

EDITORIAL COMMENT

Triple Therapy... Can We Replace More With Better?*



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Triple therapy, or the use of oral anticoagulation (OAC) in addition to dual antiplatelet therapy (DAPT), is common among patients who have undergone percutaneous coronary intervention (PCI) and have concurrent indications for anticoagulation, such as atrial fibrillation (AF) or mechanical valve replacements. Patients are started on this therapy because of a concern for thrombotic events such as myocardial infarction, stent thrombosis, or embolic stroke. Unfortunately, this potent antithrombotic regimen also exposes patients to increased bleeding. While clinicians were quick to grasp the dangers of thrombotic events, only recently have the dangers of bleeding events started to be truly understood: bleeding is more than just a nuisance, carrying its own significant risk of major adverse cardiac events (MACE) and mortality (1-3). Thus, practitioners are left with a clinical conundrum, balancing the risks of thrombosis and bleeding.

Clinicians are encountering this dilemma more frequently as the indications for both OAC and DAPT expand. Through efforts to reduce thromboembolic events, the population of patients with AF and indications for OAC has broadened significantly. The development of the CHA₂DS₂-VASc (congestive heart failure, hypertension, age \geq 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category) risk score also expanded the number of patients with indications for anticoagulation (4), as the most recent major societal

guidelines endorse a lower threshold to start OAC, using a CHA₂DS₂-VASc score of 1 as opposed to 2 (5,6). Concurrently, emerging data support longer duration of DAPT (7) to reduce stent thrombosis and MACE. With more patients on OAC and patients on DAPT for longer periods, the overlap of these 2 populations has inevitably grown as well. As physicians try to prevent adverse thrombotic events, more patients are being treated with more antithrombotic therapy. However, with the concurrent risk of bleeding, we must ask: is more antithrombotic therapy better? Or is it time to replace “more” with “better”?

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In this issue of the *Journal*, Hess et al. (8) add to the growing body of work by examining triple therapy use and its effects on MACE and bleeding. The available evidence is limited mainly to observational data but has been inconsistent in its findings regarding MACE, with a majority of studies failing to show an association between use of triple therapy and lower rates of MACE or mortality. Conversely, the current data are consistent in showing an association between triple therapy and bleeding events, with all but 1 study demonstrating increased rates of bleeding associated with triple therapy use. Hess et al. found similar relationships, showing a lack of association between triple therapy use and MACE risk but a significant association with increased bleeding among older patients with acute myocardial infarction and AF. Furthermore, although there was a trend for fewer ischemic strokes in the triple therapy group, this outcome was counterbalanced by an increase in hemorrhagic stroke. Although the question of whether triple therapy is beneficial for MACE remains troublingly uncertain, the data are convincing for bleeding. Regarding MACE, the effects of “more” remain enigmatic. When it comes to bleeding events, however, “more” appears to be

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significantly worse. In this study, use of warfarin for patients with AF was not associated with bleeding risk, suggesting an opportunity to improve selection of patients for oral anticoagulation in the setting of PCI and AF.

If more isn't better, perhaps less might be? The most insight into the "more" versus "less" question is the WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) trial, which evaluated triple therapy compared with clopidogrel and warfarin alone in post-PCI patients and found increases in both MACE and bleeding in the triple therapy arm (9). Although WOEST was the lone trial that demonstrated a better strategy with both efficacy and safety endpoints favoring warfarin and clopidogrel dual therapy over triple therapy, it did have limitations. WOEST was a small study of 573 patients, of whom only one-quarter received PCI for acute coronary syndrome, raising questions of generalizability. Thus, despite being the only randomized trial to date to explore the role of triple therapy, WOEST's treatment strategy received only a IIB recommendation in the American Heart Association/American College of Cardiology/Heart Rhythm Society 2014 guidelines for the management of AF (10). Clearly "less" is appealing, but further study is needed to declare a definite frontrunner.

Despite this gap in evidence, more recent investigations have focused not on further defining the relative safety and efficacy of DAPT and triple therapy but rather on redefining the agents in triple therapy. Rather than comparing "more" versus "less," investigation has now centered on "new." New agents and new paradigms have been proposed, while there has yet to be a randomized controlled trial comparing conventional DAPT versus triple therapy with warfarin. Evaluating incorporation of a more potent antiplatelet agent (i.e., prasugrel) into triple therapy,

Sarafoff et al. (11) found increased bleeding events with prasugrel compared with clopidogrel but no significant difference in ischemic endpoints. Other trials are underway to evaluate the role of novel oral anticoagulants, including the REDUAL-PCI trial investigating the effects of dabigatran as the anticoagulant in triple therapy and PIONEER AF-PCI trial investigating rivaroxaban (12,13). Although these analyses will provide key insights into the potential of newer agents, their designs compare novel oral anticoagulants in combination with either clopidogrel alone or DAPT versus triple therapy using warfarin, a P2Y₁₂ inhibitor, and aspirin and not the dual therapy of WOEST. At best, these trials will offer further evidence to support the use of dual therapy without aspirin but with no knowledge of their efficacy or safety compared with clopidogrel and warfarin. At worst, they may have negative results and continue the uncertainty surrounding the optimal treatment strategy for patients with indications for OAC and DAPT.

Thus, the clinical dilemma remains: what do we do with patients who have concurrent indications for OAC and DAPT? The preponderance of evidence runs contrary to the current practice of using warfarin with a P2Y₁₂ inhibitor and aspirin. With mostly observational data and a single, small randomized trial, the data may not be perfect, but they do paint a picture of uncertain benefit for MACE and convincing harm with bleeding. When it comes to antithrombotic therapy, "more" does not appear to be "better." Can we replace "more" with a better alternative? Unfortunately, the answer to date is "not yet."

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REFERENCES

1. Ndrepepa G, Guerra E, Schulz S, et al. Weight of the bleeding impact on early and late mortality after percutaneous coronary intervention. *J Thromb Thrombolysis* 2015;39:35-42.
2. Chhatriwalla AK, Amin AP, Kennedy KF, et al. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. *JAMA* 2013;309:1022-9.
3. Ko DT, Yun L, Wijeyesundera HC, et al. Incidence, predictors, and prognostic implications of hospitalization for late bleeding after percutaneous coronary intervention for patients older than 65 years. *Circ Cardiovasc Intervent* 2010;3:140-7.
4. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest* 2010;137:263-72.
5. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;64:2246-80.
6. Camm AJ, Lip GY, De Caterina R, et al. 2012 Focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation—developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;14:1385-413.
7. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;371:2155-66.

8. Hess CN, Peterson ED, Peng SA, et al. Use and outcomes of triple therapy among older patients with acute myocardial infarction and atrial fibrillation. *J Am Coll Cardiol* 2015;66:616-27.
9. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;381:1107-15.
10. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;64:e1-76.
11. Sarafoff N, Martischinig A, Wealer J, et al. Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. *J Am Coll Cardiol* 2013;61:2060-6.
12. ClinicalTrials.gov. PIONEER-AF-PCI trial: An Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention. Available at: <http://clinicaltrials.gov/ct2/show/NCT01830543>. Accessed June 25, 2015.
13. Gibson CM, Mehran R, Bode C, et al. An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin K antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI). *Am Heart J* 2015;169:472-8.e5.

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