Review Article

Interventional Cardiology

Aspirin use in chronic kidney disease: Is cardiovascular risk reduction worth the risk?

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Abstract

Chronic kidney disease patients are at increased risk of atherothrombotic cardiovascular disease but are also at high risk of bleeding complications. Aspirin is an overall safe and efficacious therapy for the secondary prevention of CVD in certain populations. However, its use as primary prevention has not been proven to be of benefit and is counterbalanced by high risk of adverse events in patients with kidney disease. In this review, we present relevant differences in pathophysiology of CVD in patients with impaired kidney function and discuss the balance between benefit and harm and review controversial aspects of aspirin therapy for both primary and secondary prevention of cardiovascular disease in patients with CKD.

Keywords: Aspirin • Chronic Kidney Disease (CKD) • Cardiovascular disease • Primary prevention

Introduction

Patients with Chronic Kidney Disease (CKD) are at increased risk of major Cardiovascular Diseases (CVD) such as myocardial infarction, stroke, and peripheral vascular disease [1,2]. Few studies have specifically addressed the impact of anti-platelet therapy for either primary or secondary prevention of cardiovascular disease in patients with CKD. Here, we highlight the uncertain and controversial aspects of aspirin therapy for cardiovascular disease prevention in the context of CKD.

CKD is defined by persistent abnormalities in kidney function or structure for more than 3 months. Such abnormalities include decreased Glomerular Filtration Rate (GFR) less than 60 ml/min/1.73 m^2, albuminuria of at least 30 mg per 24 hours, abnormalities in urine sediment, histology or imaging suggesting kidney disease, or history of kidney transplantation [3]. CKD is commonly classified into stages determined by GFR and degree of albuminuria. Staging CKD can be a helpful guide for predicting progression of kidney disease to End Stage Renal Disease (ESRD) and for risk stratification across a broad spectrum of CKD complications and clinical outcomes (Table 1). CKD staging incorporating both GFR and albuminuria can help guide treatment decisions, disease monitoring strategies and timeliness of nephrology specialist referral.

Literature Review

CKD is highly prevalent, affecting nearly 10% of the worldwide population. Over the past 20 years, global prevalence of CKD has increased 29.3%, and mortality attributable to CKD has increased 41.5% [4]. Despite the increasing prevalence of CKD worldwide, only a minority of patients with kidney disease will progress to ESRD. Most patients with CKD will die of other, non-renal causes prior to requiring renal replacement therapy.

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Table 1: Prognosis of CKD by GFR and albuminuria categories. Green, low risk of disease progression; yellow, moderately increased risk of disease progression; orange, high risk of disease progression; red, very high risk of disease progression. **Abbreviations:** CKD: Chronic Kidney Disease; GFR: Glomerular Filtration Rate; ACR: Albumin-to-Creatinine Ratio. Reprinted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) [3].

				Albuminuria (ACR) categories (mg/g)		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30	30-300	>300
GFR Categories (mL/min per 1.73 m^2)	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Mildly to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

The presence of CKD and proteinuria both independently associate highly with CVD, amplifying risk of all-cause mortality and cardiovascular mortality in graded fashion as GFR declines and as proteinuria increases [5,6]. CVD in patients with GFR <60 ml/min/1.73 m^2 accounts for 50% of all deaths, significantly greater than the 26% risk of cardiovascular death in patients with preserved renal function [7]. Mortality from cardiovascular disease attributed to CKD accounted for 4.6% of worldwide deaths in 2017 [4].

The pathogenesis of cardiovascular disease and CKD share many common, traditional risk factors such as age, diabetes mellitus, hypertension, hyperlipidemia, and tobacco use. However, the excess cardiovascular disease mortality is not fully accounted for by these entities alone. Recent meta-analyses of non-dialysis dependent CKD patients, controlling for traditional shared risk factors, showed increasing absolute risk of death with declining GFR and higher amounts of albuminuria [5,8,9]. Enhanced propensity for vascular calcification and a pro-inflammatory state in patients with declining GFR may be responsible for the excess risk.

Like patients with preserved kidney function, modification of traditional risk factors and beneficial lifestyle changes are the foundation for cardiovascular risk reduction in CKD. Despite limited representation in major cardiovascular therapeutic trials, available data concerning use of statins, blood pressure control, glycemic control and sodium-glucose cotransporter-2 (SGLT-2) inhibition, moderation of alcohol use, and smoking cessation have all been shown to limit cardiovascular mortality in patients with CKD [10-15]. While there is compelling data in the non-CKD population, relatively few studies specifically address the impact of anti-platelet therapy for prevention of cardiovascular disease in patients with CKD.

Patients with CKD tend to have an atherothrombotic predisposition yet are also prone to bleeding complications. A recent meta-analysis by Baaten et al. highlights inconsistencies in mechanisms responsible for both quantitative and functional platelet abnormalities in CKD states [16]. Overall, results of their meta-analysis point toward disordered platelet function and aggregation as well as prolonged bleeding time. Platelet exhaustion, a conceptual condition exhibiting down-regulated platelet responsiveness occurring after consistently elevated states of platelet activation, may explain the polar phenotypes.

Aspirin (acetylsalicylic acid) selectively and irreversibly acetylates platelet cyclooxygenase (COX), leading to inhibition of thromboxane A2 in platelets thus affecting platelet to platelet interactions and, indirectly, platelet aggregation [17,18]. Aspirin is primarily hepatically metabolized, with some dose and urine pH dependent renal excretion. While pharmacodynamic and pharmacokinetic mechanisms account for aspirin efficacy in individuals, multiple studies have shown a higher frequency of insufficient platelet COX-1 inhibition of thromboxane formation in patients with CKD [18]. This "aspirin resistance", along with platelet dysfunction inherent to CKD states, may account for the imbalanced risk to benefit ratio of antiplatelet agents in CKD patients [16]. Moreover, aspirin has been shown to increase risk of either developing CKD or enhancing progression of underlying CKD, particularly in subjects with more than 500 g of aspirin intake per year and also in the elderly [19,20]. Use of aspirin, one of the oldest and most widely used therapeutics in medicine, remains controversial as preventive therapy in this inherently high-risk population.

Primary prevention

Recommendations regarding the use of aspirin for primary prevention of cardiovascular disease are currently limited to specific populations at particularly high risk of developing atherosclerotic vascular disease who are not at high risk of bleeding complications [21]. Risk of developing CVD is often inferred from risk scores based on cohort data. Unfortunately, risk equations do not commonly include the unique comorbidities associated with CKD and thus tend to underpredict risk of CVD in CKD [22].

Across the spectrum of CKD, higher rates of atherothrombotic vascular disease should, at first glance, be a solid basis for aspirin use as primary preventive therapy. However, available data to date are equivocal (Table 2), leaving an undefined role for aspirin in this setting. Current KDIGO recommendations do not support the use of aspirin for primary prevention in CKD patients [3].

Post-hoc subgroup analysis of the Hypertensive Optimal Treatment (HOT) study showed that aspirin use reduced risk of major cardiovascular events [23]. Increased risk of major bleeding was non-significantly greater with more advanced CKD stage, but overall was outweighed by benefit. However, there was no delineation of outcomes between patients using aspirin as primary or secondary prevention, and only 2.9% of participants had a GFR <45 ml/min/1.73 m^2. A sub-analysis of the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial showed no benefit of aspirin use in subjects with a GFR <60 ml/min/1.73 m^2 [24]. A post-hoc, propensity matched study of participants in The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial showed no benefit of aspirin use in patients without cardiovascular disease at baseline and no increased risk of gastrointestinal bleeding [25]. Post-hoc analysis of the ASPirin in Reducing Events in the Elderly

Table 2: Major studies of aspirin therapy as primary prevention for major cardiovascular outcomes in patients with CKD.

Author, year	Study Type	Findings	Major Limitations	Reference
Jardine et al., 2010	Post hoc subgroup analysis	Progressive benefit as eGFR declined	Did not specify if primary or secondary prevention, 2.9% of patients with GFR <45 ml/min/1.73 m^2	23
Saito et al., 2011	Post hoc subgroup analysis	No benefit in eGFR <60 ml/min/1.73 m^2	Non-blinded design, only 20 patients with eGFR <30 ml/min/1.73 m^2	24
Wolfe et al., 2021	Post hoc analysis	No benefit, increased bleeding risk in CKD	Post hoc study, CKD status based only on one lab value	26
Kim et al., 2014	Retrospective propensity matched analysis	Increased risk of CVD and CKD progression	Single center, single ethnic group	30
Desai et al., 2021	Post hoc, propensity matched analysis	No benefit across all GFR strata	Focused on aspirin use at baseline, use of propensity scoring	25
Palmer et al., 2012	Meta-analysis	Reduced risk of myocardial infarction, increased bleeding risk	Included ESRD and some pre-existing CVD patients	27
Major et al., 2016	Meta-analysis	No benefit, increased risk of bleeding	Small number of studies included	28
Goicoechea et al., 2018	Randomized Controlled Trial	No benefit in CKD stage 3 and 4	Small sample size	30

(ASPREE) trial showed no differential benefit of aspirin use for prevention of major adverse cardiovascular events in subjects with CKD (eGFR <60 ml/min/1.73 m^2), although there was a protective effect in subjects with albuminuria.26 Bleeding rates were similar to non-CKD subjects.

In a 2012 meta-analysis of 44 randomized studies, Palmer et al. showed that anti-platelet agents reduced the risk of myocardial infarction independent of CKD stage, but not stroke, cardiovascular or all-cause mortality [26,27]. Bleeding risk was also found to increase similarly across all GFR categories. The authors conclude that in patients with low risk of myocardial infarction, the risk of harm outweighs any benefit of anti-platelet therapy. Notably, this analysis included studies with ESRD and some pre-existing CVD populations. In 2016, a meta-analysis by Major et al. of studies specifically addressing use of aspirin in CKD patients showed no benefit in the primary prevention of cardiovascular events, no significant reduction in mortality, and increased risk of bleeding [28,29]. One retrospective, single center study by Kim et al. showed an increased risk of CVD associated with aspirin use in CKD patients [29].

In a controlled trial, Aspirin for Primary Prevention of Cardiovascular Disease and Renal Disease Progression in Chronic Kidney Disease Patients (AASER Study), Goicoechea et al. randomized 111 patients with CKD 3 and 4 to daily low dose aspirin versus placebo for primary prevention of CVD [30]. After more than 5 years of follow up, there was no difference in incidence of the primary outcome (a composite of heart failure acute coronary syndrome peripheral vascular disease, or stroke) and there was no difference in bleeding risk. There are at least two active randomized clinical trials that are recruiting patients to prospectively study primary prevention in patients with CKD. Antiplatelet therapy for the prevention of atherosclerosis in chronic kidney disease patients (ALTAS-CKD) is a multicenter, prospective, randomized, double-blind, placebo controlled trial of Chinese subjects with advanced CKD studying the effect of aspirin use on carotid ultrasound detected atherosclerosis, combined cardiovascular events, all cause mortality, and 50% decrease in eGFR [31]. Aspirin to Target Arterial Events in Chronic Kidney Disease (ATTACK) is a large, randomized controlled trial studying the effect of aspirin use as primary prevention for the primary composite outcome of non-fatal MI, non-fatal stroke and cardiovascular death. The study is estimated to enroll 25,210 patients and should be completed by 2025 [32].

Several underlying features of patients with CKD may help explain the limited utility of aspirin as primary prevention. In addition to the traditional cardiovascular risk factors such as diabetes, dyslipidemia, hypertension, and smoking, CKD patients experience high rates of anemia, oxidative stress, altered bone mineral metabolism, and retention of uremic toxins. The additional metabolic imbalances present contribute to a different pattern of vascular disease characterized by arterial calcification, microvascular and endothelial dysfunction, vascular stiffness, and left ventricular hypertrophy. These non-atherosclerotic conditions are commonly found in CKD patients and often account for a predominance of heart failure, arrhythmia and sudden cardiac death. Such conditions are not amenable to anti-platelet therapy and complicate the extrapolation of aspirin benefits to the CKD population.

Another factor complicating aspirin use in CKD patients is the imbalanced and complex predisposition to both atherothrombotic and bleeding complications. Uremic platelets have been described as having both procoagulant and anticoagulant properties, although reports detailing quantitative and qualitative aspects of platelet dysfunction in CKD are inconsistent [33]. Overall, available data points toward impaired platelet activation, recruitment, adhesion, and aggregation in patients with CKD [16]. These findings, along with potential aspirin resistance in CKD patients may help explain the lack of benefit of aspirin relative to risk of bleeding.

Secondary prevention

Aspirin is a cornerstone of modern antiplatelet therapy. Robust evidence supports the use of aspirin to prevent new cardiovascular events in patients with established atherosclerotic cardiovascular disease. This is perhaps best demonstrated by an Antithrombotic Trialists' Collaboration (ATC) meta-analysis showing a 22% relative reduction in subsequent serious vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) with aspirin use [34].

The influence of impaired renal function on the impact of aspirin use for secondary prevention is unclear. No randomized controlled trials that inform the safety and efficacy of aspirin in prevention of atherosclerotic vascular disease in CKD patients with established CVD have been performed. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines encourage use of aspirin for secondary prevention of cardiovascular disease [3]. As the basis for this recommendation, the guideline authors cite post-hoc analysis of the Hypertensive Optimal Treatment (HOT) trial. In their study, Jardine et al showed greater proportional reduction of cardiovascular events and all-cause mortality with progressively lower eGFR. However, as previously mentioned, analysis of aspirin effectiveness for primary or secondary prevention was not reported [23].

There are data that point towards differences in the effectiveness of aspirin in patients with CKD. A post hoc analysis of the ALLHAT trial showed no benefit of aspirin use on fatal CAD or non-fatal MI outcomes in participants with established cardiovascular disease [25]. Aspirin use, while associated with a reduction in all-cause mortality for the overall study population (70% with established CVD), was limited to subjects with eGFR >60 ml/mi/1.73 m^2. Cardiovascular death was prevented with aspirin use in the overall study population but was not statistically significant in participants with eGFR <90 ml/min/1.73 m^2. Bleeding risk was similar across all GFR strata. Additionally, findings from the KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD) prospective, observational cohort study show increased risk of cardiovascular events with aspirin used as secondary prevention in patients with low body weight (<60 kg) [35]. Though optimal dosing of aspirin remains an area of active research, a recent open-label pragmatic trial comparing dosing strategies for secondary prevention of CVD found similar rates of cardiovascular events and major bleeding in the overall study population and in the CKD subgroup irrespective of high (325 mg) or low (81 mg) dose for daily aspirin use [36].

Overall, given the high risk of atherothrombotic events in CKD patients and barring any contraindications such as high risk of bleeding or low body weight, the use of aspirin as a prophylactic measure to prevent further CVD events is reasonable.

Conclusion

Patients with CKD carry an elevated risk of CVD and suffer from a complex imbalance of bleeding and thrombotic properties. Aspirin is an overall safe and efficacious therapy for the secondary prevention of CVD in certain populations of patients with CKD. However, its use as primary prevention has not been proven to be of benefit and carries a high risk of adverse events, mainly bleeding. At this time, pending completion of major randomized clinical trials of preventive aspirin use across the spectrum of CKD, its use as primary prevention should generally be discouraged.

Conflicts of Interest

None.

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