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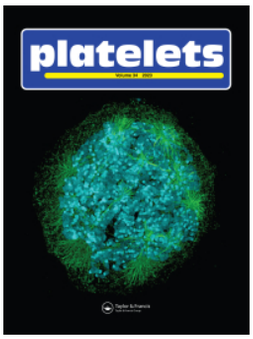

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REVIEW

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Treatment inequity in antiplatelet therapy for ischaemic heart disease in patients with advanced chronic kidney disease: releasing the evidence vacuum

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Abstract

Chronic kidney disease (CKD) is a global health problem and an independent risk factor for cardiovascular morbidity and mortality. Despite evidence-based therapies significantly improving cardiovascular mortality outcomes in the general population and those with non-dialysis-dependent CKD, this risk reduction has not translated to patients with end-stage kidney disease (ESKD). Absent from all major antiplatelet trials, this has led to insufficient safety data for $P2Y_{12}$ inhibitor prescriptions and treatment inequity in this subpopulation. This review article presents an overview of the progression of research in understanding antiplatelet therapy for ischaemic heart disease in patients with advanced CKD (defined as eGFR <30 mL/min/1.73 m^2). Beyond trial recruitment strategies, new approaches should focus on registry documentation by CKD stage, risk stratification with biomarkers associated with inflammation and haemorrhage and building a knowledge base on optimal duration of dual and single antiplatelet therapies.

Keywords

Acute coronary syndrome (ACS); antiplatelet; cardiovascular disease; chronic kidney disease (CKD); end stage kidney disease (ESKD); ischaemic heart disease (IHD); P2Y12 inhibitor; renal replacement therapy (RRT)

History

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Plain Language Summary

What is the context?

- Patients with kidney disease are more likely to experience a heart attack than those without.
- Those with advanced kidney disease have a higher risk of death following a heart attack.
- Over the past two decades, advances in treatment following a heart attack have reduced the risk of death, however this has not translated to those with advanced kidney disease.
- Progression of kidney disease influences antiplatelet (e.g. clopidogrel) treatment efficacy.

What is new?

- This contemporary review analyses registry and trial data to highlight some of the issues surrounding treatment inequity in patients with advanced kidney disease.
- This article describes potential mechanisms by which progression of kidney disease can influence clotting, bleeding and antiplatelet treatments.

What is the impact?

- Further research into antiplatelet therapy for patients with advanced kidney disease is required.
- Registry and trial data can improve upon classification of kidney disease for future research.
- Future trials in antiplatelet therapy for advanced kidney disease are anticipated.

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Introduction

Chronic kidney disease (CKD) is a major health problem worldwide and an independent risk factor for cardiovascular morbidity and mortality [1]. The 2015 global census accredited 8.92 million deaths to ischaemic heart disease (IHD) and 1.2 million to CKD [2]. Associated with an accelerated disease course, these figures do not reflect the significant proportion of deaths from IHD underpinned by CKD [3]. The incidence estimates suggest 12 ,000 excess myocardial infarctions (MIs) occurred in CKD patients in England (2009–2010) compared to the incidence of MI in age- and gender-matched controls without CKD [4]. This incurred estimated costs of £174–178 million [4]. With CKD progression, it is estimated that 70% of patients have significant coronary atherosclerosis and 40% have symptomatic IHD or heart failure by the time of dialysis [5]. Registry data of 289,699 cases of acute MI reported that a proportionally higher percentage (79%) of dialysis-treated MI patients presented with non-ST-segment elevation MI (NSTEMI) and only 21% presented with ST-segment-elevation MI (STEMI) [6]. While the greatest proportion of sudden cardiac death relates to non-atherosclerotic disease in dialysis patients [7], patients on dialysis who have an MI have twice the risk of death over the general dialysis population, and this risk has remained unchanged for more than a decade [6]. This is in stark contrast to patients experiencing MI who are not on dialysis, where there has been an impressive 3- to 5-fold reduction in risk of death over the same period [6]. Furthermore, while 1-year mortality following MI on dialysis has improved from ≈60% to 41%, this does not appear to correlate with advances in evidence-based therapies for managing acute coronary syndromes (ACS) [6]. This vast disparity in treatment outcomes for patients with advanced CKD suggests a historically neglected research population.

Recently updated, the European Society of Cardiology (ESC) guidelines [8] on management of non-ST-segment-elevation ACS subheads CKD within special populations and highlights insufficient safety data for $P2Y_{12}$ inhibitor prescription in those with end-stage kidney disease (ESKD), defined when estimated glomerular filtration rate (eGFR), an index of kidney function, is less than 15 mL/min/1.73 m^2. Contemporary reviews of $P2Y_{12}$ inhibition within the CKD subgroup demonstrate inequity through the absence of robust evidence due to underrepresentation or exclusion from the informing clinical trials [3]. Previous data have questioned the increased risk of harm, through bleeding, with more potent $P2Y_{12}$ inhibitors with advanced CKD [3] when eGFR is <30 mL/min/1.73 m^2. However, these statements are based on lower-grade evidence and neglect to consider individualised risk stratification of bleeding and thrombotic risks. Some risk scores predicting bleeding risk with dual antiplatelet therapy (DAPT) include renal function [9, 29], but none has been validated for patients with advanced CKD.

A recent systematic review and meta-analysis comprising small trials and observational data suggest that prasugrel and ticagrelor can provide beneficial clinical outcomes compared to clopidogrel with no significant increase in major bleeding events [10]. While both offer dose adjustments, these have yet to be fully evaluated in advanced CKD [11–13]. The reduced efficacy of clopidogrel in this cohort is well substantiated and is associated with poor clinical outcomes [10,14–16]. Contemporary trials are boosting efforts to understand treatments in this subpopulation [17–20]. Outcomes of the forthcoming TROUPER trial [17] – ticagrelor or clopidogrel in severe CKD patients (eGFR <30 ml/min/1.73 m^2 or chronic dialysis) undergoing percutaneous coronary intervention (PCI) for ACS – are eagerly anticipated.

Aims and objectives

This review article provides an overview of antiplatelet agents in advanced CKD with an overarching aim to highlight areas for future research. This is not a comprehensive systematic review of each topic area and is therefore limited in this regard. Evidence readily informing ESC guidelines in the management of ACSs [8] is included. Additional literature search terms were performed on PubMed to include 'advanced CKD', 'hemodialysis', 'dialysis', 'end stage kidney disease', 'end stage renal disease' and 'peritoneal dialysis', pertaining to each of the objectives. This article provides a snapshot of advanced CKD across the following areas:

(1) How is advanced CKD represented within ACS registries?
(2) Consideration of mechanisms within CKD that increase bleeding and thrombotic risk
(3) Representation of advanced CKD within major clinical trials and selection of antiplatelet regimen
(4) How relevant are bleeding and thrombotic risk scores in advanced CKD?

Advanced CKD within ACS registries

CKD is caused by abnormal function and/or structure in the kidney. It is classified into five stages according to eGFR [4]. Stages 1 and 2 are identified by albuminuria, abnormalities in urine sediments or electrolytes associated with tubular disorders, or histological changes. Stage 3 CKD is defined by eGFR 30–59 mL/min/1.73 m^2, inclusive, on two separate occasions at least 90 days apart. Criteria for referral to a nephrologist include 'advanced CKD' when eGFR is <30 mL/min/1.73 m^2 (CKD stage 4), special circumstances such as rapid disease progression or when the 5-year risk of needing renal replacement therapy (RRT) is calculated to be > 5% [4]. This includes CKD stage 5, or ESKD, defined when the eGFR is <15 mL/min/1.73 m^2, with or without dialysis therapy. Patients with cardiovascular disease (CVD) and concurrent stage 3 CKD, classified in most trials as 'moderate' renal impairment, are more likely to be managed by their cardiologist and/or general practitioner in the UK than a nephrologist.

Table I displays a subset of registries for ACS available across the globe. Spanning nearly two decades, publications evaluating patients with advanced CKD were analysed. Those without advanced CKD data were excluded. These indicate a high prevalence of CKD within the ACS population. The proportion with at least moderate CKD (eGFR <60 ml/min/1.73 m^2) ranges from 30% to 43% in the United States [11], 23% in Malaysia [28], 20% in Australia [29], 40% in Taiwan [30] and 33% in Sweden [24]. The proportion with advanced CKD (CKD stage 4 or 5; eGFR <30 ml/min/1.73 m^2) ranges from 13.4–14.5% in CRUSADE and GRACE registries [21,23] to 6.6% in SWEDEHEART [24].

Strong correlations exist between advancing CKD, recurrent thrombotic events and major bleeding events. Subgroup analysis from the PEGASUS-TIMI-54 trial showed independent, inverse and graded relationships between eGFR and ischaemic risk [33]. A literature review of 43 000 dialysis patients from the US Renal Database System (USRDS) showed heterogeneity, with in-hospital mortality outcomes following a STEMI, reported as 26% in ESKD patients on dialysis compared to 4–8% in patients not receiving dialysis [34]. Even those perceived to have relatively preserved kidney function with stage 3 CKD (eGFR 30–59 ml/min/1.73 m^2) have a substantially increased risk of cardiovascular mortality. In patients with CKD stage 3 or 4 (eGFR range 15–59 ml/min/1.73 m^2), 35–50% [5] of

Table I. Registry distribution of CKD with IHD; therapeutic patterns, mortality and bleeding events.

Author name, year	ACS Registry	Enrollment, region	Total Cohort	Distribution of CKD eGFR ml/min/1.73 m^2 or CrCl ml/min			Follow-up	All-cause and cardiovascular mortality	Bleeding risk and treatment preferences
				No CKD	Mild to moderate CKD	Advanced CKD eGFR or CrCl <30 or RRT			
Santopinto et al. [21]	**GRACE** Global Registry of Acute Coronary Events	1999–present 94 hospitals, 14 countries	$N = 11$ 774 ACS ($N = 4716$ STEMI; $N = 7058$ NSTEMI)	CrCl >60: 7591 (64.5%) STEMI $N = 3068$ (26.1%) NSTEMI $N = 4523$ (38.4%)	CrCl 30–60 $N = 3397$ (28.9%) STEMI $N = 1347$ (11.4%), NSTEMI $N = 2050$ (17.4%)	CrCl <30 $N = 786$ (6.7%) STEMI $N = 301$ (2.6%), NSTEMI $N = 485$ (4.1%)	Inpatient	Mortality double when CrCl 30–60, (Adj. OR 2.09 95% CI 1.55–2.81) and almost four times when CrCl <30 (Adj. OR 3.7 95% CI 2.57–5.37) compared to patients with CrCl >60. A 10 ml/min decrease in CrCl had similar adverse impact to 10-year increase in age.	Risk of major bleeding increased with renal dysfunction, CrCl. 30–60 adj.OR 1.52 [1.17–1.99], CrCl <30 Adj. OR 2.78 [1.96–3.94] compared to CrCl >60 mL/min. Clopidogrel prescriptions when CrCl <30 12.4% lower in ACS compared to CrCl >60 ($P < .05$).
Hemmelgarn et al. [31]	**APPROACH** Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease	1995–2001 Alberta, Canada	$N = 41$ 786	'Reference population' with creatinine <200 μmol/L: $N = 40$ 374 (96.6%)		NDDKD: Creatinine ≥200 $N = 750$ (1.8%) Dialysis $N = 662$ (1.6%)	8 years	Adjusted 8 year survival reference group for CABG Vs NR (85.5%), PCI Vs (80.4%) and NR (72.3%) $P < .001$.	Compared with reference population adjusted survival: NDDKD: CABG Vs NR 45.9% ($P < .001$), PCI Vs NR 32.7% ($P = .48$) and NR 29.7%. Dialysis: CABG Vs NR 44.8% ($P = .003$) PCI Vs NR 41.2% ($P = .03$), NR 30.4%.
Han et al. [23]	**CRUSADE** Can Rapid Risk Stratification of Unstable Angina patients suppress Adverse outcomes with Early Implementation of the ACA/AHA guidelines	2001–2003 312 US hospitals with PCI service	$N = 45$ 343 NSTEMI	'Reference population' with creatinine ≤177 μmol/L: $N = 38$ 783 (85.5%)		CKD either creatinine >177 μmol/L or on dialysis $N = 6560$ (14.5%) – exact data not available	Inpatient	In-hospital mortality and reinfarction was higher in CKD patients (adj OR 1.45 95% CI 1.30–1.61) than non-CKD	CKD patients less likely to receive aspirin (adj OR 0.86 95% CI 0.78–0.95), clopidogrel (adj OR 0.86 95% CI 0.78–0.95) nor PCI (adj OR 0.67 95% CI 0.62–0.71) compared to non-CKD
Latif et al. [32]	**EVENT** Evaluation of Drug Eluting Stents and Ischemic Events registry	2004–2005 42 US Centres	$N = 4791$ ACS	CrCl >75 mL/min: $N = 2827$ (59%)	CrCl 50–75 mL/min: $N = 1253$ (26%) CrCl 30–49 mL/min $N = 571$ (12%)	CrCl <30 mL/min: $N = 140$ (3%) 1% dialysis	Inpatient and 12 months	Death and MI increased from 5.8% CrCl >75 to 10% CrCl <30, $P = .0016$. Stent thrombosis ($P = .99$) and revascularisation ($P = .51$) showed no statistical difference compared to CrCl >75	Bleeding complications increased with progressive CKD. For CrCl <50, adjusted OR 1.6, 95% CI 1.01–2.5; and CrCl <30 OR 3.1 (95% CI 1.7–5.6). Clopidogrel prescription 9% lower at 12 months with CrCl <30 compared to >75

(*Continued*)

Table I. (Continued).

Author name, year	ACS Registry	Enrollment, region	Total Cohort	Distribution of CKD eGFR ml/min/1.73 m^2 or CrCl ml/min: No CKD	Mild to moderate CKD	Advanced CKD eGFR or CrCl <30 or RRT	Follow-up	All-cause and cardiovascular mortality	Bleeding risk and treatment preferences
Szummer et al. [24]	**SWEDEHEART** Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies register	2003–2006 71 hospitals, Sweden	*N* = 57 477 ACS	*N* = 12 344 (21.5%)	eGFR 60–90 *N* = 25 970 (45.2%) eGFR 30–59 *N* = 16 008 (27.9%)	eGFR 15–29 *N* = 2349 (4%) NDDKD with eGFR <15 *N* = 806 (1.4%) Dialysis *N* = 368 (0.6%)	Inpatient	eGFR <15/dialysis 22% STEMI compared to 41% eGFR >90. VT/VF/ cardiac arrest 6.2% eGFR <15 (adj OR 1.89 CI 1.3–2.72) compared with 2.7% eGFR ≥90. In-hospital mortality more likely eGFR <60.	Bleeding 6.1% in eGFR <15 (adj OR 3.39 CI 2.16–5.33) compared to 1.5% eGFR ≥90. Lower primary PCI in STEMI 49.4% for eGFR <15/dialysis compared with 77.3% eGFR >90.
Fox et al. [13]	**NCDR-ACTION** National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes registry	2007–present 280 ACTION hospitals, US	*N* = 30 462 NSTEMI *N* = 19 029 STEMI	NSTEMI = 17 393 (57.1%) STEMI = 13 221 (69.5%)	NSTEMI = 10 112 (33.2%) STEMI = 5001 (26.3%)	eGFR 15–29 NSTEMI = 1846 (6.1%) STEMI = 554 (2.9%) eGFR <15 NSTEMI = 1111 (3.6%) STEMI = 253 (1.3%)	Inpatient	In-hospital death 31% eGFR <15 (adj OR 8.0) compared to 2.3% no CKD in STEMI and 12.4% eGFR <15 (adj OR 4.1) compared to 1.8% in NSTEMI ($p < .0001$).	Multivariable adjusted OR for major bleeding in STEMI 2.1 (CI 1.4–2.9) when eGFR <15 and 2.0 (CI 1.6–2.5) eGFR 15–30 compared to no CKD. Not adjusted for significant overdosing of glycoprotein IIb/IIIa inhibitors in STEMI 55.6% in eGFR <15 and 40.9% in NSTEMI compared to 2.2% in those with no CKD ($p < .0001$).
Baber et al. [26]	**PARIS** Patterns of non-adherence to anti-platelet Regimen in Stented Patients	2009–2010 US and Europe	*N* = 4190 CAD treated with PCI (DES)	CrCl ≥60 mL/min *N* = 3527 (84.2%)	CrCl <60 mL/min: *N* = 663 (15.8%)		24 months	CrCl <60 independent predictor of CTE at 2 years; 3.8% (HR 2.12 95% CI 1.46–3.05, $P < .001$) compared to CrCl ≥60.	CrCl independent predictor of major bleeding CrCl <60 3.3% (HR 1.81 95% CI 1.16–2.82, $P = .01$) compared to CrCl ≥60.

(*Continued*)

Table I. (Continued).

Author name, year	ACS Registry	Enrollment, region	Total Cohort	Distribution of CKD eGFR ml/min/1.73 m^2 or CrCl ml/min: No CKD	Mild to moderate CKD	Advanced CKD eGFR or CrCl <30 or RRT	Follow-up	All-cause and cardiovascular mortality	Bleeding risk and treatment preferences
Gragnano et al. [25]	**START-ANTIPLATELET** survey on anticoagulated patients register clinical trials.gov	2014–2018 Italy	$N = 383$ High bleeding risk	CrCl >30 mL/min $N = 196$ Ticagrelor $N = 138$ Clopidogrel		CrCl <30 mL/min $N = 13$ Ticagrelor (6.2%) $N = 36$ Clopidogrel (20.7%)	12 months	Composite end point of all-cause death, MI stroke or major bleeding, after multivariate adjustment, did not differ at 1-year adverse clinical outcomes associated between clopidogrel or ticagrelor (19% versus 11%, respectively, adj HR 1.27 CI 0.71–2.27 $P = .429$)	Mean CrCl overall higher in ticagrelor group 64.6 ± 25.9 compared with clopidogrel 52.5 ± 27.1 ($P < .001$). Advanced age, high bleeding risk criteria and longer DAPT duration were independent predictors of composite end point.
De Luca et al. [27]	**PIRAEUS group** – combined registries. Included for analysis: AAPCI/DAPT, AMIS Plus, EYESHOT	2014–2019	STEMI	eGFR >60 $N = 23$ 215	eGFR <60 $N = 2968$ (12.8%)		In-hospital events	All-cause mortality lower with prasugrel/ticagrelor compared to clopidogrel (OR 0.72, 95% CI 0.62–0.84, $P < .001$). Prasugrel Vs ticagrelor non-inferior (OR 0.97, 95% CI 0.77–1.23, P = .81)	No difference in bleeding events between prasugrel and ticagrelor (OR 0.81 95% CI 0.53–1.24, $P = .335$)

ACA, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance mL/min; CTE, coronary thrombotic events; DES, Drug-eluting stent; eGFR, estimated glomerular filtration rate ml/min/1.73m^2 ; EBM, evidence based medications; ER, event rate; HTPR, high on-treatment platelet reactivity; HR, hazard ratio; OR, odds ratio; NDDKD, non-dialysis-dependent kidney disease; NSTEMI, non-ST segment elevation myocardial infarction; NR, no revascularisation; MACE, major adverse cardiovascular event; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; RRT, renal replacement therapy; STEMI, ST-segment Elevation Myocardial Infarction; US, United State; VT, ventricular tachycardia; VF, ventricular fibrillation.

mortality is ascribed to CVD, three times that of patients with eGFR >90 ml/min/1.73 m^2. An analysis of >100 000 patients with CKD demonstrated the hazard for cardiovascular mortality increases exponentially by CKD stage [1] (adjHR 5.39 (CI 3.30–8.80) for eGFR 15–29 ml/min/1.73 m^2 compared to eGFR ≥90 ml/min/1.73 m^2). Reinfarction, ventricular tachycardia, ventricular fibrillation and cardiac arrest are nearly three times more likely in those with eGFR <60 mL/min/1.73 m^2 versus those without [24]. Outcomes from the PLATO trial also showed that, for every 5 mL/min reduction in creatinine clearance (CrCl), relative increases in total mortality rates were 19%, MI 8% and major bleeding 4% (all $P < .001$) [35]. Observational studies suggest a 10 ml decrease in CrCl has a similar adverse impact to a 10-year advancement in age [21]. Notwithstanding the unmitigated proportional risk attributed to pathophysiological processes, there remains considerable potential to improve outcomes post-ACS, with targeted therapeutics in advanced CKD.

Antiplatelet options for ACS in advanced CKD

Not only is CKD an independent predictor of death and further cardiovascular events [3,36], but also it additionally is associated with increased health-care costs per event. For example, the estimated cost of stay of a patient with ACS and ESKD receiving haemodialysis (HD) is approximately 1.6 times that of patients without CKD and 1.3 times higher than non-dialysis - dependent kidney disease (NDDKD) [34].

Prescription of evidence-based medications, timing of revascularisation and selection for reperfusion or medical therapy are less predictable in this population. Despite limitations in delineation of CKD patients, registry data globally demonstrate wide variation in clinical practice and outcomes in ACS management (Table I) [21,23,24,25–2728,29,31,32]. Lower prescriptions for evidence-based medications in advanced CKD reportedly relate to concerns about drug toxicity, deterioration in renal function, bleeding and overall paucity in the evidence base [11,24,28,37,38]. Historical failure of registry datasets to capture CKD stage has also missed trends in antithrombotic prescriptions in advanced diseases. The proportion of dialysis patients prescribed DAPT following MI in 2012/13 reflects clinical practice from 10 years earlier in patients not receiving dialysis [6]. Furthermore, historically found in 40–55% [13], studies reporting in-hospital bleeding complications often neglect to consider the impact of overdosing in patients with eGFR <30 ml/min/1.73 m^2, with co-prescription of intravenous antiplatelets (i.e. glycoprotein IIa/IIIb inhibitors) during PCI.

Efficacy of DAPT with aspirin and clopidogrel is affected by CKD progression [10,25,38]. Recognition of the pharmacological challenges in managing antiplatelet therapy in advanced CKD is growing [3,10]. This demands awareness of the pharmacodynamics and pharmacokinetics of $P2Y_{12}$ inhibitors in this subgroup. Circulating platelet volume, reactivity and plasma constituents involved in platelet aggregation, coagulation and fibrinolysis all contribute to bleeding and thrombotic risks. Therapeutic targets of antiplatelets, as illustrated in Figure 1, include platelet activation via adenosine diphosphate (ADP)-mediated activation of the $P2Y_{12}$ receptor, cyclooxygenase (COX)-1-mediated production of thromboxane A_2 (TXA_2) and thrombin-mediated activation of protease-activated receptor (PAR)-1 and PAR-4 [39–41]. However, the safety profile of vorapaxar, in particular regarding the increased risk of ICH, leaves PAR-1 as an unattractive target [42], especially given higher bleeding risks associated with advanced CKD.

Aspirin therapy has proven benefit in secondary prevention of established ACS, with reported absolute risk reductions of 38 per 1000 patients treated for -month post-acute MI [44]. However, the CKD subgroup is not well evidenced in this analysis. Aspirin is a non-selective, irreversible inhibitor of COX-1 (antiplatelet) and, less sensitively, COX-2 (anti-inflammatory) enzymes. Oral bioavailability is 30–40% and peak plasma levels occur 30–40 min after ingestion of plain or dispersible aspirin [45] (or 3–4 h for enteric-coated formulations). Inactivation of COX-1 inhibits the formation and release of TXA_2, a platelet activator and vasoconstrictor, and this effect lasts for the lifespan of the platelet. The mean lifespan of the human platelet is around 7–10 days. As approximately 10% of the platelet pool is replenished per day, once-daily dosing should be sufficient to maintain almost complete inhibition [45]. However, the plasma half-life is short with differential exposure to platelet and systemic endothelium, leading to inconsistent efficacy in groups with accelerated platelet

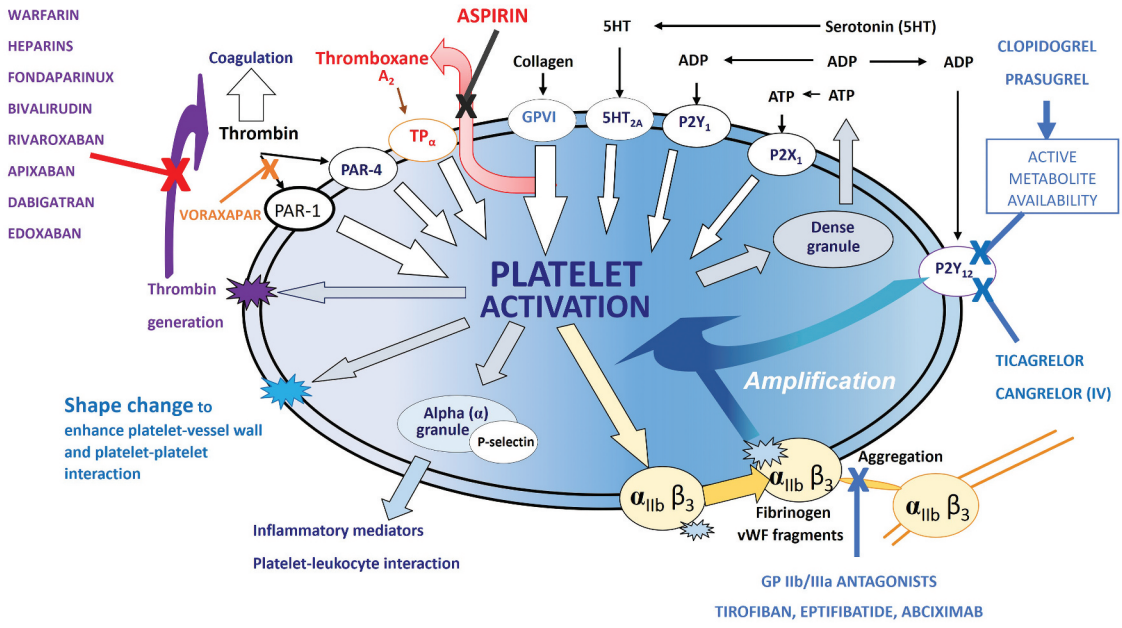

Figure 1. Graphical abstract of platelet activation pathways and mechanism of action of antiplatelet and antithrombotic therapies. Adapted from and reproduced with permission from Storey, 2006 [43].

turnover [46]. This can be improved with twice-daily dosing [46]. In those with enhanced inflammatory state, such as end-stage CKD, platelet turnover is demonstrably higher [47], but the efficacy of twice-daily dosing has yet to be evaluated in this setting.

Although aspirin is a recommended option for secondary prevention, primary prevention studies of aspirin in non-end-stage CKD showed no clear benefit, with a statistically significant doubling of major bleeding and progressive renal dysfunction [48]. Hence, despite impairment of haemostasis, COX-1 inhibition in this cohort was insufficient in primary prevention of thrombotic events. HD patients were not well represented in this meta-analysis, and only studies evaluating the patency of dialysis access were included [48]. Smaller studies have shown pharmacodynamic variation in aspirin response in CKD [49]. One cross-sectional study [49] ($N = 116$) demonstrated impaired response to aspirin with higher on-treatment TXA_2 levels indicative of high on-treatment platelet reactivity (HTPR) in patients with eGFR <60 ml/min/1.73 m^2. As an NSAID, aspirin is also potentially nephrotoxic, and even doses of 75 mg OD have shown a small, but significant, reduction in serum creatinine, which is resolved after cessation of therapy [50]. Additionally, it has been noted to have pro-inflammatory properties in a human endotoxaemia model, in contrast to the anti-inflammatory effects of $P2Y_{12}$ inhibition [51]. Further assessment of aspirin dosing and efficacy in moderate and severe CKD is required [52–54]. Trends, however, are shifting toward the benefits of single antiplatelet therapy (SAPT) with $P2Y_{12}$ inhibitor monotherapy. The TWILIGHT-CKD subgroup analysis suggested that ticagrelor monotherapy leads to a lower incidence of bleeding compared with DAPT in patients with CKD without necessarily increasing the risk of cardiovascular events although the analysis was underpowered to provide robust evidence on this [55,56]. Larger trials for monotherapy with a more potent $P2Y_{12}$ inhibitor in dialysis-dependent and advanced CKD are required.

Clopidogrel is a second-generation thienopyridine prodrug requiring intestinal absorption and metabolisation by liver enzymes to produce an active metabolite that binds irreversibly to the $P2Y_{12}$ receptor for the life of the platelet [57]. Renal dysfunction significantly suppresses biotransformation, and genetic variation in absorption and cytochrome P450 (CYP) polymorphism leads to unpredictable variations in the on-treatment platelet reactivity [14,15]. Table II shows a subset of pharmacodynamic and pharmacokinetic studies within advanced CKD across the globe to include a meta-analysis ($N = 10$) evaluating the prevalence of HTPR in CKD patients treated with clopidogrel, linked to poorer clinical outcomes [14]. HTPR with clopidogrel is reportedly up to 84% with advanced CKD [58]. This exceeds estimates of 30% within the general population [59,61,64]. Consistent evidence of poor response across a variety of research studies [14,15,52,59,61] has fuelled exploration of the safety and efficacy of newer $P2Y_{12}$ inhibitors in advanced CKD. The timely TROUPER trial – clopidogrel compared with ticagrelor following PCI in ACS [17] – is a step towards closing treatment disparities within this subgroup.

Prasugrel is a newer prodrug, with significantly enhanced potency in reduction of platelet activation compared to clopidogrel. Rapidly hydrolysed by intestinal hydroxyesterases followed by CYP bioactivation, maximum plasma concentration of the active metabolite is reached at 30–60 min [65]. Like clopidogrel, this third-generation thienopyridine blocks ADP binding to the $P2Y_{12}$ receptor irreversibly and effectively reduces multiple aspects of platelet activation and associated responses [66]. Maximum effect of platelet inhibition after loading with 60 mg prasugrel is seen at 1 h compared to clopidogrel where maximum effects of a 300 mg loading dose are seen at >6 h and 600 mg at 2–4 h [65,67]. Furthermore, small studies suggest that low-dose prasugrel, as well as clopidogrel, demonstrates a reduction in platelet inhibition post-HD (mean $P2Y_{12}$ reaction units >208), which requires further exploration [63].

Ticagrelor is a cyclopentyl triazolopyrimidine, or nucleoside analogue, that is bound 99.8% to plasma proteins and does not require metabolic activation [68]. Median time to maximum platelet inhibition is 2 h with declining plasma concentration at ~12 h, requiring twice-daily dosing [57]. Compared to clopidogrel, ticagrelor has shown more consistent $P2Y_{12}$ inhibition, with a lower proportion of HTPR [69] and the lowest proportion of non-responders, reportedly ≈10% on dialysis [52] and 0% with NDDKD [15]. Pharmacokinetic and pharmacodynamic data suggest that, unlike clopidogrel and prasugrel, ticagrelor's platelet inhibition response remains unchanged during HD [62].

Significantly higher risks of MACE, MI and stent thrombosis are associated with 'non-responders' or HTPR (identified by either light transmission aggregometry, VerifyNow $P2Y_{12}$ and/or vasodilator-stimulated phosphoprotein phosphorylation assays), as reported in a meta-analyses of 10 studies in advanced CKD [14]. Personalised antiplatelet therapy through genotyping to predict clopidogrel poor metabolisers and guide selective treatment with clopidogrel instead of ticagrelor or prasugrel was shown to be non-inferior to standard therapy with ticagrelor or prasugrel in reducing risk of MACE but did lower bleeding risk [70]. Only 10% of this sample was represented by advanced CKD and subgroup analysis of this cohort was not reported. Proportionately fewer (3%) were included in TROPICAL-ACS [60], which was also non-inferior for guided de-escalation of prasugrel therapy by platelet-function testing. Most of the dedicated trials for platelet function testing failed to meet end-points [60] and the disproportionately low recruitment of advanced CKD undermines applicability for this cohort. Despite this, a role for platelet-function testing in those with either 'on-treatment stent thrombosis', or 'recent PCI on DAPT requiring cardiac or non-cardiac surgery' remains [60]. It should be noted that low haematocrit in patients with CKD may affect results obtained with the VerifyNow $P2Y_{12}$ assay [71] and the optimal pharmacodynamic assay in advanced CKD patients remains to be established [72].

Bleeding risk on antiplatelet therapy in advanced CKD

Bleeding complications are higher in CKD compared to the general population. This has implications for antiplatelet therapy. A large observational study [73] reported a 1.6-fold (95% CI 1.2–2.2) increased risk of bleeding during antiplatelet therapy if diagnosed with CKD (defined as eGFR <60 mL/min/1.73 m^2 or albuminuria) relative to the non-CKD population [73]. In the CKD population, the majority of bleeding events (62%, $N = 172$) were unspecified nonintervention-related, followed by 30% ($N = 83$) intervention-related and 6.6% ($N = 18$) due to ruptured abdominal aneurysm [73]. These figures can be criticised for lack of risk stratification by stage since bleeding rates have been shown to increase with CKD progression. Clinically significant haemorrhage rates (of various aetiology) in ESKD reportedly range from 2.1 to 16.1 per 100 person-years [74]. The adjusted hazard ratio (HR, inclusive of aspirin use) for upper gastrointestinal bleeding in HD patients is increased to 1.27 (95% CI 1.03–1.57) compared to a population without CKD [75], with the risk of upper gastrointestinal bleeding in ESKD more than 3.5-fold higher than those with CKD stage 3 [76]. The interactions between bleeding, atherothrombosis and CKD are illustrated in Figure 2.

Table II. Efficacy of $P2Y_{12}$ inhibitors in advanced CKD.

Author, year	Design	CKD Distribution eGFR mL/min/1.73 m^2	Intervention	Platelet function test	CKD analysis	Outcome	Bleeding risk
Trials							
Alexopoulos et al. 2011 [58]	Randomised single-blinded prospective cross-over trial	HD with HTPR (PRU ≥235) on clopidogrel 75 mg od $N = 21/25$ randomised	Prasugrel 10 mg OD Vs clopidogrel 150 mg OD (47.6% concurrent aspirin)	VerifyNow $P2Y_{12}$	CKD stage 5 on HD	84% HTPR on clopidogrel prior to randomisation. PRU lower with prasugrel compared to high-dose clopidogrel (19% Vs 85.7%, $P < .001$). Genotyping for CYP2C19 × 2 unhelpful	Pharmacodynamic study, no clinical safety data
Price et al. 2011 [59]	RCT: GRAVITAS	CrCl <60 ml/min in 40.5% 441/1099 high dose 456/1096 standard dose	Standard clopidogrel 75 mg OD Vs high-dose clopidogrel 150 mg OD	VerifyNow $P2Y_{12}$	No	40.8% HRPR (PRU ≥230) on clopidogrel at randomisation of whom 40.5% had CrCl <60 ml/min compared to 28% with CrCl <60 ml/min PRU <230. No benefit in MACE despite reduction in absolute HTPR	No increase in bleeding with higher dose.
Storey et al. 2016 [12]	Substudy of RCT: PEGASUS-TIMI 54	No CKD $N = 146$ (81%) CrCl <60 mL/min $N = 9/64$ placebo (9%), $N = 5/58$ T60 (9%) $N = 9/58$ T90 (16%)	Ticagrelor 90 mg BD (T90) + aspirin and ticagrelor 60 mg BD (T60) + aspirin	VerifyNow $P2Y_{12}$ LTA VASP	No	PRU showed no significant difference between T90 and T60 though greater standard deviation in T60 group. HTPR PRU >208 in 2 patients T60 group pre-dose, 1 was due to poor compliance. No CKD subgroup analysis	In RCT: non-significant lower rates of bleeding T60. TIMI major bleeding was 2.69 (95% CI: 1.96 to 3.70) and 2.32 (95% CI: 1.68 to 3.21) for T90 and T60, respectively
Sibbing et al. 2017 [60]	RCT: TROPICAL-ACS	$N = 2106$, $N = 1304$ de-escalation and $N = 1306$ control. Renal insufficiency 3%	Prasugrel Vs PFT guided de-escalation to clopidogrel at 14 days if HTPR	Multiplate	No	PFT at 14 days. HTPR defined AU ≥ 46. HTPR noted 14% in control group and 39% in clopidogrel de-escalation group. Guided de-escalation non-inferior to standard prasugrel treatment. No CKD subgroup analysis	6% BARC 2 or higher bleeding in control and 5% in PFT group. No statistically significant reduction in bleeding events.
Pharmacodynamic and pharmacokinetic studies in advanced CKD							
Muller et al. 2012 [61]	Prospective study	1 and 2: eGFR >60 $N = 29$ 3a: eGFR 45–59 $N = 21$ 3b: eGFR 30–44 $N = 26$ 4: eGFR 15–29 $N = 14$ 5: eGFR <15 ml/min $N = 36$	Monotherapy with maintenance clopidogrel 75 mg OD	VerifyNow $P2Y_{12}$ VASP	Yes	PRI correlated inversely with eGFR (VASPr = −0.307, $P < .001$) in both assays (VerifyNowr = −0.485, $P < .001$). HRPR with PRU ≥235 (and VASP) increased with eGFR for all stages. From 17.2%, Stage 1–2 to 63.6%, stage 5 ($P < .001$). No effect of dialysis session on HRPR.	Pharmacodynamic study, no clinical safety data

(*Continued*)

Table II. (Continued).

Author, year	Design	CKD Distribution eGFR mL/min/1.73 m^2	Intervention	Platelet function test	CKD analysis	Outcome	Bleeding risk
Alexopoulos et al. 2012 [52]	2-center prospective study	HD with HTPR $N = 24/27$ had HTPR (89%) $N = 20$ included	Switch from clopidogrel 75 mg OD to ticagrelor 90 mg BD	VerifyNow $P2Y_{12}$ Multiplate	CKD stage 5 on HD	PRI decreased from 310.4 ± 52.9 to 137.7 ± 77.9 after ticagrelor treatment ($P < .001$). 10% remained poor responders (PRU ≥235) at day 15	No increased bleeding and drug tolerability was good
Wang et al. 2018 [15]	RCT in NSTEACS	$N = 60$ eGFR <60 with NSTEACS	Ticagrelor 90 mg BD + aspirin Vs clopidogrel 75 mg OD + aspirin	VerifyNow $P2Y_{12}$ CYP2C19 genotyping	CKD 3 and 4	PRU at 2 h, 8 h, 24 h and 30 days markedly lower in ticagrelor Vs clopidogrel and irrespective of eGFR or genotype. Biotransformation of clopidogrel significantly suppressed by renal dysfunction. HTPR with ticagrelor 3.3% at 24 h and 0% by 30 days compared to 58.6% on clopidogrel	No clinical safety data
Teng et al. 2018 [62]	Prospective study	14 HD 13 healthy (CrCl ≥90 mL/min)	Ticagrelor 90 mg pre-HD or 1 day post-HD	VerifyNow $P2Y_{12}$ LTA 20-μM ADP	CKD stage 5 on HD	Median time to maximum concentration was not significantly different to healthy controls. Mean IPA >90% 2 h post-dose and was consistent across all treatments, regardless of timing on HD. PRU was unchanged by dialysis, but overall values were higher than healthy subjects.	No clinical safety data
Kamada et al. 2019 [63]	Single-center prospective study	HD $N = 38$	Switched to prasugrel 3.75 mg OD from clopidogrel 75 mg OD monotherapy	VerifyNow $P2Y_{12}$	CKD stage 5 on HD	Prasugrel inhibited platelet aggregation more effectively than clopidogrel pre-(PRU 175 Vs 226) and post-HD (PRU 210 Vs 256). Significant increase in PRU for both clopidogrel and prasugrel post-HD ($p < .001$)	Pharmacodynamic study but no short-term bleeding or other adverse events after 14 days
Ohno et al. 2019 [11]	Multi-center prospective study	HD $N = 41$	Clopidogrel 75 mg OD + aspirin 100 mg OD Vs prasugrel 3.75 mg OD + aspirin 100 mg OD	VerifyNow $P2Y_{12}$ CYP2C19 genotyping	CKD stage 5 on HD	HTPR (PRU >208) in 75.7% clopidogrel prior to switching. 75% on low-dose prasugrel remained non-responders with HTPR. Difference in overall PRU was significant but remained >208 PRU. Unclear of timings of sampling in relation to HD	Pharmacodynamic study but no major bleeding at 30 days, 1 minor episode.
Wu et al. 2019 [14]	Meta-analysis	No CKD $N =$ 11138 (78.6%) CKD $N = 3028$ (21.4%) on clopidogrel	Clinical outcomes associated with HTPR	NA	'CKD' NOS	HTPR demonstrated in CKD patients OR 1.34 (95% CI 1.23–1.46). HTPR increases risk of MACE RR 2.99, (95% CI 1.19–7.53 $p < .00001$)	Cardiovascular events only, no inclusion for bleeding events.

AU, aggregation units; BARC, bleeding academic research consortium; BD, twice daily; CAD, coronary artery disease; CKD, chronic kidney disease; CrCl, creatinine clearance mL/min; CYP, cytochrome P450 enzymes; eGFR, estimated glomerular filtration rate ml/min/1.73m^2 ; HD, haemodialysis; HTPR, high on-treatment platelet reactivity; IPA, inhibition of platelet aggregation; LR, low responder (PRI ≥61%); LTA, light transmittance aggregometry to adenosine diphosphate and arachidonic acid; NOS, not otherwise specified; NSTEACS, non-ST-segment elevation acute coronary syndrome (includes unstable angina); OD, once daily; PCI, percutaneous coronary intervention; PFT, platelet function testing; PRI, platelet reactivity index; PRU, $P2Y_{12}$ reaction units; RCT, randomised controlled trial; TIMI, Thrombolysis In Myocardial Infarction; T90, ticagrelor 90 mg BD; T60, ticagrelor 60 mg BD; VASP, vasodilator-stimulated phosphoprotein phosphorylation.

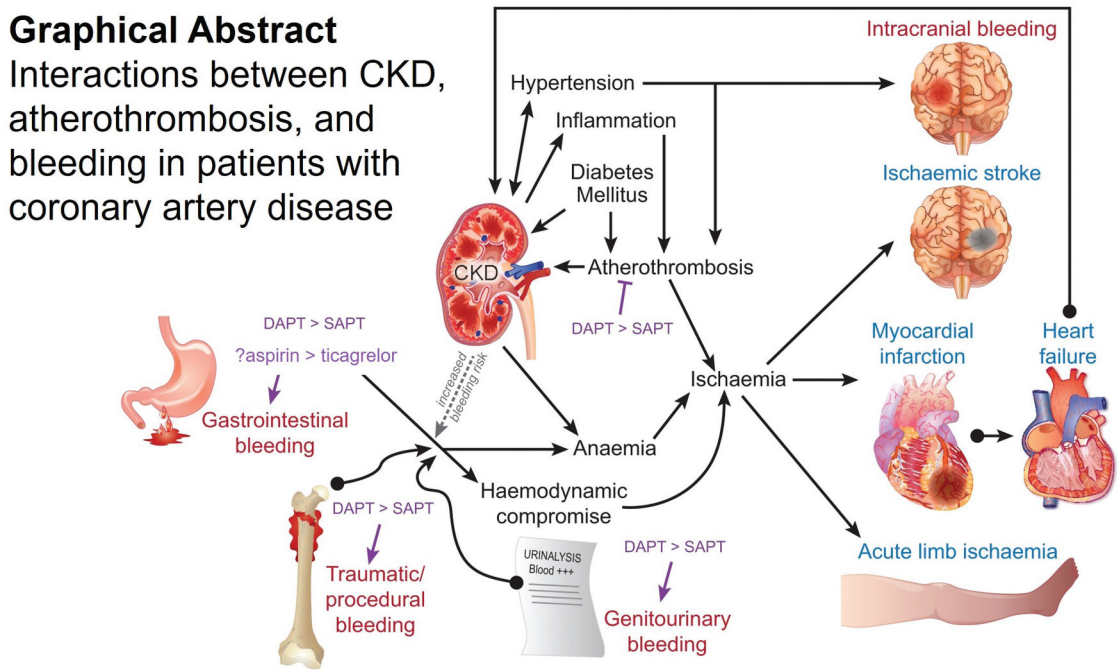

Figure 2. Graphical abstract of interactions between chronic kidney disease (CKD), atherothrombosis and bleeding in patients with coronary artery disease. CI, confidence interval; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy. Adapted from and reproduced with permission from the European Society of Cardiology. Parker, Storey, 2021 [56].

Advanced CKD in antiplatelet trials

Table III describes the distribution of CKD populations within the major trials over the past 20 years. Treatment inequalities have manifest because advanced CKD is poorly ascribed within these trials. Recruitment of patients with eGFR <60 mL/min/1.73 m^2 has historically comprised <25% across all major trials [3]. Developing robust generalised findings for DAPT/SAPT in this cohort is paramount.

Few trials segregate CKD by disease stage, dichotomising as 'non-CKD' and 'CKD' for eGFR ≥60 and <60 ml/min/1.73 m^2, respectively. Evidence is heavily reliant upon subgroup analyses. Recent head-to-head trial evaluation of more potent $P2Y_{12}$ inhibitors in ISAR-REACT-5 [20,82] also did not stratify CKD further than eGFR <60 mL/min/1.73 m^2 ($N = 760$/4012 [18.9%]), and ESKD was excluded. While a reduction in eGFR was associated with increased bleeding and ischaemic events, it was concluded that this had no significant impact on the relative benefit of a prasugrel-based strategy on the primary end point of death, MI or stroke compared to a ticagrelor-based strategy (HR 1.47 [1.04–2.08]) with no significant difference in bleeding risk [82]. PEGASUS-TIMI-54 CKD subgroup analysis (CrCl <60 ml/min = 23.2%, $N = 4849$) demonstrated a more marked relative MACE risk reduction with ticagrelor (with aspirin) in those with eGFR <60 ml/min/1.73 m^2 [RR 0.72, 95% CI 0.59–0.89] compared to those with eGFR ≥60 ml/min/1.73 m^2 [RR 0.83, 95% CI 0.72–0.96] [33], although the interaction P value for this subgroup analysis was not significant. In contrast to PEGASUS-TIMI-54, POPular AGE, comprising 37% ($N = 377$) with eGFR <60 ml/min/1.73 m^2, found clopidogrel and aspirin to be non-inferior to ticagrelor and aspirin in the older population (>70 years) following NSTEMI with fewer BARC 3 and 5 bleeding events [18]. These findings, however, are underpowered and any relationship to advanced CKD remains unclear. Further head-to-head comparisons of DAPT in advanced CKD are awaited [17].

Bleeding and thrombotic risk scores for ACS treatment in advanced CKD

Scores aimed at balancing the ischaemic and bleeding risks with DAPT prescription [83,84] are not robustly validated for patients with advanced CKD. The DAPT risk score was developed in a population treated with aspirin and clopidogrel with a low prevalence of CKD (15.8%) and validated with even fewer (7.7%) [83]. This sample is not representative of registry demographics, has no relationship to more potent $P2Y_{12}$ inhibitors and does not consider dynamic changes in renal function or duration of DAPT. PRECISE-DAPT [85] was developed to address some of these issues by integrating dynamic variation in renal function. This score utilises haemoglobin (g/dL), age (years), white blood cells (10^9/L), creatinine clearance (mL/min) and prior bleeding. Derived from eight trials ($N = 14$ 963), with median CrCl = 79.1 mL/min (range 60.8–98.0 mL/min), 44.4% had stable CAD undergoing PCI and the remainder ACS. It was validated in two cohorts, the PLATO trial ($N = 8595$) and the BernPCI registry 2009–2014 ($N = 6172$). CKD however is neither stratified by stage nor highly proportioned in either of these populations. PLATO participants with CrCl <60 mL/min comprised 21% of those with baseline measurements with median CrCl in the overall population of 84.6 mL/min (67.3–102.9 mL/min) and a similar median CrCl of 87.6 mL/min (range 65.4–105.4 mL/min) within the BernPCI registry [85]. The absence of categorisation of renal function means neither validation dataset includes an ac^{c}urately observed risk relationship with progressive renal dysfunction. Failure to capture advanced CKD means that PRECISE-DAPT risk scores can therefore be criticised for extrapolating risk percentages for such cases [83]. Pooled analysis of individual patient data could enhance validation of current risk tools; however, historically poor labeling, disproportionately low enrollment, and lack of dynamic renal assessment in advanced CKD are restrictive.

Table III. CKD distribution, efficacy of antithrombotic therapies and bleeding risk in major trials.

Author, year	RCT	Population	Intervention	CKD distribution eGFR mL/min/1.73 m^2	Outcomes	Bleeding risk
Ahmed et al. 2011 [77]	**CLARITY-TIMI −28**	$N = 3491$ eGFR data available for 3252 (93%) STEMI	Clopidogrel 75 mg Vs placebo with fibrinolysis	Excluded creatinine >220 µmol/L) eGFR ≥90 ($N = 841$, 26%) eGFR 60–89 ($N = 1897$, 58%) eGFR <60 ($n = 514$, 16%)	Ischaemic complications higher in moderate eGFR (OR 1.5, 95% CI 1.0–2.1, $P = .04$). Clopidogrel no benefit Vs Placebo when eGFR <60.	30-day bleeding increase as eGFR declines.
Bhatt et al. 2006 [78]	**CHARISMA**	$N = 15\,603$ Stable CVD	Clopidogrel + aspirin Vs placebo +aspirin	Diabetic nephropathy subgroup (eGFR undefined) $N = 1006$ (clopidogrel), $N = 1003$ (placebo) (12.9%)	Clopidogrel plus aspirin not significantly more effective in reducing MI, stroke or death from CVD, potential benefit in patients with prior MI. No subgroup analysis.	Severe bleeding RR 1.25 (95% CI 0.97–1.61, $P = .09$), Moderate bleeding RR 1.62 (95% CI1.27–2.08, $P < .001$). No subgroup analysis.
Wiviott 2007 [79]	**TRITON-TIMI-38**	$N = 13\,608$ ACS	Prasugrel Vs clopidogrel	CrCl ≥60 ml/min; $N = 11\,890$ (87%) CrCl <60 ml/min; $N = 1490$ (11%) (data missing 2%) Matched in groups 11% Prasugrel and 12% Clopidogrel	Superior efficacy of prasugrel for reduction in MI. Subgroup showed no benefit in CrCl <60 ml/min. Net harm; prior CVA, >75 years or <60 kg.	Higher rate of life-threatening bleeding with prasugrel.
Best et al. 2008 [80]	**CREDO**	$N = 2002$ Elective PCI	Clopidogrel + aspirin Vs placebo + aspirin	CrCl >90 ml/min; $N = 999$ (49.9%) Mild: CrCl 60-89 ml/min = 672 (33.5%) Moderate CrCl <60 mL/min = 331 (16.5%) Excluded creatinine >3 mg/dL or 265 µmol/L	No significant difference in outcomes in clopidogrel Vs placebo in patients with CKD.	No difference in bleeding events compares to placebo in moderate CKD group (9.8% Vs 5.1%, $P = .106$)
James et al. 2010 [35]	**PLATO**	$N = 18\,624$ PCI for ACS	Ticagrelor + aspirin Vs clopidogrel + aspirin	Excluded dialysis, median CrCl 80.3 mL/min (63–99) Crcl <60 mL/min $N = 3237$ (17.4%)	Ticagrelor reduced ischaemic end points and mortality without significant increase in major bleeding. Ticagrelor increased non-procedure-related bleeding	Increased risk of major and minor bleeding with CKD not differentiated by stage.
Roe et al. 2012 [81]	**TRILOGY**	$N = 7243$ ACS, not STEMI	Prasugrel Vs clopidogrel	Excluded dialysis Median CrCl 81 ml/min (IQR 63–102 ml/min) matched both groups	No significant difference in end point or bleeding	No significant difference in bleeding events
Magnani 2016 [33]	**PEGASUS-TIMI 54**	$N = 20\,898$ (99% of overall trial population) MI patients with history of MI	Ticagrelor 90 mg BD and 60 mg BD vs placebo	CrCl <60 mL/min $N = 4849$ (23.2%) eGFR ≥90 $N = 3251$ (15.6%) eGFR 60–90 $N = 12\,798$ (61.2%) eGFR 45 to < 60 $N = 3536$ (16.9%) eGFR <45 $N = 1313$ (6.3%) Excluded dialysis	Platelet inhibition similar with 60 mg to 90 mg dose, superior to placebo. Relative risk reduction of MACE was similar but greater absolute risk reduction with eGFR <60 as this subgroup at higher overall risk 2.7% vs 0.96%	No increased risk of major bleeding but excess minor bleeding
Schupke et al. 2019 [20]	**ISAR-REACT5**	$N = 4018$ ACS (Majority PCI)	Ticagrelor 90 mg OD Versus prasugrel 10 mg OD	Dialysis excluded N= Creatinine 88 ± 27 µmol/L Ticagrelor (5.8% <83 µmol/L) 88 ± 31 µmol/L Prasugrel (4.9% <83 µmol/L)	Incidence of composite end point including MI lower in prasugrel compared with ticagrelor, but this was not sustained when creatinine <83 µmol/L	No comparative significant increase in major bleeding

(*Continued*)

Table III. (Continued).

Author, year	RCT	Population	Intervention	CKD distribution eGFR mL/min/1.73 m^2	Outcomes	Bleeding risk
Gimbel et al. 2020 [18]	**POPular AGE**	$N = 1002$ NSTE-ACS >70 yrs	Clopidogrel + aspirin versus ticagrelor + aspirin or prasugrel + aspirin	Dialysis excluded eGFR <60: $N = 181$ (36%) Clopidogrel $N = 186$ (37%) Ticagrelor <1% Prasugrel	Clopidogrel non-inferior. Favorable alternative with lower rates of discontinuation without increased risk of MACE.	BARC 3 and 5 bleeding clopidogrel 6% Vs ticagrelor 9% (HR 0.61 CI 0.38–0.98, p = .034)
Bangalore et al. 2020 [19]	**ISCHEMIA-CKD**	N = 777	Invasive versus conservative-strategy with at least moderate ischaemia on exercise or stress testing	Renal transplant 24/777 (3.1%) eGFR <15 on dialysis $N = 415/777$ (53.4%) (83.7% HD, 14.6% PD) eGFR <30 $N = 362/777$ (46.6%) (eGFR <15 not on dialysis (51/362 (14.1%), eGFR 15 to < 30 311/262 (85.9%))	83% patients on aspirin at baseline and 87% at last FU visit. 22.6% on clopidogrel at baseline. 10% anticoagulated. Higher incidence of non-procedural stroke in invasive	No record of bleeding events
Stefanini et al. 2021 [55]	**TWILIGHT-CKD**	$N = 1111$ (16.3%) eGFR <60	3 month switch to ticagrelor (T90) + placebo Vs ticagrelor (T90) + aspirin	eGFR <60 excluding dialysis $N = 796$ eGFR 45–59 (71.6%) $N = 315$ eGFR 15–45 (28.4%)	Rates of death, MI or stroke were not significantly different between the two groups. 7.9% Vs 5.7%; HR 1.4, 95% CI 0.88–2.22	T90 + placebo reduced BARC (2,3,5) 4.6% Vs 9%; HR 0.5 95% CI 0.31–0.8.

ACS, acute coronary syndrome; BARC, bleeding academic research consortium; CKD, chronic kidney disease; CI, confidence interval; CrCl, creatinine clearance mL/min; CVA, cerebrovascular attack; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate as ml/min/1.73m^2 ; HD, haemodialysis; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome (includes unstable angina); PCI, percutaneous coronary intervention; PD, peritoneal dialysis; RCT, randomised controlled trial; RR, relative risk; STEMI, ST-segment elevation myocardial infarction.

Absent from current antiplatelet risk scores is urine albumin-to-creatinine (uACR) ratio. uACR is increasingly evidenced as an important distinguishing factor when risk profiling for CVD [86]. In patients with uACR >1.1 mg/mmol (>10 mg/g), cardiovascular mortality increases independent of CKD stage, with proportionately higher risk depending on progression of CKD and uACR [1]. Even in those with eGFR >90 ml/min/1.73 m^2, the presence of uACR 1.1–3.3 mg/mmol (10-29 mg/g) conferred an adjusted HR for cardiovascular mortality of 1.63 (CI 1.20–2.19) [1]. These figures increase exponentially with deteriorating renal function [1]. Importantly, bleeding risk is also increased with albuminuria regardless of CKD stage [73]. Monitoring uACR is recommended for diabetic patients and those with eGFR <60 ml/min/1.73 m^2 or suspected CKD [4]. Despite therapeutic implications, in-patient testing is not routinely recommended in comparison to other risk markers, such as lipid profile and HbA1c [8,87]. In-patient testing of uACR for secondary prevention of CVD in advanced CKD offers prognostic potential if utilised in targeting treatment strategies.

High-sensitivity troponin T is an additional risk biomarker, associated with a 2- to 5-fold increased risk of death in otherwise stable patients with ESKD [88,89], with further prognostic value in interval monitoring if receiving peritoneal dialysis treatment [90]. C-reactive protein has also been shown to be an independent predictor of death in patients receiving HD [91] and peritoneal dialysis [90] after adjusting for confounders. The utility of high-sensitivity CRP, as a measure of low-grade inflammation, did not show a strong predictive performance for all-cause mortality and MACE regardless of CKD stage in a large East Asian cohort [92]. Geographical and ethnic variations may, however, contribute to the lower cardiovascular event rate observed in this observational study [92]. Growth differentiation factor-15 (GDF15) is also associated with inflammatory conditions and prediction of major bleeding and cardiovascular events [93]. Levels are significantly higher in patients with ESKD and CVD and further associated with dialysis vintage [22]. The relationships between duration of DAPT, uACR, troponin and inflammatory markers, on the one hand, and bleeding and thrombotic outcomes on the other have yet to be explored.

The utility of platelet-function testing for individualisation of DAPT in HD patients with bleeding (or concerns for bleeding, such as severe anaemia) is also worth exploring, particularly as bleeding risk scores such as HAS-BLED, ATRIA, HEMORR2HAGES and ORBIT for those requiring concurrent anticoagulants have poor predictive abilities [74] and the DAPT and PRECISE-DAPT scores have yet to be validated for dialysis patients [83]. An alternative strategy for de-escalation warranting further exploration is the withdrawal of aspirin and the use of ticagrelor monotherapy in DAPT-treated patients with advanced CKD and high bleeding risk.

The future for advanced CKD patients with IHD

Table IV summarises contemporary evidence for advanced CKD patients with IHD and outlines avenues for future research.

Conclusion

This review presents an overview of advanced CKD within the ACS population. Although not exhaustive, search criteria incorporated studies targeting this sub-population to evaluate registry inclusion, antiplatelet choice and bleeding risk. Under-representation of advanced CKD in large RCT supporting guidelines for management of ACS has created a void in

Table IV. Evidence and opportunities for the CKD population with IHD.

Current evidence in advanced CKD	Opportunities for future research
• CKD progression has independent association with increased mortality and MACE	• Population studies and ACS registries to discriminate between all CKD stages • Differentiate between 'at-risk' CKD groups to further optimise and target treatment strategies for underlying CV risks (e.g. hypertension, albuminuria)
• CKD stage considered in some risk tools assessing bleeding risk, e.g. PRECISE-DAPT	• Tools not specifically validated in CKD cohorts
• Albuminuria has independent association with cardiovascular risk • High-sensitivity troponin T has an independent association with cardiovascular risk	• Benefits of routine measurement of uACR following a CV event in risk stratification for DAPT/SAPT • Utility of uACR and troponin in risk score stratification for prescription of DAPT/SAPT
• Inflammatory markers inversely associated with eGFR and uACR	• Utility of inflammatory markers for risk stratification of bleeding and thrombosis in patients on antiplatelet therapy
• Prescribing preference for clopidogrel despite lack of efficacy with HTPR	• PD studies and clinical outcomes in patients with advanced CKD on $P2Y_{12}$ inhibitor • TROUPER RCT outcomes awaited
• Lower overall prescription of antiplatelets and anticoagulants in advanced CKD	• Duration and choice of DAPT/or SAPT and combination antithrombotic therapies
• Lower bleeding risk without increased ischaemic burden for ticagrelor monotherapy after 3 months DAPT	• Adequately powered trial for ticagrelor monotherapy in advanced CKD
• Benefits of lower-dose ticagrelor long term in high-risk patients post-PCI with CKD	• Appropriate duration and timing of dose-adjustments in DAPT post-PCI in patients with advanced CKD to consider 1,3 and 12 months DAPT vs. SAPT

ACS, acute coronary syndrome; uACR, urine albumin creatinine ratio; CKD, chronic kidney disease; CV, cardiovascular; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate ml/min/1.73m^2; HTPR, high on-treatment platelet reactivity; ICH, intracranial haemorrhage; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; PD, pharmacodynamic; RCT, randomised controlled trial; SAPT, single antiplatelet therapy.

evidence for this subpopulation. In the past few years, there has been an increasing focus on this subgroup following recognition of the substantial disparity in treatments compared to those without advanced CKD. Research efforts are focussing on choice, dose and timing of antiplatelet regimens including DAPT and SAPT. Large trials specifically recruiting CKD patients offer opportunities to validate risk scores and explore markers for bleeding and thrombotic risk stratification. Study designs should involve increasing frequency of renal function measurement and consider integrating uACR, troponin and inflammatory markers into assessment. Guided de-escalation with withdrawal of aspirin and use of ticagrelor monotherapy in DAPT-treated patients with advanced CKD and high bleeding risk is also worth exploring. Such advances could help close the treatment gap for this high-risk population.

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