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EDITORIAL COMMENT

The Prematurely Stopped Clinical Trial

An Unfinished Symphony*

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The completion of a randomized clinical trial (RCT) requires extensive effort and resources. Like Schubert's eighth "Unfinished Symphony," which had an expansive first movement that was evidently unsustainable for 3 additional movements (1), RCTs often have a great start but sometimes struggle to get completed.

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In this issue of *JACC: Cardiovascular Interventions*, Nakamura et al. (2) report the results of the NIPPON (Nobori Dual Antiplatelet Therapy as Appropriate Duration) trial, which was stopped prematurely because of poor enrollment. The NIPPON trial tested the hypothesis that 6 months of dual antiplatelet therapy (DAPT) was noninferior to 18 months after implantation of biodegradable polymer drug-eluting stents (DES). The primary composite endpoint of all-cause mortality, myocardial infarction, stroke, and major bleeding occurred in 2.1% of patients receiving short-term DAPT and in 1.5% receiving long-term DAPT (difference 0.6%; 95% confidence interval [CI]: 1.5% to 0.3%). Because the lower limit of the 95% CI was inside the pre-specified margin of −2.0%, the investigators declared noninferiority of short-term DAPT.

Although the NIPPON results ostensibly suggest that a short course of DAPT after biodegradable polymer DES implantation is safe, in a strict sense the findings are inconclusive. The NIPPON trial was stopped prematurely after enrollment of 3,307 of 4,598 planned patients and had event rates that were less than one-half of expected (4.5%). Reduced event rates tend to shrink between-group differences to the null and increase the probability of achieving statistical significance within a noninferiority framework, whereas increased event rates tend to do the opposite in a conventional superiority trial and increase the chance of statistical significance. A solution is to define the noninferiority margin on a relative scale, but this was not done, likely because no one could have predicted that the NIPPON trial would be stopped early.

The NIPPON trial joins a group of 5 trials that have been stopped early for slow enrollment (2–6) among a total of 14 trials investigating DAPT duration after newer generation DES implantation (2–15). Stopping a trial for poor enrollment is not a moral failing. Loss of funding and coexistence of competing trials are several factors beyond the control of investigators that may explain why approximately 1 in 4 RCTs is terminated prematurely (16). When pre-defined stopping rules are not followed, an unplanned interim analysis may generate results that are imprecise, inaccurate, or unintentionally biased (17).

To identify whether any of these problems arose in RCTs of DAPT duration after newer generation DES implantation, we integrated the NIPPON results with the existing evidence (18). As shown in **Figure 1**, pooled results from the 5 RCTs with poor enrollment (2–6) showed no relation between DAPT duration and mortality, bleeding, stent thrombosis, and myocardial infarction. In contrast, results from the 9 trials with complete enrollment (7–15) identified a relation between prolonged DAPT and mortality, bleeding, stent thrombosis, and myocardial infarction. Apart from mortality, outcomes in the prematurely stopped trials had point estimates that were similar in direction and to some extent in magnitude to values from the completed trials (**Figure 1**). Testing for statistical

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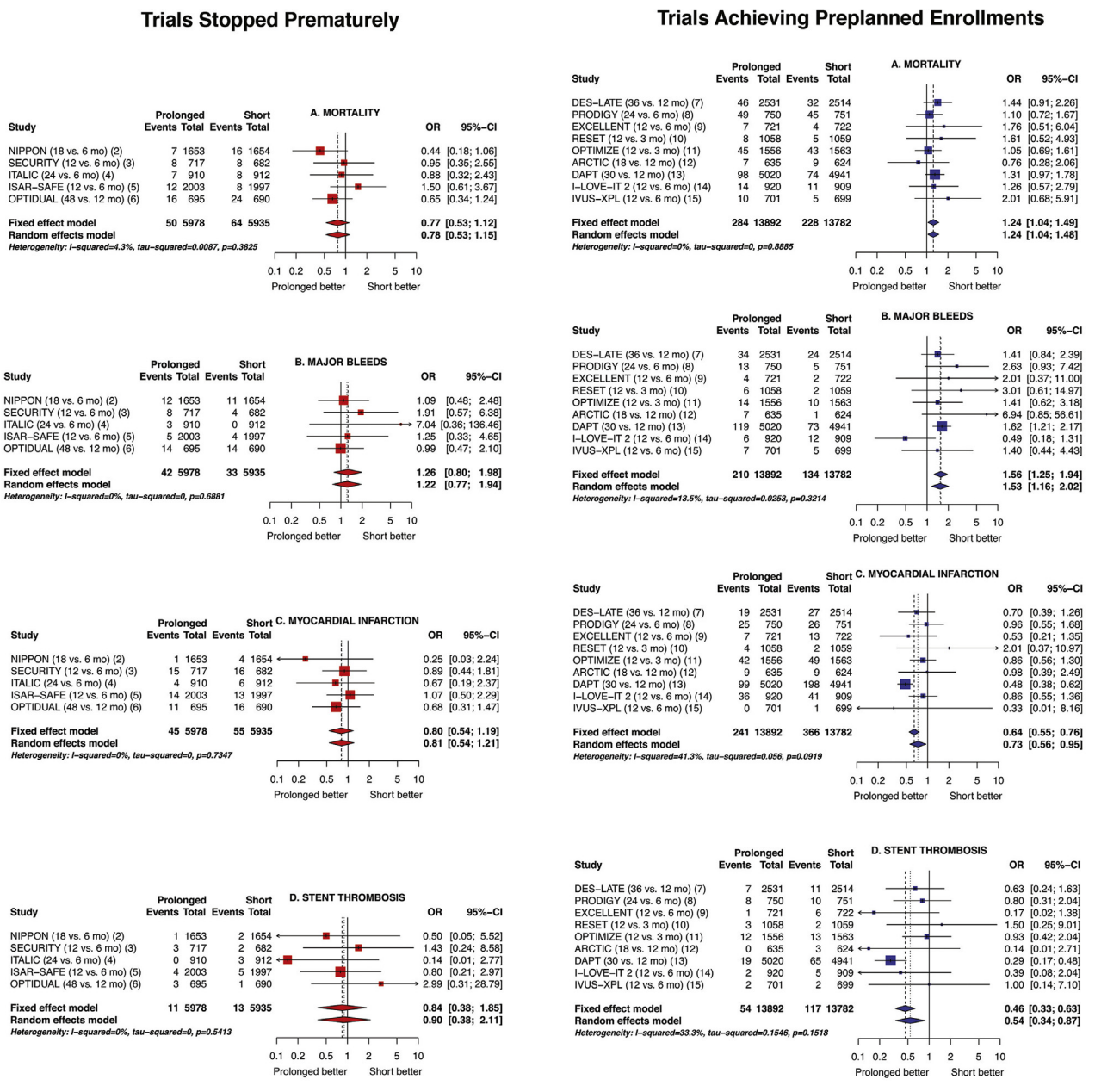
FIGURE 1 Forest Plots



Original forest plots show event rates in 5 trials stopped prematurely because of slow enrollment **(red)** and in 9 trials achieving planned enrollment **(blue)** that randomized patients to prolonged or shorter courses of dual antiplatelet therapy after drug-eluting stent implantation. CI = confidence interval; OR = odds ratio. Original figures created with the open-source statistical program R version 3.0.3 (19) and library package "meta" 3.8-0 (20).

heterogeneity showed that prematurely stopped trials provided a different estimate for mortality than did completed trials (p = 0.028), though confidence intervals overlapped.

To determine if the findings for the completed trials were driven by the DAPT results (13), we performed an elimination exercise and found that point estimates from the 8 other completed trials (7-12,14,15) for mortality (odds ratio [OR]: 1.21; 95% CI: 0.97 to 1.50), bleeding (OR: 1.40; 95% CI: 0.99 to 1.47), myocardial infarction (OR: 0.84; 95% CI: 0.67 to 1.05), and stent thrombosis (OR: 0.71; 95% CI: 0.46 to 1.11) were

more likely than the results from the 5 prematurely stopped trials (**Figure 1**) to match the results of the DAPT trial itself (13), which set a high standard for study design and met its primary endpoints (18), accomplishments in an RCT that earn comparisons to Schubert's ninth symphony, "The Great" (1).

The findings presented here require cautious interpretation. First, although prematurely stopped trials may measure event rates imprecisely or inaccurately, evidence of bias has not been suggested apart from mortality. Second, the findings do not prove that prolonged DAPT increases mortality, because stratification by trial completion was a post hoc exercise. Last, early stopping is not the only measure of trial quality.

A prematurely stopped trial such as the NIPPON trial (2) calls to mind both the beauty and the uncertainty of Schubert's eighth symphony (1), a masterwork that remains a heartfelt contribution to the repertoire, but no one knows how it would have ended. Although prematurely stopped trials may provide useful information about the safety of new treatments (17), they are underpowered and often add statistical noise to systematic reviews. Future research should determine whether the present findings are relevant only to trials of DAPT duration or whether a prematurely stopped trial in other disciplines differs from a completed trial as much as the "Unfinished Symphony" differs from "The Great" (1) and leaves the audience wishing for more.

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