Review Article

Oral Antiplatelet Agents and Chronic Kidney Disease

Dimitrios Alexopoulos, Agelliki Panagiotou

Department of Cardiology, Patras University Hospital, Patras, Greece.

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Address:
Dimitrios Alexopoulos

Department of Cardiology
Patras University Hospital
Rion 26500, Patras
Greece
e-mail: dalex@med.upatras.gr

Chronic kidney disease (CKD) is recognized as an independent predictor for myocardial infarction, stroke and all-cause mortality due to accelerated atherosclerosis.[1] Cardiovascular mortality accounts for 45% of all-cause mortality in CKD patients,[2,3] while in end-stage renal disease (ESRD) death attributable to arrhythmic mechanisms is responsible for 27% of the cardiovascular mortality observed in this population, with an annual rate of sudden death of approximately 7%.[4,5] Moreover, patients with ESRD under renal replacement therapy are prone to develop hemostatic disorders, which vary from thrombotic complications to bleeding abnormalities.[6,7] Vascular complications resulting from the thrombotic tendency are responsible for 25% of all hospitalizations in hemodialysis patients and therefore are considered as a significant burden on the health care system.[4] This review focuses on the oral antiplatelet agents that could be used as prophylaxis for the thrombotic events in CKD, with special emphasis on patients who undergo hemodialysis.

Thrombotic abnormalities in CKD

Thrombotic abnormalities may be present in all stages of CKD, but the most significant are observed in renal replacement patients and predominantly those on hemodialysis. The spectrum of thrombotic abnormalities varies from deep vein thrombosis and pulmonary embolism to hemodialysis vascular access thrombus formation, atherosclerosis-associated thrombosis (mainly in the form of acute coronary syndromes), renal allograft-associated thrombosis and heparin-induced thrombocytopenia.[8] The most frequent thrombotic event among chronic hemodialysis patients is arteriovenous access thrombosis, which occurs in 45% of the patients. It is believed that stenosis caused by intimal and muscular hyperplasia (induced by growing factors) can result in low blood flow and thus hypercoaguability, clot formation, hypotension and hypovolemia.[9] Thrombotic cardiovascular events are the major cause of death in ESRD.[10] Hypertension, hyperhomocysteinemia, disturbances in the lipidemic profile (elevated Lipoprotein (a), very low density lipoproteins and triglycerides, as well as reduced high density lipoproteins), hyperparathyroidism, extensive coronary calcification and oxidative stress are considered as factors promoting atherogenesis and thus coronary artery occlusion in ESRD. Activation of both fibrinolytic and coagulation factors as well as platelet dysfunction are thought to be the main causes of vascular changes. In addition, diabetes mellitus, the most common cause leading to CKD, is considered to be a highly prothrombotic state.[11] Insulin resistance may lead to an increase in plasminogen activator inhibi-

tor-1 and thus in fibrinolysis abnormalities, in coagulation disorders (such as elevated factor VII, von Willebrand factor, fibrinogen, factor XII), in increased platelet aggregation and adherence, and in endothelial dysfunction.

Platelet dysfunction

Excessive platelet activation occurs in CKD, even in the early stages of the disease. Specifically, the expression of P-selectin, glycoprotein 53 and activated fibrinogen receptor-1 on the platelet surface membrane is significantly increased in CKD patients.[12] In ESRD, these abnormalities are more pronounced and may lead to access site thrombosis. Several studies of hemodialysis patients have underlined the decreased membrane expression of glycoprotein Ib, especially at the end of the hemodialysis session.[13] On the other hand, Liani et al hypothesized the existence of an abnormal activation of platelet receptors (glycoprotein IIb/IIIa and glycoprotein Ib) as well as an increase in their number that might lead to thrombosis of the access site, but also to thrombotic and atherosclerotic complications.[14] Moreover, the hemodialysis procedure itself can lead to platelet activation due to the exposure to the artificial membrane[15] and the high shear stress and turbulence in the vascular access. Serum fibrinogen is increased in hemodialysis patients, promoting adhesion to inactivated platelets, thrombus formation and deposition on the access surface.[16] Both polytetrafluoroethylene grafts and native arteriovenous fistulas facilitate fibrinogen adhesion.[17] Activated platelets, by releasing factors (like platelet-derived growth factor) that promote intimal hyperplasia in the vascular access, may reduce the stability of the graft or fistula. The role of inflammation (cytokines tumor necrosis factor-a, interleukin-6) is also important, as it is associated with alterations in the expression of vascular and platelet adhesion molecules, the structure and concentration of lipoproteins (higher concentrations of lipoprotein (a)), the levels of coagulation factors and the activity of oxidants and antioxidants. Extrinsic factors such as the uremic toxins (urea, guanidinosuccinic acid, phenolic acid and parathyroid hormone),[18-20] anemia, hyperhomocysteinemia,[21,22] abnormalities of nitric oxide synthesis and abnormalities of von Willebrand factor contribute to the prothrombotic tendency in ESRD patients. The oxidative milieu may result in reduced bioavailability of nitric oxide and this has been proposed to adversely affect endothelial function, leading to vasoconstriction and further platelet adhesion/activation.[23] Furthermore, alterations in plasma factors can worsen the prothrombotic tendency that exists in CKD. A synopsis of the most significant thrombotic abnormalities in ESRD is shown in Table 1. Notably, peritoneal dialysis might produce less platelet dysfunction because of the lack of contact between artificial membranes and platelets (causing fewer disturbances in arachidonic acid metabolism) in addition to the better clearance of uremic toxins.[9] In peritoneal dialysis, platelet activation is closely related to low concentrations of serum albumin.

Treatment with oral antiplatelet agents

According to the above, platelet activation is heavily implicated in the prothrombotic state observed in CKD patients, and oral antiplatelet and sometimes anticoagulant agents have been extensively used in these patients. Oral antiplatelet agents that have been tested include dipyridamole,[24,25] aspirin,[26-30] clopi-

Table 1. Thrombotic abnormalities in end-stage renal disease.

Platelet factors:
– Increased platelet stimulation
– Abnormal membrane receptor expression(Gp Ib, GpIIb/IIIa)
– Contact with artificial circuit
– Hyperfibrinogenemia
– Release of growth factors(PDGF) that reduce blood flow in the vascular access
Endothelial factors:
– Increased levels of vWF
– Increased levels of thrombodulin
– Increased release of VCAM
– Oxidative stress and thus reduced NO synthesis
– Increased levels of PAI-1
Extrinsic factors:
– Uremic toxins
– Anemia
– Hyperhomocysteinemia
Plasma factors:
– Increased levels of d-dimers
– Reduced levels of protein C anticoagulant activity
– Increased levels of prothrombin fragments 1+2
– Increased levels of thrombin-antithrombin complex (ongoing coagulation)
– Decreased levels and reduced activity of antithrombin III
– Reduced levels of protein S
– Increased levels of tissue factor
– Elevation of antiphospholipid antibodies
– Increased levels of plasmin-antiplasmin complex (i.e. ongoing fibrinolysis)

vWF – von Willebrand factor; VCAM – vascular cell adhesion molecule; PDGF – platelet-derived growth factor; PAI-1 – plasminogen activator inhibitor; NO – nitric oxide.

dogrel, or the newer, more potent than clopidogrel $P2Y_{12}$ inhibitors, prasugrel and ticagrelor. Access thrombosis rates with antiplatelet agents in patients on hemodialysis are shown in Table 2.

Dipyridamole

Dipyridamole is a phosphodiesterase inhibitor that reversibly inhibits platelet aggregation, platelet-mediated thrombosis, as well as vascular smooth muscle proliferation *in vitro*. In patients with a new graft the lowest rate of thrombosis (17%) occurs when they are treated with dipyridamole alone, while the highest rate (50%) occurs in those treated with aspirin alone. In patients with prior graft thrombosis, thrombosis rates are higher and neither dipyridamole nor aspirin have been proved to be beneficial. However, when combined with dipyridamole, aspirin may reduce the rate of such events.[24] In a more recent study, dipyridamole and low-dose aspirin were given after the placement of a new arteriovenous graft until a first event of access occlusion. The one-year incidence of primary unassisted patency was 23% in the placebo group and 28% in the dipyridamole-aspirin group, while the hazard ratio (HR) for loss of primary unassisted graft patency in the dipyridamole-aspirin group, as compared with the placebo group, was 0.82 (95% confidence interval, CI: 0.68-0.98; p = 0.03).[25]

Aspirin

A low dose of aspirin was found to be ineffective for preventing thromboembolic accidents in low-risk hemodialysis patients while they were on treatment with recombinant erythropoietin.[26] However, in 2815 patients enrolled in the Dialysis Outcomes and Practice Pattern Study, aspirin use was related to a lower risk of thrombosis while there was no relationship between its use and bleeding.[27]

It is of interest that 28% of patients with cardiovascular disease exhibit a low or no response to aspirin ("aspirin resistance"),[28] and renal function impairment has been associated with this phenomenon. A 34.8% prevalence of aspirin resistance – defined as >550 units by the VerifyNow aspirin assay – has been described in hemodialyzed patients.[29] In a study, not only of patients receiving hemodialysis, but also those in stages 3-4 of CKD and a control group, aspirin resistance was found in 46.1%, 24.6% and 16.9%, respectively.[30] Further studies are needed in order to

Table 2. Antiplatelet agents and access thrombosis rate in hemodialysis.

Study	Year	Trial (N)	Intervention	Duration (months)	Access thrombosis rate
Dypiridamole:					
Sreedhara[24]	1994	RCT (N=107)	Dipyridamole 75 mg, aspirin 325 mg, both, placebo Type I: new graft Type II: recurrent thrombosis	72	Type I: 17% vs. 50% vs. 23% vs. 32% Type II: 83% vs. 50% vs. 100% vs. 80%
Dixon[25]	2009	RCT (N=649)	Dipyridamole 200 mg + aspirin 25 mg vs. placebo	60	40% vs. 42%
Aspirin:					
Kooistra[26]	1994	RCT crossover (N=153)	Aspirin 30 mg vs. placebo	3	16% (9.4% aspirin vs. 6.5% placebo, NS)
Clopidogrel:					
Trimarchi[36]	2005	Prospective (N=24)	Clopidogrel 75 mg vs. no antithrombotic therapy	Until diagnosis of thrombosis	8% vs. 92% (p=0.001)
Dember[37]	2008	RCT (N=877)	Clopidogrel (300 mg LD and 75 mg daily) vs. placebo	5 after AVF creation or 1 after dialysis initiation	12.2% vs. 19.5% (p=0.018)
Kaufman[38]	2003	RCT (N=200)	Clopidogrel 75 mg + aspirin 325 mg vs. double placebos	24	HR 0.81 (95% CI: 0.47-1.40) in favor of aspirin and clopidogrel therapy, (p=0.45)

AVF – arteriovenous fistula; CI - confidence interval HR – hazard ratio; LD – loading dose; MD – maintenance dose; NS – non-significant; RCT – randomized controlled trial.

define the clinical significance of aspirin resistance in CKD patients and to seek ways to overcome it.

Clopidogrel

Clopidogrel, a $P2Y_{12}$ inhibitor of platelet aggregation, is widely used for the prevention of access site thrombosis. In a small pharmacodynamic study in chronic hemodialysis patients, clopidogrel administration reduced the ADP-induced platelet aggregation to a degree comparable with that in patients with normal renal function, as reported in another study. This inhibition disappeared 7 days after clopidogrel discontinuation.[31] However, recent studies have shown that CKD is accompanied by a low platelet inhibitory response to clopidogrel administration (Table 3). Park et al,[32] in a prospective, randomized trial, described a higher platelet reactivity in patients with CKD than in those with normal renal function, while they were taking 75 mg of clopidogrel, although there was no difference between patients receiving 75 mg or 150 mg of clopidogrel. In diabetic patients with coronary artery disease treated with aspirin and clopidogrel, the presence of moderate or severe CKD is accompanied by a 2.4 to 3.8 higher rate of post-treatment increased platelet reactivity than is found in mild CKD patients or those with normal renal function.[33] In contrast, no significant effect of CKD on clopidogrel response, neither acutely (following 600 mg) nor after 1 month with 150 mg of clopidogrel was found in patients with CKD and a non-ST elevation myocardial infarction undergoing percutaneous coronary intervention (PCI).[34] The authors, however, advocate in high risk CKD patients the use of higher than usual clopidogrel doses, or alternative agents like prasugrel or ticagrelor. Interestingly, the hemodialysis itself seems to result in a reduction of platelet reactivity.[35]

The effect of clopidogrel on access thrombosis patency has been studied by several investigators (Table 2). In a small prospective study of 24 hemodialysis patients with grafts, only one thrombotic event was observed in the clopidogrel treated group, while 11 events occurred in those where no antithrombotic therapy had been used.[36] In a randomized, double-blind, placebo-controlled trial involving 877 patients, fistula thrombosis was observed less frequently with clopidogrel, although the suitability for dialysis did not differ between the two groups.[37] In 200 hemodialysis patients who received aspirin 325 mg and clopidogrel 75 mg daily or double placebos for at least 2 years, no significant effect of the antithrombotic treatment was reported.[38] However, the study was stopped because of the significantly increased bleeding risk in the active treatment group.

Table 3. Clopidogrel pharmacodynamic studies in patients with chronic kidney disease.

Study	Year	Population (N)	Clopidogrel dose	Assay	Results
Kaufman[31]	2000	Hemodialysis (N=9)	75 mg for 14 days	ADP-induced platelet aggregation 2 mM, 5 mM, 10 mM	From 48% to 23% From 59% to 38% From 66% to 44% p=0.01
Park[32]	2009	CKD (groups II, III) vs. normal renal function (group I) (N=59)	group I: 75 mg group II: 75 mg group III: 150 mg	VerifyNow (PRU)	Group I 239 ± 87 Group II 308 ± 70 Group III 302 ± 81 p=0.013
Angiolillo[33]	2010	Diabetic CAD patients categorized by the presence or absence of moderate/severe CKD (N=306)	75 mg	ADP and collagen platelet aggregation	60 ± 13% vs. 52 ± 15%, p=0.001 49 ± 20% vs. 41 ± 20%, p=0.004
Cuisset[34]	2010	PCI patients, 44 moderate/severe CKD 179 normal/mild CKD (N=223)	600 mg LD + 150 mg MD	ADP-induced platelet aggregation and VASP	1 month: 55.4% vs. 52.5% 10.5% vs. 43.8%

CKD – chronic kidney disease; ADP – adenosine diphosphate; VASP – vasodilator-stimulated phosphoprotein phosphorylation assay; LD – loading dose; LR – low responder; MD – maintenance dose; PCI – Percutaneous coronary intervention; PRU – platelet reactivity units; R – responder.

Dual antiplatelet therapy (clopidogrel and aspirin) is mainly used in coronary artery stenting and, even though these lesions are in the arterial circulation, they have similarities with the lesions observed in hemodialysis grafts.[39] CKD has been well recognized as a predictor of restenosis and stent thrombosis following PCI.[40-48] The high restenosis rates may be partially overridden by the use of drug-eluting stents.[46-48] Hemodialysis has been recognized as an independent predictor for ischemic events post PCI.[49,50] It is of great interest that recent outcome studies, like the Clopidogrel for the Reduction of Events During Observation (CREDO) and the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trials, suggest that renal function might have an impact on the clinical efficacy of clopidogrel. In fact, outcomes in clopidogrel-treated patients with CKD have been shown to be worse compared with those in patients with normal renal function, whereas clopidogrel may even be harmful in patients with diabetic nephropathy.[51,52]

In a large cross-sectional study, 440 consecutive PCI patients were tested with the vasodilator-stimulated phosphoprotein phosphorylation method and were classified as low responders or responders. At 9-month follow up, in low responder CKD patients all cause mortality, cardiac death and possible stent thrombosis were higher than in CKD responders (25.5% vs. 2.8%, 23.5% vs. 2.8% and 19.6% vs. 2.7%, respectively). In patients with preserved renal function, a low response did not affect outcomes.[53] In a retrospective evaluation of 1567 PCI patients (41% with stage III-V CKD) with adenosine diphosphate-induced platelet aggregation assessment, stage III-V CKD and a low response were independent predictors of the primary endpoint (composite of myocardial infarction, ischemic stroke, and death) within 1 year, after the administration of 600 mg clopidogrel and of 100 mg aspirin.[54] Therefore, in CKD patients the post PCI cardiovascular mortality seems to be associated with inadequate inhibition of $P2Y_{12}$ platelet receptors by clopidogrel. This high platelet reactivity may partially explain the increased prevalence of ischemic complications observed in CKD patients, as well as the previously described limited benefit of clopidogrel in the CREDO and CHARISMA trials.

Newer, more potent $P2Y_{12}$ inhibitors

The use of novel, more potent thienopyridine agents has been proposed as a way to overcome the low responsiveness to clopidogrel. Prasugrel, a third generation thienopyridine, was found to have the same pharmacokinetic and pharmacodynamic response in healthy subjects as well as in those with moderate/severe CKD and those on hemodialysis. More specifically, Small et al showed that the concentration of prasugrel's active metabolite was the same in normal renal function and in stage III-IV CKD, but was lower in stage V CKD, though without any difference in platelet inhibitory effect. There were no drug- or bleeding-related adverse events observed in this study.[55] In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI 38), the reduction in the primary endpoint (defined as death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) with prasugrel compared to clopidogrel was independent of the presence of CKD.[56] In the PLATO (Platelet Inhibition and Patient Outcomes) study, clopidogrel was compared to ticagrelor, a cyclopentyl-triazolopyrimidine reversibly binding to the $P2Y_{12}$ receptor. In 3237 patients with CKD (creatinine clearance <60 ml/L) ticagrelor reduced the primary endpoint (cardiovascular death, myocardial infarction, stroke) to 17.3% from 22.0% (HR 0.77, 95% CI: 0.65-0.90). This reduction was greater than that observed in patients with normal renal function (7.9% versus 8.9%, HR 0.90, 95% CI: 0.79-1.02). It should be mentioned that there was no significant difference in bleeding events between the two treatments in patients with normal or impaired renal function.[57] In both these important trials hemodialysis patients were excluded.

Conclusions

CKD, and especially ESRD, are characterized as a state with a prothrombotic tendency where platelet dysfunction plays a pivotal role. The beneficial action of oral antiplatelet agents like dipyridamole, aspirin and clopidogrel is rather limited in preventing the thrombotic complications that are frequently observed in this population. A low platelet responsiveness to aspirin and, mainly, clopidogrel are implicated in these moderate results. The use of new potent $P2Y_{12}$ inhibitors appears promising, although special consideration should be given to the possible bleeding events that CKD patients could demonstrate.

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