Are Drug Eluting Stents Worth Triple Therapy?

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Approximately 8% patients undergoing percutaneous coronary intervention are on anticoagulation, which creates difficult choices regarding stent type and antiplatelet use.[1] Drug eluting stents (DES) are usually preferred over bare metal stents (BMS) because of less restenosis and fewer repeat revascularization procedures. However, DES require a longer duration of dual antiplatelet therapy to minimize the chance of stent thrombosis. Typically, this is 6 months of dual antiplatelet therapy for DES compared with 1 month for BMS in patients with stable ischemic heart disease.[2] In a patient already on anticoagulation, adding dual antiplatelet therapy (now triple therapy) poses a significant risk of bleeding: a 2- to 3-fold increase per recent studies.[2] The need for triple therapy can be reduced by using a BMS, but is the decreased risk of bleeding worth the increased restenosis risk?

Ideally, we would know the benefits and risks of double versus triple therapy, different durations of each strategy, DES versus BMS, and the various permutations. Current European guidelines recommend only 1 month of triple therapy following a DES in those at high risk for bleeding, whereas North American guidelines suggest that triple therapy can be stopped after 3 months; with a switch to dual therapy, this is only a IIb recommendation.[2] However, this is only a IIb recommendation indicating it "may be considered" instead of using the usual 6 months of DAPT. These recommendations are supported, in part, by the ISAR-TRIPLE (Intracoronary Stenting and Antithrombotic Regimen-Testing of a 6-Week Versus a 6-Month Clopidogrel Treatment Regimen in Patients with Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting) study, which compared 6 weeks to 6 months of clopidogrel on top of warfarin and aspirin for those undergoing DES

implantation.[3] Among 614 patients, the primary end point of death, myocardial infarction (MI), stent, thrombosis, stroke, or major bleeding at 9 months was slightly, but not significantly, higher in those treated with the shorter 6-weeks of clopidogrel (9.8% versus 8.8%, $P=0.63$).[3] The secondary end point of Thrombolysis in Myocardial Infarction major bleeding was also slightly, but not significantly, higher in the shorter triple therapy duration arm (5.3% versus 4.0%; $P=0.44$). Although seemingly small, an absolute 1% difference in death would be important to exclude, arguing for confirmatory studies. The benefits and harms of 1 month of triple therapy as recommended by the European guidelines versus 3 months as suggested by the North American guidelines are even less clear.

A recent meta-analysis concluded that triple therapy may offer no benefit over anticoagulation with 1 platelet agent while increasing bleeding.[4] This review of observational studies (N=9) and randomized, controlled trials (n=2) including over 7000 patients compared outcomes of triple therapy (dual antiplatelet therapy and anticoagulant) with dual therapy (single antiplatelet therapy and anticoagulant) in patients taking long-term anticoagulants after percutaneous coronary intervention. At a mean 11 months of follow-up, major bleeding was higher in triple than double therapy (6.6% versus 3.8%; $P<0.01$). There was no difference in all-cause mortality (relative risk [RR], 0.98; 95% confidence interval [CI], 0.68–1.43), major adverse cardiac events (RR, 1.03; 95% CI, 0.8–1.32), and thromboembolic events (RR, 1.02; 95% CI, 0.49–2.10), though there were nonsignificant trends toward reduced MI (RR, 0.85; 95% CI, 0.67–1.09) and stent thrombosis (RR, 0.77; 95% CI, 0.46–1.3). The studies often included both DES and BMS stents. Thus, it was not clear whether the lack of benefit of triple versus dual therapy for stenting is the same for DES and BMS.

Based on this literature demonstrating a clear bleeding risk with triple therapy without a clear benefit, and the guideline recommendations recommending limitation in duration of triple therapy, one would expect that BMS would be used in those with a very high risk of bleeding where there would be less of a need for antiplatelet therapy.

However, the results presented in this issue of *JAHA* suggest that practitioners do not share this concern. Vora et al evaluated over 14 000 patients with atrial fibrillation undergoing acute percutaneous coronary intervention with acute myocardial infarction.[5] Overall, DES was used in 59% of patients

and this increased over time from 47% in 2008 to 68% in 2014. Bleeding risk was measured using the Anticoagulation and Risk Factors in Atrial Fibrillation score calculated from hemoglobin <13 mg/dL (or 12 for females, 3 points), glomerular filtration rate <30 mL/min (3 points), age ≥75 years (2 points), past hemorrhage (1 point), and history of hypertension (1 point). High-risk bleeding is a score of 5 points or greater (6% annual risk of hemorrhage). Surprisingly, the 32% of patients at highest risk for bleeding (Anticoagulation and Risk Factors in Atrial Fibrillation score ≥4) were almost as likely to receive a DES (56%) as those at low risk (Anticoagulation and Risk Factors in Atrial Fibrillation <4, 60% DES use). It appears that clinicians are not selecting stents (and need for prolonged antiplatelet use) based on bleeding risk.

Although there was little variation in use based on bleeding risk, there was substantial variation at the hospital level. The interquartile range of DES use was 50% to 74%, with the full range going from 0% to 100%. Whereas academic status, bed size, and coronary artery bypass grafting capability explained some of this variation, it appears that most of the variation remains unexplained. I suspect that cultural differences (local practice patterns) are largely responsible. The wide variation across hospitals is both intriguing and an opportunity to determine effects while limiting confounding. When comparing 2 patients receiving different treatments, it is often patient characteristics that most influence the treatment decisions. However, when comparing 2 facilities with widely different rates of use of a therapy, it is often a cultural difference in approach to therapy and not systematic patient differences that explains the difference in hospital use of treatments. Although an observational analysis at the patient level will be confounded if patient differences influence both the treatment decision and outcome, an analysis at the facility level may provide a more-accurate measure of treatment effects. However, a relatively small number of facilities limits the power of such analyses and hospital effects will not always mirror patient-level effects. As multicenter registries grow, such analyses become more feasible.

It is important to note that the authors used the ACTION Registry-GWTG, a collaboration between the National Cardiovascular Disease Registry of the American College of Cardiology and the Get With The Guidelines program of the American Heart Association. Their study adds to the over 100 published research articles originating from this successful registry collaboration. The data collected by hospitals include detailed in-hospital clinical, process of care, and outcomes for patients hospitalized with acute MI. Tools are available to allow hospitals to measure and improve care through real-time dashboards and custom reports. Participation can fulfill Chest Pain Center accreditation and lead to recognition through Registry Achievement Awards. Unfortunately, this collaboration between the American College of Cardiology and American Heart Association has dissolved, with each

organization now having its own acute MI registry (through the National Cardiovascular Disease Registry for the American College of Cardiology and Get With The Guidelines for the American Heart Association). Although research and quality improvement will continue, hospitals may choose to participate in only 1 of these registries. Having 2 smaller registries that cannot be combined is a step backward in our efforts to understand and improve cardiovascular care.

The authors were able to link clinical registry data to Medicare data to estimate subsequent mortality, stroke, MI, revascularization, and bleeding. They found that this composite outcome was nonsignificantly lower with DES (adjusted hazard ratio, 0.88 0.76−1.03). It should be noted that past comparisons of DES and BMS have shown stronger effect sizes favoring DES in observational than with randomized trials.[6] Although it is tempting to conclude that the trend toward more DES for patients on anticoagulation should continue, we do not know the type and duration of antithrombotic therapy following discharge and thus it is difficult to interpret the similar outcome for DES and BMS patients. Pending future randomized trials, registries are our best opportunity to collect these data and inform our treatment decisions.

Disclosures

None.

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