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EDITORIAL COMMENT

Another Coronary Stent for Patients at High Bleeding Risk*

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Approximately 40% of patients undergoing percutaneous coronary intervention (PCI) and stent implantation who receive dual antiplatelet therapy (DAPT) present with characteristics of high bleeding risk (HBR) (1,2). In these subjects, prescribing shorter DAPT durations (eg, 1 or 3 months) in contrast to standard durations (eg, 6 or 12 months depending on clinical presentation) is recommended among strategies for bleeding prevention (3). Shortening DAPT carries some theoretical risk of withdrawal of antithrombotic protection, especially in HBR patients who also present with characteristics of high thrombotic risk. Therefore, it seemed necessary at some point to re-evaluate the safety of currently available stents in a context specific to HBR patients who receive short DAPT. To that end, stent manufacturers have conducted a number of trials to fulfill the expectations of regulatory agencies and, eventually, be able to label their products with expanded HBR indications (4-9).

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In this issue of *JACC: Cardiovascular Interventions*, Mehran et al (10) report the results of 2 new studies of short DAPT using the Xience stent (Abbott Vascular), an extensively investigated everolimus-eluting stent with thromboresistant fluoropolymer coating. Both studies enrolled only HBR patients, were single-arm, used for comparison propensity-stratified historical cohorts of the same device with prolonged DAPT, and were powered for noninferiority on death or myocardial infarction and for superiority on bleeding (Bleeding Academic Research Consortium [BARC] type 2-5). The statistical plan prespecified blanking periods that formally make these 2 investigations corresponding comparisons of aspirin (ie, after discontinuation of the $P2Y_{12}$ inhibitor) and DAPT.

In the XIENCE 90 study (n = 2,047, of whom 1,693 discontinued DAPT at 3 months from PCI), the mean rates of death or myocardial infarction between 3 and 12 months in groups defined by quintiles of the propensity score were identical (5.4%) in the aspirin and DAPT groups (P for noninferiority = 0.0063). Reassuringly, stent thrombosis occurred in only 0.2% of patients on aspirin ($P < 0.0001$ compared with an objective performance goal of 1.2%). The mean rates of BARC type 2 to 5 bleeding were similar with aspirin and DAPT (5.1% vs 7.0%; $P = 0.069$)—with the authors acknowledging some chance of underreporting in the control group to explain the lack of a statistically significant difference—but BARC type 3 to 5 bleedings were lower with aspirin (2.2% vs 6.3%; $P < 0.0001$).

The XIENCE 28 study pooled data from 2 separate studies conducted in the United States and Canada (XIENCE 28 USA study) and in Europe and Asia (XIENCE 28 Global study), encompassing a total of 1,605 patients, of whom 1,392 discontinued DAPT at 1 month from PCI. The mean rates of death or myocardial infarction between 1 month and 6 months in groups defined by quintiles of the propensity score were 3.5% and 4.3% in the aspirin and DAPT groups, respectively (P for noninferiority = 0.0005). Stent thrombosis occurred in 0.3% in both groups. Again, the mean rates of BARC type 2 to 5 bleeding were similar (4.9% vs 5.9%; $P = 0.19$), while the composite of BARC type 3 to 5 bleeding was significantly lower with aspirin (2.2% vs 4.5%; $P = 0.016$).

The many ways stent manufacturers are designing their trials in HBR populations are schematized in

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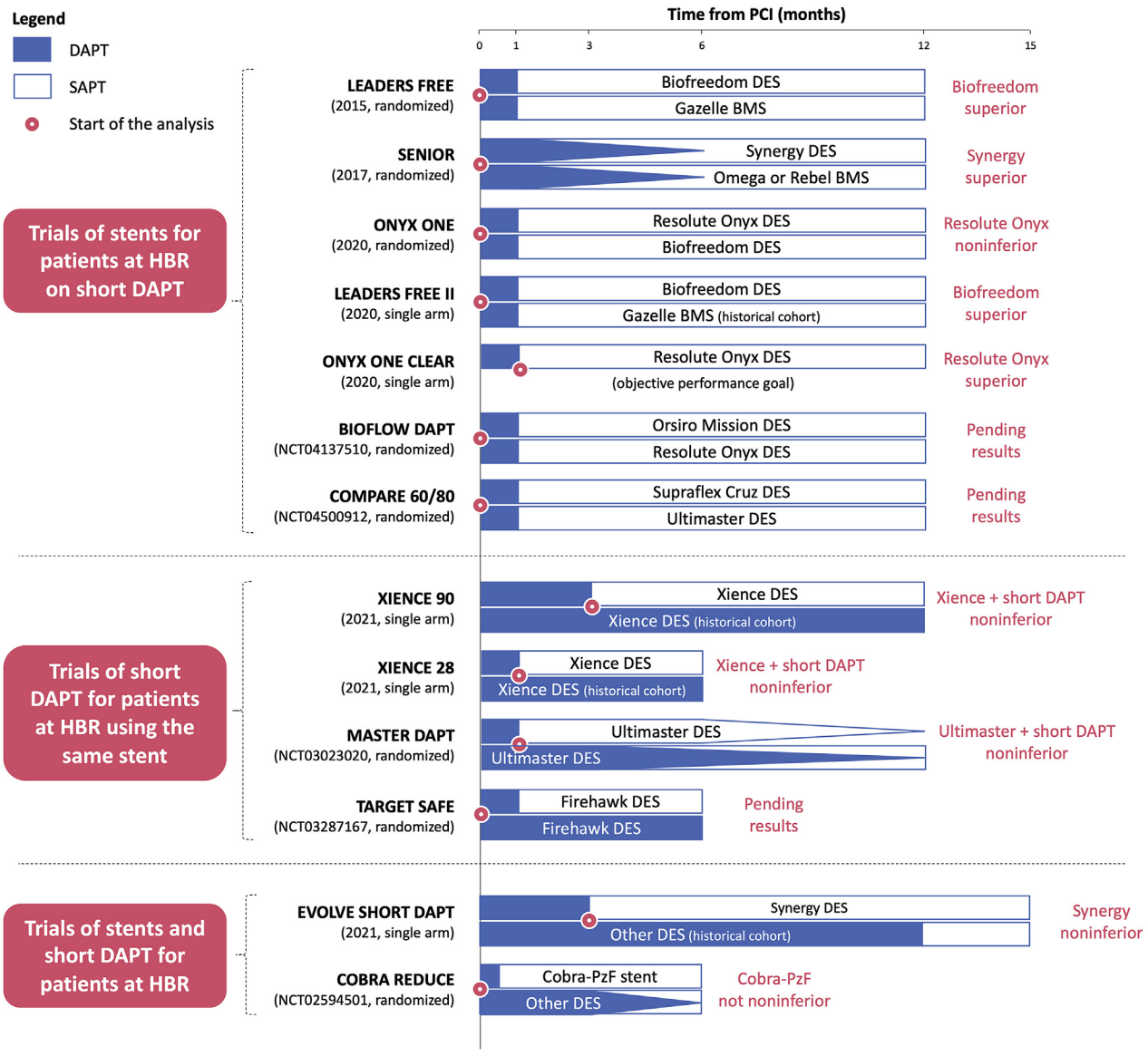
FIGURE 1 Trials of DES or Short DAPT in Patients at HBR



Study names are reported with year of publication (if published) or ClinicalTrials.gov identifier (if ongoing or unpublished at the time of writing this editorial). Tapered bars indicate study arms with dual antiplatelet therapy (DAPT) or single antiplatelet therapy (SAPT) periods ranging between shorter (beginning of tapering) and shorter durations (end of tapering). BMS = bare-metal stent; DES = drug-eluting stent; HBR = high bleeding risk; PCI = percutaneous coronary intervention.

Figure 1. Several differences in design, use of a blanking period, endpoints, choice of a synchronous or historical cohort, and especially the choice of the comparator (ie, a different stent with the same DAPT duration, the same stent with a different DAPT duration, or even different stents and DAPT durations all together) are apparent. The Academic Research Consortium, under the auspices of the Food and Drug Administration, has recently issued a set of recommendations for standardizing the design of trials of devices and DAPT strategies for patients at HBR (11). Ideally, based on these standards, stent trials should privilege the use of superiority rather than noninferiority designs, and 1-to-1 randomization in contrast to comparisons of single-arm registries with historical cohorts. The XIENCE 90 and 28 studies, like

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other trials, were designed before these nonbinding recommendations became available, which partly explains a certain degree of misalignment (11). Yet, a noninferiority design is justifiable when an effective treatment has already been established, and the investigational strategy offers greater convenience or safety (in this case, less major bleeding) while preserving a prespecified margin of efficacy. For the purists of trial design, it is more problematic to accept that in the XIENCE 90 and XIENCE 28 studies the comparator was a propensity-stratified historical cohort dated back a decade earlier (12). In that respect, the design of the XIENCE 90 study is similar to that of the EVOLVE Short DAPT study, a prior study of the Synergy stent (Boston Scientific) that was also single-arm, and similarly used a 3-month blanking period and a historical 12-month DAPT control (8). Putting the XIENCE 28 study into perspective is more problematic, because other HBR studies of drug-eluting stents in the context of 1-month DAPT followed diverse approaches: 1) by randomizing versus bare-metal (LEADERS FREE and SENIOR study) or drug-eluting (ONYX ONE study) stents (4-6); or 2) by comparing single-arm registries versus objective performance goals (ONYX ONE Clear study) or historical cohorts using the same DAPT duration (LEADERS FREE II study) (7,9).

With positive results stemming from the peculiar study design chosen by the XIENCE 90 and XIENCE 28 study investigators, the correct implication for clinical practice is not that these studies authorize upfront decisions for 3- or 1-month DAPT (ie, at the time of PCI), but rather that discontinuation of DAPT after implantation of the Xience stent is justifiable after an uneventful period of 3 months or even 1 month if dictated by clinical circumstances or medical judgment (13). These considerations apply to patients undergoing relatively noncomplex PCI procedures such as those represented in the 2 registries, in which patients with ST-segment elevation myocardial infarction were also excluded.

Interventional cardiologists now have several options for stent selection in the broad and increasingly recognized HBR population. In June 2021, based on the XIENCE 28 study, the Food and Drug Administration approved the short DAPT labeling of the Xience stent for patients at HBR. In the United States, this expanded indication adds to those similar already issued for the Resolute Onyx (Medtronic) and Synergy stents based on the ONYX ONE Clear and EVOLVE Short DAPT studies, respectively. It is noteworthy that these 3 studies have in common the use of a single arm and a blanking period, while they differ significantly in the choice of the control group, denoting a trend and some degree of flexibility allowed by the regulators. In this evolving regulatory scenario, the results of more conventional randomized trials of HBR patients comparing drug-eluting stents (eg, NCT04137510, NCT04500912) and DAPT durations (eg, NCT03023020, NCT03287167) are forthcoming.

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