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EDITORIAL COMMENT

Cherry-Picking Historical Data to Legitimize Contemporary Practice

Should Diabetic Status Influence Decision-Making in Complex CAD?*

Patrick W. Serruys, MD, PhD,[a,b] Vasim Farooq, MBChB, PhD[c]

Choosing to make selective choices among competing evidence, so as to emphasize those results that support a given position, while ignoring or dismissing any findings that do not support it, is a practice known as "cherry picking" and is a hallmark of poor science or pseudo-science.
—Richard Somerville (1)

Historically, the 15 randomized clinical trials comparing coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) were plagued with profound selection bias ("cherry-picking" of patients) that justifiably drew severe criticism from broad sections of the cardiology community (2); namely, the stringent angiographic and clinical inclusion criteria, with only 2% to 12% of screened patients actually being randomized in most trials. The result was recruitment of low-risk subjects with predominant 1-vessel or 2-vessel disease (1VD and 2VD, respectively), a low incidence of 3-vessel disease (3VD), preserved left ventricular ejection fraction (LVEF), and a low incidence of diabetes. This practice echoes a 2002 review of 31 antidepressant efficacy trials (3) that demonstrated that despite the large number of patients/trials investigated, due to the primary exclusion criteria used in determining eligibility for trial participation, only a minority of patients treated in routine clinical practice for clinical depression were actually represented. Consequently, attempting to apply any of these trial findings to real-world contemporary clinical practice is questionable at best.

SYNTAX, FREEDOM, AND BEST TRIALS

The all-comers SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial was designed to overcome the historical limitations of the trial data comparing CABG with PCI by incorporating an all-comers design in which practically no patient was refused entry, with subjects either randomized (if determined by the heart team to achieve "equivalent anatomical revascularization" between CABG and PCI) or nested in registries for CABG- or PCI-ineligible patients (4). Subsequently, the FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial (5), investigating patients with diabetes and multivessel disease, and the BEST (Randomised Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease) trial (6), utilizing contemporary drug-eluting stents in multivessel disease, have largely mirrored the findings of SYNTAX; that when complex coronary artery disease (CAD) is viewed as a whole, surgical revascularization should be considered as the primary revascularization strategy.

ANATOMIC COMPLEXITY, CLINICAL FACTORS, AND THEIR IMPACT ON DECISION-MAKING

ANATOMIC COMPLEXITY (SYNTAX SCORE). The anatomic SYNTAX score allows the heart team to more objectively assess the extent and complexity of CAD,

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From the [a]Department of Interventional Cardiology at the Erasmus University, Rotterdam, the Netherlands; [b]International Centre for Circulatory Health, NHLI, Imperial College, London, United Kingdom; and the [c]St. Georges University Hospital, London, United Kingdom. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose. Deepak L. Bhatt, MD, MPH, served as Guest Editor-in-Chief for this paper.

compared with simply eyeballing the coronary angiogram and making clinical decisions, a habit that continues to dominate contemporary clinical practice (7). The potential value of the anatomic SYNTAX score in decision-making between CABG and PCI in complex CAD was first realized in the 5-year follow-up of the ARTS (Arterial Revascularization Therapies Study) II (8), followed by prospective validation in the all-comers SYNTAX trial (4). Using tertiles of the anatomic SYNTAX score (low <23, intermediate 23 to 32, high ≥33) in SYNTAX, it was demonstrated that the more extensive and complex the CAD, the greater the potential longer-term prognostic benefit of CABG compared with PCI (4), findings that were subsequently validated in multiple registries worldwide (9).

CLINICAL FACTORS. Notably, exactly the same scenario exists with clinical comorbidity (cardiovascular risk factors such as diabetic status) as occurred with anatomic complexity in the SYNTAX trial; greater clinical comorbidity equates to a potential greater prognostic benefit for CABG compared with PCI in complex CAD, provided that the risks of surgical revascularization are not prohibitive (10). Why, one may ask, is this the case? Traditionally, it has been thought that if stents can fix all obstructive coronary lesions, then CABG and PCI will have similar outcomes, and that with improvements in stent technology, PCI outcomes will one day even surpass those of CABG (2). In our view, this way of thinking, focusing on the stent rather than a disease (atherosclerotic)-specific process, represents a single-minded approach.

On the basis of the results of the SYNTAX, FREEDOM, and BEST trials, it may be surmised that clinical outcomes in complex CAD are primarily due to excess plaque burden and/or clinical comorbidity increasing the likelihood of the presence (or future development) of vulnerable plaque (11,12). Greater anatomic complexity and/or clinical comorbidity implies an increased likelihood of the patient having a greater plaque burden and the presence (or future development) of vulnerable plaque, particularly in the proximal vessels, and risk of a future myocardial infarction.

Although excess clinical comorbidity is well established to increase the short-term surgical operative risk (13), this is counterbalanced by a potentially greater longer-term prognostic benefit for the patient undergoing CABG. The underlying rationale is that the bypass graft will confer longer-term protection (for the lifespan of the graft) by preventing the clinical consequences of plaque rupture/myocardial infarction, compared with a stent (irrespective of generation), which would treat the obstructive lesion alone (2).

SHOULD DIABETIC STATUS INFLUENCE DECISION-MAKING IN COMPLEX CAD?

Diabetes has justifiably been regarded as a unique cardiovascular risk factor that should be treated differently from other risk factors. This view is endorsed by international revascularization guidelines, which recommend that patients with diabetes mellitus be treated as having a CAD equivalent (14,15). It is well established that atherosclerosis is accelerated in diabetes (both types 1 and 2), predisposing patients with diabetes to a 2- to 4-fold lifetime increase in the development of CAD compared with patients without diabetes, with 75% of patients with diabetes dying of a cardiovascular cause (16). Patients with diabetes also have a substantially higher incidence of multivessel disease and a greater plaque burden at presentation, with the extent and severity of CAD proportional to the duration of diabetes (17). These factors are undoubtedly related to the metabolic abnormalities characteristic of diabetes provoking molecular mechanisms that contribute to vascular dysfunction (16).

THE SYNTAX SCORE II AND DIABETIC STATUS

The SYNTAX score II (18) is essentially the anatomic SYNTAX score augmented by clinical variables that alter the threshold value of the anatomic SYNTAX score in complex CAD, allowing for equipoise between CABG and PCI for long-term mortality. Notably, SYNTAX demonstrated that reduced LVEF, impaired kidney function, younger age, and female sex substantially lower the anatomic SYNTAX score, whereas older age, unprotected left main coronary artery disease, and chronic obstructive pulmonary disease markedly raise the anatomic SYNTAX score, to allow for equipoise for long-term mortality.

The absence of diabetic status from the SYNTAX score II has been a point of confusion and controversy (7). During the initial development of the SYNTAX score II, it was demonstrated that diabetes was not an independent correlate of mortality in patients with complex CAD from the SYNTAX trial (19) when corrected for the end-organ manifestations of diabetes. These factors included the anatomic SYNTAX score and age/creatinine clearance/LVEF expressed as continuous (numerical) variables. In addition, it is important to emphasize that the SYNTAX score II was built on the seminal work of a cardiac surgeon (Ranucci et al. [20,21]) who demonstrated that a simple integer, derived from 3 clinical variables (age, preoperative serum creatinine, and LVEF), expressed as a continuous variable, was at least