

## EDITORIAL



## Dual Antiplatelet Therapy after Drug-Eluting Stents — How Long to Treat?

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The rationale behind dual antiplatelet therapy after successful stenting is based upon two indications. First, the stented segment requires protection from stent thrombosis that occurs as a result of inflammation during healing. Second, the areas inside and outside the stented section require protection from the development of progressive atherosclerosis and plaque rupture. The first of these two problems is of less concern with drug-eluting stents, especially second- and third-generation drug-eluting stents.<sup>1,2</sup> However, the second issue continues to be important. The most effective duration of dual antiplatelet therapy for preventing both stent thrombosis and spontaneous myocardial infarction, while limiting bleeding risk, remains unresolved.

Mauri et al. now report in the *Journal* the results of the Dual Antiplatelet Therapy (DAPT) study,<sup>3</sup> in which 9961 patients who had completed 12 months of dual antiplatelet therapy after implantation of a drug-eluting stent were randomly assigned to an additional 18 months of thienopyridine therapy (clopidogrel or prasugrel) or placebo; all the patients continued to take aspirin. The rates of the coprimary efficacy end points of stent thrombosis and major adverse cardiovascular and cerebrovascular events (a composite of death, myocardial infarction, or stroke) at 12 to 30 months were significantly reduced with continued thienopyridine therapy. There was a significant reduction in the rate of myocardial infarction in the group that continued to receive thienopyridine therapy; myocardial infarctions that were not related to stent thrombosis represented 55% of this benefit. On the other hand, the primary safety end point — moderate or severe bleeding — was increased

with continued thienopyridine therapy. There was also an increase in overall mortality with continued thienopyridine treatment, although this increase may have been due, at least in part, to an imbalance in preexisting cancer (and subsequently in cancer-related mortality) in that group.

There has been a recent drive within the interventional cardiology community to shorten the duration of dual antiplatelet therapy after implantation of a drug-eluting stent from 12 months of therapy to 6 or even 3 months. Several previous trials and meta-analyses have shown this practice to be safe, at least in selected patients.<sup>4-10</sup> Therefore, the question of whether to continue dual antiplatelet therapy beyond 12 months may appear to be outdated. This apparent contradiction can be explained by separating the need for dual antiplatelet therapy after implantation of a drug-eluting stent into two phases: a period of “mandatory” dual antiplatelet therapy and a period of “possibly beneficial” dual antiplatelet therapy. The mandatory period is defined as the interval during which premature discontinuation of dual antiplatelet therapy would lead to an unacceptably high rate of stent thrombosis, whereas the possibly beneficial period is the subsequent interval during which the benefit versus risk of continued, uninterrupted therapy is more a matter of debate. The DAPT study addresses the possibly beneficial period rather than the mandatory period.<sup>8</sup> This study has clearly shown a reduction in both stent thrombosis and myocardial infarction when dual antiplatelet therapy is extended beyond 1 year after implantation of a drug-eluting stent. However, the observed increase in moderate or severe bleeding, as well as the possible increase in all-cause

mortality, leaves us with uncertainty regarding the incremental benefit from prolonging dual antiplatelet therapy.

Prolonged dual antiplatelet therapy is most likely to be of benefit in patients who are at high risk for stent thrombosis or myocardial infarction, but who are also at relatively low risk for bleeding. In this regard, the DAPT trial included only patients who had not had a major adverse cardiovascular or cerebrovascular event, repeat revascularization, or moderate or severe bleeding by the completion of 12 months of dual antiplatelet therapy and who were adherent to thienopyridine therapy. These and other criteria resulted in the exclusion from randomization of 23% of the patients who had initially been treated with a drug-eluting stent and were enrolled in the study. It is possible that the patients who were excluded from randomization because of a previous major adverse cardiovascular or cerebrovascular event are the very patients who would have benefited the most from prolonged treatment.

In addition, there was evidence suggesting that continued thienopyridine therapy had the greatest effect in reducing the rate of major adverse cardiovascular and cerebrovascular events among recipients of paclitaxel-eluting stents (hazard ratio, 0.52) and the least effect in reducing the rate among recipients of everolimus-eluting stents (hazard ratio, 0.89;  $P=0.05$  for the interaction). This suggests that the potential benefits of prolonged dual antiplatelet therapy may depend on the type of stent that is implanted.

The key message of the DAPT study is the suggestion that some patients who have been treated with a drug-eluting stent may benefit from extending dual antiplatelet therapy beyond 1 year, but also that the potential harm with this approach should not be overlooked. Moreover, we do not know how long this benefit extends and which patients benefit most. The safest and most effective duration of dual antiplatelet therapy therefore remains uncertain and must be individualized for each patient; pre-

sumably in making this judgment, physicians should balance risk factors favoring atherothrombosis against the risk of bleeding.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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This article was published on November 16, 2014, at NEJM.org.

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DOI: 10.1056/NEJMe1413297

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