DAPT Duration After Coronary Stenting
Assessing Risk-Benefit Tradeoffs in Individual Patients*

Gregg W. Stone, MDa,b

Following successful coronary artery stent implantation, patients remain at long-term risk for recurrent ischemic events, including stent thrombosis (ST) and myocardial infarction (MI), the latter arising either from the stented target lesion or nonrevascularized atherosclerotic plaques (1–3). In this regard, one of the most important decisions physicians make after stent implantation is choosing the duration of dual antiplatelet therapy (DAPT). DAPT reduces ischemic complications after stenting, albeit at the cost of increased bleeding, which may have direct and indirect adverse consequences to patient well-being and survival (4). Understanding the offsetting risks and benefits of extended DAPT after coronary stenting is one of the most challenging issues in cardiology today, and has been studied in no <11 randomized trials in which 33,880 patients have been assigned to DAPT, lasting from 3 to 48 months. Studies have shown that in general, the longer that DAPT is continued the greater the suppression of ST and MI, but the greater the risk of bleeding. Palmerini et al. (5) reported from a pairwise and Bayesian network meta-analysis of 10 randomized trials in 31,666 patients that “longer” rather than “shorter” DAPT after drug-eluting stents (DES) was associated with a 49% increase in noncardiac mortality, with a neutral effect on cardiac mortality. As a result, all-cause death (which within the randomized trial framework may be the benchmark via which the net risks vs. benefits of DAPT can be appraised) was increased by 22% with the nonselective application of prolonged DAPT. The enhanced safety profile of contemporary DES further shifts the risk-benefit equation toward abbreviated DAPT (6,7). Most experts thus believe an individualized approach to patient selection is warranted, wherein prolonged DAPT after coronary stenting is reserved for those in whom the ongoing probability of ST and atherothrombosis outweighs the iatrogenic bleeding risks. Accurately assessing this calculus in an individual patient, however, is easier said than done.

With 11,648 stented patients who were event free at 1 year randomized to either aspirin plus a thienopyridine or aspirin plus placebo for an additional 18 months, the aptly named DAPT trial is the largest randomized trial of DAPT duration. Recognizing the imperative to risk-stratify DAPT duration decisions, the DAPT investigators developed the DAPT score, consisting of 9 weighted clinical and angiographic variables that were identified in multivariable analysis from the DAPT trial itself to be predictive of either late ischemic events (MI or ST) or major bleeding (GUSTO [Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries] moderate or severe), but not both (8). The DAPT score ranges from -2 to 10 for individual patients, with lower and higher scores representing greater relative risks of bleeding and ischemia, respectively. As previously presented for the entire study population, a DAPT score <2 (~50% of all patients) identified a cohort in whom prolonged DAPT after 1 year was associated with a sizable increase in major bleeding with only a small reduction in MI or ST, whereas prolonged DAPT in patients with a DAPT score ≥2 was associated with substantial protection from ischemic events with only a small excess in bleeding. Perhaps most importantly, although the

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From the *New York Presbyterian Hospital, Columbia University Medical Center, New York, New York; and the Cardiovascular Research Foundation, New York, New York. Dr. Stone has reported that he has no relationships relevant to the contents of this paper to disclose.
DAPT trial as a whole found greater mortality with prolonged DAPT (2.0% vs. 1.5%; hazard ratio: 1.36; p = 0.05), this risk was confined to patients with a DAPT score <2, whereas an additional 18 months of DAPT had a neutral effect on survival in patients with a DAPT score ≥2 (8). Notwithstanding the caveats inherent in applying a study-derived risk score to the same study population (!), prolonged DAPT may be beneficial in those with a DAPT score ≥2, but in aggregate was clearly harmful in those with a DAPT score <2, at least for the patients enrolled in the DAPT trial.

Two of the variables predicting ischemic risk (but not bleeding) in the DAPT score are prior MI and MI at presentation. In this regard the DAPT investigators previously reported that MI presentation 1 year before randomization (representing 3,576 [30.7%] of all enrolled DAPT patients, and a well-described risk factor for ST and recurrent MI) (9,10) identified a subgroup with a potentially greater relative reduction of major adverse cardiovascular or cerebrovascular events with prolonged DAPT compared to those without MI, although no significant interactions were present for ST or major bleeding (11). Prolonged DAPT significantly increased all-cause mortality in patients without MI at presentation (2.1% vs. 1.1%; p = 0.04), but had a neutral effect on death in patients presenting with MI (1.4% vs. 1.6%; p = 0.61). Regarding the risk factor of prior MI, the PEGASUS (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) trial reported that in stable patients with MI (with or without stent treatment) 1 to 3 years prior plus at least 1 additional high-risk feature, an additional 3 years of ticagrelor significantly reduced the composite endpoint of cardiovascular death, MI, or stroke, while increasing bleeding, with a neutral effect on all-cause mortality (12). These 2 studies thus suggest that prior MI and MI at presentation (i.e., history of “any MI”) might be pooled and represent a subgroup in which the benefits of prolonged DAPT after stenting might outweigh its risks.

In this issue of the Journal, Kereiakes et al. (13) report the results from the DAPT trial in patients with vs. without “any MI,” according to DAPT duration randomization, and further analyzed by the DAPT score (<2 vs. ≥2). As expected, any MI patients had increased short-term (<1 year) and long-term (1 to 2.5 year) ischemic risk, while patients without any MI were older and had increased bleeding risk in both periods. Prolonged DAPT duration was of net clinical benefit in the any MI group (in whom mortality was not increased), with an approximately similar risk-benefit profile in patients with prior MI and MI at presentation. In contrast, prolonged DAPT resulted in net harm in the group without any MI, with increased mortality. However, the any MI and not any MI groups were heterogeneous, each comprised of a mix of patients at relatively higher versus lower rates of ischemia and bleeding. As such, the DAPT score provided some incremental guidance in approximately one-third of patients in each MI group as to who might benefit vs. realize harm by prolonged DAPT, although given the “subgroup of a subgroup” nature of the present analysis all reported interaction tests were negative. Yes, even the DAPT trial was not large enough to conclusively address this issue!

Several additional methodologic and practical limitations of the DAPT score deserve discussion. The DAPT score was derived to guide DAPT duration decisions between 12 and 30 months after coronary stenting, and does not apply to either shorter or longer usage intervals, or to non-stent DAPT indications. Ticagrelor was not included in the DAPT trial, and thus the utility of the DAPT score in ticagrelor-treated patients is unknown. Patients were also excluded who required chronic oral anti-coagulation (one of the strongest risk factors for bleeding) (14), and the DAPT trial and score do not provide insight into this vexing scenario (which is the focus of several ongoing randomized trials). In addition, of the 37 variables from which the DAPT score was derived, only 1 (advanced age) was predictive of major bleeding and not ischemia. Prior bleeding and baseline anemia, which are primarily predictors of bleeding, were not available from the DAPT database. Intuitively, the presence of these bleeding risk factors would favor shorter DAPT. Conversely, other unmeasured variables of increased ischemic risk (e.g., suboptimal stent results, recurrent angina, ongoing systemic inflammation, and imaging evidence of diffuse atherosclerosis) may favor prolonged DAPT. Specific definitions of MI, ST, and major bleeding were used in the DAPT trial, and whether the DAPT score would prove more useful had more or less sensitive criteria for these endpoints been incorporated is unknown. Importantly, the DAPT score has not yet been externally validated in a database in which patients were treated with contemporary DES and pharmacotherapy. Finally, emerging medical advances, such as PCSK9 inhibitors (15), may change the risk-benefit ratio of prolonged DAPT. And technology marches on as well: polymer-free DES have been developed and shown to result
in similar rates of ST and improved net clinical outcomes compared to bare metal stents in patients at high risk of bleeding with only 1 month of DAPT (16). Conversely, different DAPT durations have not yet been studied in patients receiving bioresorbable vascular scaffolds (17). Considering all of these nuances, selection of the optimal DAPT duration after coronary stenting is for the foreseeable future likely to remain more of an art than a definitive quantifiable science (with appropriate DAPT duration prescriptions for individual patients ranging from 1 month to lifelong), although the DAPT investigators are to be congratulated for taking the first major step down this challenging road.

**REFERENCES**


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