

Pivotal contemporary trials of percutaneous coronary intervention vs. coronary artery bypass grafting: a surgical perspective

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Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are the two revascularization strategies for patients with coronary artery disease (CAD). While CABG continues to be the gold standard for revascularization, advancements in PCI technology have triggered numerous, often industry-funded investigations to challenge this role. This perspective will provide a summary of previous RCTs comparing CABG vs. PCI. The recently published NOBLE and EXCEL trials will be discussed in depth. Future directions of research pertaining to CABG vs. PCI will be briefly discussed in this document.

Keywords: Coronary artery bypass grafting (CABG); percutaneous coronary intervention (PCI)



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Introduction

Since its introduction in 1968, coronary artery bypass grafting (CABG) has been the gold standard of coronary revascularization for patients with coronary artery disease (CAD). In 1977, percutaneous coronary intervention (PCI) was introduced as an alternative coronary revascularization strategy. Advances in CABG, such as better and less invasive operative techniques, perioperative care, use of arterial conduits, and enhanced myocardial protection have significantly reduced the mortality and morbidity associated with CABG. Concomitantly, the evolution of newer generations of stents and improvement of techniques have made PCI feasible for treating complex coronary lesions. As a result, several sizable RCTs have been conducted to evaluate whether PCI is as good as CABG for patients with CAD.

RCTs comparing CABG vs. PCI [2005–2015]

We have summarized the major multicenter RCTs comparing CABG vs. PCI published between 2005–2015 (1–9) (*Table 1*). Virtually each of these trials had been undertaken to demonstrate non-inferiority of PCI as

compared to CABG. Several overarching conclusions were drawn: (I) CABG yielded superior survival outcomes in long-term follow up (3,7); (II) CABG led to lower rates of MACE/MACCE (1,2,4,6,8); (III) PCI group had higher rates of repeat revascularization (1,2,4–6,8). However, stroke was more likely to occur with CABG (4,7). Based on these findings, CABG continues to remain the intervention of choice for those needing coronary revascularization.

EXCEL and NOBLE: patients with unprotected left main coronary artery disease (ULMCA) stenosis

Whether CABG vs. PCI was the optimal revascularization strategy in patients with ULMCA stenosis again became a topic of heated debate in 2017, due to the simultaneous publication of the EXCEL (10) and NOBLE (11) randomized trials. A table summarizing these 2 contemporary RCTs is provided in this perspective (*Table 2*). These two studies yielded different conclusions, despite the similar design and patient population with ULMCA stenosis. In our opinion, these apparently contradictory conclusions can be attributed to several factors.

The conclusion of a trial is largely dependent on

Table 1 Summary of RCTs comparing CABG vs. PCI [2005–2015]									
Trial	ERACI II (1)	ARTS I (2)	SoS (3)	SYNTAX (4)	CARDIA (5)	ARTS II (6)	FREEDOM (7)	BEST (8)	PRECOMBAT (9)
Journal	JACC	JACC	Circulation	NEJM	JACC	JACC	NEJM	NEJM	JACC
Year of publication	2005	2005	2008	2009	2010	2010	2012	2015	2015
Funded by PCI industry partner	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Study period	October 1996–September 1998	April 1997–June 1998	November 1996–December 1999	March 2005–April 2007	January 2002–May 2007	February 2003–November 2003	April 2005–April 2010	July 2008–September 2013	April 2004–August 2009
Regions	US & South America	Europe, US & South America	Europe	Europe & US	Europe	Europe	US, Canada, Europe, South America, Asia & Australasia	Asia	Asia
Number of sites	7	67	53	85	24	45	140	27	12
Sample size	450	1,205	988	1,800	510	607	1,900	880	600
Patient population	Multivessel CAD	With at least two <i>de novo</i> lesions located in different major epicardial coronary arteries, potentially amenable to stent implantation	Multivessel CAD	Three-vessel or left main CAD (or both)	Diabetic and symptomatic multivessel CAD	Same as ARTS-I	Diabetic and symptomatic multivessel CAD	Multivessel CAD	Unprotected left main coronary artery stenosis
Rates of at least 2 arterial grafts	NA	NA	10.2%	27.6%	17.0%	NA	<10%	66.0%	NA
Generation of stent used	Pacitaxel-coated stent	Bare metal stent	Any commercially available stent	Pacitaxel-eluting stents	Bare metal stent then sirolimus-eluting stent	Sirolimus-eluting stent	Sirolimus-eluting and pacitaxel-eluting stents	Everolimus-eluting stents	Sirolimus-eluting stent

Table 1 (continued)

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Trial	ERACI III (1)	ARTS I (2)	SoS (3)	SYNTAX (4)	CARDIA (5)	ARTS II (6)	FREEDOM (7)	BEST (8)	PRECOMBAT (9)
Primary outcome	Composite of death, Q-wave MI, stroke, and need for repeat revascularization	Composite of all-cause death, any cerebrovascular accident, nonfatal MI, or any repeat revascularization	All-cause mortality	Composite of death from any cause, stroke, MI, or repeat revascularization	Composite of all-cause mortality, MI, and stroke	Composite of all-cause death, any cerebrovascular accident, nonfatal MI, or any repeat revascularization	Composite of death from any cause, nonfatal MI, and nonfatal stroke	Composite of death, MI, or target-vessel revascularization	Composite of all-cause death, MI, stroke, or ischemia-driven target vessel revascularization
Conclusions	No survival benefits from any revascularization procedure at 5 years; patients initially treated with CABG had better freedom from repeat revascularization procedures and from MACE	No difference in mortality between BMS and CABG for multivessel CAD at 5-year; the incidence of stroke or MI was not significantly different between the two groups; overall MACCE was higher in the BMS group, driven by the increased need for repeat revascularization	Continuing survival advantage was observed in CABG group at a median follow-up of 6 years	For the primary endpoint, PCI was not non-inferior; CABG proved to be superior; PCI group had increased rate of repeat revascularization; CABG group had higher incidence of stroke	First randomized trial of coronary revascularization in diabetic patients; a non-significantly higher rate of the composite of death, MI, and stroke (driven by a higher rate of MI) in PCI as compared to CABG at 1 year; significantly higher rates of repeat revascularization in the PCI group	At 5 years, SES had a safety record comparable to CABG and superior to BMS, and a MACCE rate that was higher than in patients treated with CABG, and lower than in those treated with BMS; one-third of MACE at 5 years seen with SES were related to stent thrombosis and could be prevented	CABG was superior to PCI in that it significantly reduced rates of death and myocardial infarction; stroke was more common in the CABG group	The study was terminated early owing to slow enrollment; at 2 years, the PCI group has higher rate of primary endpoint (did not meet non-inferiority); at a median follow up of 4.6 years, CABG had significantly lower rate of primary endpoint; PCI had higher rates of repeat revascularization and spontaneous MI	During 5 years of follow-up, there was no significant difference regarding the rate of MACCE between PCI and CABG

CAD, coronary artery disease; DES, drug eluting stent; MI, myocardial infarction; MACE, major adverse cardiovascular events; MACCE, major adverse cardiac and cerebrovascular events; BMS, bare metal stent; NA, unavailable; SES, sirolimus-eluting stent.

Trial	EXCEL	NOBLE
Journal	<i>NEJM</i>	<i>LANCET</i>
Year of publication	2016	2016
Study period	September 2010–March 2014	December 2008–January 2015
Funded by PCI industry partner	Yes (Abbott Vascular)	Yes (Biosensors)
Regions	Europe, North America, South America, Asia	Europe
Number of sites	126	36
Sample size	1,905	1,201
Patient population	Patients with left main coronary stenosis of at least 70%, SYNTAX score of 32 or lower	Patients with visually assessed left main coronary stenosis diameter $\geq 50\%$ or fractional flow reserve ≤ 0.80 in the left main coronary artery, with no more than three additional noncomplex lesions
Rates of at least 2 arterial grafts	28.8%	8.0%
Generation of stent used	Everolimus-eluting stents	Biolimus-eluting stent
Primary outcome	Composite of all-cause mortality, stroke, or MI	Composite of all-cause mortality, non-procedural MI, any repeat coronary revascularization, and stroke
Conclusions	PCI was non-inferior to CABG with respect to the rate of the composite endpoint of death, stroke, or myocardial infarction at 3 years	PCI was not non-inferior to CABG as treatment of left main coronary artery disease; CABG might provide a better clinical outcome at 5 years

EXCEL, Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; NOBLE, Nordic-Baltic-British Left Main Revascularisation trial.

the preselected endpoints. Periprocedural myocardial infarction (MI) as an endpoint has been controversial due to its definition based on arbitrary enzyme release thresholds, which change from time to time. Besides, its value in representing clinical and prognostic differences between CABG and PCI remains unclear. NOBLE did not include periprocedural MI as part of its composite primary endpoint; however, EXCEL did. In fact, EXCEL adopted a new definition of periprocedural MI during the study (12), which was quite distinct from the contemporary Third Universal Definition of MI (13). Importantly, the non-inferiority of PCI compared to CABG demonstrated in the EXCEL trial was largely driven by periprocedural MI. Target vessel revascularization (TVR) has been widely used as an endpoint in the previous RCTs comparing CABG vs. PCI (1,4,5,8). However, EXCEL did not include TVR as part of its composite primary outcome (10).

The duration of follow-up in a trial is also critical to allow for correct interpretation of study data. NOBLE and EXCEL reported the 5- and 3-year follow-up results,

respectively. The longer the follow-up time, the more likely the clinical or prognostic differences between CABG and PCI, if any, can be observed. Based on the previous studies, the slopes of event rates within the CABG and PCI groups start to diverge and reach statistical significance after 2 to 3 years of follow-up (7,8). NOBLE reported that CABG was superior to PCI at 5 years of follow-up (11), while EXCEL indicated PCI was non-inferior to CABG at 3 years (10). Moreover, the event slopes of CABG and PCI in EXCEL crossed at 3 years. It will be interesting to see the 5-year follow-up data in EXCEL. Furthermore, 29.1% of the EXCEL study subjects were diabetics, whereas NOBLE only had 15% diabetics. This might have contributed to the worrisome excess death signal (8.2% vs. 5.9%, PCI vs. CABG, respectively; $P=0.11$) in the PCI group in EXCEL.

As mentioned in the earlier section, previous RCTs consistently showed that the incidence of stroke was higher in CABG. However, there was no excess stroke signal observed in the CABG groups of both NOBLE and EXCEL. In fact, NOBLE demonstrated a trend of

increasing stroke risk in the PCI group at 5 years [PCI *vs.* CABG: hazard ratio (HR) 2.20, 95% CI, 0.91–5.36, $P=0.08$] (11). This is thought to be due to improved pharmacological stroke prevention strategies in the CABG group, such as the more frequent continuation of dual anti-platelet therapy and statins both before and after CABG. It may also relate to more frequent repeat revascularization and vascular events/procedures in the PCI group.

Looking at these RCTs comparing CABG *vs.* PCI, we often forget a very important question: have we provided the best quality of CABG to compare with PCI? Surgeons should bear in mind that all of the above mentioned RCTs compared CABG with the most advanced stents at the time of the studies. Revascularization using arterial grafts have been proven to be associated with improved survival outcomes (14), superior long-term graft patency (15), and less MACE/MACCE (16). However, the utilization of arterial grafts in these RCTs was suboptimal. The proportion of patients who received total arterial grafting was only 24% and 2% in EXCEL and NOBLE, respectively. We as surgeons ought to work to optimize our surgical technique, in order to provide the best long-term results and uphold CABG as the gold revascularization standard.

The next big question: revascularization in patients with CAD and severe left ventricular systolic dysfunction

At present, we have data regarding PCI *vs.* CABG in patients with complex multivessel CAD and diabetes (4,7). The data on left main disease is evolving, as discussed in the previous section (10,11). What remains unexplored is the patient population with CAD and left ventricular systolic dysfunction. Heart failure with reduced ejection fraction represents an increasing public health issue, with its incidence expected to rise steadily in coming years. To date, there has not been a RCT investigating the optimal revascularization strategy in this patient population. Moreover, this group of patients have been routinely excluded from the trials comparing CABG *vs.* PCI. Wolff *et al.* published a meta-analysis which included 21 studies involving a total of 16,191 patients (17). The authors concluded that revascularization, regardless of modality, was superior to medical treatment in improving survival in this patient population. When compared with PCI, CABG still showed a survival benefit (HR 0.82; 95% CI, 0.75–0.90; $P<0.001$). Nevertheless, these results are only hypothesis-

generating and remain to be tested in future randomized clinical trials.

Conclusions

To date, RCTs comparing CABG and PCI have demonstrated the superiority of CABG in patients with multivessel CAD, specifically in terms of survival and MACE/MACCE. The recently published EXCEL and NOBLE trials have triggered tremendous discussion due to their apparently conflicting conclusions. There has been enthusiasm around revision of the current revascularization guideline based on the EXCEL trial. However, this is likely premature due to the controversial study endpoints, as well as short follow-up. Despite the well-demonstrated superiority and longevity of arterial grafts in CABG, their utilization in all the contemporary RCTs has been suboptimal. Future trials should focus on revascularization in patients with severe left ventricular systolic dysfunction. From the surgeon's perspective and in light of rapid advances in PCI technologies in recent years, a collaborative effort is needed to continually improve our CABG techniques for better surgical outcomes.

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Footnote

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

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