ANTIPLATELET THERAPY IN CKD

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Summary

Chronic kidney disease (CKD) patients are at increased risk of cardiovascular events (CVE) than general population. Antiplatelet agents (APA) reduce CVE in patients with normal kidney function. Whether they are of same efficacy and safety in CKD population is questionable because most of the studies did not include CKD population in their trial of APAs. At one hand there is poor response to APAs because of altered metabolism, on the other hand there is paradoxical more risk of major bleeding. This review will, address these issues of APAs use in CKD.

Key words

Antiplatelet agents; cardiovascular events; CKD

Introduction

Globally 10-16% of adults suffer from CKD [1]. CKD is associated with high cardiovascular morbidity and mortality [2]. Incidence of coronary artery disease (CAD) is around 40% in end stage renal disease (ESRD) and half of the causes of mortality in these patients is due to cardiovascular disease [3].The increased incidence of both CVE (Due to higher rate of coronary thrombosis) and paradoxical major bleeding episodes leads to composite outcome resulting in four fold higher mortality in CKD patients than patients with normal kidney function [1].

Though APAs reduce major CVE (stoke, myocardial infarction, fatal coronary heart disease) in normal patients, data using APAs in CKD is scarce due to the exclusion from large randomized trials. Besides as physicians are very much concerned regarding safety of use of cardioprotective medications, delayed risk factor modifications and late cardiovascular inteventions in CKD , the trial of APAs in CKD is sometimes omitted [4].

Search Strategy

Electronic databases from 1994-2012 using pubmed and google scholar were searched for text words "chronic kidney disease, aspirin, clopidogrel and Antiplatelet" combined with MeSH terms. The conference proceedings of the American Society of Nephrology from 2008-2012 were also searched for trials. References of the selected articles were also reviewed.

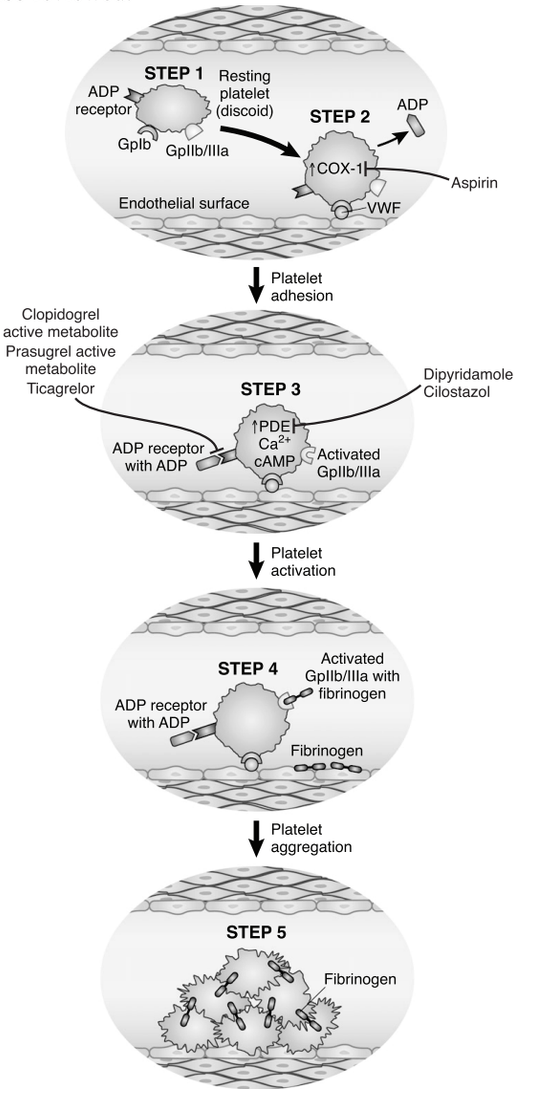

Fig 1 : Normal Platelet Activation and Aggregation. Site of action of different drug to prevent Platelet Activation and Aggregation.

Normal Platelet Activation and Aggregation (Fig 1)

Resting platelet is discoid in shape.It has five receptors such as GP1b(vWf receptor), GPIIb/IIIa (Fibrinogen receptor), Thrombin receptor, ADP receptor (P2Y12) and Thromboxane receptor [1].

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Endothelial injury causes vWf, ADP and Thrombin release. vWf interacts with GP1b. resting platelet changes to spherical shape. Thombin binds to its receptor, resulting in increase of COX-1 activity, Thromboxane and ADP are released from platelet granules. ADP and thromboxane bind to their receptors and increase intracellular Calcium(Ca 2+) and cAMP. Increased level of cAMP is maintained by enzyme called phophodiesterase(PDE). Ultimately platelets are activated and a conformational change occurs in GPIIb/IIIa recptors leading to fibringen binding. Platelet crosslinks with fibrinogen and platelet aggregation occurs.

Platelet Dysfunction in CKD

In CKD both the bleeding diathesis and paradoxical thrombotic predisposition occurs.In CKD patients especially on dialysis the bleedind tendency is due to (i)reduced expression of GPIb receptor (ii)less intracellular Ca2+ and cAMP (iii) configuration change in GP IIb/IIIa receptor.All these are due to increased Urea,Phenol,middle molecules and fibrinogen fragments accumulation in CKD [5,6]. Due to reduced clearance of middle molecules,they also interfere with vWf binding to platelets [1]. Studies also showed that though in CKD the amount of vWf is increased but they are of small sample sizes and heterogeneous population [7]. Furthermore it was postulated that desmopresin reduce bleeding risk in uremic patients by inducing release of coagulation factor viii, vWF and tissue plasminogen activator via extrarenal V2 reeptor. However if vWf levels are already increased In CKD patients, then the mechanism of whole this process raises question [8,9].

To understand the increased coagulability in CKD endothelial dysfunction was proposed. Increased inflammation and oxidative stress in CKD cause endothelial dysfunction which causes release of Thrombin which in turn causes more platelet aggregation. This pathogenesisis lies in the mechanism of increased Aspirin resistance in CKD [3, 10]. We know that aspirin inhibits COX-1 and thereby inhibiting the production of TXA2. In CKD aspirin resistance is probably due to i)increased oxidative stress producing increased cyclooxigenase-independent isoprostane (an arachidonicacid derivative with potent vasoconstrictor and proaggregatory effects similar to TXA2) ii) inflammation induced COX-2activationleading to TXA2 production iii) Oxidative stress leading to production of TXA2 through pathways not blocked by aspirin [11,12].

Types of APAs (Fig 2)

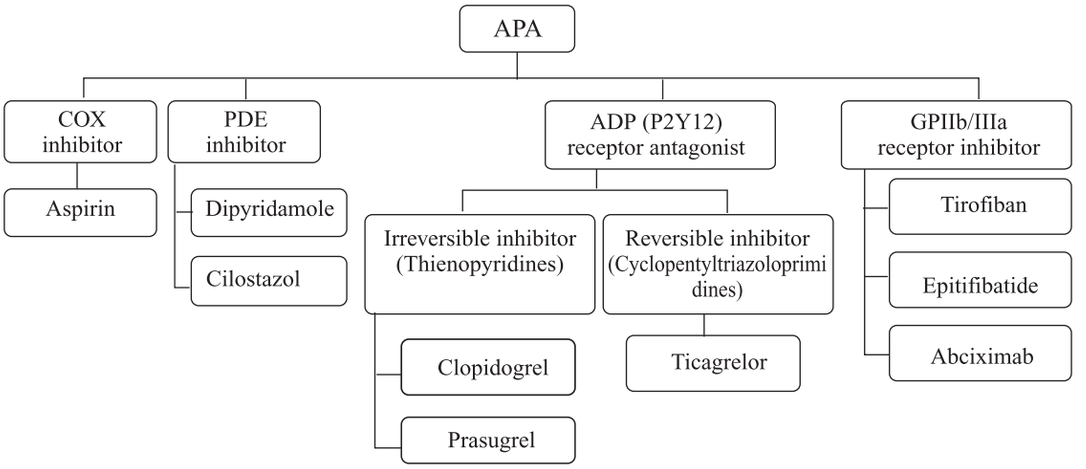

Fig 2 : Different APA

COX - Inhibitors

Aspirin inhibits COX-1 and decreases platelet thromboxane production and ultimately inhibits platelet aggregation. Its mean platelet inhibition time(Required time) is < 30 minutes. The safety and efficacy of low dose aspirin (75-100 mg/d)was tested in different studies. The First United Kingdom Heart and Renal Protection (UK-HARP) trial, a RCT and the dialysis Outcomes Practice Pattern Study (DOPPS), a case control study showed no evidence of major bleeding but three fold risk of minor bleeding(epistaxis, ecchymosis and bruising) with 100mg/d of aspirin [13,14].Both these showed no benefit of all-cause mortality but reduced risk of myocardial infarction(MI) and stroke. However a recent meta-analysis by Palmer et al.showed increase in major and minor bleeding with statistically insignificant haemorrhagic stroke [15]. So efficacy of low dose aspirin monotherapy on firm evidence ("LEVEL C") is not evident [16].

Even data is limited regarding primary prevention with low dose aspirin. The most common guidelines by National Kidney Foundation (NKF) and Kdney Disease Improving Global Outcomes (KDIGO) advocate low dose aspirin based on data from extrapolation in general population. Even the American Heart Association (AHA) / American College of Cardioloy (ACC) made no specific recommendation for APA use in CKD patients because more than 75% of their trials excluded CKD patients [17]. The aspirin should be used with caution in eGFR less than 10 ml/min/1.73 m^2 [1].

PDE inhibitors

Dipyridamole and Cilostazol are used as PDE inhibitors. They inhibit platelet aggregation by limiting intracellular cAMP increase by PDE [18]. Another advantage of Cilostazol is that in CKD patients where endothelial cells are activated by oxidative stress and thereby activating platelets,it acts as a potent APA than Dipyridamole [19,20]. No dose adjustment is required in ESRD for Dipyridamole but in creatinine clearance (CrCl)<25ml the dose of Cilostazol is to be adjusted [1].

ADP receptor (P2Y12 inhibitors)

There are three ADP receptor inhibitors such as Clopidogrel, Prasugrel and Ticagrelor.

P2Y12 receptor is G protein -coupled purinergic receptor that binds ADP leading to activation of GPIIb/IIIa receptor, granule release,amplication of platelet aggregation and stabilization of the platelet aggregate .Inhibiion of this receptor prevents platelet degranulation,deactivates GPIIb/IIIa receptor,blocks fibrinogen binding and cross linking of platelets.

Clopidogrel

It is a prodrug. Clopidogrel is more commonly used as dual APA therapy with aspirin in secondary prevention and monotherapy for primary prevention in those allergic to aspirin [15]. Its active metabolite is produced in two steps which require cytochrome monooxigenase system enzymes (fig 3) [21]. In CKD uraemia reduces expression of the organic anion transporter responsible for drug ransport into enterocyte and hepatocyte [22]. That is why Clopidogrel nonresponsiveness occur in CKD patients. This poor response increase with deterioration of CKD stages,20% in stage 2 to 38% in stage 4 and 5 [23]. Mean platelet inhibition time is 1 hour with loading dose of 300mg. and 2-3 days for daily dose of 75mg.No dose adjustment is required is ESRD [1]. Safety and efficacy of Clopidogrel was shown in different studies. Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidence (CHARISMA) trial showed increased all cause and cardiovascular mortality in elective PCI patients [23]. The Clopidogrel in Unstable angina to prevent recurrent events (CURE) showed no reduction in death and cardiovascular death in ACS patients (no STEMI) but increased risk of minor bleeding [24]. The Clopidogrel for The Reduction of Events During Observation (CREDO) revealed no difference of death , MI or stoke between Clopidogrel and placebo arms in elective PCI patients [25]. The meta- analysis by Palmer et al. also found no effect on all-cause mortality though there was increase in major and minor bleeding with uncertain risk of haemorrhgic risk in ACS/PCI or cardiovascular disease patients [15]. So all these findings are in favour of worse outcomes with Clopidogrel in CKD. Even comparing three dosages of Clopidogrel like standard therapy (75mg/d), higher- dose therapy (150mg/d)and dual therapy (75 mg of Clopidogrel daily and 100 mg of Cilostazol twice daily) showed no added benefit with higher-dose though some improvement with dual therapy [26].

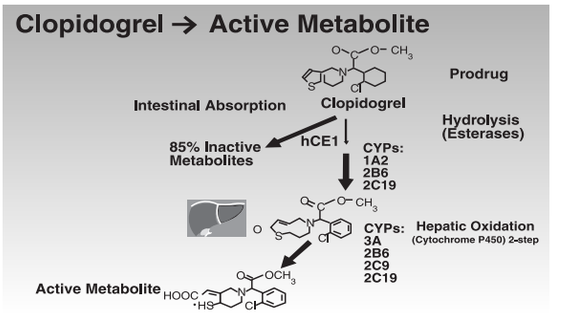

Fig 3 : Metabolism of Clopidogrel

Prasugrel

It is a newer APA approved by the Food and Drug Administration (FDA). It is not a prodrug and does not require metabolic transformation. Mean platelet inhibition time is 2-4 hours. No dose adjustment is required in CKD but no data is available for ESRD patients [1]. The Trial to Assess Improvement in Therapeutic Outcomes by optimizing Platelet Inhibition with Prasugerl-Thrombolysis in Myocardial Infarction (TRION-TIMI) showed superiority of prasugrel over clopidogrel in reduction of coronary stent thrombosis even in reduced creatinine clearance [27].

Ticagrelor

Like Prausugrel it is also not a prodrug. It is a direct ATP analogue.Its mean platelet inhibition time and dosing in CKD and ESRD are same as Prasugrel. The difference is that it induces hyperuricaemia and maintenance aspirin dose (100mg/d) reduces its efficacy [28]. Its use in Gout is contraindicated. The Platelet Inhibition and Patient Outcomes (PLATO) trial showed superiority of Ticagrelor over Clopidogrel in all patients irrespective of CrCl [29]. Loading dose of Ticagrelor is 180 mg and then it is given 90mg twice daily. No dose adjustment is required in CKD but no data is available regarding dose adjustment in ESRD [1].

GPIIb/IIIa Inhibitors [30, 31]

Abiciximab is cleared from circulation by spleen and Reticuloendothelial system, so no dose adjustment is required in renal impairment. The dose is 250µg/kg bolus followed by 0.125 µg/kg/min for 12 h . Its half life is 30 min. However, because the potential risk of bleeding is increased in patients with stage 4 CKD, the use of abciximab in CKD patients should be considered only after careful appraisal of the risks and benefits. 50% of Epitifibatide is renally cleared. In Crcl >50 ml the dose of epitifibatide is 180µg/kg bolus followed by 2.0µg/kg/min for 72 h. Its half life is 25 minutes. In patients with stage 3 to 4 CKD, the clearance of eptifibatide is reduced by 50%, and steady-state plasma levels are approximately doubled. So in CrCl <50 ml/min/1.73 m2 the dose is 180 µg/kg/min bolus followed by 1 µg/kg/min for 72 h; It is contraindicated in patients on hemodialysis. Renal excretion also contributes significantly to the elimination of tirofiban. Its half life is 1.4-1.8 hours. 40=70% of it is renally excreated. Its usual dose is 0.4 µg/kg/min 30-min bolus followed by 0.1 µg/kg/min. In patients with CrCl <30 ml/min/1.73 m^2 the dose is 0.2 µg/kg/min 30-min bolus followed by 0.05 µg/kg/min .

Other APAs (under investigation) [30]

Cangrelor is the first parenteral P2Y12 receptor antagonist which is not affected by renal impairment. It is still not approved for use in humans.Elinogrel is another P2Y12 receptor antagonist. It is excreted by kidney and liver. It can be given both orally and intravenously. There are two Thrombin receptor antagonists under advanced clinical testing for use in arterial thrombosis in CKD. These are Vorapaxar and Atopaxar.

Antiplatelet Therapy in Haemodialysis Patients [32]

Bleeding risk is higher in dialysis population than general population. Bleeding risk varies with the type, duration and individual patient characteristics. Though Clopidogrel was found to be of no more additional bleeding risk than placebo or control group in some studies but due to small number of population in these studies the fact is not firmly established. Clinical equipoise still exists regarding use of aspirin in this subgroup due to mixed result. However dual therapy should not be used. Use of APA for vascular access patency has no evidence based recommendation. It was found to be of some role only in case of Central venous catheter.

Discussion

As a whole Antiplatelets act at different sites to deactivate and prevent aggregation of platelets as shown in fig 4 [31].

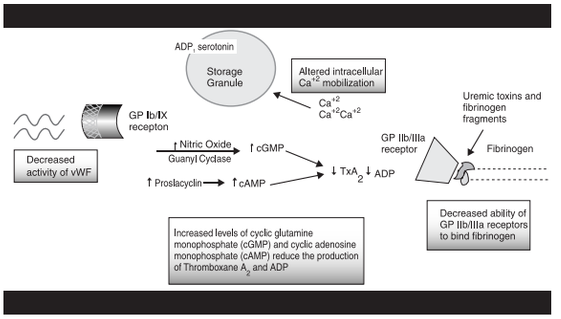

Fig 4 : Sites of Inhibition of Platelet Activation and Aggregation

The sites of inhibition of platelet activation and aggregation by all currently approved anticoagulants are detailed. ADP = adenosine diphosphate; GP = glycoprotein; TxA_2 = thromboxane A_2, wWF = von Willebrand factor.

CKD patients are at higher risk for bleeding and thrombotic events but it is difficult to identify why they are efficacious in some CKD patients and not others. Also choosing the correct type, dose, optimal duration and combination therapy to attain maximum cardiovascular and survival benefits was not universally accepted. Moreover methods of measuring degree of platelet aggregation by "residual platelet aggregability" is heterogenous. There are usually two methods: i) Whole blood platelet aggregation(WBPA) measured by ex vivo impedence aggregometry via chrono-log or multi-plate aggregometers ii) light transmittance method using platelet rich plasma. Other platelet function testings are to determine platelet (P-selectin,platelet factor-4 and vasodilator stimulated phosphoprotein) and endothelial(vWf antigen and activity, E-selectin) markers to predict clinical outcomes. But studies are very much heterogenous to use the above methods and also CKD populations enrolled in the studies are not homogenous. In fine the studies did not include other confounding variables like sex, body-mass index and Diabetes mellitus(DM) [33,34,35,36]

One of the common approaches which is clinician friendly is to follow the approach adopted by Jain et al [1]. This approach is to use low dose aspirin monotherapy for primary and secondary prevention because higher dose will only increase adverse events without added benefit. Dual therapy with aspirin and clopidogrel are advocated for secondary prevention in patients undergoing PCIs and in presence of other high risk patients (DM, longer stents and stents located at bifurcation points). There is no benefit of higher loading or maintenance dose of clopidogrel. When dual therapy is failed , platelet function testing is to be considered. In case of higher residual platelet aggregability newer agents like prasugrel and ticagrelor is prescribed.

Conclusion

Elevated vWf antigen level in CKD explains high cardiovascular thrombotic events [7]. Impaired vWf activity (due to decreased expression of GP1b on platelet surface in CKD) explain increased bleeding tendency in CKD [37]. Overall selection of APA demands individualization, patients risk factor profiles, tolerance and other clinical characteristics. Moreover studies with homogenous CKD populations and data on long term safety and efficacy of these agents is required to recommend safe use of APAs in CKD population.

Disclosure

All the authors declared no competing interest.

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