Duration of dual antiplatelet therapy after drug-eluting stent implantation: will we ever reach a consensus?

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This editorial refers to ‘ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting’, by S. Schulz-Schüpke et al., on page 1252.

“Well! Shall we go?—Yes, let’s go. ‘They do not move.’

Waiting for Godot, by Samuel Beckett.

Combined treatment with aspirin and a P2Y12 inhibitor, the so-called dual antiplatelet therapy (DAPT) regimen, exerts protection against ischaemic myocardial recurrences via a double mechanism of action.

First, it prevents sudden thrombotic occlusion of previously implanted stent(s) in the coronary arteries, thereby reducing the risk of stent thrombosis that occurs as a result of an inflammation during healing.1,2 Since the vast majority of stent thrombosis cases are known to occur within the first weeks after stent implantation, an arbitrary 30 day to 6 weeks duration of DAPT has been investigated and a 30 day duration of therapy has become the standard of care approach after uncoated stent implantation.

Secondly, DAPT has also been shown to mitigate the risk of subsequent myocardial infarction in patients not previously treated with coronary stents or arising from non-previously stented coronary segments.3,4 While the capability of DAPT to limit the progression of atherosclerosis per se has never been demonstrated, it remains likely—even if not proven—that DAPT protects the patient from the consequences of spontaneous coronary plaque rupture.

The reasons why long-term prolongation of DAPT is debated, despite its unquestionable value, are two-fold. Long-term DAPT carries a time-dependent risk of major and clinically relevant bleeding complications, which affects morbidity and mortality at least as much as ischaemic recurrences.4–7

Moreover, the advent of drug-eluting stents (DES) has prompted attention to be paid to delayed healing and persistent polymer-induced inflammation at the sites of stent placement, thereby potentially requiring long-standing DAPT continuation.

First-generation DES were associated with a four- to five-fold higher risk of very late (i.e. after the first year) stent thrombosis as compared with bare metal stents (BMS).8,9 This observation corroborated the perception of increased thrombogenicity of DES as compared with BMS and fuelled ‘the longer the better’ notion for DAPT duration in DES-treated patients.10

Yet, stent thrombogenicity is a multifactorial process and the drug-elution capability per se does not appear nowadays (i.e. at variance with the original belief) clearly related to it.11

Emerging evidence of superior safety with respect to stent thrombosis and target vessel myocardial infarction has been generated for some of the newly introduced devices when compared with first-generation DES.12–14 Moreover, there is a growing literature suggesting that at least some second-generation devices may be safer when compared not only with first-generation devices but also with the corresponding BMS counterparts.14–16 Therefore, the original belief according to which a DES per se should trigger a prolonged course of DAPT does not seem to be supported by currently available comparative safety and efficacy data amongst different stent platforms.

The complexity and importance of the topic can only be addressed by properly performed randomized clinical trials. Yet, after multiple dedicated randomized controlled studies, the issue of the optimal duration of DAPT after DES implantation remains apparently unsettled.

In this issue of the journal, Schulz-Schüpke and colleagues report on the long awaited primary findings of the Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) trial, which randomized 4000 patients, out of the previously planned 6000, to undergo 6- vs. 12-month therapy with aspirin and clopidogrel, largely after second-generation DES implantation.17

Beyond the specific clinical and scientific value of the study, this trial does represent a major academic achievement, in light of its global representativeness, and investigator-initiated and placebo-controlled design. The hurdles of conducting such a study, which led investigators to stop inclusion prematurely, reinforce the notion that it is becoming increasingly more challenging for physicians (and also expert trialists!) to provide answers to clinically relevant...
questions without the direct involvement of industries. This observation should prompt a profound reflection within the medical community on the sustainability of spontaneous research in the future and highlights the value of this specific study despite its inherent limitations, largely related to limited study power, which are well acknowledged by the authors.

Waiting for Godot?

In the tragicomedy entitled Waiting for Godot, by Samuel Beckett, Vladimir and the struggling Estragon wait for the mysterious Mr Godot, who never shows up. The ISAR-SAFE along with the DAPT trials have been eagerly awaited by the community as the studies are supposed to bring a final word on the optimal DAPT duration after DES. Unlike Mr Godot, ISAR-SAFE and DAPT trials finally arrived. However, similarly to Mr Godot, both studies, for very different reasons, did not entirely fulfill the expectations set by the community.

The incidence of the primary endpoint of the ISAR-SAFE study, consisting of death, myocardial infarction, stent thrombosis (definite or probable), stroke, or Thrombolysis in Myocardial Infarction (TIMI) major bleeding, was virtually identical in both groups at 9 months after randomization, fulfilling the pre-specified non-inferiority criteria. Absolute non-inferiority delta between the two treatment groups was set at 2%, corresponding to 20% of the anticipated background event rate (i.e. 10%). While the originally planned relative 20% non-inferiority boundary was appropriately stringent, the five-fold lower than expected observed event rate resulted in non-inferiority criteria being even greater than the actual event rate observed in the study. As a result, the ISAR-SAFE trial cannot be regarded as a conclusive investigation per se. The selection of mainly stable patients at the time of percutaneous coronary intervention (<20% myocardial infarction patients), the relatively short treatment duration difference (6 months) and follow-up (9 months), the application of a noise avoidance strategy, i.e. setting randomization at the time the treatment started to diverge in the two study groups, and perhaps the need to stick to clopidogrel instead of newer P2Y12 inhibitors may account for such an unexpected low event rate. It may be argued that in the era of more potent and consistent P2Y12 inhibitors, the need to stick to clopidogrel instead of newer P2Y12 inhibitors may add clarity to the results provided now by ISAR-SAFE itself. The mean age was comparable across these seven studies, ranging from 62 to 68 years, and the prevalence of diabetes mellitus ranged from 25% up to 39%. The prevalence of ST-segment elevation myocardial infarction at presentation varied widely amongst the included studies. Importantly, in all trials, DAPT consisted of aspirin and clopidogrel. Loss at follow-up was variable across studies: SE-CURITY19 and the ISAR-SAFE trials had the highest loss at follow-up, while in the EXCELLENT22, RESET23, PRODIGY5 and ITALIC23 trials, loss at follow-up was minimal. ISAR-SAFE is the only study among those included based on a double-blind design. No detectable heterogeneity for the explored endpoints, as assessed by the Q statistic (P = 0.08) and when the BARC (Bleeding Academic Research Consortium) classification was applied, which captures any type of actionable or non-actionable bleeding complications, the 6-month DAPT regimen was associated with 50% lower risk of events (1.4% vs. 2.8%; HR 0.49; 95% CI 0.31–0.77; P = 0.002). An interesting observation arising from the ISAR-SAFE trial is the complete lack of rebound phenomenon after DAPT discontinuation, both at 6 (experimental arm) and at 12 (control group) months. This is in agreement with the results of the patterns of non-adherence to anti-platelet regimens in stented patients (PARIS) registry,18 where only patients who discontinued DAPT due to a bleeding episode or non-compliance experienced an increased risk of adverse events thereafter. Yet, this observation appears in contrast to the results of the DAPT trial where a three-fold increased risk of myocardial infarction in the 90 days following DAPT discontinuation has been reported at both 12 (control group) and 30 months (experimental arm). The inspection of the 95% CIs of the HRs capturing events in the 90 days after DAPT discontinuation in ISAR-SAFE and DAPT trials suggests that this discrepant finding with respect to rebound effect after stopping DAPT cannot easily be attributed to a type I error. Moreover, no single randomized controlled trial (RCT) testing different DAPT durations has so far reported this observation, apart from the DAPT trial. Hence, a proper explanation for the observed rebound effect, or lack thereof, of protocol-mandated DAPT discontinuation in the DAPT trial vs. ISAR-SAFE and other RCTs remain elusive and warrants further investigation.

Pooled analysis

Including ISAR-SAFE, seven studies, recruiting 15,378 patients have so far compared <12-month DAPT duration (ranging from 3 to 6 months), with 12-month (5 studies)19–22 or 24-month (two studies)5,23 DAPT duration. Three additional studies, including the DAPT trial, evaluated the value of prolonging vs. stopping DAPT beyond 12 months. While multiple meta-analyses exist pooling together all available evidence, irrespective of actual DAPT duration in the control and experimental arm, this generates a methodological issue as it would lead to inclusion of the 12-month DAPT duration in both study arms. As the aim of ISAR-SAFE is to assess whether DAPT can be safely stopped at 6 as compared with 12 months, only including studies comparing a shorter than 12-month vs. a ≥12-month regimen may add clarity to the results provided now by ISAR-SAFE itself. The mean age was comparable across these seven studies, ranging from 62 to 68 years, and the prevalence of diabetes mellitus ranged from 25% up to 39%. The prevalence of ST-segment elevation myocardial infarction at presentation varied widely amongst the included studies. Importantly, in all trials, DAPT consisted of aspirin and clopidogrel. Loss at follow-up was variable across studies: SECURITY19 and the ISAR-SAFE trials had the highest loss at follow-up, while in the EXCELLENT22, RESET23, PRODIGY5 and ITALIC23 trials, loss at follow-up was minimal. ISAR-SAFE is the only study among those included based on a double-blind design. No detectable heterogeneity for the explored endpoints, as assessed by the Q statistic (P = 0.08) and when the BARC (Bleeding Academic Research Consortium) classification was applied, which captures any type of actionable or non-actionable bleeding complications, the 6-month DAPT regimen was associated with 50% lower risk of events (1.4% vs. 2.8%; HR 0.49; 95% CI 0.31–0.77; P = 0.002). An interesting observation arising from the ISAR-SAFE trial is the complete lack of rebound phenomenon after DAPT discontinuation, both at 6 (experimental arm) and at 12 (control group) months. This is in agreement with the results of the patterns of non-adherence to anti-platelet regimens in stented patients (PARIS) registry,18 where only patients who discontinued DAPT due to a bleeding episode or non-compliance experienced an increased risk of adverse events thereafter. Yet, this observation appears in contrast to the results of the DAPT trial where a three-fold increased risk of myocardial infarction in the 90 days following DAPT discontinuation has been reported at both 12 (control group) and 30 months (experimental arm). The inspection of the 95% CIs of the HRs capturing events in the 90 days after DAPT discontinuation in ISAR-SAFE and DAPT trials suggests that this discrepant finding with respect to rebound effect after stopping DAPT cannot easily be attributed to a type I error. Moreover, no single randomized controlled trial (RCT) testing different DAPT durations has so far reported this observation, apart from the DAPT trial. Hence, a proper explanation for the observed rebound effect, or lack thereof, of protocol-mandated DAPT discontinuation in the DAPT trial vs. ISAR-SAFE and other RCTs remain elusive and warrants further investigation.
In summary, despite the fact that ISAR-SAFE has limited power to answer the original study question (i.e. is it safe to stop DAPT at 6 months after DES as compared with 12 month therapy?) the results of this pooled analysis of all studies so far conducted comparing shorter than 12 months vs. at least 12 months or longer DAPT duration after DES implantation are consistent with the overall study results. It suggests that a shorter DAPT regimen halves the risk of major bleeding and does not seem to be associated, in return, with extra ischaemic risk. This observation is in keeping with the PARIS registry, where patients who discontinued DAPT under medical guidance were not exposed to a higher risk of major adverse cardiovascular events or stent thrombosis as compared with patients who remained on DAPT for 2 years.\(^ {18}\)

**What does the future hold?**

The lack of clear ischaemic benefit associated with an at least 12-month DAPT regimen arising from the pooled analysis of all studies comparing shorter than vs. at least 12-month DAPT duration contrasts with the results of the DAPT trial.\(^ {4}\) In that study, an unquestionable benefit in terms of both stent- and patient-oriented ischaemic endpoints has been reported, even if the excess of bleeding risk and the increase of non-cardiovascular mortality remain a matter of concern.\(^ {9}\) Reconciliation of these apparently contrasting findings in clinical practice remains challenging. Difference in patient selection, timing of randomization, proportion of patients receiving newer as compared with first-generation DES,\(^ {24,25}\) and use of newer P2Y12 inhibitors are elements which may at least partially account for these different results.

Hence, after 10 randomized controlled studies including >30 000 patients, the only possible conclusion to be drawn by the clinician is that one standard DAPT regimen does not seem to benefit all patients equally. A personalized DAPT duration based on the individual bleeding hazard or the balance of bleeding and ischaemic risk seems the most logical way for the future, which will require dedicated studies.\(^ {26}\)

The selection of which single antiplatelet agent to carry forward after DAPT discontinuation, i.e. aspirin as conventionally recommended\(^ {27}\) or the P2Y12 inhibitor and type thereof, remains an area of research for the future, but they hold promise to shorten overall DAPT duration without compromising efficacy.

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**References**


