

Prognosis after revascularization for left main coronary artery disease: insights from the crystal ball

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This editorial refers to ‘Long-term forecasting and comparison of mortality in the Evaluation of the Xience Everolimus Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial: prospective validation of the SYNTAX Score II’[†], by C.M. Campos *et al.* on page 1231.

Obstructive left main coronary artery (LMCA) disease is encountered in >5% of patients undergoing coronary angiography.¹ Because of the large area of downstream myocardium supplied by the left main stem—more than 80% of the left ventricle in right dominant systems, 100% in left dominant systems²—successful revascularization of LMCA stenosis is usually associated with considerable improvement in both symptoms and survival in comparison with medical treatment alone.³ Against this, the consequences of revascularization failure are greater and, accordingly, much debate has centred on the preferred revascularization modality—coronary stenting or bypass surgery—for patients with LMCA disease.

A number of previous randomized trials enrolling patients with LMCA disease have shown comparable mortality between patients treated by either drug-eluting stenting or bypass surgery over the short to medium term (see *Figure 1*).^{4–6} The largest of these was a pre-specified subgroup of the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial (enrolling 705 patients).⁶ This study showed not only similar rates of death with both treatments but also comparable rates of overall major adverse cardiac events at 12 months, suggesting genuine clinical equipoise between the two approaches. Moreover, recent publication of 5-year results from this study confirmed the overall comparability of outcomes with both strategies over the longer term.⁷ Accordingly, the choice of revascularization strategy is probably best made in a shared decision-making approach taking into account both individual patient characteristics and preferences as well as local considerations

relating to the availability and expertise of cardiac surgery and interventional cardiology. Indeed current European guidelines on myocardial revascularization support this approach, recommending that patients with LMCA disease can be treated with either coronary stenting (class I or IIa recommendation) or bypass surgery (class I recommendation) unless there is concomitant anatomical highly complex disease, in which circumstance bypass surgery should be preferred.⁸

However, existing trial data have certain limitations, and conclusions relating to hard clinical events must be made cautiously. First, these earlier studies were limited by small sample size and were unlikely to be able to detect differences in endpoints such as death, myocardial infarction, or stroke. Moreover, the largest study—the SYNTAX left main trial—was not primarily powered for comparison of outcomes in patients with LMCA disease and included target lesion revascularization, which is a relatively soft endpoint, as a component of the primary endpoint.⁹ Secondly, stenting was undertaken with early generation drug-eluting stents (DES). These stents have been superseded by newer generation devices with improved efficacy and higher clinical safety.^{10,11} It is conceivable that lower rates of stent failure might influence rates of survival.^{12,13} Thirdly, completeness of revascularization is associated with improved survival, and concerns exist regarding this issue in earlier trials.¹⁴ Finally, increased use of invasive haemodynamic testing may better select lesions likely to benefit from either revascularization approach. For these reasons, contemporary re-assessment of comparative efficacy with coronary stenting vs. bypass surgery is an important undertaking.

The Evaluation of XIENCE Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation (EXCEL) trial is a randomized trial comparing outcomes of patients with LMCA disease, who are allocated to either coronary stenting with new-generation DES or bypass surgery (see www.clinicaltrials.gov, identifier NCT01205776). Importantly, patients with the highest anatomic

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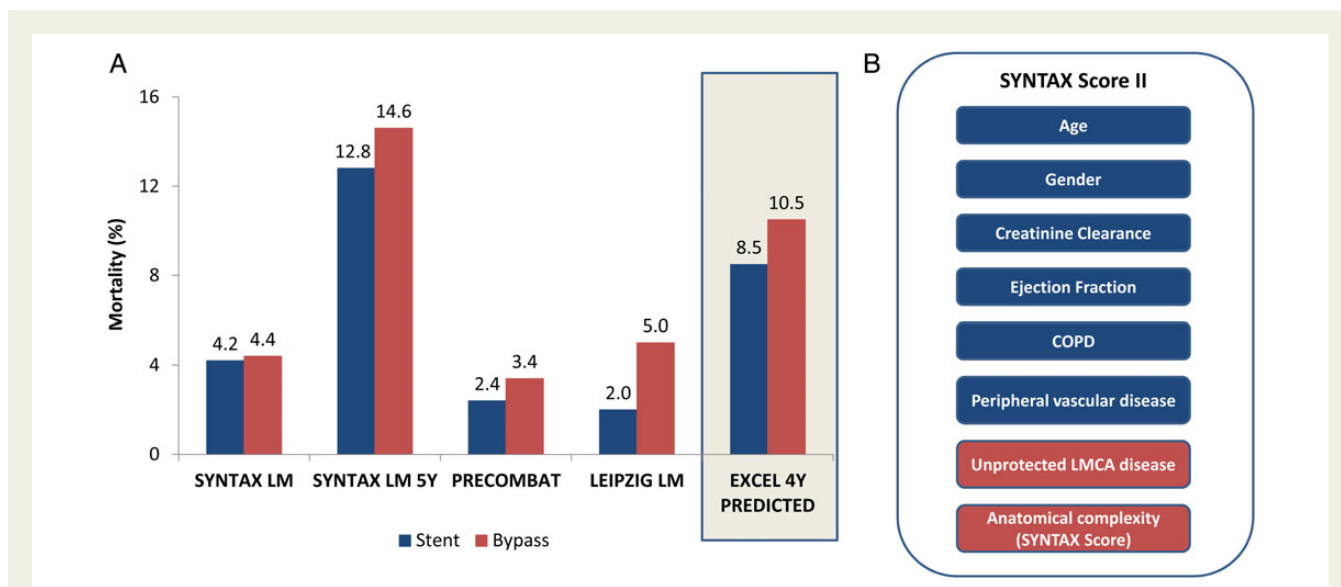


Figure 1 (A) Mortality of patients with unprotected left main stem disease treated with drug-eluting stenting vs. bypass surgery in randomized trials along with predicted mortality based on the SYNTAX Score II from the ongoing EXCEL randomized trial. (B) Principal data components for calculation of the SYNTAX Score II. In (A), rates are rounded to the nearest whole number and are shown at the time point of analysis of the primary endpoint and/or at the time point of the latest published follow-up. In (B), clinical parameters are in blue, and anatomical parameters are in red. COPD, chronic obstructive pulmonary disease; LMCA, left main coronary artery.

disease complexity are not eligible for enrolment. The basis for excluding these patients was probably concern on the investigators' behalf about outcomes with stenting in these patients, though actually in the SYNTAX left main trial there was no difference in terms of hard clinical endpoints in this group, and the subsequent availability of long-term data suggests that these patients probably need not have been excluded.^{6,7} The investigators originally planned to enrol 2600 patients but subsequently modified the trial to reduce enrolment to 1900 patients, though the precise reasons for this decision have not yet been reported. The trial is now fully enrolled and the results of the primary analysis—the composite of death, myocardial infarction, or stroke at 3 years—are awaited.

So, will the enrolment of a large sample size, the exclusion of patients with high anatomic disease complexity, and the use of new-generation DES result in different relative rates of mortality between coronary stenting and bypass surgery in the EXCEL trial in comparison with earlier studies? Although we will have to wait for the primary results of the trial, which are expected in 2016, to know for sure, in the current issue of the journal, the EXCEL trial investigators take the unique step of reporting in advance an analysis of predicted mortality in both treatment groups.¹⁵ To do this they abstracted the baseline data on enrolled patients concerning anatomical disease complexity (SYNTAX Score, as assessed by the site investigators) and six key clinical parameters of interest for each patient in order to calculate the SYNTAX Score II for each patient (see Figure 1).¹⁶ These scores were then used to predict mortality in each group. Subsequently, using bootstrapping—a standard statistical resampling technique—the authors calculated prediction intervals based on 10 000 repeated simulations of the trial. The main finding is that predicted mortality was not significantly different in both groups: 8.5% with stenting vs. 10.5% with bypass surgery (odds ratio 0.79, 95% prediction interval 0.43–1.50); in the majority of

trial simulations, 4-year mortality predictions between stenting and bypass surgery could not be separated with statistical significance.

The anatomic SYNTAX Score is a useful tool designed to assist researchers and clinicians in quantifying the aggregate complexity of all lesions requiring revascularization in a patient with obstructive coronary disease.¹⁷ Its importance is underlined by the fact that current guidelines on both sides of the Atlantic recommend its use in decision-making in patients with LMCA and multivessel disease.^{8,18} An important limitation is that it only takes into account lesion characteristics: as such it primarily predicts outcomes in patients undergoing stenting; outcomes of patients undergoing bypass surgery tend to be influenced to a greater degree by patient rather than lesion characteristics. For this reason, a variety of new scores have been developed that seek to combine the SYNTAX Score with additional patient-related factors that are known to have important impact on clinical outcomes.¹⁹ The most recent of these is the SYNTAX Score II, which used as the derivation cohort the original SYNTAX randomized trial and as the initial validation cohort the DELTA registry.¹⁶ Since then further data from a second cohort of Japanese patients have also been published.²⁰ However, although its clinical value seems promising, broader and prospective validation is necessary before we can take advantage of its utility in routine clinical practice.

By reporting predicted mortality from an ongoing trial, in some respects the current report of Campos *et al.* represents a rather original contribution to the literature.¹⁵ However, aside from the curiosity of crystal ball gazing, what are the immediate implications of the reported findings and are there dangers inherent in such an approach? First, predicted mortality in an ongoing trial is certainly of interest for the trial investigators. Conceivably—with a well-validated predictive tool—investigators could compare the rates of predicted mortality with those assumed in the sample size

calculations. Such an approach might theoretically be employed to modify the sample size during patient recruitment. However, as the current trial was not powered for mortality and the study is already completely enrolled, this opportunity does not present itself here. Secondly, although it should be acknowledged that clinicians are generally more interested in actual event rates in clinical trials rather than predicted event rates, it will nevertheless be interesting for readers to see how the predicted rates compare with the actual rates when these data become available. In addition it might also be interesting to examine predicted mortality in the patients who were not randomized but entered the registry arm of the study. In this respect, the real value of this report lies in the future: the EXCEL results will provide an excellent data set to test this risk score in LMCA disease patients, and the availability of the actual study data will help us to determine further the validity of the score. Thirdly, the risks of such a publication strategy are poorly defined. Although the authors contend otherwise, an impact of publishing these findings on ongoing data collection and event adjudication cannot be entirely excluded.

Although interesting, this prognosis experiment does not diminish the anticipation of the actual results. In fact there are reasons to expect that predicted and observed mortality might differ. First, the derivation set for both the SYNTAX Score and SYNTAX Score II are based on a trial enrolling not just left main stem disease but also complex three-vessel disease. These latter patients are excluded from the current trial. Secondly, the derivation set was based on outcomes after stenting in patients treated with a relatively poorly performing DES and may not be applicable to outcomes with newer DES devices. Ultimately, these considerations remain hypothetical and the current report may stimulate further debate on the value of predictive scores in routine practice. For example, the relative value of the SYNTAX Score II in comparison with an array of other clinical risk scores—including, for example, the logistic Euroscore, Euroscore II, and the ACEF score to name but three—requires further study.²¹ In addition, some physicians may require further reassurance before they adopt a predictive score that does not include presence or absence of diabetes mellitus, an important variable that most doctors - and indeed clinical practice guidelines - take into account when making decisions on revascularization based on data from randomized clinical trials.²² Finally, at the end of the day, most of these scores fail to capture a true metric of patient frailty, which probably plays a very significant confounding role in determining mortality with both revascularization approaches.²³ In this respect, none of these tools will replace a considered synthesis of the key clinical parameters by experienced surgeons or physicians in the clinic or at the hospital bedside.

In conclusion, the EXCEL trial represents a very important randomized trial studying a question of real clinical equipoise. The investigators should be congratulated for the design and prompt execution of the trial thus far. Its results are eagerly awaited and will undoubtedly be highly relevant for clinical practice and guideline writing committees. Moreover although the implications of the current report concerning predicted mortality in both treatment groups seem limited at present, the availability of the primary trial data set will permit further evaluation of the validity of the SYNTAX Score II. After this we will have a better idea of the value of this novel predictive tool in helping busy clinicians in daily decision-making. Perhaps more importantly, the large data set of the EXCEL trial might well permit development of even better risk scores more reliably

reflecting the outcomes of patients with LMCA disease treated with contemporary state-of-the-art revascularization methods.

Conflict of interest: R.A.B. reports receiving lecture fees from B. Braun Melsungen AG, Biotronik, and Boston Scientific. A.K. reports patent applications related to drug-eluting stent coatings.

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