EDITORIAL COMMENT

Can’t Bare It Any Longer*

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Against the background of comparative drug-eluting stent (DES) trials, iterative stent designs, and even the advancement of bioresorbable scaffolding, studies demonstrating the clinical benefit of DES over conventional bare metal stents (BMS) seem a distant afterthought, and the clinical utility of BMS appears equally remote. Indeed, the prevalence of BMS use in economically developed countries approximates 10% of all percutaneous revascularization procedures, an estimate that continues to decrease annually over the past 5 years. Were it not for perceptions of safety with abbreviated dual antiplatelet therapy (DAPT) durations for BMS compared with DES, the use of BMS might even be lower; in many ways, therefore, treatment with BMS in itself conveys a “risk factor”—a coexisting condition that challenges DAPT adherence and confers increased risk, for example, excessive bleeding hazard, advanced age, impending need for noncardiac surgery, or even noncompliance. For these reasons, patients treated with BMS often demonstrate characteristics that routinely exclude them from representation in contemporary stent trials.

The ZEUS (Zotarolimus-Eluting Endeavor sprint stent in Uncertain DES candidates) trial investigators tested the boundaries of abbreviated antiplatelet therapy and DES safety in such a patient population challenged by DAPT adherence (1). Among 1,606 randomized patients characterized as “uncertain DES candidates” based on thrombotic, bleeding, and restenosis risk features, and despite a median DAPT duration of only 32 days, the 1-year occurrence of myocardial infarction (MI) and stent thrombosis was significantly lower with the zotarolimus-eluting Endeavor stent (E-ZES) (Medtronic, Minneapolis, Minnesota) compared with BMS revascularization. In this issue of JACC: Cardiovascular Interventions, Ariotti et al. (2) provide further insight to the clinical association of stent selection, ischemic outcomes, and bleeding risk among those 828 patients identified with a high bleeding risk (HBR) (2). Broadly defined as age older than 80 years, indication for oral anticoagulant therapy, a recent bleeding episode, profound anemia, or a systemic condition that predisposed to hemorrhagic risk, among this pre-specified HBR subgroup, the 1-year occurrence of MI, stent thrombosis, and repeat target vessel revascularization each was significantly lower for those treated with the E-ZES compared with BMS. With a median DAPT duration of 30 days (notably 5-fold shorter than those without a bleeding risk), hemorrhagic complications did not differ relative to stent type.

For cardiovascular practitioners, the translation of this study and its results are readily apparent to routine clinical practice; more than one-half of patients were aged at least 80 years old, and the prevalence of an acute presentation, complex coronary anatomy, impaired renal function and other risk factors was commonplace. In addition, the frequent need for oral anticoagulation or a recent bleeding event is familiar to a real-world patient population. The analysis also highlights a commonly overlooked reality that criteria constituting bleeding risk rarely exist in isolation. Indeed, approximately one-half of HBR patients fulfilled 2 or more risk factors that forecast bleeding complications. Further, the results also reaffirm previous observations that bleeding and ischemic risk parallel one another (2). Compared with those individuals without HBR, not only were actionable bleeding events approximately 2-fold greater among patients with at least 1 risk factor, but ischemic

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events—including stent thrombosis—were also of similar higher relative risk. Expectedly, hemorrhagic complications by any measure increased proportionately with the increasing number of bleeding risk factors per patient.

That uncertainty regarding stent selection and DAPT duration might still persist now despite numerous randomized trials is not surprising, especially as most studies have not explored what might be considered the “minimum acceptable” antiplatelet therapy regimen in selected patients. This is most relevant for patients recognized with excess bleeding risk who are systematically excluded from DAPT clinical trials. Even societal guidelines advocate conflicting DAPT durations and are vague regarding the definition of bleeding risk (4,5). Because of the absence of well-crafted studies addressing this issue, guidance documents advocating BMS and/or abbreviated DAPT cross-reference each other rather than cite primary evidence. In many ways, these apparent inconsistencies underscore the unspoken reality that an “optimal” DAPT duration does not exist for all patients, making uniform recommendations impractical.

Considering the findings of the present study and others, have BMS been held to a lower standard than DES relative to both DAPT duration and ischemic risk? At present, DES are assigned a class III recommendation of harm for patients who may not adhere to prolonged DAPT or in whom compliance cannot be confirmed before revascularization (4)—in many ways the exact patient population intended for this study. However, the attention to DES, DAPT adherence, and stent thrombosis may have detracted from the consequences of restenosis and provided a false reassurance of guideline-advocated 1-month DAPT for BMS. In an era exclusive to BMS, pivotal studies that transitioned practice from oral anticoagulation to the combination of aspirin and a thienopyridine were limited to 1-month DAPT duration, a standard for BMS that until recently had not been challenged except in acute coronary syndrome patients. Delayed stent thrombosis does in fact occur with BMS (6), and ischemic events attributed to bare metal restenosis have been detailed (7). In the randomized PRODIGY trial (N = 2,013), both composite major cardiovascular events and definite/probable stent thrombosis through 2 years were significantly higher among patients receiving BMS compared with newer generation DES (8). To better characterize BMS outcomes, the DAPT trial compared major adverse events among 10,026 patients treated with DES or BMS (9). Although not designed to address stent selection at the time of revascularization, the study demonstrated a higher rate of stent thrombosis through 33 months of follow-up for BMS compared with DES. Moreover, compared with 12 months of DAPT, a 30-month DAPT regimen after BMS treatment was associated with a consistent reduction in stent thrombosis as for patients treated with DES, although these findings did not achieve statistical significance due to the smaller BMS cohort sample size (10).

Because E-ZES demonstrates more rapid drug dissolution and greater in-stent neointimal hyperplasia (and therefore considered to more closely resemble a BMS phenotype rather than iterative-generation DES), whether similar safety and greater efficacy in like patients translate to other commercially available DES is speculative. Interestingly, recent European guidelines advise <6 months DAPT after DES for patients with a bleeding risk, although this recommendation is based on 2 studies exclusively with E-ZES (5). Limited, nonrandomized data with more contemporary DES suggest a low risk of ischemic events with DAPT interruption after periods as brief as 1 month post-revascularization (11). A significant amount of aggregate data from pooled trials also suggest the risk of stent thrombosis with newer generation DES could be even lower than for BMS (12).

Although the safety of stents incorporating bioresorbable materials is intuitive but inconsistently proven, clinical study with these stents and only 1 month of DAPT is ongoing (NCT01813435). Finally, the advantage of DES may also extend to clinical settings other than those related to bleeding risk in which BMS are commonly perceived as safer than DES; in 2 large surveys of patients undergoing noncardiac surgery after stent revascularization, the occurrence of cardiovascular events was significantly higher with BMS compared with unselected DES (13,14).

Since the ZEUS study, the themes of comparative DES versus BMS safety and abbreviated DAPT in HBR patients have been amplified in the LEADERS FREE trial (15). Among 2,466 patients with HBR criteria similar to those of the ZEUS trial, patients were randomized to percutaneous revascularization with a polymer-free DES or BMS. By 30 days, less than 10% of patients remained on DAPT. At 1 year, however, both repeat revascularization and the composite outcome of death, MI, and stent thrombosis were significantly lower with DES compared with BMS. The difference in outcome was principally driven by a significantly lower rate of MI in the DES cohort, adjudicated equally as both spontaneous and restenosis related. As in the ZEUS trial, bleeding and stent thrombosis rates were higher than in conventional trials, but did not differ relative to stent type.
Altogether, in HBR patients included from both trials treated with an approximate 30-day DAPT duration, compared with BMS, the number needed to prevent a major ischemic event with DES ranges from 15 to 33, notwithstanding a consistent 50% reduction in repeat target vessel revascularization. As one of last remaining clinical situations in which they are used, these data further challenge the clinical purpose of BMS in HBR patients.

Recognizing that societal guidelines do not provide treatment options for this unique but commonly encountered patient population and are based more on opinion and inferential evidence, the ZEUS study instead informs treatment decisions for patients common to clinical practice yet underrepresented by evidence-based medicine. Applying a practical assessment of bleeding risk, the trial introduces a method by which practitioners might tailor antithrombotic and stent therapy based on individual assessment of risk and benefit. Unlike recent study that informs antiplatelet therapy prescription (but not stent selection) with the benefit of hindsight in patients free of ischemic and bleeding events at 1 year, the ZEUS trial addressed the other, less predictable end of the spectrum related to stent and DAPT decision making at the time of revascularization. Providing clarity to one of the last remaining clinical settings in which BMS are still commonly used yet unstudied, these data add to an emerging evidence base that challenges existing standards and brands the utility of BMS more a misperception than a reality.

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