

Coronary artery bypass grafting versus percutaneous coronary intervention in complex coronary artery disease: looking beyond clinical end-points

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The choice of optimal revascularization techniques for complex coronary artery disease (CAD), either unprotected left main (UPLM) or multi-vessel disease (MVD), has been a matter of debate for the last two decades. Initially, randomized controlled trials (RCTs) demonstrated a significant mortality benefit of coronary artery bypass grafting (CABG) over medical therapy in patients with complex CAD (1). However, percutaneous coronary intervention (PCI) with balloon angioplasty alone or bare metal stent (BMS) was limited by higher rates of adverse events due to restenosis when compared to CABG (2). Since then, PCI has evolved in both stent technology and delivery techniques, and drug eluting stents (DES) have been shown to decrease risk of revascularization compared with BMS (3). Therefore, further research has focused on comparing PCI using DES versus CABG for patients with complex CAD.

The Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) was a well-conducted, multi-center, RCT that was designed to compare the outcomes of PCI using DES versus CABG among 1,800 patients with triple vessel or UPLM CAD (4). At 1 year follow up, the primary results failed to show non-inferiority of PCI with higher rate of the primary composite end point [death, myocardial infarction (MI), stroke or revascularization] in PCI arm compared to CABG. At the long term follow up of 5 years, superiority of CABG over PCI persisted driven by reductions in MI and revascularization, albeit with similar survival (5). Although

hypothesis generating, pre-specified sub-group analyses of the trial suggested more favorable equipoise between PCI and CABG in participants with UPLM and low (≤ 22) versus intermediate-high (≥ 23) SYNTAX score.

While incorporating the SYNTAX trial findings into decision-making process of revascularization strategies for patients with complex CAD, few points need to be highlighted. First, patients enrolled in SYNTAX trial were determined suitable for both PCI and CABG by a team of interventional cardiologist and cardiothoracic surgeon, and thus can't be applied to the subset of patients who are suitable for only one of the modalities. Further, since similar mortality was observed with either strategy, other factors such as patient preferences, functional status and quality of life (QoL) must be taken into the realm of consideration when determining the best approach for such patients.

Recently, Abdallah *et al.* reported findings of a health status sub-study assessing any QoL differences among patients enrolled in the SYNTAX trial (6). The study was based on assessment of patient's perspective of their disease specific and generic health status after they underwent revascularization (PCI or CABG) using the Seattle Angina Questionnaire (SAQ) and Short form (SF) 36 scores respectively. While both PCI and CABG resulted in early improvements in SAQ angina frequency (AF) score, PCI was associated with faster improvement in SAQ-physical limitation (PL) and QoL as well as SF-physical function scores at 1 month compared to CABG. However, at 5 years,

CABG performed better with slightly higher scores on SAQ AF and PL scales compared to PCI. Moreover, compared to PCI, significantly higher number of patients in CABG arm was free of angina at 1 (76.8% vs. 71.5%) and 5 years (78.8% vs. 74.4%). Finally, a significant interaction with SYNTAX score was again found with differences in angina relief between two modalities observed only in patients with intermediate-high (≥ 23) complexity.

The study by Abdallah *et al.* is well conducted with utilization of standardized methodologies, however, results need to be viewed in background of other available evidence. SYNTAX trial used a hierarchical statistical design to allow analysis of pre-specified sub-groups of UPLM and 3VD (4). In the 3VD cohort, CABG was found to be superior to PCI in terms of all cause death, MI and repeat revascularizations at 5 years follow up (7). However, in the UPLM subgroup, similar rates of all cause death and MI were observed with PCI and CABG, with a higher rate of revascularization in PCI and stroke in CABG arms (8). Further, in both cohorts' degree of complexity significantly affected outcomes thus favoring CABG in higher SYNTAX score patients. Although the findings are only hypothesis generating because of failure to meet non-inferiority end point for PCI in overall population, these results are supported by other studies of UPLM CAD (9). In PRECOMBAT trial, PCI was found to be non-inferior to CABG for UPLM disease patients except a higher risk of revascularization noted in subgroup with high SYNTAX (≥ 33) score (10). While UPLM CAD has been traditionally studied within context of complex CAD, it is important to remember that LM disease patients represent a heterogeneous group with different complexities in terms of downstream CAD. This is illustrated by a recent patient level meta-analysis showing even lower rates of mortality with PCI vs. CABG in isolated LM or LM plus 1 vessel disease (11). In this regard, no significant difference between PCI and CABG in angina relief for SYNTAX ≤ 22 sub group in the study by Abdallah *et al.* remain concordant (6).

Several other points are noteworthy in respect to QoL outcomes study by Abdallah *et al.* First, the 5-year differences in SAQ scores (~2–3 points) between CABG and PCI were modest and smaller than the minimum clinically significant differences of 8–10 points. On the contrary, early improvement with PCI in physical health status scores was significant (~10–20) which could mean early return to work. Importantly, long term benefits of CABG over PCI across several health status measures translated into significant health status changes in ~5% of patients. Second, although

CABG resulted in improved SAQ AF scores at 5 years, the differences between CABG and PCI in terms of angina relief seem to have narrowed down compared to prior RCT based health status studies conducted in BMS era (6). This further brings into perspective the utilization of first generation paclitaxel eluting stent in the SYNTAX trial that has shown to be inferior to second generation DES in terms of stent thrombosis and MI. Therefore, it is expected that the difference between CABG and PCI will further converge with increased utilization of second generation DES. Third, while diabetics have been shown to gain greater benefit with CABG over PCI, the SYNTAX sub-study found no such interaction with respect to health status outcomes. This is in consistence with health status sub-study of FREEDOM trial that failed to show consistent meaningful differences in SAQ scales beyond 2 years (12). Finally, incomplete revascularization is a significant predictor of adverse outcomes in complex CAD, and thus ought to be factored in the decision-making regarding optimal revascularization strategy.

In summary, the study by Abdallah *et al.* adds support to a consistent line of evidence favoring CABG over PCI in “more” complex CAD, as could be assessed by higher SYNTAX score. However, for patients with less complex CAD (such as UPLM plus one vessel or MVD with SYNTAX ≤ 22), PCI with newer generation stents remains a viable option. Moreover, temporal patterns of symptom relief, QoL and functional status measures are increasingly important considerations in the choice of revascularization strategies particularly for an aging population. As such, the final decision concerning mode of revascularization needs to be an individualized approach based on angiographic complexity, patient preferences and comorbidities, and inclusion of heart team approach.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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