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EDITORIAL COMMENT

Too Hot? Too Cold? When Is it "Just Right" to Stop Dual Antiplatelet Therapy After PCI With DES?*

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Drug-eluting stents (DES) revolutionized cardiology by dramatically reducing the need for repeat coronary revascularization associated with percutaneous coronary intervention. Accompanying this rise to prominence, however, were reports of unexpected late stent thromboses among DES recipients, culminating in a Food and Drug Administration warning in 2003. Registries verified the risk of late stent thrombosis with DES, a syndrome often associated with devastating consequences. In response, cardiologists extended the duration of dual antiplatelet therapy (DAPT) after patients received DES, with observational data demonstrating reduced late stent thrombosis with this strategy. In accordance with these data, consensus guidelines recommended 12 months of DAPT for all patients receiving a DES (Class I recommendation).

Concurrently, however, stent technology continued to improve as novel polymers and antiproliferative drugs were developed, cell shapes changed, and strut sizes decreased—all culminating in reductions in stent thrombosis. Interventional techniques also advanced, with increasing use of intravascular imaging to minimize stent underexpansion, a known risk factor for stent thrombosis.

Given decreasing concern for stent thrombosis after the implantation of newer generation DES, several trials challenged the notion that it may be dangerous to stop DAPT within a year, with a systematic review and meta-analysis of these trials suggesting safety of discontinuation within this time period (1). Clinical questions regarding DAPT duration are common in modern cardiology. Patients may request to stop DAPT for major or nuisance bleeding, desire for an urgent/elective surgical procedure, or difficulties with medication adherence. It remained unclear how strongly to recommend extended durations of DAPT given the emerging data.

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To this end in this issue of *JACC: Cardiovascular Interventions*, Piccolo et al. (2) have provided further evidence that it may be safe to discontinue DAPT within the first year of DES implantation with newer generation DES. Recent research shows a period of increased risk for thrombotic events following discontinuation of DAPT when prescribed for at least 1 year (3). Piccolo et al. (2) aimed to identify whether this phenomenon exists with discontinuation of DAPT within the first year of initiation. They performed an individual participant data (IPD) analysis of 6 randomized trials that compared short-term (3 to 6 months) versus long-term DAPT (12 months or more) and analyzed the 90-day period after cessation of DAPT for rates of major adverse cardiac and cerebrovascular events (MACCE) defined as cardiac death, myocardial infarction, or stroke. The IPD included 6 randomized controlled trials and 11,473 patients. MACCE occurred in 0.59% of patients assigned to short-term DAPT within 90 days of discontinuation, as compared with 0.49% of patients assigned to longer term DAPT ($p = 0.52$). The composite of myocardial infarction or stent thrombosis occurred in 0.27% of patients assigned to short-term DAPT, compared with 0.29% of patients assigned to long-term DAPT ($p = 0.85$). They then performed a separate aggregate meta-analysis of 11 trials including 38,919 patients and observed an increased rate of

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early MACCE after long-term DAPT (hazard ratio: 2.28) but not short-term DAPT (hazard ratio: 1.08).

Notably, the authors made use of an IPD analysis, an increasingly popular alternative to traditional systematic review and meta-analyses (SRMA). In IPD analysis, individual patient data are obtained for each clinical trial used in the study as opposed to analyzing summary statistics of trials in an SRMA. IPD analysis allows for application of consistent inclusion/exclusion criteria between studies, accounting for missing data, inclusion of unpublished studies, standardization of statistical analyses across studies, subgroup isolation, and, importantly for the authors' current analysis, precise and serial follow-up information for trial participants (4). Despite their apparent benefits, IPD analyses remain victim to many of the flaws of SRMA, including propagation of error and bias from the participant clinical trials and heterogeneity between included trials. Additionally, IPD analyses introduce the potential for introduction of novel biases not seen in SRMA such as choosing outcomes or follow-up times that censor results from portions of the component trials.

Despite limitations, this study fits nicely into an evolving appreciation of the safety of newer generation DES. Particularly notable is the low absolute rate of stent thrombosis seen in the early period after DAPT cessation in both arms of the IPD analysis. Recently, the 2016 ACC/AHA focused update on DAPT duration included a Class I recommendation to reduce the minimum DAPT duration to 6 months after DES implantation in stable ischemic heart disease with a Class IIb recommendation to reduce DAPT duration to 3 months in patients with high bleeding risk (5). After acute coronary syndrome, there is a Class IIb recommendation for 6 months of DAPT in patients with elevated bleeding risk.

Thus, the initial concerns of late stent thrombosis necessitating prolonged courses of DAPT may be abrogated by current-generation DES, which have stent thrombosis profiles similar to bare-metal stents (6). But whereas prolonged DAPT may have diminishing use for stent thrombosis prevention, it is important to remember that patients requiring stents have high cardiovascular risk with elevated rates of recurrent ischemic events not related to the implanted stent. Most of the myocardial infarction benefit seen in the DAPT trial was not stent related (7). Percutaneous coronary intervention represents an incomplete revascularization, with remaining, unstented plaques in the coronary vasculature at risk for subsequent myocardial infarction. The true benefit of prolonging DAPT in the modern era appears to be preventing the consequences of instability of these lesions.

The aggregate SRMA portion of this publication reinforces concerns regarding a potential rebound phenomenon when DAPT is extended beyond 1 year and then halted. Though there are benefits to prolonging DAPT, subsequent discontinuation of this therapy may pose a unique risk to the patient that they may not have been subject to if DAPT had been stopped earlier. Strategies to minimize the risk of the rebound effect, such as bridging or tapering, represent areas of future investigation.

Overall, for the patient receiving DES in the current era, extended durations of DAPT to prevent recurrent thrombotic events should be considered in standard practice, acknowledging potential for the "rebound effect" with eventual cessation. However, if circumstances arise that favor discontinuation within a year, the current investigation supports the safety of this strategy. Practitioners should not allow concerns of early stent thrombosis with cessation of DAPT in the intermediate term to dissuade them from halting the therapy when clinically indicated.

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