The Eternal Debate: CABG Vs PCI. Current Status of the Literature

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While advances in revascularization strategies have dramatically altered the morbidity and mortality associated with coronary artery disease, significant equipoise remains regarding the optimal revascularization strategy for specific groups of patients. Herein, we review the 5 most impactful studies of the last 3 years and correlate this with a historical perspective.

Keywords: CABG, PCI, Revascularization

INTRODUCTION

While advances in revascularization strategies have dramatically altered the morbidity and mortality associated with coronary artery disease (CAD), significant equipoise remains regarding the optimal revascularization strategy for specific groups of patients. Starting in 1987 with the Emory Angioplasty Surgery Trial (EAST),[1] coronary artery bypass grafting (CABG) has been compared to percutaneous coronary intervention (PCI) iteratively for the last 30 years. Multiple studies have shown the benefits of either CABG or PCI in subgroups of patients with CAD. However, criticisms of each new trial include biases (in patient selection, advances in associated pharmacologic therapy, stent design, and new techniques for CABG) making comparisons between trials challenging. Herein, we summarize the most impactful studies published in the past 3 years comparing outcomes of CABG vs PCI.

THE EXCEL TRIAL (2016)

Everolimus-Eluting Stents or Bypass Surgery for Left Main CAD

The EXCEL trial was an international, open-label, multicenter, noninferiority, randomized control trial comparing CABG to PCI for patients with obstructive left main (LM) disease (70% or greater visually or 50−70% with concordant functional testing).[2] Of 1905 enrolled patients, 948 patients were randomized to PCI and 957 were randomized to CABG. In both groups, the goal was complete revascularization. Notable

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Central Message

Significant equipoise remains regarding the optimal revascularization strategy for specific patients with coronary artery disease. The Heart Team Model should be used for complex revascularization decisions and include the risks and benefits based on the literature.

exclusion criteria were a syntax score of >32, any prior CABG or LM PCI, and the need for any concomitant cardiac surgery. Approximately one-third of both groups were diabetic. Cardiopulmonary bypass was used at the surgeons' discretion in the CABG group and poststenting IVUS was "strongly recommended" in the PCI group. Of patients undergoing CABG, 96% underwent a LIMA-LAD graft. All patients were also prescribed guideline-directed optimal medical therapy (including, among others, dual antiplatelet therapy for at least 1 year). Notably, the primary endpoint of this study was a composite of all cause death, stroke, or myocardial infarction at 3 years. Salient points from this study include:

1. PCI with a second-generation drug-eluting stent Xience (Abbott, IL) was noninferior to CABG at preventing death, stroke, or myocardial infarction for patients with unprotected left main disease at 3 years.

2. At 12 months, there was no significant difference in the Seattle angina questionnaire between patients who underwent CABG vs PCI.

3. New-onset atrial fibrillation occurred more commonly in patients undergoing CABG than PCI, but resolved in 85% of patients prior to discharge.

4. Chronic kidney disease (CKD) was present in nearly 20% of the study population. Notably, patients with CKD had a higher event rate compared to the rest of the study population. However, there was no difference in patients with CKD in the event rate between the CABG and PCI groups at 3 years.

5. In keeping with prior trials, the PCI group had a higher rate of repeat revascularization and fewer 30-day adverse events than the CABG group. After 30 days, the CABG group had fewer adverse events. This difference is likely attributable to the index procedure.

THE NOBLE TRIAL

Percutaneous Coronary Angioplasty Vs CABG in Treatment of Unprotected Left Main Disease

Published simultaneously with the EXCEL trial, NOBLE was also a prospective, randomized, open-label, noninferiority trial of CABG compared to PCI for unprotected left main stenosis.[3] In this study, 36 European centers randomized 1201 patients in a 1:1 manner to CABG (603 patients) or PCI (598 patients). A notable difference between this trial and EXCEL was the longer length of follow-up and the inclusion of myocardial revascularization to the primary endpoint. Prior to randomization, a heart team comprised of an interventional cardiologist and cardiac surgeon determined that equivalent revascularization could be achieved with either PCI or CABG. Any patient with more than 3 noncomplex lesions was excluded (mean syntax score 22.5 ± 7.5 in PCI group vs 22.4 ± 8 in CABG group $P = 0.74$). Complete revascularization was attempted in each procedure (achieved in 96% of PCI). Notably, this trial had fewer diabetics (15%) in each group. The composite endpoint in this study included death from any cause, nonprocedural myocardial infarction, repeat revascularization, and stroke. Salient points from this study include:

1. CABG was superior to PCI at 5 years in both MACCE and improvements in the maximum angina pectoris score.

2. Despite differences in the composite endpoint, there was no significant difference in mortality at 5 years between CABG (12%) vs PCI (9%) ($P = 0.77$).

3. Nonprocedural MI was significantly higher in the PCI group (7%) vs the CABG group (2%) ($P = 0.0040$).

4. Patients in the PCI group underwent significantly higher rates of repeat revascularization (16%) than the CABG group (10%) ($P = 0.03$). There was a high rate of LIMA to LAD grafting (98%).

5. Eleven percent of patients in the NOBLE trial underwent PCI with a first-generation DES, unlike EXCEL where 100% of patients had a second-generation stent. It remains unclear to what degree this contributes to the primary endpoint at 5 years.

PATIENTS WITH CKD ON/OFF DIALYSIS: DATA FROM THE NEW YORK STATE REGISTRY

Revascularization in Patients With Multivessel CAD and CKD: Everolimus-Eluting Stents Vs CABG

Patients with CKD frequently have diffuse or multivessel disease which adds significant risk for complications with any kind of revasularization.[4] Most large-scale clinical trials exclude these patients. As a consequence, there are minimal data concerning this clinically challenging population. Using the New York State database, Bangalore et al attempted to better define understand optimal revascularization strategies.[4] A total of 11,305 patients with CKD (defined as a GFR <60 mL/min/1.73 m^2) undergoing revascularization with either everolimus-eluting stents or isolated CABG were propensity-matched (2960 patients matched in each group) and analyzed for the rates of death, stroke, and repeat revascularization. Patients with severe left main disease were excluded from this study. Patients were well-matched between groups. Interestingly, less than 50% of both the PCI and CABG groups had a diagnosis of diabetes. Salient points from this study include:

1. PCI was associated with a lower risk of death (1.0% vs 1.7%, $P = 0.01$) at 30 days, but this does not represent an important clinical difference. The low risk of death at 30 days is likely due to the overall low-risk profile of the patient population. At a mean follow-up of 2.9 years rates of death were similar (22.7% vs 20.5%, $P = 0.40$) and higher than would be expected in a cohort without CKD.

2. At 30 days, there was also a numerically small but lower risk of stroke (0.4% vs 1.7%, $P < 0.0001$), lower risk of repeat revascularization (0.4% vs 0.8%, $P = 0.04$), and no significant difference in MI between PCI and CABG groups.

3. During long-term follow-up, there was a higher risk of MI in patients who underwent PCI compared to CABG (10.7 vs 7.0% $P < 0.0001$) There was also a higher risk of repeat revascularization in the PCI group (26.1% vs 13.1% $P < 0.0001$). These findings were driven largely by patients with 3-vessel disease and patients who underwent incomplete revascularization.

4. In a propensity-matched subset of 486 patients on dialysis, PCI was associated with a higher risk of long-term death (2.9 years) (54.3% vs 39.1% $P < 0.05$), MI (31.9% vs 16.7% $P < 0.05$), and repeat revascularization (48.3% vs 25.0% $P < 0.05$). There was no difference in stroke rate.

5. This study is a registry and inherently limited by its retrospective nature. Given the prevalence of CKD, a dedicated trial is warranted to best delineate the optimal revascularization strategy in this cohort. The pending ISCHEMIA-CKD substudy may provide useful information to guide clinical decision-making.

THE BEST TRIAL

The Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel CAD

The BEST trial was a randomized, open-label, multicenter, noninferiority trial conducted in Asia that compared a strategy of CABG to PCI using second-generation everolimus-eluting stents in patients with multivessel CAD.[5] All patients in this study had angiographically defined stenoses of at least 70% in at least 2 coronary arteries. A heart team deemed each study participant to be a good candidate for either CABG or PCI. The aim was to study the impact of improved stent technology on clinical outcomes. Routine IVUS use was not mandated but strongly recommended during PCI (used in 72% of cases), the internal thoracic artery was preferentially used for LAD revascularization (99% of cases), and enrollment was slow and ultimately stopped prematurely. Notably, greater than 75% of patients had 3-vessel disease, approximately 30% of both groups had a lesion defined as a chronic total occlusion, and approximately 40% of both study groups were diabetic. Similar to other studies, the primary endpoint of BEST was a composite of death, myocardial infarction, or target-vessel revascularization. Salient points from this study include:

1. At 2-year follow-up, the combined primary endpoint occurred in 11% of the PCI group and 7.9% of the CABG group. PCI did not achieve the prespecified noninferiority endpoint ($P = 0.32$ for noninferiority).
2. During long-term follow-up (4.8 years), the combined primary endpoint was higher in the PCI group (15.3%) vs the CABG group (10.6%, $P = 0.04$).
3. During long-term follow-up, in the PCI group, the difference in outcomes mentioned above was driven by higher rates of target-vessel revascularization and spontaneous MI. However, there was no significant difference in death, myocardial infarction, or stroke between groups.
4. The generalizability of this study is limited by the restricted sample size, 80% screen failures, routine follow-up angiography, and lack of geographic diversity.

BYPASS SURGERY OR STENTING FOR LEFT MAIN CAD IN PATIENTS WITH DIABETES

A specified subgroup analysis of patients from the above-described EXCEL trial[2] evaluated the impact of diabetes on patients with left main disease treated with PCI vs CABG.[6] The diabetic cohort of 554 patients studied had a higher prevalence of medical comorbidities; however, these did not differ significantly based on revascularization strategy. There were notable differences between surgical revascularization strategies in diabetic patients. Only 19.6% of diabetic patients underwent bilateral internal mammary artery grafting compared to 32.4% of patients without diabetes ($P < 0.001$). Salient points from this study include:

1. At 3 years, the composite endpoint, somewhat expectedly, remained higher in the diabetic than the nondiabetic cohort (20.0% vs 12.9%; $P < 0.001$).
2. Of patients undergoing PCI, 20.7% experienced the primary endpoint while 19.3% of patients undergoing CABG experienced the primary endpoint ($P = 0.87$).
3. There was a higher rate of all-cause death at 3 years in the PCI group (13.6%) compared to the CABG group (9.0%, $P = 0.046$).
4. At 30 days, the composite endpoint of death, stroke, or MI was numerically higher after CABG than PCI (9.8% vs 5.3%, $P = 0.05$).

Synthesis

The most impactful trials published in the last 3 years comparing CABG to PCI are summarized above. Collectively, these data represent the dedicated study of over 15,000 patients and build on the historical work of EAST,[1] BARI,[7] BARI-2D,[8] FREEDOM,[9] and SYNTAX.[10] Despite this, the question remains: how does one, as a physician, counsel a patient with CAD on which revascularization strategy is optimal? Unfortunately, our summary of the last 3 years of trials helps with, but does not give a definitive answer for, an individual patient. Historical context may help as well to better answer this question (Table 1).

The EAST[1] was the first trial to compare angioplasty to CABG in patients presenting with multivessel coronary disease using the earliest generation of balloon angioplasty. Despite starting in 1987, the demographics and outcomes are incredibly similar to many of the later trials. In the EAST trial, 40−50% of patients had diabetes, 99.1% of patients in the CABG arm received full revascularization, and at 3 years, there was no significant difference in mortality at the expense of higher repeat revascularization in the angioplasty group.

Following this work, the Bypass Angioplasty Revascularization Investigation (BARI)[7] trial was an international, multicenter, randomized control trial that compared a strategy of CABG vs angioplasty in patients with multivessel CAD. A lower proportion of patients in this study, approximately 25%, were diabetic. At 5 years, there was no difference in survival in patients who had an initial strategy of angioplasty (without any form of coronary stenting) vs CABG, except in patients with diabetes. Because BARI was not powered to evaluate diabetics vs nondiabetics, the survival advantage found in diabetics undergoing

Table 1. Summary of the 5 Most Impactful Studies of the Last 3 Years as Compared to a Historical Perspective

Study	Author	Year	Diabetics	Multivessel Disease	Revascularization Strategy Favored by Trial Outcome	Critiques
EXCEL	Stone et al	2016	Yes (30%)	No Study of LM Disease	CABG or PCI	Nonblinded Differences in medical therapy postrevascularization
EXCEL (diabetic subanalysis)	Milojevic et al	2019	Yes (100%)	No Study of LM disease	CABG or PCI	Substudy analysis
NOBLE	Mäkikallio et al	2016	Yes (15%)	No Study of LM disease	CABG	11% of patients underwent PCI with first-generation DES in the era of second-generation DES
Data from the NY state registry	Bangalore et al	2015	Yes (48%)	Yes	Short-term outcomes: PCI Dialysis patients: CABG	Retrospective Observational
BEST	Park et al	2015	Yes (40%)	Yes	CABG	Limited sample size 80% screen failure rate Routine follow-up angiography
FREEDOM	Milojevic et al	2012	Yes (100%)	Yes	CABG	Slow enrollment Use of first-generation DES in the era of second-generation DES
SYNTAX	Serruys et al	2009	Yes (25%)	Yes	High syntax score: CABG Low syntax score: PCI	Use of first-generation DES in the era of second-generation DES
BARI 2D	BARI 2D Investigators	2009	Yes (100%)	Yes	CABG	Not a direct comparison of CABG to PCI Use of bare metal stents in the era of DES
BARI	BARI Investigators	1996	Yes (25%)	Yes	CABG or PCI	Performed in prestent era Inadequate power to evaluate diabetics vs nondiabetics
EAST	King et al	1994	Yes (40−50%)	Yes	CABG or PCI	Performed in the prestent era

CABG was hypothesis generating only. This study started in the prestent era and therefore underwent immediate criticism—with a belief that stent use may make PCI outcomes more comparable to CABG.

Given these findings and equipoise, the BARI-2D trial (a randomized trial of therapies for type 2 diabetes and CAD)[8] sought to evaluate both the effects of diabetes treatment strategies (insulin vs oral medications) and revascularization strategies (PCI vs CABG). Revascularization strategies were determined by the treating physician and patients were only randomized to prompt revascularization vs optimal medical therapy. In this trial, both bare metal and drug-eluting stents were used during PCI. There were no significant differences in mortality at 5 years comparing a strategy of early revascularization (with PCI or CABG) vs optimal medical therapy but there was significantly higher freedom from major adverse cardiovascular events (77.5% vs 69%, $P = 0.01$) in the CABG vs OMT group but not in PCI vs OMT group (77% vs 78.9% $P = 0.15$). This trial was not a direct comparison of CABG to PCI, but it suggested that diabetics with multivessel CAD may benefit from a revascularization strategy of CABG compared to PCI. Critics cited the use of bare metal stents as a possible etiology to explain the differences in outcomes.

The SYNTAX (Synergy between Percutaneous Intervention with Taxus and Cardiac Surgery) Trial[10] compared outcomes in patients with either 3-vessel or left main CAD undergoing revascularization with either CABG or PCI. In this trial, approximately 25% of patients had medically treated diabetes. At 12 months, CABG proved to be superior to PCI for the combined primary endpoint of major adverse cardiac or cerebrovascular event. Not surprisingly, this was driven largely by the rate of repeat revascularization in the PCI group (13.5%) compared to the CABG group (5.9%) and not affected by death at 12 months. Again, there was a higher rate of early stroke in the CABG group (2.2%) vs PCI (0.6%). An important contribution of the SYNTAX trial was the development of an angiographic grading tool (the syntax score)—which classifies patients CAD severity on lesion complexity, location, and number. Patients with a lower SYTNAX score had a similar outcome regardless of revascularization strategy while those with a higher score had better outcomes with CABG. Again, a criticism of this trial was the use of first-generation DES.

The FREEDOM trial (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease)[9] was performed to compare PCI using first-generation paclitaxel/sirolimus DES PCI vs CABG only in diabetics. This trial showed that CABG provided a 5% absolute risk reduction (16.3% vs 10.9% $P = 0.049$) of all-cause death compared to PCI in addition to a decreased rate of myocardial infarction and repeat revascularization at the expense of a 3% absolute increase in early stroke rate. Overall, the sense of FREEDOM is that in patients with complex coronary disease (median syntax score: 26) CABG had superior outcomes to PCI save for the early risk of

stroke. Again, as technology advanced, a major criticism of this study is the advent of the possible superiority of second-generation DES.

Given these findings, we believe that a patient is best counseled and treated using the following principles:

1. A heart catheterization is a diagnostic, not a therapeutic, test. With the advent of high-resolution CTA and CT FFR, the role of a diagnostic heart catheterization may become more complex.
2. Patient perception, preference, and satisfaction play an important role in determining the ultimate treatment strategy.
3. The Heart Team Model should be used for complex revascularization decisions. A discussion with the patient should include representatives of both cardiac surgery and interventional cardiology and be focused on the risks and benefits of the treatment options, with likely outcomes based on the literature.
4. Patients should be made aware of the limitations of our current understanding of this complex issue. Despite 30 years of clinical research studying thousands of patients, advances in technology, and dealing with individual variations in patients makes definite strategy recommendations difficult at best.

Given all of the above, it is our belief that:

1. CABG should be offered to appropriate surgical candidates with diabetes and LM or severe multivessel disease.
2. For patients with low syntax score, with or without LM disease, PCI or CABG may be appropriate based on the patient's clinical condition (STS score/Frailty Index) and preference.
3. For all the other patients who do not fall into these relatively small groups, clinical judgment and a careful conversation with the patient are still appropriate.
4. While more contemporary studies are needed, it is inherently difficult to finish a study before technology supersedes the outcomes.

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