Percutaneous coronary intervention for left main coronary artery disease

Intervencionismo percutáneo en la enfermedad del tronco común izquierdo

David A. Power MD[1], Anastasios Roumeliotis MD[1,2], Javed Suleman MD[1], George D. Dangas MD PhD[1]

ABSTRACT

Left main coronary artery (LMCA) is associated with significant morbidity and mortality, primarily related to the large amount of myocardium it subtends. The medical management of left mainstem disease has been associated with dismal outcomes approaching 50% mortality at 5 years. Coronary artery bypass graft (CABG) surgery historically emerged as the standard of care for the revascularization of LMCA disease. Recently, percutaneous coronary intervention (PCI) has been established as a alternative to CABG for LMCA disease. Advancements in stent design, implantation technique, and pharmacotherapy, have occurred over time. Large randomized controlled trials comparing CABG to PCI for LMCA disease have recently been published in various settings. There have been ongoing efforts to reconcile certain disparate trial results. Herein, we summarize the data behind LMCA revascularization and place the NOBLE and EXCEL trials in clinical context alongside current societal guidelines.

Keywords: *unprotected stenosis of left main coronary artery, complex lesions, SYNTAX score, multiple vessels, drug-eluting stents, stents.*

RESUMEN

La enfermedad de tronco de coronaria izquierda (TCI) se asocia a una mortalidad y morbilidad importantes, principalmente porque compromete una cantidad enorme de miocardio. El manejo médico de la enfermedad del TCI se asocia a resultados funestos con tasas de mortalidad del 50% al cabo de 5 años. Tradicionalmente, la cirugía de revascularización coronaria (CABG) ha sido su tratamiento estándar. Recientemente, la intervención coronaria percutánea (ICP) se ha establecido como una alternativa a la CABG para su tratamiento. El paso del tiempo ha traído consigo avances tanto en el diseño de los *stents*, como en las técnicas de implantación, así como en la farmacoterapia. Recientemente, se han publicado extensos ensayos clínicos controlados y aleatorizados comparando CABG frente a ICP para el tratamiento de la enfermedad del TCI en diferentes escenarios clínicos. En varias ocasiones se han intentado reconciliar resultados dispares procedentes de estos ensayos. En este artículo se resumen los datos que hay detrás de la revascularización del TCI y se ponen los ensayos NOBLE y EXCEL en contexto clínico dentro del marco establecido por las actuales guías de práctica clínica elaboradas por las diferentes sociedades médicas.

Palabras claves: *estenosis no protegida de tronco de coronaria izquierda, lesiones complejas, score de SYNTAX, múltiples vasos, stents liberadores de fármacos, stents.*

Revista Argentina de Cardioangiología Intervencionista 2022;13(1):12-15. https://doi.org/10.30567/RACI/202201/0012-0015

INTRODUCTION

The left main coronary artery (LMCA) supplies blood to approximately 75% of the total myocardium. While LMCA disease (LMCAD) accounts for less than 5% of lesions on routine coronary angiography, the large area of muscle subtended illustrates its significance as a target for revascularization[1]. Historically, coronary artery bypass graft surgery (CABG) was considered the gold standard therapy for LM stenosis. More recently, however, percutaneous coronary intervention (PCI) has been considered as a viable alternative treatment option for select patients[2].

Over the last decade, advances in stent technology, implantation technique, intravascular imaging and antiplatelet pharmacotherapy have helped PCI to emerge as an alternative for selected patients with LMCAD. To date, randomized trials directly comparing the two revascularization strategies have demonstrated non-inferiority of PCI in comparison to CABG with regards to major adverse cardiac and cerebrovascular events[2]. Furthermore, multiple observational registries have reported excellent short- and long-term outcomes in LMCAD patients treated with PCI[3]. Additional prospective registries throughout the 2010's revealed disparate results, prompting the initiation of multicenter randomized control trials to compare the two strategies.

THE FIRST GENERATION DES ERA

Early clinical trials for left main coronary artery diseaseinitially examined CABG versus PCI with predominantly 1st generation drug eluting stents (DES). Four of the most notable randomized trials of this era included SYNTAX, PRECOMBAT, Boudriot et al., and LEMANS[4-7]. The Synergy Between PCI with Taxus and Cardiac Surgery (SYNTAX) trial was a multicenter randomized control trial comparing CABG versus PCI in 1,800 patients for a composite MACCE (major adverse cardiac and cerebrovascular events) outcome of death, stroke, myocardial infarction (MI) or repeat revascularization. The PCI arm of SYNTAX notably utilized the now obsolete Paclitaxel DES. Analysis of the LMCAD subgroup (n=705) revealed no significant differences between PCI or CABG for either mortality (12.8% vs. 14.6%; p=0.53) or MACCE (36.9% vs. 31%, p=0.12) at 5-year follow up. Compared to PCI, CABG patients in SYNTAX hadsome what higher rates of stroke. Notably, CABG did provide a significant survival benefit in patients with extensive triple vessel coronary disease[6].

Building from the lessons of the SYNTAX trial, the Premier of Randomized Comparison of Bypass Surgery Ver-

1. The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York City, NY, 10029
2. Harvard Medical School, Mount Auburn Hospital Department of Medicine, 330 Mount Auburn Street, Cambridge, MA, 02138, USA

✉ Corresponding authors: *George D. Dangas MD, PhD. Zena and Michael A Wiener Cardiovascular Institute. Icahn School of Medicine at Mount Sinai. New York City, NY, 10029. United States. Tel: 212-241-7014. Fax: 212-241-0273.*

The authors declared no conflicts of interest whatsoever.

Received: 1/11/21 | Accepted: 08/11/21

sus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) study was a randomized control trial of 600 patients undergoing PCI or CABG for unprotected LMCAD in South Korea. Similar to SYNTAX, it was designed as a non-inferiority study with a primary MACCE endpoint. No differences in 1 year mortality (5.7% vs. 7.9%; p=0.32) or MACCE (17.5% vs. 14.3%; p=0.26) were detected between PCI versus CABG respectively[6].

Boudriot et al. examined 201 patients with LMCAD randomized to PCI or CABG for a primary MACE outcome of death, MI or repeat revascularization. The combined primary endpoint at 1-year follow-up for PCI versus CABG was 19% and 13.9% respectively (p=0.19)[4]. Finally, the Left Main Coronary Artery Stenting (LE MANS) trial enrolled a small number of patients (n=105) with unprotected LMCAD to either PCI or CABG with long term follow up. At 10 years, there were no differences in the secondary outcome of MACCE (death, myocardial infarction, target vessel revascularization or stroke) between revascularization strategies. The primary outcome of LE MANS was a difference in left ventricular ejection fraction and was neither statistically nor clinically significant[5].

Taken together, the relatively small number of patients with LMCAD included in individual randomized trials, generally short term follow-up time frame and the use of 1st generation DES necessitated other contemporary randomized trials to examine the role of PCI with 2nd generation DES versus CABG for LMCAD.

THE SECOND GENERATION DES ERA

The simultaneous publication of the EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and NOBLE (Nordic–Baltic–British left main revascularization trial) randomized trials in 2016 gave apparently discordant results to the topic of LM CAD revascularization with second generation drug-eluting stents (DES)[8,9]. Both trials had a non-inferiority design, attempting to demonstrate that PCI was not significantly worse than the control treatment, CABG.

In brief, the NOBLE trial was a prospective, randomized control trial carried out across 36 centers throughout Europe comparing PCI to CABG. The trial randomized 1,201 patients to either revascularization strategy (PCI, n=598; CABG, n=603) with a primary outcome of MACCE comprising all-cause mortality, stroke, non-procedural MI (peri-procedural MI was excluded) and repeat revascularization. The findings from NOBLE indicated that CABG was superior to PCI (MACCE 19% vs. 28%; HR=1.58; 95% CI: 1.24-2.01; p<0.01). There were no differences between CABG and PCI groups in terms of all-cause mortality (9% vs. 11%; 95% CI: 0.67-1.74; p=0.84)[8].

On the other hand, the EXCEL trial was a prospective, randomized, open label, non-inferiority trial of 1,905 patients undergoing either CABG or PCI with low or intermediate anatomical complexity. At an average of 3 years follow up, there was no significant difference between CABG and PCI in terms of the primary MACE outcome of cardiac death, stroke, MI or revascularization (14.7% vs. 15.4%; HR=1.00; 95% CI: 0.79-1.26; p=0.98 for superiority).There were no differences in all-cause-mortality at 3-years (5.9% vs. 8.2%; HR=1.34; 95% CI: 0.94-1.91; p=0.11)[9].

In order to reconcile these apparently contradicting trial results it is crucial to outline their major methodological differences. First, the EXCEL trial used the SCAI (Society of Cardiac Angiography and Intervention) definition forperiprocedural MI after both PCI and CABG, whereas NOBLE excluded all periprocedural MI events[10-11].

Secondly, while the NOBLE trial provides a direct comparison between CABG and PCI for the treatment of left main disease across a wide spectrum of angiographic complexity, the population included in the EXCEL trial had an overall intermediate-low anatomical complexity. It can be construed, therefore, that EXCEL may have a higher level of external generalizability given the current ESC and ACC/AHA guidelines that strongly recommend CABG for LMCAD revascularization amongst high SYNTAX populations and become more equivocal between revascularization strategies as SYNTAX scores are in the intermediate-low range[11].

Third, the stent platforms used in the two trials were different. Biolimus-eluting biodegradable stents were used exclusively in the NOBLE trial while fluoropolymer-based cobalt-chromium Everolimus eluting stents were used in the EXCEL trial. Inherent device differences may exist between stent platforms.

Finally, the primary end points were different between the two trials. The primary endpoint of NOBLE was MACCE (death, MI, stroke and repeat revascularizations), while in EXCEL, repeat revascularization was not included in the composite endpoint (death, MI and stroke). Hence, the use of different stents, MI definitions, primary outcome differences and anatomical complexity accounts for the observed differences; otherwise results are actually quite concordant.

SYNTAX AND ANATOMICAL COMPLEXITY

The 5-year follow up of both NOBLE and EXCEL confirmed the previous findings for both studies(12,13). Looking to the long term data from another notable revascularization trial, Park *et al.,*revealed the 10-year follow up of the PRECOMBAT cohorts, finding no significant difference in the primary outcome of MACCE (composite of death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization)[14]. The landmark SYNTAX Extended-Survival Study also demonstrated no difference in overall all-cause mortality between PCI and CABG in patients with LM disease not accompanied by multivessel disease. With the exception of the NOBLE trial, all previous studies have shown a significant association between cardiovascular death and the extent of multivessel disease (typically measured using the SNYTAX score). The EXCEL trial 5 year follow up study showed a mortality benefit in favor of CABG over PCI (9.9% vs. 13.0%; HR=1.38; 95% CI: 1.03-1.85), mostly of non-cardiovascular origin.

As a result of the afore mentioned data, it appears that the advantage of CABG in LM coronary revascularization perhaps relates more to the presence of triple vessel disease or comorbidities such as diabetes, rather than the pure presence of LMCAD. Furthermore, a meta-analysis of six randomized trials examining PCI and CABG from over 4,500 patients demonstrated a lower relative risk of mortality with PCI in low SYNTAX score, equivocal results between both strategies for intermediate SYNTAX scores and lower risk of mortality with CABG in high SYNTAX scores[15].

	LEMANS[5]	SYNTAX (Left Main Study)[6]	Boudriot et al.[4]	PRECOMBAT[7]	NOBLE[8]	EXCEL[9]
Publication year	2007	2010	2011	2011	2016	2016
Study design	RCT	RCT sub-analysis (pre-specified)	RCT	RCT	RCT	RCT
Number of patients	105	705	201	600	1201	1905
Length of follow up	2 years	1 year	1 year	1 year	5 years	3 years
Stent generation	1st Gen DES & BMS	1st Gen DES	1st Gen DES	1st Gen DES	2nd Gen DES	2nd Gen DES
Diabetes % (PCI/CABG)	19%/17%	28%/30%	40%/33%	34%/30%	15%/15%	30%/28%
Outcome of interest *(components)*	MACCE: *CV death, MI, stroke, repeat revascularization, ISR*	MACCE: *Death, stroke, MI, repeat re-vascularization*	MACE: *CV death, MI, TVR*	MACCE: *Death, MI, stroke, TVR*	MACCE: *Death, MI, stroke, repeat revascularization*	MACCE: *Death, Stroke, MI*
Results	PCI non-inferior to CABG	PCI non-inferior to CABG (non-randomized)	PCI inferior to CABG	PCI non-inferior to CABG	PCI inferior to CABG	PCI non-inferior to CABG
Methodological issues	Secondary endpoint	Pre-specified sub-analysis	CABG superiority driven by repeat re-vascularization;	Wide non-inferiority margins	Outcome driven by MI and repeat revascularization	Impact of periprocedural MI on early outcomes

BMS: bare metal stent. CABG: coronary artery bypass graft surgery. CV: cardiovascular. DES: drug eluting stent. MACCE: major adverse cardiac and cerebrovascular events. MACE: major adverse cardiac events, MI: myocardial Infarction, PCI: percutaenous coronary intervention, RCT: randomized controlled t rial, TVR: target vessel revascularization.

The most recent European Society of Cardiology guideline recommendations on the optimal treatment approach to LMCA disease were published in 2018 and were primarily based on the secondary analyses of the SYNTAX trial and the early results of the EXCEL trial. The most recent update from the European Society of Cardiology recommends CABG in all patients with stable LMCAD and low predicted surgical mortality (Class 1, LOE B). In LMCAD patients with low anatomical complexity (SYNTAX score: 0-22) PCI was indicated with a high level recommendation (IA) while in those with an intermediate score (SYNTAX score: 23-32) PCI should be considered as a treatment option (IIA, LOE B). PCI was not recommended (IIIB, LOE B) in cases with high SYNTAX score >32[16-17].

The recommendations for PCI for LMCA disease across SYNTAX score tertiles from the 2014 American College of Cardiology/American Heart Association focused update for the diagnosis and management of patients with stable ischemic heart disease are currently Class IIa if SYNTAX score is low, Class IIb if SYNTAX score is intermediate, and Class III if SYNTAX score is high[18]. Overall, isolated LM disease, or LM disease in combination with lesions of lower complexity can be safely and successfully treated via PCI.

LEFT MAIN LESION LOCATION AND STENT IMPLANTATION TECHNIQUE

In addition to factors such as anatomical complexity, ventricular reserve and comorbid diabetes that have been well described, much attention should focus on lesion location and stenting technique. Distal lesions of the LM bifurcation treated with PCI have been associated with inferior cardiovascular outcomes compared to ostial and body disease.This probably reflects the higher lesion complexity and unique technical difficulties encountered during interventions on the distal segment of the LM coronary artery.

A secondary analysis from the 3-year follow up of the EXCEL trial examined the comparative efficacy of PCI and CABG according to the location of the LM lesion. While no differences between PCI or CABG were reported for lesions in the ostium or the shaft, patients in the PCI arm with a distal LM lesion experienced a higher incidence of ischemia-driven revascularization (13.0% vs. 7.2%; p=0.0001). In a post-hoc analysis of the EXCEL trial, PCI with a 1-stent provisional stenting (PS) technique was associated with lower rates of the composite endpoint of death, MI or stroke at 3-years as compared to a 2-stent approach (14.1% versus 20.7%; adjusted HR=0.55; 95% CI: 0.35-0.88; p=0.01). These results were primarily driven by decreased rates of ischemia-driven revascularization in the PS group compared to the 2-stent group (7.2% vs. 16.3%; p=0.001)[19]. Despite the afore mentioned post-hoc analyses, the benefit of PS in ULMD has recently been questioned in the DKCRUSH-V (Double Kissing Crush versus Provisional Stenting for Left Main Distal Bifurcation Lesions) randomized trial.

DK-CRUSH-V randomized patients with ULMD to either a 2 stent DK-CRUSH technique or PS. At one year follow up, the DK crush strategy resulted in reduced rates of target lesion failure compared to a PS strategy (10.7% vs. 5.0%; HR=0.42; 95% CI: 0.21-0.85; p=0.02), although the study was under-powered to assess hard outcomes. Several 2-stent techniques are currently available to treat bifurcation lesions, but how these techniques compare with one another is still debated[20].

The DKCRUSH-III (Comparison of double kissing crush versus Culotte stenting for unprotected distal left main bifurcation lesions) trial compared the 2-stent DK-CRUSH technique to a 2-stent Culotte technique for LM bifurcation lesions. Patients treated with a Culotte technique had significant higher 1-year MACE rate compared to DK-CRUSH group (16.3% vs. 6.2%), mainly driven by increased TVR[21]. These results clearly indicate that not all 2-stent strategies are equal, however the choice of 2-stent vs. 1-stent technique remains unclear[22].

The European Society of Cardiology (ESC) has reflected these results in its recent recommendations advocating for the DK-Crush technique to be preferred over provisional T stenting (Class IIb, LOE B)[16]. However, the unique multi-step methodology employed for the DK-CRUSH-V trial may limit its broader adaptation in clinical practice.

CONCLUSION

Left main CAD represents an important and demonstrably complex target for revascularization. PCI appears to be a safe and feasible alternative to CABG as demonstrated by the non-inferiority of major trials according to hard outcomes for select patient populations. Importantly, low anatomical complexity as defined by SYNTAX scores is perhaps the most critical element in favor of PCI for LM disease. Rather than dogmatically applying one-stent (provisional) or

two-stent techniques to left main disease, either technique can be pragmatically employed according to specific anatomical settings.

On the other hand, patients with high anatomical complexity as defined according to the SYNTAX score are better served with CABG. As PCI techniques and stent platforms develop further to improve patient care, randomized controlled trials comparing PCI versus CABG will continue to suffer from an inevitable lag time bias. Clinical research will continue to be necessary in order to delineate the role for LM PCI in patient subsets with co-morbid diabetes, reduced left ventricular function and other conditions

REFERENCES

1. *Collet C, Capodanno D, Onuma Y, et al. Left main coronary artery disease: pathophysiology, diagnosis, and treatment. Nature Reviews Cardiology 2018;15:321-331.*
2. *Ramadan R, Boden WE, Kinlay S. Management of Left Main Coronary Artery Disease. Journal of the American Heart Association;7:e008151.*
3. *Chieffo A, Tanaka A, Giustino G, et al. The DELTA 2 Registry: A Multicenter Registry Evaluating Percutaneous Coronary Intervention With New-Generation Drug-Eluting Stents in Patients With Obstructive Left Main Coronary Artery Disease. JACC Cardiovasc Interv 2017;10:2401-2410.*
4. *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.*
5. *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;9:318-327.*
6. *Park S-J, Kim Y-H, Park D-W, et al. Randomized Trial of Stents versus Bypass Surgery for Left Main Coronary Artery Disease. New England Journal of Medicine 2011;364:1718-1727.*
7. *Serruys PW, Morice M-C, Kappetein AP, et al. Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease. New England Journal of Medicine 2009;360:961-972.*
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. The Lancet 2016;388:2743-2752.*
9. *Stone GW, Sabik JF, Serruys PW, et al. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. New England Journal of Medicine 2016;375:2223-2235.*
10. *Ruel M, Farkouh ME. Why NOBLE and EXCEL Are Consistent With Each Other and With Previous Trials. Circulation 2017;135:822-824.*
11. *Stankovic G, Milasinovic D. EXCELling in Left Main Intervention. Circulation: Cardiovascular Interventions 2018;11:e007363.*
12. *Holm NR, Mäkikallio T, Lindsay MM, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: updated 5-year outcomes from the randomised, non-inferiority NOBLE trial. The Lancet 2020;395:191-199.*
13. *Stone GW, Kappetein AP, Sabik JF, et al. Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease. New England Journal of Medicine 2019;381:1820-1830.*
14. *Park D-W, Ahn J-M, Park H et al. Ten-Year Outcomes After Drug-Eluting Stents Versus Coronary Artery Bypass Grafting for Left Main Coronary Disease. Circulation 2020;141:1437-1446.*
15. *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 Cardiology 2017;2:1079-1088.*
16. *Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal 2020;41:407-477.*
17. *Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949-3003.*
18. *Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease. Circulation 2014;130:1749-1767.*
19. *Kandzari DE, Gershlick AH, Serruys PW, et al. Outcomes Among Patients Undergoing Distal Left Main Percutaneous Coronary Intervention. Circulation: Cardiovascular Interventions 2018;11:e007007.*
20. *Chen X, Li X, Zhang JJ et al. 3-Year Outcomes of the DKCRUSH-V Trial Comparing DK Crush With Provisional Stenting for Left Main Bifurcation Lesions. JACC Cardiovasc Interv 2019;12:1927-1937.*
21. *Chen SL, Xu B, Han YL, et al. Clinical Outcome After DK Crush Versus Culotte Stenting of Distal Left Main Bifurcation Lesions: The 3-Year Follow-Up Results of the DKCRUSH-III Study. JACC Cardiovasc Interv 2015;8:1335-1342.*
22. *Power D, Roumeliotis A, Reisman A, et al. TCT CONNECT-305 Impact of Lesion Location on Cardiovascular Outcomes of Patients Undergoing Percutaneous Coronary Intervention With Drug-Eluting Stents for Unprotected Left Main Coronary Artery Stenosis. Journal of the American College of Cardiology 2020;76:B131-B132.*