Editorial Commentary

Percutaneous coronary intervention in left main disease: 10-year follow-up

Akihiro Kobayashi[1], **Naoki Misumida**[2]

[1]Banner University Medical Center Phoenix, Department of Cardiology, Phoenix, AZ, USA; [2]Gill Heart and Vascular Institute and Division of Cardiovascular Medicine, University of Kentucky, Lexington, KY, USA

Correspondence to: Naoki Misumida. Gill Heart and Vascular Institute and Division of Cardiovascular Medicine, University of Kentucky, 900S, Limestone Street, 326 Wethington Building, Lexington, KY 40536, USA. Email: misumidanaoki@gmail.com.

Provenance: This is an invited article commissioned by the Section Editor Busheng Zhang (Department of Cardiac Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).

Comment on: Park DW, Ahn JM, Yun SC, *et al.* 10-Year Outcomes of Stents Versus Coronary Artery Bypass Grafting for Left Main Coronary Artery Disease. J Am Coll Cardiol 2018;72:2813-22.

Submitted Dec 19, 2018. Accepted for publication Jan 03, 2019.
doi: 10.21037/atm.2019.01.05
View this article at: http://dx.doi.org/10.21037/atm.2019.01.05

The role of percutaneous coronary intervention (PCI) in left main revascularization

Significant left main coronary artery (LMCA) disease is found in 4.8% of patients undergoing coronary angiography (1). Historically, coronary artery bypass graft (CABG) has been the mainstay of revascularization strategy for LMCA disease (2). However, with the advances in PCI techniques and devices as well as adjunctive pharmacotherapy, PCI certainty has expanded its role in left main revascularization over the past decade (3). The previous guidelines discouraging unprotected left main PCI (Class III indication) have been challenged and modified (4): Class IIa–III in the 2012 ACC/AHA guidelines (5) and Class I–III in the 2014 ESC guidelines depending on patient-specific factors as well as anatomic considerations (6). The left main cohort of the SYNTAX trial showed the overall comparable 5-year survival between PCI and CABG, though CABG is still preferred revascularization method in patients with SYNTAX score ≥33 (7). In addition, recent two large randomized trials, representing the most contemporary data comparing PCI and CABG in patients with low to intermediate SYNTAX score, demonstrated comparable mid-term survivals between the groups (8,9). Nevertheless, grafting and stenting are fundamentally different; grafting will theoretically protect the distal vessel (if no critical stenosis beyond anastomosis), whereas stenting is, by nature, a focal "patch" to a lesion. There remains a concern for long-term (>10 years) durability of left main PCI in comparison to the well-documented long-term excellent patency of left internal mammary artery graft (10).

The optimal duration of follow-up

Follow-up length is one of the key considerations when interpreting the results of clinical studies, especially ones regarding CABG. A notable example is the STITCH trial, which compared CABG versus optimal medical therapy alone in patients with severe ischemic left ventricular dysfunction (11). While no statistically significant difference was found in all-cause death at 56-month follow-up (primary endpoint) (11), a significant mortality reduction with CABG became evident at the extended follow-up at 9.8 years (12). In the previous landmark trials comparing PCI versus CABG, the follow-up lengths for the assessment of primary endpoints were relatively short ranging from 1-year in the SYNTAX trial (13), Boudriot *et al.*'s trial (14), and PRECOMBAT trial (15,16), 3-year in the NOBLE trial (8) and the EXCEL trial (9). These relatively short follow-up durations are arguably "unfair" for CABG, which is expected to provide clinical benefits at longer follow-up after overcoming the intrinsic early hazard with surgery. In addition, with contemporary advanced medical therapy, the majority of patients with LMCA disease indeed live beyond 10-year: 10-year mortality after CABG has been reported

as 23% (17). Thus, sufficient longer follow-up is essential when comparing PCI versus CABG, while acknowledging down-side of longer follow-up such as increased cost (especially in randomized studies), loss of follow-up, and "background noise" due to events unrelated to the intended comparison.

Summary of the 10-year follow-up of MAIN-COMPARE registry

In the issue of *JACC*, Park *et al.* reported extended long-term follow-up data from the MAIN-COMPARE registry, which included 2,240 patients with LMCA disease (defined as stenosis >50%) who underwent PCI or CABG between January 2000 and June 2006 (18). The median follow-up duration was 12.0 years with an excellent follow-up rate (98.7%). This registry consisted of two phases according to the type of stent. During the first half of the enrollment period, bare-metal stents (BMS) were exclusively used. During the second half of the enrollment period, drug-eluting stents (DES) were exclusively used and a total 1,474 patients were enrolled (784 patients in DES cohort and 690 patients in CABG cohort). In the DES cohort, first-generation DESs either sirolimus-eluting stents (77.4%) or paclitaxel-eluting stents (22.6%) were used. The mean number of stents in LMCA disease was 1.2±0.5. In CABG cohort, 98.4% of the patients received at least one arterial conduit. The rate of complete revascularization was not reported in either PCI or CABG group.

After applying propensity score matching and inverse-probability-weighting adjustment to adjust baseline dissimilar characteristics inherent to observational comparison, authors found no statistically significant difference in adjusted risks of death and the composite outcome (death, myocardial infarction, or stroke) between the groups up to 10 years in the overall cohort. As expected, the rate of target-vessel revascularization was significantly higher in PCI cohort [hazard ratio (HR) 4.07; 95% confidence interval (CI), 3.43–6.44]. Considering a different time-dependent nature of treatment effects of PCI and CABG, authors performed additional pre-specified analyses dividing into two separate periods of before and after 5-year after the index procedure. There was no significant difference between PCI with DES and CABG in the risks of death and composite outcomes up to 5 years. However, after 5 years, PCI with DES, compared to CABG, was associated with a higher rate of death (HR 1.35; 95% CI, 1.00–1.81) and composite outcomes (HR 1.46; 95% CI, 1.10–1.94). In contrast, no significant difference was observed between CABG and PCI with BMS in before or after 5-year point.

Higher risk of death beyond 5-year after PCI with DES in comparison to CABG

These contrasting results between DES and BMS cohort can be explained by different clinical and anatomical characteristics of the patients in the two cohorts. In the initial registry period [2000–2003] when left main PCI was still regarded as class III indication (2), patients who underwent PCI had less complex anatomy as indicated by a lower rate of distal bifurcation lesion (31.4%) and left main plus 3-vessel disease (10.4%). In contrast, in the latter registry period [2003–2006], patients with more complex anatomy underwent PCI as indicated by the higher rate of distal bifurcation lesion (56.8%) and left main plus 3-vessel disease (30.6%). The patients in DES cohort were older and more likely to be diabetic. These high-risk clinical and anatomical characteristics in patients in DES cohort, which likely reflect our contemporary left main PCI cohort, would explain worse clinical outcomes. In contrast, it is well-known that anatomical feature such as SYNTAX score has little impact on outcome after CABG (7). The overall results of the current study suggest comparable long-term outcome between PCI and CABG after careful selection of patients with less complex coronary anatomy, but raise a concern for long-term durability of PCI, even with the use of DES, in those with highly complex coronary anatomy (18). Of note, SYNTAX score, which is a key element in guiding an optimal revascularization strategy in our contemporary practice (5-7), was not available at the time of the study and thus not reported in the current analysis. Its large cohort size and excellent long-term follow-up rate are the key strengths of the study. In addition, the nature of study being all-comer registry indicates high generalizability, although it comes with a concern for potential residual selection bias despite extensive statistical adjustments. As acknowledged by authors, frailty was not included in the adjustment method. In the nested registry cohort of SYNTAX trial, the patients who underwent PCI after deemed not a surgical candidate had a higher mortality than patients who underwent CABG after deemed not a PCI candidate (18.3% *vs.* 6.9% at 3-year) (19). The observed higher risk of death beyond 5 years in the DES cohort may still be due to residual or unmeasured confounding factors.

Prior landmark studies comparing PCI versus CABG

Prior landmark randomized controlled trials comparing percutaneous and surgical revascularization for LMCA disease are summarized in *Table 1*. Prior randomized controlled trials consistently demonstrated comparable survival between PCI cohort and CABG cohort at relatively short follow-up periods (7-9,14,16). A recent updated meta-analysis of randomized trials demonstrated comparable composite outcome (death, myocardial infarction, or stroke) at the longest follow-up (21). A few randomized studies have reported long-term follow-up beyond 10-year. The LE MANS trial randomized 105 patients with unprotected LMCA disease with low to intermediate SYNTAX score to either PCI (mainly BMS) or CABG. Although it showed comparable 10-year survival between the two revascularization strategies, obviously the study was not powered for hard endpoints such as death (20). More recently, preliminary 10-year follow-up data of the SYNTAX trial (72.3% follow-up of the original study cohort) was presented at the 2018 Transcatheter Cardiovascular Therapeutics annual conference. There was no significant difference at 10-year mortality between PCI and CABG cohorts (29.4% *vs.* 25.6%, P=0.11) in the overall cohort. In the subgroup of the patients with LMCA disease, 10-year morality was also comparable between PCI and CABG cohorts (29.7% *vs.* 31.9%, P=0.43). These lines of evidence from randomized data suggest a comparable long-term survival between percutaneous and surgical revascularization in selected patients amenable to both strategies.

A time lag inherent to long-term follow-up

The current study raised a concern about long-term durability of PCI with DES, however, one may argue that current second-generation or biodegradable polymer thin strut DES would lead to better outcomes. Indeed, first-generation sirolimus-eluting stent, in comparison to everolimus-eluting stent, resulted in higher incidences of ischemic events and mortality at 10-year follow-up at the ISAR-TEST 4 randomized trial (22). Long-term follow-up leads to an unavoidable time lag between the index procedure and the completion of long-term follow-up, resulting in significant differences between the practice at the time of the index procedure and the ever-evolving contemporary practice. This is particularly true in the field of rapidly evolving interventional cardiology. This time lag inherent to long follow-up period is an important shortcoming of long-term follow-up and it would be unrealistic to anticipate 10-year follow-up of "our contemporary practice". Assuming further sophistication in our skills and equipment, we will keep facing this dilemma of a time lag. Long-term follow-up data of the NOBLE and EXCEL trials are awaited, but will need to be interpreted in the context of the future advancements to be made during the follow-up period.

Future direction

The overall findings of the current study are in line with the large body of evidence and current guideline recommendation. PCI is a reasonable alternative to CABG in selected patients with unprotected LMCA disease with less complex coronary anatomy and comorbidities that predict adverse surgical outcomes (5-7). A comparable long-term survival can be achieved with PCI after careful selection of patients, although PCI carries a higher risk of subsequent revascularization. Perhaps a better selection of optimal revascularization strategy for each patient is clinically more important than the binary comparison between PCI versus CABG in overall cohort. The current guidelines endorse heart team approach (Class I) along with SYNTAX score calculation (Class IIa) (5-7). SYNTAX score II is another tool, which provides predicted 4-year mortality with PCI and CABG and also provides treatment recommendation as either PCI, CABG, or equipoise (23). SYNTAX II study demonstrated that the revascularization strategy incorporating heart team decision-making based on SYNTAX score II as well as "state of the art" revascularization resulted in better outcomes compared to the PCI cohort in the original SYNTAX trial (24). Patients' preference is another key factor that needs to be incorporated in decision making. Some patients may well accept the increased risk of future revascularization associated with PCI if both strategies provide similar long-term survival, and some others may value early recovery as important as long-term outcome.

In summary, the reported >10 years follow-up data provide valuable insights, but is definitely not the end of the story. More than 75% of the patients in the registry were alive beyond 10 years, and even longer follow-up is needed. Another key piece of the data is longer follow-up of the recent two large randomized clinical trials (8,9), which will further clarify the long-term durability of PCI using second-generation stents in comparison to CABG. Our

Table 1 Main characteristics and results of the referred randomized control trials (7-9,13-16,20)

Study	Enrollment period	Published year	Number of patients		Type of stent	Follow-up (year)	Primary endpoint	Main results of the referred randomized control trials							
								Mortality		MI		Stroke		Repeat revascularization	P value
			CABG cohort	PCI cohort				PCI *vs.* CABG	P value	PCI *vs.* CABG	P value	PCI *vs.* CABG	P value		
Boudriot *et al.* (14)	2003–2009	2011	101	100	Sirolimus-eluting stent	1 year	Death/MI/RR	2.0% *vs.* 5.0%	<0.001	3.0% *vs.* 3.0%	0.02	Not reported	–	14.0% *vs.* 5.9%	0.35
SYNTAX left main cohort (7,13)	2005–2007	2014	348	357	Paclitaxel-eluting stent	5 years	Death/MI/Stroke/RR	12.8% *vs.* 14.6%	0.53	8.2% *vs.* 4.8%	0.1	1.5% *vs.* 4.3%	0.03	26.7% *vs.* 15.5%	<0.01
PRECOMBAT (15,16)	2004–2009	2015	300	300	Sirolimus-eluting stent	5 years	Death/MI/Stroke/IDR	5.7% *vs.* 7.9%	0.32	2.0% *vs.* 1.7%	0.76	0.7% *vs.* 0.7%	0.99	13.0% *vs.* 7.3%	0.02
LE MANS (20)	2001–2004	2016	53	52	DES/BMS	10 years	Left ventricular ejection fraction	21.6% *vs.* 30.2%	0.41	8.7% *vs.* 10.4%	0.68	4.3% *vs.* 6.3%	0.58	26.1% *vs.* 31.3%	0.39
NOBLE (8)	2008–2015	2016	603	598	Sirolimus-/biolimus-eluting stent	3 years	Death/MI/Stroke/RR	11% *vs.* 9%	0.84	6.0% *vs.* 2.0%	0.004	5.0% *vs.* 2.0%	0.08	15.0% *vs.* 10.0%	0.03
EXCEL (9)	2010–2014	2016	957	948	Everolimus-eluting stent	3 years	Death/MI/Stroke	8.2% *vs.* 5.9%	0.11	8.0% *vs.* 8.3%	0.64	2.3% *vs.* 2.9%	0.37	12.9% *vs.* 7.6%	<0.001

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MI, myocardial infarction; RR, repeat revascularization; IDR, Ischemia driven revascularization; DES, drug-eluting stent; BMS, bare-metal stent.

never-ending endeavor to ascertain long-term outcomes of our rapidly evolving "contemporary" practice will go on.

Acknowledgements

None.

Footnote

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

References

1. Giannoglou GD, Antoniadis AP, Chatzizisis YS, et al. Prevalence of narrowing >or=50% of the left main coronary artery among 17,300 patients having coronary angiography. Am J Cardiol 2006;98:1202-5.
2. Smith SC Jr, Dove JT, Jacobs AK, et al. ACC/AHA guidelines of percutaneous coronary interventions (revision of the 1993 PTCA guidelines)--executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty). J Am Coll Cardiol 2001;37:2215-39.
3. Huang HW, Brent BN, Shaw RE. Trends in percutaneous versus surgical revascularization of unprotected left main coronary stenosis in the drug-eluting stent era: a report from the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). Catheter Cardiovasc Interv 2006;68:867-72.
4. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). Circulation 2006;113:e166-286.
5. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:e44-164.
6. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541-619.
7. Morice MC, Serruys PW, Kappetein AP, et al. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. Circulation 2014;129:2388-94.
8. Mäkikallio T, Holm NR, Lindsay M, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. Lancet 2016;388:2743-52.
9. Stone GW, Sabik JF, Serruys PW, et al. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. N Engl J Med 2016;375:2223-35.
10. Goldman S, Zadina K, Moritz T, et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. J Am Coll Cardiol 2004;44:2149-56.
11. Velazquez EJ, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med 2011;364:1607-16.
12. Velazquez EJ, Lee KL, Jones RH, et al. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. N Engl J Med 2016;374:1511-20.
13. 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;360:961-72.
14. Boudriot E, Thiele H, Walther T, et al. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. J Am Coll Cardiol 2011;57:538-45.
15. Park SJ, Kim YH, Park DW, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. N Engl J Med 2011;364:1718-27.
16. Ahn JM, Roh JH, Kim YH, et al. Randomized Trial of Stents Versus Bypass Surgery for Left Main Coronary Artery Disease: 5-Year Outcomes of the PRECOMBAT

Study. J Am Coll Cardiol 2015;65:2198-206.
17. van Domburg RT, Kappetein AP, Bogers AJ. The clinical outcome after coronary bypass surgery: a 30-year follow-up study. Eur Heart J 2009;30:453-8.
18. Park DW, Ahn JM, Yun SC, et al. 10-Year Outcomes of Stents Versus Coronary Artery Bypass Grafting for Left Main Coronary Artery Disease. J Am Coll Cardiol 2018;72:2813-22.
19. Head SJ, Holmes DR Jr, Mack MJ, et al. Risk profile and 3-year outcomes from the SYNTAX percutaneous coronary intervention and coronary artery bypass grafting nested registries. JACC Cardiovasc Interv 2012;5:618-25.
20. Buszman PE, Buszman PP, Banasiewicz-Szkróbka I, et al. Left Main Stenting in Comparison With Surgical Revascularization: 10-Year Outcomes of the (Left Main Coronary Artery Stenting) LE MANS Trial. JACC Cardiovasc Interv 2016;9:318-27.
21. Giacoppo D, Colleran R, Cassese S, et al. Percutaneous Coronary Intervention vs Coronary Artery Bypass Grafting in Patients With Left Main Coronary Artery Stenosis: A Systematic Review and Meta-analysis. JAMA Cardiol 2017;2:1079-88.
22. Kufner S, Joner M, Thannmeimer A, et al. Ten-year clinical outcomes from a trial of three limus-eluting stents with different polymer coatings in patients with coronary artery disease: results from the ISAR-TEST 4 randomised trial. Available online: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.118.038065
23. Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381:639-50.
24. Escaned J, Collet C, Ryan N, et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. Eur Heart J 2017;38:3124-34.

Cite this article as: Kobayashi A, Misumida N. Percutaneous coronary intervention in left main disease: 10-year follow-up. Ann Transl Med 2019;7(5):85. doi: 10.21037/atm.2019.01.05