Coronary Revascularization
How Can Model-Derived Probabilities Inform Clinical Judgment?*

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The study reported in this issue of JACC: Cardiovascular Interventions by Sotomi et al. (1) is the next step in addressing one of the principal challenges in coronary artery disease management: how to apply probability measures of risk and efficacy derived from population studies to identify the optimal binary treatment strategy for an individual patient.

In the 1960s, coronary artery bypass grafting (CABG) presented the first major alternative therapeutic choice in coronary disease management (2). The 1970s and 1980s witnessed prodigious clinical research efforts intended to develop an evidence base to inform the choice between surgical and medical therapies (3). The inception and refinement of percutaneous coronary intervention (PCI) in the 1980s and 1990s added a third alternative, again spawning ambitious efforts to define the relative roles of surgical and interventional revascularization (4–9).

Coronary artery disease is heterogeneous in terms of its anatomic complexity, functional severity, suitability for different treatment modalities, and types of short- and long-term outcome events. Consequently, for meaningful comparisons of alternative treatments, clinical research populations must be accurately characterized with respect to both baseline characteristics and clinical outcomes. Over time, trialists developed progressively sophisticated metrics to characterize these variables. The anatomic SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score was a major advance in this field, providing a numeric approximation of the anatomic extent, severity, and complexity of coronary disease (10). Its application in the SYNTAX trial demonstrated a strong relationship between the anatomic SYNTAX score and long-term outcomes following revascularization, with CABG proving to be superior to PCI in more complex and extensive coronary disease (11).

Concurrently, it became clear that the patient characteristics that determine outcomes in PCI and CABG are different. Whereas anatomic complexity, left ventricular ejection fraction, and renal function are major determinants of PCI outcomes, CABG outcomes are more influenced by measures of patient functional status, including age and medical comorbidities (partially quantitated by the Society of Thoracic Surgeons score and the European System for Cardiac Operative Risk Evaluation score).

This realization led to the SYNTAX score II, which was developed and calibrated by applying regression analysis to the outcomes of the SYNTAX trial. It combines the anatomic SYNTAX score with the functional parameters that figure prominently in the Society of Thoracic Surgeons and European System for Cardiac Operative Risk Evaluation scores into a single scoring system (12). The SYNTAX score II (which is well described in Figure 4 in Farooq et al. [12]) uses patient baseline characteristics to calculate an expected 4-year mortality rate for both PCI and CABG treatment. Notably, individual variables are weighted differently in the CABG and PCI models,
validating that different factors influence outcomes after CABG compared with PCI.

Once the SYNTAX score II was developed, it needed validation. This was initially undertaken using registry datasets (13,14) in which treatment assignments were not randomized. The study by Sotomi et al. (1) reported here extends that assessment to datasets from 2 trials (BEST [Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease] and PRECOMBAT [Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease]) that compared PCI and CABG in 3-vessel and unprotected left main disease patient populations in which treatment choice was by randomization assignment (15,16).

The investigators used the SYNTAX score II to calculate the 4-year mortality hazard ratio for PCI versus CABG treatment for each subject and defined 3 patient populations (PCI preferred, CABG preferred, and equipoise). For each population, there were approximately equal numbers of patients treated by PCI and CABG. Within each treatment preference population, the investigators compared the observed 4-year mortality rates for the 2 subpopulations (actual treatment consistent with vs. opposite to model recommendations). Overall, the SYNTAX score II model showed good calibration and moderate discrimination. Importantly, the analysis showed that for the model-predicted CABG-preferred and PCI-preferred subgroups, survival was better when the treatment received was congruent with model prediction. This validation analysis is limited by inadequate statistical power. As a result, these findings fail statistical significance testing. Nonetheless, in both subgroups, the point estimate trends show superior survival in the patients who were treated according to the model recommendation.

How can clinicians, who are confronted daily by the need to make treatment modality recommendations, apply this information to refine their decision making? These findings demonstrate that the choice between PCI and CABG should incorporate both coronary disease anatomic complexity, as quantitated by the anatomic SYNTAX score, and other patient characteristics and comorbidities. Clinicians already do this under the rubric of “clinical judgment,” and these findings provide an additional evidence base to support what would otherwise be a more intuition-based decision. Moreover, the SYNTAX score II recommended “equipoise” for a large fraction of the patients in these datasets, and in this population, 4-year mortality was reassuringly similar for PCI and CABG. Notably, and perhaps in favor of a PCI strategy in the equipoise population, the model overestimated risk more in the PCI arms than in the CABG arms, especially in the highest risk groups. This may have been driven by the fact that the SYNTAX score II model was developed from datasets that used paclitaxel-eluting stents, whereas second-generation drug-eluting stents were used in BEST and PRECOMBAT.

What are this study’s shortcomings and future research directions? The dataset’s strength is that it is a randomized treatment assignment population. Although the data analysis is elegant, the small number of events analyzed undermines its statistical power. The all-cause mortality endpoint included only 91 deaths, of which only 65 were due to cardiac causes. This shortcoming is most evident in the PCI-preferred group, which included 50 patients, only 17 of whom underwent CABG (with 2 deaths).

The study’s findings are also compromised by the shortcomings of the analyzed endpoint. Endpoint definition for cardiovascular disease outcome studies continues to be an ongoing challenge. The study investigators chose all-cause mortality as the analysis endpoint, even though additional endpoint events had been recorded in the source study datasets. Although death as an endpoint has the advantage of being definitive without subjectivity, it is an incomplete description of the outcomes patients and their physicians may value most. Investigators have examined other endpoints, including various criteria for other adverse cardiac events, frequently using these to create composite endpoints. These strategies are complicated by differences in the clinical importance and the subjective nature of the different endpoint components.

The goal of a cardiovascular treatment is to achieve optimal overall functionality at late follow-up balanced against the initial and continued treatment intensity experienced by the patient. All of these variables are difficult to measure accurately and more challenging to assign relative values to, explaining why investigators necessarily retreat to more readily measured, time-honored metrics. The challenge for future research directions is to develop and apply more meaningful patient-centered outcome metrics that better reflect achieved patient functionality and examine outcomes from the patient functionality perspective.

Currently, clinicians can apply the SYNTAX score II findings to inform their clinical judgment...
when making treatment choices for their coronary disease patients who require revascularization. The score provides a rational basis for weighing the contributions of all patient characteristics, including but not limited to anatomic complexity, in identifying the optimal treatment strategy.

REFERENCES


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