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EDITORIAL COMMENT

Complex Coronary Artery Disease

Would Outcomes From the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) Trial Have Differed With Newer-Generation Drug-Eluting Stents?*

Vasim Farooq, MB, ChB,
Patrick W. Serruys, MD, PhD

Rotterdam, the Netherlands

Newer-generation drug-eluting stents (DES) have unequivocally led to significant improvements in safety compared with first-generation DES (1–8). Given the substantial clinical benefits attained with newer-generation DES, the obvious question remains—would outcomes from the landmark SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial (9–12) have differed with newer-generation DES?

See page 1012

In this issue of *JACC: Cardiovascular Interventions*, Ribichini et al. (13) present important findings from the randomized, multicenter EXECUTIVE (Evaluating Xience-V in Multi-Vessel Disease) pilot trial, comparing the newer-generation everolimus-eluting stent (EES) (Xience V, Abbott Vascular, Santa Clara, California) against the first-generation paclitaxel-eluting stent (PES) (Taxus Express, Boston Scientific, Natick, Massachusetts) in the treatment of multivessel coronary artery disease. The primary outcome was angiographic, namely, late lumen loss, and demonstrated the superiority of EES (all lesions late lumen loss: EES 0.05 ± 0.51 mm vs. PES 0.24 ± 0.50 mm, $p < 0.001$). Although the study was clearly underpowered for clinical outcomes, observations of numerical differences in 1-year major adverse cardiac events of 11.1% in the randomized EES arm, and 16.5% in the randomized PES arm are difficult to ignore, and offer a unique insight into the potential benefit of newer-generation DES in the treatment of multivessel disease.

There are, however, a number of caveats to the EXECUTIVE trial that should be highlighted. Firstly, in keeping with the U.S. and European revascularization guidelines (14–16), the EXECUTIVE trial focused primarily on low SYNTAX score (<23) (11,17,18) subjects, having been recruited in approximately 95% of the EES and PES treatment arms (mean SYNTAX score: 12.7 ± 5.2). How generalizable the results of the EXECUTIVE trial are to subjects with more complex multivessel disease, therefore, remains unclear. Secondly, the EXECUTIVE trial lacked an all-comers design, with clinical and angiographic inclusion and exclusion criteria, which somewhat limits translation of the study's findings to contemporary clinical practice, even in low SYNTAX score subjects. For example, a history of congestive cardiac failure or a left ventricular ejection <30%—factors previously shown to alter the threshold value of the SYNTAX score in favor of coronary artery bypass grafting (CABG) (19)—were exclusion criteria. In the pre-SYNTAX era, such restrictive trial designs comparing CABG with percutaneous coronary intervention (PCI) were heavily criticized for "cherry-picking" patients for randomization, despite the randomized nature of these studies (20,21). Thirdly, the EXECUTIVE trial was clearly underpowered to assess clinical outcomes, and showed numerical differences in clinical outcomes that could not be statistically corroborated. Fourthly, the fact that complete revascularization almost uniquely appeared to have been achieved in all randomized patients, with consequent favorable outcomes (22,23), and that an arbitrarily defined limit of 4 planned stents per patient was placed in the angiographic inclusion criteria, does imply a further amount of selection bias in recruiting subjects.

The improved clinical outcomes with the EES in multivessel disease (despite the described shortcomings of the EXECUTIVE trial), coupled with similarly reported data from the FLM Taxus (French Left Main Taxus) and the LEMAX (LEft MAin Xience) registries, investigating left main stenting with EES (24,25), and the known reductions in stent thrombosis (ST) of newer-generation DES (1–8), does imply that if newer-generation DES had been used in the SYNTAX trial, there would have been a significant reduction in clinical events, particularly repeat revascularization and myocardial infarction.

As to whether reductions in mortality would be seen with newer-generation DES in patients undergoing contemporary PCI is entirely plausible (8). Large-scale reductions in ST and their clinical sequelae with newer-generation DES are firmly established in the literature, although the expected reduction in mortality awaits confirmation from randomized trials (1–7). Conversely, in the SYNTAX trial, if the cardiac mortality events related to ST were removed, based on Academic Research Consortium (26) definitions of ST, there would have been only a modest reduction in cardiac mortality at 5 years. Namely, for definite ST, 5-year cardiac mortality would be reduced from 9% to 8.5%, and for

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From the Department of Interventional Cardiology, Erasmus University Medical Centre, Thoraxcenter, Rotterdam, the Netherlands. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

definite and probable ST, from 9% to 7.5% (27). The main reason to account for this phenomenon may relate to the hypothesis that bypass grafts protect coronary vessels from future myocardial events for the lifespan of the graft, particularly in more complex coronary artery disease where the plaque burden and risk of a future cardiac event would potentially be higher, compared with a subject with less complex coronary artery disease. Conversely, stents would only treat individual lesions (21,28).

The potential reduction in mortality with newer-generation DES in the SYNTAX trial would therefore be unlikely to bridge the gap between CABG and PCI, particularly with more complex coronary artery disease. This is exemplified in the SYNTAX score II (19,29), in which the SYNTAX score was combined with clinical variables that were shown to alter the threshold value of the SYNTAX score so that equipoise was achieved between CABG and PCI for long-term mortality. Notably, subsets of patients were identified across all tertiles of the SYNTAX score who would have a mortality benefit from undergoing CABG or PCI (Fig. 1). It should, however, be emphasized that increasing anatomical complexity, particularly in subjects with 3-vessel disease, lead to a greater likelihood of a mortality benefit to be attained with CABG over PCI (Fig. 1).

In both the ongoing EXCEL (Evaluation of XIENCE PRIME Everolimus Eluting Stent System [EECSS] or XIENCE V EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (NCT01471522), investigating the treatment of unprotected left main coronary artery disease, and the

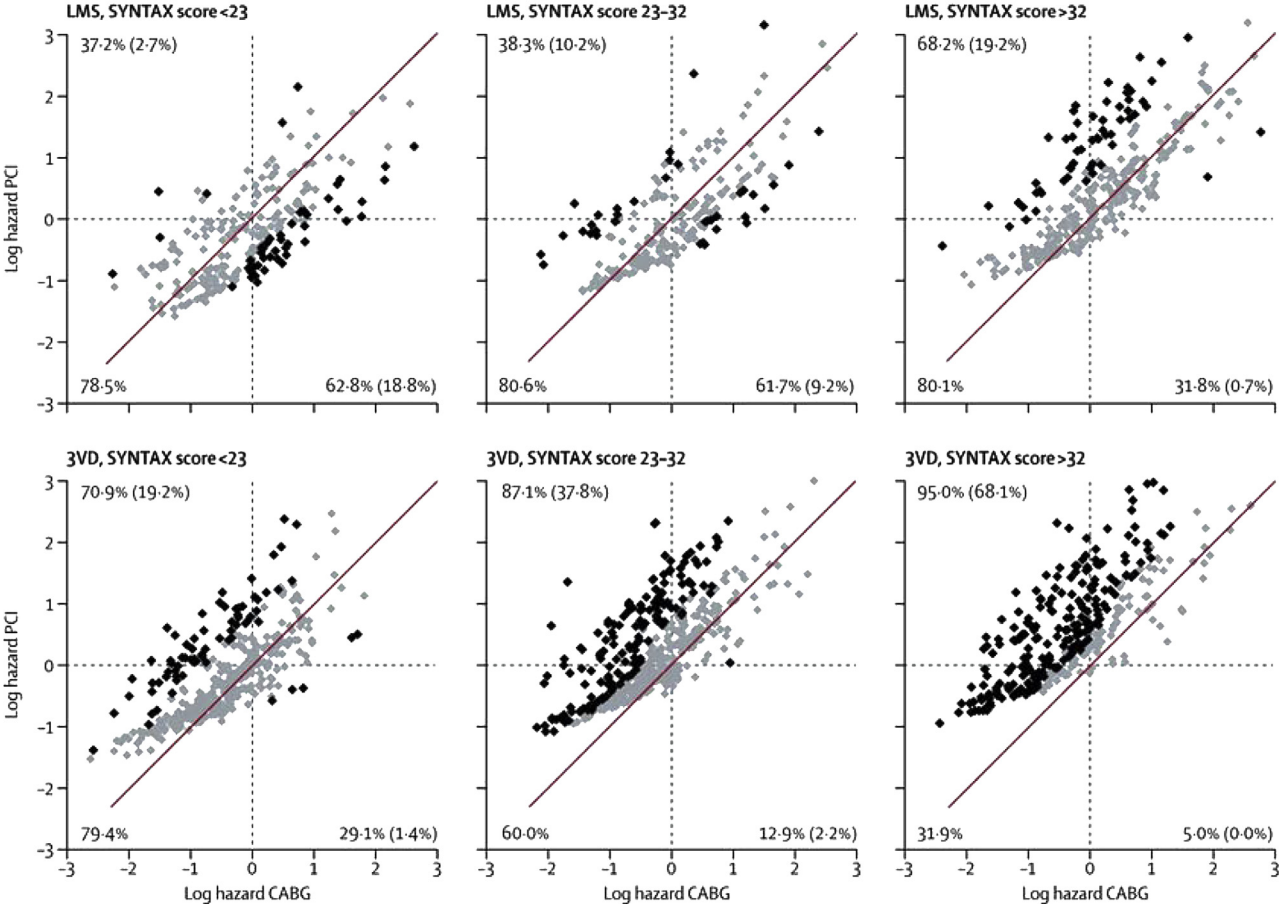

Figure 1. Scatter Plots for Individual Patients in the Left Main and 3-Vessel Disease Cohorts of the Randomized SYNTAX Trial (N = 1,800)

The scatter plots for the left main and 3-vessel disease cohorts of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial are based on the SYNTAX score II. The **diagonal line** represents identical mortality predictions for CABG and PCI. Individual mortality predictions plotted to the **left of the diagonal line** favor CABG (actual percentages shown in **top left corner**), and to the **right** favor PCI (actual percentages shown in **bottom right corner**). Individual mortality predictions for CABG or PCI that could be statistically separated with 95% confidence ($p < 0.05$) are colored **black** (actual percentage shown in parentheses in respective corners). Mortality predictions that could not be statistically separated with 95% confidence ($p > 0.05$) are highlighted in **gray**, and identify patients with similar 4-year mortality. 3VD = 3-vessel disease; CABG = coronary artery bypass grafting; LMS = left main stem; PCI = percutaneous coronary intervention. Legend and image are adapted and reproduced, with permission, from Farooq et al. (19).

planned SYNTAX Trial II, investigating the treatment of de novo 3-vessel disease, the SYNTAX score and SYNTAX score II, respectively, are being used to recruit subjects on the grounds of patient safety (30). Further delineating the boundaries between CABG and PCI is where further study is heading to help best define the optimal revascularization modality for individual patients with complex coronary artery disease.

Reprint requests and correspondence: Dr. Patrick W. Serruys, Erasmus Medical Centre, 's-Gravendijkwal 230, 3015 CE Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

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