Optimal duration of clopidogrel therapy: the shorter the longer?

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After the initial enthusiasm for drug-eluting stents (DES) based on their impressive reduction in restenosis, there was increasing concern about an increased and sustained risk for stent thrombosis (Figure 1). Consequently, the recommendation for the duration of dual antiplatelet therapy (DAPT) was gradually extended from initially 3 months for sirolimus-eluting stents (SES) and 6 months for paclitaxel-eluting stents (PES) to currently at least 12 months for all DES. This recommendation is reinforced by most cardiovascular societies including the American College of Cardiology (ACC)/American Heart Association (AHA) and the National Institute for Health and Clinical Excellence (NICE) in the UK, while the European ESC guidelines recommend at least 6–12 months of DAPT for DES,3 and at least 12 months after an acute coronary syndrome (ACS) regardless of stent type.2 Not uncommonly, cardiologists recommend indefinite DAPT if the patient has no bleeding complications during the first 12 months. The need for long-term DAPT is costly and remains the Achilles’ heel of DES; furthermore, the excess risk for stent thrombosis associated with DES is a matter of an ongoing controversy. Ongoing improvements in second- and third-generation DES drug coatings as well as other factors such as stent design may have all changed the rates of stent thrombosis. Newer generation stents have shown impressively low stent thrombosis rates and, therefore, the excessive bleeding risk of DAPT has to be reconsidered.3,4 The newest generation everolimus-eluting stents (EES) have revealed very low stent thrombosis rates,3 and, in Europe, Abbott’s Xience V and Xience PRIME stents have recently received the CE mark with 3 months DAPT, further adding to the confusion about the optimal duration for DAPT following DES.

Cassese et al. have now tried to elucidate our understanding of optimal DAPT duration with a meta-analysis of randomized controlled trials (RCTs) investigating the impact of short vs. extended DAPT.5 The primary endpoint was all-cause death, and the main safety endpoint was major bleeding. They included four trials (N = 8231 patients) and found that a median DAPT duration of 16.8 vs. 6.2 months did not reduce all-cause death [odds ratio (OR) 1.15, 95% confidence interval (CI) 0.85–1.54, P = 0.36], myocardial infarctions, or strokes. Extended DAPT duration, however, did show an increased risk for TIMI (thrombolysis in myocardial infarction) major bleeding (OR 2.64, 95% CI 1.31–5.30, P = 0.006). In addition, the authors performed an adjusted indirect comparison which confirmed a higher risk of major bleeding for 24-month vs. 3-month DAPT (P = 0.046) and for 24-month vs. 6-month DAPT (P = 0.047), while there was no difference regarding ischaemic endpoints. Therefore, the authors conclude that extending DAPT increases bleeding events without reducing ischaemic events.

Do these results support or challenge current guidelines? The study certainly raises relevant questions regarding current DAPT recommendations, by highlighting a lack of clear evidence rather than by providing a definitive answer. Furthermore, this study has important limitations which need to be considered when interpreting the data.

The four trials included in this meta-analysis tried to answer rather different questions. It therefore remains unclear which question this meta-analysis is addressing exactly. The REAL-LATE/ZEST-LATE asked the important question of how to advise a patient who comes back to clinic 12 months after DES implantation who was completely free of complications during this first year. Is it beneficial to continue clopidogrel? The study did not find any advantage for extended DAPT. The PRODIGY trial asked whether a patient having just undergone stent implantation (DES or BMS) should stay on DAPT for 6 or for 24 months. There was no benefit for the longer DAPT, but, instead, this group had an increased bleeding risk. The RESET trial asked whether a 3-month course of DAPT after a zotarolimus-eluting sent (Endeavor, Medtronic) is non-inferior to any non-Endeavor DES with standard 12 months of DAPT. The trial showed...
equivalence of these two approaches. Finally, the EXCELLENT trial compared 6 vs. 12 months DAPT after a DES implantation. The short DAPT was non-inferior. However, there were some differences between the subgroups receiving an EES and those receiving an SES; the latter group showed more target vessel failures with the short DAPT. Furthermore, the risk for stent thrombosis was numerically doubled for the short DAPT while the bleeding risk was half compared with the long DAPT (even though again not statistically significant).

In addition, each of these individual trials has important limitations. The PRODIGY trial included patients with BMS (25%) where a lack of benefit for prolonged duration clopidogrel is not surprising. A significant proportion of the enrolled patients had an ACS (74% in the PRODIGY trial) and this is probably confounding the results. There is convincing evidence that this population benefits from a longer duration treatment (at least 12 months), regardless of stent type used and even if managed medically. The RESET trial used the Endeavor stent in the short DAPT group, but this stent is seldom used in clinical practice and has been replaced by the RESOLUTE stent with a slower drug release. The main characteristic of the Endeavor stent is the very rapid drug release within 2 weeks, therefore behaving almost like a BMS.

Unfortunately, this meta-analysis does leave several key questions unanswered: what is the optimal DAPT duration for patients on oral anticoagulation? Not only does a triple therapy increase the risk for bleeding, but coumadin can also attenuate the antiplatelet oral anticoagulation? Not only does a triple therapy increase the risk for bleeding, but coumadin can also attenuate the antiplatelet treatment groups (categorical variables). Increasingly, clinical questions concern continuous variables, such as optimal dosing and optimal duration of treatments. It is highly challenging if not impossible to address such questions with a randomized trial design. To find an optimum, we would need an infinite number of patient groups, even more so if we also wanted to consider different modifying variables such as different stent types. This would lead to a countless number of possible combinations. There is an urgent need to develop new trial designs and corresponding statistical methods to test for continuous variable and multiple permutation endpoints in cardiovascular medicine.

In addition to well-powered RCTs being cost prohibitive, current RCTs also have the problem that the research question becomes outdated during the long course of the trial (given the large sample size required and prolonged follow-up). The currently ongoing largest ever trial in this field, the Dual Antiplatelet Therapy (DAPT) trial (NCT00977938), has just completed its enrolment phase in August 2012 and has randomized 26,000 patients to 12 vs. 30 months of DAPT. Will this question still be relevant by the time the follow-up period will be completed in a few years? It is unlikely that we will ever find a definite answer on optimal DAPT duration: stent designs continue to change, bioabsorbable stents may be increasingly used and will probably behave differently, newer antiplatelet drugs (such as ticagrelor and prasugrel) will be used more often, and these more potent drugs may even be used as single antiplatelet therapy, questioning the role of aspirin. In this context, optimal duration DAPT will continue to be a moving target. In the future, the golden rule will hopefully be ‘the shorter the dual antiplatelet therapy, the longer the event-free survival’.

Despite these limitations, this meta-analysis provides the best evidence on this topic to date. Based on these results, it seems safer to use a shorter duration DAPT while the optimal duration still remains unclear. According to non-randomized data, the optimal duration may be ~6 months. A cohort study of 10,778 patients followed-up for 2 years after an SES found an excess risk for stent thrombosis if DAPT was stopped during the first 6 months, but not if it was stopped after 6 months. In line with this, a German study in 6816 consecutive patients who underwent DES implantation followed the patients for 4 years and showed a rapidly decreasing risk for stent thrombosis, reaching a plateau at ~6 months (fig. 3, Schulz et al.11). Importantly, these studies were predominantly based on first-generation DES and also included patients with ACS. Newer generation DES are likely to show a different time-dependent risk, and patients with stable coronary artery disease can probably be safely treated with shorter DAPT duration.

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References


