Complete Revascularization

A Quality-Performance Metric?

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Current U.S. and European guidelines recommend coronary artery bypass graft (CABG) over percutaneous coronary intervention (PCI) for multivessel coronary artery disease (CAD) and confer a class IIb (of uncertain benefit) recommendation to PCI for improvement in survival (1,2).

Prior studies suggest that the magnitude of clinical benefit attributable to revascularization with either PCI or CABG is enhanced among patients in whom revascularization is complete (CR) versus incomplete (IR) (3,4). Although these studies demonstrate that IR is associated with hazard for death, myocardial infarction (MI), or additional revascularization, this conclusion is limited by observational, retrospective study designs, lack of randomization (IR vs. CR) and reliance on post-procedural classification of revascularization completeness by the treating physician. To elucidate the incidence and clinical consequence(s) associated with IR (vs. CR), Garcia et al. (5) provide the most systematic, comprehensive meta-analysis to date. The investigators conclude that CR: 1) is more often achieved by CABG than PCI; 2) is associated with meaningful reductions in mortality, MI, and repeat coronary revascularization; and 3) provides differential benefit (vs. IR) regardless of how CR is defined (e.g., anatomic vs. physiologic). In addition, the magnitude of relative survival benefit attributable to CR (vs. IR) was similar following either CABG or PCI revascularization, which suggests that the adequacy of revascularization influences subsequent clinical course as much or more than the method of revascularization does. Although the scope and magnitude of this meta-analysis is helpful to inform therapeutic triage for revascularization, multiple caveats exist.

First, this work has the inherent limitations of any post hoc meta-analysis of trial-level (not individual patient–level) data garnered from observational studies with heterogeneous methodologies, endpoints, and endpoint definitions. In all but 1 included study, the decision to perform IR or CR was not randomized. The prevalence of protocol-driven late angiographic follow-up across constituent studies is not provided nor is any uniform algorithm for prompting repeat revascularization. Despite efforts to avoid counting staged PCI procedures as repeat revascularizations, this possibility persists and preferentially disadvantages the PCI strategy. Similarly, medical therapy was neither optimized nor standardized across treatment groups stratified by revascularization status (CR vs. IR), and no protocol prescribed minimum duration of dual antiplatelet therapy following PCI is specified.

Second, although the association between CR and survival benefit appears sound, conclusions regarding secondary endpoints of MI or repeat revascularization are limited by power, heterogeneity of study definitions, and lack of independent adjudication. These limitations are evident in the investigators’ conclusion that “a reduction in MI was observed among PCI-treated patients (PCI: risk ratio [RR]: 0.80, 95% confidence interval [CI]: 0.71 to 0.91; p = 0.001, I² = 0%) but not among CABG-treated patients (CABG: RR: 0.69, 95% CI: 0.44 to 1.10; p = 0.12; I² = 62%)” Indeed, the point estimate for MI risk reduction by CR (vs. IR) for CABG exceeds that observed for PCI. MI definitions varied across studies and revascularization strategy and only 18 of 35 studies reported this endpoint. Thus, the possibility that CR provides similar MI reduction benefit for both PCI and CABG exists.

Third, although the benefit provided by CR (vs. IR) persists regardless of definition(s) used (anatomic vs. nonanatomic) (see Online Table 1 of Garcia et al. [5]), this observation would be strengthened by demonstrating a quantitative relationship between IR and risk of subsequent adverse outcomes. A graded, standardized quantification of IR (the residual SYNTAX [Synergy Between PCI With Taxus and Cardiac Surgery] score) has been correlated with adverse clinical events including mortality following PCI in patients with acute coronary syndromes (6), multi-vessel stable ischemic heart disease (7) and left main CAD (8). Although the residual SYNTAX score post-PCI predicts risk when applied as either a binary (0 vs. >0) or graded (tertile) function, its risk discriminatory ability appears greatest when used quantitatively (6,7). Despite linearity of baseline (pre-PCI) and residual (post-PCI) SYNTAX scores, residual SYNTAX score provides incremental predictive accuracy for late adverse clinical outcomes.

In the absence of a large-scale randomized trial comparing CR with IR in patients with multivessel CAD, the work of Garcia et al. (5) provides evidence that CR should be the goal of revascularization and is associated with optimal clinical outcomes. Further insights are gleaned by viewing this work in context with a patient-level analysis from the SYNTAX trial (9). SYNTAX prospectively employed a pre-procedural angiographic lesion complexity
score and required pre-operative consensus between the interventional cardiologist and surgeon (the Heart Team) regarding the number of vessels $\geq 1.5$ mm in diameter with $\geq 50\%$ stenosis that required revascularization. Subjects were categorized as incompletely revascularized when the number of diseased segments treated did not match the pre-operative Heart Team’s decision. Among 1,800 subjects with left main and/or 3-vessel CAD, who were randomly assigned to revascularization by either CABG or PCI, IR was more frequent following PCI (43.3\%) than CABG (36.8\%). Both the incidence of IR and the relative advantage of CABG (vs. PCI) for achieving CR were directly proportional to the complexity of CAD as reflected by SYNTAX score tertile (Fig. 1). Major adverse cardiovascular and cerebrovascular events (MACCE), the primary composite clinical endpoint of the SYNTAX trial, was significantly increased through 3 years following IR by PCI but not CABG (Fig. 2) and was largely driven by repeat revascularization among PCI-treated subjects. When only subjects with 3-vessel (non–left main) CAD are analyzed, IR is again more frequent following PCI (48.3\% vs. 42.8\% for CABG; $p = 0.07$), and MACCE through 5 years is more adversely influenced by IR after PCI than following CABG (Fig. 3). Thus, adverse clinical outcomes appear disproportionately influenced by IR (vs. CR) following PCI. Differences in the completeness of revascularization achieved by PCI and the relative “weight” of adverse events associated with IR following PCI may be reflected in the relative survival advantage attributed to CABG (vs. PCI) in recent randomized trials (9,10) and observational studies of patients undergoing multivessel revascularization (11). Although concordant, these observations must be tempered by rapid evolution in catheter-based technology and techniques for PCI, as well as wide intercenter variability in expertise and outcomes achieved by either PCI or CABG. Indeed, durable safety and efficacy of PCI revascularization is influenced by “optimal” drug–eluting stent (DES) selection. In this regard, target vessel revascularization, MI, and stent thrombosis are reduced by everolimus-eluting (EES) DES platforms (vs. non-EES DES) (12,13). Indeed, the superiority of EES for reduction in MI, target lesion revascularization, and stent thrombosis when compared with the paclitaxel-eluting DES platform employed in the SYNTAX trial, has been demonstrated by a large-scale randomized trial, pooled analysis of multiple trials, and large-scale meta-analyses (13–15). Furthermore, the relative benefit of EES (versus paclitaxel-eluting stents) for reduction in late adverse clinical outcomes is roughly proportional to the complexity (number of
lesions/vessels) of CAD being treated (16). It has been suggested that the results of the SYNTAX trial, which favored CABG (vs. PCI), particularly in subjects with intermediate SYNTAX scores (i.e., 23 to 32), complexity may have been different if EES had been used instead of the first-generation paclitaxel-eluting stents (17). Finally, in addition to ischemia guidance with fractional flow reserve (18) and optimal DES choice, long-term outcomes following PCI (including reduction in death or MI) may be improved by routine use of procedural intravascular ultrasound (19). The impact of a comprehensive, multifaceted approach to optimize PCI revascularization outcomes with EES (vs. CABG) will be evident when results of the EXCEL (Evaluation of XIENCE PRIME or XIENCE V versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) randomized trial become available. In EXCEL, patients with unprotected left main coronary disease and SYNTAX scores $\leq 32$ are randomly assigned to revascularization with either PCI using EES and adjunctive fractional flow reserve/intravascular ultrasound optimization or CABG. The experience and expertise of individual centers is as important as the technology and technique for PCI or completeness of revascularization. In this regard, wide intercenter variability in MACCE too was observed among subjects treated with either PCI or CABG in SYNTAX and was not related to center enrollment volume (20). Indeed, intercenter variability in MACCE for a given revascularization modality (PCI or CABG) exceeded any observed differences between PCI and CABG for the trial as a whole. Thus, triage for revascularization must always be made in the context of local experience and expertise.

In summary, the meta-analysis of Garcia et al. (5) suggests that CR should be the objective for either PCI or CABG and that CR is more commonly achieved by CABG. Furthermore, as CR appears to confer a survival advantage, objective assessment(s) of the completeness of revascularization should be incorporated into procedural quality/performance metrics as well as criteria for appropriate utilization. Although the benefit of CR was evident regardless of definition(s) used, a standardized, consensus definition that incorporates both anatomic and physiologic data would greatly enhance across-trial analyses of aggregate data in the future (21).

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REFERENCES


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