

CABG for Multivessel CAD

Recent studies show that CABG is still preferred over PCI for most patients.

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A decade ago, many cardiac surgeons believed that percutaneous coronary intervention (PCI) was more likely to replace coronary artery bypass grafting (CABG) in more patients with multivessel coronary artery disease than in left main disease (LMD). Today, the results of recent randomized trials in addition to large registries suggest just the opposite: CABG is still the preferred treatment for most patients with multivessel coronary artery disease.

COMPARING CABG AND PCI

To understand the role of CABG in 2012, it is important to review and understand the appropriate evidence-based indications for CABG for the last 3 decades. First performed in 1962, CABG gained prominence in the 1970s and 1980s as the mainstay of revascularization for coronary artery disease (CAD). The 2007 National Hospital Discharge Survey estimates that there were 405,000 CABG procedures performed that year.¹

In a review of the initial randomized studies comparing CABG to medical management with patients enrolled from 1972 to 1984, the appropriate role of CABG was defined with absolute survival advantages at 5 years (10.2% vs 15.8%) and at 10 years (26.4% vs 30.5%) that was more pronounced with the extent of CAD. This included CABG for LMD, three-vessel disease, and two-vessel disease with proximal left anterior descending (LAD) disease, and in diabetics or patients with low ejection fraction.² Importantly, there was no survival advantage with CABG compared to medical management in stable angina with single- and double-vessel CAD and in patients with normal left ventricular function. This distinction is important to understand for the subsequent role of PCI with respect to surgery. Because CABG was not shown to have an advantage over medical management in these subgroups, it could be predicted that CABG would not show an advantage over PCI for these patients.

A number of subsequent randomized trials compared CABG to first balloon angioplasty, then bare-metal stents (BMS), and then to drug-eluting stents (DES). These results

generally showed similar survival rates for PCI and CABG, with PCI having higher rates of revascularization. In a summary of 15 important randomized trials comparing PCI and CABG, Taggart³ made some significant observations about the inherent limits of these studies.

First, although the trials involved almost 9,000 patients, this represented only 5% of the total screened population. Second, only 35% of PCI patients had three-vessel disease, and 40% had proximal LAD disease. Third, the overwhelming majority of patients had an ejection fraction of more than 50%. Fourth, only 79% of patients received a left internal mammary artery (LIMA) graft, which is known to have a clear survival advantage over a saphenous vein graft compared to our current 92% rate of IMA utilization.⁴

Thus, surgeons were skeptical of these randomized trials and did not believe that they represented a real-world experience because they excluded the patients who were known to benefit the most from surgery based on the original randomized trials. Because it had already been established that CABG was nonsuperior over medical management in patients with single- or two-vessel disease, it should have come as no surprise that CABG was not beneficial to PCI in these studies that were focused on these low-risk groups of patients. Subsequently, the conclusions of these studies based on less complex CAD were then being used to justify widespread PCI in three-vessel disease, LMD, and more complex CAD patients. Nevertheless, despite these limitations, meta-analyses of these same studies showed a significantly lower CABG mortality rate in diabetics (hazard ratio, 0.7; confidence interval, 0.56–0.87; $P = .014$) and patients over age 65 (hazard ratio, 0.82; confidence interval, 0.70–0.97; $P = .002$).⁵

RANDOMIZED CONTROLLED TRIALS

The limitation of a randomized controlled trial (RCT) is the selection bias at the time of study enrollment. By excluding more and more patients in the screening process such that a small overall percentage of eligible patients are actually enrolled, an RCT can result in an atypical patient population sample. On the other hand, a

TABLE 1. COMPARISON OF DES VERSUS CABG TRIAL REGISTRIES

Registry	Number of Patients	Follow-Up (y)	Enrollment Period	Major Exclusion Criteria	Risk Factors (CABG > PCI)	Major Results (Odds Ratios)	Subgroup Results
NY State Registry Hannan et al, 2008 ⁶	DES, 9,963 CABG, 7,437	1.5	2003–2004	Previous revascularization LMD MI < 24 h	EF < 40%, CVD, PAD, CHF, DM, and 3VD (70% vs 25%)	CABG favored in 3VD (0.80 ^a), 2VD (0.71 ^a), DM (0.84 ^a), EF < 40% (0.67 ^a), age > 80 (0.74 ^a)	N/A
Seoul, Korea Park et al, 2011 ⁷	DES, 1,547 CABG, 1,495	5.6	2003–2005	N/A	CHF, CVD, renal failure, EF < 40%, 3VD (77% vs 44%), LMD, CTO (44% vs 7%), and SYNTAX score (29.9 vs 17.4)	Death/MI/stroke similar, DES group had higher revascularization rate overall (HR, 2.93 ^a) in DM (3.28 ^a), age > 65 (4.57 ^a), and abnormal LV function (9.23 ^a)	Mortality benefit in 2VD for DES over CABG
Beijing, China Li et al, 2009 ⁸	DES, 1,834 CABG, 1,886	3	2004–2005	N/A	CVD, PVD, EF < 50%, CHF, and 3VD (82% vs 23%)	DES with higher rate of death (1.62 ^a), MI (1.65 ^a), and TVR (6.79 ^a)	Benefit in DM, 3VD, age > 70
CREDO Kyoto ⁹	PCI, 1,825 (77% DES) CABG, 1,156	3	N/A	Acute MI, 1VD, 2VD, and LMD	SYNTAX score (CABG 30 ± 10.5 vs PCI 23.6 ± 9.2), previous MI, DM, and renal insufficiency	PCI had higher all-cause death/MI/stroke (1.47 ^a), and MI (1.62 ^a)	CABG favored even in low SYNTAX group (PCI = 1.66 ^a)

^aP < .05

Abbreviations: 1VD, single-vessel disease; 2VD, two-vessel disease; 3VD, three-vessel disease; CHF, congestive heart failure; CTO, chronic total occlusion; CVD, cardiovascular disease; DM, diabetes mellitus; EF, ejection fraction; HR, hazard ratio; LV, left ventricular; MI, myocardial infarction; PVD, peripheral vascular disease; TVR, target vessel revascularization.

real-world perspective can be obtained by analyzing registry data. Although there may be bias at the time of treatment decision, valuable information can be obtained from these studies. Important registry trials looking at CABG versus PCI using DES are illustrated in Table 1, demonstrating real-world results of comparative methods of coronary revascularization. Consistently, there appears to be a survival benefit for patients undergoing CABG of almost 5% by 3 to 5 years, although it is not apparent at 1-year follow-up. What is even more striking in each of the listed registries is that the CABG groups consistently have more comorbidities known to compromise survival; nevertheless, the CABG arms consistently outperformed DES in the real world.

SYNTAX

To address the shortcomings of the previous randomized trials, Boston Scientific Corporation (Natick, MA) support-

ed the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial that was designed as an all-comers prospective RCT at 85 sites worldwide with 5-year follow-up.¹⁰ In the trial, 4,337 patients with LMD or three-vessel disease were screened, and 3,075 (70.9%) patients were enrolled. Of that group, 1,800 patients (58.5% of total enrollment; 41.5% of total screened) were enrolled in a randomized trial of CABG versus PCI using DES, and an additional 1,275 patients were enrolled in either a nested parallel CABG registry (n = 1,077; 35% of total enrollment) due to complex coronary anatomy felt to be unsuitable for PCI (mean SYNTAX score, 37.8) or a PCI registry (n = 198) due to comorbidities precluding surgery. Thus, approximately one-third of all potential patients had CAD of such severity that PCI was believed to be either suboptimal or unsafe, and these patients were referred directly for CABG. In the randomized arm, three-vessel disease represented 66.3% in the CABG arm and 65.4% in the Taxus Express2 stent arm.

The primary conclusion of SYNTAX was that at 12 months, the composite primary endpoint (all-cause death, stroke, myocardial infarction, and repeat revascularization) was lower in the CABG versus PCI (12.4% vs 17.8%; $P = .002$) group.¹⁰ Thus, PCI noninferiority was not demonstrated and based on predetermined primary endpoints; CABG remained superior to PCI. However, the focus was on the higher rate of stroke in the CABG group (2.2% vs 0.6%) and the higher rate of repeat revascularization in the PCI group (13.5% vs 5.9%). Therefore, one interpretation of the SYNTAX trial for some was that repeat revascularization drove the primary endpoint results, so the tradeoff between repeat PCI instead of a CABG-related stroke actually favored PCI.

The stroke results deserve closer analysis. There was a total of 19 strokes in the CABG arm and five in the PCI arm at 1 year. In the CABG group, three (0.3%) strokes occurred before the actual surgery but were included in the intent-to-treat methodology. From the time of the procedure to 30 days, there were nine (1%) strokes in the CABG group and two (0.2%) in the PCI group. This is consistent with a large series over the last decade that demonstrates a 30-day CABG stroke rate in the 1.5% range.^{11,12} From 30 days to 1 year, there were seven (0.8%) strokes in the CABG group and three (0.3%) in the PCI arm.

Thus, in another interpretation of SYNTAX, a large difference in secondary prevention medical therapy may have influenced the stroke results. CABG patients were significantly undertreated with aspirin (89% vs 96% at discharge; 84% vs 91% at 1 year), clopidogrel (20% vs 97% at discharge; 15% vs 71% at 1 year), and statin medications (75% vs 87% at discharge; 82% vs 86% at 1 year) compared to the PCI group. This may have influenced the difference in 1-year stroke rates because half of the strokes in the CABG group occurred after 30 days of surgery and were likely not related to the surgery. Finally, 36.7% of the CABG arm received aprotinin (Trasylol, Bayer Pharmaceuticals, West Haven, CT) perioperatively, which was discontinued in 2008 due to concerns about higher stroke, renal failure, and mortality in CABG patients.¹³

CABG achieved a higher rate of complete revascularization (63% vs 57%) than PCI. It is worth noting that SYNTAX was the most aggressive PCI trial published with respect to average total stent length (86.1 ± 47.9 mm) and mean stents placed (4.6 ± 2.3). In a real-world setting in New York, an analysis of over 11,000 patients demonstrated a 31% rate of complete revascularization with PCI, which was associated with a lower 18-month mortality rate.¹⁴ Although there was statistical superiority in the freedom from angina in the SYNTAX CABG group (94% vs 92%), it was not clinically significant. An additional and important achievement of SYNTAX was

to provide a complete scoring system of coronary pathoanatomy, which allowed grouping of patients in terciles according to the complexity of their lesions. It is important to remember that because SYNTAX did not meet its primary statistical endpoint, any observations resulting from subgroup distinction by the SYNTAX score is hypothesis generating and, as such, worthy of further study. Drawing definitive conclusions from a subgroup analysis, despite widespread practice, cannot be statistically justified at this time to support changes in clinical practice.

Subsequent annual updates of the SYNTAX trial include the published 3-year results of the CABG and PCI arms of the trial, with 92% and 98% follow-up, respectively. This report demonstrated that CABG is the preferred treatment in terms of survival, not simply repeat revascularization for three-vessel disease in the intermediate- and high-risk SYNTAX groups.¹⁵ Overall mortality at 3 years in the three-vessel disease group was significantly lower for patients who underwent CABG than PCI (5.7% vs 9.5%; $P = .02$) as it was for cardiac-related death (2.9% vs 6.2%; $P = .01$). CABG outperformed PCI in incidence of myocardial infarction (3.3 vs 7.1%; $P = .005$) and repeat revascularization (10% vs 19.4%; $P = .0001$) without any difference seen in total strokes (2.9% vs 2.6%; $P = .001$). This was believed to be in line with previous published CABG trials compared to DES in which the benefit to CABG is typically apparent not after 1 year but after 3 to 4 years. The most recent presentation of the 4-year SYNTAX data at the 2011 European Society of Cardiology meeting confirmed the 3-year survival benefit findings, with CABG preferred to PCI for intermediate- and high-risk three-vessel disease SYNTAX groups.

The reason that the CABG benefit may manifest after a few years might be due to the intrinsic difference between CABG and PCI. It has been postulated that the prognostic benefit of CABG is that while PCI deals only with the proximal immediate culprit lesion or stenosis, CABG also deals with future distal culprit lesions because the bypass graft is anastomosed to the mid or distal vessel beyond the immediate stenosis. Therefore, CABG may be protective against future progression of proximal plaque. It is notable that, unlike PCI, the mortality results of CABG are not influenced by the severity of the SYNTAX score.^{16,17}

In multivessel CAD for survival benefit, the 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines¹⁸ and 2010 European Society of Cardiology/European Association of Cardiothoracic Surgery (ESC/EACTS) Guidelines¹⁹ are compared for CABG and PCI (Table 2). While overall sim-

TABLE 2. COMPARISON OF 2010 ESC/EACTS¹⁹ AND 2011 ACCF/AHA GUIDELINES¹⁸

	ESC/EACTS CABG	ESC/EACTS PCI	ACCF/AHA CABG	ACCF/AHA PCI
3VD ± (proximal LAD disease)	N/A	N/A	Class I (B)	N/A
Complex 3VD (SYNTAX > 22)	Class I (a)	Class III (a)	Class IIa (B)	Class IIb (B)
Simple 3VD (SYNTAX ≤ 22)	Class I (a)	Class IIa (b)	N/A	N/A
2VD with proximal LAD	Class I (a)	Class IIa (b)	Class I (B)	Class IIb (B)
2VD without proximal LAD disease	Class IIb (C)	Class I (c)	Class IIa (B) with extensive ischemia Class IIb (B) without extensive ischemia	Class IIb (B)
1V proximal LAD disease	Class I (a)	Class IIa (B)	Class IIa (B) with LIMA	Class IIb (B)
1V without proximal LAD disease	Class IIb (C)	Class I (C)	Class III (B)	Class III (B)
LV dysfunction	N/A	N/A	Class IIa (B) for EF 35%–50% Class IIb (B) for EF < 35% without significant LMCAD	Insufficient data
MVCAD and diabetes mellitus	N/A	N/A	Class IIa (B)	N/A
Survivor of sudden death with major coronary artery stenosis	N/A	N/A	Class I (B)	Class I (C)

Class I (green), procedure should be performed; class IIa (yellow), it is reasonable to perform the procedure; class IIb (yellow), the procedure may be considered; class III (red), the procedure is not useful and may be harmful.

Level of evidence A, data derived from multiple randomized clinical trials or meta-analyses; level of evidence B, data derived from a single randomized trial or nonrandomized studies; level of evidence C, consensus opinion of experts, case studies, or standard of care. Abbreviations: 1VD, single-vessel disease; 2VD, two-vessel disease; 3VD, three-vessel disease; EF, ejection fraction; LMCAD, left main coronary artery disease; LV, left ventricular; MVCAD, multivessel coronary artery disease.

ilar, it is interesting to note that the ACCF/AHA guidelines issue no higher than a class IIb recommendation to PCI for most forms of multivessel disease. The European guidelines are more generous with class IIa recommendation in lower-risk multivessel disease. Currently, approximately one-third of patients with class I indications for CABG are treated with PCI using DES, according to the National Cardiovascular Data Registry.²⁰

Contemporary results for CABG are excellent, with a mortality of 1.8% in over 1.5 million patients analyzed in the Society of Thoracic Surgeons database.²¹ The challenge for surgeons is that the SYNTAX surgical patients had 28% bilateral IMA grafting and 19% all arterial grafting. This is approximately double the current rates in the United States. However, because the major benefits of additional arterial revascularization beyond LIMA grafting tend to be demonstrated beyond 5 years,²² it is unlikely to have had a significant impact in the reported SYNTAX results up to this point. Nevertheless, the 2011 ACCF/AHA guidelines give a class IIa recommendation

for bilateral IMA grafting in selected patients and a class IIb recommendation for complete arterial revascularization in patients younger than 60 years.¹⁸

It has already been pointed out by some that the paclitaxel DES of SYNTAX is already obsolete and has given way to sirolimus- and everolimus-coated stents that appear to lower the rate of angiographic restenosis. However, it is important to remember that even though DES eclipsed BMS because of reduced restenosis, DES has not been shown to have a survival benefit over BMS in stable angina.²³ Regardless, future trials involving sirolimus- or everolimus-coated stents will have to demonstrate a similarly high enrollment percentage, as seen in the landmark SYNTAX trial, to have a similar level of credibility to both cardiologists and surgeons. Based on SYNTAX, of the 1,088 patients studied with three-vessel disease in the randomized arm and the 338 studied in the registry, CABG was preferred over PCI in 1,074 or 75% of patients with respect to major adverse cardiac and cerebrovascular events and was equivalent to PCI in 25% of patients.

The other recommendation from the 2010 European guidelines is to have a “heart team” consisting of an interventionist, a surgeon, and a general cardiologist to discuss and decide the best treatment for the patient after the diagnostic catheterization. Along these lines, ad hoc PCI, in which the diagnostic catheterization and PCI are performed at the same setting, is discouraged. In New York State, 92% of patients who underwent PCI at hospitals capable of both PCI and cardiac surgery had ad hoc PCI.²⁴ Similarly, the 2011 ACCF/AHA guidelines also offer a class I recommendation to a multidisciplinary heart team approach in unprotected LMD or complex CAD. The collaborative nature of SYNTAX and the current transcatheter aortic valve trials suggest that the interventionist, general cardiologist, and surgeon can work together in the patient’s best interests.

CONCLUSION

Unlike the rapid innovation and improvements occurring in PCI, the majority of CABGs performed in the United States have remained unchanged for a quarter century: an on-pump, heart stopped, LIMA to LAD with two or three vein grafts. The challenge for the surgical community is to continually improve upon a very good operation with respect to perfusion, arterial conduits, stroke prevention, and secondary CAD prevention. It is human nature that the least-invasive treatment carries the strongest appeal. When confronted with the prospect of having one’s “chest cracked open,” most any alternative will appeal to a patient. That belief, however, rests on the assumption that the treatments are equivalent. Genuine informed consent in which patients understand both the rationale for the treatment and a discussion of alternatives occurs far less often than we think in coronary revascularization.²⁵ Based on the SYNTAX trials and registry data, for most (75%) patients with three-vessel CAD in 2012, CABG remains the preferred treatment, with a survival advantage over PCI with DES. ■

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- Hall MJ, DeFrances CJ, Williams SN, et al. National Hospital Discharge Survey: 2007 summary. Hyattsville, MD: National Health Statistics Reports No. 29, National Center for Health Statistics; 2010. Available at: <http://www.cdc.gov/nchs/data/nhsr/nhsr029.pdf>. Accessed December 2, 2011.
- Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomized trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet*. 1994;344:563-570.
- Taggart DP. Coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to know. *Ann Thorac Surg*. 2006;82:1966-1975.
- Tabata M, Grab JD, Khalpey Z, et al. Prevalence and variability of internal mammary artery graft use in contemporary multivessel coronary artery bypass graft surgery: analysis of the Society of Thoracic Surgeons National Cardiac Database. *Circulation*. 2009;120:935-940.
- Hlatky MA, Boothroyd DB, Bravata DM, et al. Coronary artery bypass compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomized trials. *Lancet*. 2003;373:1190-1197.
- Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary artery bypass grafting in multivessel coronary disease. *New Engl J Med*. 2008;358:331-341.
- Park DW, Kim YK, Song HG et al. Long-term comparison of drug-eluting stents and coronary artery bypass grafting for multivessel coronary revascularization: 5 year outcomes from the Asan Medical Center-Multivessel Revascularization Registry. *J Am Coll Cardiol*. 2011;57:128-137.
- Li Y, Zheng Z, Xu B, et al. Comparison of drug-eluting stents and coronary artery bypass surgery for the treatment of multivessel coronary disease: three year follow-up results from a single institution. *Circulation*. 2009;119:2040-2050.
- Shiomi H, Van de Werf F. Comparison of three-year outcome after PCI and CABG stratified by the SYNTAX score in patients with triple vessel coronary artery disease: an observation from the CREDO-Kyoto PCI/CABG registry Cohort-2. Presented at The European Society of Cardiology meeting in Paris, France; August 27-31, 2011.
- Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961-972.
- Tarakji KC, Sabik JF, Bhudia SK, et al. Temporal onset, risk factors, and outcomes associated with stroke after coronary artery bypass grafting. *JAMA*. 2011;305:381-390.
- John R, Choudhri AF, Weinberg AD, et al. Multicenter review of preoperative risk factors for stroke after coronary artery bypass grafting. *Ann Thorac Surg*. 2000;69:30-35.
- Mangano DT, Miao Y, Vuylsteke A, et al. Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. *JAMA*. 2007;297:471-479.
- Hannan EL, Wu C, Walford G, et al. Incomplete revascularization in the era of drug eluting stents. *JACC Cardiovasc Interv*. 2009;2:17-25.
- Kappetein AP, Feldman TE, Mack MJ, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J*. 2011;32:2125-2134.
- Lemesle G, Bonello L, de Labriolle A, et al. Prognostic value of the Syntax score in patients undergoing coronary artery bypass grafting for three-vessel coronary artery disease. *Catheter Cardiovasc Interv*. 2009;73:612-617.
- Mohr FW, Rastan AJ, Serruys PW, et al. Complex coronary anatomy in coronary artery bypass graft surgery: impact of complex coronary anatomy in modern bypass surgery? Lessons learned from SYNTAX trial after two years. *J Thorac Cardiovasc Surg*. 2011;141:130-140.
- Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2011 Nov 7. [Epub ahead of print]
- Task Force on Myocardial Revascularization of the ESC and EACTS. Guidelines on myocardial revascularization. *Eur Heart J*. 2010;31:2501-2555.
- Fruitkin AD, Lindsey JB, Mehta SK, et al. Drug-eluting stents and the use of percutaneous coronary intervention among patients with class I indication for coronary artery bypass surgery undergoing index revascularization. *JACC Cardiovasc Interv*. 2009;2:614-621.
- Society of Thoracic Surgeons. Adult Cardiac Surgery Database—Executive Summary 10 years: period ending 03/31/2010. Available at: www.sts.org/sites/default/files/documents/20112ndHarvestExecutiveSummary.pdf. Accessed December 2, 2011.
- Stevens LM, Carrier M, Perrault LP, et al. Single versus bilateral internal thoracic artery grafts with concomitant saphenous vein grafts for multivessel coronary artery bypass grafting: effects on mortality and event-free survival. *J Thorac Cardiovasc Surg*. 2004;127:1408-1415.
- Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet*. 2007;370:937-948.
- Hannan EL, Racz MJ, Gold J, et al. Adherence of Catheterization Laboratory Cardiologists to ACC/AHA Guidelines for PCI and CABG Surgery. *Circulation*. 2010;121:267-275.
- Chandrasekharan DP, Taggart DP. Informed consent for interventions in stable coronary artery disease: problems, etiologies, and solutions. *Eur J Cardiothorac Surg*. 2011;29:912-917.