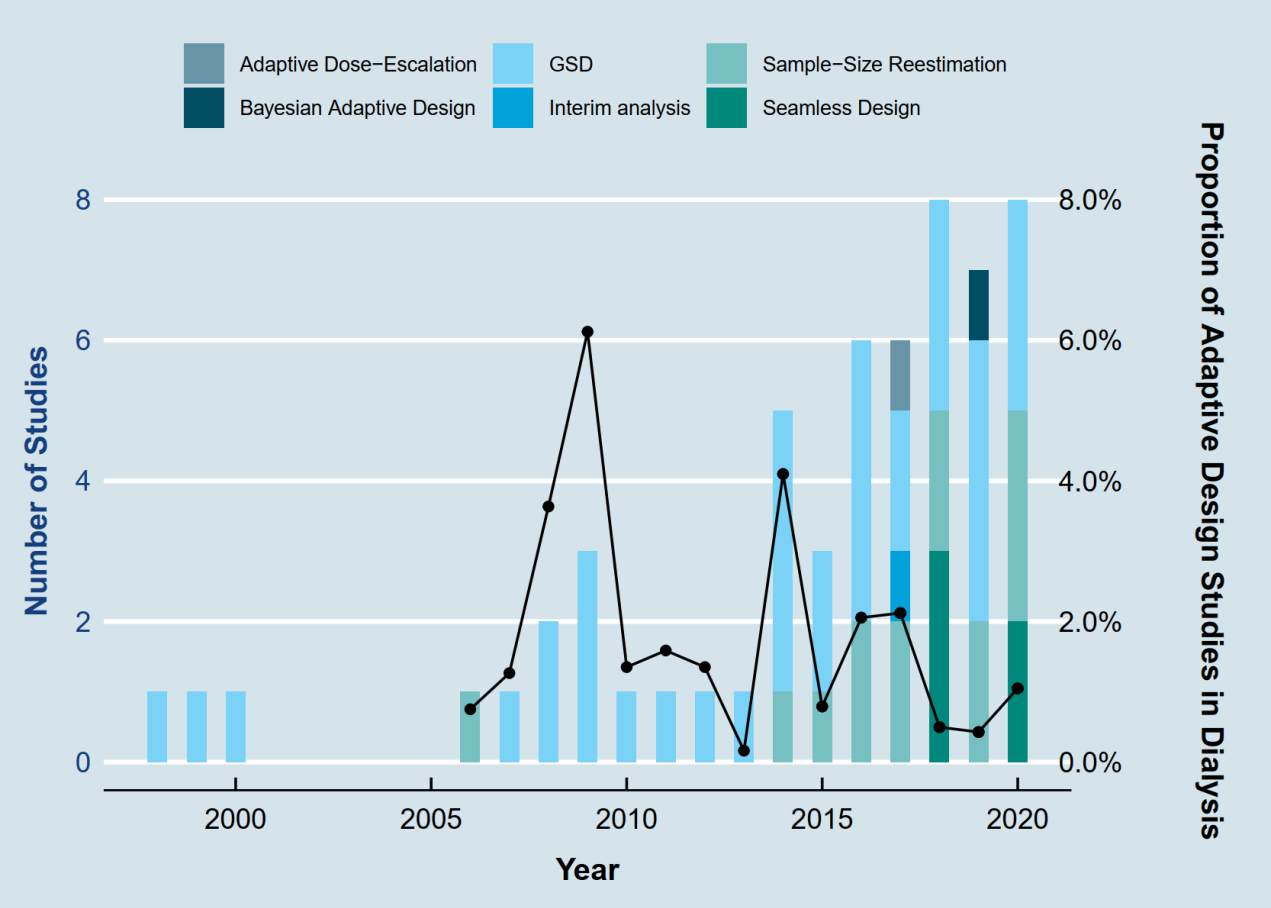
2.6.1 Study Characteristics

2.6.1.1 Frequency and Type of Adaptive Design

Figure 2-2 reports the number of adaptive designs by year and alongside the proportion of all dialysis RCTs that used adaptive design methods. The absolute amount of dialysis trials using adaptive designs has increased each year, but this has not matched the overall increase in dialysis trials and resulted in a relative decrease over time in the use of adaptive design methods in dialysis trials ranging from 6.12% in 2009 to 0.43% in 2019 with a mean of 1.82%. A one-way ANOVA was conducted to determine if the proportion of adaptive trials was different by year. Adaptive trials proportion was statistically significantly different between years, $F(17) = 3.391$, $p < 0.001$. Tukey post hoc analysis revealed statistically

significant differences between years 2009 and 2013 [-5.96 (-10.73 to -1.19), P=0.002], 2015 [-5.33 (-10.21 to -0.45), P=0.016], 2018 [-5.62 (-10.29 to -0.96), P=0.003], 2019 [-5.7 (-10.36 to -1.04), P=0.003], 2020 [-5.07 (-9.81 to -0.34), P=0.021]; and between years 2014 and 2018 [-3.6 (-6.62 to -0.58), P=0.004], 2019 [-3.67 (-6.69 to -0.65), P=0.003].

Figure 2-2 Adaptive Designs in Dialysis Randomised Clinical Trials by Year



Group sequential designs were the most common type of adaptive design method used, 35 (61.4%) trials (22 (71%) in dialysis populations and 13 (50%) in dialysis outcome trials) (Table 2-6). The O'Brien-Fleming stopping boundary was the most common stopping rule, used in 9 trials (25.7%), followed by Lan DeMets used in 8 trials (22.9%). 29 trials (50.9%) were impacted by the use of group sequential adaptive design including 7 trials (41.2%) that stopped early for futility, 3 trials (17.6%) that stopped early for efficacy and 4 trials (23.5%) that stopped early for safety.

Table 2-6 Groups Sequential Trials in Dialysis Randomised Clinical Trials

	Study Name, Year	Stopping Rule	Impact of Adaptive design	Population	Intervention	Primary Outcome	Nature of primary outcome	Dialysis Modality	Sample Size of Study	Country of lead investigator	Funder	Funder Details	Study Phase
Acute Kidney Injury													
	Acker et al., 2000, (87)	Pocock	Significant difference in mortality was observed at first analysis and trial was terminated.	Patients with acute renal failure.	Thyroxine	Medication	Percentage requiring dialysis.	Haemodialysis/haemodiafiltration	59	United States of America	Not reported	Not reported	Phase III
	ATN, 2008, (79,79)	Haybittle-Peto rule	Two interim analyses performed as planned, trial continued per protocol.	Critically ill patients with acute kidney injury and failure of at least one nonrenal organ or sepsis.	Intensive or less intensive renal-replacement therapy.	Dialysis Parameter	Death from any cause by day 60.	Haemodialysis/haemodiafiltration	1124	United States of America	Public	Cooperative Studies Program VA and by the NIDDKD.	Phase III
	Ejaz et al., 2009, (82)	Z-boundary	The study was stopped after completion of stage I.	Patients undergoing high-risk cardiac surgery.	Nesiritide	Medication	Dialysis and/or all-cause mortality within 21 days.	Haemodialysis	94	United States of America	Private	Scios, Inc.	Phase III
	IVOIRE, 2013, (70)	Not reported	One interim analysis performed as planned, trial d/c due to difficulty recruiting.	Critically ill patients with septic shock and AKI.	High-volume Haemofiltration (HVHF)	Dialysis Modality	28-day mortality.	Haemofiltration	140	France	Public	Grant from the French Health Ministry.	Phase III
	FENO HSR, 2014, (65)	Reboussin et al and Lan-DeMets Stopping Rule	Stopped due to futility after the 3rd interim analysis.	Critically ill cardiac surgery patients with acute kidney injury.	Fenoldopam	Medication	Rate of renal replacement therapy.	Any RRT	667	Italy	Public	Grant from the Italian Ministry of Health.	Phase III
	FBI, 2014, (121)	Fleming-Harrington (O Brien-Fleming	Trial not complete.	Critically ill patients with acute kidney injury receiving continuous renal	Enoxaparin	Medication	Occurrence of venous thromboembolism.	Haemodialysis/haemodiafiltration/Haemofiltration	266	Denmark	Public	Danish society of anaesthesiology & intensive medicines	Phase III

		boundary)		replacement therapy.								research initiative	
	HEROICS, 2015, (120)	Triangular test (Whitehead 1978)	At the third sequential interim analysis the trial was stopped for futility.	Patients with severe shock requiring high dose catecholamines 3 to 24 h postcardiac surgery.	Early high-volume Haemofiltration	Dialysis Modality	30-day mortality	Haemofiltration/haemodiafiltration	224	France	Public and Private	French Ministry of Health and Hospital-Gambro.	Phase III
	AKIKI, 2016, (91,92)	O Brien-Fleming boundary	Two interim analysis before final analysis. No change to trial.	Patients with severe acute kidney injury who required mechanical ventilation, catecholamine infusion, or both.	Early or a delayed strategy of renal-replacement therapy.	Dialysis Parameter	Overall survival at day 60.	Haemodialysis	620	France	Public	Funded by the French Ministry of Health.	Phase III
	ELAIN-Trial, 2016, (108,109)	O Brien-Fleming boundary	One interim analysis was performed after half of the total number of deaths across both treatment groups. No change to trial.	Critically ill patients with AKI and plasma neutrophil gelatinase-associated lipocalin level higher than 150 ng/mL.	Early or delayed initiation of RRT.	Dialysis Parameter	Mortality at 90 days.	Haemodialysis/haemodiafiltration/Haemofiltration	231	Germany	Private	Else-Kroner Fresenius Stiftung.	Phase III
	LEVO-CTS, 2017, (76,76)	O Brien-Fleming boundary	Not reported.	Patients with an EF<35% who were undergoing cardiac surgery with the use of cardiopulmonary bypass.	Intravenous levosimendan	Medication	Composite of 30-day mortality, RRT, perioperative MI, or mechanical cardiac assist device through day 5.	Haemodialysis/haemodiafiltration	882	United States of America	Private	Tenax Therapeutics.	Phase III
	CULPRIT-SHOCK, 2018, (71,72)	O Brien-Fleming boundary	Not reported.	Patients with cardiogenic shock complicating acute myocardial infarction.	Culprit lesion only Primary Coronary Intervention.	Treatment strategy	30-day mortality or AKI requiring RRT.	Haemodialysis/haemodiafiltration	706	Germany	Public	EU; German Heart Research Foundation; German Cardiac Society.	Phase III

	PRESERVE, 2018, (93)	O Brien-Fleming boundary	The sponsor stopped the trial after a prespecified interim analysis due to the absence of between-group difference.	Patients at high risk for renal complications who were scheduled for angiography.	1.26% sodium bicarbonate or intravenous 0.9% sodium chloride and 5 days of oral acetylcysteine or oral placebo.	Medication	Composite of death, the need for dialysis, or a persistent increase of at least 50% from baseline in the serum creatinine level at 90 days.	Haemodialysis	5177	United States of America	Public	U.S. Department of Veterans Affairs Office of Research and Development and the National Health and Medical Research Council of Australia.	Phase III
	VIOLET, 2018, (122)	Lan-DeMets	Study stopped for futility after first interim analysis.	Acute Respiratory Distress Syndrome, Vitamin D Deficiency and Critical Illness.	Vitamin D3	Medication	90-day all-cause mortality.	Haemodialysis	1358	United States of America	Public	National Heart, Lung, and Blood Institute (NHLBI)	Phase III
	Schanz et al., 2019, (99)	Jennison and Turnbull	The study was stopped prematurely after interim analysis due to futility.	Patients at high risk for AKI.	Screened with urinary [TIMP-2][IGFBP7]	Other	Incidence of moderate to severe AKI within the first day after admission.	Haemodialysis	100	Germany	Public	Robert-Bosch-Foundation.	Phase III
	HYVITS, 2019, (NCT03380507)	O Brien-Fleming boundary	Trial not complete.	Septic Shock and Critical Illness.	Hydrocortisone, Vitamin C and Thiamine.	Medication	Hospital Mortality at 60 days.	Haemodialysis	212	Qatar	Industry	Hamad Medical Corporation.	Phase II/III
	RICH, 2020, (104,105)	O Brien-Fleming boundary	Stopped early for efficacy.	Critically Ill Patients With Acute Kidney Injury.	Regional citrate anticoagulation, compared with systemic heparin anticoagulation.	Dialysis Parameter	Filter life span and 90-day mortality.	Haemodiafiltration	596	Germany	Public	German Research Foundation.	Phase III
	REMOVE, 2020, (NCT03266302)	Pocock	Trial not complete.	Infective Endocarditis.	Haemoadsorber for removal of cytokines.	Medical Device	Change in mean total SOFA score.	Haemodialysis	288	Germany	Public and Private	German Federal Ministry of Education and Research and CytoSorbents Europe GmbH	Phase II
Kidney Failure Requiring Dialysis													

	Besarab et al., 1998, (88)	Lan-DeMets	The trial was stopped at the third interim analysis due to concerns about safety.	Patients with clinical evidence of congestive heart failure or ischaemic heart disease who were undergoing haemodialysis.	Epoetin and target haematocrit.	Medication	Length of time to death or a first nonfatal myocardial infarction.	Haemodialysis	1233	United States of America	Private	Amgen	Phase III
	ACTION II, 1999, (123)	Lan-DeMets	ACTION II terminated enrolment due to an unfavourable perceived risk-to-benefit ratio.	Type 2 diabetic patients with renal disease.	Aminoguanidine	Medication	Doubling of serum creatinine concentration.	Haemodialysis	900	United States of America	Not reported	Not reported	Phase III
	Chapman et al., 2007, (81)	Constrained stopping boundaries	Two interim analysis, trial continued.	Liver resection, spine, peripheral arterial bypass, and dialysis access surgery.	Recombinant human thrombin (rhThrombin)	Medication	Time to haemostasis.	Haemodialysis	76	United States of America	Private	ZymoGenetics, Inc	Phase III
	DAC, 2008, (66)	Lan-DeMets	Enrolment was stopped after 877 participants were randomised based on a stopping rule for intervention efficacy.	Participants with ESKD and undergoing new fistula creation.	Clopidogrel	Medication	Fistula thrombosis.	Haemodialysis	877	United States of America	Public	National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health.	Phase III
	DAC, 2009, (89)	Lan-DeMets	Five planned interim analyses were performed before the final analysis. No change to trial.	Participants with placement of a new arteriovenous graft.	Extended-release dipyridamole plus aspirin.	Medication	Loss of primary unassisted patency.	Haemodialysis	649	United States of America	Public and Private	NIDDKD, NIH, and Boehringer Ingelheim.	Phase III
	AURORA, 2009, (118,119)	Event-driven	Continuation of the study was recommended by the data and safety monitoring board.	Patients who were undergoing maintenance haemodialysis.	Rosuvastatin	Medication	Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.	Haemodialysis	2776	Sweden	Private	AstraZeneca	Phase III

	ACCORD, 2010, (84)	Lan-DeMets	Intensive therapy was stopped before study end due to increased mortality.	Volunteers with established T2DM, HbA1c levels ≥ 7.5% and CVD or two or more CVD risk factors	Target HbA1c of <6.0%.	Treatment Target	Dialysis or renal transplantation, or serum creatinine >291.7 micromole/L, or retinal photocoagulation or vitrectomy.	Haemodialysis	10251	United States of America	Public	National Heart, Lung, and Blood Institute.	Phase III
	OPPORTUNITY, 2011, (113,114)	Event-driven	The trial was terminated early due to slow recruitment.	Adult maintenance haemodialysis patients.	Recombinant human growth hormone.	Medication	Mortality	Haemodialysis	695	United States of America	Private	Novo Nordisk	Phase III
	CONTRAST, 2012, (106,107)	Double triangular test (Whitehead 2007)	The board recommended to stop the trial because enough evidence was provided for futility.	Patients with ESRD.	Online haemodiafiltration.	Dialysis Modality	All-cause mortality	Haemodialysis/haemodiafiltration	714	The Netherlands	Public and Private	Dutch Kidney Foundation, Fresenius Medical Care, and Gambro Lundia.	Phase III
	HONEYPOT, 2014, (85,86)	Haybittle-Peto rule	Stopping rule for efficacy was not met, and the study was completed as per protocol.	Participants undergoing peritoneal dialysis	Daily topical exit-site application of antibacterial honey.	Medication	Time to first infection related to peritoneal dialysis	Peritoneal Dialysis	371	Australia	Public and Private	Baxter Healthcare, Queensland Government, Comvita, and Gambro.	Phase III
	HALT-PKD, 2014, (90)	Lan-DeMets	The study was extended due to a lower-than-expected number of end points.	Patients with autosomal dominant polycystic kidney disease.	Lisinopril and telmisartan.	Medication	Time to death, end-stage renal disease, or a 50% reduction from the baseline estimated GFR.	Haemodialysis	486	United States of America	Public	NIDDKD	Phase III
	Knoll et al., 2015, (97,98)	O Brien-Fleming boundary	Because of slower than expected recruitment, we extended follow-up to 4 years for all participants to increase statistical power.	Kidney transplant patients with proteinuria and an estimated GFR 20-55 ml/min/1.73 m2.	Ramipril	Medication	Doubling of serum creatinine, end stage renal disease or death.	Haemodialysis	528	Canada	Public	Canadian Institutes of Health Research.	Phase III

	PAVE, 2016, (124)	Lan-DeMets	Trial not complete.	Patients with a native arteriovenous fistula.	Paclitaxel-coated balloons	Medical Device	Time to end of target lesion primary patency.	Haemodialysis	211	United Kingdom	Public	National Institute for Health Research (NIHR) EME programme	Phase III
	OPN-305, 2016, (NCT01794663)	Not reported	Unknown	Kidney transplant recipients with delayed graft function.	OPN-305 (Tomaralimab)	Medication	Measure of Early Graft Function EGF.	Haemodialysis	252	Ireland	Industry	Opsona Therapeutics Ltd.	Phase II
	FAVOURED, 2017, (67,68)	Haybittle-Peto rule	Early cessation of recruitment, only 1st interim analysis was performed.	Participants with stage 4 or 5 chronic kidney disease after arteriovenous fistula creation.	Fish oil supplementation	Medication	Fistula failure, a composite of fistula thrombosis and/or abandonment and/or cannulation failure, at 12 months	Haemodialysis	567	Australia	Public and Private	Grants from National Health and Medical Research Council of Australia, Amgen Australia Pty Ltd and Mylan EPD.	Phase III
	CREDENCE, 2019, (94)	Alpha spending function	The prespecified efficacy criteria for early cessation had been achieved and recommended that the trial be stopped.	Patients with type 2 diabetes and albuminuric chronic kidney disease.	Canagliflozin	Medication	Composite of end-stage kidney disease (dialysis, transplantation, sustained GFR <15), a doubling of the serum creatinine level, or death from renal or cardiovascular causes.	Haemodialysis	4401	Australia	Private	Janssen Research and Development	Phase III
	DECLARE-TIMI 58, 2019, (95)	O Brien-Fleming boundary	Two interim analyses performed. No change to trial.	Patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease.	Dapagliflozin	Medication	Cardiovascular death, myocardial infarction, or ischaemic stroke or hospitalization for heart failure.	Haemodialysis	17160	United States of America	Private	AstraZeneca	Phase III
	CONVINCE, 2020, (125)	Haybittle-Peto rule	Trial not complete.	Patents with ESKD treated with Haemodialysis.	High-dose haemodiafiltration versus conventional high-flux Haemodialysis.	Dialysis Modality	All-cause mortality	Haemodialysis/haemodiafiltration	1800	The Netherlands	Public	European Union's Horizon 2020 research and innovation programme.	Phase III

Table 2-6 Legend – HD – Haemodialysis, HDF – Haemodiafiltration, HF – Haemofiltration, PD – Peritoneal Dialysis

Sample-Size Re-estimation was the second most common type of adaptive design, used in 14 trials (24.6%) (8 (25.8%) in dialysis populations and 6 (23.1%) in dialysis outcome trials) (Table 2-7). 8 trials (57.1%) were impacted by the use of Sample-Size Re-estimation adaptive design including 6 trials (75%) that increased sample size (Table 2-7).

Table 2-7 Sample-Size Re-estimation in Dialysis Randomised Clinical Trials

	Study Name, Year	Impact of Adaptive design	Population	Intervention	Primary Outcome	Nature of primary outcome	Dialysis Modality	Sample Size of Study	Country of lead investigator	Funder	Funder Details	Study Phase
Acute Kidney Injury												
	Hemodiafe, 2006, (83)	The sample size was adjusted to include 180 patients per group.	Critically ill patients with acute renal failure as part of multiple-organ dysfunction syndrome.	Intermittent Haemodialysis versus continuos venovenous haemodiafiltration	Dialysis Modality	60-day survival	Haemodialysis/haemodiafiltration	360	France	Public	Supported by the Société de Reanimation de Langue Françoise.	Phase III
	Riley et al., 2014, (117)	Data from the initial ten randomised patients demonstrated >50% difference in urine output, revealing adequate power would be achieved with only 20 randomised patients.	Infants <90 days old with congenital heart disease who underwent bypass surgery and were post-operatively treated with CPD.	Continue 24 h more CPD or discontinue CPD.	Dialysis Modality	Urine output (ml/kg per h)	Peritoneal Dialysis	20	United States of America	Public	Baylor College of Medicine and Cincinnati Children - Hospital Medical Centre.	Phase II
	SCD, 2015, (110)	The study was terminated by the sponsor at the interim analysis because the SCD treatment was often outside the recommended iCa range, and therefore, resulted in ineffective therapy	ICU patients with AKI	Selective Cytopheretic Device	Medical Device	60-day mortality	Haemodiafiltration	134	United States of America	Private	CytoPherx, Inc.	Phase III
	TARTARE-2S, 2016, (126)	Trial not complete.	Patients with septic shock.	Targeted tissue perfusion versus macrocirculation-guided standard care	Treatment strategy	Alive at 30 days with normal arterial blood lactate and without any inotropic or vasopressor agent.	Haemodialysis/haemodiafiltration/ haemofiltration	200	Switzerland	Public	Sigrid Juselius Foundation, Instrumentarium Foundation, and Helsinki University Hospital	Phase III

	Kwiatkowski et al., 2017, (69)	Not reported.	Infants after congenital heart surgery.	Peritoneal Dialysis	Dialysis Modality	Negative Fluid Balance	Peritoneal Dialysis	73	United States of America	Public	American Heart Association Great Rivers Affiliate and internal funding from Cincinnati Children's Hospital Medical Centre.	Phase II
	ANDROMEDA-SHOCK, 2018, (127)	Trial not complete.	Patients with septic shock.	Peripheral perfusion-targeted resuscitation	Other	28-day mortality	Haemodialysis/haemodiafiltration/ haemofiltration	422	Chile	Public	Departamento de Medicina Intensiva, Pontificia Universidad Catolica de Chile.	Phase III
	COACT, 2019, (73,74)	After this interim analysis, the data and safety monitoring committee advised that the sample size not be increased.	Post-cardiac arrest patients without signs of STEMI.	Immediate coronary angiography and percutaneous coronary intervention.	Treatment strategy	90-day mortality	Haemodialysis/haemodiafiltration	552	The Netherlands	Public	Netherlands Heart Institute.	Phase III
	FRESH, 2020, (77)	Continue enrolment and to increase the sample size to a maximum of 210 patients.	Patients presenting to the ED with sepsis or septic shock and anticipated ICU admission.	Dynamic assessment of fluid responsiveness (passive leg raise).	Treatment strategy	Difference in positive fluid balance at 72 hours or ICU discharge.	Haemodialysis/haemodiafiltration/ haemofiltration	124	United States of America	Private	Cheetah Medical	Phase III
Chronic Kidney Disease												
	PREDICT, 2020, (115,116)	The sample size was amended from 220 to 238 for each group.	Patients with CKD without diabetes.	High and low haemoglobin groups (Darbepoetin alfa)	Medication	Kidney composite end point (starting maintenance dialysis, kidney transplantation, eGFR<6 ml/min per 1.73 m2, and 50% reduction in eGFR).	Haemodialysis	491	Japan	Private	Kyowa Hakko Kirin, Otsuka, Dainippon Sumitomo, and Mochida.	Phase III
Kidney Failure Requiring Dialysis												

	Kratochwill et al., 2016, (111)	Led to premature termination of patient recruitment.	Stable Peritoneal Dialysis outpatients.	Alanyl-glutamine addition to glucose-based Peritoneal Dialysis Fluid.	Medication	Heat-shock protein 72 expression	Peritoneal Dialysis	20	Austria	Public	ZIT - Technology Agency of the City of Vienna and FFG - the Austrian Research Promotion Agency	Phase II
	IDPN-Trial, 2017, (80)	Sample size was increased. Primary outcome was significant.	Maintenance haemodialysis patients suffering from Protein-energy wasting (PEW).	Intradialytic parenteral nutrition (IDPN)	Medication	Prealbumin	Haemodialysis	107	Germany	Private	Fresenius Kabi Germany GmbH, Bad Homburg, Germany.	Phase IV
	CHART, 2018, (100,101)	Sample-Size Reestimation Not Performed.	Urologic patients undergoing elective cystectomy.	Albumin 5% or balanced hydroxyethyl starch 6%	Medication	Ratio of serum cystatin C between the last visit at day 90 and the first preoperative visit.	Haemodialysis	100	Germany	Private	CSL Behring GmbH	Phase III
	KALM-1, 2019, (96)	Not reported	Patients undergoing haemodialysis who had moderate-to-severe pruritus.	Intravenous difelikefalin	Medication	24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS)	Haemodialysis	378	United States of America	Private	Cara Therapeutics	Phase III
	Fujimoto et al., 2020, (128)	The sample size was calculated by the intermediate analysis of the first 30 samples enrolled.	Patients undergoing maintenance haemodialysis thrice/week.	Lidocaine/prilocaine cream (EMLA).	Medication	Puncture pain relief, which was measured using a 100-mm visual analogue scale.	Haemodialysis	66	Taiwan	Public	Grant-in-Aid for Young Scientists from the Japan Society for the Promotion of Science.	Phase II

Table 2-7 Legend – HD – Haemodialysis, HDF – Haemodiafiltration, HF – Haemofiltration, PD – Peritoneal Dialysis

Phase II/III seamless design was the third most common type of adaptive design, 5 trials (8.8%) (1 (3.23%) in dialysis populations and 4 (15.4%) in dialysis outcome trials) (Table 2-8). Adaptive Dose-Escalation, Bayesian Adaptive Design and Interim analysis were used in one trial each (Table 2-8).

Table 2-8 Seamless Design/Adaptive Dose-Escalation in Dialysis Randomised Clinical Trials

	Study Name, Year	Impact of Adaptive design	Population	Intervention	Primary Outcome	Nature of primary outcome	Dialysis Modality	Sample Size of Study	Country of lead investigator	Funder	Funder Details	Study Phase
Phase IIa/IIb seamless design												
	STOP-AKI, 2018, (102,103)	Combined efficacy and dose finding study.	Critically ill patients with sepsis associated AKI.	Human recombinant alkaline phosphatase	Medication	Area under the time-corrected endogenous creatinine clearance curve from days 1 to 7.	Haemodialysis	301	The Netherlands	Private	AM-Pharma	Phase IIa/IIb
Two-stage seamless adaptive design												
	Himmelfarb et al., 2018, (112)	At the end of each stage, data from the patients are used to select the THR-184 dose arms for next stage.	Patients at high risk for AKI after cardiac surgery.	THR-184	Medication	Proportion of patients who developed AKI	Haemodialysis/haemodiafiltration/haemofiltration	452	United States of America	Private	Thrasos Therapeutics, Inc.	Phase II
Adaptive Phase IIb/III												
	SEPSIS-ACT, 2018, (129)	The trial was stopped for futility at the end of part 1.	Septic shock requiring more than 5 µg/min of norepinephrine.	Selepressin	Medication	Vasopressor- and Mechanical Ventilator-free Days (PVFDson)	Haemodialysis	868	United States of America	Industry	Ferring Pharmaceuticals	Phase II/III
Phase II/III seamless design												
	COMBAT-SHINE, 2020, (130)	Trial not complete.	Patients with septic shock-induced endothelio pathy.	Infusion of iloprost	Medication	Mean daily modified Sequential Organ Failure Assessment (SOFA) score	Haemodialysis	384	Denmark	Public	Danish Independent Research Organisation	Phase II

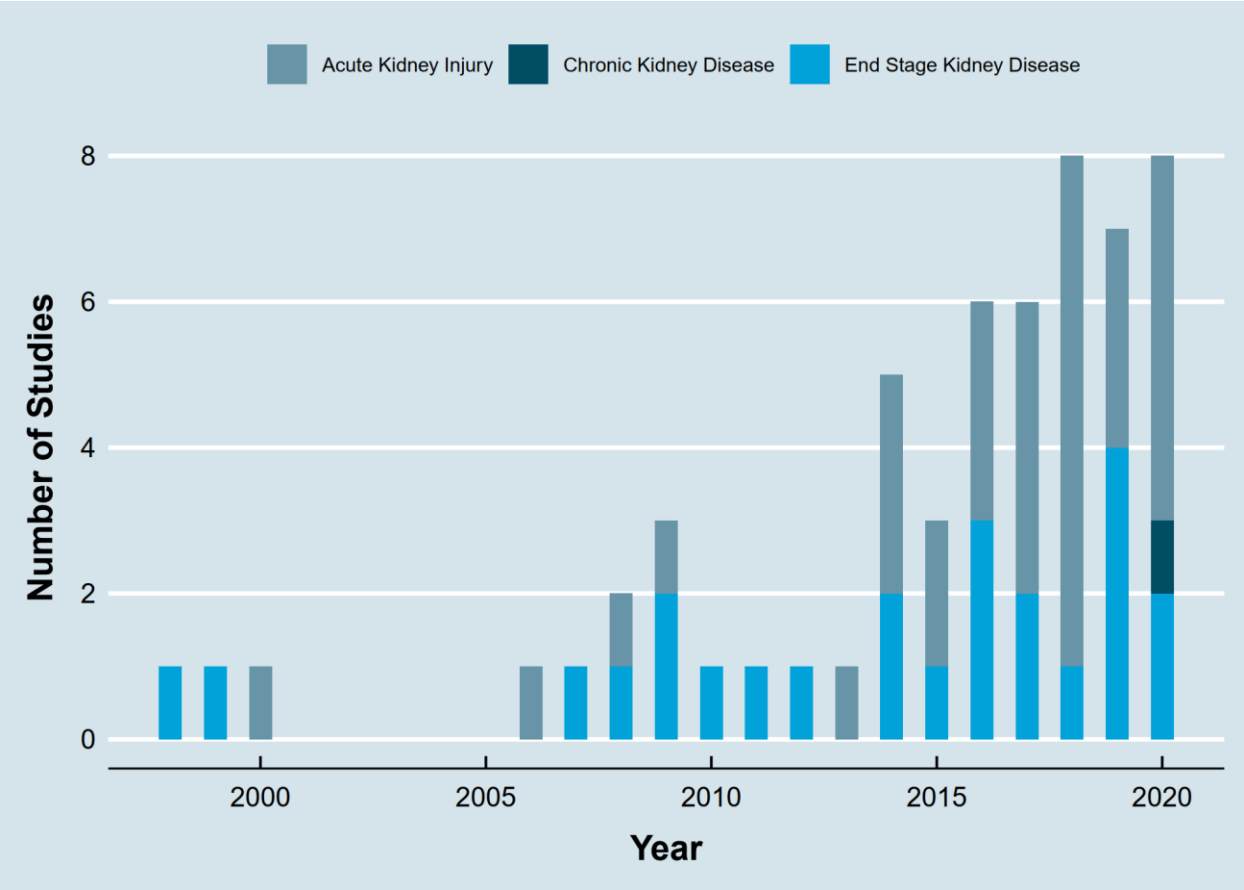
	Cohen et al., 2020, (NCT04381052)	Trial not complete.	Patients with life-threatening Coronavirus Disease 2019 (COVID-19) infection.	Clazakizumab	Medication	Cumulative incidence of serious adverse events associated with clazakizumab or placebo.	Any	30	United States of America	Public and Private	Columbia University, NYU Langone Health and CSL Behring.	Phase II
Adaptive Dose-Escalation												
	EMPIRIKAL, 2017, (131)	Trial not complete.	Patients after receiving cadaveric renal allografts.	Mirococept	Medication	Delayed graft function	Haemodialysis/haemodiafiltration/haemofiltration	560	United Kingdom	Public	Medical Research Council	Phase II
Bayesian Adaptive Design												
	ASTOUND, 2019, (NCT02723591)	Trial shortened to 1 year due to a stopping rule.	Kidney Transplantation	Tacrolimus	Medication	Percentage of Participants Who Were Positive for de Novo DSA (dnDSA) or Immune Activation (IA) Occurrence	Haemodialysis	599	United States of America	Industry	Astellas Pharma Inc	Phase IIII
Interim analysis												
	Hosgood et al., 2017, (132)	Trial not complete.	Patients receiving a kidney from a donation after circulatory death donor.	Ex vivo normothermic perfusion	Other	Rates of delayed graft function (DGF) defined as the need for dialysis in the first week post-transplant.	Haemodialysis	400	United Kingdom	Public	Kidney Research UK; University of Cambridge and University Hospitals of Cambridge Foundation Trust.	Phase II

Table 2-8 Legend – HD – Haemodialysis, HDF – Haemodiafiltration, HF – Haemofiltration, PD – Peritoneal Dialysis

2.6.1.2 Population, Intervention, and Outcome studied

Acute Kidney Injury (AKI) was studied in 32 trials (56.1%), kidney failure requiring dialysis was studied in 24 trials (42.1%) and Chronic Kidney Disease (CKD) was studied in 1 trial (1.75%). Figure 2-3 reports the number of each population under study per year and shows a larger increase in adaptive design methods in AKI populations compared to kidney failure requiring dialysis populations.

Figure 2-3 Populations with Adaptive Design in Dialysis Randomised Clinical Trials by Year



Medications were the most common intervention type, evaluated in 35 trials (61.4%), followed by Dialysis Modality in 7 trials (12.3%), and Dialysis Parameter in 4 trials (7%). Haemodialysis was the most common dialysis modality studied in 32 trials (56.1%), followed by haemodialysis and haemodiafiltration in 8 trials (14%), haemodialysis, haemodiafiltration and haemofiltration in 7 trials (12.3%) and peritoneal dialysis in 4 trials (7%). Hard clinical outcomes were selected in 34 trials (59.6%), followed by surrogate outcomes in 20 trials (35.1%) and mixed in 3 trials (5.3%). The outcome measure was continuous in 15 trials (26.3%) and dichotomous in 42 trials (73.7%). Phase III studies were the most common study phase, studied in 41 trials (71.9%) (Table 2-6, Table 2-7, Table 2-8).

2.6.2 Publication in High Impact Journals

32 studies (56.1%) were published in a high impact journal (Impact Factor > 9). 14 studies (24.6%) were published in the New England Journal of Medicine (NEJM), 6 studies (10.5%) were published in the Journal of the American Medical Association (JAMA), 4 studies (7%) were published in Trials, and 2 studies (3.5%) were published in the Journal of the American Society of Nephrology (JASN).

2.6.3 Geographic Location and Funding

The most common country of the lead author was the United States of America in 24 studies (42.1%), followed by Germany in 7 studies (12.3%), France in 4 studies (7%), The Netherlands in 4 studies (7%), Australia in 3 studies (5.3%), and the United Kingdom in 3 studies (6%) (Table 2-6, Table 2-7, Table 2-8). 49 studies (86%) were multicentre trials. 27 studies (47.4%) were supported by public funding, 21 studies (36.8%) were supported by private funding, 7 studies (12.3%) were supported by both public and private funding and 2 studies (3.5%) did not report the source of funding.

2.6.4 Reporting of Adaptive Design Method in Title and Abstract

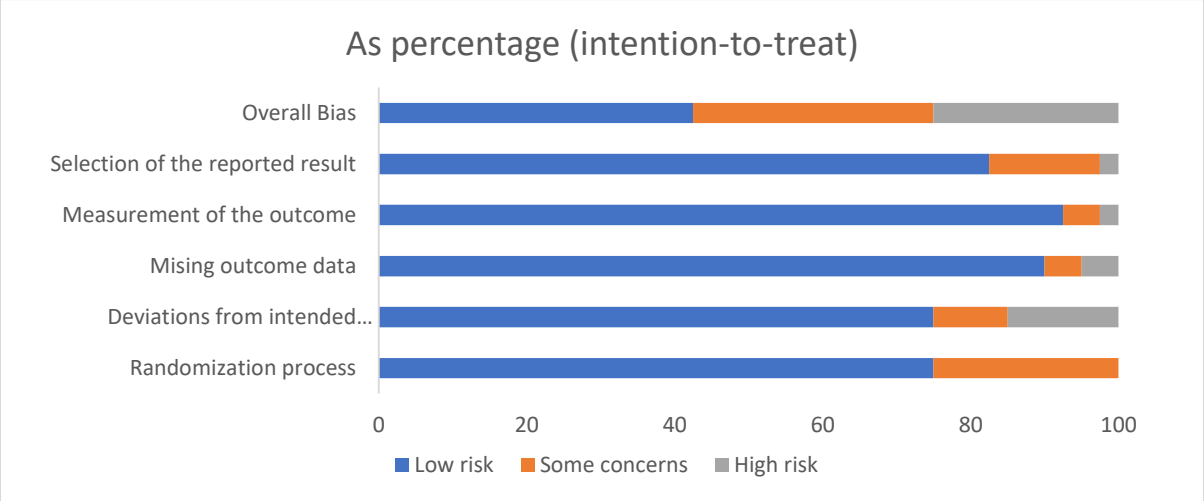
44 studies (77.2%) did not report their adaptive design method in the title or abstract and would not be detected by a standard systematic review search. 29 of the 44 studies were GSD methods and 13 of the 44 studies were sample size reestimation methods.

2.6.5 Risk Of Bias

Risk of bias was assessed for forty trials (protocols and clinicaltrials.gov were excluded) (Figure 2-4, Table 2-5). Overall risk of bias was deemed to be “low” in 17 trials (42.5%),

"some concerns" in 13 trials (32.5%), and "high risk" in 10 trials (25%). The randomisation process led to some concerns for 10 studies (25%). Deviations from intended interventions led to some concerns for 4 studies (10%) and "high risk" for 6 studies (15%). Missing outcome data were deemed to have "some concerns" for 2 studies (5%) and a 'high risk' of bias for 2 studies (5%). Measurement of outcome measures were deemed to have "some concerns" for 2 studies (5%) and a 'high risk' of bias for 1 study (2.5%). Selection of the reported result were deemed to be "some concerns" for 6 studies (15%) trials and 'high risk' of bias for 1 study (2.5%).

Figure 2-4 Risk of Bias Assessment of Dialysis Randomised Clinical Trials with Adaptive Designs



2.7 Discussion

In this systematic review, we report that adaptive design methods were used in 57 dialysis randomised clinical trials over a 20-year period. While the absolute number has increased over time, the relative use of adaptive design methods in trials in dialysis populations and trials with dialysis as an endpoint has decreased.

First, we report that the relative proportion of adaptive design methods in dialysis trials has reduced over time. The absolute number of dialysis trials using adaptive designs has increased each year, but this has not matched the overall increase in dialysis trials and therefore resulted in a relative decrease. We were unable to compare this result with other specialities because recent systematic reviews have not reported the relative use of

adaptive designs (62,133). Second, we report that group sequential designs are the most commonly used type of adaptive design in dialysis trials. This is similar to previous systematic reviews in cardiology (134), oncology (133) and in a review of registered clinical trials covering multiple specialities on clinicaltrials.gov (62). Third, we report that adaptive designs were more common in Acute Kidney Injury (AKI) (56.1% of trials) than kidney failure requiring dialysis (42.1% of trials). This may reflect increasing use of adaptive design methodology in critical care (135) and sepsis related trials (136), where AKI is most common. There were very few trials of CKD with a dialysis outcome (2%) that used an adaptive design. Many reasons for the paucity of CKD trials have been previously suggested including the use of treatments in CKD despite a lack of evidence, difficulty recruiting to CKD trials due to stringent eligibility criteria and underpowered subgroup analysis (37,40). The infrequent usage of adaptive designs in CKD trials may become a self-perpetuating barrier to using adaptive designs in future trials (62). Fourth, we report that adaptive design methods impacted the conduct of the randomised trial in most studies (50.9%). For example, 17 (48.6%) trials were impacted by the use of group sequential adaptive design including 7 trials (41.2%) stopped early for futility, 3 trials (17.6%) stopped early for efficacy and 4 trials (23.5%) stopped early for safety. This finding is similar to a systematic review of published and publicly available trials where the most common reason for stopping group sequential trials was futility (61). Fifth, we found that the most common country of the lead author was the United States of America, 24 studies (42.1%) and the most common funding source was public, 27 studies (47.4%). This finding was different to a systematic review of published and publicly available trials where 65% of trials reported industry funding (61). Funding for kidney research reached an all-time low in 2013 (45), but this has recently changed in the United States with advocacy from scientific societies such as the American Society of Nephrology, whereby an executive order was signed in 2020 to reform the US End-Stage Kidney Disease treatment industry (137). Adaptive designs are one part of the solution for optimising the design of clinical trials in dialysis and nephrology and will benefit from the improvement in the funding landscape (37).

2.7.1 Limitations

Our study has several limitations. First, we limited our search to two databases (PubMed and Clinicaltrials.gov) due to the scale of studies sourced (209,033 and 6,002 results). This

was a deviation from our protocol but necessary to make this full text review feasible. Second, we decided to include randomised clinical trials with dialysis outcomes in addition to patients currently on dialysis. This permitted a more comprehensive review of the full landscape of AKI, kidney failure requiring dialysis and CKD trials, but was a deviation from our original protocol. Third, the denominator for calculating the proportion of adaptive designs in dialysis RCTs, will include some false positives i.e., either not RCTs or not dialysis. We modified the parameters of the machine learning classifier to perform a sensitive search to include as many true positives as possible. We expect this mis-classification bias to be independent of time and bias every year equally and therefore not affect the trend. Fourth, publication bias – where negative studies are not published – will bias results towards the null, for example, our estimate of the impact of adaptive design (50.9%) would be higher if unpublished studies stopped for futility and not published were included.

2.7.2 Strengths

We developed a novel full text systematic review search strategy. 44 studies (77.2%) did not report their adaptive design method in the title or abstract and would not be detected by a standard systematic review search methodology. This could introduce a reporting bias where adaptive design methods are reported in the main paper but not in the abstract. Our novel strategy combined classical systematic review, machine learning classifiers and a novel full text systematic review. This new method has broad applications in medical evidence synthesis and evidence synthesis in general.

2.7.3 Conclusion

Adaptive design methods improve efficiency of randomised clinical trials in dialysis, but their relative use in dialysis is decreasing over time. Greater knowledge of adaptive design examples in dialysis will further improve uptake in dialysis randomised clinical trials.

Chapter 3 Effect of a dietary counselling intervention targeting low sodium intake (<2.3 g/day) versus moderate sodium intake on 24-hour ambulatory blood pressure and renal biomarkers – COSTICK Trial

Conor Judge, Martin J O'Donnell, COSTICK, (2021), GitHub repository, https://conorjudge.github.io/costick

3.1 Introduction

Reducing sodium intake to low levels (<2.3 g/day) is recommended for all adults, with some guidelines recommending a lower target (<1.5 g/day) for patients with hypertension, renal impairment and kidney failure requiring dialysis (138–141). This specific low sodium intake target is based on short-term randomised clinical trials, reporting a reduction in office blood pressure with short-term reductions in sodium intake (142,143). Longer-term trials of dietary counselling to reduce sodium intake also report a reduction in office systolic blood pressure (1.2/0.7 mmHg) over 3 years (mean intake 3.1 g/day), but did not achieve a low sodium intake target of <2.3 g/day recommended by guidelines (144).

Ambulatory blood pressure monitoring (ABPM) is a more valid and reliable method of measuring average blood pressure in individuals (145). To date, only one small randomised crossover evaluation trial (n=12) has evaluated the effect of sodium intake on 24-hour ambulatory blood pressure, reporting a difference in 24-hour blood pressure (-22.7/-9.1 mmHg) between low (1.15 g/day for 7 days) and high sodium diets (5.75 g/day for 7 days) separated by a 2-week washout period (146). Ambulatory blood pressure is a strong and independent predictor of cardiovascular outcomes, with night-time blood pressure being the strongest predictor of cardiovascular events (147). Therefore, the effect of sodium intake reduction on 24-hour ambulatory blood pressure is important for informing a public health strategy for recommended sodium intake in populations.

While prospective cohorts studies have reported a monotonic curvilinear association of sodium intake and blood pressure, they report a J-shaped association with cardiovascular disease and mortality, with increased risk at high (>5 g/day) and low (<3 g/day) sodium intakes (148). Therefore, while reductions in sodium intake from moderate to low intake levels reduce office blood pressure, they do not appear to translate into reductions in cardiovascular events. One potential explanation may be a different association with day and nocturnal blood pressure, the latter being a stronger predictor of cardiovascular disease (149).

The association of sodium intake and renal outcomes is also complex (150). While high sodium intake (>4.6 g/day) is associated with increased risk of adverse renal outcomes (151), there is conflicting data on whether low sodium intake (<3 g/day) is associated with better renal outcomes compared to moderate intake. In a peritoneal dialysis population, some observational studies have reported increased mortality associated with lower dietary sodium intake (152), while a meta-analysis of four clinical trials (n=67) reported lower systolic blood pressure in those with low sodium intake (−8.4 mmHg, 95% CI, −12.0 to −4.8) (153). In patients with mild-moderate CKD, higher urinary sodium excretion was not associated with an increased risk of adverse renal outcomes in the ONTARGET/TRANSCEND cohort, while increased urinary potassium excretion was associated with a reduced risk of adverse renal outcomes (e.g., kidney failure requiring dialysis, doubling of creatinine) (154). In contrast, the CRIC cohort study reported an increased risk of end-stage kidney disease in the group with highest urinary sodium excretion (>4.6 g/day) (155). Therefore, while guidelines recommend low sodium intake in patients with chronic kidney disease, there is insufficient evidence from clinical trials, and inconsistent information from observational studies to support this.

COSTICK-ABPM was a sub-study of two phase IIb, single-centre, randomised clinical trials in populations without cardiovascular disease or chronic kidney disease (COSIP) and those with chronic kidney disease (STICK). All participants received advice on healthy eating and were randomised to an additional intensive dietary counselling intervention to reduce sodium intake (target <2.3 g/day) or not. In this analysis, we report the between-group differences in changes of nocturnal systolic blood pressure, other ABPM parameters (nocturnal diastolic, mean systolic/diastolic, daytime systolic/diastolic, night/day ratio, and blood pressure variability) and renal outcomes (eGFR-MDRD, eGFR-CKD-EPI, creatinine clearance and proteinuria).

3.2 Methods

The Clarifying Optimal Sodium Intake in Populations (COSIP) clinical trial was designed to explore the effect of low sodium intake (<2.3 g/day) compared to moderate sodium intake in adults on a panel of cardiovascular biomarkers, over two years. The Sodium InTake In Chronic Kidney Disease (STICK) clinical trial was designed to explore the effect of low sodium intake (<2.3 g/day) compared to moderate sodium intake in adults with non-severe Chronic Kidney

Disease (CKD) on decline in renal function over two years. COSTICK is the combined cohort of both trials. The design for COSIP and STICK have been published (156). In brief, COSIP and STICK were phase IIb, two group, parallel, open-label, single centre, randomised clinical trials.

Inclusion criteria for both trials were, age >40 years, stable blood pressure – no change in antihypertensive or diuretic medications (including dose) for 3 months before screening visit, willingness to modify dietary intake and written informed consent. Exclusion criteria for both trials included abnormal sodium handling, heart failure, high dose diuretic use, immunosuppressive medication use, unable to comply with intervention or study visits, pregnancy or lactation, postural hypotension, cognitive impairment, high or low Body Mass Index (BMI) or inclusion in another clinical trial. All STICK participants were required to have a stable estimated glomerular filtration rate (eGFR) of 30-60 ml/min/1.73m^2 within three months of randomisation. For COSIP, participants were excluded for known CKD (eGFR <60 ml/min/1.73m^2) or previous cardiovascular disease.

The intervention group received a one-to-one, dietician developed and delivered, healthy eating guidance session and intensive counselling on specific behavioural and environmental factors to promote reduction in sodium intake to a target of <2.3 g/day. The intervention was based on the Trial Of Non-pharmacologic interventions in the Elderly (TONE) trial (157) and targeted: (i) reducing use of 'salt' during food preparation (encouraging the use of herbs and/or spices); (ii) reducing table 'salt' use; (iii) encouraging fresh food consumption over processed or canned foods; (iv) identification of sodium content in foods; (v) modifying the consumption of foods with high sodium content; and (vi) advice on eating outside of the home. The intervention was delivered at all patient contacts up to and including the 21-month visit with approximately 225–255 minutes of in-person contact and 155 minutes of telephone contact over the course of the trials. Participants randomised to usual care received a healthy eating guidance session, administered by a trained member of the research team, over 15 minutes following randomisation, in addition to written materials emphasising key messages (156). Telephone contact was made at months nine and 15 to follow-up on key points on healthy eating (each 15 minutes). Participants randomised to usual care did not meet with the dietitian

or receive focused recommendations on sodium intake. Participants were followed for 24 months.

Office Blood Pressure (BP) was measured using a calibrated, automated oscillometric device and followed by a 24-hour ABPM using the Spacelabs ABP 90217 device, where BP was measured every 30 minutes between 7am and 10pm, and every 60 minutes between 10pm and 7am. 24-hour ABPM was completed at screening visit and final visit (24 months). Nocturnal systolic BP was defined as the average of all systolic BP readings between 1am and 6am; daytime systolic BP was defined as the average of all systolic BP readings between 9am and 9pm (158). The 6am to 9am and 9pm to 1am transition periods are included in the overall systolic and diastolic BP. Participants were categorized by the percentage change between night and day ambulatory systolic BP: extreme dippers (≥20%), dippers (<20% and ≥10%), non-dippers (<10% and >0%), and reverse dippers (<0%) (159). Short-term BP variability was defined in two ways: the standard deviation (SD) of 24-hour average ABP and the Coefficient of Variation (CoV) which was calculated as 24-hour SD divided by the corresponding mean BP and multiplied by 100 (160). 24-hour urine collections were performed at baseline, 3 months and 24 months. A single laboratory analysed all samples using standardised storage, handling and analytical procedures, including urine protein, urine creatinine, urine sodium and urine potassium on the Roche Cobas® 8000 modular analyser series (Roche Diagnostics Limited, West Sussex, UK). All participants provided written informed consent and both trials were approved by Galway University Hospitals Research Ethics Committee.

3.2.1 Statistical Analysis

The mean difference between groups in the change from baseline to 24 months of 24-hour ABP was assessed using multiple linear regression that was adjusted for treatment allocation, age, sex, and baseline 24-hour ambulatory systolic BP. Our primary analysis was intention to treat, and our primary outcome measure was mean change in nocturnal systolic BP from baseline to 24 months. Nocturnal systolic BP was selected as the primary outcome measure, as it is reported to be a strong predictor of cardiovascular outcomes (149) and used in other randomised controlled trials of blood pressure lowering (161). Additionally, we completed a sensitivity analysis that assessed a per-protocol population that completed more than 75% of

interventional sessions. Stratified analysis in pre-specified subgroups was also performed including: COSIP population, STICK population, sex, age greater and less than median age, and baseline hypertension status. Further analyses were performed for 24-hour systolic and diastolic BP, daytime systolic and diastolic BP, nocturnal diastolic BP, night/day systolic and diastolic BP ratio and 24-hour short-term BP variability (coefficient of variation).

3.2.2 Sample size calculation

For STICK, a mean decline in creatinine clearance of 8±5ml/min/1.73m2 over the trial period and estimated a minimum clinically meaningful effect size of 25% relative reduction. Based on an alpha of 0.05 and power of 80%, a per group sample size of 99 participants was required. Assuming a dropout rate of 5% participants, a net crossover/non-adherence of 5% in favour of the control group, a total sample size of 224 participants was required (156). For COSIP, the sample size was based on the ability to detect an effect size of 0.40 in the between-group difference in mean change scores of biomarkers (80% power and alpha 0.05), equating to a difference of 0.4 of the standard deviation of the change in biomarker. Assuming a dropout rate of 5% participants, a net crossover/non-adherence of 15%, we require a total sample size of 286 participants (156).

3.3 Results

Ambulatory BP recordings at both baseline and follow-up were obtained in 323 COSTICK participants (COSIP, 230; STICK 93) referred to as COSTICK-ABPM participants (Figure 3-1). At baseline, the mean age for COSTICK-ABPM participants was 61.5 years (COSIP, 59.7 years; STICK 67.0 years), 46.75% (COSIP, 49.13%; STICK, 40.86%) were female and mean eGFR (CKD-EPI) was 71.86 mL/min/1.73m^2 (COSIP, 80.48 mL/min/1.73m^2; STICK, 50.72 mL/min/1.73m^2) (Table 3-1). There was no significant difference in baseline characteristics between participants who did and did not complete ABPM (Table 3-2).

Figure 3-1 Consort Flow Diagram

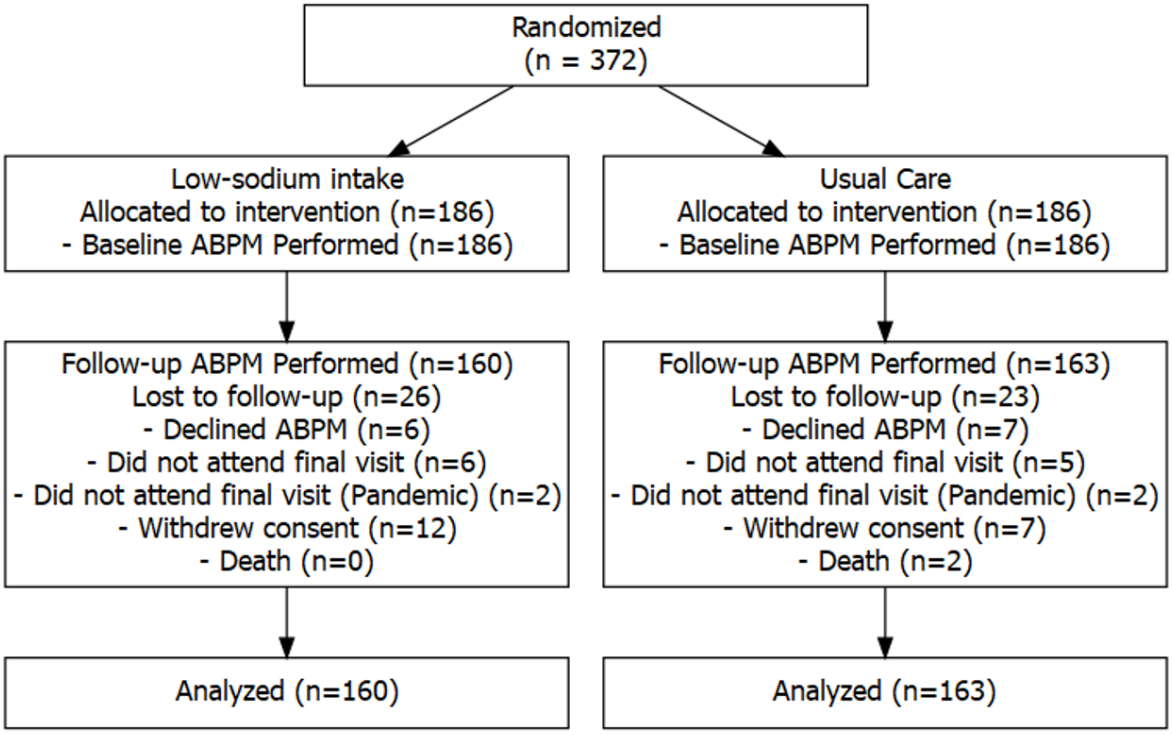


Table 3-1 Baseline Characteristics of Combined COSTICK Participants Who Completed Baseline and 24-month ABPM

Characteristic	Dietary Sodium Intake		
	Low Sodium Intake N =160[1]	Usual Care N =163[1]	p-value[2]
Age, years	61 (10)	62 (10)	0.24
Female	79 (49%)	72 (44%)	0.35
Transient ischaemic attack	4 (2.5%)	7 (4.3%)	0.37
Hypertension	82 (52%)	89 (55%)	0.59
Heart failure	4 (2.5%)	3 (1.9%)	0.72
Coronary artery disease including angina pectoris	11 (6.9%)	13 (8.0%)	0.69
Carotid endarterectomy or stent	1 (0.6%)	0 (0%)	0.50
Peripheral artery disease	3 (1.9%)	5 (3.1%)	0.72
Bioprosthetic heart valve present	1 (0.6%)	0 (0%)	0.50
Pacemaker/ ICD present	0 (0%)	2 (1.2%)	0.50
Venous thromboembolism	12 (7.5%)	6 (3.7%)	0.13
Hyperlipidaemia	87 (55%)	74 (45%)	0.095
Cancer	16 (10%)	28 (17%)	0.060
History of GI bleeding	4 (2.5%)	5 (3.1%)	>0.99
Tobacco use			0.062
Never	70 (44%)	77 (47%)	
Current	18 (11%)	7 (4.3%)	
Former	71 (45%)	79 (48%)	
Alcohol consumption	124 (78%)	121 (74%)	0.49
Office Systolic Blood Pressure (mmHg)	130 (14)	132 (14)	0.45
Office Diastolic Blood Pressure (mmHg)	75 (9)	76 (10)	0.16
eGFR (ml/min/1.73m^2)	72 (18)	72 (17)	0.88
ABP Systolic Blood Pressure (mmHg)	121 (11)	123 (12)	0.22
ABP Diastolic Blood Pressure (mmHg)	72 (7)	73 (7)	0.050

[1]Mean (SD); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 3-2 Baseline Characteristics of COSTICK Participants Who Completed and Did Not Complete Ambulatory Blood Pressure Monitoring

Characteristic	Baseline and 24-month ABPM completed		
	No N =50[1]	Yes N =323[1]	p-value[2]
Age, years	60 (11)	62 (10)	0.58
Female	29 (58%)	151 (47%)	0.14
Transient ischaemic attack	1 (2.2%)	11 (3.4%)	>0.99
Hypertension	22 (48%)	171 (53%)	0.50
Heart failure	0 (0%)	7 (2.2%)	>0.99
Coronary artery disease including angina pectoris	2 (4.3%)	24 (7.5%)	0.76
Carotid endarterectomy or stent	0 (0%)	1 (0.3%)	>0.99
Peripheral artery disease	1 (2.2%)	8 (2.5%)	>0.99
Bioprosthetic heart valve present	1 (2.2%)	1 (0.3%)	0.23
Pacemaker/ ICD present	0 (0%)	2 (0.6%)	>0.99
Venous thromboembolism	1 (2.2%)	18 (5.6%)	0.49
Hyperlipidaemia	26 (58%)	161 (50%)	0.33
Cancer	6 (13%)	44 (14%)	0.91
History of GI bleeding	4 (8.9%)	9 (2.8%)	0.062
Tobacco use			0.72
Never	21 (46%)	147 (46%)	
Current	5 (11%)	25 (7.8%)	
Former	20 (43%)	150 (47%)	
Alcohol consumption	35 (76%)	245 (76%)	0.97
Office Systolic Blood Pressure (mmHg)	NA (NA)	131 (14)	
Office Diastolic Blood Pressure (mmHg)	NA (NA)	76 (10)	
eGFR (ml/min/1.73m^2)	73 (18)	72 (17)	0.56
ABP Systolic Blood Pressure (mmHg)	121 (13)	122 (11)	0.33
ABP Diastolic Blood Pressure (mmHg)	71 (7)	72 (7)	0.11

[1]Mean (SD); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

3.3.1 Urinary Sodium Excretion

At baseline, mean urinary sodium excretion was 3.26±1.5 g/day in the low sodium group and 3.01±1.41 g/day in the usual care group (Table 3-3). At 3 months, mean change in urinary sodium excretion was -0.12 g/day (95% CI, -0.33 to 0.09) in the low sodium target group and +0.28 g/day (95% CI, 0.06 to 0.51) in the control group. At 3 months, there was a significant difference in mean change in urinary sodium excretion between groups (-0.3 g/day, 95% CI, -0.57 to -0.04), P=0.03 for between-group comparison) (Table 3-3). At 24 months, mean change in urinary sodium excretion was -0.23 g/day (95% CI, -0.48 to 0.02) in the low sodium target group and 0.05 g/day (95% CI, -0.18 to 0.28) in the control group. At 24 months, there was no significant difference in mean change in urinary sodium excretion between groups (-0.1 g/day, 95% CI, -0.36 to 0.16), P=0.47 for between-group comparison) (Table 3-3). 34.3% of participants in the low sodium target group and 28.0% of participants in the control groups reduced sodium intake to less than 2.3 g/day at 24 months (P=0.20).

3.3.2 Discretionary salt intake in the low sodium group

At 24 months, there was a 31% (21 to 41%) reduction in the proportion of participants in the low sodium group that added salt to cooking, a 27% (16 to 37%) reduction in the proportion of participants in the low sodium group that added salt at the table and there was no difference in the proportion of participants in the low sodium group that eat out for the main meal (-7.7%, (-19 to 3.5%).

Table 3-3 Urinary Sodium Excretion at 3 Months and 24 Months in COSTICK Participants

	Low Sodium Intake				Usual Care				Unadjusted Mean Difference between Groups	P Value	Adjusted* Mean Difference between Groups	P Value
	Baseline	**3 Month**	**Unadjusted Mean Difference (3 months)**	**P Value**	**Baseline**	**3 Month**	**Unadjusted Mean Difference (3 months)**	**P Value**	**(3 Months)**		**(3 Months)**	
Sodium (g/day)	(n=157)	(n=157)	(n=157)		(n=160)	(n=160)	(n=160)		(n=317)		(n=317)	
	3.25+-1.53	3.13+-1.46	-0.12 (-0.33 to 0.09)	0.26	3.02+-1.38	3.3+-1.46	0.28 (0.06 to 0.51)	0.01	-0.41 (-0.71 to -0.1)	0.01	-0.3 (-0.57 to -0.04)	0.03
	Baseline	**24 Month**	**Unadjusted Mean Difference (24 months)**	**P Value**	**Baseline**	**24 Month**	**Unadjusted Mean Difference (24 months)**	**P Value**	**(24 Months)**		**(24 Months)**	
Sodium (g/day)	(n=159)	(n=159)	(n=159)		(n=163)	(n=163)	(n=163)		(n=322)		(n=322)	
	3.29+-1.51	3.06+-1.36	-0.23 (-0.48 to 0.02)	0.07	3.02+-1.42	3.07+-1.25	0.05 (-0.18 to 0.28)	0.67	-0.28 (-0.62 to 0.06)	0.11	-0.1 (-0.36 to 0.16)	0.47

3.3.3 Primary Outcome

3.3.3.1 Sodium Reduction Intervention and Nocturnal Systolic Blood Pressure (ABPM)

At baseline, mean nocturnal systolic BP was 110.3±13.1 mmHg in the low sodium group and 111.3±13.9 mmHg in the usual care group. Mean change in nocturnal systolic BP was +0.44 mmHg (95% CI, -1.51 to 2.39) in the low sodium target group and +2.96 mmHg (95% CI, 0.81 to 5.11) in the control group. At 24 months, there was no significant difference in mean change of nocturnal systolic BP between groups (-2.64 mmHg [95% CI, -5.36 to 0.08], P=0.06 for between-group comparison) (Table 3-4). In an analysis confined to participants who adhered to the sodium lowering intervention (n=279), there was a significant difference in mean change of nocturnal systolic BP (-3.63 mmHg [95% CI, -6.5 to 0-0.75]) (

Table 3-5). There was a significant difference between participants with hypertension at baseline (p-interaction=0.04) but no difference between subgroups in sex (p-interaction=0.18), age above and below median (p-interaction=0.41), study (p-interaction=0.19), or baseline office systolic BP tertiles (p-interaction=0.57) (Figure 3-2).

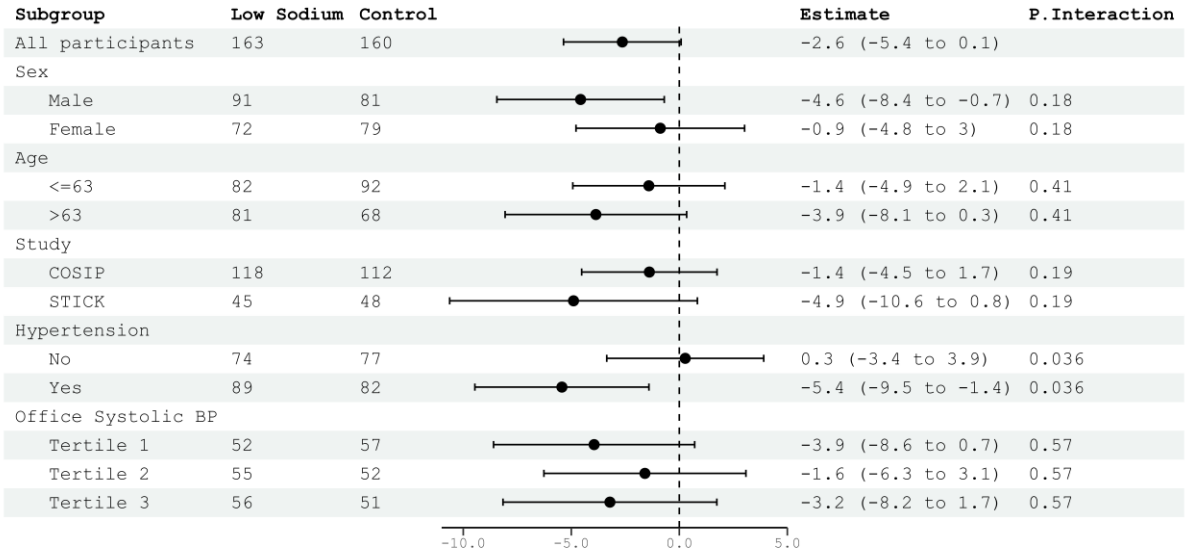
Table 3-4 Office and ABPM Baseline and 24-month Follow-up Systolic and Diastolic Blood Pressure (COSTICK)

	Low Sodium Intake				Usual Care				Difference	
	Baseline	**Month 24**	**Difference**	**P Value**	**Baseline**	**Month 24**	**Difference**	**P Value**	**Difference**	**P Value**
Primary Outcome - mm Hg										
Night Systolic	110.34+-13.13	111.09+-13.92	0.44 (-1.51 to 2.39)	0.66	111.27+-13.85	114.32+-15.8	2.96 (0.81 to 5.11)	0.01	-2.64 (-5.36 to 0.08)	0.06
Night Diastolic	63.56+-8.1	62.72+-8.45	-0.73 (-1.92 to 0.46)	0.23	63.41+-7.6	64.41+-8.75	1.02 (-0.23 to 2.26)	0.11	-1.77 (-3.35 to -0.2)	0.03
Secondary Outcomes										
ABPM - mm Hg										
Overall Systolic	121.88+-10.49	122.44+-12.08	0.33 (-1.27 to 1.93)	0.69	124.1+-11.49	125.07+-13.28	1.41 (-0.29 to 3.11)	0.1	-1.49 (-3.75 to 0.77)	0.2
Overall Diastolic	72.37+-6.88	71.77+-7.7	-0.75 (-1.61 to 0.11)	0.09	73.85+-6.77	73.58+-7.53	-0.04 (-0.95 to 0.87)	0.93	-1.11 (-2.32 to 0.1)	0.07
Day Systolic	125.79+-10.59	126.56+-12.55	0.39 (-1.34 to 2.12)	0.66	128.28+-12.15	128.47+-13.52	0.47 (-1.41 to 2.34)	0.62	-0.67 (-3.11 to 1.78)	0.59
Day Diastolic	75.64+-7.29	75.28+-8.22	-0.59 (-1.56 to 0.38)	0.23	77.44+-7.62	76.85+-7.97	-0.4 (-1.45 to 0.64)	0.45	-0.8 (-2.14 to 0.55)	0.25
Dipping Percentage (%)										
Dipping Systolic	12.2+-7.88	11.81+-8.8	-0.24 (-1.47 to 0.98)	0.69	12.98+-9.36	10.86+-8.49	-1.94 (-3.36 to -0.52)	0.01	1.24 (-0.41 to 2.9)	0.14
Dipping Diastolic	15.98+-8.94	15.89+-9.18	0.26 (-1.24 to 1.76)	0.73	17.54+-9.76	15.92+-8.87	-1.49 (-3.16 to 0.19)	0.08	0.57 (-1.28 to 2.42)	0.55
Dipping Status										
Dipper	73+-45.62	64+-40			74+-45.4	73+-44.79				
Extreme Dipper	27+-16.88	31+-19.38			34+-20.86	22+-13.5				
Non Dipper	53+-33.12	55+-34.38			40+-24.54	45+-27.61				
Reverse Dipper	7+-4.38	10+-6.25			15+-9.2	18+-11.04				
Night/day BP Ratio										
Systolic Ratio	0.88+-0.08	0.88+-0.09	0 (-0.01 to 0.01)	0.69	0.87+-0.09	0.89+-0.08	0.02 (0.01 to 0.03)	0.01		
Diastolic Ratio	0.84+-0.09	0.84+-0.09	0 (-0.02 to 0.01)	0.73	0.82+-0.1	0.84+-0.09	0.01 (0 to 0.03)	0.08		
Blood Pressure Variability										
Systolic CoV	8.95+-2.33	8.94+-2.44	-0.04 (-0.5 to 0.42)	0.86	8.86+-2.17	9.04+-2.35	0.14 (-0.33 to 0.61)	0.56		
Diastolic CoV	11.23+-3.16	11.55+-3.27	0.22 (-0.47 to 0.9)	0.54	10.88+-2.89	10.99+-3.01	0.16 (-0.49 to 0.81)	0.63		
Office - mm Hg										
Office Systolic	130.25+-13.84	129.58+-14.46	0.67 (-1.43 to 2.77)	0.53	131.69+-13.79	130.88+-16.54	0.81 (-1.58 to 3.2)	0.5	-0.53 (-3.47 to 2.41)	0.72
Office Diastolic	75.18+-9.2	74.26+-10.74	0.93 (-0.41 to 2.26)	0.17	76.28+-9.99	76.11+-10.84	0.17 (-1.22 to 1.56)	0.81	-1.37 (-3.17 to 0.43)	0.13

Table 3-5 Baseline and 24-month Follow-up Systolic and Diastolic BP (COSTICK) - Per-Protocol

	Low Sodium Intake				Usual Care				Difference	
	Baseline	**Month 24**	**Difference**	**P Value**	**Baseline**	**Month 24**	**Difference**	**P Value**	**Difference**	
Primary Outcome										
Night Systolic	110.75+-12.73	111.06+-13.41	0.16 (-1.96 to 2.29)	0.88	111.31+-14.37	115.26+-15.59	3.63 (1.39 to 5.86)	0	-3.63 (-6.5 to -0.75)	0.01
Night Diastolic	63.99+-7.68	62.85+-7.77	-1.03 (-2.35 to 0.28)	0.12	63.65+-7.59	64.64+-8.51	1.23 (-0.1 to 2.56)	0.07	-2.24 (-3.92 to -0.56)	0.01
Secondary Outcomes										
ABPM										
Overall Systolic	122.37+-10.48	123+-12.29	0.43 (-1.36 to 2.22)	0.64	123.97+-11.72	125.56+-13.34	1.69 (-0.15 to 3.53)	0.07	-1.55 (-4.03 to 0.92)	0.22
Overall Diastolic	72.81+-6.73	72.12+-7.56	-0.87 (-1.83 to 0.09)	0.07	73.95+-6.54	73.62+-7.49	-0.01 (-1.01 to 0.98)	0.98	-1.2 (-2.53 to 0.14)	0.08
Day Systolic	126.34+-10.72	127.15+-12.89	0.41 (-1.55 to 2.37)	0.68	128.04+-12.17	128.75+-13.45	0.65 (-1.35 to 2.65)	0.52	-0.64 (-3.31 to 2.04)	0.64
Day Diastolic	76.1+-7.19	75.65+-8.08	-0.74 (-1.84 to 0.36)	0.19	77.5+-7.39	76.78+-7.96	-0.48 (-1.63 to 0.66)	0.41	-0.76 (-2.25 to 0.73)	0.32
Dipping Percentage										
Dipping Systolic	12.31+-7.59	12.08+-8.63	-0.05 (-1.39 to 1.29)	0.94	12.82+-9.45	10.55+-7.82	-2.35 (-3.73 to -0.97)	0	2 (0.33 to 3.68)	0.02
Dipping Diastolic	15.89+-8.74	15.95+-8.92	0.48 (-1.18 to 2.13)	0.57	17.33+-9.81	15.61+-8.53	-1.85 (-3.61 to -0.1)	0.04	1.28 (-0.67 to 3.24)	0.2
Dipping Status										
Dipper	57+-41.91	53+-38.97			65+-45.45	67+-46.85				
Extreme Dipper	26+-19.12	29+-21.32			30+-20.98	15+-10.49				
Non Dipper	50+-36.76	46+-33.82			35+-24.48	42+-29.37				
Reverse Dipper	3+-2.21	8+-5.88			13+-9.09	15+-10.49				
Night/day BP Ratio										
Systolic Ratio	0.88+-0.08	0.88+-0.09	0 (-0.01 to 0.01)	0.94	0.87+-0.09	0.89+-0.08	0.02 (0.01 to 0.04)	0		
Diastolic Ratio	0.84+-0.09	0.84+-0.09	0 (-0.02 to 0.01)	0.57	0.83+-0.1	0.84+-0.09	0.02 (0 to 0.04)	0.04		
Blood Pressure Variability										
Systolic CoV	8.77+-2.19	8.97+-2.48	0.12 (-0.38 to 0.62)	0.63	8.88+-2.18	8.96+-2.15	0 (-0.47 to 0.48)	0.99		
Diastolic CoV	10.99+-2.92	11.47+-3.36	0.36 (-0.39 to 1.11)	0.35	10.85+-2.98	10.89+-2.97	0.09 (-0.61 to 0.79)	0.8		
Office										
Office Systolic	130.25+-13.84	129.58+-14.46	0.67 (-1.43 to 2.77)	0.53	131.69+-13.79	130.88+-16.54	0.81 (-1.58 to 3.2)	0.5	-0.53 (-3.47 to 2.41)	0.72
Office Diastolic	75.18+-9.2	74.26+-10.74	0.93 (-0.41 to 2.26)	0.17	76.28+-9.99	76.11+-10.84	0.17 (-1.22 to 1.56)	0.81	-1.37 (-3.17 to 0.43)	0.13

Figure 3-2 Forest Plots, According to Subgroups for the Nocturnal Systolic Blood Pressure. (COSTICK)



3.3.4 Secondary Outcomes

3.3.4.1 Sodium Reduction Intervention and Nocturnal Diastolic Blood Pressure (ABPM)

At baseline, the mean nocturnal diastolic BP was 63.6±8.1 mmHg in the low sodium group and 63.4±7.6 mmHg in the usual care group. Mean change in nocturnal diastolic BP was -0.73 mmHg (95% CI, -1.92 to 0.46) in the low sodium target group and +1.02 mmHg (95% CI, -0.23 to 2.26) in the control group. At 24 months, there was a significant difference in mean change of nocturnal diastolic BP between groups (-1.77 mmHg [95% CI, -3.35 to -0.2], P=0.03 for between-group comparison) (Table 3-4). In an analysis confined to participants who adhered to the sodium lowering intervention (n=279), there was a significant difference in mean change of nocturnal diastolic BP (-2.24 mmHg [95% CI, -3.92 to -0.56]) (

Table 3-5).

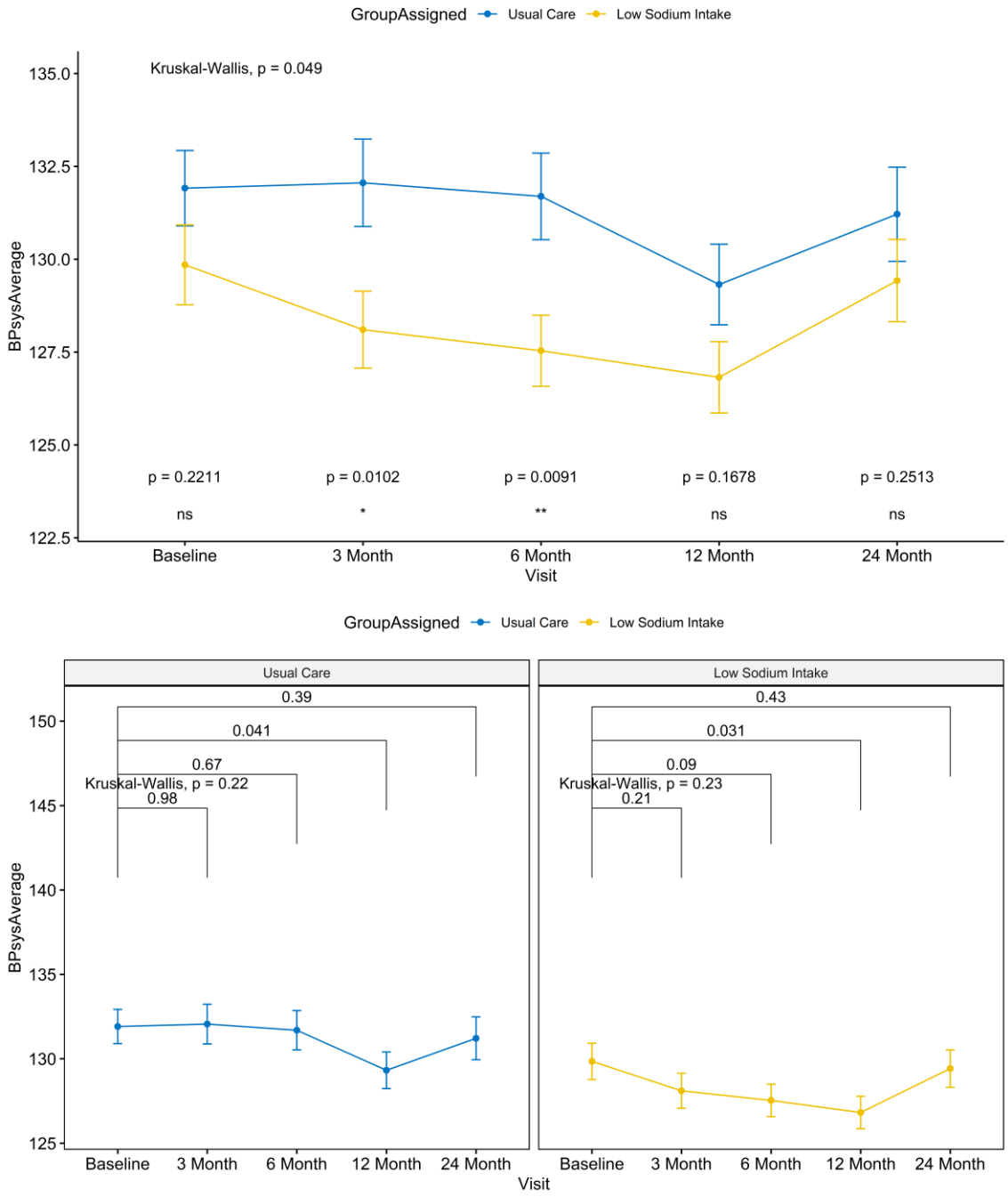
3.3.4.2 Sodium Reduction Intervention and Other ABPM Parameters

There was no significant difference between participants assigned to the low sodium intervention versus usual care for overall systolic BP (-1.49 mmHg [95% CI, -3.75 to 0.77]), overall diastolic BP (-1.11 mmHg [95% CI, -2.32 to 0.1]), daytime systolic BP (-0.67 mmHg [95% CI, -3.11 to 1.78]), daytime diastolic BP (-.08 mmHg [95% CI, -2.14 to 0.55]), office systolic BP (-0.53 mmHg [95% CI, -3.47 to 2.41]), office diastolic BP (-1.37 mmHg [95% CI, -3.17 to 0.43]), systolic dipping percentage (1.24% [95% CI, -0.41 to 2.9]), diastolic dipping percentage (0.57% [95% CI, -1.28 to 2.42]), night/day systolic BP ratio, night/day diastolic BP ratio, systolic coefficient of variation, or diastolic coefficient of variation (Table 3-4).

3.3.4.3 Sodium Reduction Intervention and Office Systolic Blood Pressure

There was a transient reduction in Office Systolic BP, but this was not sustained over two years. There was a between group difference in office systolic BP at 3 months (P=0.01) and 6 months (P=0.009) but no difference at 12 months and 24 months (Figure 3-3).

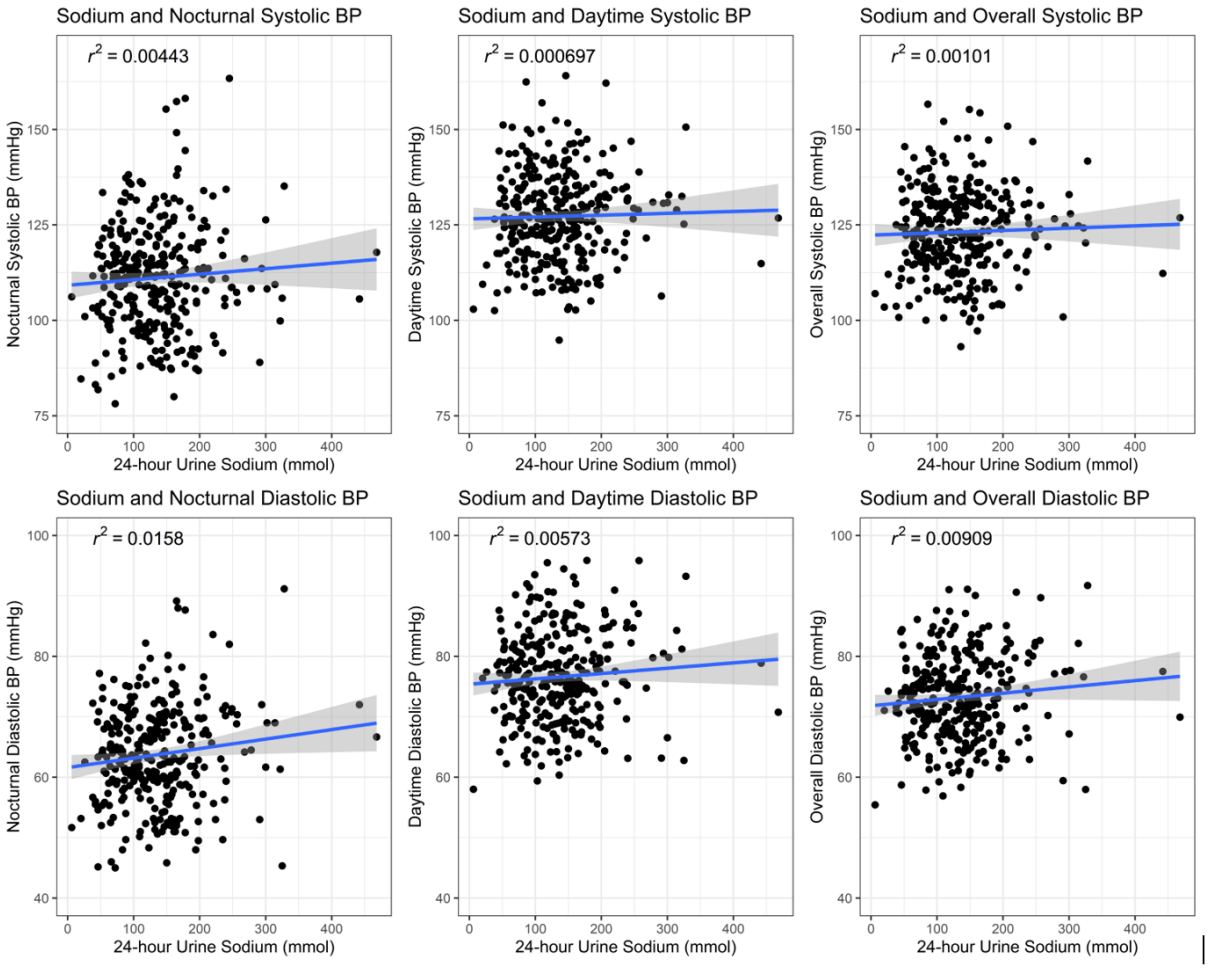
Figure 3-3 Sodium Reduction Intervention and Office Systolic Blood Pressure



3.3.4.4 Baseline 24-hour Urine Sodium Excretion and ABP Measurements

There was no significant correlation between 24-hour urine sodium excretion and nocturnal systolic BP (r^2=0.00443), nocturnal diastolic BP (r^2=0.0158), daytime systolic BP (r^2=0.000697), daytime diastolic BP (r^2=0.00573), overall systolic BP (r^2=0.00101) and overall diastolic BP (r^2=0.00909) (Figure 3-4).

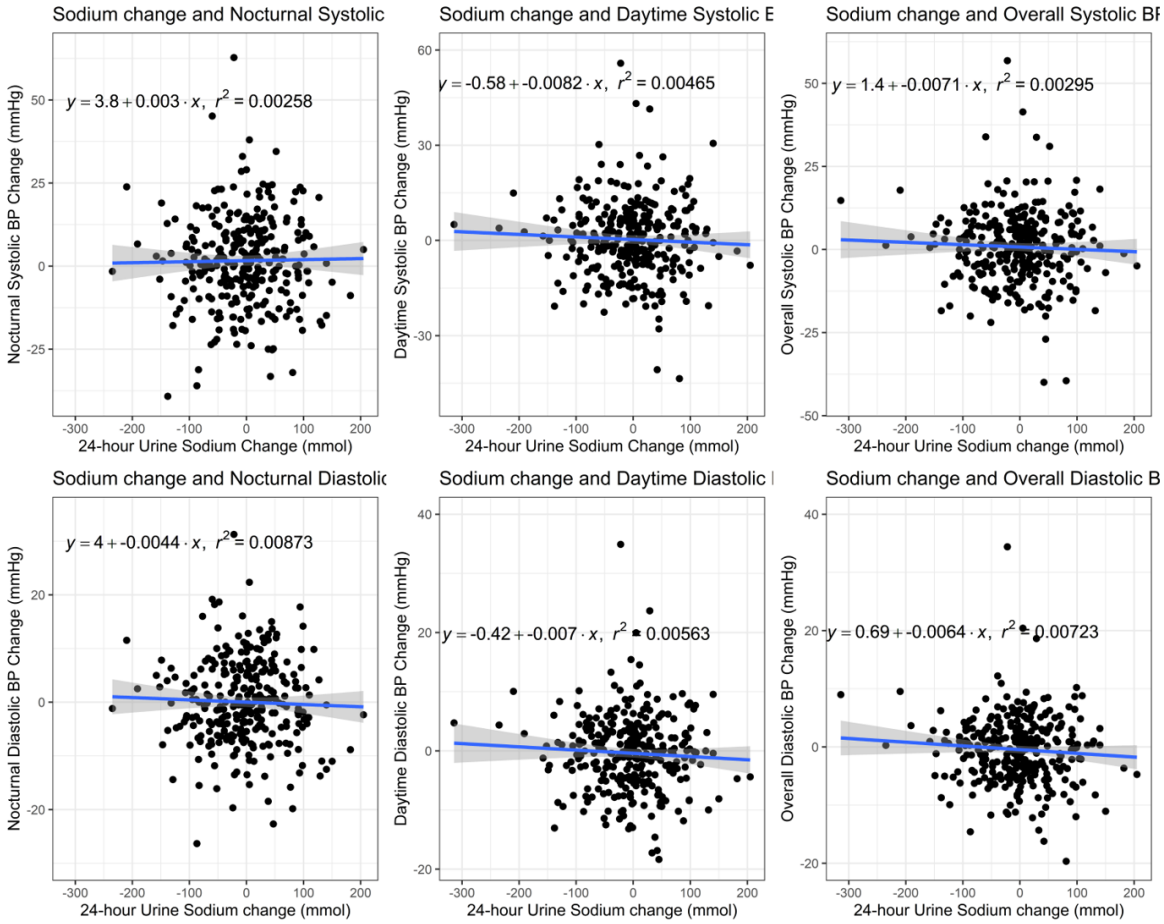
Figure 3-4 Baseline 24-hour Urine Sodium Excretion and ABP measurements



3.3.4.5 Change in 24-hour Urine Sodium Excretion and Change in ABP Measurements

There was no significant correlation between 24-hour urine sodium excretion and nocturnal systolic BP (r^2=0.00258), nocturnal diastolic BP (r^2=0.00873), daytime systolic BP (r^2=0.00465), daytime diastolic BP (r^2=0.00563), overall systolic BP (r^2=0.00295) and overall diastolic BP (r^2=0.00723) (Figure 3-5).

Figure 3-5 Change in 24-hour Urine Sodium Excretion and Change in ABP Measurements



3.3.5 Renal Outcomes

3.3.5.1 Sodium Reduction and eGFR-MDRD (Modification of Diet in Renal Disease)

3.3.5.1.1 COSTICK

At baseline, the mean eGFR-MDRD was 71.32±22.29 mL/min/1.73m^2 in the low sodium group and 73.3±21.58 mL/min/1.73m^2 in the usual care group. Mean change in eGFR-MDRD was 1.12 mL/min/1.73m^2 (95% CI, -0.8 to 3.04) in the low sodium target group and 1.32 mL/min/1.73m^2 (95% CI, -0.33 to 2.97) in the control group. At 24 months, there was no

significant difference in mean change in eGFR-MDRD between groups (-0.23 mL/min/1.73m^2 [95% CI, -2.74 to 2.27], P=0.86 for between-group comparison) (Table 3-6).

3.3.5.1.2 STICK

At baseline, the mean eGFR-MDRD was 49.4±11.08 mL/min/1.73m^2 in the low sodium group and 49.7±10.59 mL/min/1.73m^2 in the usual care group. Mean change in eGFR-MDRD was -1.5 mL/min/1.73m^2 (95% CI, -3.29 to 0.3) in the low sodium target group and -0.62 mL/min/1.73m^2 (95% CI, -2.63 to 1.39) in the control group. At 24 months, there was no significant difference in mean change in eGFR-MDRD between groups (-1.42 mL/min/1.73m^2 [95% CI, -4.04 to 1.21], P=0.29 for between-group comparison) (Table 3-7).

3.3.5.2 Sodium Reduction and eGFR-CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)

3.3.5.2.1 COSTICK

At baseline, the mean eGFR-CKD-EPI was 74.13±21.04 mL/min/1.73m^2 in the low sodium group and 75.53±21.03 mL/min/1.73m^2 in the usual care group. Mean change in eGFR-CKD-EPI was -0.64 mL/min/1.73m^2 (95% CI, -2.11 to 0.82) in the low sodium target group and 0.47 mL/min/1.73m^2 (95% CI, -1.0 to 1.94) in the control group. At 24 months, there was no significant difference in mean change in eGFR-CKD-EPI between groups (-1.27 mL/min/1.73m^2 [95% CI, -3.27 to 0.72], P=0.21 for between-group comparison) (Table 3-6)

3.3.5.2.2 STICK

At baseline, the mean eGFR-CKD-EPI was 51.09±11.92 mL/min/1.73m^2 in the low sodium group and 50.95±11.04 mL/min/1.73m^2 in the usual care group. Mean change in eGFR-CKD-EPI was -1.92 mL/min/1.73m^2 (95% CI, -3.82 to -0.02) in the low sodium target group and -0.94 mL/min/1.73m^2 (95% CI, -3.09 to 1.21) in the control group. At 24 months, there was no significant difference in mean change in eGFR-CKD-EPI between groups (-1.56 mL/min/1.73m^2 [95% CI, -4.35 to 1.23], P=0.27 for between-group comparison) (Table 3-7).

3.3.5.3 Sodium Reduction and Creatinine Clearance

3.3.5.3.1 COSTICK

At baseline, the mean Creatinine Clearance was 103.7±39.2 mL/min in the low sodium group and 100.97±38.91 mL/min in the usual care group. Mean change in Creatinine Clearance was -2.15 mL/min (95% CI, -7.62 to 3.32) in the low sodium target group and

+1.05 mL/min (95% CI, -4.28 to 6.38) in the control group. At 24 months, there was no significant difference in mean change in Creatinine Clearance between groups (-1.37 mL/min [95% CI, -7.81 to 5.07], P=0.68 for between-group comparison) (Table 3-6).

3.3.5.3.2 STICK

At baseline, the mean Creatinine Clearance was 77.75±28.16 mL/min in the low sodium group and 71.89±23.77 mL/min in the usual care group. Mean change in Creatinine Clearance was -3.98 mL/min (95% CI, -11.03 to 3.07) in the low sodium target group and -2.55 mL/min (95% CI, -8.69 to 3.6) in the control group. At 24 months, there was no significant difference in mean change in Creatinine Clearance between groups (1.01 mL/min [95% CI, -7.02 to 9.04], P=0.8 for between-group comparison) (Table 3-7).

3.3.5.4 Sodium Reduction and Proteinuria

3.3.5.4.1 COSTICK

At baseline, the mean proteinuria was 138.56±335.84 mg/day in the low sodium group and 98.24±194.81 mg/day in the usual care group. Mean change in proteinuria was +14.77 mg/day (95% CI, -29.22 to 58.76) in the low sodium target group and +11.65 (95% CI, -9.45 to 32.75) in the control group. At 24 months, there was no significant difference in mean change in proteinuria between groups (+10.76 mg/day [95% CI, -36.9 to 58.41], P=0.66 for between-group comparison) (Table 3-6).

3.3.5.4.2 STICK

At baseline, the mean proteinuria was 215.43±522.46 mg/day in the low sodium group and 163.62±341.51 mg/day in the usual care group. Mean change in proteinuria was -47.62 mg/day (95% CI, -110.85 to 15.61) in the low sodium target group and 23.5 mg/day (95% CI, -37.2 to 84.2) in the control group. At 24 months, there was no significant difference in mean change in proteinuria between groups (-54.34 mg/day [95% CI, -116.18 to 7.51], P=0.08 for between-group comparison) (Table 3-7).

Table 3-6 Renal Outcomes at 24 month Follow-up (COSTICK)

	Low Sodium Intake				Usual Care				Adjusted* Mean Difference between Groups	P Value
	Baseline	**24 Month**	**Unadjusted Mean Difference (24 months)**	**P Value**	**Baseline**	**24 Month**	**Unadjusted Mean Difference (24 months)**	**P Value**	**(24 Months)**	
eGFR-MDRD (mL/min/1.73m2)	(n=166)	(n=166)	(n=166)		(n=168)	(n=168)	(n=168)		(n=334)	
	71.32+-22.29	72.44+-26.58	1.12 (-0.8 to 3.04)	0.25	73.3+-21.58	74.62+-23.04	1.32 (-0.33 to 2.97)	0.12	-0.23 (-2.74 to 2.27)	0.86
eGFR-CKD-EPI (mL/min/1.73m^2	(n=166)	(n=166)	(n=166)		(n=168)	(n=168)	(n=168)		(n=334)	
	74.13+-21.04	73.49+-22.49	-0.64 (-2.11 to 0.82)	0.39	75.53+-21.03	76+-21.76	0.47 (-1 to 1.94)	0.53	-1.27 (-3.27 to 0.72)	0.21
Creatinine Clearance (mL/min)	(n=162)	(n=162)	(n=162)		(n=162)	(n=162)	(n=162)		(n=324)	
	103.7+-39.2	101.55+-39.47	-2.15 (-7.62 to 3.32)	0.44	100.97+-38.91	102.02+-38.82	1.05 (-4.28 to 6.38)	0.7	-1.37 (-7.81 to 5.07)	0.68
Proteinuria (mg/day)	(n=149)	(n=149)	(n=149)		(n=144)	(n=144)	(n=144)		(n=293)	
	138.56+-335.84	153.33+-381.39	14.77 (-29.22 to 58.76)	0.51	98.24+-194.81	109.88+-178.51	11.65 (-9.45 to 32.75)	0.28	10.76 (-36.9 to 58.41)	0.66

Table 3-7 Renal Outcomes at 24 month Follow-up (STICK)

	Low Sodium Intake				Usual Care				Adjusted* Mean Difference between Groups	P Value
	Baseline	**24 Month**	**Unadjusted Mean Difference (24 months)**	**P Value**	**Baseline**	**24 Month**	**Unadjusted Mean Difference (24 months)**	**P Value**	**(24 Months)**	
eGFR-MDRD (mL/min/1.73m^2)	(n=53)	(n=52)	(n=52)		(n=51)	(n=48)	(n=48)		(n=100)	
	49.4±11.04	47.73±12.34	-1.5 (-3.29 to 0.3)	0.1	49.61±10.52	49.08±12.49	-0.62 (-2.63 to 1.39)	0.54	-1.42 (-4.04 to 1.21)	0.29
eGFR-CKD-EPI (mL/min/1.73m^2)	(n=53)	(n=52)	(n=52)		(n=51)	(n=48)	(n=48)		(n=100)	
	51.29±11.89	49.17±13.28	-1.92 (-3.82 to -0.02)	0.05	50.88±11	50.01±13.33	-0.94 (-3.09 to 1.21)	0.39	-1.56 (-4.35 to 1.23)	0.27
Creatinine Clearance (mL/min)	(n=53)	(n=51)	(n=51)		(n=51)	(n=46)	(n=46)		(n=97)	
	77.98±28.75	73.76±25.87	-3.98 (-11.03 to 3.07)	0.26	72.1±23.4	69.34±20.73	-2.55 (-8.69 to 3.6)	0.41	1.01 (-7.02 to 9.04)	0.8
Proteinuria (mg/day)	(n=49)	(n=51)	(n=51)		(n=46)	(n=45)	(n=45)		(n=87)	
	206.67±513.26	243.37±671.77	-47.62 (-110.85 to 15.61)	0.14	196.78±380.61	192.91±269.55	23.5 (-37.2 to 84.2)	0.44	-54.34 (-116.18 to 7.51)	0.08

3.4 Discussion

In this randomised clinical trial of a dietary intervention to lower sodium intake (<2.3 g/day) compared to control, we report no significant difference in mean change in sodium intake or nocturnal systolic BP between groups over a 2-year period, in a population with mean sodium intake of 3.1 g/day. There was a significant difference in mean change in nocturnal diastolic BP but no significant differences in other ABP parameters (Daytime Systolic/Diastolic BP, Overall Systolic/Diastolic BP) between groups. Additionally, there was a significant difference between subgroups in hypertension at baseline but not in sex, age above and below median, study, or baseline office systolic BP tertiles. We observed no significant differences in other ABP parameters (Nocturnal Diastolic BP, Daytime Systolic/Diastolic BP, Overall Systolic/Diastolic BP) between groups.

In the intervention group of COSTICK, sodium intake was reduced by 0.23 g/day (95% CI, -0.02 to 0.48) at 24 months, which was not statistically significant. In the two largest long-term clinical trials (TOHP-II (144) and TONE (157)) of dietary counselling interventions to reduce sodium intake, mean reduction in sodium intake was 0.93±0.13 g/day at 36 months in TOHP-II and 0.91±0.12 g/day at 30 months in TONE, despite employing similar dietician led dietary sodium lowering interventions. TOHP-II showed no significant difference in their primary outcome of diastolic BP (-0.6±0.4 mmHg, P=0.17) at termination (36 months or at the final 3-visit sequence if after 36 months) or their secondary outcome of systolic BP (-1.0±0.5 mmHg, P=0.05) at termination (144). TONE showed a significant difference (HR, 0.69, 95% CI, 0.58-0.81) in their primary outcome of diagnosis of high blood pressure (a systolic BP of 190 mmHg or greater or a diastolic BP of 110 mmHg or greater at a single visit; or a mean systolic BP of 170 mmHg or greater or a mean diastolic BP of 100 mmHg or greater over 2 sequential visits; or a mean systolic BP of 150 mmHg or greater or a diastolic BP of 90 mmHg or greater over 3 sequential visits), or treatment with antihypertensive medication, or a cardiovascular event (myocardial infarction, angina, congestive heart failure, stroke, coronary artery bypass surgery or coronary artery angioplasty) at 30 months among those assigned versus not assigned to reduced sodium intake (157). In TONE, 38% assigned to sodium reduction compared to 24% of those not assigned to sodium reduction remained off antihypertensives with a BP less than 150/90 mmHg with no cardiovascular events (157). Additionally, there was no difference in cardiovascular events between those

assigned to sodium reduction versus those not (157). In TONE, the mean office blood pressure difference between those assigned to sodium reduction versus not assigned to sodium reduction at the attempted medication withdrawal (at 3 months) was SBP -3.4±0.8 mmHg and DBP -1.9±0.5 mmHg (157).

In COSTICK, the mean sodium intake at baseline was 3.1 g/day, which is lower than reported in TOHP-II (4.28 g/day) and TONE (3.6 g/day), and unlike those trials, we specifically recruited a population with moderate sodium intake, reducing the capacity for large reductions in sodium intake. Indeed, 3.1 g/day is lower than the mean (±SD) intake of 3.6±0.5 g per day reported by 129 surveys representing at least 5 decades and 45 countries (162). It is also at the lower end of the range for 90% of persons (3.07 to 4.38 g/day), a range that is potentially determined by physiologic needs rather than environmental factors (162). Additionally, 3.6 g/day coincides with an inflection point at which lower intakes have been reported to increase plasma renin activity, a potent mediator of sodium retention (163–165). Therefore, our trial addresses the question of whether individuals with moderate (average) sodium intake (3.1 g/day) benefit from dietician led interventions for dietary sodium lowering. Our findings, and those of TOHP-II (negative primary diastolic BP outcome), suggest that despite an intensive dietary counselling intervention (led by specialist dieticians), reducing sodium intake to less than 2.3 g/day is not feasible for many individuals (achieved in only 34.3% in the intervention versus 28.0% in the control groups at 24 months [P=0.20]). Potential explanations for this include the recently elucidated neurohormonal control of thirst and salt hunger which restores sodium balance by altering physiological processes and ingestive drives (166). Moreover, our observed small mean change in sodium intake, measured with repeated 24-hour urine collections, is a difference that would not be expected to reduce nocturnal blood pressure. An important implication of our study is the feasibility of dietary sodium reduction recommendations in other groups. For example, KDOQI Clinical Practice Guideline for Haemodialysis Adequacy makes a 1B recommendation to reduce dietary sodium intake in patients on dialysis (15). Our findings raise considerable concerns about the feasibility of targeting low sodium intake (<2.3 g/day) in any population, including those with renal disease.

In pre-specified subgroup analysis, we did find a statistically significant difference in participants with hypertension at baseline (-5.4 mmHg, 95% CI, -9.5 to -1.4) versus

participants with no hypertension at baseline (0.3 mmHg, 95% CI, -3.4 to 3.9) (P-Interaction = 0.036). This finding is different in magnitude from a short-term (4 week) phase II study of participants with resistant hypertension which showed a large reduction in nocturnal BP (systolic BP: -20.3 mmHg [95% CI, -32.3 to -8.3] and diastolic BP: -9.9 mmHg [95% CI, -15.0 to -4.8]). They also showed a reduction in overall and daytime BP, a finding also not seen in COSTICK. Like TOHP-II and TONE, the effect of lowering sodium and nocturnal BP is likely to decrease with time and not be present after a long follow-up period e.g., 2 years. The decrease in nocturnal systolic BP was numerically greater in participants with CKD (STICK participants) (-4.9 mmHg, 95% CI, -10.6 to 0.8) compared to Non-CKD (COSIP participants) (-1.4 mmHg, 95% CI, -4.5 to 1.7) but this was not statistically significant (P-interaction = 0.19). TONE and TOHP-II did not report differences between participants with CKD and without CKD. Additionally, there was no correlation between change in 24-hour sodium excretion between baseline and follow-up and change in Systolic or Diastolic (Nocturnal, Day, Overall) between baseline and follow-up (Figure 3-5). There was a transient reduction in Office BP, but this was not sustained over two years. There was a between group difference in office systolic BP at 3 months (P=0.01) and 6 months (P=0.009) but no difference at 12 months and 24 months. In our per-protocol analysis, confined to participants who adhered to the sodium lowering intervention (n=279), there was a significant difference in mean change of nocturnal systolic BP (-3.63 mmHg [95% CI, -6.5 to 0-0.75]), nocturnal diastolic BP (-2.24 mmHg [95% CI, -3.92 to -0.56]) at 24 months.

We found no association between a dietician-led dietary sodium reduction intervention compared to a healthy eating control group and eGFR (MDRD), eGFR (CKD-EPI), creatinine clearance, or proteinuria. A previous systematic review found an association between high (>4.6 g/day) sodium intake, compared to moderate/low sodium intake, and adverse renal outcomes including decrease in eGFR, increase in proteinuria or need for dialysis (151). One clinical trial (n=187) reported lower serum creatinine (82.3±14.7 µmol/l compared with 83.8±15.0 µmol/l while on placebo [P = 0.013]) and higher Urinary Albumin Excretion (10.2mg (IQR 6.8–18.9mg) while on sodium supplementation (3.8 g/day) compared with 9.1mg (IQR 6.6–14.0mg) while on placebo (2.5 g/day) (P < 0.001)) (167). In the STICK trial population alone, which represents the largest clinical trial completed evaluating a sodium reduction intervention on renal outcomes in a population with chronic kidney disease, we

found no significant reduction in sodium intake, nor evidence of an effect on renal outcomes. Again, our findings need to be interpreted in the context of not achieving low sodium intake targets at 24 months, and a non-significant reduction in sodium intake, meaning that we cannot draw conclusions on the effect of sustained low sodium intake on renal outcomes.

3.4.1 Limitations

Our study has several limitations. First, it was a unblinded study with potential for contamination. We tried to limit contamination by scheduling intervention groups for review on different days. Second, it was not a controlled diet study, so a reduction in dietary sodium intake could not be guaranteed. In fact, we see this as a different question that was answered by the DASH study (168), which showed a reduction in BP with a controlled low sodium diet. COSTICK-ABPM aimed to answer the question of whether an intensive dietary sodium lowering intervention would be successful in reducing nocturnal ABP in a population with moderate sodium intake. Third, 24-hour urinary collection suffers from under and over collection and transient changes to participants diet when they know they will be performing the collection.

3.4.2 Conclusion

We evaluated a dietician led dietary intervention for lowering sodium intake compared to a moderate sodium intake, in persons at low risk who did not have cardiovascular disease (COSIP), and in persons with Chronic Kidney Disease (STICK). Our data indicate that in this population of moderate sodium intake, there was no significant benefit of a dietary intervention of lowering sodium intake on nocturnal, overall, or daytime blood pressure or renal outcomes.

Chapter 4 Association of Sodium and Potassium Urinary Excretion and Acute Stroke (INTERSTROKE): Does eGFR modify the Association?

Conor S. Judge, Andrew Smyth, Martin O'Donnell. Renal Impairment Modifies the Association Between Sodium Intake and Risk of Stroke – An Analysis of INTERSTROKE. Kidney Week, American Society of Nephrology. October 25, 2018, San Diego Convention Centre. (Conference Poster)

Conor Judge, Martin J O'Donnell, Graeme J Hankey, Sumathy Rangarajan, Siu Lim Chin, Purnima Rao-Melacini, John Ferguson, Andrew Smyth, Denis Xavier, Liu Lisheng, Hongye Zhang, Patricio Lopez-Jaramillo, Albertino Damasceno, Peter Langhorne, Annika Rosengren, Antonio L Dans, Ahmed Elsayed, Alvaro Avezum, Charles Mondo, Danuta Ryglewicz, Anna Czlonkowska, Nana Pogosova, Christian Weimar, Rafael Diaz, Khalid Yusoff, Afzalhussein Yusufali, Aytekin Oguz, Xingyu Wang, Fernando Lanas, Okechukwu S Ogah, Adesola Ogunniyi, Helle K Iversen, German Malaga, Zvonko Rumboldt, Shahram Oveisgharan, Fawaz Al Hussain, Salim Yusuf, on behalf of the INTERSTROKE investigators, Urinary Sodium and Potassium, and Risk of Ischaemic and Haemorrhagic Stroke (INTERSTROKE): A Case–Control Study, American Journal of Hypertension, Volume 34, Issue 4, April 2021, Pages 414–425, https://doi.org/10.1093/ajh/hpaa176

Conor Judge, Martin J O'Donnell, INTERSTROKE, (2021), GitHub repository, https://conorjudge.github.io/interstroke

4.1 Introduction

Hypertension is a key modifiable risk factor for stroke and increasing sodium intake is positively associated with blood pressure (169,170). Reduction of sodium intake, to low intake levels of <2 g/day, has been proposed to be an effective population-level intervention to reduce blood pressure, and inferentially, reduce the burden of stroke (171–173). However, despite the modest positive association between sodium intake and blood pressure (174), the pattern of association of sodium intake with cardiovascular disease is consistently J-shaped in a number of large epidemiologic studies (175–177), despite using different methods to estimate sodium intake (24-hour urine collection, early morning fasting samples, or random non-fasting urine samples). For stroke, individual studies report an inconsistent relationship between sodium intake and stroke, with different epidemiologic studies reporting a linear association, a curvilinear relationship, or J-shaped association (178). In addition, the association of high sodium intake with stroke persists in most observational studies, after adjusting for blood pressure, suggesting mechanisms other than blood pressure may also mediate the increased cardiovascular risk (175).

Considerable public health efforts and resources are being invested in targeting low sodium intake (<2 g/day) (179), although there is controversy about whether low sodium intake represents the optimal target for cardiovascular prevention. Additionally, increased potassium intake appears to be an important target for stroke prevention, with meta-analyses reporting a linear reduction in stroke risk associated with increased potassium intake (180). Moreover, the feasibility of a combined target of low sodium and high potassium intake is challenged because only a very small proportion of the population consume this joint electrolyte target (181,182); sodium and potassium intake usually correlate positively with each other, indicating that targeting low sodium intake is more likely to be associated with reductions in potassium intake among free-living individuals, and vice versa (183). Studies also suggest that the adverse cardiovascular effects of high sodium intake may be mitigated with high potassium intake (181,184,185). Therefore, evaluating the association of sodium intake with stroke necessarily requires a combined analysis of the relationship of both electrolytes with stroke risk overall, and within stroke subtypes (185).

Chronic kidney disease is an independent risk factor for both ischaemic and haemorrhagic stroke (186). CKD is also associated with a greater neurological deficit following ischemic

stroke, a poor functional outcome and greater mortality (187). The association between sodium intake and stroke is potentially modified by renal function through several mechanisms including impaired sodium and water excretion, activation of renin-angiotensin-aldosterone, endothelial dysfunction and chronic inflammation (188–190). Altered sodium handling by the kidney in CKD, might affect the intake-excretion relationship and the degree to which sodium intake is reflected by sodium excretion has not been studied in CKD (191). In addition, increased potassium intake is associated with a lower risk of both stroke and adverse renal outcomes in prospective cohort studies (192,193).

INTERSTROKE was a standardised international case-control study that included participants from 30 countries (169). Unique aspects of this observational study include the breadth of the international population included, the standardised measurement of vascular risk factors (including diet) and the valid determination of primary stroke subtype (ischaemic or intracerebral haemorrhage) using neuroimaging.

In this chapter, we report the individual, and joint, associations of estimated sodium and potassium excretion, which are surrogates for intake, with stroke and how this association is modified by CKD.

4.2 Methods

4.2.1 Study Design and Participants

INTERSTROKE is a large, international case control study of risk factors for first stroke. 13,462 stroke patients and 13,483 matched controls were recruited between Jan 11, 2007 and Aug 8, 2015. For the current analyses, we include 9,275 cases and 9,726 controls with urinary measures of sodium and potassium (8,761 matched pairs for conditional analysis). Each case was matched for sex and age (±5 years) with control. Cases were patients with first acute stroke, either ischaemic or intracerebral haemorrhage, with confirmation by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) brain imaging. Patients with stroke were enrolled within five days of symptom onset and within 72 hours of hospital admission. Stroke severity was measured using the modified Rankin Scale at the time of recruitment and at 1-month follow-up. The study was approved by the ethics committees in all participating centres. Written informed consent was obtained from participants or their proxy.

4.2.2 Measurement of Risk Factors

Standardised questionnaires were used to collect data on demographics, lifestyle stroke risk factors and characteristics of acute stroke from all cases and controls. Physical measurements of weight, height, waist and hip circumferences, heart rate, and blood pressure were recorded in a standardised manner. In cases, blood pressure and heart rate were measured at three time-points: at admission, the next morning, and at the time of interview. A modified-Rankin scale score was collected at three time-points for cases: pre-admission, time of interview, and at one-month follow-up (either in person or by phone) and one time-point for controls (time of interview). Ischaemic stroke subtype was based on clinical assessment (baseline and one-month), neuroimaging (baseline), and results of tests to determine aetiology (ultrasound of carotids, cardiac imaging, and cardiac monitoring). Hypertension was defined as a composite of self-reported hypertension and a blood pressure reading of greater than 140/90 mmHg at recruitment. Diabetes mellitus was defined as self-reported diabetes or a HbA_{1c} of greater than 6·5% (48 mmol/mol) at recruitment.

4.2.3 Blood and Urine Collection and Analysis

Non-fasting blood and urine samples were taken from cases within 72 hours of recruitment and from controls at the time of interview. Samples were frozen at -20° to -70° and shipped to core laboratories (Hamilton-Canada, Beijing-China, Bangalore-India, and Istanbul-Turkey). Several formulae exist for estimation of 24-hour sodium and potassium excretion from spot urinary sodium/potassium measurements (194–196). These formulae have been validated against 24-hour urine collections (197) and serve as a valid measure of mean population sodium and potassium intake (198). The Tanaka formula was used to estimate 24-hour urine sodium and potassium excretion (194) and is reported to be associated with the least biased estimate for spot (non-fasting) urine samples in an international population (197).

4.2.4 Statistical Analysis

We calculated the correlation between urinary sodium and potassium excretion using Pearson's correlation coefficient, and of sodium and potassium excretion with blood pressure using an intra-class correlation coefficient (ICC) in controls (excluding those with known hypertension or taking diuretics). We used multivariable conditional logistic regression to evaluate the association of sodium and potassium excretion with stroke,

employing restricted cubic spline plots to explore the pattern of association (199). For analysis of categories of estimated sodium excretion, we set the reference group as the second quartile (2·8-3·5 g/day), as this was identified as the lowest risk category on initial univariate analyses, and consistent with the range of lowest risk on cubic splines. Similarly, we set the first quartile (<1.34 g/day) as the reference group for estimated potassium excretion.

We adjusted for covariates in four sequential models. Model 1 was adjusted for age and body mass index (BMI). Model 2 (the primary model) was additionally adjusted for education level (none-reference, 1-8 years, 9-12 years, Trade School, College/University), alcohol intake (never-reference, former, current), diabetes, atrial fibrillation or flutter, smoking (never-reference, former, current) and physical activity level (strenuous-reference, moderate, mild, mainly sedentary). Model 3 included all the variables in model 2 and added estimated excretion of potassium (Tanaka) and the alternative healthy eating index (AHEI) dietary score as an overall measure of diet quality. Model 4 included hypertension status, mean systolic blood pressure, mean diastolic blood pressure and medications which modify sodium excretion, which was a model to explore variables potentially along the causal pathway mediating the association of sodium and potassium intake with stroke. Model 4 was reproduced separately with the three components of the mean blood pressure variable: time of admission, the morning after admission, and during the interview. We examined the consistency of these associations by performing analyses in subgroups using our primary model (conditional analysis) based on key characteristics that might modify the association between sodium, potassium, and stroke (ethnicity, BMI, sex, age, hypertension, and diuretic therapy), using the Wald test to assess statistical interactions. We excluded small subgroups (<500 participants). We examined the association of sodium and potassium urinary excretion and stroke by CKD categories (CKD-EPI): G1: eGFR >90 ml/min/1.73m^2, G2: 60-89 ml/min/1.73m^2, G3: 30-59 ml/min/1.73m^2, and G4/G5: <30 ml/min/1.73m^2 (200). A Wald test was performed to test for an interaction effect of sodium and potassium urinary excretion and CKD categories.

We performed an analysis of the combined effects of sodium and potassium excretion, in which we generated eight categories (4x2), four by sodium excretion quartile (<2.8 g/day, 2.8-3.5 g/day, 3.5-4.26 g/day and >4.26 g/day) with potassium excretion above the median

(1·58 g/day) and four by sodium excretion quartile (<2.8 g/day, 2.8-3.5 g/day, 3.5-4.26 g/day and >4.26 g/day) with potassium excretion below the median (1·58 g/day). We completed a sensitivity analysis in which we excluded patients (cases) with a modified Rankin score greater than two, as such patients are more likely to not consume their usual diets and may receive co-interventions (e.g., intravenous fluids and enteric feeding due to their disability). Given that time from hospital admission to sample collection may also affect the classification of intake categories, we completed an analysis that excluded participants with samples collected greater than 48 hours after admission. All analyses were performed using R version 3.5.3 (Great Truth).

4.3 Results

4.3.1 INTERSTROKE Participants

Between Jan 11, 2007 and Aug 8, 2015, the INTERTSROKE study enrolled 9,275 cases of acute first stroke and 9,726 matched controls (8,761 matched pairs for conditional analysis) who also had urinary samples collected. Table 4-1 and Table 4-2 outline the characteristics of patients including co-morbidities, stroke type, stroke severity and blood pressure by quartiles of sodium and potassium excretion. The mean time between stroke onset and collection of urine sample was 2·08±1·27 days and the mean time between hospitalisation and collection of urine sample was 1·51±1·04 days. Figure 4-1 reports the scatterplot and a statistically significant correlation (r=0.4435, p<0.0001) between estimated urinary sodium and potassium excretion for cases and controls in the INTERSTROKE population. The mean 24-hour sodium excretion was 3.69 g/day for cases and 3.54 g/day for controls (P<0.001) (Table 4-1). The mean 24-hour potassium excretion was 1.58 g/day for cases and 1.68 g/day for controls (P<0.001) (Table 4-2).

Figure 4-1 Scatterplot of Estimated Urinary Sodium and Potassium Excretion

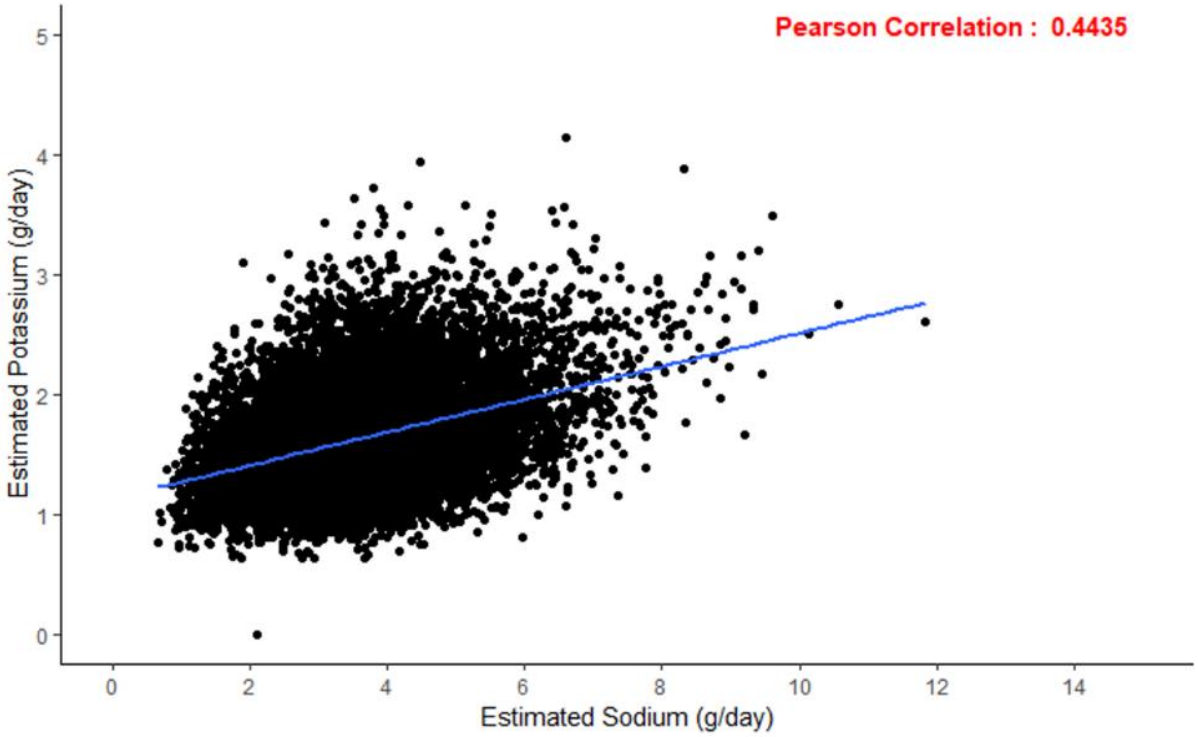


Table 4-1 Characteristics of the Study Participants at Baseline, According to Estimated Sodium Excretion (Conditional Analysis)

Characteristic	Case					Control				
	Estimated Sodium Excretion									
	All	<2.8 g/day	2.8-3.5 g/day	3.5-4.3 g/day	>4.3 g/day	All	<2.8 g/day	2.8-3.5 g/day	3.5-4.3 g/day	>4.3 g/day
	(N=8761)	(N=2214)	(N=1911)	(N=2065)	(N=2571)	(N=8767)	(N=2075)	(N=2481)	(N=2352)	(N=1859)
Estimated excretion - g/day										
Sodium	3.69±1.28	2.23±0.44	3.19±0.20	3.88±0.21	5.18±1.02	3.54±1.04	2.32±0.41	3.19±0.20	3.88±0.21	4.93±0.93
Potassium	1.58±0.38	1.43±0.30	1.49±0.33	1.56±0.34	1.78±0.42	1.68±0.42	1.48±0.35	1.62±0.39	1.75±0.40	1.88±0.44
Age - years	62.9±13.4	63.9±13.7	63.0±13.4	62.5±13.2	62.3±13.2	62.1±13.2	63.7±13.5	62.0±13.2	61.3±12.9	61.5±13.0
Female Sex - no. (%)	3574 (40.8)	959 (26.8)	770 (21.5)	797 (22.3)	1048 (29.3)	3580 (40.8)	925 (25.8)	978 (27.3)	929 (25.9)	748 (20.9)
Geographic region - no. (%)										
Western Europe / North America	1544 (17.6)	567 (36.7)	394 (25.5)	302 (19.6)	281 (18.2)	1544 (17.6)	381 (24.7)	439 (28.4)	447 (29.0)	277 (17.9)
Eastern / Central Europe / Middle East	1079 (12.3)	206 (19.1)	213 (19.7)	290 (26.9)	370 (34.3)	1079 (12.3)	211 (19.6)	287 (26.6)	322 (29.8)	259 (24.0)
Africa	587 (6.70)	278 (47.4)	126 (21.5)	90 (15.3)	93 (15.8)	587 (6.70)	213 (36.3)	192 (32.7)	118 (20.1)	64 (10.9)
China	3891 (44.4)	728 (18.7)	836 (21.5)	1053 (27.1)	1274 (32.7)	3891 (44.4)	832 (21.4)	1089 (28.0)	1051 (27.0)	919 (23.6)
Southeast Asia	615 (7.02)	155 (25.2)	123 (20.0)	125 (20.3)	212 (34.5)	615 (7.01)	204 (33.2)	214 (34.8)	126 (20.5)	71 (11.5)
South America	1045 (11.9)	280 (26.8)	219 (21.0)	205 (19.6)	341 (32.6)	1051 (12.0)	234 (22.3)	260 (24.7)	288 (27.4)	269 (25.6)
Stroke type - no. (%)										
Ischaemic	6805 (77.7)	1710 (77.4)	1537 (81.0)	1646 (80.0)	1912 (74.7)	-	-	-	-	-
ICH	1919 (21.9)	499 (22.6)	361 (19.0)	411 (20.0)	648 (25.3)	-	-	-	-	-
Hypertension - no. (%)	5243 (59.8)	1363 (61.6)	1134 (59.3)	1192 (57.7)	1554 (60.4)	3299 (37.6)	974 (46.9)	998 (40.2)	988 (42.0)	856 (46.0)
Blood pressure - mmHg										

	Systolic	148±21.2	149±22.0	147±20.8	148±20.5	149±21.3	133±18.5	133±19.1	133±18.3	133±17.8	134±18.7
	Diastolic	86.5±12.3	87.0±13.2	85.4±12.1	86.5±11.8	86.9±12.0	80.1±10.7	79.3±11.2	79.8±10.5	80.3±10.3	81.1±10.6
Cholesterol - mmol/litre											
	HDL	1.15±0.35	1.18±0.37	1.16±0.37	1.14±0.34	1.12±0.33	1.22±0.37	1.22±0.38	1.23±0.38	1.21±0.35	1.20±0.37
	LDL	2.97±1.01	3.03±1.08	2.96±0.98	2.99±0.99	2.91±0.98	2.98±0.96	2.98±1.01	3.04±0.97	2.97±0.94	2.90±0.92
Diabetes mellitus - no. (%)		1486 (17.0)	355 (16.0)	315 (16.5)	359 (17.4)	457 (17.8)	1108 (12.6)	283 (13.6)	304 (12.3)	303 (12.9)	218 (11.7)
AFIB/Atrial Flutter - no. (%)		936 (10.7)	301 (13.6)	210 (11.0)	170 (8.23)	255 (9.92)	270 (3.08)	74 (3.57)	69 (2.78)	61 (2.59)	66 (3.55)
Diuretic Pre-admission - no. (%)		1132 (12.9)	298 (13.5)	260 (13.6)	229 (11.1)	345 (13.4)	782 (8.92)	194 (9.35)	185 (7.46)	204 (8.68)	199 (10.7)
Diuretic In Hospital - no. (%)		1994 (22.8)	537 (24.3)	418 (21.9)	441 (21.4)	598 (23.3)	352 (12.8)	73 (11.3)	80 (10.2)	95 (13.7)	104 (16.3)
Current smoker - no. (%)		2623 (29.9)	610 (27.6)	591 (30.9)	666 (32.3)	756 (29.4)	1850 (21.1)	429 (20.7)	522 (21.0)	510 (21.7)	389 (20.9)

Plus–minus values are means ± Standard Deviation (SD). ICH-Intracerebral Haemorrhage. LDL-Low-Density Lipoprotein. HDL-High-Density Lipoprotein. AFIB-Atrial Fibrillation.

Table 4-2 Characteristics of the Study Participants at Baseline, According to Estimated Potassium Excretion (Conditional Analysis)

Characteristic		Case					Control				
		Estimated Potassium Excretion									
		All	<1.34 g/day	1.34-1.58 g/day	1.58-1.86 g/day	>1.86 g/day	All	<1.34 g/day	1.34-1.58 g/day	1.58-1.86 g/day	>1.86 g/day
		(N=8985)	(N=2240)	(N=1929)	(N=2079)	(N=2586)	(N=8991)	(N=2129)	(N=2519)	(N=2381)	(N=1879)
Estimated excretion - g/day											
	Potassium	1.58±0.38	1.17±1.28	1.46±0.07	1.71±0.08	2.15±0.29	1.68±0.42	1.17±0.13	1.46±0.07	1.72±0.08	2.18±0.30
	Sodium	3.68±1.28	3.16±0.97	3.50±1.08	3.80±1.14	4.52±1.58	3.53±1.04	3.01±0.86	3.32±0.88	3.63±0.90	3.97±1.15
Age – years		62.9±13.7	60.3±14.0	63.4±13.2	64.2±13.4	64.3±13.2	62.1±13.4	59.9±14.2	61.9±13.3	62.7±13.0	63.5±12.7
Female Sex - no. (%)		4401 (41.6%)	1041 (26.9%)	1074 (27.8%)	962 (24.9%)	790 (20.4%)	4411 (41.6%)	860 (21.0%)	920 (22.5%)	1027 (25.1%)	1287 (31.4%)
Geographic region - no. (%)											
	Western Europe / North America	1915 (18.1%)	191 (7.08%)	423 (16.7%)	573 (24.3%)	504 (27.1%)	1917 (18.1%)	61 (2.88%)	192 (8.40%)	406 (16.5%)	1151 (38.9%)
	Eastern / Central Europe / Middle East	1394 (13.2%)	225 (8.34%)	293 (11.6%)	368 (15.6%)	272 (14.6%)	1393 (13.2%)	180 (8.49%)	275 (12.0%)	336 (13.7%)	387 (13.1%)
	Africa	971 (9.18%)	222 (8.23%)	208 (8.22%)	180 (7.62%)	147 (7.90%)	975 (9.20%)	208 (9.81%)	199 (8.70%)	167 (6.80%)	203 (6.87%)
	China	3976 (37.6%)	1463 (54.2%)	1114 (44.0%)	804 (34.1%)	541 (29.1%)	3976 (37.5%)	1005 (47.4%)	1140 (49.8%)	1035 (42.1%)	759 (25.7%)
	Southeast Asia	855 (8.09%)	350 (13.0%)	167 (6.60%)	91 (3.85%)	60 (3.23%)	855 (8.07%)	481 (22.7%)	182 (7.96%)	99 (4.03%)	31 (1.05%)
	South America	1461 (13.8%)	246 (9.12%)	324 (12.8%)	345 (14.6%)	336 (18.1%)	1477 (13.9%)	185 (8.73%)	299 (13.1%)	413 (16.8%)	425 (14.4%)
Stroke type - no. (%)											
	Ischaemic	8265 (78.5%)	2112 (28.9%)	2000 (27.3%)	1840 (25.1%)	1365 (18.7%)	-	-	-	-	-
	ICH	2261 (21.5%)	579 (27.7%)	514 (24.6%)	515 (24.6%)	483 (23.1%)	-	-	-	-	-

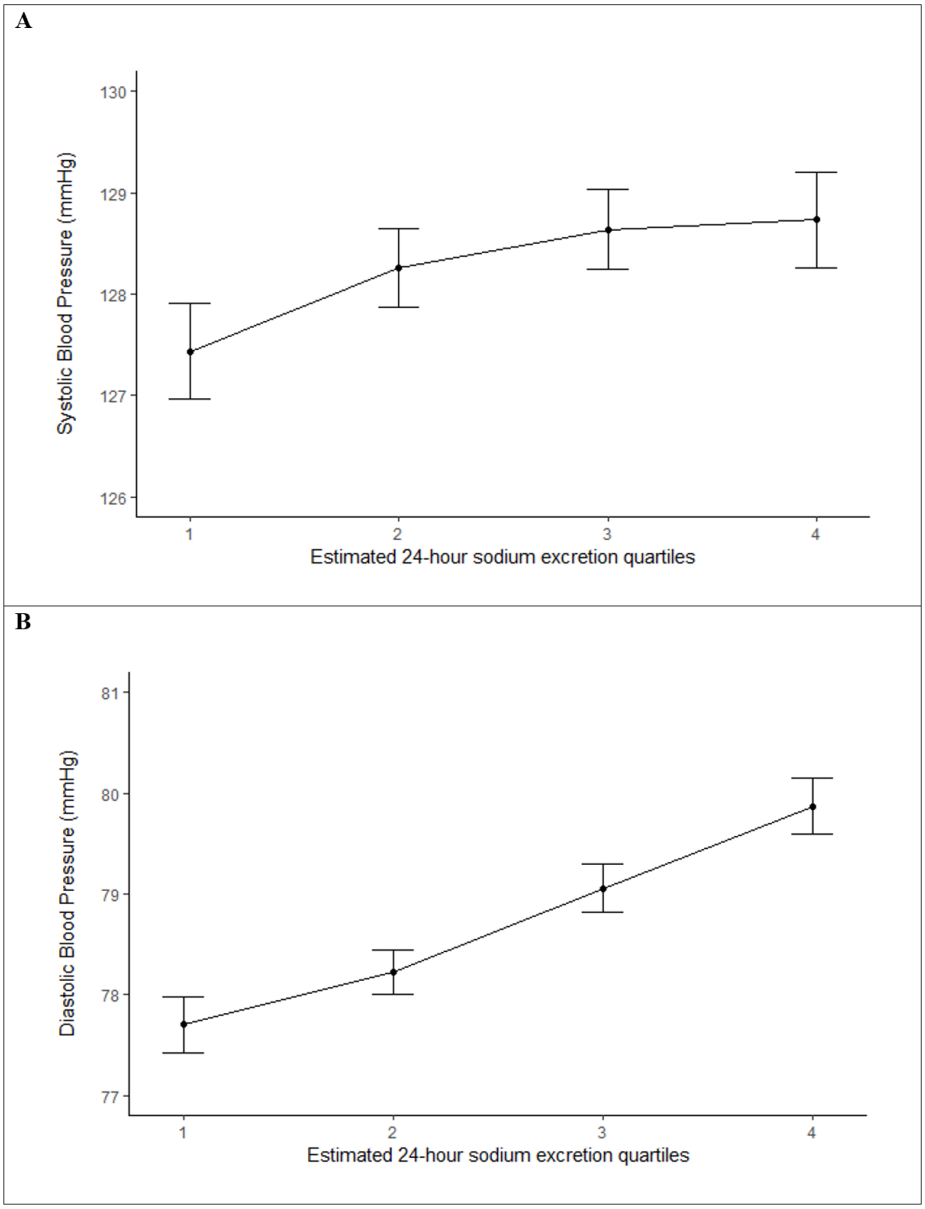
Hypertension - no. (%)	6391 (60.5%)	1502 (26.5%)	1516 (26.8%)	1462 (25.8%)	1181 (20.9%)	4094 (38.7%)	779 (20.8%)	871 (23.2%)	977 (26.0%)	1125 (30.0%)
Blood pressure - mmHg										
Systolic	149±21.6	148±21.1	148±20.9	149±21.9	150±22.1	133±18.6	133±19.6	133±18.3	133±18.4	133±18.3
Diastolic	86.4±12.5	87.2±12.2	86.0±12.2	86.3±12.8	86.8±12.7	79.9±10.8	80.6±11.1	80.4±10.9	79.7±10.4	79.3±10.6
Cholesterol - mmol/litre										
HDL	1.15±0.35	1.13±0.35	1.14±0.35	1.15±0.34	1.17±0.37	1.22±0.38	1.18±0.36	1.19±0.36	1.21±0.36	1.27±0.40
LDL	2.97±1.03	3.04±1.00	2.97±1.03	2.93±1.01	2.88±1.03	2.96±0.97	2.95±0.98	3.00±0.97	2.98±0.96	2.93±0.97
Diabetes mellitus - no. (%)	1900 (18.0)	332 (20.4)	426 (26.2)	461 (28.4)	405 (24.9)	1412 (13.3)	204 (16.0)	259 (20.3)	365 (28.6)	448 (35.1)
AFIB/Atrial Flutter - no. (%)	1187 (11.2)	171 (16.7)	280 (27.4)	294 (28.7)	278 (27.2)	343 (3.24)	42 (13.5)	54 (17.4)	83 (26.8)	131 (42.3)
Diuretic Pre-admission - no. (%)	1391 (13.2)	230 (18.7)	310 (25.2)	366 (29.7)	325 (26.4)	996 (9.41)	131 (14.4)	179 (19.6)	245 (26.9)	356 (39.1)
Diuretic In Hospital - no. (%)	2459 (23.3)	524 (24.3)	560 (26.0)	555 (25.7)	518 (24.0)	441 (12.2)	78 (19.6)	90 (22.6)	108 (27.1)	122 (30.7)
Current smoker - no. (%)	3057 (28.9)	1006 (36.0)	749 (26.8)	601 (21.5)	436 (15.6)	2132 (20.1)	554 (27.7)	591 (29.5)	460 (23.0)	397 (19.8)

Plus–minus values are means ± Standard Deviation (SD). ICH-Intracerebral Haemorrhage. LDL-Low-Density Lipoprotein. HDL-High-Density Lipoprotein. AFIB-Atrial Fibrillation.

4.3.2 Estimated Sodium Excretion (Quartiles) and Blood Pressure

Figure 4-2 reports the association of urinary sodium excretion and blood pressure among controls not receiving antihypertensive therapy or pre-hospital diuretics and indicates a graded increase in blood pressure with increasing sodium intake. For each 1-g increment in estimated sodium excretion, there was an increment of 1.01 mmHg in systolic blood pressure (P<0·001) and an increment of 0·48 mmHg in diastolic blood pressure (P<0·001).

Figure 4-2 Mean Systolic and Diastolic Blood Pressure by Sodium Quartile (Controls Excluding Baseline Hypertension and Pre-hospital Diuretic Use)



4.3.3 Estimated Sodium Excretion (Quartiles) and Risk of Stroke and Stroke Subtypes

Compared to the reference quartile Q2 (sodium excretion of 2·8-3·5 g/day), Q1 (Odds Ratio (OR) 1.39; 95% CI, 1.26-1.53, sodium excretion <2·8 g/day) and Q4 (OR 1.81; 95% CI, 1.65-2.00, sodium excretion >4·26 g/day) were associated with significant increases in the risk of all stroke (Table 4-3). The highest quartile (Q4 >4·26 g/day) was more strongly associated with ICH (OR 2.38; 95% CI, 1.93-2.92) than ischaemic stroke (OR 1.67; 95% CI, 1.50-1.87) (P<0.001). Sodium excretion <2·8 g/day was significantly associated with both ischaemic stroke (OR 1.36; 95% CI, 1.22-1.52) and ICH (OR 1.62; 95% CI, 1.32-1.99) (Figure 4-3).

Table 4-3 Association of Estimated 24-hour Sodium Excretion Quartiles and Risk of Stroke

			Estimated Sodium Excretion			
			<2.8 g/day	2.8-3.5 g/day	3.5-4.26 g/day	>4.26 g/day
			(N=4751)	(N=4750)	(N=4750)	(N=4750)
Analysis – odds ratio (95% CI)						
	Univariate analysis *		1.40 (1.28-1.52)	1.00	1.15 (1.06-1.25)	1.84 (1.69-2.01)
	Multivariate analysis					
		Model 1: Analysis including age and BMI	1.41 (1.29-1.54)	1.00	1.14 (1.05-1.25)	1.86 (1.70-2.03)
		Model 2: Primary analysis †	1.39 (1.26-1.53)	1.00	1.13 (1.03-1.24)	1.81 (1.65-2.00)
		Model 3: Analysis including dietary score and potassium excretion ‡	1.24 (1.12-1.37)	1.00	1.28 (1.16-1.41)	2.49 (2.24-2.77)
		Model 4: Analysis including HTN and medications which modify sodium excretion §	1.16 (1.03-1.30)	1.00	1.22 (1.09-1.36)	2.35 (2.08-2.65)
	Sensitivity analysis					
		Primary analysis excluding MRC > 2	1.37 (1.18-1.58)	1.00	1.08 (0.95-1.23)	1.64 (1.42-1.88)
		Primary analysis excluding urine collection >48 hours	1.28 (1.12-1.47)	1.00	1.18 (1.03-1.34)	1.91 (1.67-2.18)

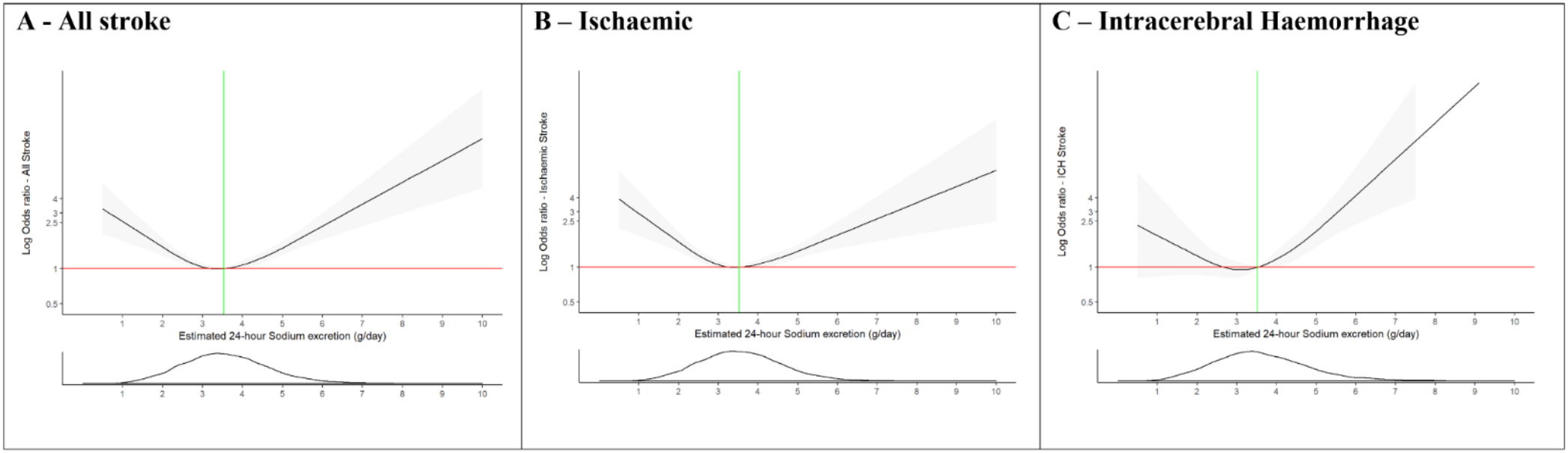
* The univariate analysis was performed using the logistic regression model.

† The primary model included age, BMI, education level, alcohol, diabetes at baseline, atrial fibrillation/flutter at baseline, smoking and physical activity level.

‡ Dietary score was the alternative healthy eating index (AHEI).

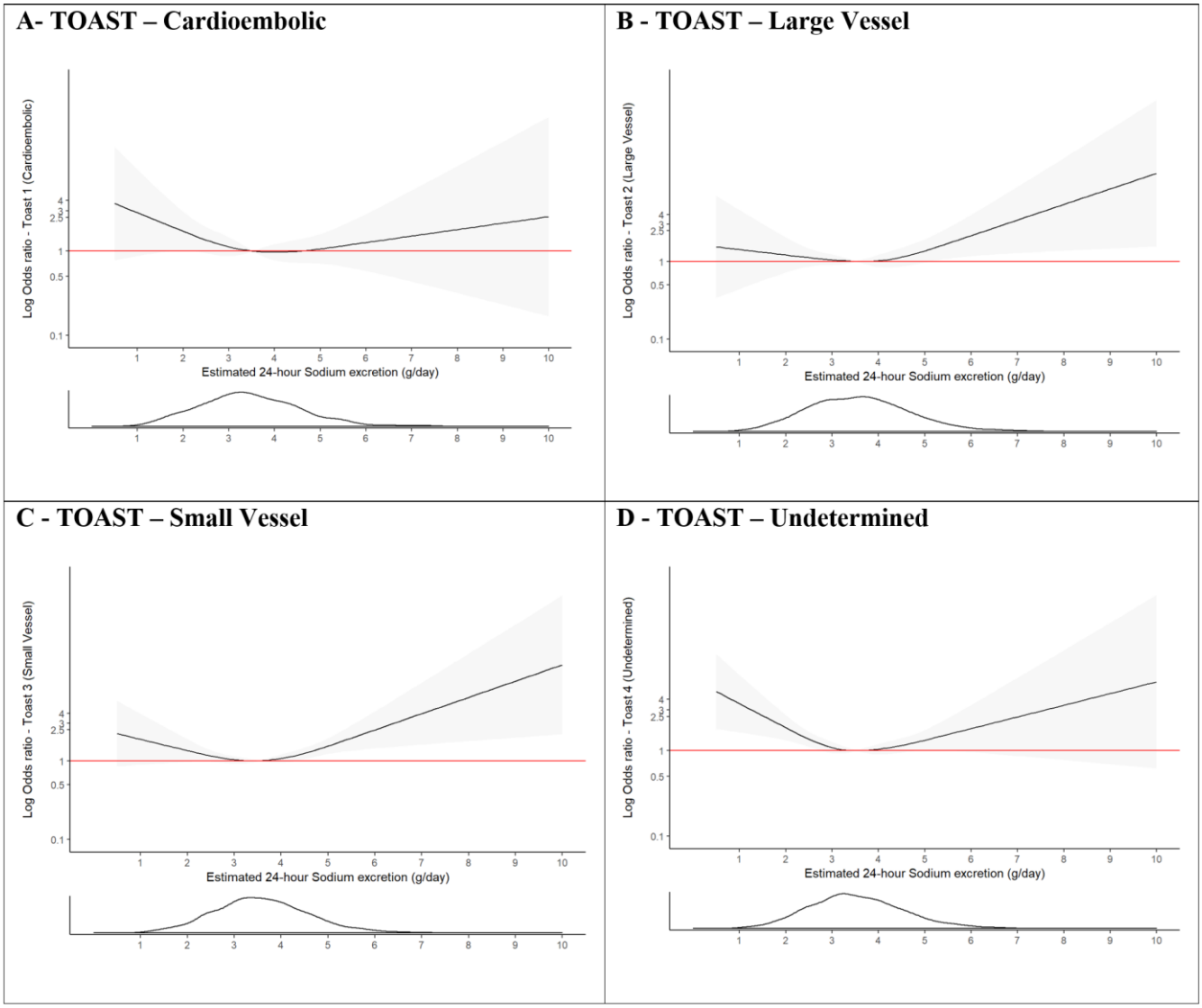
§ Hypertension variables hypertension status, systolic blood pressure and diastolic blood pressure. We adjusted for pre-hospital ace-inhibitor, angiotensin receptor blocker and diuretic use.

Figure 4-3 Association of Estimated 24-hour Sodium Excretion (Tanaka) with Risk of Stroke and Pathological Stroke Subtypes



The association of high sodium excretion (>4·26 g/day) and stroke remained significant after adjustment for blood pressure and prior history of hypertension (OR 2.35; 95% CI, 2.08-2.65). Within ischaemic stroke subtypes, the association of high sodium intake was significant for small vessel and large vessel ischaemic stroke, but not significant for cardioembolic stroke (Figure 4-4).

Figure 4-4 Association of Estimated 24-hour Sodium Excretion (Tanaka) and Risk of Ischaemic Stroke Subtypes (TOAST Classification).



4.3.4 Estimated Sodium Excretion (Quartiles) and Risk of Stroke Stratified by CKD Categories

Compared to the reference quartile Q2 (sodium excretion of 2·8-3·5 g/day), Q1 (sodium excretion of <2.8 g/day) remained significant for CKD G1 and G2 but was non-significant for G3, and G4/G5. Compared to the reference quartile Q2, Q4 (sodium excretion of >4.2 g/day) remains significant for all categories of CKD with a similar magnitude of estimate, except for a larger estimate for CKD G4/G5 (OR 3.30; 95% CI, 1.81-6.14). The overall P for interaction was significant (P-interaction=0.0039) but Q4 vs Q2 was the only individual P for interaction that was significant (P-interaction=0.033) (Table 4-4), and we did not find a statistically significant P-interaction for increased risk associated with low sodium excretion.

Table 4-4 Association of 24-hour Sodium Excretion and Risk of Stroke by CKD Category

CKD Categories (n)	<2.8 g/day	P-Interaction	2.8-3.5 g/day	3.5-4.2 g/day	P-Interaction	>4.2 g/day	P-Interaction	Overall P-Interaction
	Q1	Q1 vs Q2	Q2 (Ref)	Q3	Q3 vs Q2	Q4	Q4 vs Q2	
Overall (18944)	1.35 (1.24-1.47)		1.0	1.10 (1.01-1.20)		1.78 (1.64-1.94)		
G1 (5897)	1.44 (1.23-1.69)		1.0	0.98 (0.84-1.14)		1.95 (1.68-2.27)		
G2 (7298)	1.36 (1.19-1.56)	0.53	1.0	1.09 (0.95-1.25)	0.1	1.57 (1.37-1.80)	0.033	0.0039
G3 (4936)	1.14 (0.97-1.34)		1.0	1.22 (1.04-1.44)		1.83 (1.54-2.17)		
G4/G5 (543)	1.42 (0.85-2.40)		1.0	2.00 (1.08-3.77)		3.30 (1.81-6.14)		

4.3.5 Estimated Potassium Excretion and Risk of Stroke and Stroke Subtypes

Compared to the reference quartile Q1 (potassium excretion of <1.34 g/day), Q2 (OR 0.83; 95% CI, 0.76-0.92, potassium excretion 1·34-1·58 g/day), Q3 (OR 0.68; 95% CI, 0.62-0.75, potassium excretion 1·58-1·86 g/day), and Q4 (OR 0.46; 95% CI, 0.41-0.51, potassium excretion >1·86 g/day) were all associated with a significant lower risk of all stroke, which was largely related to the association of potassium excretion with ischaemic stroke and there was no significant association with ICH (Table 4-5, Figure 4-5).

Table 4-5 Association of Estimated 24-hour Potassium Excretion Quartiles and Risk of Stroke

Estimated Potassium Excretion Quartiles					
		Quartile 1	Quartile 2	Quartile 3	Quartile 4
		<1.34 g/day	1.34-1.58 g/day	1.58-1.86 g/day	>1.86 g/day
		(N=4817)	(N=4816)	(N=4817)	(N=4816)
Analysis – odds ratio (95% CI)					
Univariate analysis *		1.00	0.80 (0.73-0.87)	0.67 (0.61-0.73)	0.43 (0.39-0.47)
Multivariate analysis					
	Model 1: Analysis including age and BMI	1.00	0.80 (0.73-0.88)	0.64 (0.59-0.71)	0.42 (0.38-0.46)
	Model 2: Primary analysis †	1.00	0.83 (0.76-0.92)	0.68 (0.62-0.75)	0.46 (0.41-0.51)
	Model 3: Analysis including dietary score and sodium excretion ‡	1.00	0.75 (0.68-0.83)	0.56 (0.51-0.63)	0.33 (0.29-0.37)
	Model 4: Analysis including HTN and medications which modify potassium excretion §	1.00	0.76 (0.68-0.86)	0.57 (0.51-0.65)	0.33 (0.29-0.38)
Sensitivity analysis					
	Primary analysis excluding MRC > 2	1.00	0.70 (0.60-0.81)	0.48 (0.41-0.56)	0.24 (0.20-0.28)
	Primary analysis excluding urine collection >48 hours	1.00	0.87 (0.76-0.99)	0.78 (0.68-0.89)	0.67 (0.58-0.77)

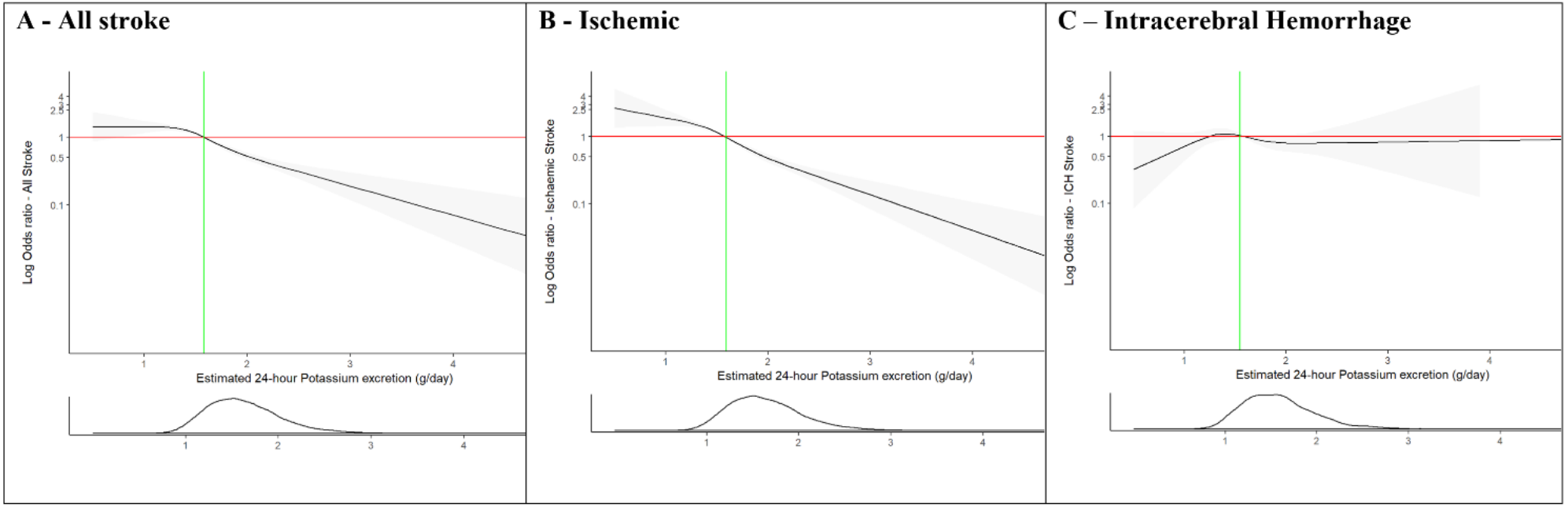
* The univariate analysis was performed using the logistic regression model.

† The primary model included age, BMI, education level, alcohol, diabetes at baseline, atrial fibrillation/flutter at baseline, smoking and physical activity level.

‡ Dietary score was the alternative healthy eating index (AHEI).

§ Hypertension variables hypertension status, systolic blood pressure and diastolic blood pressure. We adjusted for pre-hospital ace-inhibitor, angiotensin receptor blocker and diuretic use.

Figure 4-5 Association of Estimated 24-hour Potassium Excretion (Tanaka) with Risk of Stroke and Pathological Stroke Subtypes



4.3.6 Estimated Potassium Excretion (Quartiles) and Risk of Stroke Stratified by CKD Categories

Compared to the reference quartile Q1 (potassium excretion of <1.34 g/day), Q2 (potassium excretion of 1.34-1.58 g/day) remained significant for CKD G1, G2, and G3 but was non-significant for G4/G5. Compared to Q1 [reference], Q3 (potassium excretion of 1.58-1.86 g/day) remains significant for all categories of CKD with a similar magnitude of estimate, apart from CKD G4/G5 (OR 1.46; 95% CI, 0.84-2.55). Compared to Q1 [reference], Q4 (potassium excretion of >1.86 g/day) remains significant for all categories of CKD with a similar magnitude of estimate, apart from CKD G4/G5 (OR 1.60; 95% CI, 0.88-2.94). The overall P for interaction was significant (P-interaction<0.001) but Q4 was the only individual P for interaction that was significant (P-interaction<0.001) (Table 4-6).

Table 4-6 Association of 24-hour Potassium Excretion and Risk of Stroke by CKD Category

CKD Category (n)	**<1.34 g/day**	**1.34-1.58 g/day**	**1.58-1.86 g/day**	**>1.86 g/day**	**Overall P-Interaction**
	Q1 (Ref)	**Q2**	**Q3**	**Q4**	
Overall (19207)	1.0	0.82 (0.75-0.89)	0.70 (0.64-0.77)	0.46 (0.42-0.50)	<0.001
G1 (5974)	1.0	0.84 (0.72-0.98)	0.62 (0.53-0.72)	0.40 (0.34-0.47)	
G2 (7382)	1.0	0.79 (0.69-0.90)	0.68 (0.59-0.79)	0.39 (0.34-0.46)	
G3 (5005)	1.0	0.80 (0.68-0.94)	0.74 (0.63-0.87)	0.60 (0.50-0.71)	
G4/G5 (571)	1.0	1.16 (0.68-2.00)	1.46 (0.84-2.55)	1.60 (0.88-2.94)	

4.3.7 Joint Urinary Sodium and Potassium Excretion and Risk of Stroke

For all stroke, compared with a joint reference category of moderate sodium excretion (2.8-3.5 g/day) and high potassium excretion (>=1·58 g/day) (lowest risk category), all other categories were associated with an increased risk of stroke, with sodium excretion >4.26 g/day and potassium excretion <1·58 g/day reporting the highest magnitude of risk (OR 4.17; 95% CI, 3.51-4.96). The magnitude of association was reduced for both low (<2.8 g/day) and high (>4.26 g/day) sodium excretion when potassium excretion was high (>=1.58 g/day) (P-interaction <0.001) (Table 4-7).

Table 4-7 Association of Joint Urinary Sodium and Potassium Excretion with Stroke

Joint Association of Urinary Sodium and Potassium Excretion with Stroke					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for interaction
	<2.8 g/day	2.8-3.5 g/day	3.5-4.26 g/day	>4.26 g/day	
Potassium less than the median (<1.58 g/day)	OR_{Joint} 2.10 (1.89-2.50)	OR_{Joint} 1.94 (1.69-2.24)	OR_{Joint} 2.62 (2.26-3.05)	OR_{Joint} 4.17 (3.51-4.96)	<0.001
	(n=3176)	(n=2600)	(n=2217)	(n=1471)	
Potassium greater than or equal to the median	OR_{Joint} 1.69 (1.44-1.98)	Ref 1·0	OR_{Joint} 1.10 (0.95-1.26)	OR_{Joint} 2.26 (1.97-2.59)	
(>=1.58 g/day)	(n=1575)	(n=2149)	(n=2530)	(n=3278)	

4.3.8 Subgroup and Sensitivity Analysis of the Associations Between Sodium and Potassium Excretion and Risk of Stroke

There was a significantly increased risk of stroke for Q4 (>4.26 g/day) versus Q2 (2.8-3.5 g/day) in participants with a BMI less than or equal to 30 (OR 1.92, 95% CI, 1.72-2.15) compared to participants with a BMI greater than 30 (OR 1.35, 95% CI, 0.81-2.26) (P-interaction=0.009). The association of high sodium excretion with stroke (>4.26 g/day) versus Q2 (2.8-3.5 g/day) was significant for European (OR 1.34, 95% CI, 1.11-1.63), Chinese (OR 1.85, 95% CI, 1.59-2.14), Other Asian (OR 10.83, 95% CI, 6.35-18.48), Latin American (OR 1.61, 95% CI, 1.23-2.13), Black African (OR 1.95, 95% CI, 1.10-3.47), and "Other" African ethnicity (OR 1.96, 95% CI, 1.12-3.43). The association of low sodium excretion with stroke (<2.8 g/day) versus Q2 (2.8-3.5 g/day) was significant for European (OR 1.57, 95% CI, 1.30-1.89), Arab (OR 2.51, 95% CI, 1.13-5.56), Latin American (OR 1.40, 95% CI, 1.06-1.87), Black African (OR 2.21, 95% CI, 1.37-3.55), and Other ethnicity (OR 2.21, 95% CI, 1.43-3.41) (P-

interaction <0.001). The associations for both high sodium excretion (OR 1.46, 95% CI, 0.77-2.76) and low sodium excretion (OR 1.55, 95% CI, 0.71-3.41) compared to Q2 (2.8-3.5 g/day) were non-significant for participants with diuretic use at baseline (P-interaction=0.1505). Sex, age, or baseline hypertension status did not alter the association significantly between both high and low estimated sodium excretion and stroke (Table 4-8).

Table 4-8 Multivariate (Conditional) Association Between Estimated 24-Hour Urinary Sodium Excretion and Stroke in Subgroups

	<2.8 g/day	2.8-3.5 g/day	3.5-4.26 g/day	>4.26 g/day	P
	N=4751	N=4750	N=4750	N=4750	
European (5885)	1.57 (1.30-1.89)	1.00	0.85 (0.71-1.03)	1.34 (1.11-1.63)	<0.001
Chinese (8009)	1.16 (0.98-1.36)	1.00	1.28 (1.10-1.47)	1.85 (1.59-2.14)	
Other Asian (1397)	1.06 (0.70-1.62)	1.00	1.91 (1.22-2.97)	10.83 (6.35-18.48)	
Arab (502)	2.51 (1.13-5.56)	1.00	1.55 (0.57-4.18)	2.18 (0.71-6.72)	
Latin American (2812)	1.40 (1.06-1.87)	1.00	0.90 (0.67-1.20)	1.61 (1.23-2.13)	
Black African (993)	2.21 (1.37-3.55)	1.00	1.31 (0.79-2.19)	1.95 (1.10-3.47)	
Other (1114)	2.21 (1.43-3.41)	1.00	0.90 (0.54-1.50)	1.96 (1.12-3.43)	
BMI >30 (3514)	1.14 (0.68-1.93)	1.00	0.95 (0.58-1.55)	1.35 (0.81-2.26)	0.009
BMI <=30 (17522)	1.33 (1.19-1.48)	1.00	1.15 (1.03-1.28)	1.92 (1.72-2.15)	
Male (12353)	1.43 (1.26-1.62)	1.00	1.14 (1.01-1.29)	1.83 (1.62-2.07)	0.88
Female (8812)	1.34 (1.15-1.56)	1.00	1.11 (0.95-1.29)	1.79 (1.54-2.09)	
Age >75 (3929)	1.32 (1.04-1.68)	1.00	1.17 (0.90-1.51)	1.78 (1.38-2.30)	0.41
Age <=75 (17236)	1.41 (1.27-1.58)	1.00	1.12 (1.01-1.24)	1.84 (1.65-2.05)	
Previous HTN (10485)	1.19 (0.99-1.44)	1.00	1.08 (0.89-1.31)	1.51 (1.25-1.82)	0.22
No HTN (10679)	1.43 (1.19-1.73)	1.00	1.25 (1.04-1.49)	1.92 (1.59-2.32)	
Diuretic (2387)	1.55 (0.71-3.41)	1.00	1.06 (0.53-2.12)	1.46 (0.77-2.76)	0.15
No Diuretic (18766)	1.40 (1.26-1.56)	1.00	1.14 (1.03-1.27)	1.87 (1.68-2.09)	

The exclusion of cases with modified Rankin scale greater than two, and the exclusion of cases with urine collected greater than forty-eight hours after symptom onset did not materially alter findings (Table 4-3, Table 4-5). We repeated all analyses with the Kawasaki formula, urinary sodium/creatinine ratio and urinary sodium, which revealed consistent

patterns of association, but as expected, different thresholds of sodium and potassium excretion (g/day) were associated with stroke risk.

4.4 Discussion

In this large, international, case-control study, we report an overall J-shaped association between sodium intake and stroke risk, with the lowest risk at moderate sodium intake (2·8-3·5 g/day), employing estimated 24-hour urinary excretion of sodium as a surrogate for intake. The association of high sodium intake was modified by CKD category (P-interaction=0.033) and showed the greatest association with stroke for CKD G4/G5. The association between low sodium intake and stroke was not modified by CKD stage (P-interaction=0.53). The association of high sodium intake was stronger for intracerebral haemorrhage compared to ischaemic stroke and within ischaemic stroke subtypes, was significant for small vessel and large vessel ischaemic stroke, but not significant for cardioembolic stroke. The association between estimated potassium excretion and risk of ischaemic stroke was inverse and linear, but not significant for ICH. The magnitude of association for both low (<2.8 g/day) and high (>4.26 g/day) sodium excretion was diminished in those with high potassium intake (≥1·58 g/day) (P-interaction <0.001). Chronic kidney disease, based on eGFR alone, modified the association of high sodium excretion and risk of acute stroke whereby the magnitude of odds ratio was higher in populations with lower eGFR. In contrast, eGFR did not modify the association of low sodium intake and risk of stroke. We also report a modifying effect of eGFR for the association of urinary potassium excretion with risk of acute stroke, in that the magnitude of odds ratio diminished with reducing eGFR, suggesting that the potential advantage of high potassium intake may be diminished in populations with chronic kidney disease.

Most national and international guidelines recommend low sodium intake in the entire population, for stroke prevention (e.g., WHO recommend an intake of <2·0 g/day). Primarily, the target of low sodium is based on the short-term phase IIa DASH-Sodium trial which reported a blood pressure reduction when reducing sodium intake to less than 1·5 g/day by providing all meals to the participants (168), and the longer-term trials (TONE and TOHP-II) which achieved mean sodium intakes of 2.3 g/day and 3.11 g/day (despite targeting a sodium intake of 1.8 g/day or lower) through intense dietary counselling (201,202). While a target of <2.0 g/day can be achieved in a highly controlled food environment, we report that

a very low proportion of the population consume a low sodium intake, and an even lower proportion consume a combined low sodium and high potassium intake. Our findings are consistent with other epidemiologic studies, and support the contention that a lower limit of sodium intake exists among free living populations due to neurohormonal control mechanisms that auto regulate the consumption of sodium (166). Activation of the renin–angiotensin–aldosterone system occurs when sodium intake falls below approximately 3.0 g/day. An analysis of the HOPE study reported a positive association between higher quintiles of plasma renin activity and cardiovascular outcomes including stroke (203), and consistently, the relative risk for the highest quintile of plasma renin activity was 1.43, identical to our estimate for the stroke risk associated with sodium excretion <2.8 g/day. In addition, we report a different pattern of association between sodium intake and blood pressure (positive and monotonic) compared to the pattern of association with stroke risk (J-shaped). These patterns have also been reported in several recent large cohort studies (175,204), and challenge assumptions that underpin current guidelines (i.e., that all reductions in blood pressure will reduce stroke, regardless of baseline sodium intake level) (177). Our findings do however, support public health interventions to reduce sodium intake among populations with high sodium intake and support transitioning populations from high to moderate sodium intake in order to reduce stroke (205). Our data suggest that the risk associated with a higher sodium intake may be greater in regions outside of Europe and North America.

Our findings suggest that reducing high sodium intake (>4 g/day) is especially important in patients with reduced eGFR. We report a modifying effect of CKD category on the association of urinary sodium excretion and risk of acute stroke, and raise the possibility that a lower intake target may be appropriate in the population, compared to the a population with normal renal function. However, our analysis also reports a consistent increased in risk with low sodium intake across CKD categories, arguing against the current target of <2.3 g/day in any population. We did not find that CKD category modified the association of low sodium excretion and risk of acute stroke, lending some additional exclusionary information on the mechanism that may influence a potential increased cardiovascular risk associated with low sodium intake.

Current guidelines recommend high potassium intake in the general population (>3.51 g/day) (206), while guidelines in patients with chronic kidney disease (CKD G4-G5) recommend a reduced potassium intake (207). Our analysis looking at combined sodium and potassium intake found a positive correlation of both electrolytes, meaning that achieving high potassium intake combined with low sodium intake is difficult, and achieving joint target intakes is uncommon. In population with reduced eGFR, we did find evidence that the association of higher potassium intake and stroke risk is altered for patients with CKD G4-G5, where we observed a change in the direction of association, albeit non-significant. An observational analysis of the ONTARGET/TRANSCEND dataset, which reported an overall reduced risk of adverse renal outcomes with increasing potassium excretion, also reported a loss of association in those with more advanced renal disease (154). As such, our findings lend some evidence to support current guideline recommendations for potassium intake in patients with advanced renal disease (CKD G4-G5), but not those with mild or moderate impairment.

Our data also provide important insights into the anticipated effects of reducing high sodium intake on patterns of stroke and its subtypes; reducing high sodium intake is likely to have a greater effect on reducing ICH than ischaemic stroke, but is nevertheless expected to also reduce ischaemic stroke, and thereby the global burden of all stroke. In ecological studies of stroke incidence in China, for example, population-level reductions in high sodium intake parallel reductions in stroke incidence, and are more marked for ICH than ischaemic stroke (208). In the INTERSTROKE study, about 40% of the control population were consuming high sodium intake in a range associated with stroke risk, supporting a targeted-population approach to sodium reduction, rather than a population-wide approach.

Our analyses also suggest that increases in potassium intake may be of comparable, or greater, importance to stroke prevention than reductions in sodium intake (181,184,185). This finding is consistent with reports that high potassium intake is a marker of a healthy diet i.e., rich in fruit and vegetables (209).

A recent analysis of the PURE cohort study reported that the combination of moderate sodium intake and high potassium intake was associated with the lowest cardiovascular risk, and our analyses are further evidence that such a combined target may be optimal (181). A cluster randomised controlled trial reported significant reductions in cardiovascular risk with

potassium salt substitution (210). Potassium salt substitution not only increased potassium intake but also reduced high sodium intake (but not to low intake levels) (210). An ongoing large cluster randomised controlled trial in China is currently evaluating potassium salt substitutes for prevention of stroke (211). Our analyses, and those of other studies, raise major concerns about the feasibility of increasing potassium intake, while simultaneously achieving low sodium intake. They suggest that populations should target moderate sodium intake and high potassium intake as the optimal balance, as the former is expected to make the latter more achievable.

Measurement of sodium and potassium intake is a major challenge, and there is no "gold" standard for estimating usual sodium and potassium intake (212). The reference standard (213) (repeated 24-hour urinary collections) is impractical in large epidemiologic studies and would invariably lead to the exclusion of a substantial proportion of participants and a biased sample. In our study, the mean intake of sodium in the control group was 3.54 g/day, which is close to the mean intake reported by the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (3·95 g/day) and the PURE study (4·9 g/day) (175,214). In the PURE study, a fasting morning urine sample was collected, and the Kawasaki formula was used to estimate sodium excretion. In contrast, we collected a random urine sample and used the Tanaka formula to estimate sodium excretion. A validation study of 1083 participants from the PURE study showed a similar differences between mean sodium estimated using the Kawasaki equation and Tanaka equation (197). Importantly, however, irrespective of the method we employed in INTERSTROKE, which included urinary sodium/creatinine ratio, Tanaka formula or Kawasaki formula, the J-shaped pattern of association were consistent among all analyses, and median intake levels are associated with lowest cardiovascular risk. Collectively, despite the study-by-study variation in methods of estimating sodium intake, there is a remarkable consistency in findings from large epidemiologic studies that the optimal range of sodium intake resides within a range between 2·7-5·0 g/day. This is also the range identified in a meta-analysis of prospective cohort studies published before 2014 (177), by Graudal et al., and consistent with prospective cohort studies reported since then, including PURE (181), CRIC (191), and PREVEND (215) studies.

4.4.1 Limitations

The case control design has inherent limitations, including sampling bias (selection of cases and controls) and measurement bias (recall bias). Sensitivity analysis by control type (community versus hospital) did not alter our findings and estimated urinary sodium excretion is an objective lab measurement and not susceptible to recall bias.

Another limitation is the potential acute effects of stroke on excretion of sodium intake, particularly the change in oral intake and use of intravenous fluids in those with severe stroke. To address this issue, we performed several sensitivity analyses by excluding patients with a modified Rankin score greater than two as these patients are likely have received intravenous fluids and enteric feeding due to their disability. Excluding these patients did not materially alter our findings. In addition, increasing time from admission to urinary sample measurement may reduce the correlation of usual (pre-stroke) diet with urinary estimate. Confining the analyses to those with early urine collections did not alter conclusions. Moreover, we are unable to quantify whether some of the reductions in eGFR were related to acute kidney injury, which is common in patients with acute stroke, and may introduce a misclassification when considering stage of eGFR, and expected to be more common in cases than controls. However, our eligibility criteria only allowed those within 96 hours of hospitalisation to be included, which is expected to reduce this source of bias. Another limitation is the narrow spread of estimated potassium excretion (0.85 to 2.97 grams/day) compared to the spread of estimated sodium excretion (1.22 to 7.38 grams/day). This discrepancy in range does alter their respective abilities to detect a J-shaped association. There are a lower proportion in the high intake range for potassium intake, resulting in an inability to detect whether there is an increased risk in high intake ranges. However, this issue is not unique to our study, whereby range of intakes are lower for potassium compared to sodium intake. Unlike sodium intake, where intakes can come from discretionary and non-discretionary sources (with large variability in both sources), potassium is derived exclusively from within dietary items. Finally, we defined chronic kidney disease with eGFR alone, and do not have measurements of albuminuria to include in our analysis, which is a major limitation of our analyses.

4.4.2 Strengths

A key strength of the INTERSTROKE study was the availability of neuroimaging to classify all cases of stroke. INTERSTROKE is the only large study which reliably examines whether the associations of sodium and potassium differs between ischaemic stroke, ischaemic stroke subtypes and ICH. Obtaining such information from cohort studies is impractical. The diverse international population included in our results are widely generalisable.

4.4.3 Conclusion

In conclusion, an estimated sodium excretion <2·8 g/day and >4·26 g/day are both associated with an increased risk of stroke (reference 2·8-3·5 g/day). An estimated potassium excretion of greater than 1.34 g/day were both associated with a reduced risk of stroke (reference <1.34 g/day). Reduced eGFR modifies the association of high sodium excretion (but not low sodium excretion) and acute stroke, and modifies the association of high potassium excretion and acute stroke. In the absence of large randomised controlled trials, the collective information from observational data is that the optimal intake of sodium is a moderate intake level in all populations combined with high potassium intake in populations without stage 4/5 chronic kidney disease.

Chapter 5 Cardiovascular Risk Associated with Stopping Antihypertensive Therapy in Patients with and without Chronic Kidney Disease – An Analysis of the SPRINT Trial

Judge, Conor S., Alvarez-Iglesias, Alberto, Ferguson, John P., Costello, Maria, Smyth, Andrew, O'Donnell, Martin. Did Non-Standard Withdrawal of Antihypertensive Agents Exaggerate Treatment Effect in SPRINT? Kidney week, American Society of Nephrology. November 03, 2017, Morial Convention Centre, New Orleans. (Conference Poster)

5.1 Introduction

The SPRINT trial compared a systolic blood pressure target of less than 120 mmHg (intensive group) to a target of 130-140 mmHg (control group) in participants at intermediate risk of cardiovascular events (216). The trial reported a lower rate of cardiovascular events with intensive blood pressure lowering, compared to standard treatment, and has had a major influence on revised guideline recommendations (217,218). In the control group of SPRINT, a specific systolic blood pressure range of 130-140 mmHg was targeted, rather than the conventional guideline threshold of <140 mmHg, with instructions for investigators to withdraw or reduce antihypertensive therapy when systolic blood pressure was less than 130 mmHg (or <135 mmHg on two occasions) (216). While such an approach had the advantage of ensuring a clear contrast in mean blood pressure between intensive and control groups, it would not be considered routine, or ”standard”, clinical care (219). For example, most clinicians would not discontinue antihypertensive therapy with systolic blood pressure between 110-130 mmHg, in the absence of adverse effects. It is unclear whether withdrawal of antihypertensive therapy, in a normal systolic blood pressure range, is associated with adverse cardiovascular effects and if this association is modified by Chronic Kidney Disease (CKD) status. However, given the cardio-protective effects of some antihypertensive therapies (220–226) (e.g. ACE inhibitors, beta-blockers), independent of their blood pressure lowering benefit, such an approach to the “standard care” in the SPRINT trial may have increased the cardiovascular event rate in the control group, thereby potentially exaggerating a true treatment effect compared to real-life clinical practice (219). Moreover, this approach to antihypertensive management is expected to result in higher mean blood pressures in the control group (227), than would be expected in routine clinical care. It may also be speculated that patients with CKD may be most vulnerable to the effects of interruption of antihypertensive medications, given their overall higher cardiovascular risk and greater net benefits from antihypertensives such as ACE inhibitors and ARBs. For example, withdrawal of diuretic antihypertensives is associated with a marked increase in hospitalisation for heart failure in patients with advancing stages of CKD (228).

We hypothesised that non-standard withdrawal or per-protocol reductions of antihypertensive therapy, in the control group of the SPRINT trial, were associated with an

increased risk of cardiovascular events, which may have biased the treatment effect in favour of intensive blood pressure lowering.

5.2 Methods

We obtained access to the SPRINT dataset through participation in the New England Journal of Medicine SPRINT Challenge (229). Ethical approval for participation was obtained from the Galway University Hospital ethics committee. A data use agreement was signed between Health Research Board-Clinical Research Facility and a representative of the National Institutes of Health's National Heart, Lung, and Blood Institute (NHLB).

5.2.1 Study Population

The details of the SPRINT population have been published elsewhere (216). In summary, participants were those at high cardiovascular risk, and inclusion criteria included: age of at least 50 years, systolic blood pressure at baseline between 130 to 180 mmHg and an increased cardiovascular risk. Increased cardiovascular risk was defined as clinical or subclinical cardiovascular disease (excluding stroke), chronic kidney disease (eGFR 20-60 mL/min/1.73m^2), a ten-year risk of 15% or greater on the Framingham risk score or an age of 75 years or greater. Patients with diabetes or prior stroke were excluded.

5.2.2 Outcome Measures

The primary outcome of the SPRINT trial was the composite outcome of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure and death from a cardiovascular cause. Secondary outcomes included individual components of the composite.

5.2.3 Statistical Analysis Plan

All participants in the SPRINT trial were included. Withdrawal of antihypertensive agents were identified from changes in the number of medications reported at each clinic visit. Antihypertensive agents were defined as FDA-approved antihypertensive drugs at dose ranges considered to have a therapeutic antihypertensive effect. We were unable to account for the impact of medication switches that did not alter the number of antihypertensive medications. Standard withdrawal of antihypertensive agents was defined as a reported withdrawal for systolic blood pressure less than 100 mmHg at the current visit,

or a reported, related adverse event occurring between the previous and current visit for any blood pressure value. Related adverse events included hypotension, syncope, bradycardia, electrolyte abnormality, injurious fall, or acute kidney injury. Non-standard withdrawal was defined as reported withdrawal of antihypertensive medication at blood pressures greater than 100 mmHg without an adverse event, as per protocol. As dose of antihypertensive medication was not available in the open access dataset, we imputed that dose reduction occurred as per-protocol in the control group. The protocol specified that down titration should be carried out if the systolic blood pressure is <130 mmHg at a single visit or <135 mmHg at two consecutive visits, at visits where antihypertensive agents were not withdrawn. We summarised, for intensive and control groups: non-standard antihypertensive withdrawal, additions, net change and mean systolic blood pressure at baseline and 4-year follow-up, overall and within tertiles of baseline systolic blood pressure, which have been reported previously (230).

We calculated net change as the total number of antihypertensive agent additions minus removals, including both standard and non-standard, and examined this by tertiles of baseline systolic blood pressure. We did not include medication changes during visits after a primary outcome event had occurred. We evaluated the association of non-standard antihypertensive withdrawal and antihypertensive dose reduction with time to first cardiovascular event during follow-up using the Cox proportional-hazards regression model. The effect of withdrawal of antihypertensive agents was investigated for two hazard time-periods between study visits, to explore a temporal gradient of risk. We reported only the first two periods after withdrawal of medications because during exploratory analysis there was no increased risk for the period 3, 4, and 5 after withdrawal. As the interval between visits differed (one-month interval between visits for the first three follow-up visits, and three-month intervals between subsequent follow-up) the hazard periods varied in duration between one month and three months, based on initial exploration of the data. The first follow-up visit had two subsequent 1-month hazard periods, the second follow-up visit had an initial one-month hazard period and a subsequent three-month hazard period, and all visits thereafter had two hazard periods of three month's duration. We included two consecutive hazard periods in the analyses, based on exploratory analyses of the association of antihypertensive withdrawal and the composite outcome. We replicated the primary

analysis of the SPRINT trial, comparing the time to first occurrence of a primary outcome between treatment groups, and then performed an analysis that adjusted for non-standard withdrawal or per-protocol reduction in antihypertensive regimens, treated as time-dependant covariates, to estimate an adjusted effect of intensive blood pressure lowering compared to control blood pressure lowering. For these analyses, non-standard withdrawals of antihypertensive medications were included for both treatment groups (as data were available), while per-protocol antihypertensive reductions were included for the control group only. Chronic Kidney Disease was defined as a baseline eGFR less than 60 mL/min/1.73m^2 and non-CKD was defined as a baseline eGFR greater or equal to 60 mL/min/1.73m^2. The hazard period analysis and the primary analysis of the SPRINT trial was repeated in CKD and non-CKD subgroups for all outcomes. A Wald test was performed to test for an interaction effect of antihypertensive withdrawal with eGFR category. Kaplan-Meier curves were generated for the intensive blood pressure group, the control group, and an adjusted control group (adjusted for non-standard withdrawals or per-protocol reductions in antihypertensives on follow-up). We also explored the association of systolic blood pressure and the primary composite outcome in the control and intensive groups, to determine whether the non-standard approach to antihypertensive therapy altered the pattern of association between blood pressure and risk of cardiovascular events. For these analyses, we evaluated the association of visit blood pressure to risk of the primary outcome measure during the subsequent visit to visit follow-up period. All analyses were performed using R Statistical Software (V3.4.3).

5.3 Results

In total, 9361 participants were included in our analyses. Descriptive baseline characteristics are reported in Table 5-1. The mean age of participants was 67.9 years and 64.4% were male. At baseline, no antihypertensive agent was prescribed in 882 (9.4%) participants, 1 agent in 2753 (29.4%), 2 agents in 3292 (35.2%), 3 agents in 1920 (20.5%) and more than 3 agents in 514 (5.5%) participants. Mean eGFR was similar in the Intensive Treatment group (71.8±20.7 ml/min/1.73m^2) and the Control group (71.7±20.5 ml/min/1.73m^2). The number and percent of participants with CKD was similar in the Intensive Treatment group (1332, 29%) and the Control group (1318, 28%).

Table 5-1 Baseline Characteristics of Study Population

Characteristic	Intensive Treatment Group (N = 4678)	Control Group (N = 4683)
Female sex — no. (%)	1684 (36.0)	1648 (35.2)
Mean age — years ± SD	67.9±9.4	67.9±9.5
Race or ethnic group — no. (%)		
Non-Hispanic black	1379 (29.5)	1423 (30.4)
Hispanic	503 (10.8)	481 (10.3)
Non-Hispanic white	2698 (57.7)	2701 (57.7)
Black race	1454 (31.1)	1493 (31.9)
Other	98 (2.1)	78 (1.7)
Baseline blood pressure — mmHg ± SD		
Systolic	139.7±15.8	139.7±15.4
Diastolic	78.2±11.9	78.0±12.0
Estimated Glomerular filtration rate — ml/min/1.73 m^2 ± SD	71.8±20.7	71.7±20.5
Chronic Kidney Disease (CKD) – no. (%)		
Non-CKD (eGFR >= 60 mL/min/1. 73m^2)	3330 (71)	3344 (72)
CKD (eGFR <60 mL/min/1. 73m^2)	1332 (29)	1318 (28)
-CKD 3a (eGFR 45 - 59 mL/min/1. 73m^2)	886 (19)	873 (19)
-CKD 3b (eGFR 30 - 44 mL/min/1. 73m^2)	370 (7.9)	366 (7.9)
-CKD 4/5 (eGFR <30 mL/min/1. 73m^2)	76 (1.6)	79 (1.7)
Ratio of urinary albumin (mg) to creatinine (g) ± SD	44.1±178.7	41.1±152.9
Statin use — no./total no. (%)	1978/4645 (42.6)	2076/4640 (44.7)
Aspirin use — no./total no. (%)	2406/4661 (51.6)	2350/4666 (50.4)
Smoking status — no. (%)		
Never smoked	2050 (43.8)	2072 (44.2)
Former smoker	1977 (42.3)	1996 (42.6)
Current smoker	639 (13.7)	601 (12.8)
Framingham 10-yr cardiovascular disease risk score — % ± SD	20.1±10.9	20.1±10.8
Body mass index ± SD	29.9±5.8	29.8±5.7
Antihypertensive agents — no./patient ± SD	1.8±1.0	1.8±1.0
Not using antihypertensive agents — no. (%)	432 (9.2)	450 (9.6)

Figure 5-1 reports the frequency of non-standard antihypertensive agent withdrawals during the trial, which were more common in the control group (5569 withdrawals involving 3236 (70.1%) participants) compared to the intensive blood pressure group (3067 withdrawals involving 2172 (46.9%) participants) (P < 0.001).

Figure 5-1 Frequency of Non-Standard Antihypertensive Agent Withdrawals During the Trial

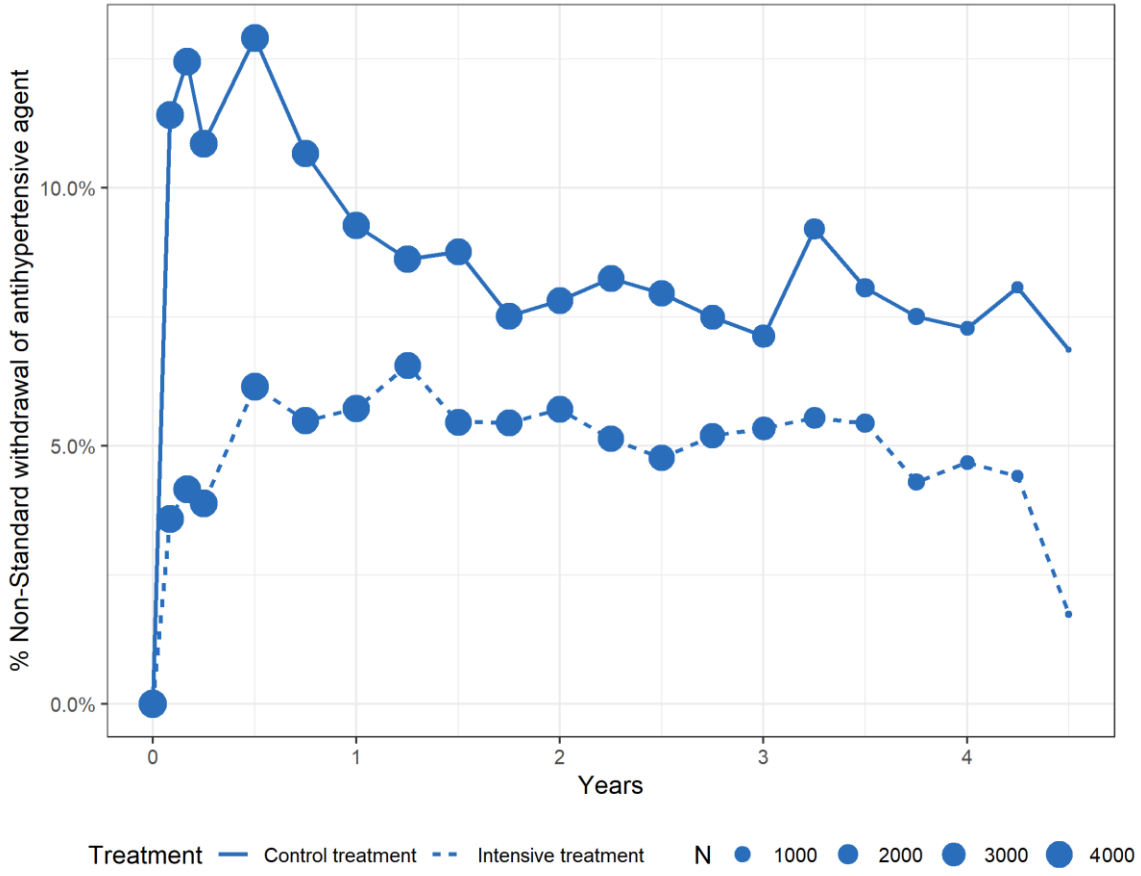


Figure 5-1 Legend – Area of dot represents size of group.

Figure 5-2 reports the frequency of non-standard withdrawals at different ranges of systolic blood pressure in both treatment groups, demonstrating adherence with the trial protocol for withdrawal of antihypertensive therapy in the control group, within a normal blood pressure range.

Figure 5-2 Frequency of Non-Standard Withdrawals at Different Ranges of Systolic Blood Pressure in Both Treatment Groups

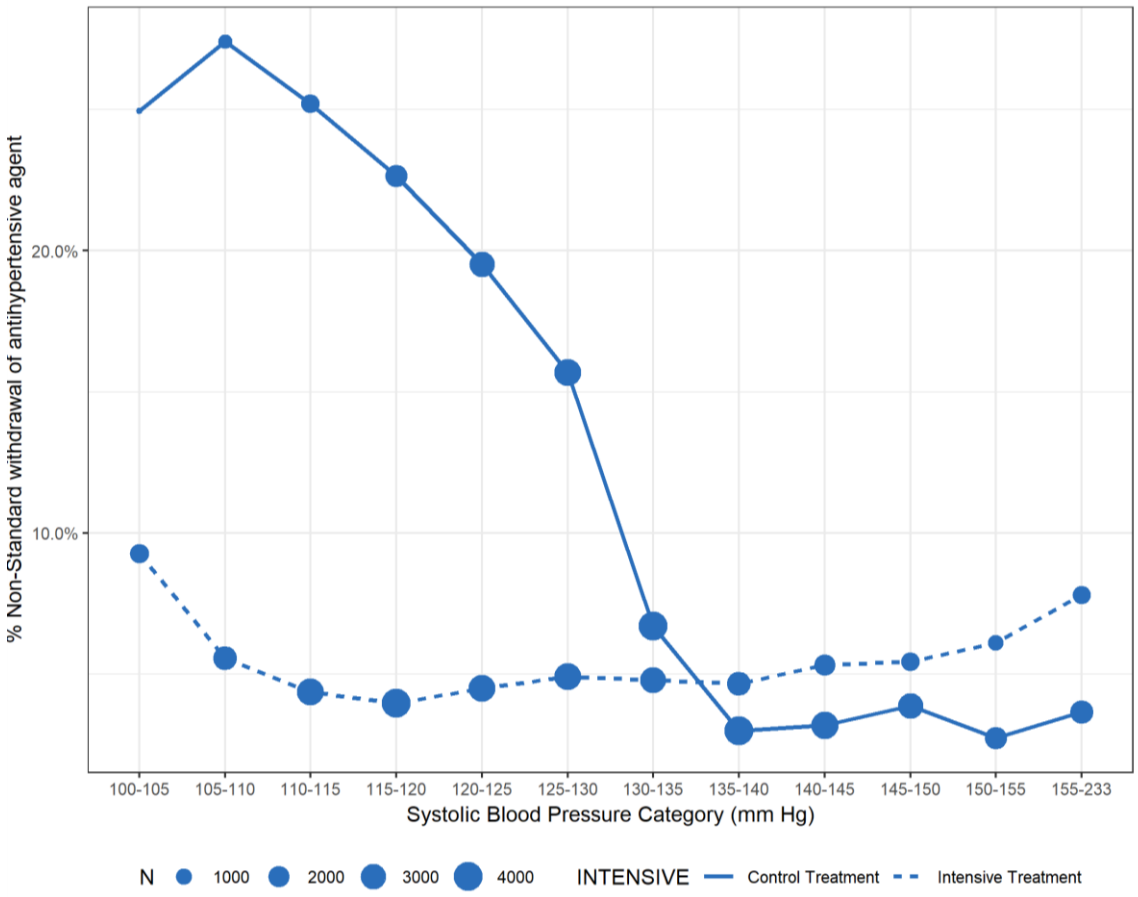
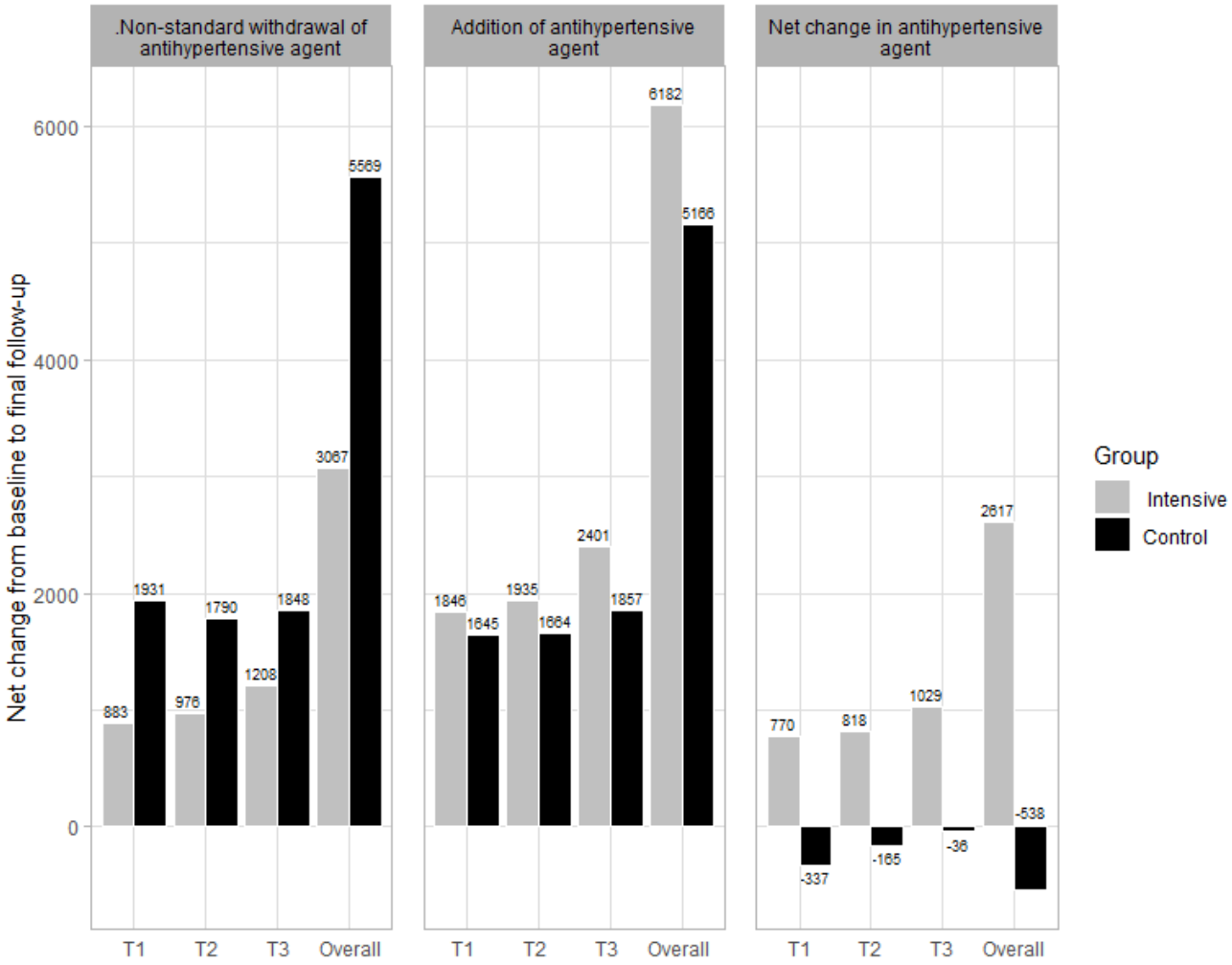


Figure 5-2 Legend – Area of dot represents size of group.

Figure 5-3 reports the frequency of antihypertensive additions and withdrawals among tertiles of baseline systolic blood pressure, for intensive and control groups. Net absolute changes in antihypertensive medication were +2617 in the intensive group and -538 in the control group during follow-up.

Figure 5-3 Frequency of Antihypertensive Additions and Withdrawals Among Tertiles of Baseline Systolic Blood Pressure, for Intensive and Control Groups



Non-standard withdrawal of antihypertensive agents was associated with an increased risk of the composite outcome, which was significant for two hazard periods (HR 1.65; 95% CI, 1.26 to 2.16 for the first hazard period, HR 1.47; 95% CI, 1.12 to 1.95 for the second hazard period after withdrawal). For subsequent hazard periods, there was no significant association of non-standard withdrawal with the composite outcome. Within the individual components of the composite outcome, non-standard antihypertensive withdrawal was significantly associated with heart failure for both periods (HR 2.39; 95% CI, 1.52 to 3.76 for the first period, HR 2.04; 95% CI, 1.30 to 3.21 for the second period) and myocardial infarction for the second period (HR 1.82; 95% CI, 1.21 to 2.74 for the second period), but not significantly associated with stroke, acute coronary syndrome or cardiovascular death (Table 5-2).

Table 5-2 Association of Non-Standard Withdrawal in Antihypertensive Therapy with Clinical Outcomes, and Effect of Intensive Versus Control Blood Pressure Target (Adjusted and Unadjusted)

	Association of Non-Standard Withdrawal		**Between-Group Comparison**	
Outcome	**HR (95% CI)** **Initial period after withdrawal**	**HR (95% CI)** **Second period after withdrawal**	**HR (95% CI)** **Unadjusted***	**HR (95% CI)** **Adjusted****
Primary Outcome	1.65 (1.26-2.16)	1.47 (1.12-1.95)	0.75 (0.64–0.89)	0.81 (0.67-0.97)
Secondary Outcomes				
~ Myocardial Infarction	1.38 (0.86-2.22)	1.82 (1.21-2.74)	0.83 (0.64–1.09)	0.88 (0.65-1.2)
~ Acute Coronary Syndrome	1.35 (0.63-2.87)	1.31 (0.60-2.85)	1.00 (0.64–1.55)	1.06 (0.65-1.75)
~ Stroke	1.61 (0.92-2.85)	1.16 (0.62-2.18)	0.89 (0.63–1.25)	0.91 (0.62-1.34)
~ Heart Failure	2.39 (1.52-3.76)	2.04 (1.30-3.21)	0.62 (0.45–0.84)	0.71 (0.50-1.02)
~ Cardiovascular Death	1.58 (0.84-2.98)	0.98 (0.45-2.10)	0.57 (0.38–0.85)	0.64 (0.41-0.99)

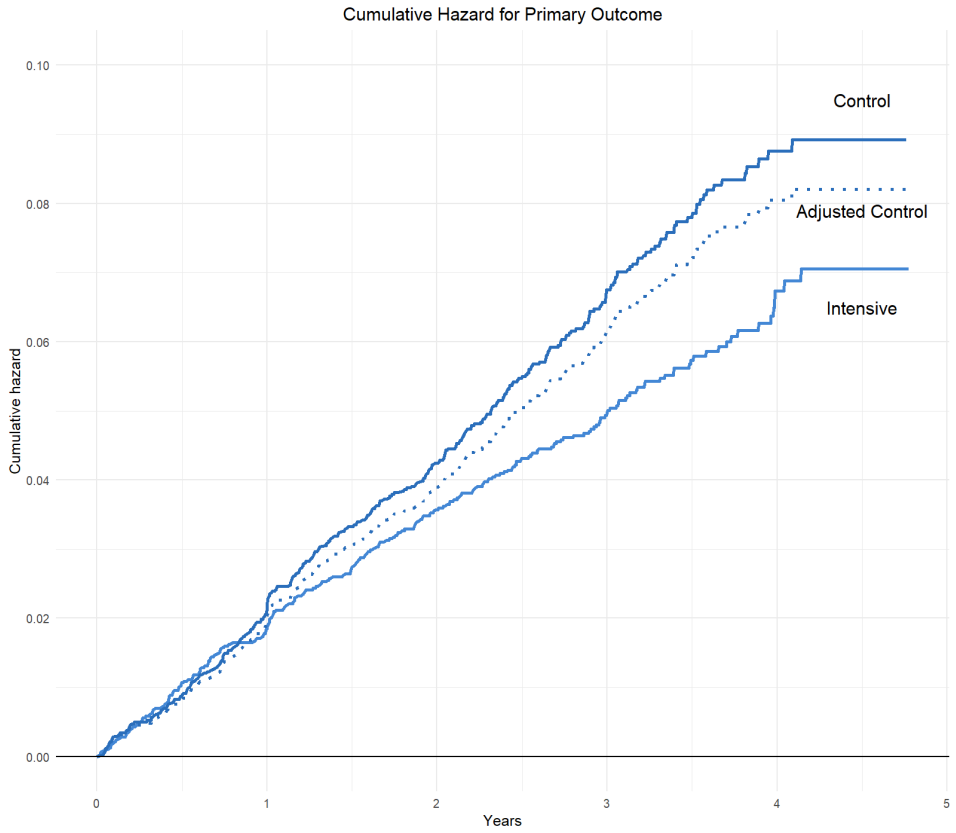
* Original reported estimates for treatment effect of intensive blood pressure lowering group compared to control (216). HR=hazard ratio, CI=confidence interval

** Adjusted for non-standard withdrawal and per-protocol reductions

Non-standard reductions of antihypertensive agents were not associated with a significantly increased risk of the composite outcome (HR 1.13; 95% CI, 0.85 to 1.50). There were 19,370 visit episodes (involving 4,189 (89.5%) participants) with systolic blood pressure that required per protocol reductions of antihypertensive agents in the control group.

In the between-treatment group analysis of the primary outcome measure, the adjusted treatment effect for intensive-treatment group versus control was HR 0.81 (95% CI, 0.67 to 0.97 - after adjustment for non-standard withdrawal and reduction) compared to HR 0.75 (95% CI, 0.64 to 0.89 - without adjustment) (Figure 5-4).

Figure 5-4 Adjusted Treatment Effect for Intensive-Treatment Group Versus Control



Within individual components of the composite, adjusted estimates were HR 0.71 (95% CI, 0.50 to 1.02) for heart failure, HR 0.91 (95% CI, 0.62 to 1.34) for stroke, HR 0.88 (95% CI, 0.65 to 1.20) for myocardial infarction and HR 0.64 (95% CI, 0.41 to 0.99) for cardiovascular death (Table 5-2). CKD status amplified the magnitude of association of non-standard antihypertensive withdrawal with adverse cardiovascular outcomes but was statistically significant for heart failure only (P-interaction=0.031) (Table 5-3).

Table 5-3 Association of Non-Standard Withdrawal in Antihypertensive Therapy with Clinical Outcomes, and Effect of Intensive Versus Control Blood Pressure Target (Adjusted and Unadjusted) with CKD and Non-CKD Subgroups and Interactions

	Association of Non-Standard Withdrawal		
	HR (95% CI) Initial period after withdrawal	**P-Interaction**	
		eGFR Stage	**eGFR**
Composite Outcome			
Overall	1.65 (1.25-2.16)		
Non-CKD	0.96 (0.66-1.41)	0.073	0.29
CKD	2.80 (1.99-3.93)		
Myocardial Infarction			
Overall	1.38 (0.86-2.22)		
Non-CKD	0.78 (0.39-1.55)	0.18	0.33
CKD	2.45 (1.37-4.40)		
Acute Coronary Syndrome			
Overall	1.35 (0.63-2.87)		
Non-CKD	0.96 (0.34-2.72)	0.33	0.51
CKD	2.03 (0.75-5.50)		
Stroke			
Overall	1.61 (0.92-2.85)		
Non-CKD	1.49 (0.76-2.91)	0.39	0.06
CKD	1.60 (0.66-3.87)		
Heart Failure			
Overall	2.39 (1.52-3.76)		
Non-CKD	0.68 (0.30-1.54)	0.073	0.031
CKD	5.15 (3.10-8.54)		
CVD Death			
Overall	1.59 (0.84-2.98)		
Non-CKD	0.69 (0.26-1.88)	0.29	0.79
CKD	3.20 (1.48-6.91)		

** Adjusted for non-standard withdrawal and per-protocol reductions. HR=hazard ratio, CI=confidence interval. eGFR=Estimated Glomerular Filtration Rate

The association of visit systolic blood pressure and subsequent visit-visit interval risk of the composite outcome was positive and linear in the intensive treatment group but J-shaped in the control group, with an increased risk for systolic blood pressure above 160mmHg and below 130mmHg (compared to reference of 140-150mmHg). Adjustment for non-standard per-protocol withdrawal or reduction of antihypertensive medications did not materially alter the patterns of association, which may suggest the presence of residual confounding with our approach to multivariable modelling to adjust for the effect of non-standard reductions in antihypertensive therapy (Figure 5-5).

Figure 5-5 Association of Visit Systolic Blood Pressure and Subsequent Visit-visit Interval Risk of the Composite Outcome

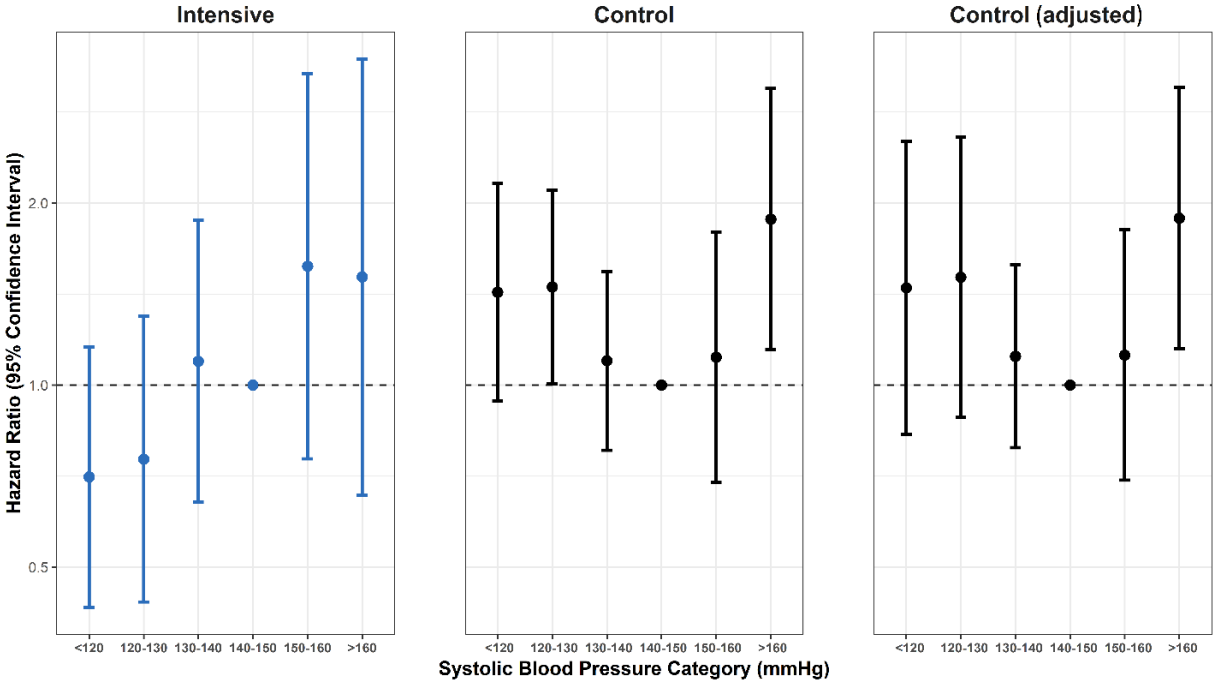


Table 5-4 reports the change in mean systolic blood pressure and net change in number of antihypertensive medications from baseline to four-year follow-up, by tertiles of baseline systolic blood pressure. Systolic blood pressure was reduced in all tertiles of the intensive group and there were positive net changes in antihypertensive medications, with the largest mean change in the highest tertile. In contrast, there was an increase in mean systolic blood pressure and net loss of antihypertensive therapy in the lowest tertile of the control group, and a small reduction in blood pressure with net loss of antihypertensive agents in the middle tertile. The highest tertile of the control group had a net decrease in blood pressure and a small net loss in antihypertensive therapy.

Table 5-4 Medication Changes in SPRINT Trial by Baseline Systolic Blood Pressure Tertile

	Tertile 1 (≤132 mmHg)		**Tertile 2 (>132 to <145 mmHg)**		**Tertile 3 (≥145 mmHg)**		**Overall**	
	Control	**Intensive**	**Control**	**Intensive**	**Control**	**Intensive**	**Control**	**Intensive**
Mean Systolic Blood Pressure (mmHg)								
Randomisation *	123.75	123.64	138.37	138.40	156.56	156.67	139.65	139.68
Follow-up (48 months) *	134.37	118.65	135.81	120.75	139.34	122.19	136.50	120.47
Net Antihypertensive Medication Change (net change)								
Non-standard medication removal	1931	883	1790	976	1848	1208	5569	3067
Medication addition	1645	1846	1664	1935	1857	2401	5166	6182
Net medication change	-337	770	-165	818	-36	1029	-538	2617
* Previously reported (230).								

5.4 Discussion

5.4.1 Principal Findings

In our post-hoc analysis of the SPRINT trial, we found an association of non-standard antihypertensive withdrawal with increased cardiovascular risk, specifically for heart failure and myocardial infarction, which was most marked within the first period between visits and attenuated thereafter with no significant increase in risk after two periods. Non-standard withdrawal of antihypertensive therapy occurred more often in the control group than the intensive treatment group. An analysis of the primary outcome of the SPRINT trial, which attempted to adjust for reported non-standard antihypertensive withdrawals and imputed per-protocol antihypertensive dose reductions, revealed an attenuated relative treatment effect of intensive blood pressure lowering compared to control, but the treatment effect remained significant. For most outcome, we found that CKD status amplified the magnitude of association of non-standard antihypertensive withdrawal with adverse cardiovascular outcomes.

5.4.2 Findings in Relation to Other Studies

The SPRINT trial was an open-label clinical trial, comparing two different blood pressure targets. Findings from the SPRINT trial have resulted in a change to guideline recommendations from the American College of Cardiology/American Heart Association (217), which now recommends a lower target systolic blood pressure (<130 mmHg). The European Society of Cardiology and the European Society of Hypertension have also revised their target blood pressure recommendation (<130/80 mmHg), but are more cautious in their recommendation, especially in >65 age group (target 130-139 mmHg) (218). ESC/ESH guidelines suggest a lower limit for the blood pressure target (120 mmHg), citing concerns about methodological limitations of the SPRINT trial, including the methodological issue addressed in our analysis (231–233). While the intensive blood pressure lowering group in SPRINT targeted a blood pressure threshold (<120 mmHg), the control group targeted a range of 130-140 mmHg, employing a pre-defined antihypertensive management protocol to keep participants within this blood pressure range. As such, the comparison was of a target threshold (<120 mmHg) to a target range (130-140 mmHg) of systolic blood pressure, rather than two different cut-off thresholds for systolic blood pressure. Other clinical trials have adopted a similar approach (234,235), which has the advantage of ensuring a clear

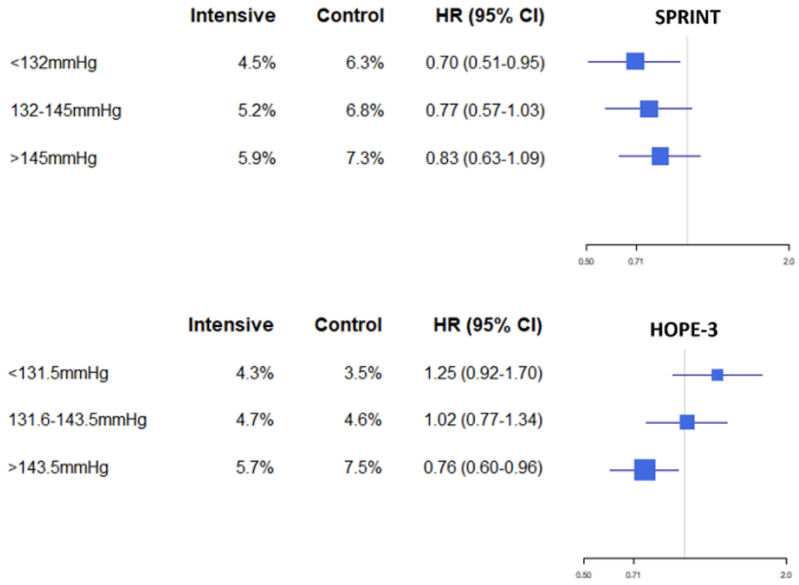
blood pressure difference between intervention and control groups. However, control groups are usually designed to replicate standard clinical care, which this approach does not since antihypertensive medications were down titrated in the control group of the SPRINT trial in circumstances where they would likely be continued in routine clinical practice (i.e., within systolic blood pressure range of 100-130 mmHg). Three main mechanisms potentially mediate the increased cardiovascular risk associated with this management approach. First, the mean blood pressure in the control group is expected to be higher than in real-life clinical practice, given the target of a range between 130-140 mmHg, with down-titration of antihypertensive regimens to achieve this range. Second, some antihypertensive agents have cardiovascular benefits, beyond their antihypertensive effect, and their withdrawal may have a triggering effect. Of note, we found the strongest association between antihypertensive agent withdrawal and heart failure, which is an expected association for withdrawal of β-blockers, diuretics, ACE inhibitors and ARBs (227). Type of antihypertensive agent was not available in the open access dataset to explore this further, which meant we were unable to specifically determine a within antihypertensive class effect. Third, more frequent titration of antihypertensive agents is expected to increase blood pressure variability over the course of the trial, which is known to be associated with increased cardiovascular risk (236) including all-cause mortality (237). Our analyses primarily tested one of these mechanisms and demonstrated that non-standard withdrawal of antihypertensive agents to achieve a blood pressure range of 130-140 mmHg was associated with increased cardiovascular risk. Adjusting for all proposed non-standard reductions and withdrawals in antihypertensive intensity resulted in an attenuated hazard ratio for the treatment effect of intensive group to control, but the estimate of treatment effect remained significant, although the upper limit confidence interval for hazard ratio was 0.97. However, our adjusted analyses for the association of blood pressure and composite outcome would suggest a high likelihood of residual confounding.

In our analysis by eGFR subgroups, we observed a higher magnitude of risk for all outcomes associated with interruption of antihypertensive therapy in participants with reduced eGFR but this was statistically significant for heart failure only (P-interaction=0.031) (Table 5-3). An increased cardiovascular risk (hospitalisation for heart failure) has been reported with interruption of diuretics in patients with advance chronic kidney disease (228). Several

factors may account for this observation. Patients with chronic kidney disease may be at higher risk of cardiovascular events, particularly heart failure which commonly co-exist with renal disease (238). These patients may also be more dependent on diuretic therapy to prevent exacerbation of heart failure. Use of ACE inhibitors and ARBs, more commonly prescribed in patients with chronic kidney disease, are known to have beneficial effects beyond blood pressure lowering in patients at high cardiovascular risk, and especially in patients with renal disease (239). Interruption of these medications may result in temporary 'rebound' increases in renin, known to increase rapidly increase BP (48-hours) and cardiovascular risk (240). Temporary interruption of antihypertensive therapy may also exacerbate lability in blood pressure, which is more common in patients with chronic kidney disease, and also reported to increased cardiovascular risk (241).

The HOPE-3 trial, which addressed a similar clinical research question to SPRINT, randomised participants with intermediate cardiovascular risk (mean baseline blood pressure of 138/82 mmHg) to combination antihypertensive therapy or placebo, and did not report a significant reduction in major cardiovascular events (HR 0.93; 95% CI, 0.79 to 1.10) (242). Figure 5-6 reports a summary comparison of SPRINT and HOPE-3, by baseline systolic blood pressure categories. In HOPE-3, there was evidence of greater treatment effect with increasing baseline blood pressure, which is expected biologically and epidemiologically. In contrast, however, the SPRINT trial reported the greatest benefit in those in the lowest third of mean baseline blood pressure, which is unexpected. For the subgroups in the highest tertile of baseline blood pressure, estimates of treatment effect between HOPE-3 (HR 0.76; 95% CI, 0.60 to 0.96) and SPRINT (HR 0.83; 95% CI, 0.63 to 1.09) were the most consistent, as were the event rates in the control groups of HOPE-3 (7.5%) and SPRINT (7.3%), and this is the subgroup least affected by down-titration of antihypertensive therapy in the control group of SPRINT. An additional difference is the association of baseline systolic blood pressure in the intervention and control groups of HOPE-3 and SPRINT trials, with a greater magnitude of association in the control group of HOPE-3 (compared to intervention group), which is expected since blood pressure is being lowered in the intervention group, while the association of blood pressure and cardiovascular events is similar between groups in the SPRINT trial (Figure 5-6).

Figure 5-6 Summary Comparison of SPRINT and HOPE-3, by Baseline Systolic Blood Pressure Categories



This observation links with our finding of a different pattern of association between visit systolic blood pressure and subsequent risk of cardiovascular events in the intensive group compared to the control group (Figure 5-5), which demonstrates a linear increase in risk in the intensive group, and a J-shaped associated in the control group. One explanation for these counterintuitive findings in SPRINT is that the control group with the lowest baseline blood pressure are those with the highest frequency of non-standard antihypertensive withdrawals, and where this source of bias exerts the largest magnitude of effect, as illustrated in Figure 5-3 and Table 5-4 and reported in a previous post-hoc analysis of SPRINT, with a mean increase of 10.6 mmHg in systolic blood pressure from baseline to final follow-up (230). The participants in the control group of this blood pressure tertile also had the largest absolute and relative change in non-standard and total medication changes (Table 5-4), and also have a marked difference in control event rate of 6.3% compared to an event rate of 3.5% in the lowest tertile baseline blood pressure subgroup in the HOPE-3 trial. This finding contrasts the near identical event rates in SPRINT and HOPE-3 (7.3% versus 7.5%) in the highest blood pressure tertile. Our primary findings suggest one potential explanation for these contrasting observations, namely the increased cardiovascular risk associated with higher frequency of non-standard antihypertensive reductions in this subgroup.

We report a linear association between multi-visit systolic blood pressure and events in intensive arm but a j shaped relationship in the standard arm. This finding is different from an analysis by Kalkman et. al. However, Kalkman's analysis relates to the difference between achieved mean on-treatment SBP and the SBP target (120 mmHg in intensive and 140mmHg in standard). Both higher and lower BP values (than the target) were associated with an increased risk of cardiovascular events with the lowest risk at 3mmHg below the target BP. The J shape of association was similar for both intensive and standard groups, but standard had a wider (and non-significant) confidence interval for BP <-20 mmHg difference. Kalkman's analysis is not directly comparable to ours as the lower strata in our analysis was <120mmHg.

5.4.3 Study Limitations

Our study has limitations. While we identified an increased risk associated with non-standard withdrawal of antihypertensive medications, it is likely that our approach to adjusting for the associated adverse cardiovascular effects was associated with residual confounding. Specifically, we were unable to adjust for the unmeasured loss of blood pressure lowering effect, or increased blood pressure variability which is also associated with increased cardiovascular risk (236), compared to usual care. Moreover, we were unable to determine whether the association of antihypertensive withdrawal with cardiovascular events was related to specific classes of antihypertensive medications, as this information was not available from the open access dataset. In addition, we did not have information on whether dose reduction of antihypertensive agents definitely occurred, and our approach was to assume that dose reductions occurred in the control groups as per study protocol, for which there may have been misclassification bias. This is a potential weakness of our analysis, however, Figure 5-1 would support that there was generally good adherence with the trial protocol for withdrawal of antihypertensive and we would expect this to be similar for dose reduction, as dose reduction is expected to be more acceptable to clinicians than antihypertensive withdrawal. In addition, the mean change in blood pressure from baseline to follow-up in the lowest tertile of the control group demonstrates an increase in systolic blood pressure (Table 5-4), supporting the contention that investigators adhered with the protocol for reducing antihypertensive therapy. Finally, some of what we defined as non-standard changes in antihypertensive regimens may have been prompted by clinical

reasons, which were unmeasured, but this potential source of error is expected to be balanced between treatment groups, and we adjusted for antihypertensive withdrawals in both treatment groups.

5.4.4 Conclusion

In conclusion, non-standard withdrawal of antihypertensive medications was associated with increased cardiovascular risk and were more common in the control group of SPRINT compared to the intensive group and is most evidence in patients with chronic kidney disease. Our analyses suggest that non-standard withdrawal and per-protocol reductions in antihypertensive therapy, in the control group, may have inflated the magnitude of treatment effect reported for intensive blood pressure lowering but the treatment effect remained statistically significant.

Chapter 6 The Effect of a Run-In Period on Estimated Treatment Effects in Cardiovascular Randomised Clinical Trials – A Meta-Analytic Review

Murphy R, McGrath E, Nolan A, Smyth A, Canavan M, O'Donnell M**, Judge C**. The impact of a run-in period on treatment effects in cardiovascular prevention randomised control trials: A protocol for a comprehensive review and meta-analysis. HRB Open Research. 2020 Nov 11;3(82):82.

Murphy R, O'Donnell MJ, Nolan A, McGrath E, O'Conghaile A, Ferguson J, Alvarez-Iglesias A, Costello M, Loughlin E, Reddin C, Ruttledge S, Gorey S, Hughes D, Smyth A, Canavan M, **Judge C**. The Effect of a Run-In Period on Estimated Treatment Effects in Cardiovascular Randomized Clinical Trials: A Meta-analytic Review (Article under review with the Journal of the American Heart Association, August 2021)

6.1 Introduction

A pre-randomisation run-in period is intended to improve the precision of treatment-effect estimates, by excluding participants who are non-adherent with study intervention or trial protocol (243–247). During a run-in period, participants receive an intervention (either active or placebo) and only those deemed adherent and tolerant of the intervention during the run-in period are randomised into the trial. The main proposed advantage of a run-in period is improved drug adherence rates of randomised participants and improved rates of follow-up (248). However, if populations who are non-adherent with medications are also those at higher cardiovascular risk (e.g., higher prevalence of co-morbidities), use of a run-in period may result in a trial population with lower event rates (249).

An unproven concern of run-in trials, given the systematic exclusion of non-adherent individuals, is the introduction of a selection bias, thereby affecting the external validity of the trial (250). This issue is most relevant to phase III randomised clinical trials where analyses are based on the intention-to-treat principle, whose purpose is to represent summary treatment effects for a general population including those who are non-adherent with the trial intervention. As such, one may speculate that the treatment effects reported in run-in trials may be closer to an 'on-treatment' analysis than intention-to-treat, given that a run-in period is expected to increase the proportion adherent with treatment. Moreover, if participants who fail the run-in period are systematically different to those who succeed the run-in period, especially if differences relate to treatment efficacy, estimates of treatment efficacy and safety may also differ between run-in and non-run-in trials. To date, evidence to support or refute differences in treatment effect estimates is lacking, despite widespread use of run-in periods (251,252). It has also not been established whether the proposed benefits of run-in, i.e., improved adherence with intervention and trial protocol, are substantiated in clinical practice. Employing a run-in period increases the complexity of randomised clinical trials, adds more burden to study participants and researchers, and may increase trial costs (253). Accordingly, it is necessary to confirm the proposed benefits of run-in periods, and reliably exclude any association with biased treatment estimates.

In this study, we evaluated whether the use of a run-in period in cardiovascular prevention trials is associated with differences in relative treatment effects, and rates of adverse events resulting in drug discontinuation, cardiovascular events, mortality, and loss to follow-up.

6.2 Methods

6.2.1 Data Sources

A protocol detailing design and methods of the current meta-analysis has been published previously (254). In summary, we identified eleven systematic reviews published between 2010 and 2019 which reported both primary and secondary prevention trials of effective therapies for cardiovascular prevention, namely antihypertensive, lipid lowering, and glucose lowering medications (255–265) (Figure 6-1, Table 6-1).

Figure 6-1 Flow Chart of Included Studies

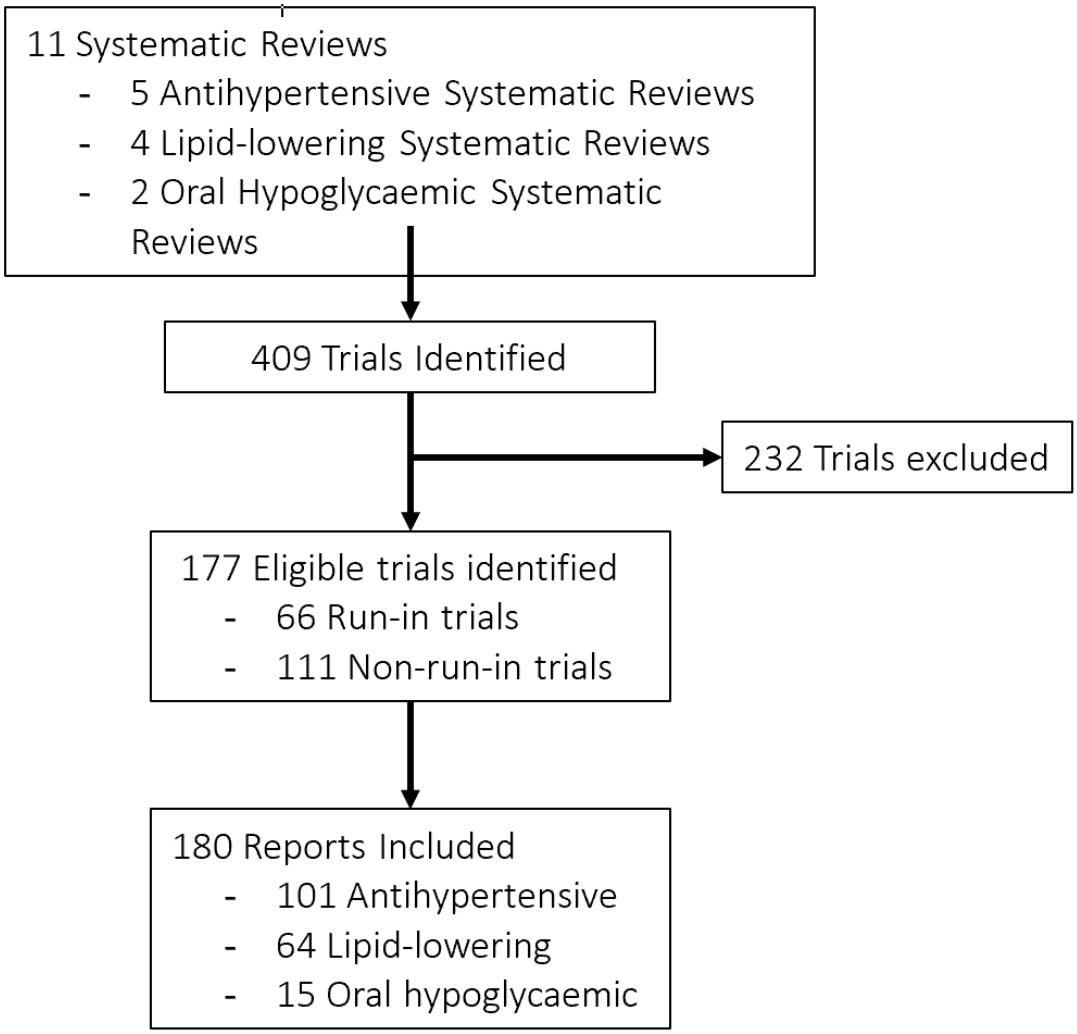


Table 6-1 Source Systematic Reviews

Antihypertensive Therapies	
Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis (259)	The Lancet, 2016
Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels: A Systematic Review and Meta-analysis (256)	JAMA internal medicine, 2018
Blood pressure-lowering drugs and secondary prevention of cardiovascular disease: systematic review and meta-analysis (264)	Journal of hypertension, 2018
Antihypertensive Treatment and Secondary Prevention of Cardiovascular Disease Events Among Persons Without Hypertension: A Meta-analysis (263)	JAMA, 2011
The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials (258)	Journal of hypertension, 2011
Lipid Lowering Therapies	
Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force (257)	JAMA, 2016
Effect of statins and non-statin LDL-lowering medications on cardiovascular outcomes in secondary prevention: a meta-analysis of randomised trials (261)	European Heart Journal, 2018
Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials (255)	Lancet, 2010
Proprotein convertase subtilisin/kexin 9 inhibitors in reducing cardiovascular outcomes: a systematic review and meta-analysis (260)	Heart, 2019
Glucose Lowering Therapies	
Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials (262)	The Lancet, Diabetes & Endocrinology, 2019
SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials (265)	The Lancet, 2018

We selected systematic reviews of proven cardiovascular prevention benefit where the overall summary estimate of the meta-analysis was significant, to test the hypothesis that run-in trial might bias estimates of efficacy. The strategy of sourcing trials for inclusion from a range of high quality published systematic reviews allowed us to reduce research waste (266). We included all phase III randomised clinical trials from these systematic reviews where an effective medicinal product for cardiovascular prevention (i.e., recommended by current cardiovascular prevention guidelines) was compared with a placebo or a standard of care control. Given that none of these published meta-analyses selected trials based on run-in status, we considered this approach to be associated with lower risk of selection bias. We conducted primary data extraction independently from the primary trial report, with double-checking of data by a second independent researcher. Any discrepancies were reviewed by both reviewers and resolved by consensus of the data extraction team, or if required, review with a senior author.

6.2.2 Matching Process

We integrated a methodological approach based on previous meta-analyses evaluating the effect of loss to follow-up and early trial stopping rules on effect estimates of interventions in randomised clinical trials (267,268).

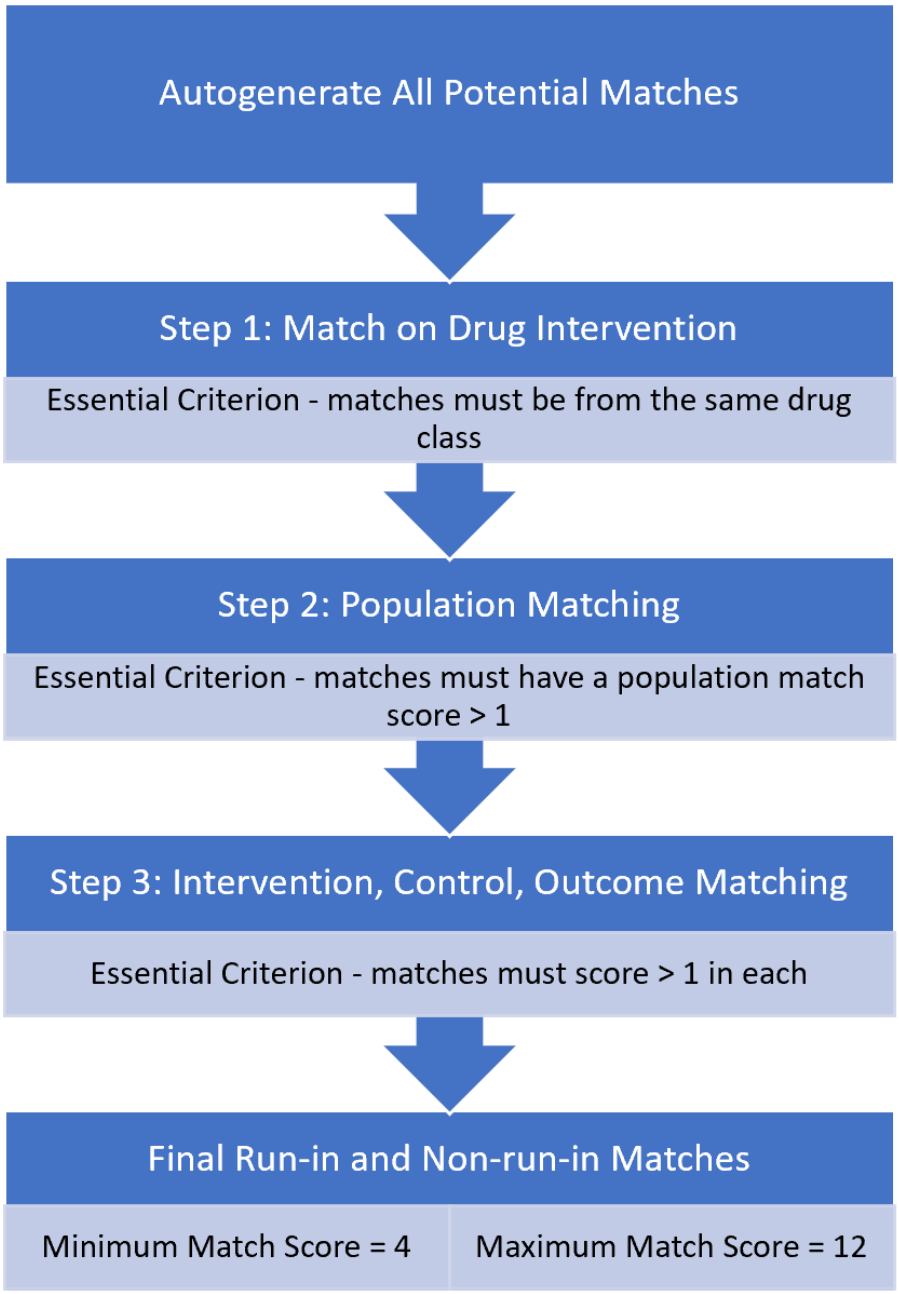
We completed the matching of run-in trials with non-run-in trials using the following approach. Step 1, we matched run-in and non-run-in trials by intervention, as we considered matching on drug class to be an essential criterion (e.g., match ACE inhibitor with ACE inhibitor). Therefore, a mandatory matching criterion was an exact match for intervention (i.e., needed to be the within the same drug class). Following Step 1, we generated a score for each potential run-in/non-run-in trial pairing, based on similarity of population, control and outcome. A score of 0 was defined as not a match, 1 an acceptable match, 2 a close match, and 3 an exact match, based on pre-specified criteria (Table 6-2).

Table 6-2 Run-in and Non-run-in Matching Score Considerations

Population • Main considerations: prevention type (primary vs secondary), population summary, mean age, gender match • Studies that compare primary prevention and secondary prevention populations are not a match • Chronic stable secondary prevention populations do not match with studies that include populations who recruit patients with acute events • Inclusion criteria should be similar in age, cardiovascular comorbidity population and inclusion criteria
Intervention • Main considerations: drug and dose • Same drugs - scored 3 • Same drug class and pharmacologically similar - scored 2 • Same drug class but pharmacologically dissimilar - scored 1 • Different drug class – scored 0
Control • Main considerations: placebo control vs standard treatment • If both studies are placebo controlled - scored 3 • If placebo is compared with standard treatment and an additional medication - scored 2 • If placebo is compared with standard treatment - scored 1
Outcome • Similar cardiovascular composite/primary outcome - scored 3 • Report multiple outcomes for mortality/stroke/myocardial infarction - scored 2 • If report one of mortality/stroke/myocardial infarction - scored 1 • If report no similar outcome - score 0

In Step 2, we included all potential matches from Step 1, and applied a population score criterion of 1 or more (i.e., minimum acceptable match). Therefore, following Step 2, all potential matches had a minimum score of 4. Following this step, we had 1,359 unique potential matches between run-in and non-run-in trials. In Step 3, we assigned a matching score for all potential matched trial pairs, ranging from minimum 4 (a score of "acceptable match" in each domain of PICO) to maximum of 12 (a score of "exact match" in each domain of PICO) (Figure 6-2).

Figure 6-2 PICO Scoring Steps



6.2.3 Statistical Analysis

For each run-in and non-run-in trial we calculated the individual trial relative risk for each outcome measure. If multiple non-run-in trials matched to a single run-in trial, we performed a random effects meta-analysis of the non-run-in trials to calculate the summary estimate to give a single non-run-in relative risk to compare to the run-in trial. This meant, that for each matched comparison, a run-in trial relative risk could either be matched

against a single non-run-in trial relative risk, or a meta-analysis of multiple non-run-in relative risks. Following this, for each matched comparison, we calculated a ratio of relative risks and 95% confidence interval by subtracting the log(non-run-in trial relative risk) from the log(run-in trial relative risk) with standard error (se) calculated as the square root of ($se(\text{Run-in RR})^2 + se(\text{Non-run-in RR})^2$). We conducted a random effects meta-analysis of the ratio of relative risks between run-in and matched non-run-in trials to obtain a summary estimate of the ratio of relative risks. A ratio of < 1 indicates a greater treatment effect in run-in trials (compared to matched non-run-in trials). We used a random effects model because run-in trials were matched to variable numbers of non-run-in trials, and we considered this approach to best represent the 'average' log RR in this setting. Additionally, we performed sensitivity analysis using fixed effects meta-analysis to ensure consistent findings regardless of the exact form of meta-analysis used. We used Cochran's Q test to test for heterogeneity and the I^2 statistic to estimate the percentage of variability.

Our primary analysis was a comparison of the relative risk reported in run-in trials compared to matched non-run-in trials for the primary outcome (cardiovascular composite) and was confined to 'best-matched' trials (i.e., maximum PICO matched score) for this outcome. Non-run-in trials could only be matched once to prevent trials with large treatment effects biasing the estimate. For a non-run-in trial pre-matched to several run-in trials, we selected the run-in and non-run-in pair with the largest PICO score, or, if several trials had equal PICO matches, we further selected by run-in trial sample size (Figure 6-3). We completed analysis of secondary clinical outcomes, all-cause mortality, adverse events leading to medication discontinuation, non-fatal myocardial infarction, non-fatal stroke, and loss to follow-up.

Figure 6-3 Visual Representation of Different PICO Matching Scenarios

Scenario 1: Highest PICO scenario

Non-run-in trials were matched to their corresponding highest PICO score run-in trial(s) e.g. Trial A and Trial C with total PICO 12/12.

Run-in Trials	Run-in Participants	Non-run-in Trials	Population /3	Intervention /3	Control /3	Outcome /3	Total /12
Trial A	6000	Trial C	3	3	3	3	12
Trial A	6000	Trial D	2	1	3	3	9
Trial A	6000	Trial E	3	2	2	3	10
~~Trial B~~	~~8000~~	~~Trial C~~	~~3~~	~~3~~	~~2~~	~~3~~	~~11~~
Trial B	8000	Trial F	3	3	3	3	12
Trial B	8000	Trial G	3	1	2	3	9

Scenario 2: Equal PICO scenario

If several trials have equal PICO matches, we selected the trials with the largest non-run-in sample size e.g. Trial B and Trial C with run-in sample size of 8000.

Run-in Trials	Run-in Participants	Non-run-in Trials	Population /3	Intervention /3	Control /3	Outcome /3	Total /12
~~Trial A~~	~~6000~~	~~Trial C~~	~~3~~	~~3~~	~~2~~	~~3~~	~~11~~
Trial A	6000	Trial D	2	1	3	3	9
Trial A	6000	Trial E	3	2	2	3	10
Trial B	8000	Trial C	3	3	2	3	11
Trial B	8000	Trial F	3	3	3	3	12
Trial B	8000	Trial G	3	1	2	3	9

Sensitivity analyses were conducted where non-run-in trials were permitted to match multiple times to different run-in trials. We also completed a robustness analysis using a parametric bootstrapping method with 1000 iterations. The bootstrap algorithm considers variability (at study level), variability due to the selection of studies, and correlation structure due to non-independence of matched pairs. During each iteration, we resampled each relative risk from a normal distribution with mean of the log(relative risk) and standard deviation (SD) equal to the relative risk variance to account for the sampling error of each trials relative risk estimate. For each possible run-in and non-run-in match, we calculated the log-relative risk ratio by subtracting the corresponding log-relative risks and resampled all pairs with replacement. In this analysis, we calculated the mean, 2.5% quantile, and 97.5% quantile from the 1000 summary estimates of relative risk ratios to obtain a parametric bootstrapping summary estimate and confidence interval.

To address the degree to which our matching ameliorates confounding, we completed an analysis without individual trial matching (i.e., comparison of meta-analytic estimate of the two groups of trials). First, we calculated the summary run-in and non-run-in relative risk estimates using random effects meta-analysis, then we calculated the log(run-in RR) – log(non-run-in RR) to obtain a relative risk ratio. We then calculated the corresponding E-Value for the upper bound of this confidence interval (UL* = 1/UL and E-value = UL* + sqrt{UL* × (UL* − 1)) (269).

We additionally performed a random-effects meta-regression analysis with log transformed treatment effect as our outcome and run-in status as our predictor variable, both univariate and multivariable adjusting for mean age, sex, trial sample size, duration of follow-up, primary versus secondary prevention, and year of publication.

To explore differences in clinical event rates between run-in and non-run-in trial populations, we compared incidence rates of clinical events and loss to follow-up in the controls groups of trials using an inverse variance weighted meta-analysis, to give higher importance to studies of larger sample sizes.

6.2.4 Assessment of the Quality of the Studies: Risk Of Bias

We used the Cochrane Risk of Bias Tool to assess methodological quality of eligible trials including random sequence generation, allocation concealment, blinding of participants and healthcare personnel, blinded outcome assessment, completeness of outcome data,

evidence of selective reporting and other biases (270). Risk of bias assessments were performed independently by two reviewers, and disagreements resolved by a third reviewer.

6.3 Results

6.3.1 Comparison of Characteristics of Run-in and Non-Run-in Trials

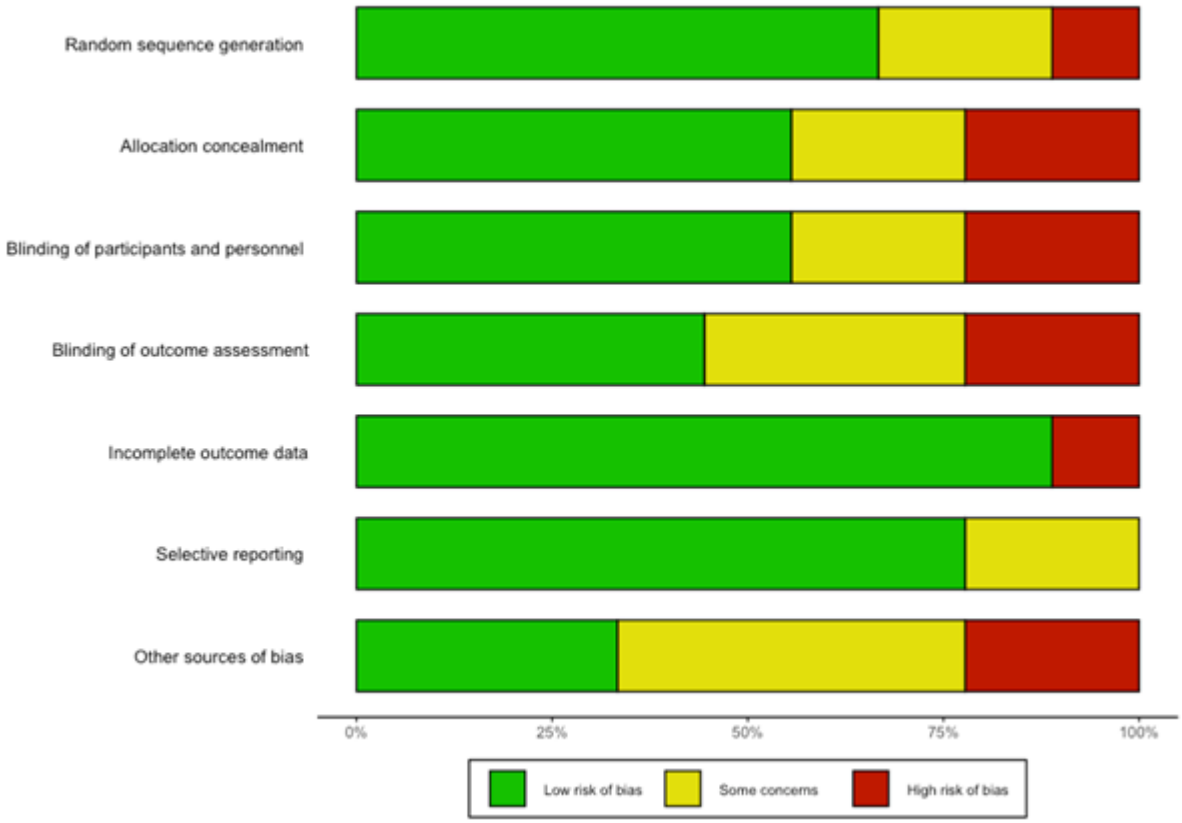
From the eleven identified systematic reviews, a total of 177 randomised clinical trials were identified, with 66 eligible run-in trials and 111 eligible non-run-in trials with a total sample size of 668,901 patients. Table 6-3 describes the characteristics of the run-in and non-run-in studies included in our primary cardiovascular composite outcome analysis, with 32 run-in trials and 76 non-run-in trials (i.e., best matches). The majority (88%) were parallel group trials. Run-in trials had older populations (mean age 64.5±6.28 vs 61.0±6.20, P=0.01) and larger samples sizes (mean n=6,604±7,243 vs 3,471±4,036, P=0.03) compared to non-run-in trials. Overall, 78% of run-in trials were reported in high-impact journals, compared to 59% of non-run-in trials (P=0.09). Risk of bias comparisons were similar between run-in and non-run-in studies (Table 6-3 and Figure 6-4). The mean duration of follow-up was similar (42.8±17.7 months vs 42.7±17.5 months, P=0.97). A meta-analysis of the matched run-in and non-run-in trials found no significant difference for loss to follow-up (RRR 1.04, 95% CI, 0.84 to 1.30).

Table 6-3 Characteristics of Run-in and Non-run-in Trials Matched by Cardiovascular Composite Outcome

	Run-in (N=32)	Non-run-in (N=76)	P Value
Year of Publication:			0.37
Before 1990	1 (3.12%)	5 (6.58%)	
1990-2000	8 (25.0%)	9 (11.8%)	
2001-2010	13 (40.6%)	32 (42.1%)	
2011-2020	10 (31.2%)	30 (39.5%)	
Experimental Design:			0.52
Factorial	5 (15.6%)	8 (10.5%)	
Parallel	27 (84.4%)	68 (89.5%)	
Study Characteristics:			1
Blood Pressure Lowering Agent	16 (53.3%)	38 (52.1%)	
Glucose Lowering Agent	1 (3.33%)	2 (2.74%)	
Lipid Lowering Agent	13 (43.3%)	33 (45.2%)	
Prevention Type:			0.89
Primary Prevention	18 (56.2%)	40 (52.6%)	
Secondary Prevention	14 (43.8%)	36 (47.4%)	
Published in high impact journal:			0.1
No	7 (21.9%)	31 (40.8%)	
Yes	25 (78.1%)	45 (59.2%)	
Industry Supported:			1
No	1 (3.12%)	4 (5.26%)	
Not Reported	0 (0.00%)	2 (2.63%)	
Yes	31 (96.9%)	70 (92.1%)	
Mean Age (Years):	64.9 (6.28)	61.0 (6.20)	0.01
Composite Primary Outcome:			0.09
No	10 (31.2%)	39 (51.3%)	
Yes	22 (68.8%)	37 (48.7%)	
Number of Patients Randomised:	6604 (7243)	3471 (4036)	0.03
Duration of Follow-up (Months):	42.8 (17.5)	42.7 (17.7)	0.97
Total Loss to Follow-up (%):	1.80 (3.84)	1.26 (2.65)	0.55
Random Sequence Generation:			0.04
Low	21 (65.6%)	56 (73.7%)	
Unclear	8 (25.0%)	20 (26.3%)	
High	3 (9.38%)	0 (0.00%)	
Allocation Concealment:			0.4
Low	21 (65.6%)	53 (69.7%)	
Unclear	9 (28.1%)	22 (28.9%)	
High	2 (6.25%)	1 (1.32%)	
Blinding of Participants and Personnel:			0.15
Low	30 (93.8%)	59 (77.6%)	
Unclear	0 (0.00%)	5 (6.58%)	
High	2 (6.25%)	12 (15.8%)	
Blinding Outcome Assessors:			0.69
Low	26 (81.2%)	65 (85.5%)	

Unclear	6 (18.8%)	10 (13.2%)	
High	0 (0.00%)	1 (1.32%)	
Selective Reporting:			0.86
Low	30 (93.8%)	68 (89.5%)	
Unclear	1 (3.12%)	2 (2.63%)	
High	1 (3.12%)	6 (7.89%)	
Other Bias:			0.21
Low	25 (78.1%)	67 (88.2%)	
Unclear	0 (0.00%)	1 (1.32%)	
High	7 (21.9%)	8 (10.5%)	

Figure 6-4 Risk of Bias Overall Summary for Trials included in Cardiovascular Composite Outcome Analysis



Differences between placebo run-in and active run-in studies are included in the Table 6-4. Active run-in was more commonly performed in antihypertensive studies than in studies of lipid lowering or glucose lowering agents (P=0.05).

Table 6-4 Comparison of Placebo Run-in and Active Run-in Studies

	Placebo Run-in (N=42)	Active Run-in (N=14)	P Value
Year of Publication:			0.92
Before 1990	2 (4.76%)	0 (0.00%)	
1990-2000	10 (23.8%)	3 (21.4%)	
2001-2010	16 (38.1%)	7 (50.0%)	
2011-2020	14 (33.3%)	4 (28.6%)	
Experimental Design:			0.26
Factorial	2 (4.76%)	2 (14.3%)	
Parallel	40 (95.2%)	12 (85.7%)	
Study Characteristics:			0.05
Blood Pressure Lowering Agent	18 (45.0%)	11 (78.6%)	
Glucose Lowering Agent	6 (15.0%)	2 (14.3%)	
Lipid Lowering Agent	16 (40.0%)	1 (7.14%)	
Prevention Type:			0.35
Primary Prevention	26 (61.9%)	6 (42.9%)	
Secondary Prevention	16 (38.1%)	8 (57.1%)	
Published in High Impact Journal:			0.73
No	13 (31.0%)	3 (21.4%)	
Yes	29 (69.0%)	11 (78.6%)	
Industry Supported:			1
No	1 (2.38%)	0 (0.00%)	
Yes	41 (97.6%)	14 (100%)	
Composite Primary Outcome:			0.88
No	18 (42.9%)	7 (50.0%)	
Yes	24 (57.1%)	7 (50.0%)	
Number of Patients Randomised:	5423 (6937)	5762 (4622)	0.84
Duration of Follow-up (Months):	36.6 (15.6)	45.3 (17.3)	0.14
Random Sequence Generation:			0.23
Low	25 (59.5%)	12 (85.7%)	
Unclear	15 (35.7%)	2 (14.3%)	
High	2 (4.76%)	0 (0.00%)	
Allocation Concealment:			0.23
Low	25 (59.5%)	12 (85.7%)	
Unclear	15 (35.7%)	2 (14.3%)	
High	2 (4.76%)	0 (0.00%)	
Blinding of Participants and Personnel:			0.15
Low	41 (97.6%)	12 (85.7%)	
High	1 (2.38%)	2 (14.3%)	
Blinding Outcome Assessors:			1

Low	35 (83.3%)	12 (85.7%)	
Unclear	7 (16.7%)	2 (14.3%)	
Selective Reporting:			0.53
Low	39 (92.9%)	12 (85.7%)	
Unclear	2 (4.76%)	1 (7.14%)	
High	1 (2.38%)	1 (7.14%)	
Other Bias:			0.18
Low	34 (81.0%)	14 (100%)	
High	8 (19.0%)	0 (0.00%)	

6.3.2 Outcome Cardiovascular Composite

Thirty-two run-in trials matched with one or more non-run-in trials, of which fifteen were matched with multiple non-run-in trials. There was no significant difference in treatment effect for cardiovascular events between run-in trials (RR 0.83, 95% CI, 0.80-0.87) compared to non-run-in trials (RR 0.88, 95% CI, 0.84-0.91), (RRR 0.95, 95% CI, 0.90-1.01) (Figure 6-5). Sensitivity analysis including multiple matches analysis and parametric bootstrapping analysis increased the precision of our estimate but were not statistically significant (Table 6-5).

Figure 6-5 Pooled Ratio of Relative Risks for Matched Run-in and Non-run-in Randomised Controlled Trials Which Reported a Cardiovascular Composite Outcome.

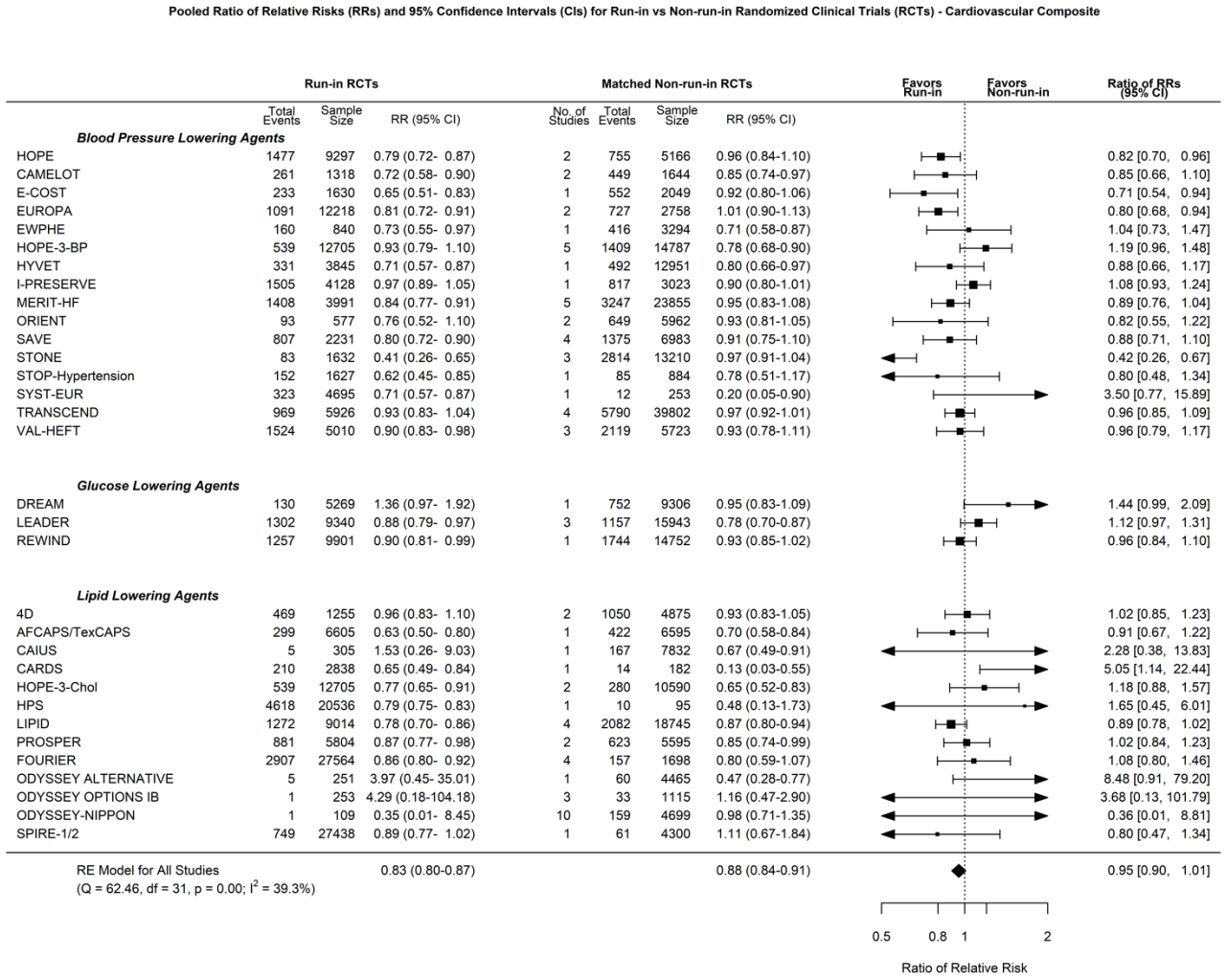


Table 6-5 Summary Estimates of Relative Treatment Estimates

Outcome	**Run-in Summary Estimate**	**Non-run-in Summary Estimate**	**Single Best Match**	**Univariate Meta-regression**	**Multivariable Meta-regression**	**Multiple Matches**	**Parametric Bootstrapping**
	Relative Risk, 95% CI	Relative Risk, 95% CI	Ratio of Relative Risk, 95% CI	Ratio of Relative Risk, 95% CI	Ratio of Relative Risk, 95% CI	Ratio of Relative Risk, 95% CI	Ratio of Relative Risk, 95% CI
Composite CVD Outcome	0.83 (0.80-0.87)	0.88 (0.84-0.91)	0.95 (0.90-1.01)	0.94 (0.90-0.99)	0.95 (0.90–1.00)	0.97 (0.93-1.02)	0.98 (0.94-1.02)
All-cause Mortality	0.89 (0.86-0.93)	0.95 (0.92-0.98)	0.97 (0.91-1.03)	0.95 (0.90-1.00)	0.94 (0.89-1.00)	0.98 (0.95-1.01)	0.98 (0.93-1.03)
Adverse Events	1.22 (1.06-1.40)	1.19 (1.06-1.34)	1.05 (0.85-1.29)	0.90 (0.73-1.12)	0.86 (0.68-1.07)	1.03 (0.87-1.21)	0.93 (0.74-1.09)
Non-fatal Myocardial Infarction	0.82 (0.75-0.89)	0.83 (0.75-0.92)	1.01 (0.85-1.19)	0.95 (0.85-1.07)	0.99 (0.88-1.12)	0.99 (0.90-1.08)	0.98 (0.88-1.11)
Non-Fatal Stroke	0.77 (0.72-0.83)	0.83 (0.75-0.93)	1.00 (0.87-1.16)	0.92 (0.84-1.02)	0.98 (0.87-1.10)	0.99 (0.89-1.11)	0.97 (0.90-1.06)

Multivariable Meta-regression adjusted for Mean Age, Prevention Type, Duration of Follow-up (months), Sex, Publication Year, and Sample Size.

Our latent confounding sensitivity analysis suggested that an unmeasured confounder, associated with run-in and relative risk, with a risk ratio of 1.16 could explain away the upper confidence limit, but weaker confounding could not. Post-hoc exploratory univariate meta-regression analysis showed that on average a run-in period was associated with a statistically significant difference in treatment effects (RRR 0.94; 95% CI, 0.90 to 0.99) for cardiovascular composite outcome. This was not statistically significant on multivariable meta-regression analysis adjusting for mean age, sex, trial sample size, duration of follow-up, primary versus secondary prevention, and year of publication (RRR 0.95; 95% CI, 0.90 to 1). Sensitivity analysis using fixed effects meta-analysis of the non-run-in trials did not alter our findings (RRR 0.95, 95% CI 0.90 to 1.01).

6.3.3 Outcome All-Cause Mortality

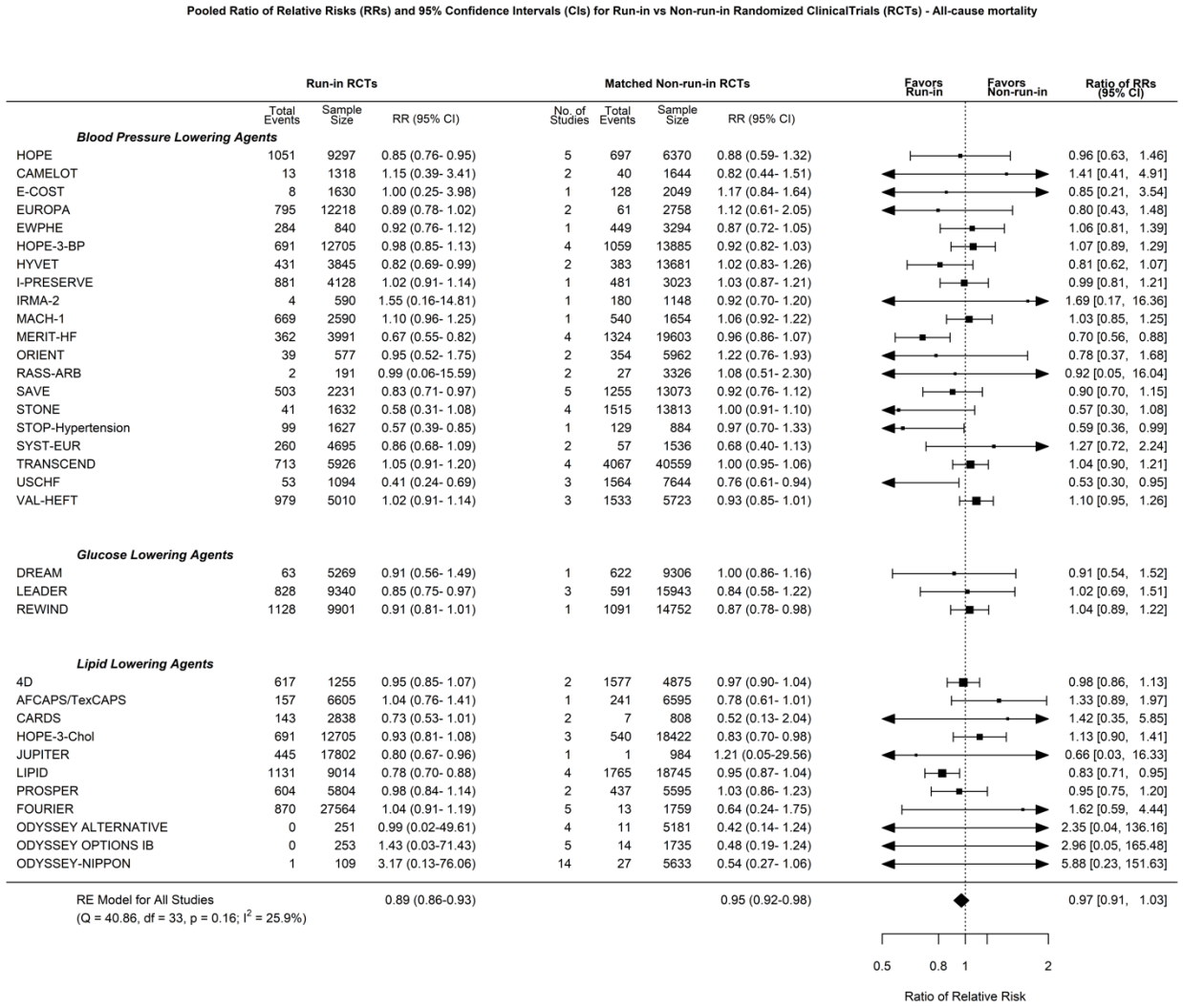
Thirty-four run-in trials matched with one or more run-in trials, of which twenty-four were matched with multiple non-run-in trials. There was no difference in mortality incidence rate in control groups of run-in studies (24.7 per 1000 person-years) compared to non-run-in studies (27.9 per 1000 person-years) (incidence difference -5.3, 95% CI, -24.69 to 14.09) (Table 6-6).

Table 6-6 Comparison of Incidence Rates

Outcome	Run-in Incidence per 1000 person-years	Non-run-in Incidence per 1000 person-years	Incidence Difference per 1000 person-years
CVD Composite	52.96 (14.48-91.45)	41.81 (25.05-58.56)	6.6 (-35.88 to 49.07)
All-cause Mortality	24.74 (12.58-36.9)	27.92 (14.73-41.11)	-5.3 (-24.69 to 14.09)
Non-fatal Myocardial Infarction	12.71 (7.7-17.72)	12.26 (5.39-19.13)	0.6 (-6.52 to 7.71)
Non-fatal Stroke	9.86 (6.57-13.15)	14.66 (4.87-24.44)	-4.82 (-11.25 to 1.62)
Adverse Events	12.76 (6.55-18.97)	34.93 (18.53-51.33)	-9.49 (-28.07 to 9.1)
Loss to Follow-up	10.61 (0.71-20.51)	8.17 (2.07-14.28)	1.53 (-9.9 to 12.95)

There was no significant difference in treatment effect for mortality in run-in trials (RR 0.89, 95% CI, 0.86-0.93) compared to non-run-in trials (RR 0.95, 95% CI, 0.92-0.98) (RRR 0.97, 95% CI, 0.91-1.03) (Figure 6-6). Sensitivity analysis including multiple matches, bootstrapping analysis or meta-regression did not alter the findings (Table 6-5).

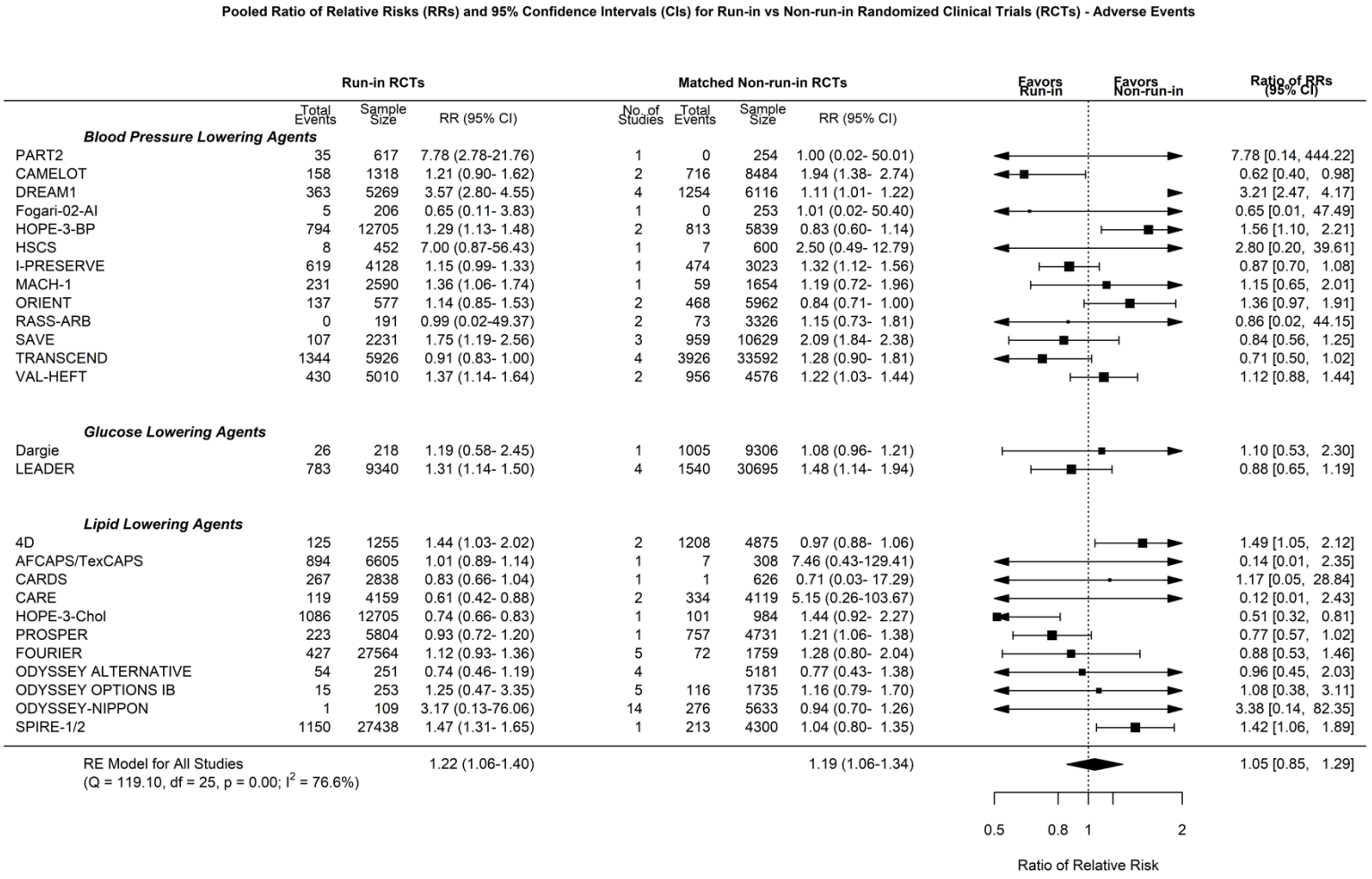
Figure 6-6 Pooled Ratio of Relative Risks for Matched Run-in and Non-run-in Randomised Controlled Trials Which Reported Mortality Outcomes.



6.3.4 Outcome Adverse Events Leading to Permanent Medication Discontinuation

Twenty-six run-in trials were matched with non-run-in trials, of which fifteen were matched with multiple non-run-in trials. There was no statistically significant difference in the incidence rate of adverse events leading to permanent medication discontinuation among control groups between run-in studies (12.8 per 1000 person-years) and non-run-in studies (34.9 per 1000 person-years) (incidence difference -9.49, 95% CI, -28.1 to 9.1) (Table 6-6). There was no significant difference in adverse events leading to permanent discontinuation between run-in trials (RR 1.22, 95% CI, 1.06-1.40) and non-run-in trials (RR 1.19, 95% CI, 1.06-1.34) (RRR 1.05, 95% CI, 0.85-1.21) (Figure 6-7). Sensitivity analysis including multiple matches analysis, bootstrapping analysis or meta-regression did not alter the findings (Table 6-5).

Figure 6-7 Pooled Ratio of Relative Risks for Matched Run-in and Non-run-in Randomised Controlled Trials Which Reported Adverse Events Leading to Discontinuation of Study Medication.



6.3.5 Outcome Non-Fatal Myocardial Infarction and Non-Fatal Stroke

A random effects meta-analysis of the ratio of relative risks between run-in and matched non-run-in studies showed no statistically significant difference in treatment effects for non-fatal myocardial infarction (RRR 1.01, 95% CI, 0.85-1.19) or non-fatal stroke (RRR of 1.00, 95% CI, 0.87-1.16 (Table 6-5). Sensitivity analysis including multiple matches analysis, bootstrapping analysis or meta-regression did not alter the findings (Table 6-5).

6.3.6 Quality of Reporting for Run-in

Authors reported the reason for a run-in design in 48 out of 66 trials (72%) (Table 6-7). Thirty-eight of the run-in trials (58%) reported the absolute number of exclusions during the run-in period. Individual reasons for participant exclusions during run-in was reported in 30 run-in trials (45%), with 20 trials clearly reporting the total number of exclusions during run-in due to adverse events during the run-in period. Placebo run-in alone was conducted in 42 trials, active run-in alone was conducted in 14 trials and nine trials had both an active and placebo run-in period. In one trial it was unclear whether placebo or active run-in was utilised. Loss to follow-up during the run-in period was reported in 38 trials (58%). The median reported duration of placebo run-in was 4 weeks (range 1 week to 4 months). The median reported duration of active run-in was 4 weeks (range 1 day to 3 months). The median reported percentage of patients excluded during active run-in was 13.5%. The median reported percentage of patients excluded during placebo run-in was 12.3%.

Table 6-7 Characteristics of all Run-in Trials Identified

Characteristics of Run-In Trials	**N=66 (%)**
Both Placebo and Active Run-in	9 (13.63)
Placebo Run-in Only	42 (63.63)
Active Run-in Only	14 (21.21)
Type of Run-in Not Reported	1 (1.51)
Reported Reason for Run-in Phase	48 (72.72)
Reported Total Exclusions During Run-in	38 (57.57)
Reported Individual Reasons for Exclusions	30 (45.45)
Reported Adverse Events During Run-in	20 (30.30)
Timing of Active and Placebo Run-in	9
Placebo Run-in First	5
Active Run-in First	3
Simultaneous with Factorial Design	1
Median Duration Active Run-in (Weeks)	4 (1 day - 3-month range)
Median Duration Placebo Run-in (Weeks)	4 (1 week - 4-month range)

6.4 Discussion

We did not find a significant difference in the relative treatment effect of run-in trials compared to matched non-run-in trials for several clinical outcomes – a composite of cardiovascular outcomes, mortality, adverse events, non-fatal myocardial infarction, and non-fatal stroke. We also failed to identify differences in adverse events leading to medication withdrawal, or proportion of participants lost to follow-up, which are expected advantages of using run-in periods in randomised clinical trials.

Our central hypothesis was that treatment effects reported in clinical trials that used run-in may be larger than those reported in trials that did not use a run-in period, which may have implications for guideline recommendations. The rationale to suspect differences is based on the contention that populations included in trials that used run-in would differ from those in non-run-in trials, as suspected and reported by previous researchers (248,250). In previous meta-analyses, comparisons of run-in and non-run in trials have been confined to smaller groups of trials (271). In our larger analyses, the lower bound of the confidence interval for ratio of relative risk ranged from 0.90-0.94, based on approaches of bootstrapping analysis and meta-regression, meaning that a treatment difference in this range is still possible, but unlikely. The only analysis reporting a significant association was our univariate meta-regression, which reported a 6% difference in relative risk associated with run-in, but this was not significant on adjusting for factors that differed between run-in and non-run-in trials (e.g., sample size). By comparison, a previous analysis evaluating the effect of early stopping of clinical trials reported a relative risk ratio of 30% (272), resulting in revision to the GRADE system for guideline recommendations with rating down quality due to risk of bias for trials that stopped early due to efficacy (273). In our analyses, we did not find a significant difference in ratio of relative risk associated with run-in period trials, and our findings suggest that if a difference does exist, it is of a magnitude that should not affect quality of evidence assessments in guideline recommendations, or influence physician prescribing patterns.

We expected to find differences in clinical event rates, adverse events leading to drug discontinuation and loss to follow-up, given that a run-in period is intended to exclude participants at higher risk of adverse events and non-adherence with trial protocol. While adverse events were numerically more common in non-run-in trials, it was not statistically

significant, and the relative risk of adverse events was similar in both trial groups. These observations provide empirical evidence that relative adverse treatment effects derived from run-in trials are unlikely to be biased, compared to non-use of a run-in period. However, our findings would also appear to challenge whether a run-in period is truly associated with the intended effect on trial populations, given that we did not observe significant differences in adverse event rates or loss to follow-up. Moreover, the similar rates of mortality and cardiovascular events does not support a major selection bias of cardiovascular risk in populations included in trials employing a run-in period. Against this observation, individual trial analyses of populations excluded during run-in, report differences in risk and event rates, which may reflect different effects depending on the clinical population (248). Of note, our analysis may have been underpowered to show differences in control incidence rates, which may become more apparent and significant in a larger study (243).

Reviews of the reporting quality of published randomised clinical trials have shown inconsistent quality of reporting, and some trials fail to record participant flow clearly, which is particularly common in the stages before randomisation (274). We also found inconsistencies in reporting the proportion of patients excluded during the run-in period, and the reasons for their exclusion. Our findings are in keeping with similar findings of prior meta-analysis, which reported inconsistent documentation of randomisation, blinding, and attrition (275–277). Previous research has found that when improved reporting standards have been adopted, such as the Consolidated Standards of Reporting Trials (CONSORT) checklist for randomised clinical trials, this has been associated with improved reporting of RCTs (278,279). It would appear reasonable that the CONSORT statement includes requirements for standardised description of run-in periods.

6.4.1 Limitations

Limitations of our study include the number of clinical trials included in our analyses, and that our analyses were restricted to cardiovascular prevention trials of medicines, meaning that these finding may not be extended to other populations or interventions. However, confining our analyses to one clinical area may also be considered a strength, as it reduces heterogeneity in clinical trial design, population, and outcome measures. In some of our analyses, a low proportion of trials were included, such as loss to follow-up. We did not

include an outcome for all adverse event, due to inconsistent reporting, and therefore we are unable to report on the association of run-in period with rate of all adverse events. We do report the more valid and reliable outcome of adverse event leading to drug discontinuation. Finally, while our findings have implications to all clinical trials employing a run-in period, they are only directly relevant to cardiovascular prevention trials of established preventative medications (280).

6.4.2 Strengths

The strengths of our study include a robust methodology, with use of a matching strategy, resulting in a comprehensive meta-analytic examination of run-in periods among cardiovascular prevention trials. We included a large number of RCTs (n=177) which were systematically and independently reviewed, across a range of journals, covering a broad time period, from 1990 to 2019. We chose cause-specific clinical outcomes which can be classified with reasonable reproducibility, which reduces the risk of ascertainment bias (281,282). We also completed a range of secondary analyses, which we undertook for each clinical outcome (283,284).

6.4.3 Conclusion

In conclusion, the use of a run-in period was not associated with a significant difference in the magnitude of treatment effect among randomised clinical trials evaluating medications to prevent cardiovascular events.

Chapter 7 Identifying the DialysatE SodIum GradieNt with the Best Efficacy/Tolerability Profile in an Adaptive Phase IIb Dose-Finding Crossover Study in Haemodialysis (DESIGN Trial)

Table 7-1 Study Synopsis of DESIGN Trial

Title	Identifying the DialysatE SodIum GradieNt with the Best Efficacy/Tolerability Profile in an Adaptive Phase IIb Dose-Finding Crossover Study in Haemodialysis (DESIGN Trial)
Scientific Queries	Dr Conor Judge, HRB Clinical Research Facility Galway
Public Title	Dialysis Sodium in Patients with Kidney Failure requiring Dialysis
Countries involved	Republic of Ireland
Health Condition	Kidney failure requiring dialysis
Interventions	Control: Dialysate sodium of 138 mmol/L and usual care including treatment of fluid volume status, dialysis adequacy, hypertension, anaemia, mineral-bone disease, comorbidities, and other dietary guidelines according to local practices. Experimental Group 1 (Hypothesis testing): Sodium Gradient (0 mmol/L) and usual care including treatment of fluid volume status, dialysis adequacy, hypertension, anaemia, mineral-bone disease, comorbidities, and other dietary guidelines according to local practices. Experimental Group 2-3 (Exploratory): Adaptive Sodium Gradient (+2, -2 mmol/L) and usual care including treatment of fluid volume status, dialysis adequacy, hypertension, anaemia, mineral-bone disease, comorbidities, and other dietary guidelines according to local practices.
Key Inclusion Criteria	(i) Age ≥18 years. (ii) Kidney failure requiring dialysis for 3 months. (iii) Kidney failure attributed to diabetes, hypertension, vascular disease, obstructive uropathy, polycystic kidney disease, glomerular disease, or a combination (which does not have to be biopsy proven). (iv) Pre-dialysis systolic blood pressure 140-180 mmHg at screening visit. (v) Signed informed consent.
Key Exclusion Criteria	(i) Severe heart failure (Left Ventricular Ejection Fraction ≤20%). (ii) Pregnancy or lactation. (iii) Cognitive impairment defined as a known diagnosis of dementia, or inability to provide informed consent due to cognitive impairment in the opinion of the investigator. Patients with mild cognitive impairment are eligible, provided they are considered able to provide informed consent in the opinion of the local investigator. (iv) Body Mass Index (BMI) <20 or >35 kg/m^2. (v) Prescribed sodium profiling for intradialytic hypotension. (vi) Hyponatremia (Serum Sodium <135 mmol/L)
Study Type	A phase IIb, dose-finding, randomised crossover, exploratory response adaptive randomised intervention, double-blinded, multi-centre, controlled trial.
Enrollment	Q4 2022
Sample Size	240 participants are required to detect a change of 0.20 kg in interdialytic weight gain with the proposed crossover design, using an estimated within-participant standard deviation of 0.77 kg and a power of 0.80 and $\alpha = 0.05$. A recruitment goal of 264 participants has been set to account for the potential participant drop out.

Primary Outcome	Efficacy: Interdialytic weight gain (IDWG)
Secondary Outcomes	Safety: Intradialytic hypotension (IDH) Efficacy: Interdialytic systolic blood pressure (44-hour ABP) Efficacy: Extracellular Water / Total Body Water Ratio Efficacy: Health Related Quality of Life (Kidney Disease Quality Of Life Scale) Efficacy: Pre- and post- dialysis systolic blood pressure Efficacy: Post-dialysis weight Efficacy: Number of antihypertensive medications
Exploratory	Efficacy: Interdialytic weight gain (IDWG) Safety: Intradialytic hypotension (IDH)
Protocol Contributors	Dr Conor Judge and Prof Martin O'Donnell (Co-Principal Investigators) Prof Donal Reddan and Prof Matthew Griffin (Co Investigators) Dr Alberto Alvarez-Iglesias (Biostatistician)

7.1 Background and Rationale

7.1.1 Burden of Kidney Failure Requiring Dialysis

More than 850 million people have kidney disease worldwide and it is estimated that by 2040, kidney disease will be the fifth leading cause of years of life lost (285). Approximately 3.9 million individuals are treated with renal replacement therapy annually worldwide and this figure is rising by 4.5% per year (285). At the end of 2020, there were 4,931 patients with kidney failure requiring replacement therapy in Ireland. This includes 2,014 patients attending in-centre dialysis, 58 on home haemodialysis, 238 on peritoneal dialysis and 2,621 with a functioning renal transplant (286). In kidney failure, mortality due to cardiovascular disease is 10 to 30 times higher than the general population (287). The increase is due to a mix of traditional cardiovascular risk factors, such as hypertension and diabetes, with non-traditional cardiovascular risk factors such as volume overload, hyperphosphatemia, anaemia and uraemia (288). There is a need to develop low cost, effective, generalisable and simple interventions to reduce risk factors especially hypertension and volume overload.

7.1.2 Kidney Failure Requiring Dialysis and Hypertension

Hypertension affects 70-80% of haemodialysis patients and is an important modifiable risk factor for cardiovascular disease in kidney failure requiring dialysis (289). The burden of hypertension in kidney failure requiring dialysis is not fully represented by peri-dialytic measurements, for example, pre-dialysis blood pressure overestimates BP, while post-dialysis blood pressure underestimates BP (290). Both home monitoring and ambulatory

blood pressure monitoring can be applied to patients with kidney failure requiring dialysis and correlate well with cardiovascular prognosis (291). Most excess fluid ingestion is driven by ingestion of excess sodium (292). Excess fluid is a major driver of hypertension and end organ changes including left ventricular hypertrophy and heart failure (293).

7.1.3 Dietary Sodium and Hypertension in Dialysis

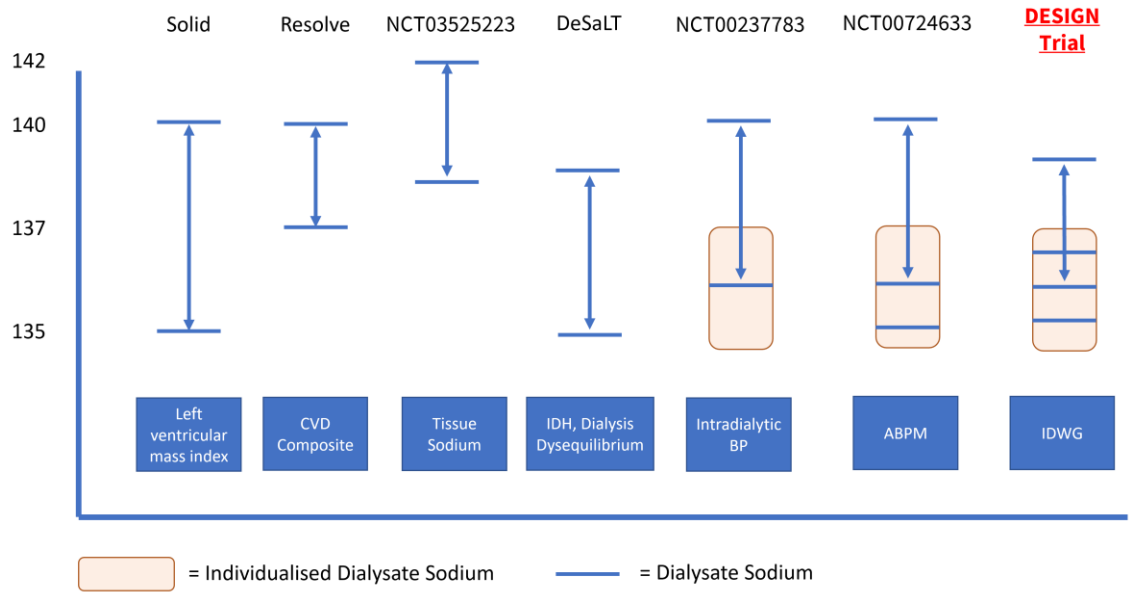
Blood pressure control is an essential component of dialysis adequacy and sodium intake reduction is a cornerstone of its management (294). Unfortunately, achieving adequate volume status and blood pressure control is often very difficult (295). As demonstrated in chapter 3 of this thesis, an intensive dietary sodium lowering intervention did not show sustained reduction in sodium excretion at two years. We hypothesised that a dietary sodium lowering intervention would therefore also not be effective at sustained dietary sodium reduction (to low intake levels) in patients with kidney failure requiring dialysis.

7.1.4 Dialysate Sodium and Hypertension

An alternative strategy is net sodium reduction through modifications of dialysate sodium concentrations (32). Observational studies have shown a positive association between lower dialysate sodium and lower blood pressure, lower interdialytic weight gain and lower antihypertensive medication use (296). However, the Sodium Lowering in Dialysate (SoLID) study conducted in New Zealand, randomised participants to dialysate sodium of 135 mmol/L of sodium compared to 140 mmol/L of sodium. There was no difference in their primary outcome of left ventricular mass index at 12 months despite differences in interdialytic weight gain and B-type natriuretic peptide. Participants randomised to 135 mmol/L of sodium had increased intradialytic hypotension at 6 months but not at 12 months (OR, 7.5; 95% CI, 1.1 to 49.8 at 6 months and OR, 3.6; 95% CI, 0.5 to 28.8 at 12 months) (27). A related study is the Randomised Evaluation of Sodium Dialysate Levels on Vascular Events (RESOLVE) trial. RESOLVE is a pragmatic, cluster-randomised, open-label trial designed to evaluate, in real-world conditions, the comparative effectiveness of two fixed dialysate sodium concentrations (137 mmol/L versus 140 mmol/L). It is currently recruiting and has an estimated primary completion date of December 2023 (28). The primary outcome is a composite of major cardiovascular events (hospitalised acute myocardial infarction, hospitalised stroke) and all-cause mortality. Figure 7-1 summarises all clinical trials registered on clinicaltrials.gov related to dialysate sodium alongside the

DESIGN trial. Six trials were found (four trials investigating fixed dialysate sodium concentration and two trials investigating fixed dialysate sodium versus individualised dialysate sodium).

Figure 7-1 Clinical Trials Registered on Clinicaltrials.gov Related to Dialysate Sodium.



Another important concept is sodium gradient, defined as dialysate sodium minus pre-dialysis plasma sodium. A cross-sectional study on 1084 clinically stable patients on haemodialysis found a direct correlation between interdialytic weight gain and sodium gradient ($r = 0.21$, $P < 0.0001$) (297). However, they did not find a significant association between sodium gradient and blood pressure parameters e.g., pre-HD systolic ($r = -0.02$), diastolic ($r = -0.06$) or mean arterial pressure ($r = -0.04$) (297). Another important concept is the lag period between change in sodium balance and achievement of blood pressure control (296). This must be carefully considered when deciding outcomes for interventional trials of sodium balance and would make blood pressure an unsuitable outcome for a trial with a short duration of follow-up. It has previously been estimated that there is a 2 to 3 litre difference between hypertensive and normotensive dialysis patients, changes of this magnitude could only be tested in a trial of long duration (298). In contrast to a change in blood pressure, a change in volume reflected by interdialytic weight gain happens sooner with a change in sodium balance and is therefore more suitable as a phase II efficacy outcome (297).

7.1.5 Holding Antihypertensive Medications Prior to Dialysis

Antihypertensive medications are usually held on the day of dialysis to reduce the risk of intradialytic adverse advents such as intradialytic hypotension (35). Our hypothesis is that the practice of holding antihypertensives is unnecessary and may be associated with adverse health outcomes by masking chronic fluid overload. Additionally, in Chapter 5 of this thesis, we showed an increased risk with withdrawal of antihypertensives in the SPRINT randomised clinical trial. In the DESIGN trial, we will mandate that antihypertensives are given pre-dialysis during a run-in period with the fixed dialysate sodium (138 mmol/L). If participants experience intradialytic symptoms such as intradialytic hypotension, they will have a protocolised reduction and/or removal of the antihypertensive medications prior to randomisation. Reduction and/or removal of medications will apply to all days i.e. not just prior to dialysis. We will also mandate that antihypertensives are given pre-dialysis during the crossover stage of the trial with fixed (138 mmol/L), zero sodium gradient and adaptive sodium gradient.

7.1.6 Clinical Equipoise for Dialysate Sodium

The UK Renal Association, in their 2019 clinical practice guideline on haemodialysis, state that “there is insufficient consistency in the literature for a clear recommendation on dialysate sodium” (26). Cross-sectional studies have reported wide variation in dialysate sodium in dialysis centres ranging from 136 to 149 mmol/L, with a median of 140 mmol/L (297). A Cochrane review of Dialysate sodium levels for chronic haemodialysis concluded that “We are uncertain about whether low sodium in dialysis fluid improves overall health and well-being for people on haemodialysis” and that “Larger and up-to-date definitive studies are needed to evaluate the medium to long-term effects of low sodium levels in dialysis fluid” (299).

7.1.7 Impact of Trial

Effective, simple, inexpensive interventions are essential to lower cardiovascular risk in patients with kidney failure requiring dialysis. However, it is critical that these interventions are proven to be effective. There is a complex interplay between dialysate sodium, dietary sodium intake, hypertension, volume overload, and antihypertensive medication use. One component cannot be modified in isolation without consideration of the others. For example, reducing dialysate sodium without also reducing antihypertensive medications

could cause intradialytic complications like intradialytic hypotension. In addition, we have shown in Chapter 4 of this thesis, that both high and low estimated sodium excretion (a surrogate for dietary intake) are associated with increased cardiovascular outcomes e.g., stroke. The results of this trial will have important implications for designing a phase III, definite intervention trial of fixed sodium versus some variation of sodium gradient.

7.2 Study Objectives

7.2.1 Primary Research Question

In adult patients with hypertension and kidney failure requiring dialysis, does dialysing against a dialysate sodium concentration with zero sodium gradient compared to dialysing against a fixed dialysate sodium concentration of 138 mmol/L result in lower interdialytic weight gain over a one-month period?

7.2.2 Secondary Research Questions

In adult patients with hypertension and kidney failure requiring dialysis, does dialysing against a dialysate sodium concentration with zero sodium gradient compared to dialysing against a fixed dialysate sodium concentration of 138 mmol/L result in:

(i) an increase in intradialytic hypotension episodes (systolic BP <90 mmHg),
(ii) lower interdialytic systolic blood pressure measured using 44-hour ambulatory blood pressure monitoring,
(iii) reduction in Extracellular Water (ECW)/Total Body Water (TBW) Ratio) measured using bioimpedance spectroscopy,
(iv) increase in Health related Quality of Life using the Kidney Disease Quality of Life scale,
(v) reduction in pre-dialysis systolic blood pressure,
(vi) reduction in post-dialysis systolic blood pressure,
(vii) reduction in post-dialysis weight,
(viii) reduction in number of antihypertensive medications,
(ix) reduction in NT-ProBNP

over a one-month period?

7.2.3 Exploratory Research Questions

In adult patients with hypertension and kidney failure requiring dialysis, does dialysing against a dialysate sodium concentration with +2 mmol/L sodium gradient compared to dialysing against a fixed dialysate sodium concentration of 138 mmol/L result in:

(i) a lower interdialytic weight gain,

(ii) an increase in intradialytic hypotension episodes,

over a one-month period?

In adult patients with hypertension and kidney failure requiring dialysis, does dialysing against a dialysate sodium concentration with -2 mmol/L sodium gradient compared to dialysing against a fixed dialysate sodium concentration of 138 mmol/L result in:

(i) a lower interdialytic weight gain,

(iii) an increase in intradialytic hypotension episodes,

over a one-month period?

7.2.4 Study Design

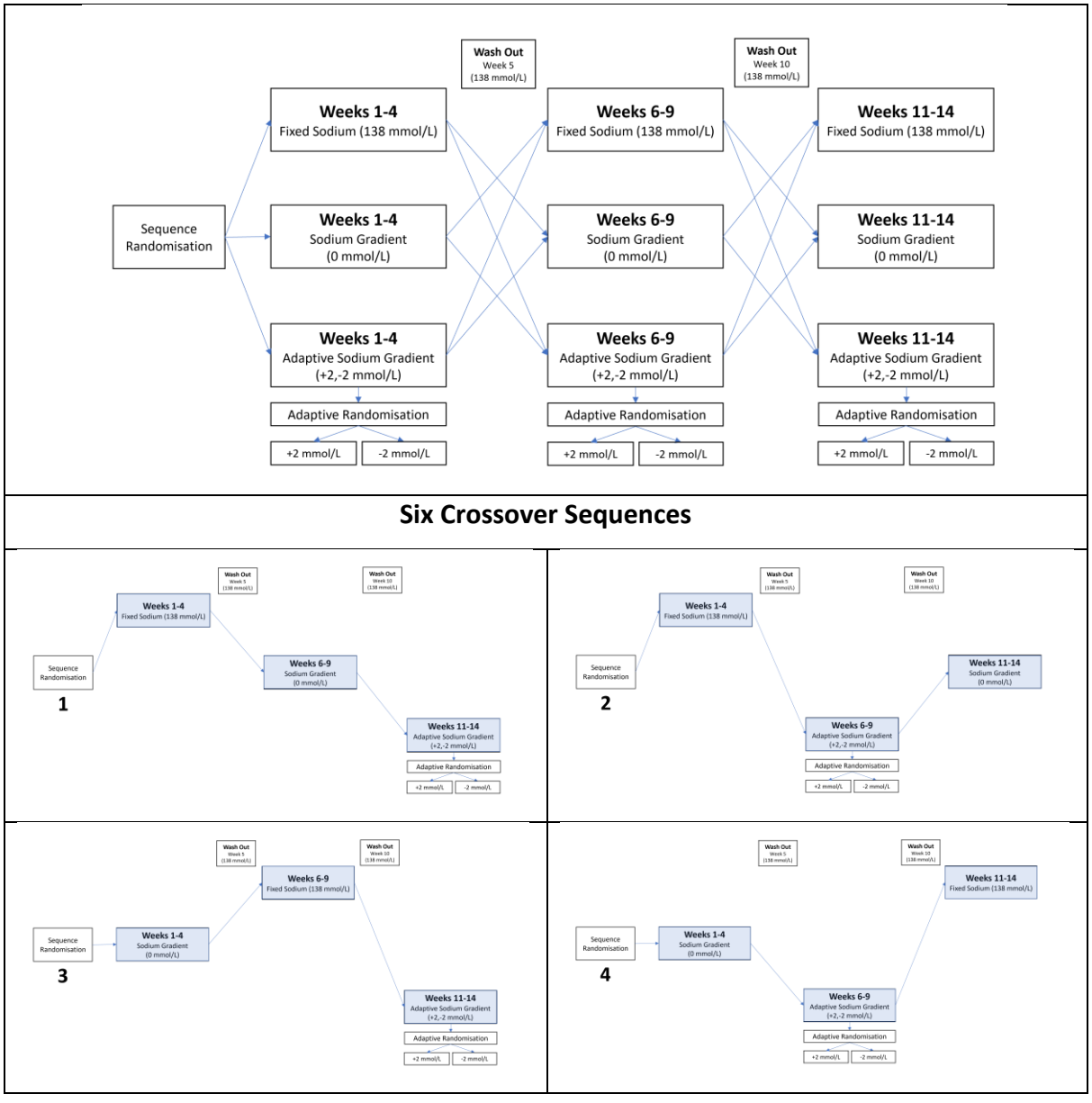
A phase IIb, dose-finding, randomised crossover, exploratory response adaptive randomised intervention, double-blinded, multi-centre (Galway University Hospitals [GUH], University Hospital Limerick [UHL], Tallaght University Hospital [TUH] and Beaumont University Hospital [BUH]) controlled trial.

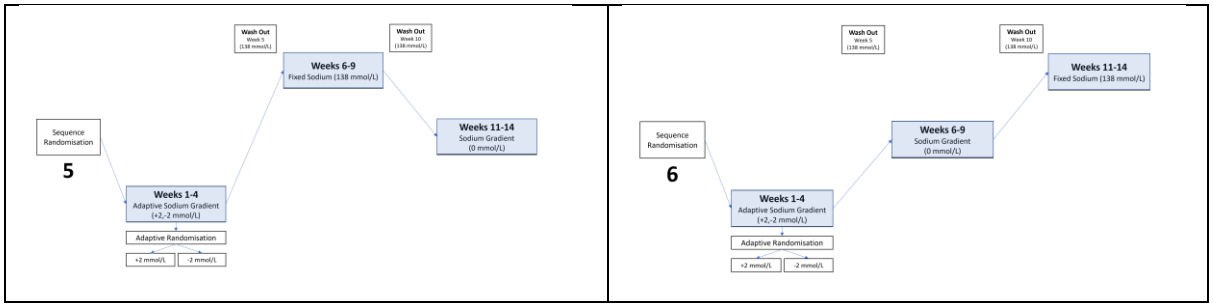
7.2.5 Sampling Frame and Clinical Setting

The sampling frame includes patients with kidney failure requiring dialysis attending the haemodialysis units and associated satellite units at GUH, UHL, TUH and BUH. All attending patients will be screened using the eligibility criteria. Established kidney failure requiring dialysis is defined as greater than three months of dialysis therapy. Patients meeting the criterion will be invited to participate and informed consent obtained (by a research nurse). All patients enrolled into the trial will continue to receive standard care. First, eligible participants will be randomised to one of the following six treatment sequences, which specifies the order of treatments received by the patient: ABC, BCA, CAB, ACB, BAC, CBA, where A=Experimental Treatment (Zero Sodium Gradient), B=Control (Fixed Sodium – 138 mmol/L) and C=Experimental Treatment (Adaptive Sodium Gradient) (Figure 7-2). Second,

eligible participants will be randomised to one of two sodium gradients (+2 mmol/L, -2 mmol/L). We selected +2/-2 mmol/L to ensure a between group difference of 4 mmol/L as the median measured minus delivered sodium is +1 mmol/L on most haemodialysis machines (300). This randomisation will be a response-adaptive randomisation (RAR) and allow modifications of the randomisation schedules during the conduct of the trial. The allocation probability is based on the response of the previous patients. It can be considered a drop the loser design with a seamless allocation probability moving from an inferior arm (either positive or negative sodium gradient) to a superior arm (either positive or negative sodium gradient).

Figure 7-2 Randomised to One of Six Crossover Sequences





7.2.6 Population

This study is a phase IIb, dose-finding, randomised crossover, exploratory response adaptive randomised intervention, double-blinded, multi-centre, controlled trial for a secondary prevention population of patients with established kidney failure requiring dialysis. All patients with kidney failure requiring dialysis are routinely followed-up every week on dialysis where they undergo clinical and laboratory assessment including measurement of blood pressure, haemoglobin, residual urine output, volume status, bone-mineral assessment, and cardiovascular risk. Therefore, the proposed clinical trial is aligned with routine care.

7.2.7 Feasibility

There is a high prevalence of hypertension in dialysis patients, up to 80% (301). There is also a lot of variation in dialysate sodium used (297). Most modern haemodialysis machines can alter sodium concentration (300). An advantage of the crossover design is that each patient acts as their own control, this allows a within-subject comparison between treatments by removing between subject variability, this includes variability among haemodialysis machines and haemodialysis centres (302).

7.3 Eligibility Criteria

7.3.1 Inclusion Criteria

(i) Age ≥18 years.

(ii) Kidney failure requiring dialysis for 3 months.

(iii) Kidney failure attributed to diabetes, hypertension, vascular disease, obstructive uropathy, polycystic kidney disease, glomerular disease, or a combination (which does not have to be biopsy proven).

(iv) Pre-dialysis systolic blood pressure 130 – 180 mmHg at screening visit.

(v) Signed informed consent.

7.3.2 Exclusion Criteria

(vi) Severe heart failure (Left Ventricular Ejection Fraction ≤20%).

(vii) Pregnancy or lactation.

(viii) Cognitive impairment defined as a known diagnosis of dementia, or inability to provide informed consent due to cognitive impairment in the opinion of the investigator. Patients with mild cognitive impairment are eligible, provided they are considered able to provide informed consent in the opinion of the local investigator.

(ix) Body Mass Index (BMI) <20 or >35 kg/m^2.

(x) Prescribed sodium profiling for intradialytic hypotension.

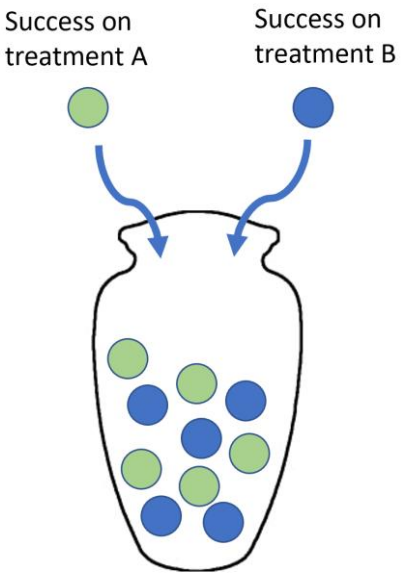
(xi) Hyponatraemia (Pre-dialysis serum sodium <135 mmol/L).

7.4 Randomisation

7.4.1 Primary Objective

For the primary objective of this trial, we will use a fixed probability randomisation strategy for the crossover order, where each participant has an equal probability of assignment to one of the six crossover order groups (Figure 7-2). A response-adaptive randomisation (RAR) will be used for selection of sodium gradient (+2mmol/L, -2 mmol/L) and allow modifications of the randomisation schedules during the conduct of the trial. The allocation probability is based on the response of the previous patients and the main purpose is to increase the chance of randomising a participant to the superior treatment group. We will use a generalised urn model suitable for multiple-arm trials with various endpoints. At the start of the clinical trial, an urn contains five balls representing treatment A (sodium gradient +2 mmol/L) and five balls representing treatment B (sodium gradient -2 mmol/L). We denote these balls as type A, and type B balls. When a subject is recruited, a ball is drawn and replaced. If it is a type A ball, the subject receives treatment A (sodium gradient +2 mmol/L) and if it is a type B ball, the subject receives treatment B (sodium gradient -2 mmol/L). When a subject's outcome is available, the urn is updated as follows: A success on treatment A (sodium gradient +2 mmol/L) will generate an additional one type-A ball in the urn. In this way, the urn builds up more balls representing the more successful treatment (Figure 7-3).

Figure 7-3 Generalised Urn Model for Response Adaptive Randomisation



7.4.2 Allocation Sequence Generation

The randomisation schedule for the crossover will be constructed using a computer-generated list of pseudo-random numbers. A centrally administered, computer-generated randomisation scheme will be used to randomly assign participants in a 1:6 ratio using randomly permuted blocks. The response adaptive randomisation will be generated by R code embedded in the electronic Case Report Form.

7.4.3 Allocation Concealment

Once a patient returns for the randomisation visit, the research nurse will use a central computer application to check eligibility criteria and confirm that the participant has provided consent, prior to assigning a unique study identification number to the participant and an individual patient treatment assignment using the online web service Sealed Envelope. A central record (at the HRB-CRFG) will be kept of all participants who have been randomised.

7.4.4 Blinding

This study is a double-blinded randomised clinical trial. The patient and dialysis staff will be blinded to the dialysate sodium concentration. A software patch for the B-Braun machine will be developed that sets the sodium concentration based on a central register of participant ID, randomisation group and crossover period. The investigator will also be blinded for the purposes of outcome assessment and the statistician completing the final

analyses will also be blinded to treatment allocation. The randomisation schedule will be securely maintained by the central randomisation facility throughout the trial. At trial completion, treatment assignments will be compared to the randomisation list, to detect any incorrect assignments.

7.5 Intervention and Usual Care

7.5.1 Pre-Randomisation and Screening Visit

All eligible participants who provide written informed consent will be included in an initial run-in period prior to randomisation. The run-in period will consist of a standardisation of dialysate sodium to 138 mmol/L, a protocolised assessment of dry weight by study staff, a protocolised standardisation of antihypertensive administration, and a sodium food frequency questionnaire. The key aim of the screening period is to standardise dialysate sodium and use of antihypertensive medications prior to randomisation. Participants will not be randomised if:

1. They have uncontrolled hypertension (Systolic BP > 180 mmHg) at randomisation. They should have their antihypertensives titrated further.
2. Two or more episodes of intradialytic hypotension (Intradialytic systolic BP < 90 mmHg) during run-in phase.

7.5.2 Usual Care

For all participants, standard care includes treatment of hypertension, fluid volume status, anaemia, mineral-bone disease, and cardiovascular disease risk according to trial protocol. Changes in antihypertensive medications are permitted throughout the trial and should be altered according to the trial protocol for all groups with an emphasis on strategies to reduce excess volume prior to increasing antihypertensive medications. No restriction on routine clinical care, including possible co-interventions, will be enforced during the trial. Usual care sessions will be delivered to all enrolled patients at all visits during the trial.

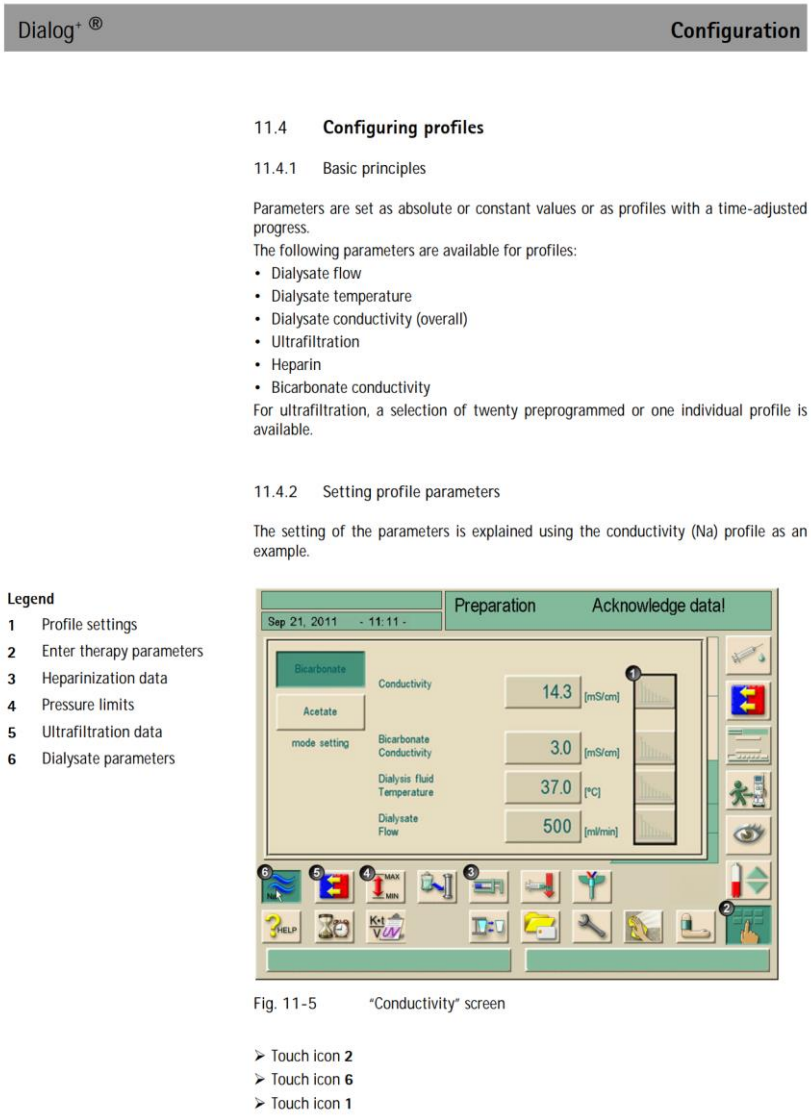
7.5.3 Follow-Up Review

Each visit will consist of a review of the baseline assessment and status to determine changes since the previous visit as well as a review of laboratory and anthropometric data. The visits will be conducted during the patient's routine dialysis time.

7.5.4 Dialysate Sodium Gradient Intervention

The pre-dialysis serum sodium will be a rolling average of the previous three pre-dialysis serum sodium levels. Dialysate sodium is set to pre-dialysis serum sodium plus/minus randomised intervention gradient, or pre-dialysis serum sodium, or a fixed dialysate sodium of 138 mmol/L. Instructions for modifying the sodium concentration on the Dialog+ B-Braun machine are included (Figure 7-4). The final determination of dialysate sodium will be at the discretion of the treating clinician. Deviations from the treatment protocol will need a documented clinical reason.

Figure 7-4 Instructions for Modifying the Sodium Concentration on the Dialog+ B-Braun Hemodialysis Machine



Dialog+ ® Configuration

11.4 **Configuring profiles**

11.4.1 Basic principles

Parameters are set as absolute or constant values or as profiles with a time-adjusted progress.
The following parameters are available for profiles:

- Dialysate flow
- Dialysate temperature
- Dialysate conductivity (overall)
- Ultrafiltration
- Heparin
- Bicarbonate conductivity

For ultrafiltration, a selection of twenty preprogrammed or one individual profile is available.

11.4.2 Setting profile parameters

The setting of the parameters is explained using the conductivity (Na) profile as an example.

Legend

1 Profile settings
2 Enter therapy parameters
3 Heparinization data
4 Pressure limits
5 Ultrafiltration data
6 Dialysate parameters

Fig. 11-5 "Conductivity" screen

➢ Touch icon **2**
➢ Touch icon **6**
➢ Touch icon **1**

7.5.5 Follow-Up Schedule

Apart from the interval between the pre-randomisation (Week -2) and randomisation (Time zero) visits, all other scheduled visits will occur three times per week throughout the study period. Patients who attend the first follow-up visit at week one (Time zero) will be randomised to one of the six crossover order groups and randomised to one sodium gradient (+2 mmol/L, -2 mmol/L). Study specific measurements will be carried out at randomisation (T0), Week 1-4, Week 5, Week 6-9, Week 10, Week 11-14. Patients will not be followed up after Week 14 (Table 7-2).

Table 7-2 Follow-up Schedule in the DESIGN Trial

Timing Window	**Routine Data Collection**	**Week -2 (Run-in)**	**Time Zero (Randomisation)**	**Week 1-4**	**Week 5**	**Week 6-9**	**Week 10**	**Week 11-14**
				Crossover Period 1	**Washout**	**Crossover Period 2**	**Washout**	**Crossover Period 3**
Eligibility Criteria Review	No	X						
Informed Consent	No	X						
Demographics	No	X						
Comorbidities	No	X						
Food Frequency Questionnaire	No		X					
Crossover Sequence Randomisation	No		X					
Sodium Gradient Randomisation	No		X					
Routinely Collected Data								
Pre-dialysis Systolic & Diastolic BP	Yes	X	X	X		X		X
Post-dialysis Systolic & Diastolic BP	Yes	X	X	X		X		X
Medications	Yes	X	X	X		X		X
Anthropometrics (Height)	Yes	X						
Pre-dialysis Weight	Yes	X	X	X		X		X
Post-dialysis Weight	Yes	X	X	X		X		X
Study Specific Data Collection								
44-hour Ambulatory Blood Pressure	No		X		X		X	
Pre-dialysis Serum sodium, potassium, urea	No	X	X	X	X	X	X	X
Post-dialysis Serum sodium, potassium, urea	No	X	X	X	X	X	X	X
Adherence	No	X	X	X	X	X	X	X
Outcomes - Intradialytic hypotension	No	X	X	X	X	X	X	X
HrQOL Survey	No	X	X	X	X	X	X	X

7.5.6 Standardisation of Intervention and Follow-Up

Patients in all groups will attend for standardised usual care at the same visit frequency. There will be a standardised operations manual for usual care and for the application of the intervention to ensure that all sessions are conducted in the same way for every participant.

7.5.7 Methods to Maximise Participant Adherence

All follow-up visits will be scheduled during the patient's regular haemodialysis time. A written pamphlet will also be provided to participants.

7.6 Measurements

7.6.1 Screening

At the pre-randomisation (Week -2) visit, eligibility criteria will be reviewed, and informed consent will be obtained by study staff.

7.6.2 Baseline Characteristics

Data will be collected at pre-randomisation (Week -2) for relevant participant demographic and clinical characteristics and entered into an electronic case report form including:

(i) Demographics: date of birth, age, sex, ethnicity, employment status.

(ii) Co-morbidities: diabetes mellitus, hypertension, congestive heart failure, dyslipidaemia, cardiovascular disease (including myocardial infarction, stroke, congestive heart failure), atrial fibrillation, peripheral vascular disease, current smoking status (never vs. former vs. current smoker [within last six months], number of cigarettes smoked per day), alcohol intake and physical activity.

(iii) Pre- and post- dialysis blood pressure.

(iv) Pre- and post- dialysis weight.

(v) Current medications: antihypertensive agents, diuretics, lipid lowering therapies, analgesics, treatments for diabetes mellitus (oral hypoglycaemic agents, insulin, or other therapies).

(vi) Height (using a wall-mounted non- stretchable standard tape measure) used to calculate body mass index.

7.6.3 Measurements at Randomisation

Participants who complete the run-in phase between Week -2 and Time Zero will compete 44-hour ambulatory blood pressure monitoring and laboratory measurements. Laboratory samples will be analysed at local laboratory using standardised storage, handling, and analytical procedures. Results will be electronically imported into the trial database. Laboratory measurements taken at randomisation will include:

(i) Serum sodium, potassium, urea
(ii) HbA1c
(iii) Troponin
(iv) ProBNP/NT-ProBNP
(v) Haemoglobin
(vi) Phosphate
(vii) Renin
(viii) Aldosterone

7.6.4 Measurements at Follow-Up Visits

At all follow-up visits, data on clinical outcomes (pre and post weight) and intradialytic hypotension will be recorded. Routinely collected data will also be recorded including pre-dialysis systolic and diastolic BP, post-dialysis systolic and diastolic BP and medications.

7.6.5 Measurements at Final Visit

At the final study visit (14 weeks after randomisation), participants will be asked about clinical events, current medications, and complete a 44-hour ambulatory blood pressure monitor. Laboratory measurements will include:

(i) Serum sodium, potassium, urea, creatinine
(ii) HbA1c
(iii) Troponin
(iv) ProBNP/NT-ProBNP
(v) Haemoglobin
(vi) Phosphate
(vii) Renin
(viii) Aldosterone

7.6.6 Criteria for Permanent Withdrawal of Intervention

(i) Intradialytic systolic BP ≤90mmHg on ≥2 occasions.

(ii) Prescription of salt or sodium bicarbonate therapy or treating physician recommends against sodium restriction.

(iii) Pregnancy.

(iv) Patient request.

7.7 Study Outcomes

7.7.1 Primary Outcome

Change in interdialytic weight gain from baseline of crossover period to end of crossover period (Modelled as time-averaged value over one-month).

7.7.2 Secondary Outcomes

(i) Safety: Intradialytic hypotension, defined as (a nadir (lowest) systolic BP less than 90 mmHg) from baseline of crossover period to end of crossover period (one-month).

(ii) Change in interdialytic systolic blood pressure measured using 44-hour ambulatory blood pressure monitoring from baseline of crossover period to end of crossover period (one-month).

(iii) Hypervolaemia (Extracellular Water (ECW)/Total Body Water (TBW) Ratio) measured using bioimpedance spectroscopy (Body composition monitor - Fresenius Medical Care) from baseline of crossover period to end of crossover period (one-month).

(iv) Health related Quality of Life using the Kidney Disease Quality of Life scale from baseline of crossover period to end of crossover period (one-month).

(v) Change in pre-dialysis systolic blood pressure from baseline of crossover period to end of crossover period (one-month).

(vi) Change in post-dialysis systolic blood pressure from baseline of crossover period to end of crossover period (one-month).

(vii) Change in post-dialysis weight from baseline of crossover period to end of crossover period (one-month).

7.7.3 Change in number of antihypertensive medications from baseline of crossover period to end of crossover period (one-month).Exploratory Outcomes (Adaptive Sodium Gradient)

(i) Efficacy: Change in interdialytic weight gain from baseline of crossover period to end of crossover period (one-month).

(ii) Safety: Intradialytic hypotension, defined as (a nadir (lowest) systolic BP less than 90 mmHg) from baseline of crossover period to end of crossover period (one-month).

7.7.4 Outcome Events of Interest

(i) Cardiovascular Events including:

a. Myocardial infarction defined as rise in troponin and one of: ischaemic signs or symptoms, ECG changes (Q waves, ST elevation, ST depression), coronary artery intervention or new cardiac wall motion abnormality on echocardiography.
b. Stroke defined as new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting >24 hours or leading to death.
c. Cardiac revascularization procedures including percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery.

(ii) Serious Adverse Events including:

a. Admission for hypervolaemia.
b. Intradialytic saline administration.
c. Reduction in Residual Urine Volume.
d. Arteriovenous fistula clotting.
e. Falls.
f. Death.

7.8 Statistical Analysis

7.8.1 Sample Size Considerations

The primary outcome is mean change in interdialytic weight gain during the crossover period (4 weeks). A random effects model with the treatment as a fixed effect, the period as a fixed effect and the participant as a random effect with baseline interdialytic weight gain as a covariate will be used to detect a difference in the mean change between crossover

periods. The sample size is primarily based on the hypothesis testing comparison of zero sodium gradient versus fixed dialysate sodium (138 mmol/L) control. Over 3 months follow-up, an estimated mean decrease in interdialytic weight gain between the intervention group (135 mmol/L) and the control group (140 mmol/L) of 0.47±0.82kg is expected based on the findings of the Sodium Lowering in Dialysate (SoLID) study (33). We have selected an estimated mean decrease in interdialytic weight gain of 0.20 kg (10% reduction in IDWG) as the minimum important 4-week difference in interdialytic weight gain. For the purpose of the power calculation, this difference applies to the zero sodium gradient versus fixed sodium (138 mmol/L) only. The R Package PowerTOST was used to perform sample size calculations (303). A total sample size of 240 participants was calculated as required to detect a change in 0.20 kg (10% reduction) in interdialytic weight gain with the proposed crossover design between zero sodium gradient and fixed sodium (138 mmol/L), using an estimated within-participant standard deviation of 0.82 kg * sqrt(1-Rho), where Rho is the correlation for measurements in the same subject (Conservative Rho=0.1), and a power of 0.80 and $\alpha = 0.05$. A recruitment goal of 264 participants has been set to account for the potential participant drop out. We will test for a carryover effect using the Mainland-Gart test. If a carryover effect exists, we will adjust for this in our mixed model using a period and group interaction term.

7.8.2 Descriptive Statistics and Baseline Characteristics

Descriptive statistics will be used to describe the baseline characteristics of the study population, the flow of trial participants and the level of missing data for both predictor and outcome variables. All losses to follow-up and dropouts will be accounted for and reasons documented. Categorical variables will be described using frequencies and percentages. Histograms and boxplots will be used to evaluate the distribution of continuous variables and to identify any outliers or potential errors in the data, with follow-up verification from CRFs. For continuous variables, the mean and standard deviation will be reported and if not normally distributed, the median and interquartile range will be reported. All tests of significance will be two-sided and conducted at an alpha of 0.05 for statistical significance. The intention-to-treat dataset will be used for the analysis of all outcomes. A secondary per-protocol analysis will also be carried out for all outcomes, with post randomisation exclusions due to ineligibility, non-compliance, loss to follow-up and missing data.

7.8.3 Statistical Analysis of Primary Outcome

A random effects model with the treatment as a fixed effect, the period as a fixed effect and the participant as a random effect with baseline IDWG as covariate will be used to compare the mean IDWG from baseline of each crossover period to end of each crossover period (modelled as time-averaged value over 4 weeks) and 95% CI reported to indicate precision. If there are any chance imbalances in the baseline distribution of important covariates between treatment groups, an adjusted secondary analysis will also be performed with the intention to treat dataset and the relevant covariates, in a linear mixed model for a continuous response.

7.8.4 Statistical Analysis of Secondary Outcomes

For continuous outcome variables (BP, Weight, Extracellular Water/Total Body Water Ratio, and number of antihypertensive medications), a random effects model with the treatment as a fixed effect, the period as a fixed effect and the participant as a random effect with baseline value as covariate will be used to compare changes from baseline of each crossover period to end of each crossover period, including 95% CI. For categorical outcomes (Intradialytic hypotension), a Chi-square or Fisher's exact test will be used, depending on the number of outcome events after checking underlying statistical assumptions.

7.8.5 Subgroup and Sensitivity Analyses

The primary outcome will be analysed by subgroups based on age (<60 versus ≥60 years), gender, smoking status (never smoker vs. ever smoker), and duration of dialysis (<1 year, ≥ 1 year). Statistical tests of interaction (Wald test) will be performed for all subgroup analyses. A sensitivity analysis will be performed to assess the effect of participant reported compliance on treatment effect.

7.8.6 Missing Data

First, by including a run-in period and only randomising those that adhere to the run-in protocol, this will reduce the dropout rate during the trial. Second, by integrating with routine clinical care, the trial will not be a significant burden to patients. Third, the informed consent form will distinguish between withdrawing from the treatment allocation and withdrawal from the study, allowing the collection of outcome data on patients that discontinue the intervention. Fourth, this small, feasibility proof-of concept trial, will be used to inform the conduct and design of a larger trial, if indicated.

7.8.7 Data Safety and Monitoring Board

To ensure the safety of participants, two interim analyses will be performed and reviewed by the data and safety monitoring board (DSMB) when 25% (A1) and 50% (A2) of participants have completed 14 weeks of follow-up. The DSMB will be chaired by a clinician scientist with experience in clinical trials in nephrology who will appoint the remainder of the DSMB, which will include an odd number of members and, at a minimum, an ethicist, and an independent, non-voting biostatistician, all of whom are knowledgeable about the question being studied. All members of the DSMB will provide written declarations of freedom from conflicts of interest.

The DSMB will be blinded and review outcomes whilst considering three stopping guidelines: (i) the proportion of serious adverse events for an unacceptable safety risk at A1 and A2; (ii) new external information that convincingly answers the primary research question or raises serious safety issues with either the intervention or usual care at A1 and A2; and (iii) overwhelming benefit from either the intervention or usual care approach.

Results of interim analysis will not be disclosed to investigators or study participants (unless the DSMB makes a formal recommendation to stop the trial is made) but will be published along with the DSMB recommendations on trial completion. The evidence derived from the interim analyses may not be conclusive and concealing the findings prevents any influence on study participants or investigators, by disturbing the assumption of clinical equipoise – i.e., it could make physicians hesitant to continue to recruit patients and/or adversely affect adherence.

7.8.8 Ethical Considerations

This study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH-GCP) and the requirements of the research ethics committee, from whom ethical approval will be sought prior to study initiation. Informed consent forms, patient information leaflets and other study documentation (including case report forms) will be developed prior to submission to the research ethics committee.

7.8.9 Patient Confidentiality

There is a risk to patient confidentiality with this study, which could result in mental discomfort and distress to involved participants if breached. The risk is estimated to be

low/moderate. To preserve patient confidentiality, all information obtained in this study will be handled with strict privacy and electronic data security standards. Unique subject identifiers will be assigned to each participant to prevent unauthorised identification of research participants. In addition, all primary data will be stored in the database devoid of any personal information or identifiers. All computers and laptops used to store the data will have password protection and encryption software in place.

7.8.10 Risk-Benefit Ratio

Although there are risks associated with this trial and interim analyses are planned, based on available evidence these risks are anticipated to be low with reasonable chance of benefit. As such, there is a reasonable chance of benefit, and the overall risk benefit ratio is favourable. The DSMB will continue to monitor risks and may recommend study discontinuation if the risk-benefit ratio changes significantly.

7.8.11 Limitations and Methods to Control Bias

First, individuals who participate in studies are often healthier than those who refuse to provide consent (volunteer bias) and the actual sample of individuals included in the trial (i.e., trial participants) may not be representative of the target population, limiting the generalisability of the results. A screening log will be compiled to determine if participants and non-participants differ significantly. Second, the primary outcome measure is absolute reduction in interdialytic weight gain, which although clinically relevant, is a surrogate measure for volume control in kidney failure requiring dialysis. Third, to minimize within and between subject variability in the administration of the intervention, all specialists administering the intervention will be trained, certified, and periodically observed. Finally, to maximize study quality, all components of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement were considered during the drafting of this protocol.

7.9 Trial Administration

7.9.1 Site

This multi-centre study will be conducted at Galway University Hospital, University Hospital Limerick, Tallaght University Hospital, and Beaumont University Hospital and the co-ordinating centre will be the Health Research Board – Clinical Research Facility Galway (HRB-

CRFG). Completed case report forms and other paperwork relating to the trial, including the trial master file, will be held at the coordinating centre (HRB-CRFG).

7.9.2 Steering, Local Operations and Publication Committees

As this is a multi-site study, one committee will deal with steering, operations and publications and consist of Dr. Conor Judge and Prof. Martin O'Donnell (Co-Principal Investigators), Prof. Donal Reddan and Prof. Matthew Griffin (Consultant Nephrologists at GUH), and Dr. Alberto Alvarez-Iglesias (Biostatistician). The steering committee will meet every three months to review progress of the clinical trial, identify problems and implement solutions. The local operations committee will meet every month to review progress, recruitment update, quality of data, etc. and will include the research nurse, research assistant, Dr Conor Judge and Prof Martin O'Donnell.

Specifically, in the first year the committee will closely review recruitment to ensure that all study participants are randomised by a specific date to complete 14 weeks of follow-up by study end. This process strives to minimise missing data.

7.9.3 Study Monitoring

Members of the steering committee will be responsible for the overall conduct and on-site monitoring of the study and for ensuring that all study procedures are compliant with ICH-GCP. Monitoring will be independent of the study funder and free from competing interests. Progress meetings will be held to monitor:

(i) recruitment and adherence to procedures for informed consent.

(ii) adherence to the protocol and any protocol amendments by reviewing a random subsample of patient consent forms and CRFs.

(iii) adherence to the intervention and to follow-up visits.

(iv) quality of the data collected.

(v) verification that the data collected is valid and consistent on import into the study database. Ongoing training will occur to ensure that a good understanding of the protocol and of standardised operating procedures is maintained, to resolve problems and to promote staff commitment and enthusiasm for the study. As this is a multi-centre study on-site monitoring will be conducted. One internal audit by the

Quality and Regulatory Affairs Manager from the HRB-CRFG will be performed during the conduct of the trial.

7.9.4 Data Collection and Quality Control

All data collection and study outcome measurements will be conducted locally and entered into electronic case report forms by the attending research nurse and transferred into the study database by trial staff. Routine data collected by the renal clinical information system, eMed, will be transferred once per day to the study database. Data to be extracted from CRFs will include participant identification numbers, verification of eligibility criteria, verification of written informed consent, relevant participant demographic and clinical characteristics, current medications, physical parameters (e.g., BMI and BP), adherence with follow-up, patient reported adherence with the intervention and outcome events. Laboratory results will be electronically imported into the trial database.

7.9.5 Study Timeline

It is expected that 6 potentially eligible patients will be reviewed at the haemodialysis unit per week per centre, of which 50% are expected to participate in the trial. Therefore, a minimum of 12 patients per week will be recruited. Patients will not be followed up after completion of the final visit.

7.9.6 Dissemination Strategy

It is anticipated that this research may demonstrate the benefits of a dialysate sodium reduction intervention on interdialytic weight gain in patients with kidney failure requiring dialysis. Study results will be presented locally, nationally, and internationally by the study Co-PIs. The primary study results will be submitted in manuscript form for publication to peer reviewed, internationally recognized, journals with a high impact factor. The focus will be on broad medical journals as well as those specific to kidney failure requiring dialysis. The database created at HRB-CRFG will be available for further research studies.

7.9.7 Protocol Amendments

The investigator will not implement any deviation from or changes of the trial protocol without review and documented approval/favourable opinions from the Research Ethics Committee, except to eliminate an immediate hazard to the trial participants. Changes will

be recorded in writing, signed by the principal investigator, and filed with the protocol. Approval from the REC must be received prior to implementation of changes.

7.9.8 Declaration of Interests

The Co-PIs, collaborators and other protocol contributors have no financial or other competing interests to declare.

Chapter 8 Conclusions

8.1 Summary and Conclusions

Kidney failure requiring dialysis is increasing in prevalence and associated with significant morbidity and mortality (4). Hypertension and volume overload play key roles in the mechanism of both cardiovascular and non-cardiovascular mortality (9). Sodium balance is a key determinant of hypertension, and it is imperative that low-cost interventions are found to reduce the burden of volume and hypertension in dialysis (12). Additionally, more efficient methods to perform clinical research in dialysis populations are urgently needed (40,45). In this thesis, I used observational, experimental and evidence synthesis methodology to develop a trial protocol for optimisation of sodium balance in dialysis. Chapter 2 examined the use of adaptive design methods in dialysis clinical trials and found a relative decrease in these methods. Chapter 3 examined the association between a dietician lead counselling intervention for lowering dietary sodium compared to healthy eating alone on blood pressure and renal outcomes in a randomised controlled trial in CKD (STICK) and non-CKD populations (COSIP) and found that dietary sodium lowering is likely not a feasible intervention. Chapter 4 also examined the association of sodium excretion (surrogate for intake) with stroke in an international case-control study (INTERSTROKE) and how this association is modified by CKD. Chapter 5 examined the association of antihypertensive medication withdrawal with cardiovascular events in CKD and non-CKD participants in a post-hoc analysis of an international randomised clinical trial (SPRINT). Chapter 6 examined the association between trials with run-in periods compared to trials without run-in periods on treatment effects in cardiovascular prevention trials. The data from these observational and experimental studies were used to design a protocol for a phase IIb, dose-finding, randomised crossover, exploratory response adaptive randomised intervention, double-blinded, multi-centre, controlled trial that tests fixed dialysate sodium versus gradients of dialysate sodium concentration on short term efficacy (Interdialytic weight gain) and safety outcomes (Intradialytic hypotension).

8.2 Chapter 2 - Trends in adaptive design methods in dialysis clinical trials – a systematic review

I completed a systematic review to explore the use of adaptive design methods in dialysis clinical trials. For this chapter, I developed the research question, drafted the protocol,

developed the search strategy, created the novel full text systematic review method, utilised a Support Vector Machine (SVM) machine learning classifier, performed first reviewer for abstract and full text screening, extracted the data, summarised the results, performed all the statistical analysis, created the figures, drafting and submission of the manuscript. Fifty-seven studies, available as 68 articles and 7 clinicaltrials.gov summaries, were included after full text review (initial search 209,033 PubMed abstracts and 6,002 clinicaltrials.gov summaries). Thirty-one studies were conducted in a dialysis population and 26 studies included dialysis as a primary or secondary outcome. The key findings were as follows: while the absolute number of adaptive design methods is increasing over time, the relative use of adaptive design methods in dialysis trials is decreasing over time (6.12% in 2009 to 0.43% in 2019 with a mean of 1.82%). Group sequential designs were the most common type of adaptive design method used. Adaptive design methods impacted the conduct of 50.9% of trials, most commonly resulting in early stopping for futility (41.2%), or safety (23.5%). Acute Kidney Injury (AKI) was studied in 32 trials (56.1%), kidney failure requiring dialysis was studied in 24 trials (42.1%) and Chronic Kidney Disease (CKD) was studied in 1 trial (1.75%). 27 studies (47.4%) were supported by public funding. Forty-four studies (77.2%) did not report their adaptive design method in the title or abstract and therefore would not be detected by a standard systematic review. The overall conclusion was that there has been a relative decline in adaptive design methods in dialysis trials. The infrequent usage of adaptive designs in dialysis trials may become a self-perpetuating barrier to using adaptive designs in future trials. Greater knowledge of adaptive design examples in dialysis should further improve uptake in dialysis randomised clinical trials.

8.3 Chapter 3 - Effect of a dietary counselling intervention targeting low sodium intake (<2.3 g/day) versus moderate sodium intake on 24-hour ambulatory blood pressure and renal outcomes – COSTICK Trial

In this chapter, I completed an analysis of two phase IIb randomised clinical trials – STICK and COSIP – exploring the association between dietary sodium lowering compared to healthy eating on blood pressure and renal outcomes. For this chapter, I processed and cleaned the raw ABPM data, performed all the analysis in R, developed the models following the prespecified statistical analysis plan, created a new R package (https://conorjudge.github.io/costick/), created the tables and figures and drafted the

manuscript. At baseline, the mean 24-hour urinary sodium excretion was 3.1 g/day, and mean ABP was 122/72 mmHg, which is a moderate sodium intake at baseline and a normotensive population. Mean change in 24-hour urinary sodium excretion did not differ significantly between groups at 24 months (-0.14 g/day, 95% CI, -0.45 to 0.17). There was no difference in nocturnal SBP (-1.45 mmHg, 95% CI, -4.69 to 1.79) between groups at 24 months. There was no significant difference in between-group change in nocturnal diastolic, overall or daytime ABP between groups. There was no difference between subgroups in sex, age above and below median, study, hypertension, or baseline office systolic BP tertiles. Additionally, the failure of a dietician led sodium lowering intervention to lower sodium at two years in a CKD population is important for sodium lowering in dialysis. Extrapolating this to kidney failure requiring dialysis provides evidence that a similar intervention in patients with kidney failure requiring dialysis would also not be feasible. Overall, there was no association between dietary sodium lowering at a moderate intake level for ambulatory blood pressure outcomes or renal outcomes. Prior to these analyses, we were considering a clinical trial to evaluate the efficacy and safety of low sodium intake (<2.3 g/day) versus moderate sodium intake in patients receiving chronic dialysis. However, findings from the COSTICK trial strongly suggested that such a trial would not be feasible due to inability to achieve sustained low sodium intake.

8.4 Chapter 4 - Association of Sodium and Potassium Urinary Excretion and Acute Stroke (INTERSTROKE): Does eGFR modify the Association?

In this chapter, I completed an analysis of the association of urinary sodium and potassium excretion and the risk of stroke and how this association is modified by Chronic Kidney Disease. For this chapter, I developed the research question and the statistical analysis plan with MOD, performed all statistical analysis in R, created a new R package (https://conorjudge.github.io/interstroke), created the tables and figures and drafted and submitted the manuscript. In these analyses, the mean estimated 24-hour sodium and potassium urinary excretion was 3·29 g/day and 1·57 g/day, with 0·01% of participants having both low sodium (<2·0 g/day) and high potassium excretion (>3·5 g/day). Compared with an estimated urinary sodium excretion of 2·8-3·5 g/day (second quartile, reference), higher (>4·26 g/day) (OR 1.81; 95% CI, 1.65-2.00) and lower (<2·8 g/day) sodium excretion (OR 1.39; 95% CI, 1.26-1.53) were significantly associated with increased risk of stroke. The

stroke risk associated with the highest quartile of sodium intake (sodium excretion >4·26 g/day) was significantly greater (P<0.001) for intracerebral haemorrhage (ICH) (OR 2.38; 95% CI, 1.93-2.92) than for ischaemic stroke (OR 1.67; 95% CI, 1.50-1.87), and greater for large vessel and small vessel ischaemic stroke than for cardioembolic ischaemic stroke. Urinary potassium was inversely and linearly associated with risk of stroke, and stronger for ischaemic stroke than ICH (P=0.026). In an analysis of combined sodium and potassium excretion, the combination of high potassium intake (>1·58 g/day) and moderate sodium intake (2.8-3.5 g/day) was associated with the lowest risk of stroke. The association of sodium intake and stroke is J-shaped, high sodium intake is modified by CKD category and low sodium intake is not modified by CKD category.

8.5 Chapter 5 - Cardiovascular Risk Associated with Stopping Antihypertensive Therapy in Patients with and without Chronic Kidney Disease – An Analysis of the SPRINT Trial

In this chapter, I completed an analysis of the association of antihypertensive medication withdrawal or reduction and cardiovascular events in participants with and without Chronic Kidney Disease. For this chapter, I developed the research question and the statistical analysis plan with MOD, I sourced the data, I performed the statistical analysis in R with JF and AAI, collation and interpretation of the results, creation of figures and drafting of the manuscript. In these analyses, non-standard withdrawals of antihypertensive medications were associated with increased cardiovascular risk in the control group of SPRINT. Non-standard withdrawal of antihypertensive agents was associated with an increased risk of cardiovascular events in the subsequent follow-up periods (HR 1.65; 95% CI, 1.26 to 2.16 for the first hazard period; HR 1.47; 95% CI, 1.12 to 1.95 for the second hazard period). The analyses suggest that non-standard withdrawal and per-protocol reductions in antihypertensive therapy, in the control group, inflated the magnitude of treatment effect for a composite cardiovascular outcome reported for intensive blood pressure lowering. We observed a statistically significant association for interruption of antihypertensive therapy and heart failure in participants with reduced eGFR (P-interaction=0.031). Prior to these findings, we had considered a clinical trial protocol to evaluate routine stopping of antihypertensive therapy (versus continuation) in the peri-dialysis period. We decided

against such a trial, due to safety concerns, but findings influenced the decision to include a population with stable use of antihypertensive therapy in the DESIGN trial.

8.6 Chapter 6 - The Effect of a Run-In Period on Estimated Treatment Effects in Cardiovascular Randomised Clinical Trials – A Meta-Analytic Review

In this chapter, I completed an analysis of the association of a run-in period in trials compared to not having a run-in period in trials with inflation of the treatment effect. For this chapter, I developed the research question and the statistical analysis plan with MOD, designed data collection, managed a team of researchers to extract and score data from trials, completed all statistical analysis in R, created the tables and figures, and drafted the manuscript with RM. On meta-analysis of the primary outcome, there was no statistically significant difference in the magnitude of treatment effect between run-in trials (relative risk (RR) 0.83, 95% CI, 0.80-0.87) compared to non-run-in trials (RR 0.88, 95% CI, 0.84-0.91) (ratio of relative risk (RRR) 0.95, 95% CI, 0.90-1.01). There was no significant difference in the RRR for secondary outcomes of all-cause mortality (RRR 0.97, 95% CI, 0.91-1.03), medication discontinuation due to adverse events (RRR 1.05, 95% CI, 0.85-1.21), non-fatal myocardial infarction (RRR 1.01, 95% CI, 0.85-1.19), and non-fatal stroke (RRR 1.00, 95% CI, 0.87-1.16). Post-hoc exploratory univariate meta-regression analysis showed that on average a run-in period is associated with a statistically significant difference in treatment effects (RRR 0.94; 95% CI, 0.90 to 0.99) for cardiovascular composite outcome, but this was not statistically significant on multivariable meta-regression analysis (RRR 0.95; 95% CI, 0.90 to 1). Overall, the use of a run-in period was not associated with a difference in the magnitude of treatment effect among cardiovascular prevention trials. In the DESIGN trial, we employ a run-in period, to include an enriched population of patients who are adherent with the clinical trial protocol.

8.7 Chapter 7 - Identifying the DialysatE SodIum GradieNt with the Best Efficacy/Tolerability Profile in an Adaptive Phase IIb Dose-Finding Crossover Study in Haemodialysis (DESIGN Trial)

In this chapter, I developed a protocol for a phase IIb, dose-finding, randomised crossover, exploratory response adaptive randomised intervention, double-blinded, multi-centre, controlled trial to test what dialysate sodium gradient is associated with lowest interdialytic

weight gain and lowest number of intradialytic hypotension episodes. For this chapter, I developed the research question, study design, methodological approaches and drafted the protocol with MOD. I will colead a funding application (with my PhD Supervisor, Professor Martin O'Donnell) to the Health Research Board of Ireland, Definitive Interventions and Feasibility Awards (DIFA) in 2022. It will incorporate adaptive design methodology (Chapter 2), a run-in period (Chapter 6), mandate that antihypertensives are not held (Chapter 4), not include a dietary intervention (Chapter 3) and will study optimal sodium balance in patients with kidney failure requiring dialysis (Chapter 1/4). It is anticipated that the findings of this trial will lead to a larger definitive phase III trial and a longer follow-up period that will be powered to detect differences in clinical endpoints to definitively answer this research question.

8.8 Conclusion and Impact

There is a need to identify the optimal peri-dialytic sodium, volume, and blood pressure environment that is associated with lowest morbidity and mortality. Sodium lowering, through dialysate sodium lowering, has the potential to safely reduce hypervolemia, hypertension and potentially, the mortality and morbidity associated with these conditions. The results of the DESIGN trial will provide key information as to the optimal approach for dialysate sodium lowering, and may guide future phase III clinical trials. Dialysate sodium modification represents a low-cost, simple intervention that offers the potential to significantly reduce the global morbidity and mortality associated with fluid overload in kidney failure requiring dialysis.

Bibliography

1. Bikbov B, Purcell CA, Levey AS, Smith M, Abdoli A, Abebe M, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2020 Feb 29;395(10225):709–33.

2. Cockwell P, Fisher L-A. The global burden of chronic kidney disease. The Lancet. 2020 Feb;395(10225):662–4.

3. Levey AS, Eckardt K-U, Dorman NM, Christiansen SL, Hoorn EJ, Ingelfinger JR, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int. 2020 Jun 1;97(6):1117–29.

4. RA P, J H, N T-R, P C, RL W, RM H. Prognosis of patients with acute renal failure requiring dialysis: results of a multicenter study. Am J Kidney Dis Off J Natl Kidney Found. 1998;32(3):432–43.

5. National Renal Office. National Renal Office Ireland - End of Year statistics Dec 31 2020 [Internet]. [cited 2021 Jun 29]. Available from: https://www.hse.ie/eng/about/who/cspd/ncps/renal/resources/nro-end-of-year-statistics-2020.pdf

6. Himmelfarb J, Ikizler TA. Hemodialysis. N Engl J Med. 2010 Nov 4;363(19):1833–45.

7. Mehrotra R, Devuyst O, Davies SJ, Johnson DW. The Current State of Peritoneal Dialysis. J Am Soc Nephrol. 2016 Nov;27(11):3238–52.

8. Tong J, Liu M, Li H, Luo Z, Zhong X, Huang J, et al. Mortality and Associated Risk Factors in Dialysis Patients with Cardiovascular Disease. Kidney Blood Press Res. 2016;41(4):479–87.

9. de Jager DJ, Grootendorst DC, Jager KJ, van Dijk PC, Tomas LMJ, Ansell D, et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. JAMA. 2009 Oct 28;302(16):1782–9.

10. Georgianos PI, Agarwal R. Blood Pressure and Mortality in Long-Term Hemodialysis—Time to Move Forward. Am J Hypertens. 2017 Mar;30(3):211–22.

11. Agarwal R. Blood pressure and mortality among hemodialysis patients. Hypertens Dallas Tex 1979. 2010 Mar;55(3):762–8.

12. Sarafidis PA, Persu A, Agarwal R, Burnier M, de Leeuw P, Ferro CJ, et al. Hypertension in dialysis patients: a consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH)*. Nephrol Dial Transplant. 2017 Apr 1;32(4):620–40.

13. Levin NW, Kotanko P, Eckardt K-U, Kasiske BL, Chazot C, Cheung AK, et al. Blood pressure in chronic kidney disease stage 5D—report from a Kidney Disease: Improving Global Outcomes controversies conference. Kidney Int. 2010 Feb 2;77(4):273–84.

14. Lowrie EG, Laird NM, Parker TF, Sargent JA. Effect of the hemodialysis prescription of patient morbidity: report from the National Cooperative Dialysis Study. N Engl J Med. 1981 Nov 12;305(20):1176–81.

15. Daugirdas JT, Depner TA, Inrig J, Mehrotra R, Rocco MV, Suri RS, et al. KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 Update. Am J Kidney Dis. 2015 Nov;66(5):884–930.

16. Agarwal R, Nissenson AR, Batlle D, Coyne DW, Trout JR, Warnock DG. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. Am J Med. 2003 Sep;115(4):291–7.

17. Alborzi P, Patel N, Agarwal R. Home blood pressures are of greater prognostic value than hemodialysis unit recordings. Clin J Am Soc Nephrol CJASN. 2007 Nov;2(6):1228–34.

18. Ekart R, Kanič V, Balon BP, Bevc S, Hojs R. Prognostic Value of 48-Hour Ambulatory Blood Pressure Measurement and Cardiovascular Mortality in Hemodialysis Patients. Kidney Blood Press Res. 2012;35(5):326–31.

19. Agarwal R. Volume Overload in Dialysis: The Elephant in the Room, No One Can See. Am J Nephrol. 2013;38(1):75–7.

20. Chazot C. Can Chronic Volume Overload Be Recognized and Prevented in Hemodialysis Patients? Semin Dial. 2009 Sep;22(5):482–6.

21. Zoccali C, Moissl U, Chazot C, Mallamaci F, Tripepi G, Arkossy O, et al. Chronic Fluid Overload and Mortality in ESRD. J Am Soc Nephrol JASN. 2017 Aug;28(8):2491–7.

22. Himmelfarb J. Hemodialysis Complications. Am J Kidney Dis. 2005 Jun 1;45(6):1122–31.

23. K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. Am J Kidney Dis. 2005 Apr 1;45:16–153.

24. Kooman J, Basci A, Pizzarelli F, Canaud B, Haage P, Fouque D, et al. EBPG guideline on haemodynamic instability. Nephrol Dial Transplant. 2007 May 1;22(suppl_2):ii22–44.

25. Ashby D, Borman N, Burton J, Corbett R, Davenport A, Farrington K, et al. Renal Association Clinical Practice Guideline on Haemodialysis. BMC Nephrol. 2019 Oct 17;20(1):379.

26. Hirakata H, Nitta K, Inaba M, Shoji T, Fujii H, Kobayashi S, et al. Japanese Society for Dialysis Therapy Guidelines for Management of Cardiovascular Diseases in Patients on Chronic Hemodialysis: JSDT Guidelines for CVD in HD Patients. Ther Apher Dial. 2012 Oct;16(5):387–435.

27. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of Mortality Risk with Various Definitions of Intradialytic Hypotension. J Am Soc Nephrol. 2015 Mar 1;26(3):724–34.

28. Palmer BF, Henrich WL. Recent Advances in the Prevention and Management of Intradialytic Hypotension. J Am Soc Nephrol. 2008 Jan 1;19(1):8–11.

29. Aymé S, Bockenhauer D, Day S, Devuyst O, Guay-Woodford LM, Ingelfinger JR, et al. Common Elements in Rare Kidney Diseases: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2017 Oct 1;92(4):796–808.

30. Krautzig S, Janssen U, Koch KM, Granolleras C, Shaldon S. Dietary salt restriction and reduction of dialysate sodium to control hypertension in maintenance haemodialysis patients. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 1998 Mar;13(3):552–3.

31. Ozkahya M, Ok E, Cirit M, Aydin S, Akçiçek F, Başçi A, et al. Regression of left ventricular hypertrophy in haemodialysis patients by ultrafiltration and reduced salt intake without antihypertensive drugs. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 1998 Jun;13(6):1489–93.

32. Santos SFF, Peixoto AJ. Revisiting the Dialysate Sodium Prescription as a Tool for Better Blood Pressure and Interdialytic Weight Gain Management in Hemodialysis Patients. Clin J Am Soc Nephrol. 2008 Mar 1;3(2):522–30.

33. Marshall MR, Vandal AC, de Zoysa JR, Gabriel RS, Haloob IA, Hood CJ, et al. Effect of Low-Sodium versus Conventional Sodium Dialysate on Left Ventricular Mass in Home and Self-Care Satellite Facility Hemodialysis Patients: A Randomized Clinical Trial. J Am Soc Nephrol. 2020 May;31(5):1078–91.

34. The George Institute. Randomised Evaluation of Sodium Dialysate Levels on Vascular Events [Internet]. clinicaltrials.gov; 2020 Nov [cited 2021 Jul 15]. Report No.: NCT02823821. Available from: https://clinicaltrials.gov/ct2/show/NCT02823821

35. Krishnan N, Peixoto AJ. We Hold Antihypertensives Prior To Dialysis. Semin Dial. 2016 Jul;29(4):323–5.

36. McCallum W, Sarnak MJ. Blood Pressure Target for the Dialysis Patient. Semin Dial. 2019 Jan;32(1):35–40.

37. Perkovic V, Craig JC, Chailimpamontree W, Fox CS, Garcia-Garcia G, Benghanem Gharbi M, et al. Action plan for optimizing the design of clinical trials in chronic kidney disease. Kidney Int Suppl. 2017 Oct;7(2):138–44.

38. Dember LM, Archdeacon P, Krishnan M, Lacson E, Ling SM, Roy-Chaudhury P, et al. Pragmatic Trials in Maintenance Dialysis: Perspectives from the Kidney Health Initiative. J Am Soc Nephrol. 2016 Oct 1;27(10):2955–63.

39. Levin A, Tonelli M, Bonventre J, Coresh J, Donner J-A, Fogo AB, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. The Lancet. 2017 Oct 21;390(10105):1888–917.

40. Baigent C, Herrington WG, Coresh J, Landray MJ, Levin A, Perkovic V, et al. Challenges in conducting clinical trials in nephrology: conclusions from a Kidney Disease—Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2017 Aug 1;92(2):297–305.

41. Strategies to Reduce Sodium Intake in the United States [Internet]. Washington, D.C.: National Academies Press; 2010 [cited 2019 Jun 6]. Available from: http://www.nap.edu/catalog/12818

42. Gkza A, Davenport A. Estimated dietary sodium intake in haemodialysis patients using food frequency questionnaires. Clin Kidney J. 2017 Oct 1;10(5):715–20.

43. Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the Gold Standard — Lessons from the History of RCTs. N Engl J Med. 2016 Jun 2;374(22):2175–81.

44. Kovesdy CP. Clinical trials in end-stage renal disease—priorities and challenges. Nephrol Dial Transplant. 2019 Jul 1;34(7):1084–9.

45. Bryan L, Ibrahim T, Zent R, Fischer MJ. The Kidney Research Predicament. J Am Soc Nephrol JASN. 2014 May;25(5):898–903.

46. Chatzimanouil MKT, Wilkens L, Anders H-J. Quantity and Reporting Quality of Kidney Research. J Am Soc Nephrol. 2019 Jan 1;30(1):13–22.

47. Yaseen M, Hassan W, Awad R, Ashqar B, Neyra J, Heister T, et al. Impact of Recent Clinical Trials on Nephrology Practice: Are We in a Stagnant Era? Kidney Dis. 2019;5(2):69–80.

48. Chow S-C, Chang M, Pong A. Statistical Consideration of Adaptive Methods in Clinical Development. J Biopharm Stat. 2005 Jul 1;15(4):575–91.

49. Pallmann P, Bedding AW, Choodari-Oskooei B, Dimairo M, Flight L, Hampson LV, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. BMC Med [Internet]. 2018 Dec [cited 2020 Apr 23];16(1). Available from: https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-018-1017-7

50. Research C for DE and. Adaptive Design Clinical Trials for Drugs and Biologics [Internet]. U.S. Food and Drug Administration. 2019 [cited 2019 Nov 18]. Available from: http://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics

51. Novak JE, Inrig JK, Patel UD, Califf RM, Szczech LA. Negative trials in nephrology: what can we learn? Kidney Int. 2008 Nov;74(9):1121–7.

52. Chaitman BR. Effects of Ranolazine With Atenolol, Amlodipine, or Diltiazem on Exercise Tolerance and Angina Frequency in Patients With Severe Chronic AnginaA Randomized Controlled Trial. JAMA. 2004 Jan 21;291(3):309.

53. Wanner C, Krane V, März W, Olschewski M, Mann JFE, Ruf G, et al. Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis. N Engl J Med. 2005 Jul 21;353(3):238–48.

54. Cheung BMY, Lauder IJ, Lau C-P, Kumana CR. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. Br J Clin Pharmacol. 2004 May;57(5):640–51.

55. Velenosi TJ, Urquhart BL. Pharmacokinetic considerations in chronic kidney disease and patients requiring dialysis. Expert Opin Drug Metab Toxicol. 2014 Aug;10(8):1131–43.

56. Pushpakom S, Kolamunnage-Dona R, Taylor C, Foster T, Spowart C, García-Fiñana M, et al. TAILoR (TelmisArtan and InsuLin Resistance in Human Immunodeficiency Virus [HIV]): An Adaptive-design, Dose-ranging Phase IIb Randomized Trial of Telmisartan for the Reduction of Insulin Resistance in HIV-positive Individuals on Combination Antiretroviral Therapy. Clin Infect Dis [Internet]. 2019 Jul 3 [cited 2020 Apr 23]; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciz589/5527878

57. Moher D, Liberati A, Tetzlaff J, Altman DG, for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009 Jul 21;339(jul21 1):b2535–b2535.

58. Judge C, Murphy RP, Cormican S, Smyth A, O'Halloran M, O'Donnell M. Adaptive design methods in dialysis clinical trials: a systematic review protocol. BMJ Open. 2020 Aug 27;10(8):e036755.

59. Beaubien-Souligny W, Kontar L, Blum D, Bouchard J, Denault AY, Wald R. Meta-analysis of Randomized Controlled Trials Using Tool-Assisted Target Weight Adjustments in Chronic Dialysis Patients. Kidney Int Rep. 2019 Jul;S2468024919314044.

60. Marshall IJ, Noel-Storr A, Kuiper J, Thomas J, Wallace BC. Machine learning for identifying Randomized Controlled Trials: An evaluation and practitioner's guide. Res Synth Methods. 2018 Dec;9(4):602–14.

61. Bothwell LE, Avorn J, Khan NF, Kesselheim AS. Adaptive design clinical trials: a review of the literature and ClinicalTrials.gov. BMJ Open. 2018 Feb 1;8(2):e018320.

62. Hatfield I, Allison A, Flight L, Julious SA, Dimairo M. Adaptive designs undertaken in clinical research: a review of registered clinical trials. Trials [Internet]. 2016 Dec [cited 2020 Aug 21];17(1). Available from: http://www.trialsjournal.com/content/17/1/150

63. Higgins JP. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). In RoB2 Development Group; 2019. Available from:

https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2

64. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343(oct18 2):d5928–d5928.

65. Bove T, Zangrillo A, Guarracino F, Alvaro G, Persi B, Maglioni E, et al. Effect of Fenoldopam on Use of Renal Replacement Therapy Among Patients With Acute Kidney Injury After Cardiac Surgery: A Randomized Clinical Trial. JAMA. 2014 Dec 3;312(21):2244.

66. Dember LM, Beck GJ, Allon M, Delmez JA, Dixon BS, Greenberg A, et al. Effect of Clopidogrel on Early Failure of Arteriovenous Fistulas for Hemodialysis: A Randomized Controlled Trial. JAMA. 2008 May 14;299(18):2164.

67. Irish AB, Viecelli AK, Hawley CM, Hooi L-S, Pascoe EM, Paul-Brent P-A, et al. Effect of Fish Oil Supplementation and Aspirin Use on Arteriovenous Fistula Failure in Patients Requiring Hemodialysis: A Randomized Clinical Trial. JAMA Intern Med. 2017 Feb 1;177(2):184.

68. Viecelli AK, Polkinghorne KR, Pascoe EM, Paul-Brent P-A, Hawley CM, Badve SV, et al. Fish oil and aspirin effects on arteriovenous fistula function: Secondary outcomes of the randomised omega-3 fatty acids (Fish oils) and Aspirin in Vascular access OUtcomes in REnal Disease (FAVOURED) trial. Puebla I, editor. PLOS ONE. 2019 Mar 26;14(3):e0213274.

69. Kwiatkowski DM, Goldstein SL, Cooper DS, Nelson DP, Morales DLS, Krawczeski CD. Peritoneal Dialysis vs Furosemide for Prevention of Fluid Overload in Infants After Cardiac Surgery: A Randomized Clinical Trial. JAMA Pediatr. 2017 Apr 1;171(4):357.

70. Joannes-Boyau O, Honoré PM, Perez P, Bagshaw SM, Grand H, Canivet J-L, et al. High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. Intensive Care Med. 2013 Sep;39(9):1535–46.

71. Thiele H, Akin I, Sandri M, de Waha-Thiele S, Meyer-Saraei R, Fuernau G, et al. One-Year Outcomes after PCI Strategies in Cardiogenic Shock. N Engl J Med. 2018 Nov;379(18):1699–710.

72. Thiele H, Desch S, Piek JJ, Stepinska J, Oldroyd K, Serpytis P, et al. Multivessel versus culprit lesion only percutaneous revascularization plus potential staged revascularization in patients with acute myocardial infarction complicated by cardiogenic shock: Design and rationale of CULPRIT-SHOCK trial. Am Heart J. 2016 Feb;172:160–9.

73. Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen M, et al. Coronary Angiography after Cardiac Arrest without ST-Segment Elevation. N Engl J Med. 2019 Apr 11;380(15):1397–407.

74. Lemkes JS, Janssens GN, Straaten HMO, Elbers PW, van der Hoeven NW, Tijssen JGP, et al. Coronary angiography after cardiac arrest: Rationale and design of the COACT trial. Am Heart J. 2016 Oct;180:39–45.

75. Mehta RH, Leimberger JD, van Diepen S, Meza J, Wang A, Jankowich R, et al. Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery. N Engl J Med. 2017 May 25;376(21):2032–42.

76. Mehta RH, Van Diepen S, Meza J, Bokesch P, Leimberger JD, Tourt-Uhlig S, et al. Levosimendan in patients with left ventricular systolic dysfunction undergoing cardiac surgery on cardiopulmonary bypass: Rationale and study design of the Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery Requiring Cardiopulmonary Bypass (LEVO-CTS) trial. Am Heart J. 2016 Dec;182:62–71.

77. Douglas IS, Alapat PM, Corl KA, Exline MC, Forni LG, Holder AL, et al. Fluid Response Evaluation in Sepsis Hypotension and Shock. Chest. 2020 Oct;158(4):1431–45.

78. Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury. N Engl J Med. 2008 Jul 3;359(1):7–20.

79. Sharma S, Kelly YP, Palevsky PM, Waikar SS. Intensity of Renal Replacement Therapy and Duration of Mechanical Ventilation. Chest. 2020 Oct;158(4):1473–81.

80. Marsen TA, Beer J, Mann H. Intradialytic parenteral nutrition in maintenance hemodialysis patients suffering from protein-energy wasting. Results of a multicenter, open, prospective, randomized trial. Clin Nutr. 2017 Feb;36(1):107–17.

81. Chapman WC, Singla N, Genyk Y, McNeil JW, Renkens KL, Reynolds TC, et al. A Phase 3, Randomized, Double-Blind Comparative Study of the Efficacy and Safety of Topical Recombinant Human Thrombin and Bovine Thrombin in Surgical Hemostasis. J Am Coll Surg. 2007 Aug;205(2):256–65.

82. Ejaz AA, Martin TD, Johnson RJ, Winterstein AG, Klodell CT, Hess PJ, et al. Prophylactic nesiritide does not prevent dialysis or all-cause mortality in patients undergoing high-risk cardiac surgery. J Thorac Cardiovasc Surg. 2009 Oct;138(4):959–64.

83. Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. The Lancet. 2006 Jul;368(9533):379–85.

84. Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. The Lancet. 2010 Aug;376(9739):419–30.

85. Johnson DW, Badve SV, Pascoe EM, Beller E, Cass A, Clark C, et al. Antibacterial honey for the prevention of peritoneal-dialysis-related infections (HONEYPOT): a randomised trial. Lancet Infect Dis. 2014 Jan;14(1):23–30.

86. Pascoe EM, Lo S, Scaria A, Badve SV, Beller EM, Cass A, et al. The Honeypot Randomized Controlled Trial Statistical Analysis Plan. Perit Dial Int J Int Soc Perit Dial. 2013 Jul;33(4):426–35.

87. Acker CG, Singh AR, Flick RP, Bernardini J, Greenberg A, Johnson JP. A trial of thyroxine in acute renal failure. Kidney Int. 2000 Jan;57(1):293–8.

88. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The Effects of Normal as Compared with Low Hematocrit Values in Patients with Cardiac Disease Who Are Receiving Hemodialysis and Epoetin. N Engl J Med. 1998 Aug 27;339(9):584–90.

89. Dixon BS, Beck GJ, Vazquez MA, Greenberg A, Delmez JA, Allon M, et al. Effect of Dipyridamole plus Aspirin on Hemodialysis Graft Patency. N Engl J Med. 2009 May 21;360(21):2191–201.

90. Torres VE, Abebe KZ, Chapman AB, Schrier RW, Braun WE, Steinman TI, et al. Angiotensin Blockade in Late Autosomal Dominant Polycystic Kidney Disease. N Engl J Med. 2014 Dec 11;371(24):2267–76.

91. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med. 2016 Jul 14;375(2):122–33.

92. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Tubach F, Pons B, et al. Comparison of two strategies for initiating renal replacement therapy in the intensive care unit: study protocol for a randomized controlled trial (AKIKI). Trials [Internet]. 2015 Dec [cited 2020 Oct 27];16(1). Available from: http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-015-0718-x

93. Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin S-S, et al. Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine. N Engl J Med. 2018 Feb 15;378(7):603–14.

94. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019 Jun 13;380(24):2295–306.

95. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380(4):347–57.

96. Fishbane S, Jamal A, Munera C, Wen W, Menzaghi F. A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus. N Engl J Med. 2020 Jan 16;382(3):222–32.

97. Knoll GA, Fergusson D, Chassé M, Hebert P, Wells G, Tibbles LA, et al. Ramipril versus placebo in kidney transplant patients with proteinuria: a multicentre, double-blind, randomised controlled trial. Lancet Diabetes Endocrinol. 2016 Apr;4(4):318–26.

98. Knoll GA, Cantarovitch M, Cole E, Gill J, Gourishankar S, Holland D, et al. The Canadian ACE-inhibitor trial to improve renal outcomes and patient survival in kidney transplantation study design. Nephrol Dial Transplant. 2007 Aug 17;23(1):354–8.

99. Schanz M, Wasser C, Allgaeuer S, Schricker S, Dippon J, Alscher MD, et al. Urinary [TIMP-2]·[IGFBP7]-guided randomized controlled intervention trial to prevent acute kidney injury in the emergency department. Nephrol Dial Transplant. 2019 Nov 1;34(11):1902–9.

100. Kammerer T, Brettner F, Hilferink S, Hulde N, Klug F, Pagel J-I, et al. No Differences in Renal Function between Balanced 6% Hydroxyethyl Starch (130/0.4) and 5% Albumin for Volume Replacement Therapy in Patients Undergoing Cystectomy. Anesthesiology. 2018 Jan 1;128(1):67–78.

101. Kammerer T, Klug F, Schwarz M, Hilferink S, Zwissler B, von Dossow V, et al. Comparison of 6 % hydroxyethyl starch and 5 % albumin for volume replacement therapy in patients undergoing cystectomy (CHART): study protocol for a randomized controlled trial. Trials [Internet]. 2015 Dec [cited 2020 Oct 27];16(1). Available from: http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-015-0866-z

102. Pickkers P, Mehta RL, Murray PT, Joannidis M, Molitoris BA, Kellum JA, et al. Effect of Human Recombinant Alkaline Phosphatase on 7-Day Creatinine Clearance in Patients With Sepsis-Associated Acute Kidney Injury: A Randomized Clinical Trial. JAMA. 2018 Nov 20;320(19):1998.

103. E P, RL M, PT M, J H, M J, JA K, et al. Study protocol for a multicentre randomised controlled trial: Safety, Tolerability, efficacy and quality of life Of a human recombinant alkaline Phosphatase in patients with sepsis-associated Acute Kidney Injury (STOP-AKI). BMJ Open. 2016;6(9):e012371.

104. Zarbock A, Küllmar M, Kindgen-Milles D, Wempe C, Gerss J, Brandenburger T, et al. Effect of Regional Citrate Anticoagulation vs Systemic Heparin Anticoagulation During Continuous Kidney Replacement Therapy on Dialysis Filter Life Span and Mortality Among Critically Ill Patients With Acute Kidney Injury: A Randomized Clinical Trial. JAMA. 2020 Oct 27;324(16):1629.

105. Meersch M, Küllmar M, Wempe C, Kindgen-Milles D, Kluge S, Slowinski T, et al. Regional citrate versus systemic heparin anticoagulation for continuous renal replacement therapy in critically ill patients with acute kidney injury (RICH) trial: study protocol for a multicentre, randomised controlled trial. BMJ Open. 2019 Jan;9(1):e024411.

106. Grooteman MPC, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AHA, et al. Effect of Online Hemodiafiltration on All-Cause Mortality and Cardiovascular Outcomes. J Am Soc Nephrol. 2012 Jun;23(6):1087–96.

107. the CONTRAST study group, Penne EL, Blankestijn PJ, Bots ML, van den Dorpel MA, Grooteman MP, et al. Effect of increased convective clearance by on-line hemodiafiltration on all cause and cardiovascular mortality in chronic hemodialysis

patients – the Dutch CONvective TRAnsport STudy (CONTRAST): rationale and design of a randomised controlled trial [ISRCTN38365125]. Curr Control Trials Cardiovasc Med [Internet]. 2005 Dec [cited 2020 Oct 27];6(1). Available from: http://trialsjournal.biomedcentral.com/articles/10.1186/1468-6708-6-8

108. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, et al. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. JAMA. 2016 May 24;315(20):2190.

109. Zarbock A, Gerß J, Van Aken H, Boanta A, Kellum JA, Meersch M. Early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury (The ELAIN-Trial): study protocol for a randomized controlled trial. Trials [Internet]. 2016 Dec [cited 2020 Oct 27];17(1). Available from: http://www.trialsjournal.com/content/17/1/148

110. Tumlin JA, Galphin CM, Tolwani AJ, Chan MR, Vijayan A, Finkel K, et al. A Multi-Center, Randomized, Controlled, Pivotal Study to Assess the Safety and Efficacy of a Selective Cytopheretic Device in Patients with Acute Kidney Injury. Cravedi P, editor. PLOS ONE. 2015 Aug 5;10(8):e0132482.

111. Kratochwill K, Boehm M, Herzog R, Gruber K, Lichtenauer AM, Kuster L, et al. Addition of Alanyl-Glutamine to Dialysis Fluid Restores Peritoneal Cellular Stress Responses – A First-In-Man Trial. Eller K, editor. PLOS ONE. 2016 Oct 21;11(10):e0165045.

112. Himmelfarb J, Chertow GM, McCullough PA, Mesana T, Shaw AD, Sundt TM, et al. Perioperative THR-184 and AKI after Cardiac Surgery. J Am Soc Nephrol. 2018 Feb;29(2):670–9.

113. Kopple JD, Cheung AK, Christiansen JS, Djurhuus CB, El Nahas M, Feldt-Rasmussen B, et al. OPPORTUNITY : a large-scale randomized clinical trial of growth hormone in hemodialysis patients. Nephrol Dial Transplant. 2011 Dec 1;26(12):4095–103.

114. Kopple JD, Cheung AK, Christiansen JS, Djurhuus CB, El Nahas M, Feldt-Rasmussen B, et al. OPPORTUNITY^{TM}: A Randomized Clinical Trial of Growth Hormone on Outcome in Hemodialysis Patients. Clin J Am Soc Nephrol. 2008 Nov;3(6):1741–51.

115. Hayashi T, Maruyama S, Nangaku M, Narita I, Hirakata H, Tanabe K, et al. Darbepoetin Alfa in Patients with Advanced CKD without Diabetes: Randomized, Controlled Trial. Clin J Am Soc Nephrol. 2020 May 7;15(5):608–15.

116. Imai E, Maruyama S, Nangaku M, Hirakata H, Hayashi T, Narita I, et al. Rationale and study design of a randomized controlled trial to assess the effects of maintaining hemoglobin levels using darbepoetin alfa on prevention of development of end-stage kidney disease in non-diabetic CKD patients (PREDICT Trial). Clin Exp Nephrol. 2016 Feb;20(1):71–6.

117. Riley AA, Jefferies JL, Nelson DP, Bennett MR, Blinder JJ, Ma Q, et al. Peritoneal Dialysis does not Adversely Affect Kidney Function Recovery after Congenital Heart Surgery. Int J Artif Organs. 2014 Jan;37(1):39–47.

118. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis. N Engl J Med. 2009 Apr 2;360(14):1395–407.

119. Fellström B, Holdaas H, Jardine AG, Rose H, Schmieder R, Wilpshaar W, et al. Effect of Rosuvastatin on Outcomes in Chronic Haemodialysis Patients: Baseline Data from the AURORA Study. Kidney Blood Press Res. 2007;30(5):314–22.

120. Combes A, Bréchot N, Amour J, Cozic N, Lebreton G, Guidon C, et al. Early High-Volume Hemofiltration versus Standard Care for Post–Cardiac Surgery Shock. The HEROICS Study. Am J Respir Crit Care Med. 2015 Nov 15;192(10):1179–90.

121. Robinson S, Zincuk A, Larsen UL, Ekstrøm C, Toft P. A feasible strategy for preventing blood clots in critically ill patients with acute kidney injury (FBI): study protocol for a randomized controlled trial. Trials [Internet]. 2014 Dec [cited 2020 Oct 27];15(1). Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-15-226

122. The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early High-Dose Vitamin D_3 for Critically Ill, Vitamin D–Deficient Patients. N Engl J Med. 2019 Dec 26;381(26):2529–40.

123. Freedman BI, Wuerth J-P, Cartwright K, Bain RP, Dippe S, Hershon K, et al. Design and Baseline Characteristics for the Aminoguanidine Clinical Trial in Overt Type 2 Diabetic Nephropathy (ACTION II). Control Clin Trials. 1999 Oct;20(5):493–510.

124. Karunanithy N, Mesa IR, Dorling A, Calder F, Katsanos K, Semik V, et al. Paclitaxel-coated balloon fistuloplasty versus plain balloon fistuloplasty only to preserve the patency of arteriovenous fistulae used for haemodialysis (PAVE): study protocol for a randomised controlled trial. Trials [Internet]. 2016 Dec [cited 2020 Oct 27];17(1). Available from: http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1372-7

125. Blankestijn PJ, Fischer KI, Barth C, Cromm K, Canaud B, Davenport A, et al. Benefits and harms of high-dose haemodiafiltration versus high-flux haemodialysis: the comparison of high-dose haemodiafiltration with high-flux haemodialysis (CONVINCE) trial protocol. BMJ Open. 2020 Feb;10(2):e033228.

126. Pettilä V, Merz T, Wilkman E, Perner A, Karlsson S, Lange T, et al. Targeted tissue perfusion versus macrocirculation-guided standard care in patients with septic shock (TARTARE-2S): study protocol and statistical analysis plan for a randomized controlled trial. Trials [Internet]. 2016 Dec [cited 2020 Oct 27];17(1). Available from: http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1515-x

127. The ANDROMEDA-SHOCK Study Investigators, Hernández G, Cavalcanti AB, Ospina-Tascón G, Zampieri FG, Dubin A, et al. Early goal-directed therapy using a physiological holistic view: the ANDROMEDA-SHOCK—a randomized controlled trial. Ann Intensive Care [Internet]. 2018 Dec [cited 2020 Oct 27];8(1). Available from: https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-018-0398-2

128. Fujimoto K, Adachi H, Yamazaki K, Nomura K, Saito A, Matsumoto Y, et al. Comparison of the pain-reducing effects of EMLA cream and of lidocaine tape during arteriovenous fistula puncture in patients undergoing hemodialysis: A multi-center, open-label, randomized crossover trial. Wu P-H, editor. PLOS ONE. 2020 Mar 25;15(3):e0230372.

129. Laterre P-F, Berry SM, Blemings A, Carlsen JE, François B, Graves T, et al. Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock: The SEPSIS-ACT Randomized Clinical Trial. JAMA. 2019 Oct 15;322(15):1476–85.

130. Bestle MH, Clausen NE, Søe-Jensen P, Kristiansen KT, Lange T, Johansson PI, et al. Efficacy and safety of iloprost in patients with septic shock-induced endotheliopathy—Protocol for the multicenter randomized, placebo-controlled, blinded, investigator-initiated trial. Acta Anaesthesiol Scand. 2020 May;64(5):705–11.

131. Kassimatis T, Qasem A, Douiri A, Ryan EG, Rebollo-Mesa I, Nichols LL, et al. A double-blind randomised controlled investigation into the efficacy of Mirococept (APT070) for preventing ischaemia reperfusion injury in the kidney allograft (EMPIRIKAL): study protocol for a randomised controlled trial. Trials [Internet]. 2017 Dec [cited 2020 Oct 27];18(1). Available from: http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-1972-x

132. Hosgood SA, Saeb-Parsy K, Wilson C, Callaghan C, Collett D, Nicholson ML. Protocol of a randomised controlled, open-label trial of ex vivo normothermic perfusion versus static cold storage in donation after circulatory death renal transplantation. BMJ Open. 2017 Jan;7(1):e012237.

133. Mistry P, Dunn JA, Marshall A. A literature review of applied adaptive design methodology within the field of oncology in randomised controlled trials and a proposed extension to the CONSORT guidelines. BMC Med Res Methodol. 2017 Jul 18;17(1):108.

134. Clayton JA, Arnegard ME. Taking cardiology clinical trials to the next level: A call to action. Clin Cardiol. 2018 Feb;41(2):179–84.

135. van Werkhoven CH, Harbarth S, Bonten MJM. Adaptive designs in clinical trials in critically ill patients: principles, advantages and pitfalls. Intensive Care Med. 2019 May 1;45(5):678–82.

136. Talisa VB, Yende S, Seymour CW, Angus DC. Arguing for Adaptive Clinical Trials in Sepsis. Front Immunol [Internet]. 2018 Jun 28 [cited 2021 Jan 14];9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6031704/

137. Zoccali C, Vanholder R, Wagner CA, Anders H-J, Blankestijn PJ, Bruchfeld A, et al. Funding kidney research as a public health priority: challenges and opportunities. Nephrol Dial Transplant [Internet]. 2020 Sep 4 [cited 2021 Jan 14];(gfaa163). Available from: https://doi.org/10.1093/ndt/gfaa163

138. Lloyd-Jones Donald M., Hong Yuling, Labarthe Darwin, Mozaffarian Dariush, Appel Lawrence J., Van Horn Linda, et al. Defining and Setting National Goals for Cardiovascular Health Promotion and Disease Reduction. Circulation. 2010 Feb 2;121(4):586–613.

139. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018 Sep 1;39(33):3021–104.

140. Gunn JP, Barron JL, Bowman BA, Merritt RK, Cogswell ME, Angell SY, et al. Sodium Reduction Is a Public Health Priority: Reflections on the Institute of Medicine's Report, Sodium Intake in Populations: Assessment of Evidence. Am J Hypertens. 2013 Oct 1;26(10):1178–80.

141. World Health Organization (Who). Guideline: Sodium intake for adults and children. Place of publication not identified: World Health Organization; 2016.

142. Sacks FM, Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, et al. A dietary approach to prevent hypertension: a review of the Dietary Approaches to Stop Hypertension (DASH) Study. Clin Cardiol. 1999 Jul;22(7 Suppl):III6-10.

143. Huang L, Trieu K, Yoshimura S, Neal B, Woodward M, Campbell NRC, et al. Effect of dose and duration of reduction in dietary sodium on blood pressure levels: systematic review and meta-analysis of randomised trials. BMJ. 2020 Feb 25;368:m315.

144. Effects of Weight Loss and Sodium Reduction Intervention on Blood Pressure and Hypertension Incidence in Overweight People With High-Normal Blood Pressure: The Trials of Hypertension Prevention, Phase II. Arch Intern Med. 1997 Mar 24;157(6):657–67.

145. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. J Am Coll Cardiol. 2018 May;71(19):e127–248.

146. Pimenta Eduardo, Gaddam Krishna K., Oparil Suzanne, Aban Inmaculada, Husain Saima, Dell'Italia Louis J., et al. Effects of Dietary Sodium Reduction on Blood Pressure in Subjects With Resistant Hypertension. Hypertension. 2009 Sep 1;54(3):475–81.

147. Dolan Eamon, Stanton Alice, Thijs Lut, Hinedi Kareem, Atkins Neil, McClory Sean, et al. Superiority of Ambulatory Over Clinic Blood Pressure Measurement in Predicting Mortality. Hypertension. 2005 Jul 1;46(1):156–61.

148. O'Donnell M, Mente A, Alderman MH, Brady AJB, Diaz R, Gupta R, et al. Salt and cardiovascular disease: insufficient evidence to recommend low sodium intake. Eur Heart J. 2020 Sep 14;41(35):3363–73.

149. Yang W-Y, Melgarejo JD, Thijs L, Zhang Z-Y, Boggia J, Wei F-F, et al. Association of Office and Ambulatory Blood Pressure With Mortality and Cardiovascular Outcomes. JAMA. 2019 Aug 6;322(5):409.

150. Borrelli S, Provenzano M, Gagliardi I, Ashour M, Liberti ME, De Nicola L, et al. Sodium Intake and Chronic Kidney Disease. Int J Mol Sci. 2020 Jul 3;21(13):4744.

151. Smyth A, O'Donnell MJ, Yusuf S, Clase CM, Teo KK, Canavan M, et al. Sodium intake and renal outcomes: a systematic review. Am J Hypertens. 2014 Oct;27(10):1277–84.

152. Dong J, Li Y, Yang Z, Luo J. Low Dietary Sodium Intake Increases the Death Risk in Peritoneal Dialysis. Clin J Am Soc Nephrol. 2010 Feb 1;5(2):240–7.

153. Cole NI, Swift PA, He FJ, MacGregor GA, Suckling RJ. The effect of dietary salt on blood pressure in individuals receiving chronic dialysis: a systematic review and meta-analysis of randomised controlled trials. J Hum Hypertens. 2019 Apr;33(4):319–26.

154. Smyth A, Dunkler D, Gao P, Teo KK, Yusuf S, O'Donnell MJ, et al. The relationship between estimated sodium and potassium excretion and subsequent renal outcomes. Kidney Int. 2014 Dec 1;86(6):1205–12.

155. He J, Mills KT, Appel LJ, Yang W, Chen J, Lee BT, et al. Urinary Sodium and Potassium Excretion and CKD Progression. J Am Soc Nephrol JASN. 2016 Apr;27(4):1202–12.

156. Smyth A, Yusuf S, Kerins C, Corcoran C, Dineen R, Alvarez-Iglesias A, et al. Clarifying Optimal Sodium InTake In Cardiovasular and Kidney (COSTICK) Diseases: a study protocol for two randomised controlled trials. HRB Open Res. 2021 Feb 1;4:14.

157. Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger, Jr WH, Kostis JB, et al. Sodium Reduction and Weight Loss in the Treatment of Hypertension in Older Persons: A Randomized Controlled Trial of Nonpharmacologic Interventions in the Elderly (TONE). JAMA. 1998 Mar 18;279(11):839.

158. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens. 2014 Jul;32(7):1359–66.

159. Chadachan VM, Ye MT, Tay JC, Subramaniam K, Setia S. Understanding short-term blood-pressure-variability phenotypes: from concept to clinical practice. Int J Gen Med. 2018 Jun;Volume 11:241–54.

160. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. Nat Rev Cardiol. 2013 Mar;10(3):143–55.

161. Drawz PE, Pajewski NM, Bates JT, Bello NA, Cushman WC, Dwyer JP, et al. Effect of Intensive Versus Standard Clinic-Based Hypertension Management on Ambulatory Blood Pressure: Results From the SPRINT (Systolic Blood Pressure Intervention Trial) Ambulatory Blood Pressure Study. Hypertension. 2017 Jan;69(1):42–50.

162. McCarron DA, Kazaks AG, Geerling JC, Stern JS, Graudal NA. Normal range of human dietary sodium intake: a perspective based on 24-hour urinary sodium excretion worldwide. Am J Hypertens. 2013 Oct;26(10):1218–23.

163. Graudal N, Hubeck-Graudal T, Jurgens G. Influence of sodium intake and change in sodium intake on plasma-renin in man. EClinicalMedicine [Internet]. 2021 Mar 1 [cited 2021 Aug 14];33. Available from: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00030-4/abstract

164. Judge C, O'Donnell M. Low sodium intake increases plasma renin activity. EClinicalMedicine. 2021 Mar;33:100803.

165. Hall JE, Guyton AC, Mizelle HL. Role of the renin-angiotensin system in control of sodium excretion and arterial pressure. Acta Physiol Scand Suppl. 1990;591:48–62.

166. Lowell BB. New Neuroscience of Homeostasis and Drives for Food, Water, and Salt. N Engl J Med. 2019 Jan 31;380(5):459–71.

167. He FJ, Marciniak M, Visagie E, Markandu ND, Anand V, Dalton RN, et al. Effect of modest salt reduction on blood pressure, urinary albumin, and pulse wave velocity in white, black, and Asian mild hypertensives. Hypertens Dallas Tex 1979. 2009 Sep;54(3):482–8.

168. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on Blood Pressure of Reduced Dietary Sodium and the Dietary Approaches to Stop Hypertension (DASH) Diet. N Engl J Med. 2001 Jan 4;344(1):3–10.

169. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. The Lancet. 2016 Aug;388(10046):761–75.

170. Mente A, O'Donnell MJ, Rangarajan S, McQueen MJ, Poirier P, Wielgosz A, et al. Association of Urinary Sodium and Potassium Excretion with Blood Pressure. N Engl J Med. 2014 Aug 14;371(7):601–11.

171. World Health Organization (WHO). Guideline: Sodium intake for adults and children. [Internet]. Geneva; 2012 [cited 2018 Nov 19]. Available from: http://www.who.int/nutrition/publications/guidelines/sodium_intake_printversion.pdf

172. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease

reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation. 2010 Feb 2;121(4):586–613.

173. Cao J, Eshak ES, Liu K, Gero K, Liu Z, Yu C. Age-Period-Cohort Analysis of Stroke Mortality Attributable to High Sodium Intake in China and Japan. Stroke. 2019 Jul;50(7):1648–54.

174. He FJ, Li J, Macgregor GA. Effect of longer-term modest salt reduction on blood pressure. Cochrane Database Syst Rev. 2013 Apr 30;(4):CD004937.

175. O'Donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L, et al. Urinary Sodium and Potassium Excretion, Mortality, and Cardiovascular Events. N Engl J Med. 2014 Aug 14;371(7):612–23.

176. Cogswell ME, Mugavero K, Bowman BA, Frieden TR. Dietary Sodium and Cardiovascular Disease Risk — Measurement Matters. N Engl J Med. 2016 Aug 11;375(6):580–6.

177. Graudal N, Jürgens G, Baslund B, Alderman MH. Compared With Usual Sodium Intake, Low- and Excessive-Sodium Diets Are Associated With Increased Mortality: A Meta-Analysis. Am J Hypertens. 2014 Sep 1;27(9):1129–37.

178. Zhu Y, Zhang J, Li Z, Liu Y, Fan X, Zhang Y, et al. Association of sodium intake and major cardiovascular outcomes: a dose-response meta-analysis of prospective cohort studies. BMC Cardiovasc Disord [Internet]. 2018 Oct 19 [cited 2019 Sep 21];18. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6194706/

179. Collins M, Mason H, O'Flaherty M, Guzman-Castillo M, Critchley J, Capewell S. An Economic Evaluation of Salt Reduction Policies to Reduce Coronary Heart Disease in England: A Policy Modeling Study. Value Health. 2014 Jul;17(5):517–24.

180. Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. BMJ. 2013 Apr 3;346(apr03 3):f1378–f1378.

181. O'Donnell M, Mente A, Rangarajan S, McQueen MJ, O'Leary N, Yin L, et al. Joint association of urinary sodium and potassium excretion with cardiovascular events and mortality: prospective cohort study. BMJ. 2019 Mar 13;l772.

182. Drewnowski A, Rehm CD, Maillot M, Mendoza A, Monsivais P. The feasibility of meeting the WHO guidelines for sodium and potassium: a cross-national comparison study. BMJ Open. 2015 Mar 20;5(3):e006625–e006625.

183. Yang Q. Sodium and Potassium Intake and Mortality Among US Adults: Prospective Data From the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2011 Jul 11;171(13):1183.

184. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A Clinical Trial of the Effects of Dietary Patterns on Blood Pressure. N Engl J Med. 1997 Apr 17;336(16):1117–24.

185. Cook NR. Joint Effects of Sodium and Potassium Intake on Subsequent Cardiovascular Disease: The Trials of Hypertension Prevention Follow-up Study. Arch Intern Med. 2009 Jan 12;169(1):32.

186. Smyth A, Judge C, Wang X, Pare G, Rangarajan S, Canavan M, et al. Renal Impairment and Risk of Acute Stroke: The INTERSTROKE Study. Neuroepidemiology. 2021;55(3):206–15.

187. Ovbiagele B, Sanossian N, Liebeskind DS, Kim D, Ali LK, Pineda S, et al. Indices of kidney dysfunction and discharge outcomes in hospitalized stroke patients without known renal disease. Cerebrovasc Dis Basel Switz. 2009;28(6):582–8.

188. Ovbiagele B. Microalbuminuria: risk factor and potential therapeutic target for stroke? J Neurol Sci. 2008 Aug 15;271(1–2):21–8.

189. Lee M, Ovbiagele B. Reno-cerebrovascular disease: linking the nephron and neuron. Expert Rev Neurother. 2011 Feb;11(2):241–9.

190. Ellison DH. Treatment of Disorders of Sodium Balance in Chronic Kidney Disease. Adv Chronic Kidney Dis. 2017 Sep;24(5):332–41.

191. Mills KT, Chen J, Yang W, Appel LJ, Kusek JW, Alper A, et al. Sodium Excretion and the Risk of Cardiovascular Disease in Patients With Chronic Kidney Disease. JAMA. 2016 May 24;315(20):2200–10.

192. Jablonski KL, Kendrick J. Renal Outcomes and Dietary Potassium: The Overshadowed Electrolyte? Kidney Int. 2014 Dec;86(6):1077–8.

193. Vinceti M, Filippini T, Crippa A, de Sesmaisons A, Wise LA, Orsini N. Meta-Analysis of Potassium Intake and the Risk of Stroke. J Am Heart Assoc Cardiovasc Cerebrovasc Dis. 2016 Oct 6;5(10):e004210.

194. Tanaka T, Okamura T, Miura K, Kadowaki T, Ueshima H, Nakagawa H, et al. A simple method to estimate populational 24-h urinary sodium and potassium excretion using a casual urine specimen. J Hum Hypertens. 2002 Feb;16(2):97–103.

195. Kawasaki T, Itoh K, Uezono K, Sasaki H. A simple method for estimating 24 h urinary sodium and potassium excretion from second morning voiding urine specimen in adults. Clin Exp Pharmacol Physiol. 1993 Jan;20(1):7–14.

196. Brown IJ, Dyer AR, Chan Q, Cogswell ME, Ueshima H, Stamler J, et al. Estimating 24-Hour Urinary Sodium Excretion From Casual Urinary Sodium Concentrations in Western Populations. Am J Epidemiol. 2013 Jun 1;177(11):1180–92.

197. Mente A, O'Donnell MJ, Dagenais G, Wielgosz A, Lear SA, McQueen MJ, et al. Validation and comparison of three formulae to estimate sodium and potassium excretion from a single morning fasting urine compared to 24-h measures in 11 countries: J Hypertens. 2014 May;32(5):1005–15.

198. O'Brien E. Salt—too much or too little? The Lancet. 2016 Jul;388(10043):439–40.

199. Harrell FE. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. Second edition. Cham Heidelberg New York: Springer; 2015. 582 p. (Springer series in statistics).

200. Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013 Jun 4;158(11):825–30.

201. Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger WH, Kostis JB, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. JAMA. 1998 Mar 18;279(11):839–46.

202. Effects of Weight Loss and Sodium Reduction Intervention on Blood Pressure and Hypertension Incidence in Overweight People With High-Normal Blood Pressure: The Trials of Hypertension Prevention, Phase II. Arch Intern Med. 1997 Mar 24;157(6):657.

203. Verma S, Gupta M, Holmes DT, Xu L, Teoh H, Gupta S, et al. Plasma renin activity predicts cardiovascular mortality in the Heart Outcomes Prevention Evaluation (HOPE) study. Eur Heart J. 2011 Sep;32(17):2135–42.

204. Stolarz-Skrzypek K. Fatal and Nonfatal Outcomes, Incidence of Hypertension, and Blood Pressure Changes in Relation to Urinary Sodium Excretion. JAMA. 2011 May 4;305(17):1777.

205. Hyseni L, Elliot-Green A, Lloyd-Williams F, Kypridemos C, O'Flaherty M, McGill R, et al. Systematic review of dietary salt reduction policies: Evidence for an effectiveness hierarchy? Shankar B, editor. PLOS ONE. 2017 May 18;12(5):e0177535.

206. WHO | Increasing potassium intake to reduce blood pressure and risk of cardiovascular diseases in adults [Internet]. WHO. World Health Organization; [cited 2021 Aug 23]. Available from: http://www.who.int/elena/titles/potassium_cvd_adults/en/

207. Clase CM, Carrero J-J, Ellison DH, Grams ME, Hemmelgarn BR, Jardine MJ, et al. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2020 Jan;97(1):42–61.

208. Li Y, Huang Z, Jin C, Xing A, Liu Y, Huangfu C, et al. Longitudinal Change of Perceived Salt Intake and Stroke Risk in a Chinese Population. Stroke. 2018 Jun;49(6):1332–9.

209. Mente A, Irvine EJ, Honey RJD, Logan AG. Urinary Potassium Is a Clinically Useful Test to Detect a Poor Quality Diet. J Nutr. 2009 Apr 1;139(4):743–9.

210. Chang H-Y, Hu Y-W, Yue C-SJ, Wen Y-W, Yeh W-T, Hsu L-S, et al. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. Am J Clin Nutr. 2006 Jun 1;83(6):1289–96.

211. Neal B, Tian M, Li N, Elliott P, Yan LL, Labarthe DR, et al. Rationale, design, and baseline characteristics of the Salt Substitute and Stroke Study (SSaSS)—A large-scale cluster randomized controlled trial. Am Heart J. 2017 Jun;188:109–17.

212. Versi E. "Gold standard" is an appropriate term. BMJ. 1992 Jul 18;305(6846):187.

213. McLean R. Measuring Population Sodium Intake: A Review of Methods. Nutrients. 2014 Oct 28;6(11):4651–62.

214. Mozaffarian D, Fahimi S, Singh GM, Micha R, Khatibzadeh S, Engell RE, et al. Global Sodium Consumption and Death from Cardiovascular Causes. N Engl J Med. 2014 Aug 14;371(7):624–34.

215. Kieneker LM, Eisenga MF, Gansevoort RT, de Boer RA, Navis G, Dullaart RPF, et al. Association of Low Urinary Sodium Excretion With Increased Risk of Stroke. Mayo Clin Proc. 2018 Dec;93(12):1803–9.

216. The SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26;373(22):2103–16.

217. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. J Am Coll Cardiol. 2018 May;71(19):e127–248.

218. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018 Sep 1;39(33):3021–104.

219. Luscher TF, Kjeldsen SE, Mancia G, Papademetriou V. From "essential" hypertension to intensive blood pressure lowering: the pros and cons of lower target values. Eur Heart J. 2017 Nov 21;38(44):3258–71.

220. Effects of an Angiotensin-Converting–Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients. N Engl J Med. 2000 Jan 20;342(3):145–53.

221. Fox KM, EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet Lond Engl. 2003 Sep 6;362(9386):782–8.

222. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after

myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992 Sep 3;327(10):669–77.

223. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet Lond Engl. 2006 Aug 12;368(9535):581–8.

224. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001 May 31;344(22):1651–8.

225. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet Lond Engl. 1999 Jun 12;353(9169):2001–7.

226. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. N Engl J Med. 1998 Aug 20;339(8):489–97.

227. van der Wardt V, Harrison JK, Welsh T, Conroy S, Gladman J. Withdrawal of antihypertensive medication: a systematic review. J Hypertens. 2017 Sep;35(9):1742–9.

228. Segall L, Nistor I, Covic A. Heart Failure in Patients with Chronic Kidney Disease: A Systematic Integrative Review. BioMed Res Int. 2014 May 15;2014:e937398.

229. Burns NS, Miller PW. Learning What We Didn't Know — The SPRINT Data Analysis Challenge. N Engl J Med. 2017 Jun 8;376(23):2205–7.

230. Shapiro BP, Ambrosius WT, Blackshear JL, Cushman WC, Whelton PK, Oparil S, et al. Impact of Intensive Versus Standard Blood Pressure Management by Tertiles of Blood Pressure in SPRINT (Systolic Blood Pressure Intervention Trial)Novelty and Significance. Hypertension. 2018 Jun;71(6):1064–74.

231. Lüscher TF. From 'essential' hypertension to intensive blood pressure lowering: the pros and cons of lower target values. Eur Heart J. 2017 Nov 21;38(44):3258–71.

232. Volpe M, Citoni B, Coluccia R, Battistoni A, Tocci G. Hypertension Across the Atlantic: A Sprint or a Marathon? High Blood Press Cardiovasc Prev. 2017 Jun;24(2):99–102.

233. Parati G, Ochoa JE, Bilo G, Zanchetti A. SPRINT Blood Pressure: Sprinting Back to Smirk's Basal Blood Pressure? Hypertension. 2017 Jan;69(1):15–9.

234. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. N Engl J Med. 2010 Apr 29;362(17):1575–85.

235. Appel LJ, Wright JT, Greene T, Agodoa LY, Astor BC, Bakris GL, et al. Intensive Blood-Pressure Control in Hypertensive Chronic Kidney Disease. N Engl J Med. 2010 Sep 2;363(10):918–29.

236. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. The Lancet. 2010 Mar;375(9718):895–905.

237. Chang TI, Reboussin DM, Chertow GM, Cheung AK, Cushman WC, Kostis WJ, et al. Visit-to-Visit Office Blood Pressure Variability and Cardiovascular Outcomes in SPRINT (Systolic Blood Pressure Intervention Trial). Hypertension. 2017 Oct;70(4):751–8.

238. He J, Shlipak M, Anderson A, Roy JA, Feldman HI, Kallem RR, et al. Risk Factors for Heart Failure in Patients With Chronic Kidney Disease: The CRIC (Chronic Renal Insufficiency Cohort) Study. J Am Heart Assoc. 6(5):e005336.

239. Zhang Y, He D, Zhang W, Xing Y, Guo Y, Wang F, et al. ACE Inhibitor Benefit to Kidney and Cardiovascular Outcomes for Patients with Non-Dialysis Chronic Kidney Disease Stages 3–5: A Network Meta-Analysis of Randomised Clinical Trials. Drugs. 2020;80(8):797.

240. Vaur L, Bobrie G, Dutrey-Dupagne C, Dubroca I, Vaisse B, Bouvier d'Yvoire M, et al. Short-Term Effects of Withdrawing Angiotensin Converting Enzyme Inhibitor Therapy on Home Self-Measured Blood Pressure in Hypertensive Patients. Am J Hypertens. 1998 Feb 1;11(2):165–73.

241. Bidani AK, Griffin KA, Epstein M. Hypertension and Chronic Kidney Disease Progression: Why the Suboptimal Outcomes? Am J Med. 2012 Nov;125(11):1057.

242. Lonn EM, Bosch J, López-Jaramillo P, Zhu J, Liu L, Pais P, et al. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. N Engl J Med. 2016 May 26;374(21):2009–20.

243. Pablos-Méndez A, Barr RG, Shea S. Run-in periods in randomized trials: implications for the application of results in clinical practice. JAMA. 1998 Jan 21;279(3):222–5.

244. Liu L, Wang Z, Gong L, Zhang Y, Thijs L, Staessen JA, et al. Blood pressure reduction for the secondary prevention of stroke: a Chinese trial and a systematic review of the literature. Hypertens Res Off J Jpn Soc Hypertens. 2009 Nov;32(11):1032–40.

245. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA. 2004 Nov 10;292(18):2217–25.

246. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991 01;325(5):293–302.

247. Fox KM, EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised,

double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet Lond Engl. 2003 Sep 6;362(9386):782–8.

248. Lang JM, Buring JE, Rosner B, Cook N, Hennekens CH. Estimating the effect of the run-in on the power of the Physicians' Health Study. Stat Med. 1991 Oct;10(10):1585–93.

249. Munger MA, Van Tassell BW, LaFleur J. Medication nonadherence: an unrecognized cardiovascular risk factor. MedGenMed Medscape Gen Med. 2007 Sep 19;9(3):58.

250. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" Lancet Lond Engl. 2005 Jan 1;365(9453):82–93.

251. Fralick M, Avorn J, Franklin JM, Bartsch E, Abdurrob A, Kesselheim AS. Application and Impact of Run-In Studies for the Evaluation of Statin Efficacy and Safety. J Gen Intern Med. 2018 Jun;33(6):792–4.

252. Fralick M, Avorn J, Franklin JM, Abdurrob A, Kesselheim AS. Application and impact of run-in studies. J Gen Intern Med. 2018;33(5):759–63.

253. Huo X, Armitage J. Use of Run-in Periods in Randomized Trials. JAMA. 2020 Jul 14;324(2):188–9.

254. Murphy R, McGrath E, Nolan A, Smyth A, Canavan M, O'Donnell M, et al. The impact of a run-in period on treatment effects in cardiovascular prevention randomised control trials: A protocol for a comprehensive review and meta-analysis. HRB Open Res. 2020 Nov 11;3:82.

255. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet Lond Engl. 2010 Nov 13;376(9753):1670–81.

256. Brunstrom M, Carlberg B. Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels: A Systematic Review and Meta-analysis. JAMA Intern Med. 2018 Jan 1;178(1):28–36.

257. Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2016 Nov 15;316(19):2008–24.

258. Czernichow S, Zanchetti A, Turnbull F, Barzi F, Ninomiya T, Kengne A-P, et al. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials. J Hypertens. 2011 Jan;29(1):4–16.

259. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet Lond Engl. 2016 Mar 5;387(10022):957–67.

260. Du H, Li X, Su N, Li L, Hao X, Gao H, et al. Proprotein convertase subtilisin/kexin 9 inhibitors in reducing cardiovascular outcomes: a systematic review and meta-analysis. Heart Br Card Soc. 2019 Aug;105(15):1149–59.

261. Koskinas KC, Siontis GCM, Piccolo R, Mavridis D, Räber L, Mach F, et al. Effect of statins and non-statin LDL-lowering medications on cardiovascular outcomes in secondary prevention: a meta-analysis of randomized trials. Eur Heart J. 2018 07;39(14):1172–80.

262. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol. 2019 Oct;7(10):776–85.

263. Thompson AM, Hu T, Eshelbrenner CL, Reynolds K, He J, Bazzano LA. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. JAMA. 2011 Mar 2;305(9):913–22.

264. Xie W, Zheng F, Evangelou E, Liu O, Yang Z, Chan Q, et al. Blood pressure-lowering drugs and secondary prevention of cardiovascular disease: systematic review and meta-analysis. J Hypertens. 2018;36(6):1256–65.

265. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Lond Engl. 2019 05;393(10166):31–9.

266. Clarke M, Brice A, Chalmers I. Accumulating research: a systematic account of how cumulative meta-analyses would have provided knowledge, improved health, reduced harm and saved resources. PloS One. 2014;9(7):e102670.

267. Akl EA, Briel M, You JJ, Sun X, Johnston BC, Busse JW, et al. Potential impact on estimated treatment effects of information lost to follow-up in randomised controlled trials (LOST-IT): systematic review. BMJ. 2012 May 18;344:e2809.

268. Briel M, Lane M, Montori VM, Bassler D, Glasziou P, Malaga G, et al. Stopping randomized trials early for benefit: a protocol of the Study Of Trial Policy Of Interim Truncation-2 (STOPIT-2). Trials. 2009 Jul 6;10:49.

269. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017 Aug 15;167(4):268.

270. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343(oct18 2):d5928–d5928.

271. Physicians' health study: aspirin and primary prevention of coronary heart disease. N Engl J Med. 1989 28;321(26):1825–8.

272. Bassler D. Stopping Randomized Trials Early for Benefit and Estimation of Treatment EffectsSystematic Review and Meta-regression Analysis. JAMA. 2010 Mar 24;303(12):1180.

273. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. 2011 Apr;64(4):407–15.

274. Hopewell S, Hirst A, Collins GS, Mallett S, Yu L-M, Altman DG. Reporting of participant flow diagrams in published reports of randomized trials. Trials. 2011 Dec 5;12:253.

275. Hopewell S, Dutton S, Yu L-M, Chan A-W, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. BMJ. 2010 Mar 23;340:c723.

276. Hewitt C, Hahn S, Torgerson DJ, Watson J, Bland JM. Adequacy and reporting of allocation concealment: review of recent trials published in four general medical journals. BMJ. 2005 May 7;330(7499):1057–8.

277. Altman DG, Moher D, Schulz KF. Improving the reporting of randomised trials: the CONSORT Statement and beyond. Stat Med. 2012 Nov 10;31(25):2985–97.

278. Plint AC, Moher D, Morrison A, Schulz K, Altman DG, Hill C, et al. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. Med J Aust. 2006 Sep 4;185(5):263–7.

279. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010 Mar 23;340:c869.

280. Arnett Donna K., Blumenthal Roger S., Albert Michelle A., Buroker Andrew B., Goldberger Zachary D., Hahn Ellen J., et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Sep 10;140(11):e563–95.

281. Ferreira-González I, Permanyer-Miralda G, Domingo-Salvany A, Busse JW, Heels-Ansdell D, Montori VM, et al. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. BMJ. 2007 Apr 14;334(7597):786.

282. Yusuf S, Negassa A. Choice of clinical outcomes in randomized trials of heart failure therapies: disease-specific or overall outcomes? Am Heart J. 2002 Jan;143(1):22–8.

283. Trivedi MH, Rush H. Does a placebo run-in or a placebo treatment cell affect the efficacy of antidepressant medications? Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 1994 Aug;11(1):33–43.

284. Affuso O, Kaiser KA, Carson TL, Ingram KH, Schwiers M, Robertson H, et al. Association of run-in periods with weight loss in obesity randomized controlled trials. Obes Rev Off J Int Assoc Study Obes. 2014 Jan;15(1):68–73.

285. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication—worldwide more than 850 million individuals have kidney diseases. Kidney Int. 2019 Nov;96(5):1048–50.

286. Mellotte G. National Renal Office, Ireland - End of year statistics [Internet]. Available from: nro-end-of-year-statistics-2020.pdf

287. Cozzolino M, Mangano M, Stucchi A, Ciceri P, Conte F, Galassi A. Cardiovascular disease in dialysis patients. Nephrol Dial Transplant. 2018 Oct;33(Suppl 3):iii28–34.

288. Yao Q, Pecoits-Filho R, Lindholm B, Stenvinkel P. Traditional and non-traditional risk factors as contributors to atherosclerotic cardiovascular disease in end-stage renal disease. Scand J Urol Nephrol. 2004;38(5):405–16.

289. Shafi T, Waheed S, Zager PG. Management of Hypertension in In-Center Hemodialysis Patients – An Opinion–Based Update. Semin Dial. 2014 Mar;27(2):146–53.

290. Agarwal R, Peixoto AJ, Santos SFF, Zoccali C. Pre- and postdialysis blood pressures are imprecise estimates of interdialytic ambulatory blood pressure. Clin J Am Soc Nephrol CJASN. 2006 May;1(3):389–98.

291. Agarwal R, Flynn J, Pogue V, Rahman M, Reisin E, Weir MR. Assessment and Management of Hypertension in Patients on Dialysis. J Am Soc Nephrol JASN. 2014 Aug;25(8):1630–46.

292. B C, C C, G J, Jm H, Jc T, T V, et al. Role of sodium in dialysis. Minerva Urol E Nefrol Ital J Urol Nephrol. 2004 Sep 1;56(3):205–13.

293. Zoccali C, Moissl U, Chazot C, Mallamaci F, Tripepi G, Arkossy O, et al. Chronic Fluid Overload and Mortality in ESRD. J Am Soc Nephrol. 2017 Aug 1;28(8):2491–7.

294. Flythe JE, Chang TI, Gallagher MP, Lindley E, Madero M, Sarafidis PA, et al. Blood pressure and volume management in dialysis: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2020 May 1;97(5):861–76.

295. Pinter J, Chazot C, Stuard S, Moissl U, Canaud B. Sodium, volume and pressure control in haemodialysis patients for improved cardiovascular outcomes. Nephrol Dial Transplant. 2020 Mar 1;35(Supplement_2):ii23–30.

296. Shah A, Davenport A. Does a reduction in dialysate sodium improve blood pressure control in haemodialysis patients? Nephrol Carlton Vic. 2012 May;17(4):358–63.

297. Munoz Mendoza J, Sun S, Chertow GM, Moran J, Doss S, Schiller B. Dialysate sodium and sodium gradient in maintenance hemodialysis: a neglected sodium restriction

approach? Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2011 Apr;26(4):1281–7.

298. Charra B, Bergström J, Scribner BH. Blood pressure control in dialysis patients: importance of the lag phenomenon. Am J Kidney Dis Off J Natl Kidney Found. 1998 Nov;32(5):720–4.

299. Dunlop JL, Vandal AC, Marshall MR. Low dialysate sodium levels for chronic haemodialysis. Cochrane Database Syst Rev [Internet]. 2019 Jan 16 [cited 2021 Mar 16];2019(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6353061/

300. Shendi AM, Davenport A. The difference between delivered and prescribed dialysate sodium in haemodialysis machines. Clin Kidney J. 2021 Mar 1;14(3):863–8.

301. Sarafidis PA, Persu A, Agarwal R, Burnier M, de Leeuw P, Ferro CJ, et al. Hypertension in dialysis patients: a consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Kidney working group of the European Society of Hypertension (ESH). Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2017 Apr 1;32(4):620–40.

302. Sibbald B, Roberts C. Understanding controlled trials Crossover trials. BMJ. 1998 Jun 6;316(7146):1719–20.

303. Labes D, Schütz H, Lang B. PowerTOST: Power and Sample Size for (Bio)Equivalence Studies [Internet]. 2021 [cited 2021 Aug 22]. Available from: https://CRAN.R-project.org/package=PowerTOST

Appendix 1 Other Publications during PhD

1. **Judge C**, Ruttledge S, Costello M, Murphy R, Loughlin E, Alvarez-Iglesias A, Ferguson J, Gorey S, Nolan A, Canavan M, O'Halloran M. Lipid lowering therapy, low-density lipoprotein level and risk of intracerebral hemorrhage–a meta-analysis. Journal of Stroke and Cerebrovascular Diseases. 2019 Jun 1;28(6):1703-9.

2. **Judge C**, Ruttledge S, Murphy R, Loughlin E, Gorey S, Costello M, Nolan A, Ferguson J, Halloran MO, O'Canavan M, O'Donnell MJ. Aspirin for primary prevention of stroke in individuals without cardiovascular disease—A meta-analysis. International Journal of Stroke. 2020 Jan;15(1):9-17.

3. Barrett PM, McCarthy FP, Kublickiene K, Cormican S, **Judge C**, Evans M, Kublickas M, Perry IJ, Stenvinkel P, Khashan AS. Adverse Pregnancy Outcomes and Long-term Maternal Kidney Disease: A Systematic Review and Meta-analysis. JAMA Network Open. 2020 Feb 5;3(2):e1920964. Doi: 10.1001/jamanetworkopen.2019.20964. PMID: 32049292.

4. Murphy RP, Dennehy KA, Costello MM, Murphy EP, **Judge CS**, O'Donnell MJ, Canavan MD. Virtual geriatric clinics, and the COVID-19 catalyst: a rapid review. Age Ageing. 2020 Oct 23;49(6):907-914. Doi: 10.1093/ageing/afaa191. PMID: 32821909; PMCID: PMC7546041.

5. Costello M, Murphy R, **Judge C**, Ruttledge S, Gorey S, Loughlin E, Hughes D, Nolan A, O'Donnell MJ, Canavan M. Effect of non-vitamin-K oral anticoagulants on stroke severity compared to warfarin: a meta-analysis of randomised controlled trials. Eur J Neurol. 2020 Mar;27(3):413-418. Doi: 10.1111/ene.14134. Epub 2020 Jan 8. PMID: 31774244.

6. Synnott P, Murphy RP, **Judge C**, Costello M, Reddin C, Dennehy K, Loughlin E, Smyth A, Mylotte D, O'Donnell MJ, Canavan M. Stroke Severity in Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement: A Systematic Review and Meta-Analysis. J Stroke Cerebrovasc Dis. 2021 Jul 9;30(9):105927. Doi: 10.1016/j.jstrokecerebrovasdis.2021.105927. Epub ahead of print. PMID: 34252826.

7. Curneen JM, **Judge C**, Traynor B, Buckley A, Saiva L, Murphy L, Murray D, Fleming S, Kearney P, Murphy RT, Aleong G, Kiernan TJ, O'Neill J, Moore D, Nicaodhabhui B, Birrane J, Hall P, Crowley J, Gibson I, Jennings CS, Wood D, Kotseva K, McEvoy JW. Interhospital and interindividual variability in secondary prevention: a comparison of outpatients with a

history of chronic coronary syndrome versus outpatients with a history of acute coronary syndrome (the iASPIRE Study). Open Heart. 2021 Jun;8(1):e001659. Doi: 10.1136/openhrt-2021-001659. PMID: 34172561; PMCID: PMC8237732.

8. Smyth A, **Judge C**, Wang X, Pare G, Rangarajan S, Canavan M, Chin SL, Al-Hussain F, Yusufali AM, Elsayed A, Damasceno A, Avezum A, Czlonkowska A, Rosengren A, Dans AL, Oguz A, Mondo C, Weimar C, Ryglewicz D, Xavier D, Lanas F, Malaga G, Hankey GJ, Iversen HK, Zhang H, Yusoff K, Pogosova N, Lopez-Jamarillo P, Langhorne P, Diaz R, Oveisgharan S, Yusuf S, O'Donnell M; INTERSTROKE investigators. Renal Impairment and Risk of Acute Stroke: The INTERSTROKE Study. Neuroepidemiology. 2021;55(3):206-215. Doi: 10.1159/000515239. Epub 2021 May 5. PMID: 33951632.

9. Reddin C, **Judge C**, Loughlin E, Murphy R, Costello M, Alvarez A, Ferguson J, Smyth A, Canavan M, O'Donnell MJ. Association of Oral Anticoagulation With Stroke in Atrial Fibrillation or Heart Failure: A Comparative Meta-Analysis. Stroke. 2021 Jul 20:STROKEAHA120033910. Doi: 10.1161/STROKEAHA.120.033910. Epub ahead of print. PMID: 34281383.