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COMMENTARY

Optimal Antiplatelet Therapy: Lessons Learned from PCI Applicable to PAD and PPI

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Patti et al. have further added to the mounting evidence that optimal antiplatelet therapy translates to clinical benefits in PCI by reporting the results of the ARMYDA-2 trial, which was a prospective, randomized trial between a pretreatment (mean 6 hours) with 600 mg versus 300 mg loading dose of clopidogrel (Plavix, Sanofi-Synthelabo, Inc., New York City, NY). The 600mg dose had less periprocedural myocardial infarction (50% risk reduction) and improved 30-day event-free survival (96% versus 86%, p = 0.017). This underscores the critical role of platelets in PCI but identifies the need for data regarding the role of more optimal antiplatelet and anticoagulant strategies in percutaneous peripheral interventions (PPI), especially considering the favorable results of both the PCI-CURE and CREDO trials in which subset analysis of the PAD patients actually received the most clinical benefits.

So, what do we know about the role of platelets in PAD? Well, not much, but certainly more than just 3–4 years ago. Besides the technical differences in PPI versus PCI (longer diseased vessels, therefore longer intervened segments, increased atherosclerotic and thrombus burden, longer procedural times, and a “low-flow” environment), there are other distinctive patient differences that may be responsible for the overall poorer outcomes characteristic of PPI vs. PCI. Shammas et al. have recently reported exceedingly high bleeding and ischemic complications in PPI cases and have suggested the need for a different anticoagulation strategy in PPI versus PCI.[1] Shammas is also investigating the role of inflammation in PAD and PPI with the recent identification that inflammation probably plays a larger role in PCI than previously known. Distinctive differences in the PPI versus PCI patient potentially leading to poorer PPI outcomes include a significant increase in the incidence of diabetes, chronic renal disease (CRD), advanced age, calcification, and hypercoaguablity.[2]

Recent evidence has shown that in the patients with diabetes, CRD, and PAD, individually each has shown elevation of almost every “hypercoaguable parameter” measured and “platelet dysfunction” is increasingly being incriminated as a culprit in both hemorrhagic and thrombotic PPI complications.[2] The impact of bleeding complications post-PPI is unknown, but recent reports have documented the high clinical and economic costs of these complications post-PCI, both acutely and out to 1 year, where an increase in adverse events of 7.5% versus 1.8% at 1-year was reported in patients who had major and minor bleeding complications post-PCI.[3] Almost a decade ago, work began to identify and improve both ischemic and hemorrhagic PCI outcomes, and questions were asked regarding the existing PCI anticoagulation and antiplatelet strategies. Increasing limitations of heparin were identified, introducing GP IIb/IIIas, direct thrombin inhibitors and oral antiplatelet agents, all as possible pharmacological solutions to improved outcomes.

Since PCI device and pharmacology technology has been only recently refined, it is important that these same questions be applied to PPI where the need for antiplatelet and anticoagulation data appears to be even greater when considering the distinct differences in the PCI and PPI patients. Heparin limitations and recent evidence that the PAD patient may even have an ASA and heparin resistance underscore the need for a better understanding of platelet dysfunction in PPI. The recently published APPROVE trial has shown the safety and feasibility of using bivalirudin in treating PAD, and the role of GPIIb/IIIas are currently being investigated, especially in the treatment of end-stage lower extremity PAD or CLI.[4] GPIIb/IIIa agents recently have been shown to possess significant anti-inflammatory properties, further implying potential benefits in the CLI patient.[5]

Clearly, it is time we consider strategies to optimize our current anticoagulation and antiplatelet strategies in PPI. It is of interest that after almost 20 years of tremendous resources invested into “perfecting PCI” that something as simple (yet not really simple) as doubling a dose of an oral antiplatelet drug could significantly improve contemporary PCI results, as has been reported with the ARMYDA-2 results. The discipline of PPI is still in its infancy, and only recently has there been a concentration of resources being dedicated to PPI by industry and physicians alike. The results of PPI have been inferior as compared to PCI, therefore, there are lessons to be learned from PCI data. Novel PPI devices are “sexy,” but it is this editor's opinion that we have much to learn from the PCI pharmacology literature and that the PAD patient, especially CLI, need even a more optimal antiplatelet and anticoagulation strategy for successful PPI than the patient with coronary artery disease. More data is needed on both PPI and the “endopharmacotherapy” of treating PAD. Similar resources must be dedicated to “perfecting PPI” as has been resourced to “perfecting PCI.” Let us not forget about the importance of anticoagulation and optimal antiplatelet therapy in the treatment of PAD.

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