

Oral Antiplatelet Agents in Dialysis Patients: Friends or Foes?

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Thrombotic cardiovascular events are one of the main causes of morbidity and mortality in dialysis patients [1] and vascular access thrombosis remains the Achilles' heel for patients undergoing maintenance hemodialysis (HD) [2]. HD and uremia are characterized by two simultaneous but opposite hematological abnormalities: a thrombotic predisposition and a bleeding tendency mainly due to impaired platelet-platelet and platelet-vessel wall interactions [3-5].

In the general population, oral antiplatelet agents have been reported to reduce vascular deaths by 15% and serious cardiovascular events by 20% in high risk persons [6] but evidence based proof for HD patients is scant. A thorough review of the literature can reveal that most data come from small and under-powered single center studies with rather conflicting results [5,7]. Oral antiplatelet agents are frequently administered in HD patients as primary or secondary prophylaxis against vascular access thrombosis, after myocardial infarction or for the treatment of peripheral vascular disease. Acetylsalicylic acid (aspirin) and clopidogrel (a P2Y₁₂ receptor inhibitor) are currently the most commonly prescribed agents of this category, whereas dipyridamole and ticlopidine which were in vogue in the nineties are rarely used nowadays [7].

Palmer et al. have recently reviewed data regarding antiplatelet agent therapy in patients with chronic kidney disease (CKD) [7] and their impact on the prevention of vascular access thrombosis in HD patients [8,9]. Regarding vascular access thrombosis, they reported that these agents may protect native fistulas but have a little or no effect on synthetic HD grafts' patency. Similar results have been reported by another meta-analysis from 10 studies with almost 2000 patients by Coleman et al. [10]. In addition, based on the study of Dember et al. [11], Palmer et al. reported that clopidogrel use may be associated with problems in fistula maturation. The study of Dember et al. [11] was the largest ever performed randomized controlled study in HD patients regarding fistula maturation, but it has also been criticized for various reasons [12].

The meta-analysis of the studies in CKD patients [8,9] showed that antiplatelet therapy was accompanied by a reduced risk of fatal or non fatal myocardial infarction, but the results did not reach statistical significance for HD patients. One of the main reasons for this discrepancy may be that the studies included in the analysis were referring to acute coronary syndromes treated by percutaneous coronary interventions (PCIs) with non drug-eluting stents, which have been associated worse outcomes in high risk populations [13]. Another reason for the lower than expected outcomes with the use of clopidogrel in dialysis patients may rely on the residual platelet reactivity (aggregability) that persists at a higher level than that required for optimal anti-ischemic effect ("high on clopidogrel platelet reactivity"). This is highly prevalent in HD patients even with increased dosing of clopidogrel (150 mg daily) [5,14].

Newer antiplatelet agents such as prasugrel (a prodrug) [15] or ticagrelor (an active drug) [16], which are also P2Y₁₂ receptor inhibitors, have been associated with better platelet inhibition in HD patients but these studies included a small number of patients for a limited time period. Of interest, a level of laboratorial "resistance" to the treatment was observed in 19% of these cases even with prasugrel

inhibition which has been considered as more potent compared with clopidogrel [15]. The inadequate platelet inhibition achieved by these agents may be associated with various reasons such as cytochrome P450 monooxygenase system (CYP) polymorphisms, altered drug metabolism from uremia [5] or the rather continuous production of "fresh" platelets with active receptors, mainly due to the exogenous erythropoietin administration, which acts as a promoter of platelet production from the bone marrow via iron deficiency [14,17-19].

On the other hand, HD patients present higher bleeding rates compared with the general population especially with the combination of these agents [3,20]. Although the exact bleeding rates in dialysis patients under antiplatelet therapy remains poorly defined [3]. Kaufman et al. reported a rate of

approximately 0.5 episodes/patient-yr of follow-up monitoring in the placebo arm of their randomised study for the prevention of HD synthetic graft thrombosis and a significantly increased rate of bleeding (almost double) in the aspirin plus clopidogrel arm [20]. The meta-analysis of Palmer et al. [9] established these adverse effects, reporting an increased risk of major (33%) or minor (49%) bleeding in CKD patients under antiplatelet therapy for various reasons. In addition, many transplant centres are reluctant to list CKD patients under clopidogrel therapy for renal transplantation, due to the increased risk of perioperative bleeding, which can be life-threatening and be treated only by massive transfusions of fresh platelets.

According to current data, antiplatelets remain a double edged sword and physicians dealing with HD patients should be very cautious regarding the prescription of these agents without definite indications, as national and international guidelines and recommendations make no clear statements for CKD ("level C" of evidence or lower) [5]. Low dose aspirin seems to be safe for primary and secondary prophylaxis and dual therapy with aspirin and clopidogrel should be used only for HD patients undergoing PCIs. Prospective studies including large numbers of patients with pre-specified outcomes and well defined terms of adverse events (major and minor bleeding) are warranted in order to clarify the exact role of these agents in HD patients.

References

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