EDITORIAL

Dual Antiplatelet Therapy
Is It Time to Cut the Cord With Aspirin?

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Since evidence of increased risk of stent thrombosis with first-generation drug-eluting stents surfaced in 2005[1,2] and the US Food and Drug Administration advised interventional cardiologists to use dual antiplatelet therapy (DAPT) for 12 months following implantation of drug-eluting stents, the appropriate duration of DAPT has been widely studied and hotly debated. Dual antiplatelet therapy consists of concurrent administration of aspirin and a P2Y12 inhibitor. Determining the duration of DAPT requires a balance between 2 objectives: lowering the risk of ischemic events with more intense and longer antiplatelet therapy vs lowering the risk of bleeding events with less intense and shorter antiplatelet therapy. Because second-generation drug-eluting stents are associated with lower rates of stent thrombosis,[3] the argument against longer DAPT was revisited. The updated guidelines incorporated such considerations by recommending a shorter duration of DAPT for selected patients, namely those with stable clinical status in whom risk of ischemic events is low.[4,5]

In this issue of *JAMA*, 2 groups of investigators studied iterations of shorter-duration DAPT with a novel twist—discontinuation of aspirin rather than discontinuation of the P2Y12 inhibitor as has commonly been the approach. Watanabe et al[6] randomized 3045 patients in Japan who received everolimus-eluting stents to receive 12 months of DAPT vs 1 month of DAPT followed by clopidogrel monotherapy. Hahn et al[7] conducted a similar study in Korea with 2993 patients who received a current-generation drug-eluting stent and were randomized to receive 12 months of DAPT vs 3 months of DAPT followed by P2Y12 (mostly clopidogrel) monotherapy.

The studies used somewhat different 1-year efficacy and safety end points but reached the same conclusions. The shorter DAPT regimens were noninferior to the more traditional 12-month regimens regarding major ischemic events. In the study by Watanabe et al in Japan, the rates of major secondary cardiovascular events (cardiovascular death, myocardial infarction, ischemic or hemorrhagic stroke, and definite stent thrombosis) at 12 months were 1.96% for the 1-month DAPT group and 2.51% for the 12-month DAPT group. In the study by Hahn et al in Korea, the rates of major adverse cardiovascular events (all-cause death, myocardial infarction, and stroke) at 12 months were 2.9% in the monotherapy group and 2.5% in the DAPT group. Both studies also demonstrated a statistically significant reduction in bleeding complications with shorter DAPT: TIMI major or minor bleeding rates of 0.4% compared with 1.5% in the Japanese study and Bleeding Academic Research Consortium (BARC) type 2 to 5 rates of 2.0% compared with 3.4% in the Korean study.

The conclusions of both reports are welcome and important news—shortening the duration of DAPT and continuing with P2Y12 monotherapy reduced bleeding complications without increasing risk of death or ischemic events. But the question is, how much do these investigations offer new solutions that can be used to address the risk of ischemic and bleeding complications after coronary stenting? There were 2 components to the experimental intervention of each study: shorter duration of DAPT and discontinuation of aspirin for the remaining study period. In regard to the shorter (≤3 months) vs traditional (12 months) DAPT duration, several prospective randomized trials have previously tested this issue.[8-11] Shorter DAPT regimens were 1 to 3 months in duration, and aspirin monotherapy followed. The main conclusions were similar to those reported by Watanabe et al and Hahn et al; ie, no increase in ischemic complications. However, in these previous trials, there was no apparent reduction in bleeding events. The noninferiority of shorter DAPT duration in reducing ischemic complications in the 2 new trials confirms the observation and may extend it to a broader group of patients and other types of drug-eluting stents.

Discontinuation of aspirin and continuation of P2Y12 inhibitor monotherapy has not been extensively studied. There is supportive pharmacodynamic evidence for this approach, as P2Y12 inhibitors provide more effective platelet inhibition than aspirin alone.[12] The 1 large-scale, randomized trial that tested such an approach among patients undergoing percutaneous coronary intervention, GLOBAL LEADERS, did not show superiority over a traditional DAPT duration.[13] This trial was based on DAPT for 1 month followed by ticagrelor monotherapy for 23 months vs a control group receiving 12 months of DAPT followed by 12 months of aspirin monotherapy. At 2 years, there was no difference in ischemic or bleeding complications.[13] The lack of adjudication of events and the nonadherence to monotherapy in 15% to 20% of patients randomized to the short DAPT intervention may partly explain the failure of the study to elicit differences between the groups at 2 years. In the studies by Watanabe et al and Hahn et al, the less potent P2Y12 inhibitor clopidogrel was predominantly used, the treatment interventions were of shorter duration, and the study groups had shorter follow-up. This may have favorably lowered the bleeding risk

and resulted in a more net positive result than in the GLOBAL LEADERS trial, in which the results favored ticagrelor monotherapy at 1-year follow-up but not at 2 years. Overall, these and the other studies do support the use of shorter DAPT regimens without increasing the risk of ischemic complication rates.

To our knowledge, there has been no direct comparison of aspirin monotherapy and P2Y12 monotherapy since the CAPRIE trial,[14] which demonstrated a modest reduction in ischemic events with no excess bleeding with clopidogrel when used for secondary prevention. However, it is unclear whether these findings can be extrapolated to the post–drug-eluting stent setting. In addition, it is unclear whether all P2Y12 inhibitors are similar to one another as monotherapy. The present studies were not intended to address such comparisons, but answers to these questions will help determine whether the proposed approach will become standard clinical practice.

With the low rate of adverse events following contemporary coronary stenting, superiority or noninferiority of new therapies or strategies is difficult to prove statistically and typically requires large study groups. In both current reports, ischemic event rates were substantially lower than the rates estimated for the sample size calculation, thus reducing the statistical power. The authors estimated the event rates based on previously published but not strictly comparable trials. Likewise, it is difficult to account for the conscious or unconscious bias of the enrolling physicians, which may have led to exclusion of higher-risk patients. Watanabe et al described the characteristics of the eligible patients who were not included, and this description confirmed the predilection to exclude some patients with high-risk features. More than 60% of patients enrolled in the trial had stable symptoms, which is higher than expected in a contemporary coronary intervention trial with few exclusion criteria, in which stable patients represent 30% to 40% of those enrolled.[15] Hahn et al did not provide a comparison between enrolled and excluded patients, but biomarker-positive presentations were relatively infrequent (<30%). Thus, there is reasonable evidence that shorter DAPT is safer in stable patients but may not be as safe in patients with acute coronary syndrome, those with complex coronary anatomy, or those with poor response to clopidogrel.[16]

It is also important to consider that both studies were conducted in East Asian populations, which have distinct phenotypic and genotypic features that influence risk of adverse outcomes and response to pharmacotherapeutics.[17,18] For example, patients in these studies had an average body mass index of 24, whereas patients in similar studies conducted in the United States had an average body mass index of approximately 30.[19] Higher body mass index may diminish the response to P2Y12 inhibition. The East Asian population is also known to have a higher prevalence of *CYP2C19* loss-of-function alleles and, hence, a higher percentage of patients with poor metabolization of clopidogrel,[20] but the risk of ischemic complications is also influenced by the underlying susceptibility to adverse ischemic events.[18] In addition, a high proportion of drug-eluting stent procedures performed in Japan and Korea use intravascular imaging to optimize outcomes, whereas such technology is used in a minority of procedures in Europe and North America. Such observations warrant caution before extending the conclusions of these studies to patients of other ethnicities or in regions where interventional practices are different.

Will the new studies by Watanabe et al and Hahn et al influence clinical practice? It is likely that shorter DAPT duration will gain more support with the accumulating evidence of lack of excess ischemic complications, especially when used in conjunction with contemporary stents, optimal implantation techniques, and aggressive atherosclerosis risk factor reduction. It is important to emphasize that a degree of selectivity is needed when considering a short DAPT approach, particularly in reference to clinical presentation and underlying risk of ischemic complications. Whether aspirin or P2Y12 monotherapy should follow shorter-course DAPT remains unclear. The present studies using clopidogrel monotherapy have demonstrated a meaningful reduction in bleeding, but direct comparison with aspirin monotherapy is not available to fully resolve this question. The Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention Study (TWILIGHT) will report the outcomes of approximately 9000 high-risk patients randomized to 1 month of DAPT including ticagrelor followed by ticagrelor monotherapy compared with 12 months of DAPT.[21] This study should provide data to help address some of the remaining issues regarding monotherapy. Until then, and while it is possible to shorten the DAPT duration in selected cases, the evidence is not sufficient to fully cut the cord with traditional DAPT or aspirin monotherapy—not for all patients and not just yet.

ARTICLE INFORMATION

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