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A Tale of Two Techniques: Demystifying the Myth

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*It was the best of times, it was the worst of times,
it was the age of wisdom, it was the age of foolishness,
it was the epoch of belief, it was the epoch of incredulity,
it was the season of Light, it was the season of Darkness,
it was the spring of hope, it was the winter of despair,
we had everything before us, we had nothing before us,
we were all going direct to Heaven, we were all going
direct the other way. . . .*

-A Tale of Two Cities, by Charles Dickens

Forty-eight years since the introduction of coronary artery bypass surgery (CABG) in 1967¹ and 38 years after the first reported percutaneous coronary intervention (PCI) in a human in 1977,² the battle for supremacy between cardiac surgery and interventional cardiology as the preferred treatment modality for complex coronary artery disease (CAD) — specifically, three-vessel or multivessel disease (3VD) with or without unprotected left main coronary artery disease (ULMCA) — shows no signs of receding.³⁻⁶ Interventional cardiologists have made rapid additions to their armamentarium for treating complex CAD through the development of newer-generation drug-eluting stents (DES) and novel antithrombotic drugs. At the same time, cardiac surgeons have improved revascularization procedures through the implementation of bilateral left internal mammary artery grafts as well as off-pump and minimally invasive surgery.

Before SYNTAX

Historically, numerous randomized and multicenter studies (e.g. ERACI, EAST, GABI, CABRI, MASS, BARI, SIMA, LAUSANNE, RITA and TOULOUSE)⁷ demonstrated the superiority of CABG over PCI

(mainly percutaneous transluminal coronary angioplasty at that time), which led to the abandonment of balloon angioplasty and the emergence of new stents. In this more recent era (up to 2009), the results of percutaneous transluminal coronary angioplasty and stenting with bare-metal stents were compared in multiple studies (e.g. AWESOME, ARTS, SOS, ERACI, MASS, among others). Although the results in the first year were similar for patients treated with either surgery or stent, at 5 years, the reoperations in the stent group were higher due to multiple restenoses, reaffirming that CABG was the better option for patients with 3VD/ULMCA disease. Almost all of these studies were criticized, as they included a very small number of randomized patients (~5%) and few patients with ULMCA,⁷ inconsistent with real-world experience.

After SYNTAX

In 2009, the 1-year results of the SYNTAX trial^{8,9} prepared the contemporary framework in which patients with 3VD/ULMCA are now evaluated. This randomized, prospective, multicenter trial (85 centers in 18 countries) incorporated an “all-comers” design and consisted of patients with ULMCA disease (isolated or associated with one to three vessels) or de novo 3VD. Patients were randomized on a 1:1 basis to either CABG or PCI with a paclitaxel-eluting stent (TAXUS Express, Boston Scientific Corp., Natick, MA) or placed in nested registries when considered unsuitable for randomization by the Heart Team (i.e. a CABG nested registry for PCI-ineligible patients and a PCI nested registry for CABG-ineligible patients). CABG techniques between the randomized and nested registry were broadly similar, except that double left and right internal mammary artery grafts were more frequently performed in the randomized CABG population (27.6%) than in the CABG nested registry (16.1%). Of the 589 stents implanted within the PCI nested registry, 57% were the TAXUS Express, 19% were another paclitaxel-eluting stent and 24% were bare-metal. Four PCI-nested patients did not receive a stent.

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The “final episode” of this landmark trial was released in 2013.¹⁰ The primary endpoint was noninferiority of PCI with paclitaxel-eluting stent versus CABG for the incidence of major adverse cardiovascular and cerebrovascular events (MACCE) at 12 months. At 5-year follow-up, CABG was associated with lower rates of MACCE (37.5% vs. 24.2%, $P<0.01$), death (14.6% vs. 9.2%, $P<0.01$), myocardial infarction (10.6% vs. 3.3%, $P<0.01$) and repeat revascularization (25.4% vs. 12.6%, $P<0.01$) compared with PCI. No difference in the rate of stroke was observed between the groups (3.0% vs. 3.4%, $P=0.66$). The final 5-year follow-up in patients with ULMCA disease also was published.¹¹ In contrast to patients with 3VD, no significant differences in MACCE were observed between PCI and CABG in patients with ULMCA disease (36.9% PCI vs. 31% CABG, $P=0.12$). However, CABG was associated with an increased rate of stroke (5% vs. 14%, $P=0.03$), which was counterbalanced by a higher revascularization rate in the PCI group (26.7% vs. 15.5%, $P<0.01$). After stratification for SYNTAX score tertiles, an increase in survival was observed in PCI-treated patients with a score ≤ 32 . Conversely, CABG was associated with a reduced incidence of MACCE in patients with a score > 32 .

The anatomical SYNTAX score, with low (<23), intermediate (23–32) or high (>32) categories,^{8,12} became a sentinel tool in the SYNTAX trial and pioneered the now-popular “Heart Team” approach, in which a cardiac surgeon and interventional cardiologist determine the optimal revascularization modality for patients with 3VD/ULMCA disease. It combines the importance of diseased vessel segment weighting (Leaman score), adverse lesion characteristics (American College of Cardiology/American Heart Association lesion classification, and total occlusion characteristics from the European TOTAL Surveillance Study) and the Medina classification system for bifurcation lesions.^{13–16} However, the SYNTAX score is open to criticism since it relies solely on scoring coronary anatomy and does not take potentially important prognostic information into consideration in the absence of clinical factors.^{17,18} Consequently, several risk stratification tools have attempted to merge the SYNTAX score with clinically based risk scores to improve the risk stratification of patients with 3VD/ULMCA disease undergoing CABG or PCI

compared with the SYNTAX score alone. Examples include the Clinical SYNTAX score (a combination of the SYNTAX score and the modified ACEF score [i.e. age/ejection fraction + 1 point for every 10 ml/min reduction in creatinine clearance below 60 ml/min/1.73 m² (up to a maximum of 6 points)]), the Global Risk score (a combination of the SYNTAX score and EuroSCORE) and the EuroHeart score.^{18–27}

The latest addition to this risk stratification mélange is the SYNTAX score II, which includes a nomogram for bedside application to obtain long-term mortality predictions for individual patients considering CABG or PCI.²⁸ This score, which was externally validated in the multinational DELTA ($n=2,891$) and Credo-KYOTO ($n=3,896$) registries,^{8,29} consists of two anatomical (SYNTAX score and ULMCA disease) and six clinical (age, creatinine clearance, left ventricular ejection fraction, sex, chronic obstructive pulmonary disease and peripheral vascular disease) variables. Unlike the anatomical SYNTAX score, which is more predictive of clinical outcomes in patients undergoing PCI than in those undergoing CABG, for whom it is not predictive,^{18,30} the SYNTAX score II provides individual mortality predictions for both CABG and PCI in addition to a measure of the magnitude of their differences, with clinically applicable accuracy. Currently, validation of the SYNTAX score II is a prespecified endpoint in the ongoing randomized EXCEL trial (NCT01205776) and the planned SYNTAX II trial, both of which will use SYNTAX score II to recruit patients on the grounds of patient safety. Early findings indicate the SYNTAX score II is equally predictive for long-term mortality between CABG and PCI in subjects with ULMCA disease up to an intermediate anatomical complexity. Both anatomical and clinical characteristics had a clear impact on long-term mortality predictions and decision-making between CABG and PCI.³¹

In this issue of *Journal of Patient-Centered Research and Reviews*, Nfor et al.³² report on the clinical outcomes after PCI with newer-generation DES (everolimus or zotarolimus in ~80% patients) versus CABG in 3VD/ULMCA on a nonrandomized “high risk” surgical cohort of select patients in their tertiary care institution. These patients were identified as “high risk” based on Society of Thoracic Surgeons

(STS)-predicted operative mortality of > 5%. Of note, approximately 40% of this cohort had an STS score ≥ 15 , qualifying them to be considered “extreme risk.” Although, the mean STS score between the PCI and CABG groups did not significantly differ, more patients revascularized with PCI fell in the extreme risk category (63.9% vs. 28.9%, $P < 0.001$). Mean age of the population in the study was 77 ± 9 years with 42% of these being above the age of 80 years. In this high-risk surgical population there was no significant difference in the mean SYNTAX score between the PCI and CABG groups (37.0 ± 12 vs. 40.0 ± 15 , $P = 0.12$). Given these characteristics of the population, it is quite evident the investigators were dealing with a subset of patients with advanced atherosclerotic cardiovascular disease demanding excellent clinical acumen and technical skills to achieve the best possible means of revascularization.

After a mean follow-up of approximately 3 years, the primary endpoint, a composite of death, myocardial infarction or stroke, occurred in 42.2% of PCI patients and 39.6% of CABG patients, an insignificant difference. The investigators also report no differences in the individual components of the primary endpoint between PCI and CABG as well as MACCE rates (50.6% in PCI group vs. 42.2% in CABG group, $P = 0.23$). However, the authors do report a threefold higher incidence of repeat revascularization in the PCI group compared with the CABG group.

The authors chose to retrospectively apply the STS risk model^{33,34} to predict the risk of operative mortality and morbidity after adult cardiac surgery based on patient demographic and clinical variables. It is the most frequently used risk profile system in the United States and comprises more than 40 preoperative variables stratifying patients into low risk (STS score ≤ 3), intermediate risk ($>3-8$) and high risk (>8). Although the STS score does not include variables like frailty, malnutrition, porcelain aorta and liver disease, and the cut-off STS scores may be arbitrary at best, it continues to be the best stratification process at present. The authors conclude that in patients with 3VD/ULMCA and STS score $> 5\%$, PCI or CABG are similar with respect to long-term death, myocardial infarction or stroke, irrespective of individual SYNTAX scores.

These findings appear to contradict the landmark SYNTAX trial, the results and impact of which have already been detailed. These findings also are in contrast to a substudy of the SYNTAX trial¹⁸ that suggested patients with high clinical comorbidity, i.e. additive EuroSCORE ≥ 6 with 3VD irrespective of the anatomical complexity (SYNTAX score),¹⁹ might derive a prognostic benefit from undergoing CABG rather than PCI provided an acceptable threshold of operative risk is not exceeded.

The combination of angiographic and clinical profiles allows clinicians to consider that PCI in subjects with ULMCA disease and a low-risk anatomical profile may be associated with a prognostic benefit, whereas more complex disease and a higher-risk clinical profile would remain the domain of CABG on the grounds of prognosis. Anatomical complexity of CAD can vary from a single lesion in the shaft of the left main coronary artery to distal trifurcation disease or involve left main disease with more complex downstream (three-vessel) disease. These variances may influence the capacity of PCI to achieve complete revascularization, the number of stents implanted and complexity of interventional techniques employed. Moreover, incomplete revascularization and anatomical complexity (residual SYNTAX score) have been directly correlated to late all-cause mortality following PCI.^{11,35,36} This was demonstrated in the PCI arm of the ULMCA subgroup of SYNTAX, for which the incidence of 5-year all-cause mortality was shown to markedly increase in subjects with a SYNTAX score ≥ 33 (5-year mortality of 20.9%) compared with subjects with a SYNTAX score < 33 (5-year mortality of 7.9%). Conversely, in subjects undergoing CABG, anatomical complexity was shown to not affect long-term prognosis, as exemplified in the CABG arm of the ULMCA subgroup of SYNTAX, for which the incidence of 5-year all-cause mortality remained almost unchanged in subjects with a SYNTAX score ≥ 33 (5-year mortality of 14.1%) compared with subjects with a SYNTAX score < 33 (5-year mortality of 15.1%).¹¹

SYNTAX in the Contemporary Era

It is important to note that improved clinical outcomes with the everolimus-eluting stent — the most used stent in Nfor et al.’s study (~59%³²) — in multivessel disease,³⁷ coupled with similarly reported data from the

French Left Main Taxus and LEMAX registries that investigated left main stenting with everolimus-eluting stents^{38,39} and the known reductions in stent thrombosis of newer-generation DES,⁴⁰⁻⁴⁷ implies that if newer-generation DES had been used in the SYNTAX trial, there would have been a significant reduction in repeat revascularization and myocardial infarction. It is also plausible that reductions in mortality would have been seen with the newer-generation DES.⁴⁷ Thus, because the SYNTAX trial used the first-generation paclitaxel-eluting stent exclusively, it is not inconceivable that contemporary PCI using everolimus stents may outperform results of paclitaxel since randomized comparisons of everolimus- versus paclitaxel-eluting stents have consistently shown everolimus to be associated with more favorable outcomes.^{45,48-50} In addition, the largest patient population meta-analysis (N=4,989) of the SPIRIT clinical program showed that everolimus-eluting stents were superior to paclitaxel-eluting stents in reducing all-cause mortality (3.2% vs. 5.1%, hazard ratio: 0.65, 95% confidence interval: 0.49–0.86, P=0.003).⁵¹ However, in the SYNTAX trial, if the cardiac mortality events related to stent thrombosis (as defined by Academic Research Consortium⁵²) were removed, there would have been only a modest reduction in cardiac mortality at 5 years: 9% to 8.5% for definite stent thrombosis, and 9% to 7.5% for definite or probable stent thrombosis.⁵³ The main hypothesis behind this is that bypass grafts protect coronary vessels from future myocardial infarctions for the lifespan of the graft, particularly in more complex CAD for which the plaque burden and risk of future myocardial infarction is potentially higher than in less complex CAD. Conversely, stents would only treat individual lesions.^{18,54}

Thus, the potential reduction in mortality with newer-generation DES in the SYNTAX trial would be unlikely to bridge the gap between CABG and PCI, particularly with more complex CAD.⁵⁵ This is exemplified in the SYNTAX score II, which identifies subsets of patients across all tertiles of the SYNTAX score who would have a mortality benefit from undergoing one type of revascularization over the other. It should be emphasized that increased anatomical complexity, particularly in subjects with 3VD, led to a greater mortality benefit with CABG as opposed to PCI.⁵⁵ Investigators in the EXCEL trial recruited 1,905

patients with left main disease and mild-to-moderate anatomical complexity (SYNTAX score ≤ 32) and randomly assigned them to undergo either PCI with second-generation DES or CABG surgery. This study could be pivotal in providing support for the efficacy and safety of PCI in this lesion type.

With consistent improvement in PCI outcomes, a wider spectrum of patients with complex CAD is being treated in this fashion. Currently, both European and North American guidelines recommend PCI as a valuable treatment option for patients with ULMCA disease and as an alternative to CABG in patients with less complex 3VD (SYNTAX score < 23).^{56,57} For prudent decision-making, it is essential to consider the risk/benefit ratio of PCI and CABG for 3VD, weighing procedural invasiveness and associated short-term complications against the long-term event rates of death, myocardial infarction, repeat revascularization and health-related quality of life.

Striking a Balance

The clinician must never underestimate the role of the individual patient and his or her personal preferences or perception of risk related to CABG and PCI. Individual patients may value the risk/benefit trade-off between CABG and PCI differently. Remaining active in their professional/personal lives may be vital for some. Those people would thus be more prepared to accept the longer-term risks of PCI (in particular an increased risk of repeat revascularization) compared to the short-term morbidity effects associated with the more invasive nature of CABG in order to obtain short-term pain relief and a rapid return to full mobility.^{58,59} Others may prefer to endure short-term pain to obtain a higher probability of avoiding a subsequent revascularization. Some patients may prefer to risk undergoing multiple PCI procedures compared with a single CABG, or they may prefer to undergo CABG initially to avoid the risk of requiring CABG subsequent to PCI. Consequently, from the patient's perspective, the balance between these conflicting considerations plays a crucial role in selecting the preferred revascularization strategy. Applying this concept to quantify the trade-off between the risks and benefits of PCI versus CABG (such as freedom from chest pain and improvement in health-related quality-of-life measures) for patients with multivessel disease, it was recently shown for the first

HEART TEAM APPROACH

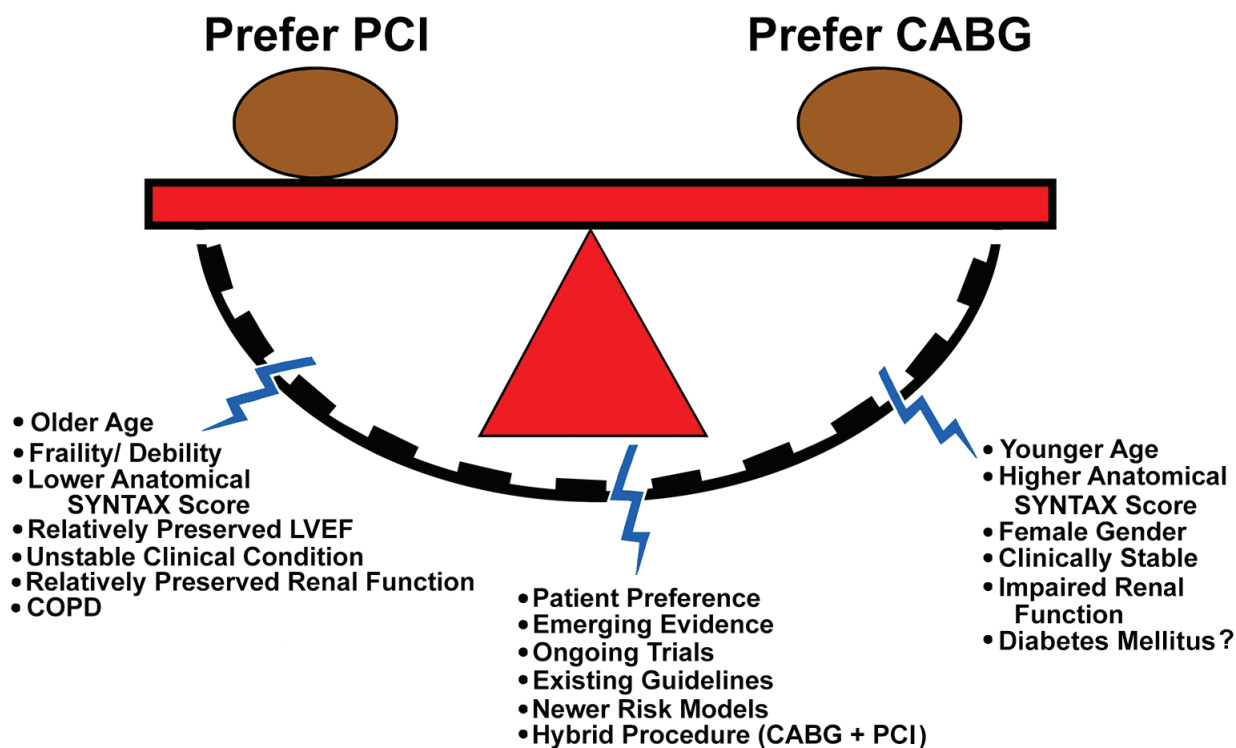


Figure 1. The balancing act between CABG and PCI. The fundamental principal behind revascularization of coronary artery disease in patients with multivessel disease and/or unprotected left main disease should not be viewed as a principal of war between the two strategies (as in *A Tale of Two Cities*). Revascularization should be viewed as a continuum of the evolution of the best possible strategy wherein patient preferences are taken into account. International guidelines, particularly those from the American College of Cardiology, American Heart Association and European Society of Cardiology, aim to be balanced, practical, patient-oriented and evidence-based, and should form the general framework of local, regional and national protocols for revascularization. Practice should regularly be audited to ensure best practices. There are clearly trade-offs between the two revascularization strategies that need to be discussed with patients as part of the shared decision-making process. The early hazard of CABG (risk of stroke) may be unacceptable to some patients, whereas others might want to avoid the later hazards of PCI (risk of needing a repeat PCI or having a myocardial infarction). The decision also should take into account whether complete revascularization with PCI appears to be feasible (i.e. residual SYNTAX score).

time that it is possible to quantify a level of risk that a patient would be able to accept in order to maintain present functional state.⁶⁰

To achieve a reasonable balance in the clinical approach to revascularization of multivessel disease, key factors in decision-making will require a Heart Team to weigh patient wishes, approved guidelines, local expertise and skills, available resources, and regional medical,

legal and ethical considerations (Figure 1). Therefore, risk stratification (SYNTAX, SYNTAX II, STS, euroSCORE, etc.) should be used only as a guide; clinical judgment and review by a Heart Team remain indispensable. Finally, surgeons and interventional cardiologists should remember that ongoing optimal medical therapy and risk-factor management is essential for the best long-term prognosis after CABG surgery or PCI.

Whether the preferred revascularization modality will change with advances in technology is the subject of ongoing and future trials. In both the EXCEL trial and the SYNTAX II trial, the SYNTAX score and SYNTAX score II, respectively, are being used to recruit subjects on the grounds of patient safety. Further study will continue to delineate the boundaries between CABG and PCI to best define the optimal revascularization modality for individual patients with complex CAD. Irrespective of the results of these trials, it should be emphasized that treatment recommendations for patients with complex CAD need to be undertaken in the context of the multidisciplinary Heart Team, in open dialogue with the patient, rather than by an individual practitioner. This is because individual patient perceptions of short- and long-term risk are important factors in decision-making. The goal should be to fit the patient with the best technique, not to force the patient into the technique. To paraphrase Hippocrates: It is more important to know what sort of person has a high SYNTAX or STS score than to know what sort of SYNTAX or STS score a person has.

Conflicts of Interest

None.

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