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EDITORIAL COMMENT

Art and Science*

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Professional society guidelines are founded on randomized clinical trials (RCTs), thought to be the highest level of science. However, medical practice is not only science-based, but an art, requiring data integration into a wisdom matrix, which is then focused and individualized for the specific patient. In this latter regard, scientific study is crucial, but has well-known limitations, highlighted by considerations related to RCTs. These limitations include (among others) typical trial enrollments of a small, very carefully selected subset of the total group of patients with the disease/therapy being studied; constrained, highly focused endpoints; and rigid protocols. Furthermore, background treatment strategies may change over the course of the study, which can affect its power to reach unequivocal conclusions. Finally, the target endpoint's incidence may be so low that a composite endpoint is used, leaving the most important single endpoint unresolved. Such issues make it difficult to translate science into the art of caring for a specific patient, who may not fit exactly into the RCT framework.

The SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy) trial (1), which studied the impact of 6 months versus 12 months of dual antiplatelet therapy (DAPT) in patients treated with 1 of several second-generation drug-eluting coronary stents (DES), exemplifies the conundrum resulting from this situation. This question is of great clinical interest, initially focused on the occurrence of stent thrombosis, a highly morbid, even mortal event (2). Early in the field, a variety of stent thrombosis definitions were used, confounding scientific study efforts. The development of specific, widely accepted definitions (3,4) greatly improved the situation. This problem was the subject of multiple single registry and multiregistry experiences, as well as smaller RCTs, resulting in varying guidelines and practice patterns around the world (5–13). The etiology has been accorded great attention. Initially, crucial small observations focused on the central role of platelets as the most important putative mechanism. Accordingly, a variety of antiplatelet strategies were put into place, of which DAPT is dominant. Such a strategy carries multiple issues including: 1) bleeding, for which the risk increases the longer a patient is on these agents; 2) its cost and side effects; and 3) the clinical need to consider drug discontinuation should subsequent surgery be required. Each of these issues has great patient care implications. Given that stent thrombosis timing ranges from early to very late (up to several years after implantation), DAPT duration is of substantial interest. Early on, different regimens were recommended without a substantial scientific basis, generally on the basis of expert consensus. For example, the American College of Cardiology/American Heart Association guidelines currently recommend 12 months of DAPT in patients treated with DES "if the patient is not at high risk of bleeding" (5).

By contrast, the European Society of Cardiology guidelines state, "routine extension of DAPT beyond 6 months after new-generation DES implantation in stable coronary artery disease cannot be recommended and observational data…suggest that even shorter durations of DAPT may be sufficient." (6). Even longer DAPT duration is currently being tested in the largest RCT, to be presented in the fall of 2014 (12). Both professional guidelines were initially developed for first-generation DES (which may have a different profile and higher frequency of stent thrombosis) and were often on the basis of expert consensus and smaller RCTs that were often

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underpowered to provide definitive conclusions. Ideally, a study such as the SECURITY trial might answer the question of DAPT duration. The SECURITY trial included 1,399 patients in a prospective, randomized, noninferiority multicenter international trial, who were treated with 1 of several second-generation DES types. The patient groups were well matched: 31% had diabetes; 20.7% had a prior myocardial infarction; 43.8% had more than single-vessel disease; and 38.4% had unstable angina. Conventional treatment with clopidogrel 75 mg/day for at least 3 days before the procedure, or a loading dose of at least 300 mg in patients not on chronic clopidogrel was used. Although newer antiplatelet agents were allowed by protocol amendment after their approval, >95% of patients were treated with clopidogrel. Post-procedure, acetylsalicylic acid (aspirin) was prescribed indefinitely. Randomization focused on administering 75 mg of clopidogrel for either 6 or 12 months. At the 12-month primary endpoint follow-up, DAPT was still used clinically in 33.8% of the 6-month group (thus muddying the water) and was continued in 96.1% of the 12-month group. The primary endpoint was the composite of cardiac death, myocardial infarction, stroke, Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding, and (very importantly) definite or probable stent thrombosis at 12 months. A noninferiority design was used with an absolute margin of 2.0% in the difference of event proportions. Using this margin, a power of 0.80, and a 1-tailed 0.05 significance level, an estimated 1,370 patients were needed per group. Very low complication rates in both treatment arms led to early termination of the trial as a result of "enrollment futility because of minimal differences in the rate of the primary endpoint between the 2 groups…" (1). There were no significant differences in the primary composite endpoint or in any individual components. In particular, there were no significant differences in either definite or probable stent thrombosis at either 12 months (0.3%) or 24 months (0.4%), which occurred very infrequently. Notably, despite the longer DAPT duration, type 3 or 5 BARC bleeding was not significantly increased in the 12-month therapy group, although event numbers and rates were very small (4 [0.6 %] vs. 8 [1.1%]; $p = 0.283$).

The investigators provide an excellent discussion of previously published studies with different trials and trial designs, illustrating the field's complexity, with some studies focusing on target vessel failure, others on varying composites, and substantial variability in DAPT duration. With respect to the latter, some prior studies evaluated 3 versus 12 months, others evaluated 6 versus 24 months. Confounding variables included patient demographics (either acute coronary syndromes or more stable patients), and noninferiority boundaries for statistical assessment. In this issue of the *Journal,* Colombo et al. (1) conclude with their trial's limitations, which have much in common with previous studies. These include: that their trial is underpowered; results cannot be generalized to higher-risk patients and lesions; approximately one-third of the 6-month control group continued with DAPT, and the primary endpoint was lower than expected; there were several different second-generation DES used; and there was a wide margin of noninferiority used for analysis. Using multivariable adjustment, they found that DAPT duration does not independently predict the primary endpoint, but stenting procedure–related factors (e.g., mean stent length, size, and number) were strong, independent primary endpoint predictors, as were some baseline characteristics, such as age. No conclusions could be made regarding specific stent type because of the small sample sizes. Such limitations have very real clinical implications for day-to-day practice.

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The scientific underpinnings of the crucial debate on the duration of DAPT required to optimize the safety and efficacy of current, more advanced-generation DES remain somewhat wobbly; different societal guideline documents reviewing the same data reached somewhat different conclusions. In this case, art and some attempt at wisdom are needed to help decide what to recommend for Mr. or Mrs. Smith, whom you have just treated with 1 of several second-generation DES. That process must include information about exactly who they are, what their lesions were like, details of the specific stent approach (e.g., number and size of stents, adequacy of the result), how the procedure went, their risk for bleeding, the potential need for subsequent surgical procedures, their tolerance of unknowns, and often other mitigating, unmeasurable data. In considering these issues, art plays a prominent role. With patients similar to those in the SECURITY trial, and in the absence of rigorous data to the contrary, shorter DAPT duration seems very reasonable to consider and is increasingly used in the art of taking care of these patients.

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