These results are not surprising, since we know that the SYNTAX score (a surrogate for coronary disease complexity) lies within the causal pathway for PCI and late outcomes, and behaves as a mediator of outcomes.^{2,5} In contrast, there is no direct relationship between the SYNTAX score and outcomes after CABG because this mediating effect is absent.² In fact, the complexity of the coronary artery lesions has little effect on the quality of the revascularization because surgeons bypass the diseased portions of the vessel.² Surgeons approach the conundrum of coronary insufficiency not by unravelling the knot but by distal bypass rendering coronary complexity moot in the same manner as Alexander the Great handled the Gordian Knot.

See Article page 1405.

Commentary: Does the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score even matter?

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The advent of revascularization trials comparing drug-eluting stents (DES) with coronary artery bypass grafting (CABG) prompted the need to more accurately quantify the complexity of coronary artery disease (CAD). In the design of the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial of DES versus CABG for multivessel CAD, the realization that CAD severity measured by the number of diseased epicardial vessels alone was

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CENTRAL MESSAGE

In patients with multivessel disease, coronary artery bypass grafting is associated with improved outcomes compared with drug-eluting stents regardless of anatomical complexity.

not sufficient gave way to the development of the SYNTAX score.¹ The SYNTAX score incorporates several important factors to quantify the severity and complexity of CAD, some of which include lesion location, vessel caliber and length, degree of stenosis, the amount of myocardium at risk, and degree of calcification. Retrospective early validation was performed in 306 patients from the percutaneous coronary intervention (PCI) arm of the Arterial Revascularization Therapies Study part II (ARTS-II) trial, which showed an association between major adverse cardiac or cerebrovascular events (MACCE) and increasing SYNTAX score tertiles (low, medium, high) at 30 days, with greater 1-year MACCE rates in the greatest tertile.²

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Since then, several larger studies have shown that the SYNTAX score is an independent predictor of adverse events in those undergoing PCI only.^{3,4} Furthermore, in patients with left main or multivessel CAD, the calculation of the SYNTAX score is a Class I recommendation (Level of Evidence: B) in the 2018 European guidelines and considered “reasonable” in the 2014 American guidelines.^{5,6} Interestingly, a residual SYNTAX score >8 after PCI was associated with greater 5-year MACCE, highlighting the correlation between complete revascularization and optimal long-term outcomes.⁷ This has led to the use of the SYNTAX score in subgroup analyses of several major revascularization trials, or its use to exclude patients in recent left main revascularization trials (such as the EXCEL [Evaluation of XIENCE versus Coronary Artery Bypass Graft Surgery for Effectiveness of Left Main Revascularization] trial, where patients with high SYNTAX scores were excluded).

In this issue of *The Journal*, Gaudino and colleagues⁸ present an elegant meta-analysis examining the association between SYNTAX score tertiles and long-term outcomes of all-cause mortality and MACCE, in randomized clinical trials that compared CABG with PCI. Overall, there was improved freedom from MACCE with CABG as compared with PCI. However, the key finding was that there was no association between SYNTAX score tertiles subgroups and freedom from MACCE (interaction P value = .40). In examining interaction terms, the null hypothesis is that there is no difference between subgroups.⁹ As such, when the interaction P value for a subgroup analysis is not significant, the main effect findings, viz. the benefits of CABG over PCI with regards to MACCE, would hold true across all subgroups of SYNTAX score tertiles. This suggests that CABG is superior to PCI across all SYNTAX tertiles and should be the revascularization strategy of choice regardless of SYNTAX score. Importantly, these findings remained robust regardless of whether patients had multivessel disease and/or left main disease and are consistent with the outcomes of the 6 individual trials included in the meta-analysis. Previous data from the FREEDOM trial had also shown that the SYNTAX score should not be used to select the best mode of revascularization in patients with diabetes and multivessel CAD, as the benefits of CABG were similar across all SYNTAX score tertiles.¹⁰ To date, no randomized controlled trial has found significant subgroup differences between SYNTAX tertiles for the primary outcome in PCI versus CABG revascularization trials; yet, as the authors have highlighted, SYNTAX score remains a key determinate in guideline-directed recommendations for PCI in those with complex coronary artery disease.

This begs the question, how did the use of the SYNTAX tertiles become so prominently used in major revascularization guidelines from North America and Europe?^{5,6} One explanation is that nonsignificant results were interpreted with

spin—a well-studied phenomenon whereby nonsignificant results are interpreted in a positive light to show that the intervention arm is beneficial when this may not necessarily be supported by strict interpretation of the data.¹¹ For example, in the original reporting of the 5-year outcome of the SYNTAX study, authors concluded in the discussion that “results suggest that patients with intermediate or high SYNTAX scores are best treated with CABG, but that patients with less complex disease (ie, SYNTAX score ≤ 22) can be treated with first-generation DES with equivalent outcomes” based on the post-hoc subgroup analysis of SYNTAX score tertiles, where there was no difference in MACCE between PCI and CABG in the lowest SYNTAX tertile but a significant difference favoring CABG in the intermediate and high tertiles.¹² However, the interaction P was not significant ($P = .07$) and, thus, the main effects that CABG was superior to PCI should be applied across all subgroups (rather than only in the intermediate and high SYNTAX score groups). The correct interpretation of that SYNTAX score analysis—and all other revascularization studies in which the interaction P -value for SYNTAX score subgroups was not significant—should be that CABG is superior to PCI across all subgroups of SYNTAX tertiles. Issues with performing and interpreting treatment effects in subgroups have been long standing.¹³ Yusuf and colleagues¹³ have highlighted those key issues in their landmark paper in 1991, bringing to light some important conclusions: quantitative differences (ie, differences in degree) are more probable than true qualitative interactions (ie, differences in kind) between subgroups; issues with subgroup analyses include multiple comparisons (ie, multiple testing) that may lead to more type 1 error and lower power in subgroups to detect real differences (type 2 error). Overall, the interpretation of subgroup analyses should be analyzed across independent trials, formally subjected to a statistical subgroup interaction test, and only performed in the context of plausible, a priori stipulated biological mechanisms.

The study by Gaudino and colleagues highlights an important point: coronary artery disease severity and complexity is only one of the many factors in determining the best treatment option for patients with CAD. To address both patient factors and coronary anatomy in helping determine long-term outcomes, the SYNTAX II score was developed by incorporating the anatomic SYNTAX score along with 8 patient-level predictors (such as age, creatinine, left ventricular function, and other comorbidities); it was shown to be a predictor of all-cause mortality in those undergoing PCI or CABG.¹⁴

In patients with multivessel CAD who are suitable surgical candidates, CABG should be the treatment of choice, regardless of SYNTAX score. However, in those at greater surgical risk, the SYNTAX score may be helpful in formally evaluating the feasibility and technical success of PCI,

enabling a heart team discussion, which may be important in these situations, itself having achieved a Class I recommendation in the European guidelines.^{6,15}

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