Revista Portuguesa de Cardiologia 41 (2022) 953–968

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

REVIEW ARTICLE

Percutaneous coronary intervention versus coronary artery bypass grafting in left main coronary artery disease: A review☆

Manuel Neto Martins

Faculdade de Medicina, Universidade do Porto, Porto, Portugal

Received 2 April 2021; accepted 1 June 2021
Available online 22 July 2022

KEYWORDS
Percutaneous coronary intervention;
Coronary artery bypass grafting;
Left main coronary artery disease

Abstract The left main coronary artery is responsible for most of the irrigation of the left ventricle. Left main coronary artery disease (LMCAD) therefore leads to important morbidity and mortality. Coronary artery bypass grafting (CABG) is considered the standard treatment, however, percutaneous coronary intervention (PCI) has become a frequent alternative in the treatment of LMCAD. In the current review, four randomized clinical trials comparing PCI with CABG in patients with LMCAD, including new longer follow-up results, are reviewed. Major adverse cardiac and cerebrovascular event rates were similar between the two intervention groups in both the SYNTAX and PRECOMBAT trials, and favored the CABG group in the EXCEL and NOBLE trials. The composite of death, stroke and myocardial infarction was similar in all trials. Mortality rates were similar across all trials except for the EXCEL trial at five years, which favored CABG. Cardiac mortality was similar in all trials. Stroke rates were similar, apart from the SYNTAX trial, which favored PCI. CABG was more favorable concerning myocardial infarction in the NOBLE trial, but not in the other trials. Repeat revascularization was generally less frequent in the CABG group. Stent thrombosis and graft occlusion were less frequent with PCI in the EXCEL trial, with no differences in the other trials. Based on the overall similarity in the primary endpoint rates, as well as favorable short-term outcomes, it is plausible to state that PCI can be considered a good alternative to CABG, although the higher risk of repeat revascularization should be taken into consideration.
© 2022 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

☆ This article has two Editorial Comments that reflect the importance of the topic. They are published following the alphabetical order of their authors.

E-mail address: manelnetomartins@gmail.com

https://doi.org/10.1016/j.repc.2021.06.026
0870-2551/© 2022 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

PALAVRAS-CHAVE
Intervenção coronária percutânea;
Cirurgia de revascularização do miocárdio;
Doença de tronco comum

Intervenção coronária percutânea *versus* cirurgia de revascularização do miocárdio na doença de tronco comum: uma revisão

Resumo O tronco comum é responsável pela maior parte da irrigação do ventrículo esquerdo. Assim, a doença do tronco comum leva a morbilidade e mortalidade importantes. A cirurgia de revascularização do miocárdio (CABG) tem sido o tratamento padrão, contudo, a intervenção coronária percutânea (ICP) tem-se tornado uma alternativa frequente no tratamento da doença de tronco comum. Nesta revisão, quatro ensaios clínicos randomizados comparando a ICP com CABG em pacientes com doença de tronco comum foram revistos. As taxas de MACCE foram semelhantes entre os dois grupos de intervenção em ambos os ensaios SYNTAX e PRECOMBAT, e favoreceram o grupo de CABG nos ensaios EXCEL e NOBLE. O *outcome* combinado de morte, AVC e enfarte do miocárdio foi semelhante em todos os ensaios. As taxas de mortalidade foram semelhantes em todos os ensaios, exceto no EXCEL aos cinco anos, que favoreceu a CABG. Morte cardíaca, no entanto, foi semelhante em todos os ensaios. As taxas de AVC foram semelhantes, exceto no ensaio SYNTAX, que favoreceu a ICP. CABG foi mais favorável em relação ao enfarte do miocárdio no ensaio NOBLE, mas não nos restantes ensaios. A repetição da revascularização foi globalmente menos frequente no grupo CABG. As taxas de trombose do *stent* ou oclusão do enxerto foram menos frequentes com ICP no ensaio EXCEL, sem diferenças nos restantes ensaios. Com base na semelhança global dos *outcomes* primários, assim como os resultados favoráveis a curto prazo, é plausível concordar que a ICP pode ser considerada uma boa alternativa à CABG, embora o risco mais alto de repetição de revascularização deve ser tido em consideração.
© 2022 Sociedade Portuguesa de Cardiologia. Publicado por Elsevier España, S.L.U. Este é um artigo Open Access sob uma licença CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Due to its irrigation territory, obstruction of the left main (LM) coronary artery compromises blood flow to the left ventricle, leading to symptoms in most patients and a high risk of cardiovascular events.[1] Based on its clinical significance, optimization of treatment is of major importance for these patients.

Since the early clinical trials, CABG has been regarded as the standard of treatment for patients with left main coronary artery disease (LMCAD), with the randomized Veterans Affairs Cooperative Study showing evidence of the superiority of CABG in survival rate over traditional medical therapy for LMCAD,[2] supported by the 15-year median survival of the Coronary Artery Surgery Study (CASS) registry, which showed significant superiority in the CABG group versus the medical therapy group in the subgroup of patients with LMCAD.[3]

Contemporary guidelines recommend that LMCAD should be stratified based on anatomical complexity using the SYNTAX score. Those with low SYNTAX scores (<22) have the same class of recommendation for PCI or CABG (class I). For intermediate SYNTAX scores (23-32), CABG is the preferred option (class I) with PCI going down one level of recommendation (IIa), while patients with high SYNTAX scores (≥33) should be treated with CABG (class I) rather than PCI (class III).[4] CABG is therefore considered the standard treatment for LMCAD, with PCI being considered a good alternative in those with low or intermediate anatomical complexity.[4,5]

However, information from clinical trials does not always lead to a consensus, and there are now results of long-term follow-up (five or even 10 years) from trials that have not yet been considered for the updated guidelines. The aim of the present review is to identify the best intervention for patients with LMCAD with the most up-to-date treatment options available.

The current report was not funded by any interested party, either governmental or industry, and the decision to carry out this review was taken exclusively by the author.

Methods

The research was conducted using the PubMed database. The following query was used: ''Left Main Coronary Artery Disease'' AND ''Percutaneous Coronary Intervention''. Based on the results, the aim was to find randomized clinical trials that compared percutaneous coronary intervention (PCI) with the standard of treatment, CABG, in patients with LMCAD. Four clinical trials were chosen based on their follow-up duration and clinical importance: SYNTAX,[6–9] EXCEL,[10,11] NOBLE[12,13] and PRECOMBAT.[14–16]

Main randomized clinical trials comparing percutaneous coronary intervention with drug-eluting stents versus coronary artery bypass grafting

The individual trial results are summarized in Tables 1-10 and a general overview is presented in Tables 11 and 12.

SYNTAX trial (2009): 12-month results, left main coronary artery disease subgroup

In the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial, a

Table 1 Some major results of the SYNTAX trial in the subgroup of left main coronary artery disease, at 12 months.

Endpoints	PCI (n=357)	CABG (n=348)	p
Primary endpoint	15.8 (56/355)	13.7 (46/336)	0.44
MACCE[a]			
SYNTAX score ≤22	7.7	13.0	0.19
			p for interaction
SYNTAX score 23-32	12.6	15.5	0.54
			0.03
SYNTAX score ≥33	25.3	12.9	0.008
Death, stroke or myocardial infarction	7.0 (25/355)	9.2 (31/336)	0.29
Death from any cause	4.2	4.4	0.88
Cardiac death	3.9	2.4	0.24
Stroke	0.3	2.7	0.009
Myocardial infarction	4.3	4.1	0.97
Repeat revascularization	11.8 (42/335)	6.5 (22/336)	0.02

Data are % (n). Adapted from [6,7].
CI: confidence interval; CABG: coronary artery bypass graft surgery; MACCE: major adverse cardiac and cerebrovascular events; PCI: percutaneous coronary intervention.
[a] Composite of death from any cause, stroke, myocardial infarction and repeat revascularization.

prospective, multicenter, multinational, randomized clinical trial with an all-comer design, 1800 patients with three-vessel disease or LMCAD (or both) who were suitable for both CABG and PCI (assessed by a local cardiologist and a cardiac surgeon at each site), were randomized to undergo either CABG (n=897) or PCI with paclitaxel-eluting stents (n=903).[6]

The primary analysis was a non-inferiority comparison of PCI versus CABG based on the rates of the primary endpoint of major adverse cardiac and cerebrovascular events (MACCE), a composite of death from any cause, stroke, myocardial infarction (MI) and repeat revascularization, at 12 months after randomization. Secondary endpoints were the individual components of MACCE at 12 months.

From the beginning, patients were stratified according to the presence of LMCAD. This subgroup had a good statistical power. Nevertheless, because the main statistical test in the study was non-inferiority of PCI versus CABG, which was not proven, analysis of subgroups can only be hypothesis-generating.

Of the 1800 patients in the SYNTAX trial, 705 patients were prespecified to have LMCAD. Of these, 357 were treated with PCI and 348 with CABG.[7]

The 12-month rates of the MACCE primary endpoint were similar between the two groups (15.8% in the PCI group vs. 13.7% in the CABG group; p=0.44). SYNTAX score was associated with significant differences in MACCE rates (p for interaction=0.03). Low (≤22; 7.7% in the PCI group vs. 13.0% in the CABG group; p=0.19) and intermediate (23-32; 12.6% in the PCI group vs. 15.5% in the CABG group; p=0.54) SYNTAX scores had similar MACCE rates between the two compared interventions. High SYNTAX scores had higher MACCE rates in the PCI group (≥33; 25.3% vs. 12.9% in the CABG group; p=0.008).

The rate of repeat revascularization was higher in the PCI group than in the CABG group (11.8% and 6.5%, respectively; p=0.02) and stroke rates were lower in the PCI group (0.3% vs. 2.7% in the CABG group; p=0.009). No other significant differences were found among the other endpoints. Some of the main results are shown in Table 1.

SYNTAX trial (2014): five-year results, left main coronary artery disease subgroup

As with the 12-month analysis, the LMCAD subgroup (n=705) was also analyzed separately at five years; 96.9% of patients in the PCI arm and 92.5% of the CABG arm were followed for the five-year period.[8]

Primary endpoint MACCE rates at five years remained similar in both groups (36.9% in the PCI group vs. 31.0% in the CABG group; hazard ratio [HR]=1.23, 95% confidence interval [CI] 0.95-1.59, p=0.12). Rates of MACCE in patients of the two lower SYNTAX score tertiles (0-32) were similar in both PCI and CABG groups (31.3% vs. 32.1%, respectively; HR=0.94, 95% CI 0.67-1.33, p=0.74) but were significantly higher in the PCI group for high SYNTAX scores (≥33; 46.5% vs. 29.7% in the CABG group; HR=1.78, 95% CI 1.21-2.63, p=0.003). Stroke rates continued to be higher in the CABG group (4.3% vs. 1.5% in the PCI group; HR=0.33, 95% CI 0.12-0.92, p=0.03) and repeat revascularization remained higher in the PCI group (26.7% vs. 15.5% in the CABG group; HR=1.82, 95% CI 1.28-2.57, p<0.001). No other significant differences were found among the other endpoints. Some of the main results are shown in Table 2.

SYNTAXES study (2019): 10-year results, left main coronary artery disease subgroup

In the SYNTAX Extended Survival (SYNTAXES) study, the population from the SYNTAX trial was assessed up to 10 years.[9] The primary endpoint was all-cause death at 10 years and the secondary endpoint was all-cause death at maximum available follow-up. A total of 705 patients in the LMCAD subgroup were analyzed.

All-cause death rates at 10 years showed no differences between the two groups (27% in the PCI group vs. 28% in the CABG group; HR=0.92, 95% CI 0.69-1.22). There was no association between SYNTAX score and the 10-year primary endpoint (SYNTAX scores ≤22: HR=1.08, 95% CI 0.62-1.89; scores 23-32: HR=0.66, 95% CI 0.37-1.17; scores ≥33: HR=1.14, 95% CI 0.76-1.71). All-cause death at maximum follow-up also had similar results for both interventions

Table 2 Some major results of the SYNTAX trial in the subgroup of left main coronary artery disease, at five years.

Endpoints	PCI (n=357)	CABG (n=348)	HR (95% CI)	p
Primary endpoint	36.9 (130)	31.0 (103)	1.23 (0.95-1.59)	0.12
MACCE[a]				
SYNTAX score 0-32	31.3 (68)	32.1 (60)	0.94 (0.67-1.33)	0.74
YNTAX score ≥33	46.5 (62)	29.7 (43)	1.78 (1.21-2.63)	0.003
Death, stroke or myocardial infarction	19.0 (67)	20.8(69)	0.91 (0.65-1.27)	0.57
Death from any cause	12.8 (45)	14.6 (48)	0.88 (0.58-1.32)	0.53
Cardiac death	8.6 (30)	7.2 (23)	1.23 (0.71-2.11)	0.46
Stroke	1.5 (5)	4.3 (14)	0.33 (0.12-0.92)	0.03
Myocardial infarction	8.2 (28)	4.8 (16)	1.67 (0.91-3.10)	0.10
Repeat revascularization	26.7 (90)	15.5 (49)	1.82 (1.28-2.57)	<0.001
Stent thrombosis or graft occlusion	5.1 (17)	4.4 (14)	1.15 (0.57-2.33)	0.70

Data are % (n). Adapted from [8].
CI: confidence interval; CABG: coronary artery bypass graft surgery; HR: hazard ratio; MACCE: major adverse cardiac and cerebrovascular events; PCI: percutaneous coronary intervention.
[a] Composite of death from any cause, stroke, myocardial infarction and repeat revascularization.

Table 3 Some major results of the SYNTAXES study in the subgroup of left main coronary artery disease, at 10 years.

Endpoints	PCI (n=357)	CABG (n=348)	HR (95% CI)
Primary endpoint	27 (95)	28 (98)	0.92 (0.69-1.22)
SYNTAX score ≤22	-	-	1.08 (0.62-1.89)
SYNTAX score 23-32	-	-	0.66 (0.37-1.17)
SYNTAX score ≥33	-	-	1.14 (0.76-1.71)
All-cause death at maximum follow-up	-	-	0.97 (0.75-1.25)

Data are % (n). Adapted from [9].
CI: confidence interval; CABG: coronary artery bypass graft surgery; HR: hazard ratio; PCI: percutaneous coronary intervention.

(HR=0.97, 95% CI 0.75-1.25). Some of the main results are shown in Table 3.

EXCEL trial (2016): three-year results

The Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial is a randomized, open-label, multicenter, international trial that compared PCI using everolimus-eluting stents with CABG. A total of 1905 patients with LMCAD, eligible for either PCI or CABG as assessed by a heart team, were randomized into two treatment groups, PCI (n=948) and CABG (n=957). Exclusion criteria included SYNTAX score ≥33 (determined by the heart team).[10]

The trial's objective was to analyze the non-inferiority of PCI over CABG regarding the primary endpoint, a composite of death from any cause, stroke or MI at three years. Secondary end-points were defined as the primary endpoint at 30 days; a composite of death from any cause, stroke, MI or ischemia-driven revascularization at three years; and the components of the primary endpoint at three years. Additional endpoints can be seen in Table 4..

Primary endpoint rates at three years were similar between the two groups (15.4% in the PCI group vs. 14.7% in the CABG group; HR=1.00, 95% CI 0.79-1.26, p=0.98), in contrast to the results at 30 days, which showed that PCI had an advantage regarding the same composite (4.9% vs. 7.9% in the CABG group; HR=0.61, 95% CI 0.42-0.88, p=0.008). The results at three years according to a subgroup analysis for SYNTAX scores maintained the similarity between the two treatment groups for both SYNTAX scores ≤22 (14.3% in the PCI group vs. 14.4% in the CABG group; HR=0.95, 95% CI 0.70-1.31) and SYNTAX scores 23-32 (17.0% in the PCI group vs. 15.4% in the CABG group; HR=1.05, 95% CI 0.73-1.51). Thus, there was no significant interaction between the primary endpoint and SYNTAX score (p for interaction=0.70).

Endpoints at 30 days were as follows: MI rates were higher in the CABG group (6.2% vs. 3.9% in the PCI group; HR=0.63, 95% CI 0.42-0.95, p=0.02), as were rates of the composite of death, stroke, MI or ischemia-driven revascularization in the same group, which occurred in 8.4% of these patients and in 4.9% of the PCI group (HR=0.57, 95% CI 0.40-0.82, p=0.002). Furthermore, rates of blood transfusion (3.2% in the PCI group vs. 12.7% in the CABG group; HR=0.24, 95% CI 0.16-0.36, p<0.001), bleeding (7.3% in the PCI group vs. 13.0% in the CABG group; HR=0.55, 95% CI 0.41-0.74, p<0.001) and definite stent thrombosis or symptomatic graft occlusion (0.3% in the PCI group vs. 1.2% in the CABG group; HR=0.27, 95% CI 0.08-0.97, p=0.03) were significantly higher in the CABG group.

At three years, secondary endpoint rates showed significant differences only in terms of ischemia-driven revascularization, which were higher in the PCI group with 12.6% of patients undergoing repeat revascularization in this group (vs. 7.5% in the CABG group; HR=1.72, 95% CI 1.27-2.33, p<0.001), and definite stent thrombosis or symptomatic graft occlusion, which favored PCI (0.7% in the PCI

Table 4 Some major results of the EXCEL trial at 30 days and at three years.

Endpoints	PCI (n=948)	CABG (n=957)	HR (95% CI)	p	p for non-inferiority
Endpoints at 30 days					
Primary endpoint					
Death, stroke or myocardial infarction	4.9 (46)	7.9 (75)	0.61 (0.42-0.88)	0.008	<0.001
MACCE[a]	4.9 (46)	8.4 (80)	0.57 (0.40-0.82)	0.002	-
Death	1.0 (9)	1.1 (10)	0.90 (0.37-2.22)	0.82	-
Stroke	0.6 (6)	1.3 (12)	0.50 (0.19-1.33)	0.15	-
Myocardial infarction	3.9 (37)	6.2 (59)	0.63 (0.42-0.95)	0.02	-
Ischemia-driven revascularization	0.6 (6)	1.4 (13)	0.46 (0.18-1.21)	0.11	-
Definite stent thrombosis or symptomatic graft occlusion	0.3 (3)	1.2 (11)	0.27 (0.08-0.97)	0.03	-
Bleeding	7.3 (69)	13.0 (123)	0.55 (0.41-0.74)	<0.001	-
Blood transfusion	3.2 (30)	12.7 (120)	0.24 (0.16-0.36)	<0.001	-
Endpoints at 3 years					
Primary endpoint					
Death, stroke or myocardial infarction	15.4 (137)	14.7 (135)	1.00 (0.79-1.26)	0.98	0.02
SYNTAX score ≤22	14.3 (75/560)	14.4 (81/590)	0.95 (0.70-1.31)	p for interaction	-
SYNTAX score 23-32	17.0 (62/386)	15.4 (54/365)	1.05 (0.73-1.51)	0.70	-
MACCE[a]	23.1 (208)	19.1 (174)	1.18 (0.97-1.45)	0.10	0.01
Death from any cause	8.2 (71)	5.9 (53)	1.34 (0.94-1.91)	0.11	-
Cardiac death	4.4 (39)	3.7 (33)	1.18 (0.74-1.87)	0.48	-
Stroke	2.3 (20)	2.9 (26)	0.77 (0.43-1.37)	0.37	-
Myocardial infarction	8.0 (72)	8.3 (77)	0.93 (0.67-1.28)	0.64	-
Ischemia-driven revascularization	12.6 (112)	7.5 (66)	1.72 (1.27-2.33)	<0.001	-
Ischemia-driven target-lesion revascularization	9.5 (84)	6.9 (60)	1.40 (1.00-1.95)	0.05	-
Definite stent thrombosis or symptomatic graft occlusion	0.7 (6)	5.4 (48)	0.12 (0.05-0.28)	<0.001	-

Data are % (n). Adapted from [10].
CI: confidence interval; CABG: coronary artery bypass graft surgery; HR: hazard ratio; MACce: major adverse cardiac and cerebrovascular events; PCI: percutaneous coronary intervention.
[a] Composite of death from any cause, stroke, myocardial infarction and ischemia-driven revascularization.

group vs. 5.4% in the CABG group; HR=0.12, 95% CI 0.05-0.28, p<0.001).

In the specific non-inferiority analysis, three composites were tested and all three proved to be significant for non-inferiority: composite of death, stroke or MI at three years (p for non-inferiority=0.02), death, stroke or MI at 30 days (p for non-inferiority <0.001) and death, stroke, MI or ischemia-driven revascularization at three years (p for non-inferiority=0.01). Some of the main results are shown in Table 4.

EXCEL trial (2019): five-year results

The EXCEL trial was powered to show non-inferiority of PCI to CABG with respect to the primary endpoint at three years, nonetheless, secondary outcomes at five years were prespecified. Of the initial 1905 patients, 93.2% in the PCI group and 90.1% in the CABG group achieved five-year follow-up.[11]

Rates of the primary composite of death, stroke or MI in the PCI group continued to present no statistical differences compared with the CABG group at five years (22.0% vs. 19.2%, respecti vely; OR=1.19, 95% CI 0.95-1.50, p=0.13). These results were not consistent throughout the five-year period, as seen in the landmark analysis, in which PCI had fewer primary outcome events in the first 30 days (4.9%% vs. 8.0% in the CABG group; HR=0.61, 95% CI 0.42-0.88); from 30 days to one year these events occurred similarly in the two groups (4.1% in the PCI group vs. 3.8% in the CABG group; HR=1.07, 95% CI 0.68-1.70). On the other hand, in the period from one to five years the CABG group had lower rates of this composite (9.7% vs. 15.1% in the PCI group; HR=1.61, 95% CI 1.23-2.12). For both SYNTAX scores ≤22 (21.9% in the PCI group vs. 18.7% in the CABG group; OR=1.21, 95% CI 0.90-1.62) and 23-32 (22.2% in the PCI group vs. 20.0% in the CABG group; OR=1.16, 95% CI 0.81-1.67) the results were also similar between the two treatment groups.

With regard to the secondary endpoints, the composite of death, stroke, MI or ischemia-driven revascularization occurred more frequently in the PCI group than in the CABG

Table 5 Some major results of the EXCEL trial at five years.

Endpoints	PCI (n=948)	CABG (n=957)	95% CI	p
Primary endpoint				
Death, stroke or myocardial infarction	22.0 (203)	19.2 (176)	1.19 (0.95-1.50)	0.13
SYNTAX score ≤22	21.9 (119/560)	18.7 (106/588)	1.21 (0.90-1.62)	-
SYNTAX score 23-32	22.2 (84/386)	20.0 (70/366)	1.16 (0.81-1.67)	-
MACCE[a]	31.3 (290)	24.9 (228)	1.39 (1.13-1.71)	0.002
Death from any cause	13.0 (119)	9.9 (89)	1.38 (1.03-1.85)	-
Definite cardiovascular death	5.0 (45)	4.5 (40)	1.13 (0.73-1.74)	-
Stroke	2.9 (26)	3.7 (33)	0.78 (0.46-1.31)	-
Myocardial infarction	10.6 (95)	9.1 (84)	1.14 (0.84-1.55)	-
Ischemia-driven revascularization	16.9 (150)	10.0 (88)	1.84 (1.39-2.44)	-
Therapy failure[b]	1.1 (10)	6.5 (58)	0.16 (0.08-0.32)	-
Cerebrovascular events[c]	3.3 (29)	5.2 (46)	0.61 (0.38-0.99)	-

Data are % (n). Adapted from [11].
CI: confidence interval; CABG: coronary artery bypass graft surgery; MACCE: major adverse cardiac and cerebrovascular events; PCI: percutaneous coronary intervention.
[a] Composite of death from any cause, stroke, myocardial infarction and ischemia-driven revascularization.
[b] Defined as stent thrombosis or symptomatic graft stenosis or occlusion.
[c] Including stroke and transient ischemic attack.

group (31.3% vs. 24.9%; OR=1.39, 95% CI 1.13-1.71, p=0.002), as did ischemia-driven revascularization (16.9% in the PCI group vs. 10.0% in the CABG group; OR=1.84, 95% CI 1.39-2.44). All-cause death rates were also higher in the PCI group (13.0% vs. 9.9% in the CABG group; OR=1.38, 95% CI 1.03-1.85), whereas definite cardiovascular death did not differ significantly between the two groups (5.0% in the PCI group vs. 4.5% in the CABG group; OR=1.13, 95% CI 0.73-1.74). Rates of both therapy failure (1.1% in the PCI group vs. 6.5% in the CABG group; OR=0.16, 95% CI 0.08-0.32) and all cerebrovascular events (3.3% in the PCI group vs. 5.2% in the CABG group; OR=0.61, 95% CI 0.38-0.99) were lower in the PCI group compared with the CABG group. No other significant differences were found between the two groups. Some of the main results are shown in Table 5.

NOBLE (2016): three-year results

The Nordic-Baltic-British Left Main Revascularization Study (NOBLE) is a prospective, randomized, open-label, international, non-inferiority trial that compared PCI, mainly with biolimus-eluting stents, with CABG in patients with LMCAD.[12]

The objective of the trial was to analyze non-inferiority of PCI compared to CABG, initially at two years of follow-up, regarding the MACCE primary endpoint, a composite of death, non-procedural MI, repeat revascularization or stroke, set as hazard ratio (HR) not higher than 1.35. After predicting that at two years of follow-up the minimum number of MACCE events (n=275) to make the trial powered for non-inferiority of PCI would not be reached, the investigators decided to report estimated results at a median of three years of follow-up,[12] followed by reporting five-year follow-up results later to confirm the estimates.[13]

Secondary endpoints included components of MACCE, definite stent thrombosis and symptomatic graft occlusion.

An initial total of 1201 patients for whom it was determined that revascularization could be equally achieved with PCI or CABG were randomly assigned to undergo PCI (n=592) or CABG (n=592). However, after various exclusions, the analyzed population was composed of 1184 patients, 592 for each treatment arm. Median follow-up was 3.1 years.

The main finding of the NOBLE trial was that PCI was inferior to CABG with regard to the primary endpoint five-year estimate rates (28% in the PCI group vs. 18% in the CABG group; HR=1.51, 95% CI 1.13-2.00, p=0.0044).

However, results at 30 days and one year showed that this inferiority was not stable throughout follow-up. At 30 days CABG had higher rates of stroke (0 in the PCI group vs. <1% in the CABG group; difference -0.7%, 95% CI -1.3 to -0.1, p=0.04), reoperation for bleeding (<1% in the PCI group vs. 4% in the CABG group; difference -3.7%, 95% CI -5.3 to -2.1, p<0.0001), blood transfusion (2% in the PCI group vs. 28% in the CABG group; difference -25.4%, 95% CI -29.3 to -21.5, p<0.0001), as well as longer hospitalization (two days in the PCI group vs. nine days in the CABG group; p for difference <0.0001). At one year there were no significant differences between the two treatment groups in terms of MACCE rates, at 7% for both (difference 0.0%, 95% CI -2.9 to -2.9; p=1). Some of the main results at both 30 days and one year are shown in Table 6.

NOBLE (2020): five-year results

Follow-up was continued and at a median of 4.9 years of follow-up the minimum number of MACCE events was reached (n=275). The results at five years of follow-up are therefore presented next.[13] As with the early results published in 2016, non-inferiority of PCI regarding MACCE rates was not obtained, with HRs surpassing the 1.35 limit (28.4% in the PCI group vs. 19.0% in the CABG group; HR=1.58, 95% CI 1.24-2.01, p=0.0002). SYNTAX score was not associated with differences in MACCE rates (p for interaction=0.16). Although low SYNTAX scores (≤22) had higher MACCE rates in the PCI group (27% vs. 14% in the CABG group; HR=2.05, 95% CI 1.41-2.98, p=0.0001), intermediate (23-32) (30% in the

Table 6 Some major results of the NOBLE trial at 30 days and at one year.

Endpoints	PCI (n=592)	CABG (n=592)	Risk difference (95% CI)	p
Endpoints at 30 days				
Death from any cause	<1 (2)	1 (7)	-0.8% (-1.8 to 0.1)	0.09
Cardiac death	<1 (2)	1 (7)	-0.8% (-1.8 to 0.1)	0.09
Procedural myocardial infarction	5 (16/296)	7 (16/238)	-1.3% (-5.4 to 2.8)	0.52
Non-procedural myocardial infarction	1 (3)	0	0.5% (-0.06 to 1.1)	0.08
Stroke	0	<1 (4)	-0.7% (-1.3 to -0.01)	0.04
Revascularization	1 (7)	2 (10)	-0.5% (-1.8 to 0.8)	0.46
Symptomatic graft occlusion or definite stent thrombosis	<1 (1)	<1 (2)	-0.1% (-0.7 to 0.4)	0.56
Reoperation for bleeding	<1 (1)	4 (23)	-3.7% (-5.3 to -2.1)	<0.0001
Reoperation for sternum infection	0	<1 (3)	-0.5% (-1.1 to 0.07)	0.08
Blood transfusion	2 (11)	28 (150)	-25.4% (-29.3 to -21.5)	<0.0001
Duration of index treatment admission (days)	2 (1-4)	9 (7-13)	-	<0.0001
Endpoints at 1 year				
MACCE[a]	7 (42)	7 (42)	0.0% (-2.9 to -2.9)	1.00
Death from any cause	2 (9)	3 (17)	-1.3% (-3.0 to 0.3)	0.11
Cardiac death	1 (8)	2 (13)	-0.8% (-2.3 to 0.6)	0.27
Non-procedural myocardial infarction	2 (11) 1 (8)	0.5% (-0.9 to 1.9)	0.5% (-0.9 to 1.9)	0.49
Stroke	<1 (2)	1 (6)	-0.7% (-1.6 to 0.3)	0.16
Revascularization	5 (32)	4 (24)	1.4% (-1.1 to 3.8)	0.27
Symptomatic graft occlusion or definite stent thrombosis	<1 (2)	1 (7)	-0.8% (-1.8 to 0.1)	0.09

Data are % (n). Adapted from [12].
CI: confidence interval; CABG: coronary artery bypass graft surgery; MACCE: major adverse cardiac and cerebrovascular events; PCI: percutaneous coronary intervention.
[a] Composite of death, non-procedural myocardial infarction, repeat revascularization and stroke.

PCI group vs. 25% in the CABG group; HR=1.24, 95% CI 0.87-1.77, p=0.30) and high (≥33) scores (33% in the PCI group vs. 25% in the CABG group; HR=1.41, 95% CI 0.68-2.93, p=0.40) had similar rates for the two groups.

Rates of the secondary endpoints non-procedural MI (7.6% in the PCI group vs. 2.7% in the CABG group; HR=2.99, 95% CI 1.66-5.39, p=0.0002) and revascularization (17.1% in the PCI group vs. 10.2% in the CABG group; HR=1.73, 95% CI 1.25-2.40, p=0.0009) were significantly higher in the PCI group. No additional significant differences between the two treatment arms were found in the other secondary endpoint rates. Some of the main results are shown in Table 7.

PRECOMBAT trial (2011): one- and two-year results

The Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) trial is a prospective, randomized, open-label trial conducted in Korea that compared PCI using sirolimus-eluting stents versus CABG in patients with LMCAD.[14]

The primary analysis was a non-inferiority comparison of PCI versus CABG based on the rates of the MACCE primary endpoint, a composite of all-cause death, MI, stroke or ischemia-driven target-vessel revascularization, at one year. A seven percentage-point margin of absolute risk difference was set for non-inferiority.

Secondary endpoints included individual components of the primary endpoint, the composite of death, MI or stroke, and stent thrombosis. Because one-year rates were lower than anticipated, two-year rates were also analyzed.

A total of 600 patients, eligible for both PCI and CABG, were randomly assigned to undergo either PCI (n=300) or CABG (n=300). Median follow-up was 24.0 months.

Non-inferiority of PCI in relation to the primary endpoint at one year was reached (8.7% in the PCI group vs. 6.7% in the CABG group; difference 2.0%, 95% CI -1.6 to 5.6; p for non-inferiority=0.01).

Endpoint rates at two years are as follows. The primary endpoint did not have significantly different rates between the two groups (12.2% in the PCI group vs. 8.1% in the CABG group; HR=1.50, 95% CI 0.90-2.52, p=0.12). Subgroup analysis of the same endpoint based on SYNTAX scores showed no significant differences (p for interaction=0.80).

Ischemia-driven target-vessel revascularization rates were higher in the PCI group than in the CABG group (9.0% vs. 4.2%; HR=2.18, 95% CI 1.10-4.32, p=0.02). However, clinically-driven target-vessel revascularization rates were similar (6.9% vs. 3.8%; HR=1.81, 95% CI 0.87-3.78, p=0.11). On the other hand, patients in the CABG group had longer hospitalizations after procedure (8.4±14.5 days vs.

Table 7 Some major results of the NOBLE trial at five years.

Endpoints	PCI (n=592)	CABG (n=592)	HR (95% CI)	p
Primary endpoint				
MACCE[a]	28.4 (165)	19.0 (110)	1.58 (1.24-2.01)	0.0002
SYNTAX score ≤22	27 (78/297)	14 (43/316)	2.05 (1.41-2.98)	0.0001
				p for interaction
SYNTAX score 23-32	30 (72/249)	25 (53/220)	1.24 (0.87-1.77)	0.30
				0.16
SYNTAX score ≥33	33 (15/46)	25 (14/56)	1.41 (0.68-2.93)	0.40
Death from any cause	9.4 (54)	8.7 (50)	1.08 (0.74-1.59)	0.68
Cardiac death	4 (25)	4 (25)	0.99 (0.57-1.73)	0.99
Stroke	3.8 (21)	2.2 (12)	1.75 (0.86-3.55)	0.1109
Non-procedural myocardial infarction	7.6 (43)	2.7 (15)	2.99 (1.66-5.39)	0.0002
Revascularization	17.1 (97)	10.2 (58)	1.73 (1.25-2.40)	0.0009
Target lesion revascularization	12 (67)	8 (46)	1.51 (1.04-2.20)	0.039
De novo lesion revascularization	7 (40)	3 (15)	2.66 (1.47-4.81)	0.0006
Symptomatic graft occlusion or definite stent thrombosis	2 (13)	4 (21)	0.64 (0.32-1.27)	0.17

Data are % (n). Adapted from [13].
CI: confidence interval; CABG: coronary artery bypass graft surgery; HR: hazard ratio; MACCE: major adverse cardiac and cerebrovascular events; PCI: percutaneous coronary intervention.
[a] Composite of death, non-procedural myocardial infarction, repeat revascularization and stroke.

3.1±5.8 days in the PCI group, p<0.001). The other endpoints showed no significant differences between the two treatment groups. Some of the main results are shown in Table 8.

PRECOMBAT trial (2015): five-year results

Of the original PRECOMBAT cohort of 600 patients, 279 of the PCI group (93%) and 275 of the CABG group (91.7%) completed five years of follow-up.[15]

Primary endpoint MACCE rates at five years were similar for those assigned to PCI and for those who underwent CABG (17.5% vs. 14.3%, respectively; HR=1.27, 95% CI 0.84-1.90, p=0.26). There were also no differences in MACCE rates when divided into the three SYNTAX score groups (p for interaction=0.49).

All secondary endpoints were similar at five years except for rates of ischemia-driven target-vessel revascularization, which were significantly higher in the PCI group (11.4% vs. 5.5% in the CABG group; HR=2.11, 95% CI 1.16-3.84, p=0.012). However, as described at two years, clinically-driven target-vessel revascularization rates remained similar (9.3% vs. 5.2%; HR=1.83, 95% CI 0.97-3.44, p=0.057). Some of the main results are shown in Table 9.

PRECOMBAT trial (2020): 10-year results

Although the initial maximum follow-up was set as five years, all participating centers agreed to extend follow-up to 10 years. Of the original 600 patients, 96.0% of those in the PCI groups (n=288) and 96.0% of those in the CABG group (n=288) completed 10 years of follow-up, with a median follow-up of 11.3 years.[16]

Similarly to the results at one, two and five years, MACCE primary endpoint rates at 10 years were not significantly different between the two groups (29.8% in the PCI group vs. 24.7% in the CABG group (HR=1.25, 95% CI 0.93-1.69). SYNTAX score did not have significant interaction with MACCE rates (p for interaction=0.63).

In addition, the secondary outcomes remained consistent, with significantly higher ischemia-driven target-vessel revascularization rates in the PCI group (16.1% vs. 8.0% in the CABG group; HR=1.98, 95% CI 1.21-3.21). No other significant differences were found. Some of the main results are shown in Table 10.

Limitations

The main objective of the SYNTAX trial was a non-inferiority analysis of PCI versus CABG in the main study population, which was not met, leading to all subgroup analyses being at most hypothesis-generating because of the hierarchical primary endpoint testing that was used.[6,7]

In the EXCEL trial, patients with high SYNTAX scores (≥33) were excluded, however, this assessment was site reported, with later core laboratory assessment showing that there were 67 patients who actually belonged to the highest SYNTAX score group.[10]

In the NOBLE trial, first-generation drug-eluting stents were initially used, with 73 patients undergoing PCI with these. However, in the other 519 patients, second-generation biolimus-eluting stents were used. Furthermore, as mentioned above, analysis of the primary endpoint timing was changed from two years to a median of three years of follow-up due to lack of events, which the trial was not powered for.[12]

Table 8 Some major results of the PRECOMBAT trial at one and two years.

Endpoints	PCI (n=300)	CABG (n=300)	HR (95% CI)	Risk difference (95% CI)	p	p for non-inferiority
Primary endpoint						
MACCE[a]						
At 1 year	8.7 (26)	6.7 (20)	-	2.0% (-1.6 to 5.6)	-	0.01
At 2 years	12.2 (36)	8.1 (24)	1.50 (0.90-2.52)	-	0.12	-
SYNTAX score ≤19	15.9 (14/89)	11.1 (10/91)	1.60 (0.73-3.54)	-	0.24	
SYNTAX score 20-29	13.9 (14/105)	5.7 (5/93)	2.32 (0.82-6.57)	-	0.11	p for interaction 0.80
SYNTAX score ≥30	8.5 (8/95)	5.9 (5/85)	1.38 (0.40-4.21)	-	0.57	
Death, myocardial infarction or stroke						
At 1 year	3.3 (10)	4.0 (12)	-	-	-	-
At 2 years	4.4 (13)	4.7 (14)	0.92 (0.43-1.96)	-	0.83	-
Death from any cause						
At 1 year	2.0 (6)	2.7 (8)	-	-	-	-
At 2 years	2.4 (7)	3.4 (10)	0.69 (0.26-1.82)	-	0.45	-
Myocardial infarction						
At 1 year	1.3 (4)	1.0 (3)	-	-	-	-
At 2 years	1.7 (5)	1.0 (3)	1.66 (0.40-6.96)	-	0.49	-
Stroke						
At 1 year	0	0.3 (2)	-	-	-	-
At 2 years	0.4 (1)	0.7 (2)	0.49 (0.04-5.40)	-	0.56	-
Ischemia-driven target-vessel revascularization						
At 1 year	6.1 (18)	3.4 (10)	-	-	-	-
At 2 years	9.0 (26)	4.2 (12)	2.18 (1.10-4.32)	-	0.02	-
Clinically-driven target-vessel revascularization[b]						
At 1 year	4.4 (13)	3.1 (9)	-	-	-	-
At 2 years	6.9 (20)	3.8 (11)	1.81 (0.87-3.78)	-	0.11	-
Stent thrombosis or symptomatic graft occlusion						
At 1 year	0	1.0 (3)	-	-	-	-
At 2 years	0.3 (1)	1.4 (4)	0.25 (0.03-2.22)	-	0.25	-

Data are % (n). Adapted from [14].
CI: confidence interval; CABG: coronary artery bypass graft surgery; HR: hazard ratio; MACCE: major adverse cardiac and cerebrovascular events; PCI: percutaneous coronary intervention.
[a] Composite of death from any cause, myocardial infarction, stroke and ischemia-driven target-vessel revascularization.
[b] Clinically-driven revascularization excluded lesions without ischemic symptoms or signs.

The PRECOMBAT trial was underpowered due to unexpectedly low event rates. The seven percentage point margin for non-inferiority initially set for PCI was almost equivalent to a 100% increase in the observed event rate of the primary endpoint at one year in the comparison group of CABG.[14] Thus, caution should be exercised when extrapolating non-inferiority. Furthermore, the trial was initially designed for a maximum of five years of follow-up, the authors extending it to 10 years without proper yearly follow-up from five to 10 years, possibly leading to adverse events being unreported.[16]

Further limitations can be added. First, because all analyses were performed according to the intention-to-treat principle and because there were crossovers between groups, the results may be biased. Second, secondary endpoint analysis should be interpreted with caution, as trials were powered for the primary endpoint. Third, the SYNTAX and PRECOMBAT trials used first-generation DES, unlike the NOBLE (most patients) and EXCEL trials, which used second-generation DES, which have been acknowledged to be the best option in PCI.[17] Lastly, double blinding of patients and investigators was not possible due to the nature of the two treatments, possibly leading to biased results.

Discussion

Irrigation of the left ventricle is mainly due to the LM, which makes its obstruction a serious condition with high risk of mortality and morbidity, and prompting efforts to find the best possible treatment for these patients.

Regarding the main analysis of the trials, EXCEL and PRECOMBAT found PCI to be non-inferior to CABG with regard to the primary endpoint, and SYNTAX found no significant differences in the primary outcome; however, this trial was designed for a different analysis, including not only LMCAD but also three-vessel coronary artery disease, in which PCI was inferior to CABG. By contrast, the NOBLE trial

Table 9 [ll1]Some major results of the PRECOMBAT trial at five years.

Endpoints	PCI (n=300)	CABG (n=300)	HR (95% CI)	p	
Primary endpoint					
MACCE[a]	17.5 (52)	14.3 (42)	1.27 (0.84-1.90)	0.26	
SYNTAX score ≤22	12.5 (16/129)	13.0 (13/104)	0.98 (0.47-2.05)	0.97	
SYNTAX score 23-32	21.7 (22/102)	12.6 (12/97)	1.85 (0.91-3.73)	0.083	p for interaction 0.49
SYNTAX score ≥33	24.2 (14/58)	19.2 (13/68)	1.37 (0.64-2.91)	0.41	
Death, myocardial infarction or stroke	8.4 (25)	9.6 (28)	0.89 (0.52-1.52)	0.66	
Death from any cause	5.7 (17)	7.9 (23)	0.73 (0.39-1.37)	0.32	
Cardiac death	3.8 (11)	6.9 (20)	0.54 (0.26-1.13)	0.098	
Myocardial infarction	2.0 (6)	1.7 (5)	1.20 (0.37-3.93)	0.76	
Stroke	0.7 (2)	0.7 (2)	0.99 (0.14-7.02)	0.99	
Ischemia-driven target-vessel revascularization	11.4 (33)	5.5 (16)	2.11 (1.16-3.84)	0.012	
Clinically-driven target-vessel revascularization[b]	9.3 (27)	5.2 (15)	1.83 (0.97-3.44)	0.057	

Data are % (n). Adapted from [15].
CI: confidence interval; CABG: coronary artery bypass graft surgery; HR: hazard ratio; MACce: major adverse cardiac and cerebrovascular events; PCI: percutaneous coronary intervention.
[a] Composite of death from any cause, myocardial infarction, stroke and ischemia-driven target-vessel revascularization.
[b] Clinically-driven revascularization excluded lesions without ischemic symptoms or signs.

Table 10 Some major results of the PRECOMBAT trial at 10 years.

Endpoints	PCI (n=300)	CABG (n=300)	HR (95% CI)	p for interaction
Primary endpoint	29.8 (87)	24.7 (72)	1.25 (0.93-1.69)	-
MACCE[a]				
SYNTAX score ≤22	21.6 (27/131)	22.2 (23/109)	1.01 (0.59-1.73)	
SYNTAX score 23-32	31.8 (32/102)	22.2 (21/98)	1.61 (0.92-2.81)	0.63
SYNTAX score ≥33	46.2 (26/58)	45.7 (24/68)	1.18 (0.67-2.09)	
Death, myocardial infarction or stroke	18.2 (53)	17.5 (51)	1.00 (0.70-1.44)	-
Death from any cause	14.5 (42)	13.8 (40)	1.13 (0.75-1.70)	-
Cardiac death	7.8 (22)	8.7 (25)	0.96 (0.56-1.65)	-
Myocardial infarction	3.2 (9)	2.8 (8)	0.76 (0.32-1.82)	-
Stroke	1.9 (5)	2.2 (6)	0.71 (0.22-2.23)	-
Ischemia-driven target-vessel revascularization	16.1 (45)	8.0 (22)	1.98 (1.21-3.21)	-
Stent thrombosis or symptomatic graft occlusion	1.4 (4)	3.7 (10)	0.56 (0.20-1.55)	-

Data are % (n). Adapted from [16].
CI: confidence interval; CABG: coronary artery bypass graft surgery; HR: hazard ratio; MACCE: major adverse cardiac and cerebrovascular events; PCI: percutaneous coronary intervention.
[a] Composite of death from any cause, myocardial infarction, stroke and ischemia-driven target-vessel revascularization.

concluded that PCI was inferior to CABG at five years. It is worth noting that in the EXCEL trial, the primary composite endpoint of death, stroke or myocardial infarction, although similar at five years of follow-up, from one to five years favored CABG, with the possibility of rates in the PCI group becoming significantly higher than those in the CABG group for this study population with longer follow-up. It should be noted that the primary composite endpoint in the EXCEL trial differed from the others by excluding repeat revascularization. MACCE, which include this outcome, were more frequent in the PCI group at five years in this trial.

Mortality rates were similar across all studies except for the EXCEL trial, which found higher all-cause mortality at five years in the PCI group. However, these higher rates were mostly due to non-cardiovascular death, which could at least in part be due to chance.

Across all trials reviewed, rates of repeat revascularization were higher in the PCI group. It is important to note that definitions of repeat revascularization differed

Table 11 Some major findings of trials on percutaneous coronary intervention versus coronary artery bypass grafting in left main coronary artery disease.

Study (date)	n	Intervention	Endpoints	Major findings
SYNTAX trial (2009) 12-month results: LMCAD subgroup	705	PCI with paclitaxel-eluting stents versus CABG	Primary endpoint: MACCE (death from any cause, stroke, myocardial infarction and repeat revascularization) at 12 months. Secondary endpoints: Components of MACCE at 12 months	MACCE rates at 12 months were similar in the PCI group and CABG group. MACCE rates at 12 months were similar for both groups in low and intermediate SYNTAX scores, but in the high SYNTAX scores favored CABG. The PCI group had higher revascularization rates while the CABG group had higher stroke rates. The other secondary endpoints showed no significant differences.
SYNTAX trial (2014) Five-year results: LMCAD subgroup		PCI with paclitaxel-eluting stents versus CABG	Primary endpoint: MACCE (death from any cause, stroke, myocardial infarction and repeat revascularization) at five years. Secondary endpoints: Components of MACCE at five years.	MACCE rates at five years were similar between the PCI and CABG groups. MACCE rates at five years in the two lower SYNTAX score tertiles were similar for the two groups, but in the higher SYNTAX scores ($\geq$33) were significantly higher in the PCI group. Stroke rates were higher in the CABG group, as opposed to repeat revascularization, which was more frequent in the PCI group. The other secondary endpoints showed no significant differences.
SYNTAXES study (2019) 10-year results: LMCAD subgroup	705	PCI with paclitaxel-eluting stents versus CABG	Primary endpoint: all-cause death at 10 years. Secondary endpoint: all-cause death at maximum follow-up.	MACCE rates at five years were similar between the PCI and CABG groups. MACCE rates at five years in the two lower SYNTAX score tertiles were similar for the two groups, but in the higher SYNTAX scores ($\geq$33) were significantly higher in the PCI group. Stroke rates were higher in the CABG group, as opposed to repeat revascularization, which was more frequent in the PCI group. The other secondary endpoints showed no significant differences.
EXCEL trial (2016) Three-year results	1905	PCI with everolimus-eluting stents versus CABG	Primary endpoint: composite of death from any cause, stroke or myocardial infarction at three years. Secondary endpoints: primary endpoint at 30 days; composite of death from any cause, stroke, myocardial infarction or ischemia-driven revascularization at 30 days and three years; components of the primary and secondary endpoints at 30 days and three years; definite stent thrombosis or symptomatic graft occlusion at 30 days and three years.	Primary endpoint rates were similar for PCI and CABG at three years, showing non-inferiority of PCI compared to CABG for this endpoint. Primary endpoint rates were similar for both low and intermediate SYNTAX scores At 30 days, the primary endpoint, composite of death, stroke, myocardial infarction or ischemia-driven revascularization, myocardial infarction, blood transfusion, bleeding and definite stent thrombosis or symptomatic graft occlusion rates favored PCI. At three years, ischemia-driven revascularization rates favored the CABG group, while definite stent thrombosis or symptomatic graft occlusion rates favored PCI. The other secondary endpoints showed no significant differences

Table 11 (*Continued*)

Study (date)	n	Intervention	Endpoints	Major findings
NOBLE trial (2016) Three-year results	1905	PCI with everolimus-eluting stents versus CABG	Secondary endpoints: death from any cause, stroke, myocardial infarction or ischemia-driven revascularization at five years; components of the primary and secondary endpoints at five years; cerebrovascular events and therapy failure at five years.	There were no significant differences in primary endpoint rates at five years between the two treatment groups. However, while rates from 30 days to one year were similar, those from one to five years favored the CABG group. Primary endpoint rates were similar for both low and intermediate SYNTAX scores. Death and repeat revascularization rates were lower in the CABG group, whereas cerebrovascular events and therapy failure rates favored PCI. The other secondary endpoints showed no significant differences.
NOBLE trial (2016) Three-year results	1184	PCI mainly with biolimus-eluting stents versus CABG	Primary endpoint: MACCE (death, non-procedural myocardial infarction, repeat revascularization or stroke) at a median of three years. Secondary endpoints: MACCE at 1 year; components of MACCE, definite stent thrombosis and symptomatic graft occlusion at 30 days and one year.	PCI was inferior to CABG for the MACCE endpoint at a median of 3.1 years of follow-up. At 30 days, CABG had higher rates of stroke, reoperation for bleeding and blood transfusion as well as longer hospitalization duration. At one year, MACCE rates were the same for both interventions. The other secondary endpoints showed no significant differences.
NOBLE trial (2016) Five-year results	1184	PCI mainly with biolimus-eluting stents versus CABG	Primary endpoint: MACCE (death, non-procedural myocardial infarction, repeat revascularization or stroke) at five years. Secondary endpoints: components of MACCE, definite stent thrombosis and symptomatic graft occlusion at five years.	PCI was inferior to CABG for the MACCE endpoint at five years of follow-up. SYNTAX score did not have significant interaction with MACCE rates for both treatments, even though low SYNTAX scores (<22) favored CABG over PCI. Non-procedural myocardial infarction and need for repeat revascularization rates favored CABG. The other secondary endpoints showed no significant differences.
PRECOMBAT trial (2011) One- and two-year results	600	PCI with sirolimus-eluting stents versus CABG	Primary endpoint: MACCE (all-cause death, myocardial infarction, stroke or ischemia-driven target-vessel revascularization) at one year. Secondary endpoints: MACCE at 2 years; components of MACCE at two years; composite of all-cause death, myocardial infarction or stroke at two years; stent thrombosis or symptomatic graft occlusion at two years.	MACCE rates at one year in the PCI group were non-inferior to the CABG group. SYNTAX score was not associated with differences in the primary endpoint rates at two years. Ischemia-driven target-vessel revascularization rates favored CABG at two years. The other secondary endpoints showed no significant differences.
PRECOMBAT trial (2015) Five-year results	600	PCI with sirolimus-eluting stents versus CABG	Primary endpoint: MACCE (all-cause death, myocardial infarction, stroke or ischemia-driven target-vessel revascularization) at five years. Secondary endpoints: components of MACCE at five years; composite of all-cause death, myocardial infarction or stroke at five years; clinically driven target-vessel revascularization at five years.	MACCE rates at five years were similar in both groups. SYNTAX score was not associated with differences in primary endpoint rates at five years. Ischemia-driven target-vessel revascularization rates favored CABG. The other secondary endpoints showed no significant differences.

Table 11 (*Continued*)

Study (date)	n	Intervention	Endpoints	Major findings
PRECOMBAT trial (2020) 10-year results	600	PCI with sirolimus-eluting stents versus CABG	Primary endpoint: MACCE (all-cause death, myocardial infarction, stroke or ischemia-driven target-vessel revascularization) at 10 years. Secondary endpoints: components of MACCE at 10 years; composite of all-cause death, myocardial infarction or stroke at 10 years; stent thrombosis or symptomatic graft occlusion at 10 years.	MACCE rates at 10 years were similar among both groups. SYNTAX score was not associated with differences in primary endpoint rates at five years. Ischemia-driven target-vessel revascularization rates favored CABG. The other secondary endpoints showed no significant differences.

Adapted from [6–16].
CABG: coronary artery bypass graft surgery; MACCE: major adverse cardiac or cerebrovascular events; n: study population; PCI: percutaneous coronary intervention.

between the trials. The higher revascularization rates may, in part, be due to a higher frequency of angiography performed in those who underwent PCI; this is supported by the fact that revascularization rates that excluded those with no symptoms had similar rates, as seen in the PRECOMBAT trial.[14,15] Another possible explanation is that CABG could protect against future lesions outside the initially treated lesion, especially if proximal to it, which PCI does not. Supporting this hypothesis, in the NOBLE trial, the higher rates of repeat revascularization in the PCI group were more significant in de novo lesion revascularization, a finding that correlates with the fact that in the EXCEL trial, the rates of ischemia-driven target-lesion revascularization at three years were similar for both PCI and CABG groups, suggesting that the higher revascularization rates were due to other lesions. Thus, efforts to prevent coronary artery disease progression could solve the problem of higher revascularization rates in the PCI group.

On the other hand, several outcomes favored PCI, mainly at early follow-up. Adverse post-procedure outcomes were more frequent in those treated with CABG, with higher rates of stroke, reoperation and blood transfusion and longer hospital stay in the NOBLE trial at 30 days.[12] Rates of the primary endpoint, myocardial infarction, MACCE, definite stent thrombosis or symptomatic graft occlusion, bleeding and blood transfusion were also higher in those treated with CABG in the EXCEL trial at 30 days. This should be taken into account when deciding which intervention to choose, and PCI might be a better option for those with low life expectancy.

CABG was associated with more cerebrovascular events in two of the trials. SYNTAX found higher stroke rates in this group at both one and five years, while the EXCEL trial had higher rates of cerebrovascular events at five years for those treated with CABG, although stroke rates were similar, which suggests that transient ischemic attacks were more frequent than strokes. One explanation for these higher rates could be the systematic use of dual antiplatelet therapy in the PCI group across all trials, which could be a protective factor for cerebrovascular events. No other trial found any association, but transient ischemic attacks were not assessed other than in the EXCEL trial at five years. Further analysis of this outcome could be of interest, as could assessment of the use of antiplatelet therapy in patients undergoing CABG.

Overall, other outcomes did not show significant differences apart from some cases, such as rates of non-procedural myocardial infarction, which were higher in the PCI group at five years in the NOBLE trial. Also, symptomatic graft occlusion after CABG was significantly more frequent than stent thrombosis after PCI in the EXCEL trial, at both three and five years of follow-up. These findings contrast with those from SYNTAX at five years, which had similar rates of stent thrombosis and symptomatic graft occlusion, possibly due to the use of first-generation stents. However, the NOBLE trial, which mainly used second-generation stents, also found similar rates of stent thrombosis and symptomatic graft occlusion at five years.

In a recent meta-analysis including five-year follow-up results of the trials included in this review, Ahmad et al. concluded that both all-cause mortality (RR=1.03, 95% CI 0.82-1.30; p=0.779; I2=42.9%) and cardiac death (RR=1.03, 95% CI 0.79-1.34; p=0.817; I2=0.0%) were similar for the two procedures, as were myocardial infarction (RR=1.22, 95% CI 0.96-1.56; p=0.110; I2=0.0%) and stroke (RR=0.74, 95% CI 0.36-1.50; p=0.40; I2=59.9%). However, unplanned revascularization was more frequent in the PCI group (RR=1.73, 95% CI 1.49-2.02; p<0.001; I2=0.0%).[18] These findings corroborate those discussed previously in this review.

Analysis of outcomes stratified by SYNTAX scores was performed in all trials, but results were diverse. In the SYNTAX trial, high SYNTAX scores were associated with higher primary endpoint rates at both 12 months and five years. However, SYNTAXES, EXCEL and PRECOMBAT showed no significant differences between different SYNTAX scores in relation to the primary endpoints. Moreover, in the NOBLE trial, the PCI group surprisingly had worse primary endpoint rates regarding low SYNTAX scores, with intermediate and high scores similar between the two treatment options. One possible explanation for these disparate results is that the SYNTAX score was initially created based on multivessel

Table 12 Overview of outcomes across all trials.

Endpoints	SYNTAX 12-month results	SYNTAX 5-year results	SYNTAXES 10-year results	EXCEL 3-year results	EXCEL 5-year results	NOBLE 1-year results	NOBLE 5-year results	PRECOMBAT 2-year results	PRECOMBAT 5-year results	PRECOMBAT 10-year results
MACCE[a]	Similar[b]	Similar[b]	-	Similar	Favored CABG	Similar[b]	Favored CABG[b]	Similar[b]	Similar[b]	Similar[b]
Death, stoke or myocardial infarction	Similar	Similar	-	Similar[b]	Similar[b]	-		Similar	Similar	Similar
Death	Similar	Similar	Similar[b]	Similar	Favored CABG	Similar	Similar	Similar	Similar	Similar
SYNTAX score ≤22[c]	Similar	Similar	Similar	Similar	Similar	-		Similar[d]	Similar[d]	Similar[d]
SYNTAX score 23-32[c]	Similar	Similar	Similar	Similar	Similar	-	Similar	Similar[d]	Similar[d]	Similar[d]
SYNTAX score ≥33[c]	Favored CABG	Favored CABG	Similar	-	-	-	Similar	Similar[d]	Similar[d]	Similar[d]
Cardiac death	Similar	Similar	-	Similar	Similar	Similar	Similar	-	Similar	Similar
Stroke	Favored PCI	Favored PCI	-	Similar	Similar	Similar	Similar	Similar	Similar	Similar
Myocardial infarction	Similar	Similar	-	Similar	Similar	Similar	Favored CABG	Favored CABG	Similar	Similar
Repeat revascularization	Favored CABG	Favored CABG	-	Favored CABG	Favored CABG	Similar	Favored CABG	Favored CABG	Favored CABG	Favored CABG
Stent thrombosis or graft occlusion		Similar	-	Favored PCI	Favored PCI	Similar	Similar	Similar	-	Similar

Adapted from [6–16]. Endpoint definitions may vary between trials. CABG: coronary artery bypass graft surgery; MACCE: major adverse cardiac or cerebrovascular events; PCI: percutaneous coronary intervention.

[a] Composite of death from any cause, stroke, myocardial infarction and repeat revascularization.

[b] Primary endpoint of the respective trial.

[c] SYNTAX score subgroup analyses based on the primary endpoint of each trial.

[d] SYNTAX scores used in the PRECOMBAT trial were ≤19, 20-29, and ≥30.

coronary artery disease, not LMCAD. Moreover, this score does not include patient and clinical factors, which should be taken into account when deciding which treatment to opt for. Based on the information presented, decision-making based on the SYNTAX score, as recommended in the current guidelines,[4,5] should be reassessed in future guidelines, as evidence does not support it as a suitable treatment decision tool in patients with LMCAD. A new version, SYNTAX Score II, has been developed, and proved to be superior in decision guidance to the original SYNTAX score, based on the original SYNTAX trial cohort (multivessel disease and/or LMCAD).[19] A recent update, with SYNTAX Score II 2020, promises to help improve guidance at the time of choosing the best option for treatment of coronary artery disease.[20] Future trials should use this newer anatomical complexity score to further evaluate its utility.

Conclusion

To conclude, LMCAD is a condition with significant associated morbidity and mortality, and so efforts should be made to find the best individual treatment. There is no clear answer to the question of the situations in which PCI or CABG should be used, as there are some contradictory findings between the different trials. However, based on the overall similarity in the primary endpoint rates, as well as favorable short-term outcomes, it is plausible to state that PCI can be considered a good alternative to CABG, not disregarding the higher risk of repeat revascularization in these patients. Nonetheless, decisions should be patient-centered and new coronary anatomical complexity scores to aid decision-making should be further investigated and validated.

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Conley MJ, Ely RL, Kisslo J, et al. The prognostic spectrum of left main stenosis. Circulation. 1978;57:947–52.
2. Murphy ML, Hultgren HN, Detre K, et al. Treatment of chronic stable angina. A preliminary report of survival data of the randomized Veterans Administration cooperative study. N Engl J Med. 1977;297:621–7.
3. Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease. Long-term CASS experience. Circulation. 1995;91:2325–34.
4. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2019;40:87–165.
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. Circulation. 2012;126:e354–471.
6. 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.
7. Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. Circulation. 2010;121:2645–53.
8. 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.
9. Thuijs D, Kappetein AP, Serruys PW, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. Lancet. 2019;394:1325–34.
10. 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.
11. Stone GW, Kappetein AP, Sabik JF, et al. Five-year outcomes after PCI or CABG for left main coronary disease. N Engl J Med. 2019;381:1820–30.
12. Makikallio 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.
13. Holm NR, Makikallio 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. Lancet. 2020;395:191–9.
14. 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.
15. 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.
16. Park DW, Ahn JM, Park H, et al. Ten-year outcomes after drug-eluting stents versus coronary artery bypass grafting for left main coronary disease: extended follow-up of the PRECOMBAT trial. Circulation. 2020;141:1437–46.
17. Piccolo R, Bonaa KH, Efthimiou O, et al. Drug-eluting or bare-metal stents for percutaneous coronary intervention: a systematic review and individual patient data meta-analysis of randomised clinical trials. Lancet. 2019;393:2503–10.
18. Ahmad Y, Howard JP, Arnold AD, et al. Mortality after drug-eluting stents vs. coronary artery bypass grafting for left main coronary artery disease: a meta-analysis of randomized controlled trials. Eur Heart J. 2020;41:3228–35.
19. 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.
20. Takahashi K, Serruys PW, Fuster V, et al. Redevelopment and validation of the SYNTAX score II to individualise decision making between percutaneous and surgical revascularisation in patients with complex coronary artery disease: secondary analysis of the multicentre randomised controlled SYNTAXES trial with external cohort validation. Lancet. 2020;396: 1399–412.