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Medication prescription to improve outcomes in advanced chronic kidney disease

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Thesis Title and Abstract

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Thesis Abstract

Chronic kidney disease (CKD) is a major public health issue affecting 10% of the global population and resulting in 1.2 million deaths. The risk of all-cause and cardiovascular mortality is inversely proportional to declining eGFR such that individuals with CKD are more likely to die, primarily due to a cardiovascular cause, than survive to the point of requiring dialysis. These poor outcomes are related to a myriad of factors including multimorbidity, medial vascular calcification and underlying haemostatic dysfunction.

Polypharmacy is a key consequence of the disease burden experienced by CKD patients. It is linked with poor adherence, adverse drug reactions, falls and increased hospitalisations. A post-hoc analysis of the CKD-FIX study was conducted to assess the prevalence and predictors of polypharmacy in CKD patients. It found that polypharmacy, defined as ≥5 medications, and hyperpolypharmacy, defined as ≥10 medications, were found in 77.5% and 34.3% of patients respectively. Age ≥65 yrs, diabetes, cardiovascular disease and hyperlipidemia were independently associated with polypharmacy.

However, limiting polypharmacy via appropriate prescribing is hampered by the lack of data in patients with advanced CKD. Despite the disproportionate cardiovascular disease burden in CKD, the benefits and risks of dual antiplatelet therapy are not known. Therefore a systematic review of randomised controlled trials on the effectiveness of dual antiplatelet therapy in CKD was conducted. Nineteen trials with 27,308 participants were analysed with all but 3 trials excluding participants with dialysis-dependent kidney failure. Compared with aspirin monotherapy or no study medication, P2Y12 inhibitor-based dual antiplatelet therapy significantly reduced the risks of major adverse cardiovascular events, myocardial infarction and stroke; but increased the risk of major bleeding. There was insufficient evidence to conclude whether patients with advanced stages of CKD and dialysis-dependent kidney failure derived benefit.

In conclusion, CKD patients represent an expanding population that is at high risk of adverse outcomes. Polypharmacy is common in patients with CKD and is related to age and multimorbidity. Further research on medication appropriateness and deprescribing are needed. In particular, adequately powered randomized trials are required to evaluate the effectiveness of dual antiplatelet therapy in patients with advanced stages of CKD and cardiovascular disease.

Declarations

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Contributions by others to the thesis

For chapter 2, Dr Badve and I conceived and designed the study. I conducted the statistical analysis with Dr Badve's assistance based on the data collected by Dr Badve and the other co-authors of the CKD-FIX trial (Elaine M. Pascoe, Anushree Tiku, Neil Boudville, Fiona G. Brown, Alan Cass, Philip Clarke, Nicola Dalbeth, Richard O. Day, Janak R. de Zoysa, Bettina Douglas, Randall Faull, David C. Harris, Carmel M. Hawley, Graham R.D. Jones, John Kanellis, Suetonia C. Palmer, Vlado Perkovic, Gopala K. Rangan, Donna Reidlinger, Laura Robison, Robert J. Walker, Giles Walters, and David W. Johnson). Dr Badve assisted with manuscript drafting and editing.

For chapter 3, Dr Badve and I conceived and designed the study together. Literature search, selection of studies and data extraction were carried out by me and supervised by Dr Badve and A/Professor Jardine. Data extraction was also independently carried out by Matthew Tong (MT). I conducted the statistical analysis and wrote the chapter. Dr Badve supervised the analysis and assisted with manuscript drafting and editing.

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ACE	angiotensin converting enzyme
ARB	angiotensin receptor blocker
ATC	anatomic therapeutic chemical
BD	twice daily
CI	confidence intervals
CKD	chronic kidney disease
CrCl	creatinine clearance
eGFR	estimated glomerular filtration rate
GFR	glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IQR	interquartile range
MI	myocardial infarction
mL	millilitres
OD	once daily
PTFE	polytetrafluoroethylene
RCT	randomised control trial
RR	risk ratio
SD	standard deviation
TDS	three times daily
UACR	urinary albumin-to-creatinine ratio
WHO	World Health Organisation

Chapter 1. INTRODUCTION

1.1 Global disease burden of chronic kidney disease

Chronic kidney disease (CKD) is a major public health issue with approximately 10% of the global population affected and increasing to more than 50% in high-risk subpopulations such as those above 70 years of age (1,2). CKD is defined as at least 3 months of an estimated glomerular filtration rate (eGFR) <60ml/min/1.73m2 and/or markers of kidney damage which include albuminuria, urine sediment abnormalities, abnormalities due to tubular disorders, abnormalities detected by histology or imaging, and history of kidney transplantation (3). Prevalence in Australian adults is estimated to be 1.7 million with majority of those in earlier stages of CKD (stages 1-3)(4), with approximately 3,000 Australians each year progressing to kidney failure requiring treatment either through kidney transplantation or dialysis (5). In 2018, CKD was the underlying cause, or was an associated cause, of 11% of deaths in Australia (4). In 2017, CKD resulted in 1.2 million deaths globally, a number which has been projected to rise to 2.2 - 4 million by 2040 (6).

1.2 Risk factors for poor outcomes in CKD

CKD is associated with significantly increased cardiovascular morbidity and mortality, even after adjustment for comorbid cardiovascular disease risk factors (7,8). Globally, 1.4 million deaths from cardiovascular disease were attributable to impaired kidney function (6). The risk of developing these outcomes is inversely proportional to absolute eGFR: compared to those with eGFR of 95 mL/min/1.73m^2, the risk of all-cause mortality is increased by 18%, 57% and 314% for eGFRs of 60, 45, and 15 mL/min per 1.73m^2, respectively. The impacts on cardiovascular mortality were similar (9). The rate of decline in eGFR is also correlated with negative outcomes with all-cause mortality increased by 25% in those with slope of -6 mL/min per 1.73m^2 per year compared with 0 mL/min per 1.73m^2 (10,11). Patients with CKD also have

more extensive coronary artery disease and experience poorer outcomes post-coronary revascularisation (12,13) or coronary artery bypass grafting (14,15). Furthermore, congestive heart failure, left ventricular hypertrophy, and arrhythmias frequently co-occur in patients with advanced CKD (16,17), defined as an eGFR <30mL/min/1.73m^2. Overall, cardiovascular causes account for approximately 50% of deaths in patients with CKD stage 4 and greater than 50% in those with CKD stage 5 or dialysis-dependent kidney failure (18).

The increased cardiovascular burden seen in patients with CKD likely reflects high prevalence of 'traditional' risk factors such as hypertension, hyperlipidaemia, diabetes mellitus, and advanced age (9,19). In 2019, 53% of Australians who were started on dialysis had type 2 diabetes mellitus (T2DM), 31% had coronary artery disease, 19% had peripheral vascular disease, and 10% had cerebrovascular disease (20). Patients with CKD also frequently feature 'non-traditional' risk factors including chronic inflammation, abnormal calcium-phosphorus metabolism, medial vascular calcification, anaemia, oxidative stress, and volume overload (9,21-24).

These factors are further compounded by a prothrombotic state that is thought to promote cardiovascular and thrombotic events. A meta-analysis of cohort studies found that the risk of stroke increased by 7% for every 10 mL/min/1.73 m^2 decrease in eGFR (25). Furthermore, patients with dialysis-dependent kidney failure have a 61% higher risk of venous thromboembolism compared to those with normal kidney function (26), and up to 40% of arterio-venous fistula or grafts thrombose (27). Mechanisms of hypercoagulability include higher circulating levels of procoagulants such as factor VIII, von Willebrand factor, tissue factor, D-dimer, fibrinogen and plasminogen activator inhibitor type 1 (28-32), chronic inflammation (29), and erythropoietin therapy (33).

Paradoxically, patients with CKD are also at a greater risk of bleeding with a 9% increasing risk of haemorrhage per each 10 mL/min/1.73m^2 increase in eGFR (34). 14% of dialysis patients were found to have had a major haemorrhage within 3 years of dialysis

initiation (35). This bleeding diathesis is potentially related to impaired platelet adhesion, aggregation, activation, and vessel wall interaction. Patients with CKD have been previously found to have platelet dysfunction secondary to increased prostacyclin generation (36), decreased membrane expression of glycoprotein (GP) Ib (37), decreased thromboxane A_2 synthesis (38), decreased GPIIb/GPIIIa receptor expression and competitive binding to GPIIb/GPIIIa receptors by fibrinogen fragments or uraemic toxins (36,37). Abnormal von Willebrand factor, altered thrombin generation, abnormal endothelial function, and uraemic toxins such as phenol, phenolic acid and guanidinosuccinic acid could also impair platelet aggregation (37,39), predisposing to bleeding.

1.3 Polypharmacy in CKD

Polypharmacy, defined as daily intake of ≥ 5 medications, has been recognised as an increasing global challenge by the World Health Organization. While the global prevalence has been difficult to estimate, it is expected to increase given that the population subset over the age of 65 years is predicted to double by 2050 (40). In 2017, 36% of Australians older than 70 years demonstrated polypharmacy, with the rate increasing to 46% for those between 85 and 89 years of age (41). Polypharmacy is associated with drug-drug interactions, poor medication adherence, as well as increased adverse drug reactions, falls, functional impairment, hospitalisations and health burden (42,43). It has been estimated that 2 - 3% of hospital admissions in Australia are medication-related, corresponding to 250,000 admissions per year, at a cost to the healthcare system of $1.4 billion (44). In addition, up to 55% of people admitted to hospital over the age of 65 years were on a potentially inappropriate medication (45). Risk factors for polypharmacy are multiple and include patient-related and system-related factors. Patient-related factors include multimorbidity, chronic mental health conditions, multiple specialists, and being an aged care resident, and systems-related factors include poorly updated

medical records and transition of care, the development of a 'prescribing cascade', automatic prescription filling, and prescribing to fulfil disease specific guidelines (46-48).

In Europe, for people over the age of 65 years with advanced CKD, 91% experienced polypharmacy and 43% experienced hyperpolypharmacy (defined as daily intake of ≥10 medications) at rates three times higher than age-matched patients without CKD (49). Patients with CKD are prescribed a myriad of medications to mitigate symptoms, reduce progression of disease and address associated complications. This is likely attributable to several factors, including the multimorbidity with conditions such as diabetes mellitus, hyperlipidaemia, and hypertension, in addition to older age, higher body mass index, and smoking (50). Unsurprisingly, the number of medications increases conversely as eGFR declines (50,51).

Compared to the general population, patients with advanced CKD are also at higher risk of potential adverse drug reactions due to altered pharmacodynamics and pharmacokinetics. Despite this, there is limited evidence and guidance to assist with decisions regarding many commonly used drugs (52). It can therefore be challenging to balance over- and under-prescribing appropriately while matching the needs of the patient with disease-specific clinical practice guidelines. For patients with advanced CKD, the appropriateness of interventions, particularly for coronary artery disease, is complicated by the lack of clinical trial data as those with advanced disease are either excluded or included in too few numbers to permit confident estimation of treatment benefits (53-55).

1.4 Limitations of the currently available therapeutic interventions in CKD

Overarching treatment of CKD is predominantly aimed at preventing progression, management of comorbidities, and managing complications such as anaemia, metabolic bone disease and acidosis (56). Medications with proven benefit for slowing CKD progression are limited to blood pressure agents such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) (57-61), and sodium-glucose co-transporter-2 (SGLT-2)

inhibitors (62,63). Despite long term use of ACE inhibitors and ARB in this population, benefit has not been proven with advanced CKD (64).

Similarly, agents to reduce cardiovascular risk and mortality are limited to medical management of cardiovascular risk factors (7,65) such as blood pressure lowering medications (66), statins (67), SGLT-2 inhibitors (62,63), and finerenone (68). Although used and recommended in all stages of CKD, blood pressure agents and statins only have known benefits in specific patient populations such as in non-dialysis dependent patients with CKD for statins (69), and beta-adrenergic antagonists in patients with CKD who have comorbid heart failure (70,71). Demonstrated benefits of SGLT-2 inhibitors and finerenone are also limited to those with eGFR >25 mL/min/1.73 m^2 and proteinuria (63,68). Phosphate binding agents in those with hyperphosphataemia and bicarbonate supplementation in those with metabolic acidosis are also recommended to manage complications of dialysis-dependent kidney failure despite inconsistent evidence of benefit (72-74).

1.5 Limitations and evidence for the currently available antiplatelet interventions in CKD

Dual antiplatelet therapy is the cornerstone of treatment for acute and chronic coronary artery disease. However, despite the disproportionate cardiovascular disease burden in patients with CKD, the decision to implement medical therapy is not straightforward. The risk-benefit profile for antiplatelet use in advanced CKD may differ compared to those without kidney disease due to their state of paradoxical haemostatic dysfunction and altered response to antiplatelet agents (75,76). Limited data suggests that clopidogrel responsiveness may be diminished in CKD independent of CYP2C19 polymorphism effects (77). The mechanisms are poorly understood but could be due to increased platelet turnover rate, poor bioavailability of the active clopidogrel metabolite, and alterations in procoagulant factors, thromboxane A2 and nitric oxide synthesis (78). The studies into the variable antiplatelet response to clopidogrel,

high residual platelet reactivity, and "clopidogrel resistance" have led to a focus on the more pharmacodynamically potent P2Y12 inhibitors ticagrelor and prasugrel (79,80). Ticagrelor remains promising in CKD as it is not renally cleared, does not require dose adjustment, and small studies have shown more rapid and greater platelet inhibition, compared with that of clopidogrel and prasugrel (81).

Observational data has suggested that antiplatelet therapy was associated with greater rates of hospitalisation for bleeding in dialysis patients (82). Although these findings may be confounded by the indication to use these agents, observational data in dialysis-dependent kidney failure has also shown an increased risk of all-cause and cardiovascular mortality (83). Similarly, limited data from randomised control trials (RCT) suggests that clopidogrel may increase the risks of death and bleeding in CKD (84,85). For those in the general population with acute coronary syndrome, landmark clinical trials with ticagrelor and prasugrel have shown improved cardiovascular outcomes, albeit with an elevated bleeding risk (86,87). Registry data in CKD populations have again shown conflicting results; no difference was found in propensity adjusted data from PROMETHEUS (88), while a reduction in the cardiovascular composite outcome was found in SWEDEHEART (89). A previous systematic review found generally low quality evidence with uncertain effects on the risks of major adverse cardiovascular events and all-cause mortality, but increased risk of major bleeding (90). Therefore, it remains unclear whether indications for antiplatelet agents in advanced CKD and dialysis-dependent kidney failure may be extrapolated from data from the general population with the same expectation of benefit.

1.6 Research objectives, method and outline of chapters

The main research objectives of this thesis were to first, assess the prevalence and predictors of polypharmacy in patients with stage 3-4 CKD in the Australian population, and second, conduct a systematic review of randomised controlled trials on the effectiveness of dual

antiplatelet therapy in patients with CKD. The first study (chapter 2) presents a post-hoc analysis of the CKD-FIX trial which involved 369 adults with CKD stage 3 or 4 identified as being at risk of progression (either urinary albumin-to-creatinine ratio ≥ 265 mg/g or eGFR decrease ≥ 3.0 mL/min/1.73m^2 in the preceding year). This study analysed the prevalence of polypharmacy and utilised multivariable logistic regression to explore predictors.The second study (chapter 3), presents a systematic review of the effectiveness of dual antiplatelet therapy in patients with CKD.

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Chapter 2. POLYPHARMACY IN CHRONIC KIDNEY DISEASE

2.1 Abstract

Introduction: Polypharmacy is common in patients with chronic kidney disease (CKD). We conducted a post-hoc analysis of the CKD-FIX trial to study the prevalence and predictors of polypharmacy in patients with CKD at high risk of CKD progression.

Methods: The CKD-FIX trial involved 369 adults with CKD stage 3 or 4, no history of gout, and who were at risk of progression (identified by either urinary albumin-to-creatinine ratio [UACR] ≥ 265 mg/g or eGFR decrease ≥ 3.0 mL/min/1.73 m^2 in the preceding year). Polypharmacy and hyperpolypharmacy were defined as ≥ 5 and ≥ 10 medications per day, respectively, including non-oral and non-prescription medications. The predictors of polypharmacy were evaluated using multivariable logistic regression.

Results: Data on medication use at baseline were available in 362 patients (mean age 62.4 years (±12.7 SD); mean eGFR 31.8 mL/min/1.73 m^2 (±12.0 SD); median UACR 719.6 mg/g (IQR 244.3, 1855); diabetes 58%; cardiovascular disease 34%). The prevalence of polypharmacy and hyperpolypharmacy were 77.6% (281 patients of 362) and 34.3% (124 patients of 362) respectively and did not differ according to CKD stage or albuminuria. The median number of daily medications was 8 (IQR 5, 11). The most commonly used medications were antihypertensive agents, statins, diuretics, antithrombotic agents and proton pump inhibitors. Variables of age ≥ 65 yrs, diabetes, cardiovascular disease and hyperlipidaemia, were each independently associated with polypharmacy.

Conclusion: Polypharmacy is common in patients with CKD at high risk of CKD progression. Further research on medication appropriateness and deprescribing are needed in this patient population.

2.2 Introduction

Polypharmacy, defined as regular use of at least 5 medications per day, is a growing problem in at-risk patient populations, including chronic kidney disease (CKD) (1-3). Polypharmacy is associated with clinical outcomes ranging from adverse drug reactions, medication errors, medication nonadherence, falls, hospitalisations, death and increased healthcare costs (4-7). Common risk-factors for polypharmacy include advanced age, lack of a primary care physician, multiple chronic conditions and involvement of multiple specialists in care (4,8). These risk factors are highly prevalent in patients with CKD. Patients with CKD are at a greater risk of disease progression, cardiovascular events, and death. The excess risk of cardiovascular and kidney-related outcomes in CKD is due to the high prevalence of risk factors, such as advanced age, hypertension, diabetes, proteinuria, hyperlipidaemia and co-existing cardiovascular disease. In addition, several non-traditional risk factors, such as hyperuricemia and hyperphosphataemia are highly prevalent in this patient population. These patients are often prescribed medications that are aimed at preventing cardiovascular and kidney-related outcomes, including proven and unproven treatments. There is a need for improved delineation of polypharmacy in patients with CKD, especially those at high risk of CKD progression, so that interventions to systematically address this problem be evaluated and implemented appropriately. This post-hoc analysis of the Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase (CKD-FIX) aimed to evaluate the prevalence, pattern and risk factors of polypharmacy in patients with CKD.

2.3 Methods

The CKD-FIX trial was an investigator-initiated, randomized, double-blind, placebo-controlled trial that was conducted by the Australasian Kidney Trials Network (University of Queensland) at 31 centres in Australia and New Zealand (Australian New Zealand Clinical Trials Registry number, ACTRN12611000791932). Patients were all recruited from renal units

providing comprehensive CKD care. The study protocol was approved by ethics committees at all participating sites in Australia, and the Northern Region A Health and Disability Ethics Committee for sites in New Zealand. All patients provided written informed consent prior to participation in the trial.

The main findings of the CKD-FIX trial have been published elsewhere (9). Briefly, between 21 March 2014 and 31 December 2016, 369 adults with stage 3 or 4 CKD and an elevated risk of progression to kidney failure were randomized to allopurinol (100-300 mg daily) or placebo. An elevated progression risk was defined as urinary albumin-to-creatinine ratio ≥ 265 mg/g (≥ 30 mg/mmol) or decrease in estimated glomerular filtration rate ≥ 3.0 mL/min/1.73 m^2 in the preceding 12 months (calculated as the difference between the first and last of at least 3 estimated glomerular filtration rate tests, each test done at least 4 weeks apart). Patients meeting these criteria have been shown to be at a substantially increased risk of progression to kidney failure (10,11). Key exclusion criteria were history of gout, allopurinol hypersensitivity, clinical indication for allopurinol and unresolved acute kidney injury in the previous 3 months. Eligible patients were randomly assigned to receive allopurinol or placebo in a 1:1 ratio with an adaptive allocation algorithm. Patients were followed for 104 weeks. The primary outcome of the CKD-FIX trial was the change in the eGFR from baseline to 104 weeks.

Data on patient demographic characteristics, comorbidities and concomitant medications at baseline were collected at the randomization visit. Polypharmacy was defined as the use of 5 or more chronic medications, and hyperpolypharmacy as the use of 10 or more medications. Medications administered by a non-oral route and over the counter medications were also included in medication count. Apart from inhalers, combination medications were counted separately if their components had a clinical indication to be prescribed in their individual forms. Data on the number of pills were not collected. Medications were classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system (12).

Statistical analysis

This post-hoc analysis included only the baseline data collected at the randomization visit. Results were reported as frequencies (percentages) for categorical variables, mean ± standard deviation (SD) for continuous normally distributed variables, and median (interquartile range [IQR]) for continuous, non-normally distributed variables. Data was assessed for normality using Skewness and Kurtosis measures. The Mann-Whitney test was used to determine differences in the number of medications and patient sub-groups. The predictors of polypharmacy and hyperpolypharmacy were evaluated using multivariable logistic regression. The variables included in the multivariable logistic regression were age (dichotomised as < 65 yr or ≥ 65 yr), sex, race, diabetes mellitus, cardiovascular disease and hyperlipidaemia. Statistical analyses were performed using Stata/MP (version 16.1, StataCorp, College Station, Texas).

2.4 Results

Patient characteristics

Data on medications at baseline were available for 362 of 369 (98.1%) randomized patients. Baseline characteristics of the study population are described in Table 2.1. The mean age was 62.4 years, with 175 (48.3%) patients ≥ 65 years of age. Self-reported ethnicity was Caucasian in 272 (75.1%) patients. At baseline, 209 (57.7%) patients had diabetes mellitus, 122 (33.7%) had cardiovascular disease, and 267 (73.8%) patients had hyperlipidaemia. Mean eGFR was 31.8 mL/min/1.73 m^2; 178 (49.2%) and 184 (50.8%) patients had CKD stage 3 and stage 4, respectively. The median urinary albumin-to-creatinine ratio was 716.9 mg/g, and 253 (70.9%) patients had urinary albumin-to-creatinine ratios ≥ 300 mg/g.

Number of medications and polypharmacy

The median number of medications taken daily was 8 (IQR 5, 11) (see Figure 2.1, Table 2.2). The median number of daily medications was greater in those ≥ 65 years of age, and those with diabetes mellitus, cardiovascular disease and/or hyperlipidaemia (see Figure 2.2).

Figure 2.1. Number of daily medications

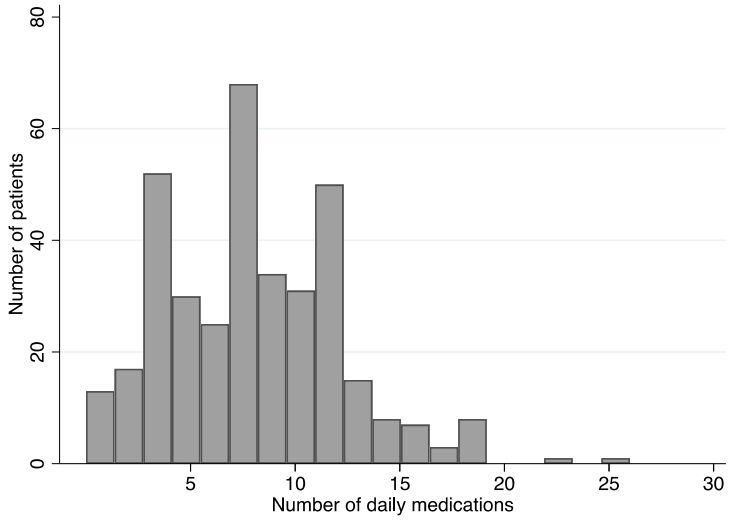
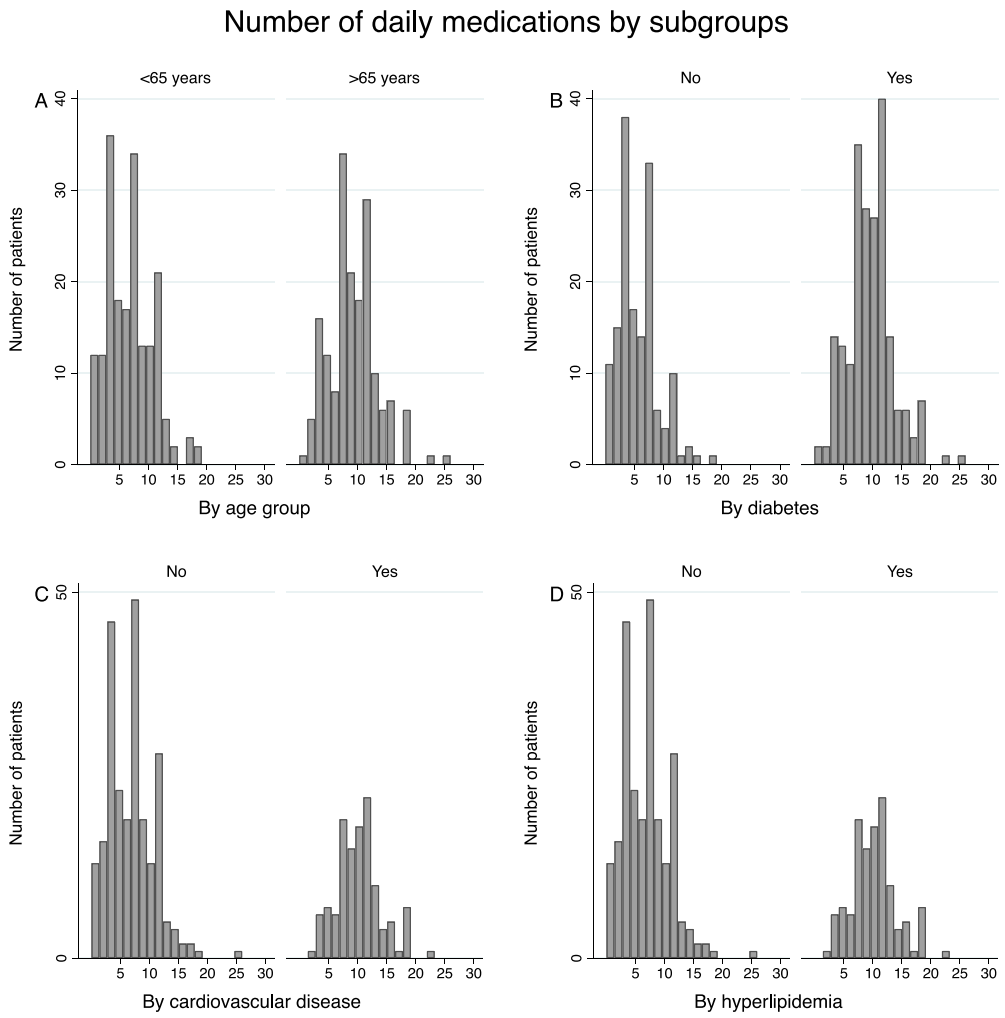


Figure 2.2. Number of daily medications by subgroup



There was no significant difference in the number of daily medications by patient sex, ethnicity, CKD stage, or albuminuria. At baseline, 77.6% (281 patients of 362) and 34.3% (124 patients of 362) were receiving ≥ 5 and ≥ 10 medications per day, respectively. The prevalence of polypharmacy was greater among those over the age of 65 years (87.4%), non-Caucasian race (86.7%), and those with diabetes mellitus (91.9%), cardiovascular disease (94.3%), or hyperlipidaemia (86.1%). The prevalence of hyperpolypharmacy was greater among those aged over 65 years (44.6%), and in those with diabetes mellitus (50.2%), cardiovascular disease (55.7%), or hyperlipidaemia (41.6%).

On multivariable logistic regression (Table 2.3), age ≥ 65 years (OR 2.05; 95% CI 1.09, 3.84), diabetes mellitus (OR 5.11; 95% CI 2.69, 9.70), cardiovascular disease (OR 4.08; 95% CI

1.70, 9.79) and hyperlipidaemia (OR 3.23; 95% CI 1.77, 5.88) were independently associated with polypharmacy. Diabetes mellitus (OR 5.88; 95% CI 3.21, 10.78), cardiovascular disease (OR 3.13; 95% CI 1.83, 5.34) and hyperlipidaemia (OR 2.55; 95% CI 1.27, 5.12) were independently associated with hyperpolypharmacy. Age ≥ 65 years was not associated with hyperpolypharmacy.

Medications

Excluding glucose-lowering medications (Table 2.4), the most prescribed medications were blood pressure-lowering medications (341 patients, 94.2%), statins (261 patients, 72.1%) and diuretics other than mineralocorticoid-receptor antagonists (146 patients, 40.3%). Only 102 patients (28.2%) were treated with a single blood pressure-lowering medication, whereas 112 patients (30.9%), 94 patients (26%), 29 patients (8%) and 4 patients (1.1%) were treated with a combination of 2, 3, 4 or 5 blood pressure-lowering medications, respectively. Among the inhibitors of renin-angiotensin-aldosterone system, 146 patients (40.3%) were treated with ACE inhibitors, 130 patients (35.9%) with angiotensin-receptor inhibitor and 21 patients with (5.8%) mineralocorticoid-receptor antagonists. Next commonly prescribed medications were antithrombotic medications in 182 patients (50.3%) and proton-pump inhibitors in 130 patients (35.9%). Single- and dual-antiplatelet therapies were prescribed in 135 (37.3%) and 24 (6.6%) patients, respectively, whereas anticoagulant agents were prescribed in 25 patients (6.9%). Among 209 patients with diabetes mellitus, 186 patients (89%) were prescribed at least one glucose-lowering medication and 128 patients (81.2%) were prescribed at least two glucose-lowering medications.

2.5 Discussion

This post-hoc analysis of the CKD-FIX trial found that polypharmacy and hyperpolypharmacy were highly prevalent in patients with CKD stages 3 and 4 with elevated progression risk. The observed high prevalence of polypharmacy in this population was due to

old age and the presence of multiple co-existing chronic conditions such as diabetes, cardiovascular disease and hyperlipidaemia. Previous studies have identified polypharmacy in patients with CKD with mean or median number of daily medications ranging between 8 and 11, and prevalence estimates ranging between 60% to 97% for polypharmacy, and 16% to 63% for hyperpolypharmacy (1,2,13,14). Similar to the German Chronic Kidney Disease study, diabetes, cardiovascular disease and hyperlipidaemia were independently associated with polypharmacy (2). However, CKD stage was not associated with polypharmacy in the current study. This could have been a result of the small sample size. Alternatively, selection bias should be considered given that the CKD-FIX cohort were enrolled on the high progression criterion and as such, did not include patients with stage CKD 1 and 2 and therefore do not represent the wider CKD population. As expected, blood pressure-lowering medications and cardiovascular treatments such as lipid-lowering and antithrombotic medications were the most prescribed medications.

Considering the association between polypharmacy and clinical outcomes, the results of the current study have several important clinical and research implications. There is a need to deprescribe medications that are not beneficial or those with uncertain benefit-risk profile. For example, despite the high burden of cardiovascular disease, anticoagulant and antiplatelet agents have not been systematically evaluated in patients with advanced stages of CKD. The CKD-FIX trial showed that urate-lowering treatment with allopurinol did not slow decline in eGFR, despite the wide use of urate-lowering in CKD and asymptomatic hyperuricemia (15). On the other hand, recent studies have shown that sodium–glucose co-transporter-2 inhibitors and nonsteroidal mineralocorticoid receptor antagonist finerenone reduce a variety of renal and cardiovascular outcomes in patients with CKD and high risk factors for progression that were similar to the CKD-FIX population (16-18).

Despite their benefits, the use of these medications add to the burden of polypharmacy, thus highlighting the need to be pragmatic in medication optimisation by choosing treatments that provide the greatest benefit with smallest harm while also considering the concept of

diminishing returns (19). Shared decision making with patients optimises medication use for the best possible outcomes, but again requires clear information about treatment outcomes. Therefore, further research on medication appropriateness, deprescribing, and prescribing of omitted therapies is needed in order to bolster the limited evidence for CKD medication guidelines. Further research evaluating the safety and efficacy combination polypills would also be informative.

An additional challenge facing medication rationalisation is determining who is responsible for co-ordinating and implementing any changes. Depending on the patient's stage of CKD, comorbidities, and healthcare arrangements, the recognition and management of polypharmacy may lie primarily with the nephrologist/renal centre, other medical specialist, the primary care provider and/or the community pharmacist. A single provider could see significantly increased workload, however if multiple health practitioners are involved without a designated co-ordinator this may lead to fragmentation of care. For those in renal centres, medication audits or reviews co-ordinated by a clinical pharmacist could be considered, as it has been shown to have benefit in those on haemodialysis to reduce medication use and hospitalisations (20). Similarly, reviews by the community pharmacist as part of the Medicare funded Domiciliary Medication Management Review in Australia have been shown to have some positive impacts on inappropriate prescribing, cost of healthcare provisions, and patient medication literacy (21,22). Further research into the impact of these types of multidisciplinary intervention on medication rationalisation should be conducted.

The strengths of this analysis include systematically collected data for a randomized controlled trial and the use of the Anatomical Therapeutic Chemical classification system. These strengths need to be balanced against its limitations. Unfortunately, as the participant number was small and did not include patients in all stages of CKD, findings cannot be generalised to a wider CKD population. Furthermore, pill count data was lacking. This can be a risk factor for low medication adherence and poorer quality of life, especially in those prescribed phosphate-binders (23,24). Moreover, this analysis did not include an evaluation of

medication appropriateness, which would be beneficial to assess prescription patterns. It would also assist with deprescription by identifying medications of inadequate clinical benefit, at increased risk for adverse reactions, or those which require renal dose adjustment.

In summary, polypharmacy is common in patients with CKD at high risk of CKD progression and associated with old age and co-existing chronic conditions. Further research on medication appropriateness and deprescribing are needed in this patient population.

2.6 Perspectives

Competency in medical knowledge: Polypharmacy was highly prevalent in patients with chronic kidney disease stages 3 or 4 who were at risk of progression. Older age, diabetics, cardiovascular disease, and hyperlipidaemia were each independently associated with polypharmacy. Clinicians should recognise the importance of medication reconciliation in reducing the burden of polypharmacy in this comorbid population.

Translational outlook: Further research on medication appropriateness, deprescription, and the effectiveness of medication reconciliation are needed in this patient population.

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Table 2.1. Baseline characteristics

Characteristic	Total (N=362)
Age - yr	62.4 (±12.7)
Age ≥65 yr - n (%)	175 (48.3%)
Female sex - n (%)	135 (37.3%)
Race or ethnic group - n (%) †	
White	272 (75.1%)
Australian Aboriginal/ Torres Strait Islander	4 (1.1%)
New Zealand Māori	28 (7.7%)
Asian	18 (5%)
Other	40 (11.1%)
Body-mass index - kg/m^2 (IQR) ‡	30 (26, 36)
Blood pressure □	
Systolic - mm Hg	139.2 (±19.1)
Diastolic - mm Hg	76.6 (±11.6)
Primary cause of kidney disease - n (%)	
Diabetic kidney disease	164 (45.3%)
Non-diabetic kidney disease	198 (54.7%)
Diabetes mellitus - n (%)	209 (57.7%)
Cardiovascular disease - n (%)	122 (33.7%)
Hyperlipidemia - n (%)	267 (73.8%)
Smoking - n (%)	
Never smoked	157 (43.4%)
Previous smoker	168 (46.4%)
Current smoker	37 (10.2%)
eGFR - mL/min/1.73 m^2	31.8 (±12.0)
Stage 3	178 (49.2%)
Stage 4	184 (50.8%)
Median urinary ACR - mg/g (IQR) §	716.9 (244.3, 1855)
<30 - n (%)	37 (10.4%)
≥30-300 - n (%)	67 (18.7%)
≥300 - n (%)	253 (70.9%)
Serum urate - mg/dL #	8.2 (±1.7)

* Plus–minus values are means ±SD. IQR, interquartile range. ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate.

† Race and ethnic group were reported by the patients.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 5 patients.

□ Data were missing for 1 patient.

¶ Scores on the 36-Item Short-Form Health Survey (SF-36) quality-of-life summary score range from 0 to 100, with higher scores indicating better quality of life. Data were missing for 1 patient.

§ Data were missing for 5 patients.

Data were missing for 11 patients.

Table 2.2. Number of medications

Characteristic	Mean (SD)	Median (IQR)	Range	Polypharmacy n (%)	Hyperpolypharmacy n (%)
All patients	8.0 (4.2)	8 (5, 11)	0 - 26	281 (77.6%)	124 (34.3%)
Age group					
<65 yr	6.9 (3.8)	6 (4, 9)	0 - 18	128 (68.5%)	46 (24.6%)
≥65 yr	9.3 (4.1)	9 (7, 12)	1 - 26	153 (87.4%)	78 (44.6%)
Sex					
Men	7.7 (3.7)	8 (5, 10)	0 – 18	176 (77.5%)	74 (32.6%)
Women	8.5 (4.7)	8 (5, 12)	1 – 26	105 (77.8%)	50 (37%)
Race					
White	7.9 (4.2)	8 (4, 11)	0 – 26	203 (74.6%)	91 (33.5%)
Non-White	8.5 (3.9)	9 (6, 10)	1 – 22	78 (86.7%)	33 (36.7%)
Diabetes mellitus					
No	5.7 (3.4)	5 (3, 8)	0 – 18	89 (58.2%)	19 (12.4%)
Yes	9.7 (3.9)	10 (7, 12)	1 – 26	192 (91.9%)	105 (50.2%)
Cardiovascular disease					
No	6.9 (3.9)	7 (4, 9)	0 – 26	166 (69.2%)	56 (23.3%)
Yes	10.2 (3.8)	10 (8, 12)	2 – 22	115 (94.3%)	68 (55.7%)
Hyperlipidemia					
No	5.6 (3.4)	5 (3, 8)	0 - 17	51 (53.7%)	13 (13.7%)
Yes	8.9 (4.1)	9 (6, 11)	1 – 26	230 (86.1%)	111 (41.6%)
CKD stage					
Stage 3	8.0 (4.3)	8 (5, 11)	0 – 26	138 (77.5%)	60 (33.7%)
Stage 4	8.1 (4.0)	8 (5, 11)	1 – 22	143 (77.2%)	64 (34.8%)
Urinary ACR in mg/g					
< 30 - n (%)	8.0 (3.9)	8 (5, 11)	2 – 18	29 (78.4%)	11 (29.7%)
≥ 30-300 - n (%)	7.7 (4.4)	7 (4, 11)	1 – 19	45 (67.2%)	22 (32.8%)
≥ 300 - n (%)	8.1 (4.1)	8 (5, 11)	0 – 26	203 (80.2%)	89 (35.2%)

Table 2.3. Multivariate logistic analysis of factors associated with polypharmacy and hyperpolypharmacy

Clinical characteristic	Polypharmacy Odds ratio (95% CI), P value	Hyperpolypharmacy Odds ratio (95% CI), P value
Age group		
< 65 yr	Reference	Reference
≥ 65 yr	2.05 (1.09, 3.84), P = 0.026	1.67 (0.99, 2.81), P = 0.055
Sex		
Men	Reference	Reference
Women	1.43 (0.78, 2.65), P = 0.248	1.76 (1.03, 3.01), P = 0.039
Race		
Non-Caucasian	Reference	Reference
Caucasian	0.61 (0.28, 1.33), P = 0.212	1.51 (0.83, 2.75), P = 0.177
Diabetes mellitus		
No	Reference	Reference
Yes	5.11 (2.69, 9.70), P < 0.001	5.88 (3.21, 10.78), P < 0.001
Cardiovascular disease		
No	Reference	Reference
Yes	4.08 (1.70, 9.79), P = 0.002	3.13 (1.83, 5.34), P < 0.001
Hyperlipidemia		
No	Reference	Reference
Yes	3.23 (1.77, 5.88), P < 0.001	2.55 (1.27, 5.12), P = 0.008

Table 2.4. Commonly used medications according to the WHO ATC classification

Medication	Number of patients (%)
A: ALIMENTARY TRACT AND METABOLISM	
A02 Drugs for acid related disorders	
Proton pump inhibitor	130 (35.9%)
Sodium bicarbonate †	34 (9.4%)
A10 Drugs used in diabetes *	
A10A Insulins and analogues	130/209 (62.2%)
A10B Blood glucose lowering drugs, excl. insulins	
Sulfonylurea	49/209 (23.4%)
Biguanide	62/209 (29.7%)
DPP-4 inhibitor	27/209 (12.9%)
SGLT2 inhibitor	4/209 (2%)
GLP-1 receptor agonist	2/209 (1%)
A11 Vitamins	
Vitamin supplement (excluding vitamin D and analogues)	37 (10.2%)
Nutritional vitamin D	88 (24.3%)
Calcitriol	21 (5.8%)
A12 Mineral supplements	
Calcium	43 (11.9%)
Potassium	7 (1.9%)
Magnesium	32 (8.8%)
B: BLOOD AND BLOOD FORMING ORGANS	
B01 Antithrombotic agents	
Anticoagulants	25 (6.9%)
Antiplatelet agents	159 (43.9%
B03 Antianemic preparations	
Erythropoiesis stimulating agent	28 (7.7%)
C: CARDIOVASCULAR SYSTEM	
C02 Antihypertensives	
Antiadrenergic agents, centrally acting	39 (10.8%)
Alpha-adrenoreceptor antagonists	58 (16%)
Agents acting on arteriolar smooth muscle	21 (5.8%)
C03 Diuretics	

Medication	Number of patients (%)
Thiazides and loop diuretics	146 (40.3%)
Spironolactone	21 (5.8%)
C07 Beta blocking agents	137 (37.9%)
C08 Calcium channel blockers	
Dihydropyridine derivatives	160 (44.2%)
Selective calcium channel blockers with direct cardiac effects	53 (14.6%)
C09 Agents acting on the renin-angiotensin system	
ACE inhibitors	146 (40.3%)
Angiotensin II receptor blockers	130 (35.9%)
C10 Lipid modifying agents	
HMG CoA reductase inhibitors	261 (72.1%)
Fibrates	21 (5.8%)
N: NERVOUS SYSTEM	
N02 Analgesics	
Opioids	29 (8%)
Other analgesics and antipyretics (e.g. paracetamol)	69 (19.1%)
N03 Antiepileptics	28 (7.7%)
N06 Psychoanaleptics (antidepressants)	55 (15.2%)
V: VARIOUS	
Sodium or Calcium polystyrene sulfonate	16 (4.4%)

* The proportion of glucose-lowering medication is calculated among 209 patients with diabetes mellitus.

† Although sodium bicarbonate is classified as an antacid according to the ATC classification system, it is likely to be used for the correction of metabolic acidosis in patients with CKD.

Chapter 3. BENEFITS AND HARMS OF DUAL ANTIPLATELET THERAPY IN CHRONIC KIDNEY DISEASE: A SYSTEMATIC REVIEW AND ANALYSIS OF RANDOMISED CONTROLLED TRIALS

3.1 Abstract

Background: Despite the high burden of cardiovascular disease in chronic kidney disease (CKD), the effects of dual antiplatelet therapy in this population are uncertain.

Objectives: The aim of this systematic review was to study the benefits and harms of dual antiplatelet therapy in CKD.

Methods: Medline, Embase and Cochrane databases were searched for randomized controlled trials with ≥ 3 months follow-up in patients with CKD stages 3 to 5 or proteinuria that reported efficacy and/or bleeding outcomes. Treatment effects were summarized using random-effects analysis.

Results: Fifteen trials comparing $P2Y_{12}$ inhibitor-based dual therapy with aspirin monotherapy or no study medication, $P2Y_{12}$ inhibitor-based monotherapy or dual therapy, and four trials evaluating dipyridamole-based dual therapy were included. All but 3 trials excluded participants with dialysis-dependent kidney failure. Compared with aspirin monotherapy or no study medication, $P2Y_{12}$ inhibitor-based dual antiplatelet therapy significantly reduced the risks of major adverse cardiovascular events (RR 0.89; 95% CI 0.81, 0.98), myocardial infarction (RR 0.75; 95% CI 0.59, 0.91) and stroke (RR 0.73; 95% CI 0.52, 0.95), but increased the risk of major bleeding (RR 1.60; 95% CI 1.19, 2.01). There were no differences in the risks of major adverse cardiovascular events (RR 0.86; 95% CI 0.61, 1.11) and major bleeding (RR 1.19; 95% CI 0.82, 1.57) between clopidogrel-based and ticagrelor- or prasugrel-based dual antiplatelet therapies.

Conclusions: Dual antiplatelet therapy improved cardiovascular outcomes in patients with early stages of CKD. However, there is insufficient evidence to conclude whether patients with advanced stages of CKD and kidney failure derive benefit from dual antiplatelet therapy.

3.2 Introduction

Chronic kidney disease (CKD) is a major public health problem affecting approximately 15% of the US adult population or 37 million adults (1). More than 500,000 people are currently receiving dialysis for kidney failure (2). Compared with the general population, people with CKD are at a greater risk of cardiovascular events and associated mortality (3,4). The risk of major adverse cardiovascular events (MACE) increases with decreasing estimated glomerular filtration rate (eGFR) (3,5). The presence of CKD is one of the most potent known risk factors for cardiovascular disease with a cardiovascular cause accounting for up to 50% of all deaths in patients with CKD stages 4-5 and 60% of deaths in patients with kidney failure receiving dialysis (6). Individuals with CKD are more likely to die, primarily due to cardiovascular disease, than survive to the point of requiring dialysis (7,8). The excess cardiovascular disease burden is likely to be partly due to the high prevalence of traditional cardiovascular risk factors, such as hypertension, hyperlipidaemia, and diabetes (9,10). In addition, non-traditional risk factors such as chronic inflammation, oxidative stress, medial arterial calcification, bone mineral disorder and hypercoagulability may also contribute to the elevated cardiovascular risk (10,11).

Dual antiplatelet therapy is a core intervention in the secondary prevention of cardiovascular events in patients with acute coronary syndrome and those undergoing coronary artery stenting (12-14). However, patients with advanced stages of CKD and kidney failure are less likely to receive established cardiovascular interventions, including clopidogrel (15). The low rates of antiplatelet therapy use in CKD may be due to the increased risk of bleeding (16). The risk of major bleeding increases linearly with worsening eGFR and albuminuria. This risk is aggravated further with the incremental use of antithrombotic agents (17). The exclusion of patients with CKD from nearly 60% of trials evaluating antiplatelet therapy has contributed to uncertainty about the role of antiplatelet therapy in CKD (18). This systematic review aimed to evaluate the benefits and harms of dual antiplatelet therapy on clinical endpoints in patients with CKD stages 3 to 5, including those on dialysis.

3.3 Methods

The systematic review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (19). The protocol of this systematic review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO).[1]

Search Strategy, study selection, and data extraction

Study eligibility requirements were: (i) randomized controlled trials; (ii) at least 3 months follow-up post randomization; (iii) inclusion of people with CKD (creatinine clearance [CrCl] <60 mL/min or eGFR <60 mL/min/1.73m^2, or dialysis-dependent kidney failure; (iv) comparison of dual antiplatelet therapy with placebo, no study medication, aspirin monotherapy, or another dual antiplatelet therapy; and (v) reported efficacy and/or bleeding outcomes. Trials evaluating both $P2Y_{12}$ inhibitor- and dipyridamole-based dual antiplatelet therapies were eligible for inclusion. Trials evaluating dual antiplatelet therapy in combination with anticoagulant agent were excluded. Relevant studies were identified by searching MEDLINE (inception to October 2020), EMBASE (inception to October 2020), and the Cochrane Central Register of Controlled Trials (November 2020) databases with English language restriction (see Table A3.1 for complete search strategy). If multiple secondary publications of the same trial were identified, the publication with the most complete data was used and additional data from secondary sources were extracted. Many of the identified RCTs had limited published CKD population data obtained via post hoc analyses. Therefore, the principal investigator from each study was contacted regarding the provision of individual-patient data or further information on relevant unreported outcomes. In addition, four potentially eligible RCTs were contacted to ascertain if further data would allow inclusion in this

[1] The protocol can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=79721

systematic review (20-23). However, in all cases the authors were not able to be contacted, did not respond, or no longer had access to the relevant data.

The following data were extracted using a standardized form: study design, patient demographic details, indication for antiplatelet therapy, dose of drug, follow-up duration, outcome events, and bleeding events. The methodological quality of each study included was assessed using the risk of bias assessment tool developed by the Cochrane Bias Methods Group (24). Data extraction was carried out independently by two authors (LPC and MT). Disagreements were resolved via consultation with two other authors (SVB and MJ).

Outcomes Assessed

The outcomes of this systematic review were MACE (a composite outcome of cardiovascular or all-cause death, non-fatal myocardial infarction, or stroke), cardiovascular death, all-cause death, myocardial infarction, stroke, loss of vascular dialysis access patency, and major or non-major bleeding. Subgroup analysis was conducted according to $P2Y_{12}$ inhibitor- or dipyridamole-based dual antiplatelet therapy, CKD stage (dialysis-dependent kidney failure or non-dialysis CKD), and indication for dual antiplatelet therapy.

Statistical analysis

Results were expressed as risk ratios (RR) with 95% confidence intervals (CI). The DerSimonian and Laird method were used to obtain summary estimates by the random effects model (25). If data on the number of events and participants were not reported, generic inverse variance meta-analysis was performed by calculating log hazard ratio and its standard error from the reported hazard ratio and respective CI. Statistical heterogeneity across studies was estimated using the I^2 test. I^2 values of 0% to 40%, 30% to 60%, 50% to 90%, and 75% to 100% were considered to correspond to low, moderate, substantial and considerable levels of heterogeneity respectively (26). Statistical analyses were performed using Stata/MP, version 16.1 (StataCorp College Station, Texas).

Certainty in the evidence was summarised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, based on the following domains: within-study risk of bias, indirectness of evidence, unexplained heterogeneity or inconsistency of results, and imprecision of results (27). Disagreements were resolved via consultation with 2 other authors (SVB and MJ). Because all meta-analyses involved fewer than 10 trials, small-study effects (publication bias) were not assessed and publication bias was not included in ratings of certainty of evidence (28).

3.4 Results

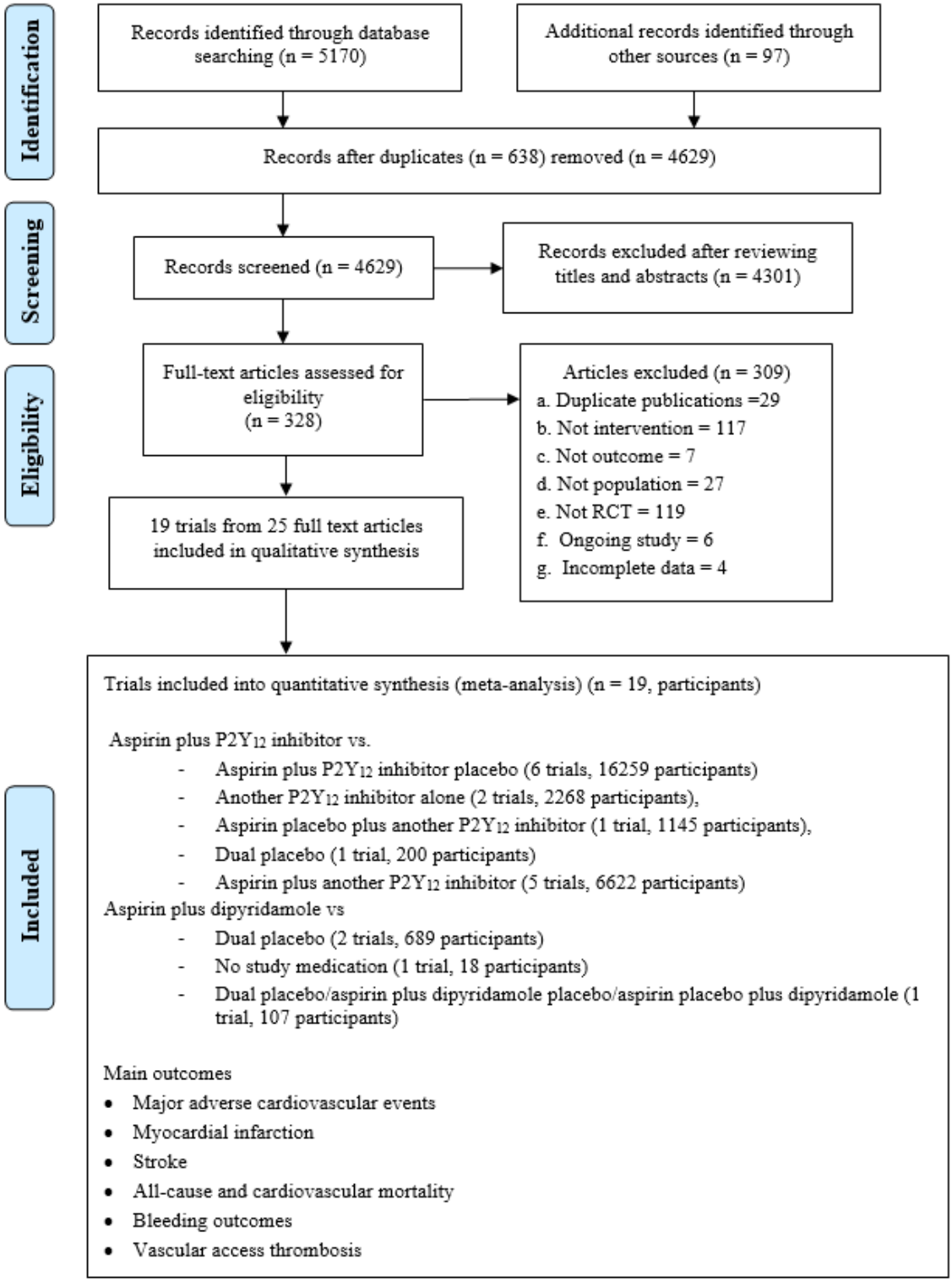
Selection and Description of Studies

Nineteen trials involving 27,308 participants with CKD (median sample size 649 [range 16 to 4,849], median follow-up 12 [range 3 to 40] months) evaluating dual antiplatelet therapy were included in the systematic review (Figure 3.1). Details of included trials are described in Table 3.1. Of these trials, only three included 956 participants with CKD stage 5, including those with dialysis-dependent kidney failure (median sample size 200 [range 107 to 649], median follow up 18 [range 10.5 to 23.5] months) evaluating dual versus monotherapy or no antiplatelet therapy for the maintenance of dialysis access patency (29-31). Of the remaining 16 trials, 2 trials evaluated dual antiplatelet therapy for the prevention of progression of CKD in 58 participants with proteinuric kidney disease (median sample size 29 [range 18 to 40], median follow up 24 [range 12 to 36] months) (32,33), and 14 trials evaluated dual antiplatelet therapy for the prevention of cardiovascular events in 26,294 participants with coronary artery disease or stroke (median sample size 1,501 [range 16 to 4,849], median follow up 12 [range 3 to 40] months) with non-dialysis dependent CKD (defined as CrCl <60 mL/min or eGFR <60 mL/min/1.73 m^2) (34-54). Data from these 14 cardiovascular outcome trials involving participants with coronary artery disease or stroke were obtained exclusively from CKD subgroup analyses of large cardiovascular outcome trials. 8 trials included 12,654 participants (median sample size 1,317.5 [range 16 to 4,087], median follow up 12 [range 12 to 24] months)

with symptomatic coronary artery disease requiring percutaneous coronary intervention (34-45), 5 trials included 13,286 participants (median sample size 2,009 [range 367 to 4,849], median follow up 30 [range 12 to 40] months) with acute or stable coronary artery disease for medical management (46-52),and 1 trial included 354 participants (follow up 3 months) with stroke (53,54). 1 trial including 411 participants (37,38), and another including 97 participants (45), assessed dual antiplatelet therapy versus dual antiplatelet therapy for the first 1 and 3 months respectively, after which the comparison arm changed to monotherapy for the remainder of the total 12 months of treatment. These two trials were considered to be dual antiplatelet therapy versus monotherapy for the purposes of analysis in this review.

Dual antiplatelet therapy comprising of aspirin and a $P2Y_{12}$ inhibitor was compared with aspirin plus $P2Y_{12}$ inhibitor placebo (6 trials, 16,259 participants) (34,35,37,38,46,47,49-51,53,54), another $P2Y_{12}$ inhibitor alone (2 trials, 2,268 participants) (41,45), aspirin placebo plus another $P2Y_{12}$ inhibitor (1 trial, 1,145 participants) (44), dual placebo (1 trial, 200 participants) (30), and aspirin plus another $P2Y_{12}$ inhibitor (5 trials, 6,622 participants) (36,39,40,42,43,48,52). Dual antiplatelet therapy comprising of aspirin and dipyridamole was compared with dual placebo (2 trials, 689 participants) (31,32), and no study medication (1 trials, 18 participants) (33), and one trial involving 107 participants had three control interventions including dual placebo, aspirin plus dipyridamole placebo and aspirin placebo plus dipyridamole (29).

Figure 3.1. PRISMA Flow Diagram Showing Selection of Studies



Nineteen trials were included in the systematic review. Of these 3 trials included participants with dialysis-dependent kidney failure and 16 trials included participants with non-dialysis CKD.
CKD = chronic kidney disease; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses

Risk of bias

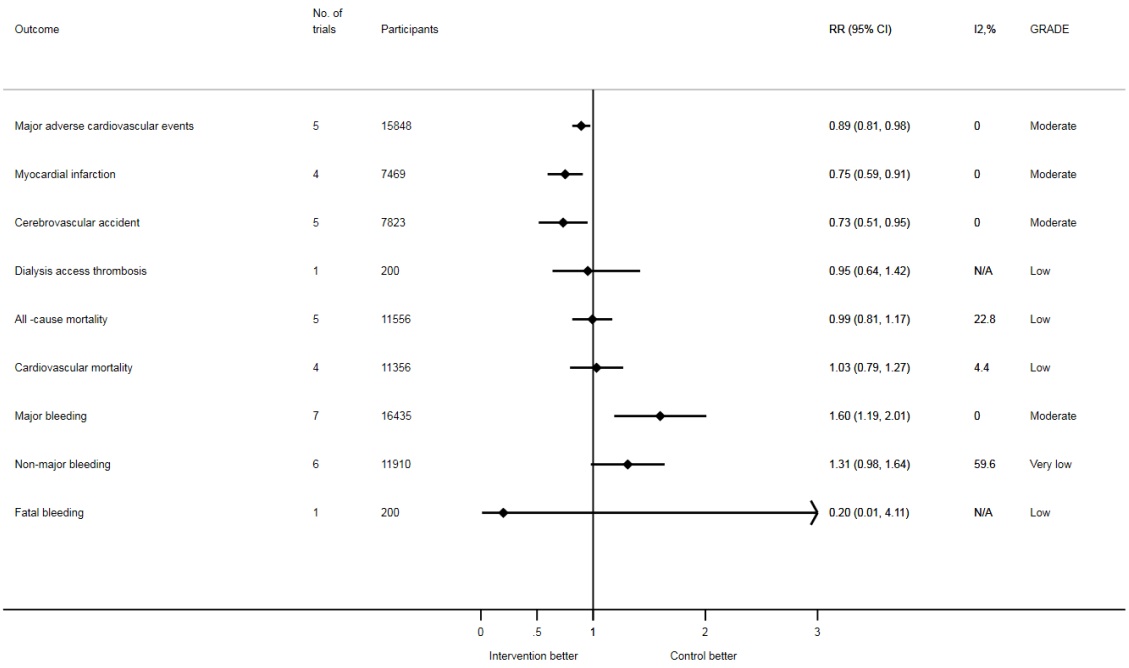
Random sequence generation and allocation concealment were reported using low risk methods in 11 (58%) and 15 (79%) trials, respectively (Figure A3.1, A3.2). Seventeen (89%) trials reported blinding of participants and investigators to the allocated intervention, while blinding of outcome assessment was reported in 12 (63%) trials. Twelve (63%) and 4 (21%) trials were assessed to have low risk for incomplete outcome data and other bias, respectively.

Effects of interventions

$P2Y_{12}$ inhibitor-based dual antiplatelet therapy versus aspirin monotherapy or no study medication

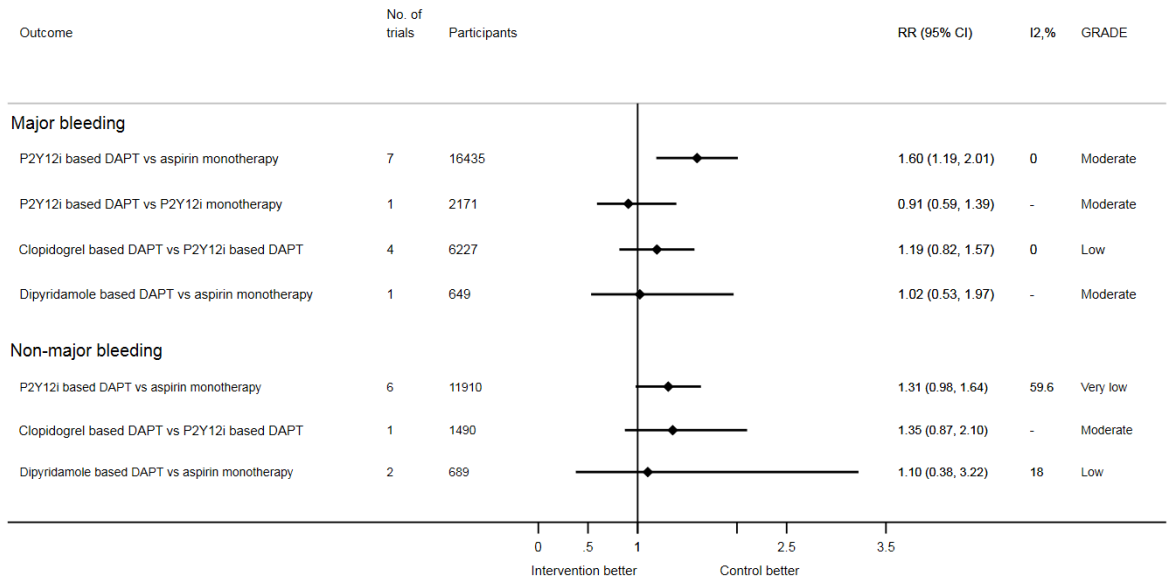
Compared with aspirin monotherapy or no study medication, $P2Y_{12}$ inhibitor-based dual antiplatelet therapy (Figure 3.2, Table A3.2) significantly reduced the risks of major adverse cardiovascular events (5 trials, 15,848 participants; RR 0.89; 95% CI 0.81, 0.98, I^2 = 0%, moderate certainty evidence; Figure A3.3), myocardial infarction (4 trials, 7,469 participants; RR 0.75; 95% CI 0.59, 0.91, I^2 = 0%, moderate certainty evidence; Figure A3.4) and stroke (5 trials, 7,823 participants; RR 0.73, 95% CI 0.52, 0.95, I^2 = 0%, moderate certainty evidence; Figure A3.5), but had uncertain effect for cardiovascular mortality (4 trials, 11,356 participants; RR 1.03, 95% CI 0.79, 1.27, I^2 = 4.4%, low certainty evidence) and all-cause mortality (5 trials, 11,556 participants; RR 0.99, 95% CI 0.81, 1.17, I^2 = 22.8%, low certainty evidence). $P2Y_{12}$ inhibitor-based dual antiplatelet therapy increased the risk of major bleeding (7 trials, 16,435 participants; RR 1.60, 95% CI 1.19, 2.01; I^2 = 0%, moderate certainty evidence; Figure 3.3 and Figure A3.6), however, there was no statistically significant difference in the risk of non-major bleeding between the two groups (6 trials, 11,910 participants; RR 1.31, 95% Cl 0.98, 1.64; I^2 = 59.6%, very low certainty evidence).

Figure 3.2. Treatment effects in trials comparing $P2Y_{12}$ inhibitor-based dual antiplatelet therapy with aspirin monotherapy or no study medication



Compared with aspirin monotherapy or no study medication, $P2Y_{12}$ inhibitor-based dual antiplatelet therapy significantly reduced the risks of major adverse cardiovascular events, myocardial infarction and stroke; but had uncertain effect for cardiovascular mortality and all-cause mortality; and increased the risk of major bleeding.

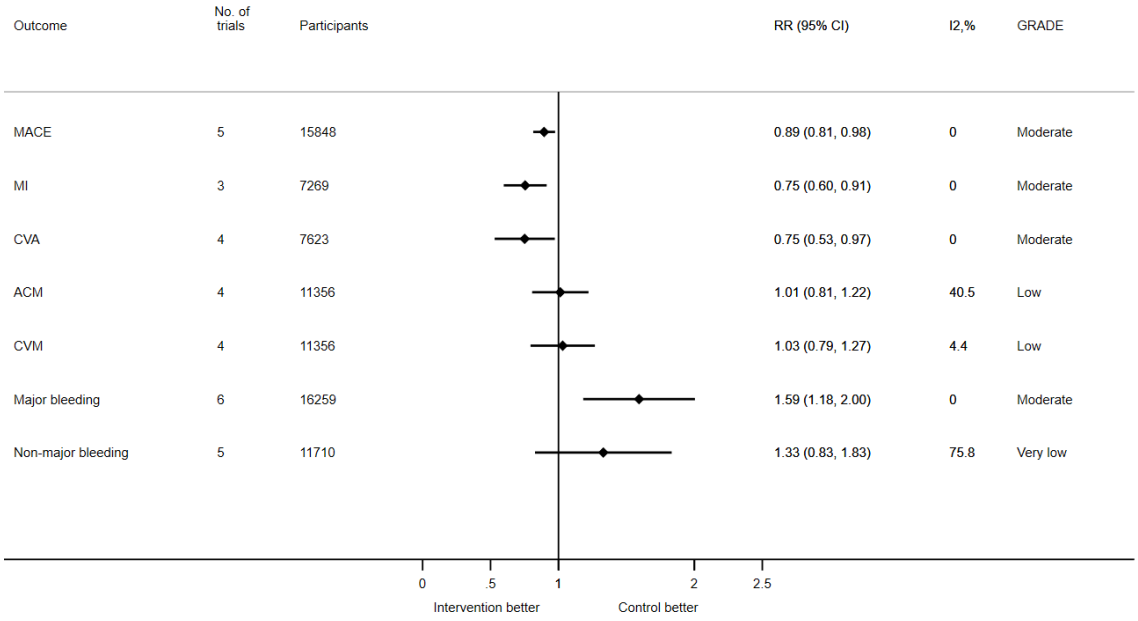
Figure 3.3 Treatment effects of dual antiplatelet therapy on bleeding outcomes



Summary of treatment effects of dual antiplatelet therapy on bleeding outcomes according to different comparisons.

Only 1 trial included patients with dialysis-dependent kidney failure, and the overall results were not significantly changed by the exclusion of this trial (Figure 3.4). In this trial (200 participants), $P2Y_{12}$ inhibitor-based dual antiplatelet therapy did not reduce the risk of loss of dialysis access patency (RR 0.95, 95% CI 0.64, 1.42), but increased the risks of major bleeding (RR 3.69, 95% CI 0.80, 16.96) and non-major bleeding (RR 1.51, 95% CI 1.11, 2.06).

Figure 3.4 Summary of treatment effects of $P2Y_{12}$ inhibitor-based dual antiplatelet therapy in trials involving participants with non-dialysis CKD

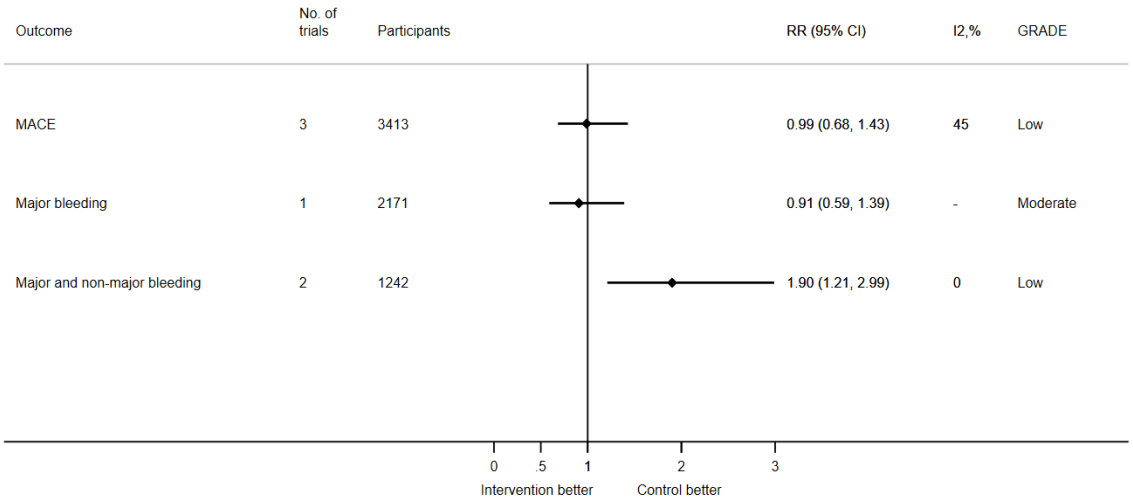


Significant outcomes were unchanged by the exclusion of the 1 trial including patients with dialysis-dependent kidney failure

$P2Y_{12}$ inhibitor-based dual antiplatelet therapy versus $P2Y_{12}$ inhibitor-based monotherapy

Compared with $P2Y_{12}$ inhibitor-based monotherapy, $P2Y_{12}$ inhibitor-based dual antiplatelet therapy (Figure 3.5) had uncertain effects on major adverse cardiovascular events (3 trials, 3,413 participants; RR 0.99, 95% CI 0.68, 1.429; $I^2 = 45\%$, low certainty evidence) and major bleeding (1 trial, 2,171 participants, RR 0. 91, 95% CI 0.59, 1.39, moderate certainty evidence); and increased the risk of combined major and non-major bleeding (2 trials, 1,242 participants, RR 1.90, 95% CI 1.21, 2.99; $I^2 = 0\%$, low certainty evidence). None of these trials included patients with dialysis-dependent kidney failure.

Figure 3.5 Summary of treatment effects of $P2Y_{12}$ inhibitor-based dual antiplatelet therapy versus $P2Y_{12}$ inhibitor monotherapy

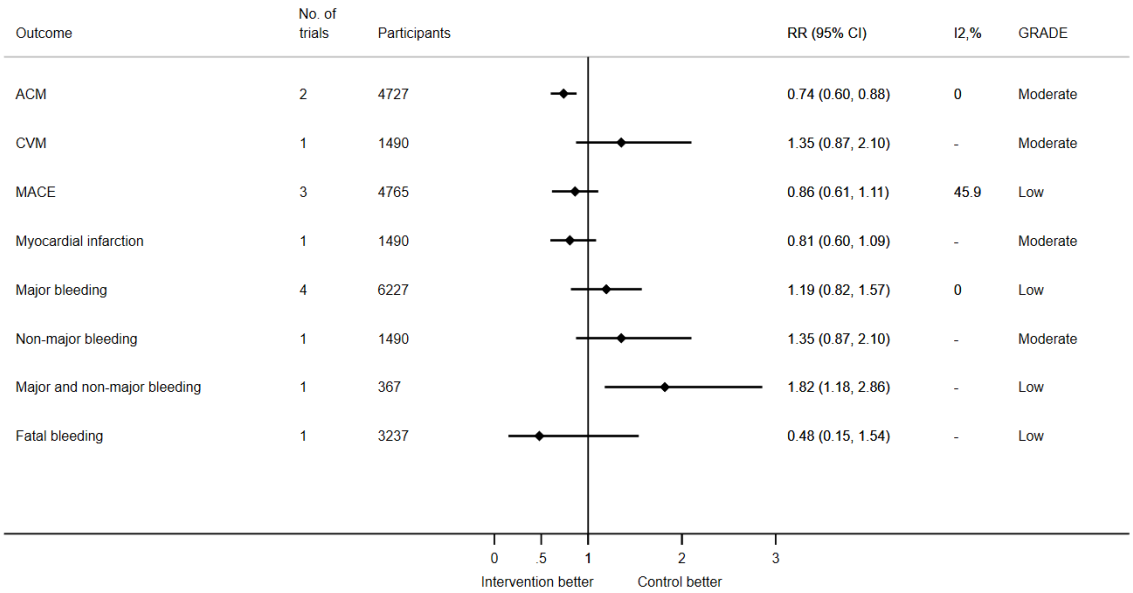


Compared with P2Y12 inhibitor-based monotherapy, P2Y12 inhibitor-based dual antiplatelet therapy had uncertain effects on major adverse cardiovascular events and major bleeding

Clopidogrel-based dual antiplatelet therapy versus P2Y12 inhibitor-based dual antiplatelet therapy

Compared with clopidogrel-based dual antiplatelet therapy, ticagrelor- or prasugrel-based dual antiplatelet therapy (Figure 3.6) had uncertain effects on major adverse cardiovascular events (3 trials, 4,765 participants; RR 0.86, 95% CI 0.61, 1.11; $I^2 = 45.9\%$, low certainty evidence) and major bleeding (4 trials, 6,227 participants; RR 1.19, 95%CI 0.82, 1.57; $I^2 = 0\%$, low certainty evidence); but decreased the risks of all-cause mortality (2 trials, 4,727 participants RR 0.74, 95% CI 0.60, 0.88; $I^2 = 0\%$, moderate certainty evidence). Data on myocardial infarction and cardiovascular mortality were reported in 1 trial.

Figure 3.6 Summary of treatment effects of clopidogrel-based dual antiplatelet therapy versus P2Y12 inhibitor-based dual antiplatelet therapy

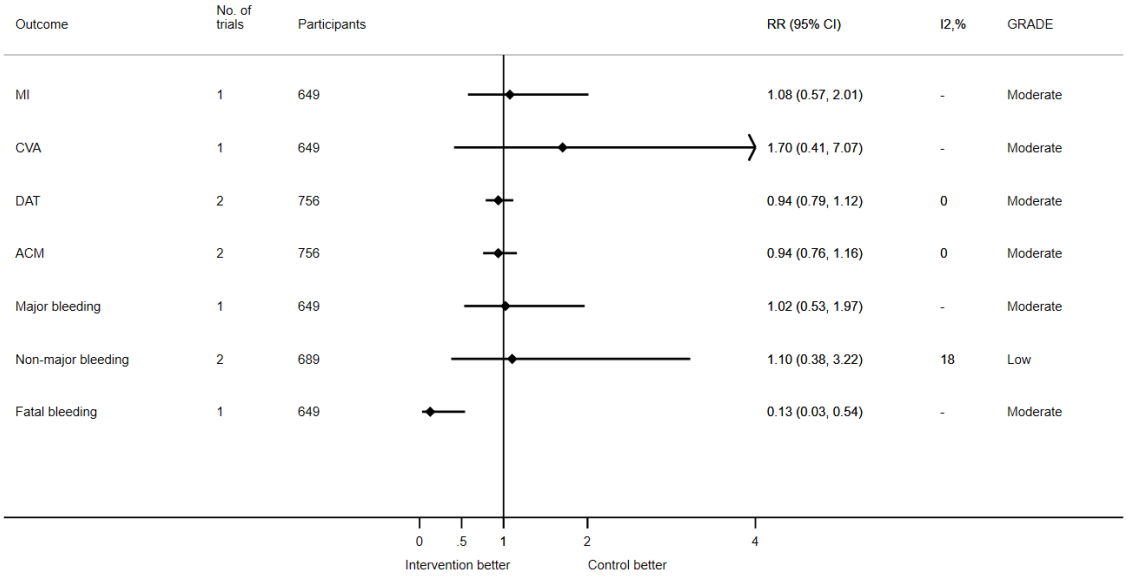


Analysis of clopidogrel-based dual antiplatelet therapy versus P2Y12 inhibitor-based dual antiplatelet therapy showed uncertain effects on major adverse cardiovascular events and major bleeding but decreased risk of all-cause mortality

Dipyridamole-based dual antiplatelet therapy versus monotherapy or no antiplatelet therapy

Compared with monotherapy or no antiplatelet therapy, dipyridamole-based dual antiplatelet therapy (Figure 3.7) had uncertain effects on myocardial infarction (1 trial, 649 participants; RR 1.08, 95% CI 0.58, 2.01), stroke (1 trial, 649 participants; RR 1.7, 95% CI 0.41, 7.01), all-cause mortality (2 trials, 756 participants; RR 0.94, 95% CI 0.76, 1.16; $I^2 = 0\%$), and dialysis access patency (2 trials, 756 participants; RR 0.94, 95% CI 0.79, 1.12; $I^2 = 0\%$). There were no significant differences in the risks of major bleeding (1 trial, 649 participants; RR 1.02, 95% CI 0.53, 1.97) and non-major bleeding (2 trials, 689 participants; RR 1.1, 95% CI 0.38, 3.2; $I^2 = 18\%$) between the two groups. In trials involving patients with dialysis-dependent kidney failure, there were no differences in the risks of myocardial infarction, stroke, and all-cause mortality between the two groups (Figure A3.7), and no trial reported data on cardiovascular mortality.

Figure 3.7 Summary of treatment effects of dipyridamole-based dual antiplatelet therapy



Limited available evidence for dipyridamole-based dual antiplatelet therapy showed uncertain effects on myocardial infarction, stroke, all-cause mortality, and dialysis access patency with no significant differences for bleeding risk

3.5 Discussion

This meta-analysis demonstrated that compared with aspirin monotherapy or no study medication, $P2Y_{12}$ inhibitor-based dual antiplatelet therapy was beneficial in reducing cardiovascular events in patients with non-dialysis CKD, with relative risk reductions of 11% for major adverse cardiovascular events, 25% for myocardial infarction and 27% for stroke. However, $P2Y_{12}$ inhibitor-based dual antiplatelet therapy increased the risk of major bleeding by 60% and did not modify the risks of cardiovascular and all-cause mortality. There appears to be no significant difference in the risk of major bleeding with $P2Y_{12}$ inhibitor-based dual antiplatelet therapy when compared with $P2Y_{12}$ inhibitor-based monotherapy or dual antiplatelet therapy, however, further data are required to assess the effect of this regimen on cardiovascular outcomes. Data on the effects of dipyridamole-based dual antiplatelet therapy were scant. No data were available on the effects of dual antiplatelet therapy on the prevention of cardiovascular events for patients with advanced stages of CKD, including those with dialysis-dependent kidney failure.

Cardiovascular thrombotic events constitute major causes of morbidity and mortality in patients with CKD, particularly those with kidney failure requiring dialysis. Given the greater rates of cardiovascular thrombotic events in patients with advanced CKD compared with patients with normal kidney function, the absolute risk reduction with dual antiplatelet therapy in this population may be greater. The potential benefit of dual antiplatelet therapy needs to be weighed against the risk for bleeding in this population. In a recently published prospective cohort study, the reported rates of major bleeding in patients on haemodialysis and peritoneal dialysis were 60.8 and 34.6 per 1,000 person-years, respectively (55). These rates increased to 65 and 47.4 per 1,000 person-years, respectively among patients with cardiovascular disease, and 67.3 and 56.4 per 1,000 person-years, respectively among those treated with antithrombotic treatment. Due to the increased bleeding risk, patients with advanced stages of CKD and kidney failure present a therapeutic conundrum.

Adding to the therapeutic conundrum is the limited evidence to guide optimal duration of dual antiplatelet therapy in patients with CKD. A 2019 meta-analysis of five RCTs containing 1902 patients with CKD, demonstrated that shorter DAPT duration therapy of ≤6 months was not inferior to longer DAPT therapy of 12 months in those with drug eluted stents. There was a similar incidence of the primary composite outcome of all-cause mortality, myocardial infarction, stroke, and stent thrombosis with no significant differences in major bleeding (56). However, there were few patients with CKD stage 4-5 included in the trials analysed and there was insufficient power to make definitive estimates.

This systematic review highlights the absence of evidence in patients with advanced CKD, particularly in those with dialysis-dependent kidney failure. We also found scant data on the efficacy of newer antiplatelet agents, such as ticagrelor and prasugrel.

Study strengths and limitations

The current review differs from previous reviews of antiplatelet agents in CKD by focusing on dual antiplatelet therapy, including recent data on prasugrel and ticagrelor, increasingly used in clinical practice (57,58). Other strengths were the inclusion of a large

number of participants, the robust evaluation of efficacy and bleeding outcomes, and the use of the GRADE approach to assess the body of evidence. These strengths should be weighed against the review's limitations, which were largely due to the limitations of the underlying literature. These include exclusion of patients with dialysis-dependent kidney failure, limited information on demographic characteristics of the CKD subgroup, underreporting of organ-specific bleeding data (especially gastrointestinal bleeding) and lack of individual-patient data.

In summary, this systematic review demonstrated that $P2Y_{12}$ inhibitor-based dual antiplatelet therapy was superior to aspirin monotherapy or no study medication in reducing cardiovascular events in patients with CKD but increased the risk of major bleeding. However, evidence was insufficient to recommend widespread use of dual antiplatelet therapy in patients with dialysis-dependent kidney failure. Adequately powered randomized trials are required to evaluate the benefits and harms of dual antiplatelet therapy in this patient population.

3.6 Perspectives

Competency in medical knowledge: In patients with chronic kidney disease not requiring dialysis, $P2Y_{12}$ inhibitor-based dual antiplatelet therapy reduced the risk of major adverse cardiovascular events; but increased the risk of bleeding. There are insufficient data to conclude whether patients with advanced stages of chronic kidney disease, including those needing dialysis, derive benefit from dual antiplatelet therapy. Clinicians should exercise caution before prescribing dual antiplatelet therapy in this patient population.

Translational outlook: Adequately powered trials are required to study the benefits and harms of dual antiplatelet therapy in patients with advanced stages of chronic kidney disease and cardiovascular disease.

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Table 3.1 Characteristics of Included studies

Study year	Inclusion criteria	N	Kidney function (eGFR, CrCl, or CKD stage)	Lower threshold of kidney function for exclusion	Experimental intervention	Control intervention	Follow-up (months)	MACE definition	Bleeding definition
Trials evaluating the effect of dual antiplatelet therapy on dialysis vascular access patency									
Sreedhara 1994 (25)	Kidney failure requiring new PTFE graft, or thrombectomy or revision of existing PTFE graft	107	Kidney failure	NA	Aspirin 325 mg OD plus dipyridamole 75 mg TDS	Aspirin plus dipyridamole placebo; or aspirin placebo plus dipyridamole; or double placebo	18	NA	NR
Kaufman 2003 (26)	Kidney failure requiring new PTFE graft	200	Kidney failure	NA	Aspirin 325 mg OD plus clopidogrel 75 mg OD	Double placebo	10.5	NA	§
DAC 2009 (27)	Kidney failure requiring new PTFE graft	649	Kidney failure	NA	Aspirin 25 mg BD plus dipyridamole 200 mg BD	Double placebo	23.5	NA	§
Trials evaluating the effect of dual antiplatelet therapy on progression of kidney disease									
Donadio 1984 (28)	Membranoproliferative glomerulonephritis	40	Mean mGFR 62.6 to 69.5 mL/min/1.73 m^2	Dialysis-dependent kidney failure	Aspirin 325 mg TDS plus dipyridamole 75 mg TDS	Double placebo	12	NA	NR
Zauner 1994 (29)	Membranoproliferative glomerulonephritis	18	Mean serum creatinine 1.79 mg/dL	NR	Aspirin 500 mg OD plus dipyridamole 75 mg OD	No study medication	36	NA	NR
Trials involving patients with symptomatic coronary artery disease requiring percutaneous coronary intervention									
CURE 2007 (30,31)	Non–ST-segment elevation myocardial infarction	4087	GFR <64 mL/min (lower tertile)	NR	Aspirin 325 mg OD plus clopidogrel 75 mg OD	Aspirin 75-325 mg OD plus placebo	12	CV death, MI, stroke	¶

Study year	Inclusion criteria	N	Kidney function (eGFR, CrCl, or CKD stage)	Lower threshold of kidney function for exclusion	Experimental intervention	Control intervention	Follow-up (months)	MACE definition	Bleeding definition
TRITON 2007 (32)	Acute coronary syndrome	1490	CrCl <60 mL/min	NR	Aspirin 75-162 mg OD plus prasugrel 10 mg OD	Aspirin 75-162 mg OD plus clopidogrel 75 mg OD	15	CV death, MI, stroke	TIMI
CREDO 2008 (33,34)	Symptomatic coronary artery disease	411	CrCl <60 mL/min	NR	Aspirin 81-325 mg OD plus clopidogrel 75 mg OD	Aspirin 81-325 mg OD plus clopidogrel 75 mg OD for 28 days, followed by Aspirin 81-325mg OD plus placebo	12	All-cause death, MI, stroke	TIMI
PLATO 2010 (35,36)	ST-Elevation or Non–ST-segment Myocardial Infarction	3237	CrCl <60 mL/min	Dialysis-dependent kidney failure	Aspirin 325 mg OD plus ticagrelor 90 mg BD	Aspirin 75-325 mg OD plus clopidogrel 75 mg OD	12	CV death, MI, stroke	TIMI
GLOBAL LEADER 2018 (37)	Acute coronary syndrome or coronary artery disease	2171	eGFR <60 mL/min/1.73 m^2	NR	Aspirin 75-150 mg OD plus ticagrelor 90 mg BD or clopidogrel 75 mg OD	Ticagrelor 90 mg BD	24	All-cause death, MI	BARC
PRAGUE-18 2018 (38,39)	Acute coronary syndrome	16	NR	NR	Aspirin 100 mg OD plus ticagrelor 90 mg BD	Aspirin 100 mg OD plus prasugrel 5-10 OD	12	CV death, MI, stroke	TIMI and BARC
TWILIGHT 2019 (40)	Acute coronary syndrome or coronary artery disease	1145	eGFR <60 mL/min/1.73 m^2	Dialysis-dependent kidney failure	Aspirin 81-100 mg OD plus ticagrelor 90 mg BD	Placebo plus ticagrelor 90 mg BD	12	All-cause death, MI, stroke	BARC
SMART-CHOICE 2019 (41)	Acute coronary syndrome or coronary artery disease	97	eGFR <60 mL/min/1.73 m^2	NR	Aspirin 100 mg OD plus ticagrelor 90 mg BD or	Aspirin plus Ticagrelor 90 mg BD or	12	All-cause death, MI, stroke	BARC

Study year	Inclusion criteria	N	Kidney function (eGFR, CrCl, or CKD stage)	Lower threshold of kidney function for exclusion	Experimental intervention	Control intervention	Follow-up (months)	MACE definition	Bleeding definition
					clopidogrel 75 mg OD or prasugrel 10 mg OD	clopidogrel 75 mg OD or prasugrel 10 mg OD for 3 months, followed by $P2Y_{12}$ inhibitor alone			
Trials involving patients with acute coronary syndrome or stable coronary artery disease for medical management									
CHARISMA 2009 (42,43)	Established CV disease or multiple CV risk factors	2009	Diabetes and microalbuminuria ≥30 µg/mL, kidney function not recorded.	NR	Aspirin 75-162 mg OD plus clopidogrel 75 mg OD	Aspirin 75-162 mg OD plus placebo	28	CV death, MI, stroke	GUSTO
TRILOGY 2012 (44)	Unstable angina or Non–ST-segment Myocardial Infarction and at least one CV risk factor	1512	CrCl <60 mL/min	Dialysis-dependent kidney failure	Aspirin 75-162 mg OD plus prasugrel 5-10 mg OD	Aspirin 75-162 mg OD plus clopidogrel 75 mg OD	30	CV death, MI, stroke	TIMI
PEGASUS 2016 (45,46)	Prior myocardial infarction and at least 1 CV risk factor including CrCl <60 mL/min	4849	eGFR <60 mL/min/1.73 m^2	Dialysis-dependent kidney failure	Aspirin 75-150 mg OD plus ticagrelor 60-90 mg BD	Aspirin 75-150 mg OD plus placebo	36	CV death, MI, stroke	TIMI
THEMIS 2019 (47)	Stable coronary artery disease and type 2 diabetes	4549	eGFR <60 mL/min/1.73 m^2	Dialysis-dependent kidney failure	Aspirin 75-150 mg OD plus ticagrelor 60-90 mg BD	Aspirin 75-150 mg OD plus placebo	40	CV death, MI, stroke	TIMI
POPular AGE 2020 (48)	Age ≥70 yr, non-ST-elevation acute coronary syndrome	367	eGFR <60 mL/min/1.73 m^2	Dialysis-dependent kidney failure	Aspirin plus ticagrelor 90 mg BD or prasugrel 10 mg OD	Aspirin plus clopidogrel 75 mg OD	12	NA	PLATO
Trials evaluating the effect of dual antiplatelet therapy on recurrent stroke									

Study year	Inclusion criteria	N	Kidney function (eGFR, CrCl, or CKD stage)	Lower threshold of kidney function for exclusion	Experimental intervention	Control intervention	Follow-up (months)	MACE definition	Bleeding definition
CHANCE 2016 (49)	Acute ischemic stroke or high-risk transient ischemic attack	354	eGFR <60 mL/min/1.73 m^2	Serum creatinine >1.5 times of upper normal range	Aspirin plus clopidogrel 75 mg OD	Aspirin plus placebo	3	CV death, MI, stroke	GUSTO

BARC: Bleeding Academic Research Consortium; CV: cardiovascular; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; GUSTO: Global Use of Strategies to Open Occluded Arteries; MACE: major adverse cardiovascular event; mGFR: measured glomerular filtration rate; MI: myocardial infarction; NA: not applicable; NR: not reported; PLATO: Platelet Inhibitionand Patient Outcomes; PTFE: polytetrafluoro-ethylene; TIMI: Thrombolysis in Myocardial Infarction

¶ Major bleeding was defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of blood.

§ Major bleeding was defined as confirmed retroperitoneal, intra-articular, intraocular, or cerebral hemorrhage or any bleeding that resulted in a 2 g/dl decrease in hemoglobin concentration and required hospitalization or transfusion.

Chapter 4. SUMMARY AND CONCLUSION

The research studies presented in this thesis were aimed at delineating the burden of polypharmacy and the evidence for medical interventions in the treatment of the cardiovascular comorbidities and associated morbidity and mortality in CKD. Key findings of these studies, their strengths and limitations, and their implications for patient care and future research are discussed in this chapter.

4.1 Polypharmacy in Patients with Chronic Kidney Disease at High Risk of CKD Progression

What was known before: Polypharmacy is a growing problem in patients with CKD in the context of multimorbidity and a lack of evidence based prescribing guidelines

Key findings: The prevalence of polypharmacy and hyperpolypharmacy were 77.6% (281 patients of 362) and 34.3% (124 patients of 362) respectively, and were associated with age, diabetes, cardiovascular disease, and hyperlipidaemia but not CKD stage. Glucose and blood pressure lowering medications were the most prescribed.

Strengths: (i) Inclusion of systematically collected data from an RCT; (ii) use of the Anatomical Therapeutic Chemical classification system.

Limitations: (i) Lack of inclusion of CKD stage 5; (ii) selection for high progression criterion limits generalisability to the wider CKD population; (iii) lack of data on the pill count; and (iv) no evaluation of medication appropriateness.

Implications for patient care: Clinicians should consider the medication burden of their patients carefully and deprescribe where possible.

Implications for future clinical research: The utility of multidisciplinary medication audits with inclusion of a clinical pharmacist and performing community medication reviews should be an area of further research.

4.2 Benefits and harms of dual antiplatelet therapy in chronic kidney disease: A systematic review and meta-analysis of randomised controlled trials

What was known before: Cardiovascular disease is highly prevalent in patients with CKD and is a major cause of morbidity and mortality. However, the role of dual antiplatelet therapy in reducing major cardiovascular events or death had not been systematically studied.

Key findings: For early stage CKD, dual antiplatelet therapy with $P2Y_{12}$ inhibitors improved cardiovascular outcomes but increased the risk of major bleeding. The effect was uncertain for cardiovascular or all-cause mortality. There was insufficient evidence to draw any conclusions regarding those patients with advanced CKD.

Strengths: (i) Comprehensive evaluation of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system; (ii) rigorous risk of bias assessment; and (iii) inclusion of only RCTs.

Limitations: (i) Lack of patient level data; (ii) inability to formally assess publication bias in some analyses due to the small number of trials; and (iii) reliance on post hoc or small CKD subgroup data.

Implications for patient care: There is insufficient evidence to currently recommend dual antiplatelet therapy in patients with advanced CKD, including those on dialysis.

Implications for future clinical research: Adequately powered randomised trials aimed at patients with advanced CKD are needed.

4.3 Future directions for clinical practice

Currently therapeutic interventions for clinical outcomes in patients with CKD are limited to a small number of agents with modest benefit. From a clinician's point of view, this research has confirmed that dual antiplatelet therapy can be applied to early stages of CKD for the improvement of cardiovascular outcomes in comparison to monotherapy. However, recommendations for one P2Y12 inhibitor over another are not possible in patients with advanced CKD, particularly the dialysis population, due to lack of evidence.

The high prevalence of polypharmacy has been confirmed within at-risk CKD populations. Although the findings of these papers have not added any effective intervention to improve clinical outcomes, they nevertheless caution clinicians against the use of unproven interventions given the potential for harm. Clinicians should recognise that current definitions of polypharmacy are arbitrary and need to be re-evaluated. As such, assessment solely based on an arbitrarily defined high number of medications being prescribed to patients with CKDfails to appreciate that the appropriate number of medications varies according to clinical needs. Hence, omitting medications for the sake of reducing polypharmacy per se, could inadvertently have a negative impact on clinical outcomes.

4.4 Future directions for clinical research

Challenges faced by those conducting clinical research in the CKD population have been exemplified by the systematic review. Data collection was problematic given a significant proportion of the available data was obtained from post hoc studies with limited information on CKD specific outcomes and baseline GFRs. CKD focused studies were small in both number and size, with frequent exclusion of advanced stage CKD and patients with dialysis-dependent kidney failure -- the highest risk population. Both of these factors hamper the creation of appropriate guidelines, as well as limit the generalisability of any results to patients with advanced stage CKD. Thus, larger trials are needed with inclusion of a broader spectrum of patients with CKD, with design allowing for evaluation of the benefits and harms of pharmacological interventions in people with CKD.

Polypharmacy will continue to be a growing problem in an increasingly aged and comorbidpopulation with CKD. Considering the association with negative clinical outcomes, further research on medication appropriateness, deprescribing and prescribing omitted appropriate treatments is needed. However, there are multiple challenges separate from the need to bolster the limited evidence for patients with CKD. These are the fragmentation of care across multiple specialists, and the fact that quantifying polypharmacy fails to consider specific

patient preferences or areas where guidelines may not be applicable. Therefore, investigation into whether medication reviews could be delivered through primary care physicians and community pharmacies is required given their increasingly important role in organising care for patients with chronic diseases. Given the time intensive nature of medication reconciliations, further studies in adverse drug events associated with polypharmacy would allow for identification of those patients with CKD most at risk.

Several additional strategies require further investigation to optimise outcomes in patients with CKD regarding the correct type, dose duration and combination of antiplatelet agents. Given the complex vascular milieu and variable platelet reactivity in patients with CKD, an individualised platelet function testing approach could be helpful. This may guide agent choice and dual antiplatelet therapy de-escalation schedules that could reduce bleeding without increasing the risk for ischaemic complications. In addition, risk scores have been established in the general population to help guide decision making regarding thrombotic versus bleeding risk. Finally, it is unknown whether longer duration antiplatelet therapy is protective in patients with CKD due to their higher thrombotic risk, or whether it merely increases bleeding complications in this population. The utility of these approaches warrants specific investigation in patients with CKD with dedicated studies and analyses.

4.5 Conclusion

This research demonstrated there is a paucity of high quality RCT-level evidence for the use of dual antiplatelet therapy in patients with advanced CKD. This is compounded by the well-established burden of polypharmacy in a population at high risk for complications. Adequately powered, head-to-head, randomised trials aimed at patients with advanced CKD are urgently needed.

Appendix

Figure A3.1 Risk of bias assessment of the included studies

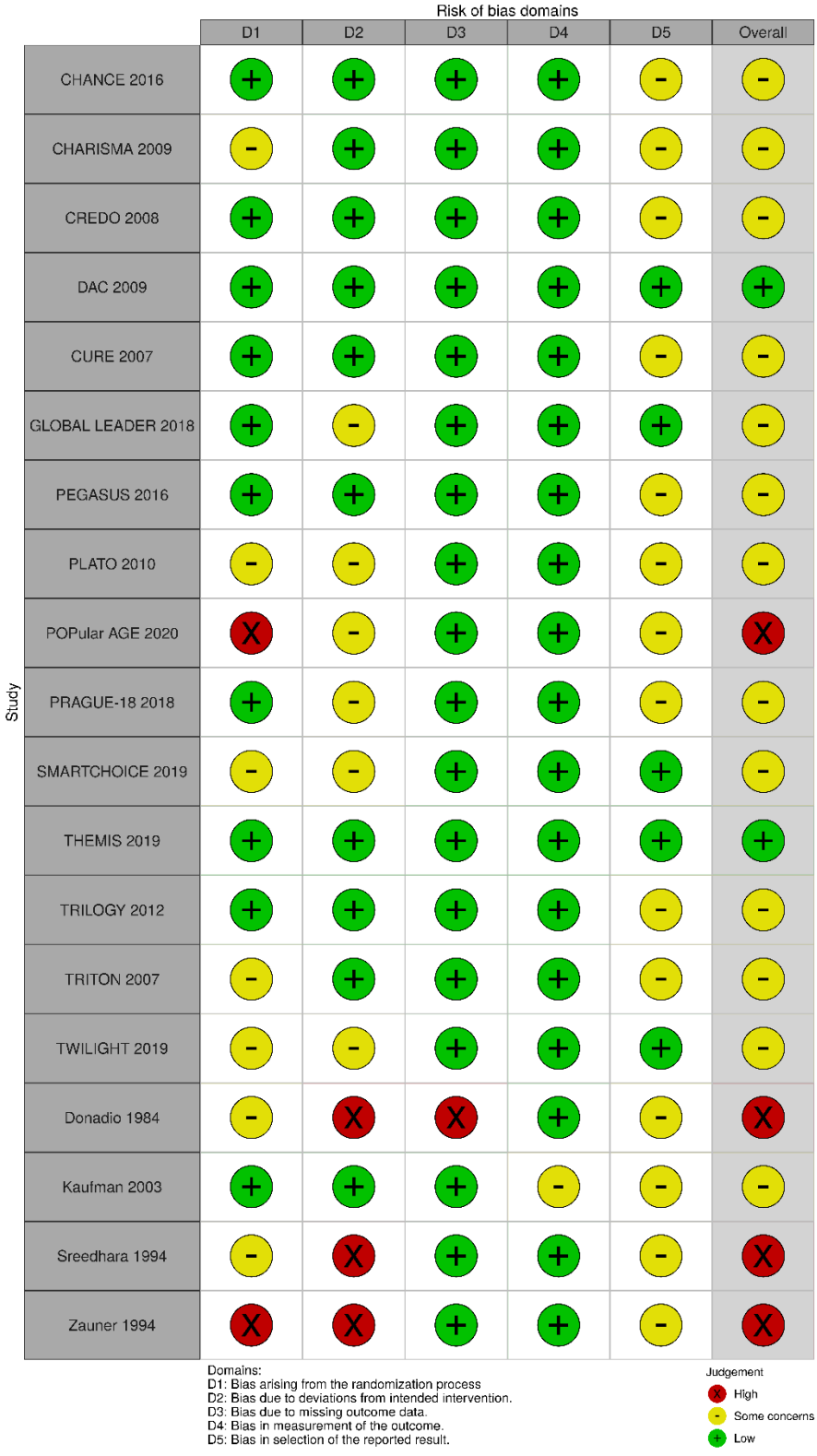

Figure A3.2 Summary of risk of bias assessment

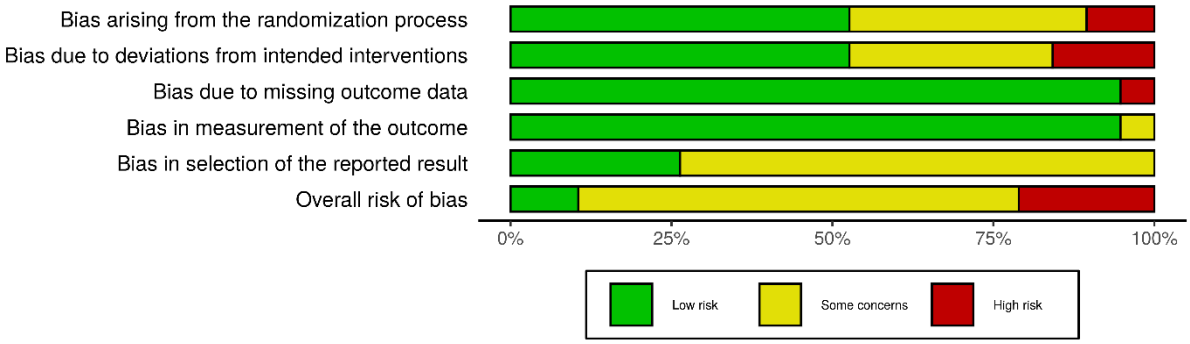

Figure A3.3. Relative effects of $P2Y_{12}$ inhibitor-based dual antiplatelet therapy vs aspirin monotherapy or no study medication on major adverse cardiovascular events

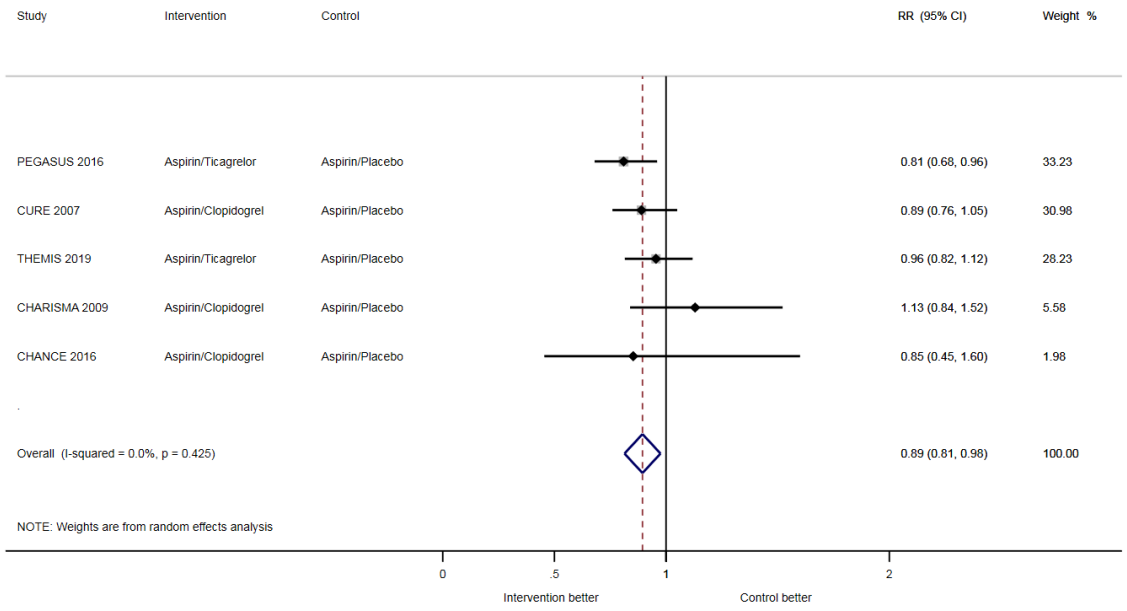

Figure A3.4 Relative effects of $P2Y_{12}$ inhibitor-based dual antiplatelet therapy vs aspirin monotherapy or no study medication on myocardial infarction

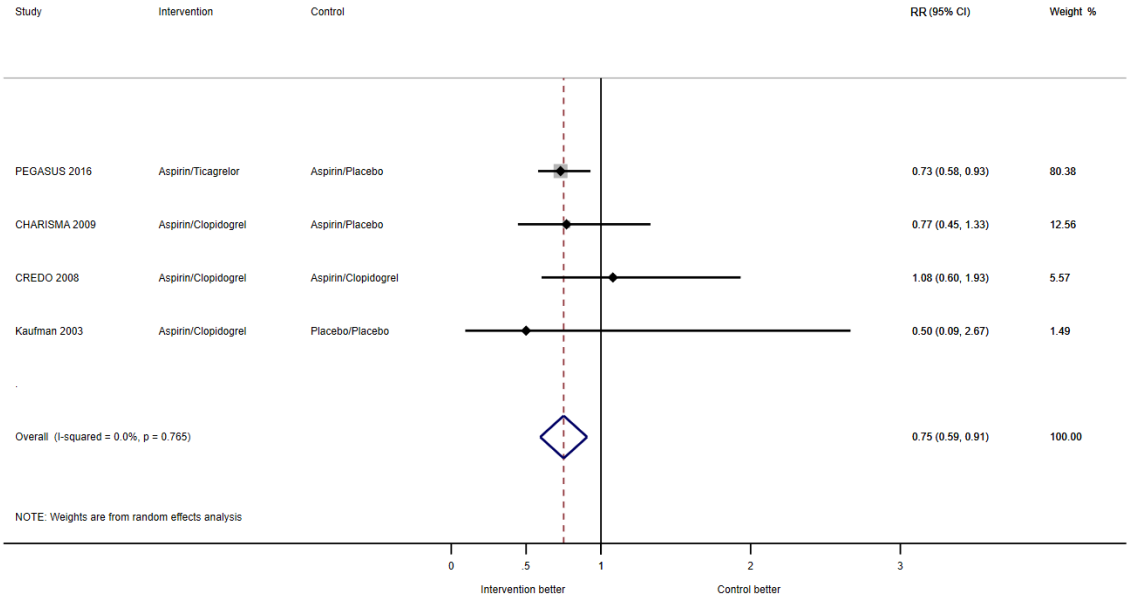

Figure A3.5 Relative effects of $P2Y_{12}$ inhibitor-based dual antiplatelet therapy vs aspirin monotherapy or no study medication on stroke

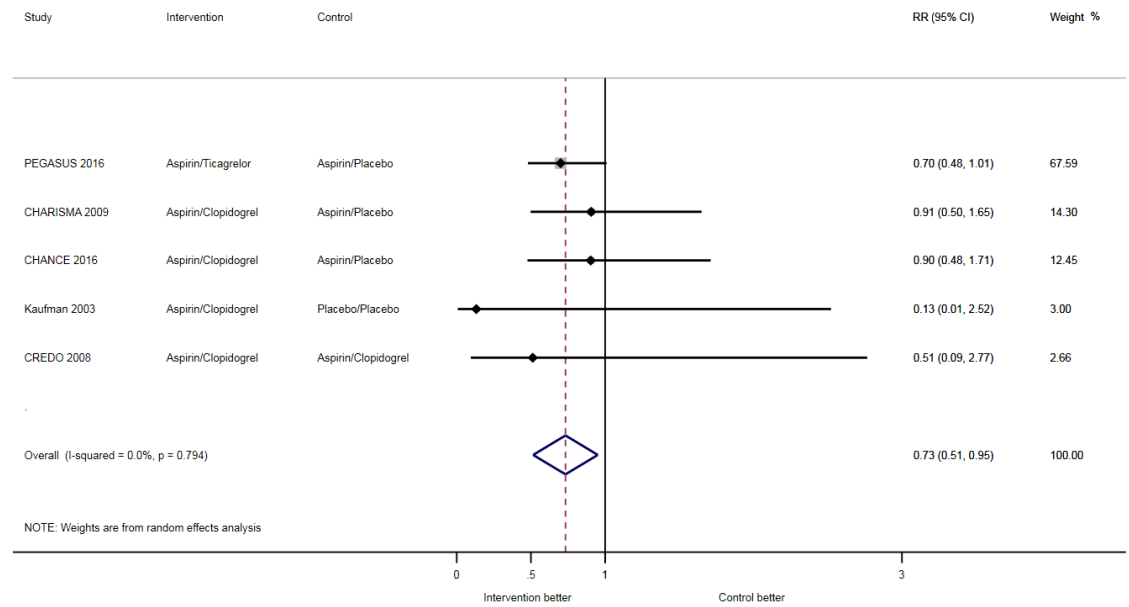

Figure A3.6 Relative effects of $P2Y_{12}$ inhibitor-based dual antiplatelet therapy vs aspirin monotherapy or no study medication on major bleeding

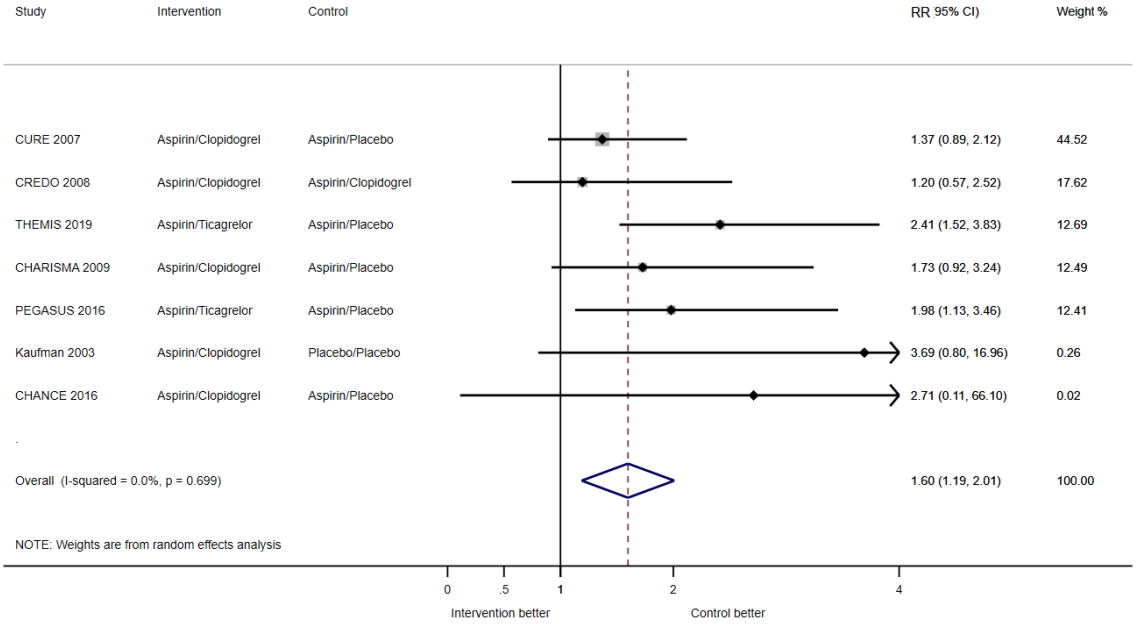

Figure A3.7 Summary of treatment effects of dipyridamole-based dual antiplatelet therapy in trials involving dialysis-dependent kidney failure

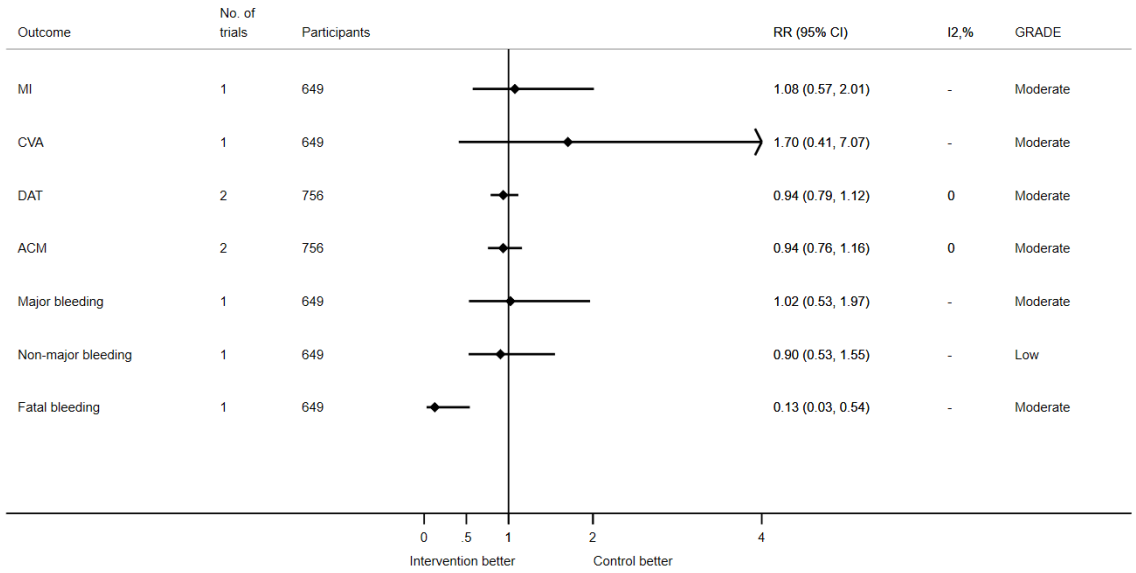

Table A3.1 Electronic search strategy

Database	Search terms
MEDLINE (Ovid)	1. exp Platelet Aggregation Inhibitors/ or exp Aspirin/ or exp Salicylates/ or exp Dipyridamole/ or exp Aspirin, Dipyridamole Drug Combination/ or exp Purinergic P2Y Receptor Antagonists/ or exp Thienopyridines/ or exp Ticlopidine/ or exp Prasugrel Hydrochloride/ or (triflusal or cilostazol or clopidogrel or ticagrelor or cangrelor or dual antiplatelet therapy or DAPT).tw. 2. exp Renal Dialysis/ or exp Renal Replacement Therapy/ or exp Kidney Failure, Chronic/ or exp Renal Insufficiency/ or Renal Insufficiency, Chronic/ or exp Kidney Diseases/ or exp Kidney Transplantation/ or exp glomerular filtration rate/ or exp kidney function test/ or exp creatinine/ or creatinine clearance.tw. 3. exp Clinical trial/ or exp Controlled clinical trial/ or exp Randomized Controlled Trials/ or exp Random Allocation/ 4. 1 and 2 and 3 5. limit 4 to humans
EMBASE (Ovid)	1. exp acetylsalicylic acid/ or exp triflusal/ or exp dipyridamole/ or exp acetylsalicylic acid plus dipyridamole/ or exp cilostazol/ or exp purinergic P2Y receptor antagonist/ or exp ticlopidine/ or exp clopidogrel/ or exp elinogrel/ or exp prasugrel/ or exp ticagrelor/ or exp cangrelor/ or exp dual antiplatelet therapy/ 2. exp chronic kidney disease/ or exp chronic kidney failure/ or exp renal replacement therapy/ or exp hemodialysis/ or exp peritoneal dialysis/ or exp creatinine blood level/ or exp creatinine clearance/ or exp kidney function/ or exp renal clearance/ or exp estimated glomerular filtration rate/ or exp glomerular filtration rate/ 3. exp controlled clinical trial/ or exp clinical trial/ or exp controlled study/ or exp randomized controlled trial/ 4. 1 and 2 and 3 5. limit 4 to humans
CENTRAL	1. MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees 2. MeSH descriptor: [Aspirin] explode all trees 3. MeSH descriptor: [Salicylates] explode all trees 4. MeSH descriptor: [Dipyridamole] explode all trees 5. MeSH descriptor: [Aspirin, Dipyridamole Drug Combination] explode all trees 6. MeSH descriptor: [Purinergic P2Y Receptor Antagonists] explode all trees 7. MeSH descriptor: [Ticlopidine] explode all trees 8. MeSH descriptor: [Prasugrel Hydrochloride] explode all trees 9. triflusal or cilostazol or clopidogrel or ticagrelor or cangrelor or "dual antiplatelet therapy" or DAPT:ti,ab,kw 10. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9) 11. MeSH descriptor: [Glomerular Filtration Rate] explode all trees 12. MeSH descriptor: [Kidney Function Tests] explode all trees 13. MeSH descriptor: [Creatinine] explode all trees 14. "creatinine clearance":ti,ab,kw

Table A3.2 Certainty of evidence using the GRADE approach

Certainty Assessment							Effect		Certainty
Outcome	**No. of studies**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Relative (95% CI)**	**Absolute (95% CI)**	
$P2Y_{12}$ inhibitor-based dual antiplatelet therapy versus aspirin monotherapy or no study medication									
Major adverse cardiovascular events	5 randomised trials	serious [a]	not serious	not serious	not serious	none	**RR 0.89** (0.81 to 0.98)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE
Myocardial infarction	4 randomised trials	serious [a]	not serious	not serious	not serious	none	**RR 0.75** (0.59 to 0.91)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE
Cerebrovascular accident	5 randomised trials	serious [a]	not serious	not serious	not serious	none	**RR 0.73** (0.51 to 0.95)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE
Dialysis access thrombosis	1 randomised trials	serious [a,b]	not serious	not serious	serious [c]	none	**RR 0.95** (0.64 to 1.42)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⊕⊕◯◯ LOW
All-cause mortality	5 randomised trials	serious [a]	not serious	not serious	serious [c]	none	**RR 0.99** (0.81 to 1.17)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⊕⊕◯◯ LOW
Cardiovascular mortality	4 randomised trials	serious [a]	not serious	not serious	serious [c]	none	**RR 1.03** (0.79 to 1.27)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⊕⊕◯◯ LOW

Certainty Assessment							Effect		Certainty
Outcome	**No. of studies**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Relative (95% CI)**	**Absolute (95% CI)**	
Major bleeding	7 randomised trials	serious[1]	not serious	not serious	not serious	none	**RR 1.60** (1.19 to 2.01)	**2 fewer per 1,000** (from 2 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE
Non-major bleeding	6 randomised trials	serious	serious [d]	not serious	serious [c]	none	**RR 1.31** (0.98 to 1.64)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⊕◯◯◯ VERY LOW
Fatal bleeding	1 randomised trials	serious	not serious	not serious	serious [c]	none	**RR 0.20** (0.01 to 4.11)	**0 fewer per 1,000** (from 4 fewer to 0 fewer)	⊕⊕◯◯ LOW
$P2Y_{12}$ inhibitor-based dual antiplatelet therapy versus $P2Y_{12}$ inhibitor-based monotherapy									
Major cardiovascular event	3 randomised trials	serious [e,f]	not serious	not serious	serious [c]	none	**RR 0.99** (0.68 to 1.43)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⊕⊕◯◯ LOW
Major bleeding	1 randomised trials	not serious	not serious	not serious	serious [c]	none	**RR 0.91** (0.59 to 1.39)	**4 fewer per 1,000** (from 16 fewer to 15 more)	⊕⊕⊕◯ MODERATE
Major and non-major bleeding	2 randomised trials	serious [e,f]	not serious	not serious	serious [g]	none	**RR 1.90** (1.21 to 2.99)	**39 more per 1,000** (from 9 more to 87 more)	⊕⊕◯◯ LOW

Certainty Assessment							Effect		Certainty
Outcome	**No. of studies**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Relative (95% CI)**	**Absolute (95% CI)**	
Dual antiplatelet therapy versus dual antiplatelet therapy									
Major cardiovascular event	3 randomised trials	serious [a,e,f]	not serious	not serious	serious [c]	none	**RR 0.86** (0.61 to 1.11)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁◯◯ LOW
Myocardial infarction	1 randomised trials	not serious	not serious	not serious	serious [c]	none	**RR 0.80** (0.60 to 1.09)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE
All-cause mortality	2 randomised trials	serious [a,e]	not serious	not serious	not serious	none	**RR 0.74** (0.60 to 0.88)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE
Cardiovascular mortality	1 randomised trials	not serious	not serious	not serious	serious [c]	none	**RR 1.35** (0.87 to 2.10)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE
Major bleeding	4 randomised trials	serious [a,e,f]	not serious	not serious	serious [c]	none	**RR 1.19** (0.82 to 1.57)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁⨁◯◯ LOW
Non-major bleeding	1 randomised trials	not serious	not serious	not serious	serious [c]	none	**RR 1.35** (0.87 to 2.10)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE
Fatal bleeding	1 randomised trials	serious [a,e,f]	not serious	not serious	serious [c]	none	**RR 0.48** (0.15 to 1.54)	**0 fewer per 1,000**	⨁⨁◯◯ LOW

Certainty Assessment							Effect		Certainty
Outcome	**No. of studies**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Relative (95% CI)**	**Absolute (95% CI)**	
								(from 2 fewer to 0 fewer)	
Major and non-major bleeding	1 randomised trials	serious [a,e,f]	not serious	not serious	serious [g]	none	**RR 1.82** (1.18 to 2.86)	**2 fewer per 1,000** (from 3 fewer to 1 fewer)	⨁⨁◯◯ LOW
Dipyridamole-based dual antiplatelet therapy versus monotherapy or no antiplatelet therapy									
Myocardial infarction	1 randomised trials	not serious	not serious	not serious	serious [c]	none	**RR 1.08** (0.57 to 2.01)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE
Cerebrovascular accident	1 randomised trials	not serious	not serious	not serious	serious [c]	none	**RR 1.70** (0.41 to 7.07)	**2 fewer per 1,000** (from 7 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE
Dialysis access thrombosis	2 randomised trials	not serious	not serious	not serious	serious [c]	none	**RR 0.94** (0.79 to 1.12)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE
All-cause mortality	2 randomised trials	not serious	not serious	not serious	serious [c]	none	**RR 0.94** (0.76 to 1.16)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE
Major bleeding	1 randomised trials	not serious	not serious	not serious	serious [c]	none	**RR 1.022** (0.53 to 1.97)	**1 fewer per 1,000** (from 2 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE

Certainty Assessment							Effect		Certainty
Outcome	**No. of studies**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Relative (95% CI)**	**Absolute (95% CI)**	
Non-major bleeding	2 randomised trials	serious [f,h]	not serious	not serious	serious [c]	none	**RR 1.10** (0.38 to 3.22)	**1 fewer per 1,000** (from 3 fewer to 0 fewer)	⊕⊕◯◯ LOW
Fatal bleeding	1 randomised trials	not serious	not serious	not serious	serious [g]	none	**RR 0.13** (0.03 to 0.54)	**0 fewer per 1,000** (from 1 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **RR**: Risk ratio

Explanations

a. Potential bias for selection of reporting
b. Potential bias in outcome measurement
c. Imprecise as confidence intervals include potential for important benefit or harm
d. Wide variation of point estimates and high heterogeneity that cannot be explained
e. Potential bias due to randomisation process
f. Potential bias due to deviation of intention
g. Optimal information size criterion not met
h. Potential bias due to missing outcome data