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ORIGINAL ARTICLE

Drug-eluting stents Versus Coronary Artery Bypass Grafting in Multivessel Disease and Left Main Obstruction: Meta-analysis of Randomized Clinical Trials

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Abstract

Background: The choice between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) remains controversial.

Objective: To conduct a meta-analysis of randomized studies comparing drug-eluting stents (DES) and CABG in multivessel disease or obstruction of the left main coronary artery.

Method: Electronic databases were searched systematically to evaluate results of randomized trials comparing PCI with DES versus CABG in multivessel disease and obstruction of the left main coronary artery. Ten studies were identified.

Results: In the aggregated results (n = 9268), mortality at 30 days and incidence of stroke favored PCI (0.8% versus 1.5%, $p = 0.005$; 0.4% versus 1.5%, $p < 0.0001$, respectively). There was no difference in mortality at 1 year (3.4% versus 3.5%, $p = 0.50$). The late mortality favored CABG (10.1% versus 8.5%, $p = 0.01$). In patients with diabetes derived from four studies (n = 3830), late mortality favored CABG (12.5% versus 9.7%, $p < 0.0001$). In six studies of left main coronary artery obstruction (n = 4700), the incidence of stroke favored PCI (0.3% versus 1.5%, $p < 0.001$) and there was no difference in mortality at 30 days (0.8% versus 1.3%, $p = 0.15$), mortality at 1 year, or late mortality (8.1% versus 8.1%). The subgroups with high SYNTAX score and diabetes were those influencing most strongly and adversely the PCI results.

Conclusion: When compared with PCI, CABG was superior in regards to late mortality and inferior in regards to 30-day mortality and incidence of stroke. Diabetes and SYNTAX score strongly impacted the results. (Int J Cardiovasc Sci. 2018;31(2)152-162)

Keywords: Myocardial Revascularization; Drug Eluting Stents; Randomized Controlled Trials as Topic; Meta-Analysis.

Introduction

Percutaneous coronary intervention (PCI or angioplasty) and coronary artery bypass grafting (surgery or CABG) are well-accepted, safe, and effective alternatives in the treatment of coronary insufficiency. A large number of randomized clinical trials has been published comparing both procedures.[1-12] In light of these studies, there seems to be a slight superiority of surgery over PCI in the ability to reduce anginal symptoms and a significant difference in its ability to prevent new revascularization procedures. Such studies are generally undersized to evaluate outcomes like death, stroke, and acute myocardial infarction (AMI).

The objective of this study was to perform a meta-analysis of randomized clinical trials comparing PCI and CABG in multivessel disease and obstruction of the left main coronary artery in the era of drug-eluting stents, with emphasis on mortality and stroke.

Methods

Randomized studies comparing PCI with drug-eluting stents *versus* CABG in multivessel lesions and / or obstruction of the left main coronary artery published between January 2002 and November 2016 were searched in the databases MEDLINE and Cochrane Library, and in bibliographical

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references of reviews published on the subject. The date of January 2002 was chosen as the initial period since drug-eluting stents began to be established as a therapeutic method after that. Clinical trials were included in the review if they were randomized, had compared surgery and coronary angioplasty, used drug-eluting stents, involved exclusively multivessel disease or left main coronary artery obstruction, had a minimum follow-up of 1 year, and were published in international journals with an impact factor > 2.0. We used the following terms in the search: *coronary artery bypass surgery*, *coronary stents*, and *randomized controlled trials.* Studies exclusively using balloon or bare-metal stents, or which assessed predominantly one-vessel disease were not included. Studies using drug-eluting and bare-metal stents[1,4] were included as studies of the drug-eluting stent era. Works resulting from observational studies (registries) or only published as meetings proceedings were not considered.

We identified 10 randomized studies that satisfied the requirements: LE MANS,[1] SYNTAX,[2-3] CARDia,[4] Boudriot et al.,[5] PRECOMBAT,[6] VA CARDS,[7] FREEDOM,[8] BEST,[9] NOBLE,[10] and EXCEL.[11] Three authors (PJNA, BAAF, and JLAAF) evaluated the studies, which were all considered to be of high quality.

The main outcomes of interest were mortality and stroke. The incidence of AMI was not evaluated because the definition of this event varied widely in the studies. We also did not evaluate the incidence of new revascularization, because the superiority of surgery on this outcome is well established. Mortality was divided into early mortality, mortality at 1 year, and late mortality. Early mortality was defined as death occurring up to 30 days after the procedure, including deaths occurring after randomization but before the procedure. This mortality was obtained from seven studies, whereas three studies did not provide this information.[2,4,7] Mortality at 1 year was defined as death occurring up to 1 year after the procedure, including early mortality. This mortality was obtained from nine studies, while one study did not provide such information.[9] Late mortality was defined as death recorded at the end of follow-up, after at least 3 years. This mortality was obtained from eight studies, six of which performed a follow-up for 5 years, one for 3 years[2] and one for 10 years.[1] We were unable to obtain this information from two studies.[5,7] For the incidence of stroke, we considered the events occurring up to 1 year after the procedure. In eight studies, we obtained the results up to 30 days and in one of them,[2] up to 1 year, while in one of the studies, this information was unavailable.[9] We evaluated separately the results of studies in the left main coronary artery and late mortality in the subgroup of patients with diabetes. We also performed analysis of combined major adverse cardiac and cerebrovascular events (MACCE) and assessed the variables age, gender, presence of diabetes, SYNTAX score, and compromised ejection fraction in subgroups based on data published in five trials.[2,4,6,8,9] Combined MACCE comprised death, AMI, and new revascularization in two of these trials,[6,9] and death, AMI, and stroke in the remaining ones.

In order to aggregate the outcomes of mortality and stroke, as well as those of MACCE (in subgroups), we considered whenever possible the absolute number of events and the number of patients followed up. Otherwise, percentages were transformed into absolute numbers.

Statistical analysis

We measured the relative risk and the risk difference after grouping the results of each outcome. In order to assess the statistical significance of the differences between the drug-eluting stent and the surgery groups, we performed a meta-analysis using the Mantel-Haenszel method, with a fixed-effect model. We calculated the heterogeneity of the studies using Cochran's Q test and the significance of the measure of the meta-analytic effect using the Z test. The differences between the results in the stent and CABG groups were considered significant if $p < 0.05$.

The statistical analyses were performed using the program Review Manager (RevMan), version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

In order to represent the heterogeneity of the studies, we constructed Forest plots. We used the risk difference to plot these graphs since this is a more stable index. We refrained from using odds ratio or relative risk due to the inclusion of some clinical trials with zero or near zero events.

Results

Characteristics of the trials are shown in table 1

The studies included a total of 9268 patients (4642 in the stent group and 4626 in the CABG group). The mean age of the patients was 64 years, 75% were male, 51% were diabetic, 24% were smokers, 64% were hypertensive, and 31% had unstable angina. The mean ejection fraction (reported in seven studies) was 59%, the mean EuroSCORE (reported in five studies) was 2.9, and the mean SYNTAX score (reported in seven studies) was 26. In regards to the number of affected vessels, 7% affected only two vessels, 43% affected only three vessels, and 50% presented obstruction of the left main coronary artery, associated or not with disease in other vessels. Some characteristics of the studies deserve special mention: the LE MANS[1] used drug-eluting and bare-metal stents, reserving the drug-eluting stents for left main coronary arteries with a reference diameter < 3.8 mm; CARDia[4] used initially bare-metal stents and only assessed patients with diabetes and multivessel disease; SYNTAX[2] evaluated left main coronary artery obstruction and multivessel disease and used first-generation drug-eluting stents (TAXUS); FREEDOM[8] and VA CARDS[7] exclusively assessed patients with diabetes and multivessel disease; BEST[9] evaluated patients with multivessel disease and used only everolimus-eluting stents; the study by Boudriot et al.[5] evaluated left main coronary artery obstruction and used only sirolimus-eluting stents; EXCEL[11] evaluated left main coronary artery obstruction and used only everolimus-eluting stents; NOBLE[10] evaluated left main coronary artery obstruction and used mostly a biolimus-eluting stent.

Outcomes

The outcomes are summarized in Figures 1 to 6. The incidence of stroke up to 1 year had a low heterogeneity ($I^2 = 0$). The results favored PCI (0.4% *versus* 1.5%, $p < 0.00001$). In regards to 30-day mortality, the studies showed low heterogeneity ($I^2 = 0$) and favored the stent group (0.8% *versus* 1.5%, p = 0.005). As for mortality up to 1 year, the studies presented low heterogeneity ($I^2 = 0\%$) and no difference between the groups (3.4% *versus* 3.5%, p = 0.50). In late mortality, the studies showed low heterogeneity ($I^2 = 0\%$) and favored CABG (10.1% *versus* 8.5%, p = 0.01). After exclusion of patients with diabetes from four studies (SYNTAX,[2] FREEDOM,[8] BEST,[9] and CARDIa[4]), the differences in late mortality tended to disappear (8.5% *versus* 8.1%, p = 0.6).

In the six studies evaluating left main coronary artery obstruction (LE MANS,[1] SYNTAX LEFT MAIN,[12] PRECOMBAT,[6] EXCEL,[11] NOBLE,[10] and the study by Boudriot et al.[5]) totaling 4700 patients, there was no difference in mortality at 30 days (0.8% *versus* 1.4%, p = 0.15), 1 year (3.0% *versus* 3.7%, p = 0.18), or in late mortality (8.1% *versus* 8.1%). There was a significant difference in favor of the stent group in the incidence of stroke (0.3% *versus* 1.5%, p < 0.0001).

Four studies reported late mortality in patients with diabetes (SYNTAX,[3] CARDIa,[4] FREEDOM,[8] and BEST[9]). In the combined results (n = 3223), mortality up to 5 years was 12.5% in the stent group *versus* 9.7% in the surgery group (p < 0.0001).

Five studies provided the outcomes of the late incidence of combined adverse events (MACCE) divided into subgroups, which are represented in Figure 7. The combined MACCE outcomes in these subgroups (Figure 7) show that a SYNTAX

Study or Subgroup	Stent Events	Stent Total	CABG Events	CABG Total	Weight	Risk Difference M-H, Fixed, 95% CI
BEST 2015	3	438	7	442	9.7%	–0.01 [–0.02, 0.00]
Boudriot et al. 2011	0	100	1	101	2.2%	–0.01 [–0.04, 0.02]
EXCEL 2010	9	948	10	957	21.9%	–0.00 [–0.01, 0.01]
FREEDOM 2012	8	953	15	947	20.9%	–0.01 [–0.02, 0.00]
LE MANS 2008	0	52	2	53	1.2%	–0.04 [–0.10, 0.02]
NOBLE 2016	2	592	7	592	13.0%	–0.01 [–0.02, 0.00]
PRECOMBAT 2011	4	300	9	300	6.6%	–0.02 [–0.04, 0.01]
Subtotal (95 CI)		**3383**		**3392**	**74.7%**	**–0.01 [–0.01, –0.00]**
Total events	26		51			

Heterogeneity: $Chi^2 = 3.65$, df = 6 (p = 0.72); $I^2 = 0\%$
Test for overall effect: Z = 2.83 (p = 0.005)

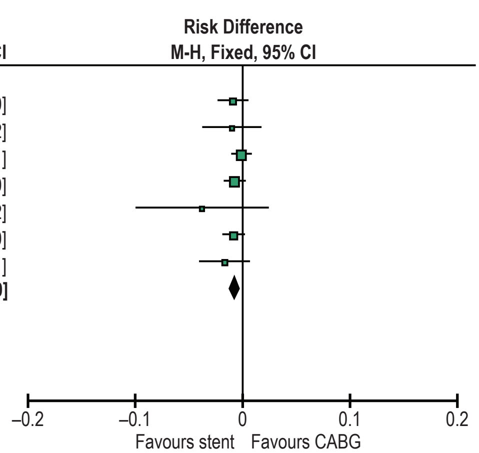

Figure 1 – *Mortality at 30 days: stent versus coronary artery bypass grafting.*
The size of the squares is proportional to the number of patients. The bars represent 95% confidence intervals. The diamond represents the synthesis of the results. Abbreviations: CABG: coronary artery bypass grafting; LE MANS: Left Main Coronary Artery Stenting; FREEDOM: Future Revascularization Evaluation in Patients with Diabetes Mellitus; BEST: Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease; PRECOMBAT: Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; EXCEL: Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NOBLE: Nordic-Baltic-British Left Main Revascularization; Boudriot: study by Boudriot et al.: J Am Coll Cardiol. 2011; 57: 538-545. **.**
Graph obtained using the software Review Manager (RevMan), version 5.3.

Study or Subgroup	Stent Events	Stent Total	CABG Events	CABG Total	Weight	Risk Difference M-H, Fixed, 95% CI
Boudriot et al. 2011	2	100	5	101	1.7%	–0.03 [–0.08, 0.02]
CARDIa 2010	8	254	8	246	4.2%	–0.00 [–0.03, 0.03]
EXCEL 2010	38	948	38	948	16.0%	–0.00 [–0.02, 0.02]
FREEDOM 2012	32	953	30	953	16.1%	–0.00 [–0.01, 0.02]
LE MANS 2008	1	52	4	52	0.9%	–0.06 [–0.14, 0.02]
NOBLE 2016	9	592	17	592	10.0%	–0.01 [–0.03, 0.00]
PRECOMBAT 2011	6	300	8	300	5.1%	–0.01 [–0.03, 0.02]
SYNTAX LM 2009	39	891	30	849	14.7%	0.01 [–0.01, 0.03]
VA-CARDIS 2013	8	101	5	97	1.7%	0.03 [–0.04, 0.10]
Subtotal (95% CI)		**4191**		**4138**	**70.3%**	**–0.00 [–0.01, 0.01]**
Total events	143		145			

Heterogeneity: Chi² = 7.31, df = 8 (p = 0.50); I² = 0%
Test for overall effect: Z = 0.25 (p = 0.080)

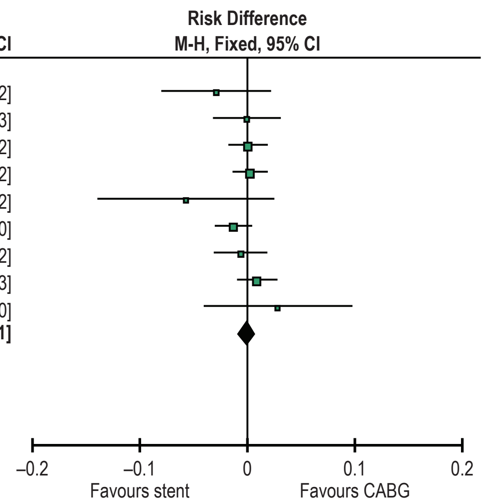

Figure 2 – *Mortality at 1 year: stent versus coronary artery bypass grafting.*
The size of the squares is proportional to the number of patients. The bars represent 95% confidence intervals. The diamond represents the synthesis of the results. Abbreviations: CABG: coronary artery bypass grafting; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; CARDia: Coronary Artery Revascularization in Diabetes; LE MANS: Left Main Coronary Artery Stenting; FREEDOM: Future Revascularization Evaluation in Patients with Diabetes Mellitus; VA CARDS: Coronary Artery Revascularization in Diabetes; BEST: Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease; NOBLE: Nordic-Baltic-British Left Main Revascularization; Boudriot: study by Boudriot et al.: J Am Coll Cardiol. 2011; 57: 538-545. ***Graph obtained using the software Review Manager (RevMan), version 5.3.***

Study or Subgroup	Stent Events	Stent Total	CABG Events	CABG Total	Weight	Risk Difference M-H, Fixed, 95% CI
BEST 2015	28	437	22	440	7.3%	0.01 [–0.02, 0.04]
CARDIa 2010	35	254	31	248	4.2%	0.01 [–0.05, 0.07]
EXCEL 2010	71	913	53	903	15.2%	0.02 [–0.00, 0.04]
FREEDOM 2012	114	894	83	859	14.7%	0.03 [0.00, 0.06]
LE MANS 2008	11	52	16	53	0.9%	–0.09 [–0.26, 0.08]
NOBLE 2016	36	592	33	592	9.9%	0.01 [–0.02, 0.03]
PRECOMBAT 2011	17	279	23	275	4.6%	–0.02 [–0.07, 0.02]
SYNTAX LM 2009	123	871	92	805	14.0%	0.03 [–0.00, 0.06]
Subtotal (95% CI)		**4292**		**4175**	**70.9%**	**0.02 [0.00, 0.03]**
Total events	435		353			

Heterogeneity: Chi² = 6.85, df = 7 (p = 0.44); I² = 0%
Test for overall effect: Z = 2.58 (p = 0.010)

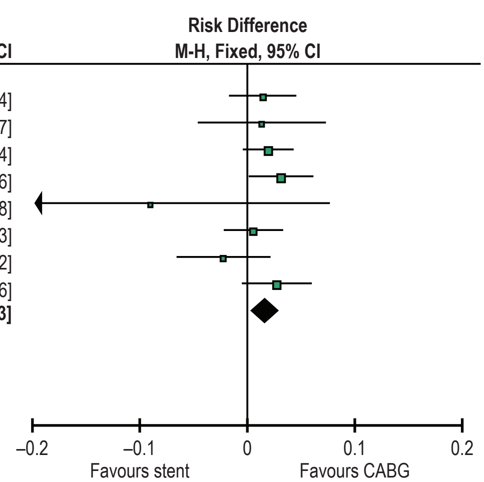

Figure 3 – *Late mortality: stent versus coronary artery bypass grafting.*
The size of the boxes is proportional to the number of patients. The bars represent 95% confidence intervals. The diamond represents the synthesis of the results. Abbreviations: CABG: coronary artery bypass grafting; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; CARDia: Coronary Artery Revascularization in Diabetes; LE MANS: Left Main Coronary Artery Stenting; FREEDOM: Future Revascularization Evaluation in Patients with Diabetes Mellitus; VA CARDS: Coronary Artery Revascularization in Diabetes; BEST: Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease; PRECOMBAT: Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; EXCEL: Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NOBLE: Nordic-Baltic-British Left Main Revascularization Study; Boudriot: study by Boudriot et al.: J Am Coll Cardiol. 2011; 57: 538-545. ***Graph obtained using the software Review Manager (RevMan), version 5.3.***

score in the upper tertile and the occurrence of diabetes had a strong negative influence on the PCI outcome. In patients in the lower SYNTAX tertile and in those without diabetes, there was no significant difference in terms of MACCE between the CABG and PCI groups. The elderly condition and the female gender contributed to the difference in results but to a lesser degree. An ejection fraction < 50% did not contribute significantly to the difference in results.

Study or Subgroup	Stent Events	Stent Total	CABG Events	CABG Total	Weight	Risk Difference M-H, Fixed, 95% CI
Boudriot et al. 2011	0	100	2	101	1.7%	–0.02 [–0.05, 0.01]
CARDIa 2010	1	254	7	248	4.2%	–0.02 [–0.05, –0.05]
EXCEL 2010	5	948	12	948	15.9%	–0.01 [–0.02, 0.00]
FREEDOM 2012	3	953	16	947	16.0%	–0.01 [–0.02, –0.00]
LE MANS 2008	0	52	2	54	0.9%	–0.04 [–0.10, 0.02]
NOBLE 2016	1	593	4	592	10.0%	–0.01 [–0.01, 0.00]
PRECOMBAT 2011	0	300	2	300	5.0%	–0.01 [–0.02, 0.00]
SYNTAX LM 2009	6	903	19	897	15.1%	–0.01 [–0.03, –0.00]
VA-CARDIS 2013	0	101	1	97	1.7%	–0.01 [–0.04, 0.02]
Subtotal (95% CI)		**4204**		**4184**	**70.5%**	**–0.01 [–0.02, –0.01]**
Total events	16		65			

Heterogeneity: Chi² = 7.53, df = 8 (p = 0.48); I² = 0%
Test for overall effect: Z = 5.37 (p = 0.00001)

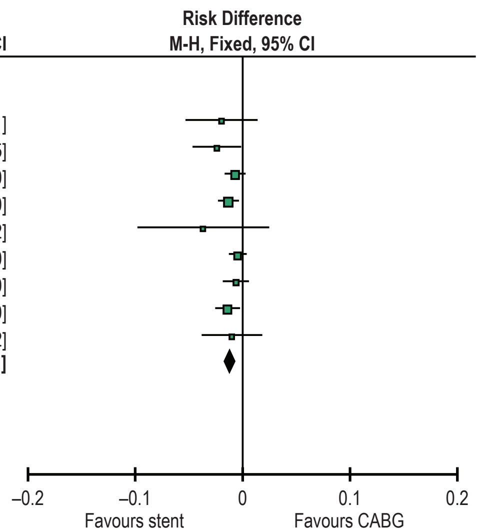

Figure 4 – *Stroke: stent versus coronary artery bypass grafting.*
The size of the boxes is proportional to the number of patients. The bars represent 95% confidence intervals. The diamond represents the synthesis of the results. Abbreviations: CABG: coronary artery bypass grafting; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; CARDia: Coronary Artery Revascularization in Diabetes; LE MANS: Left Main Coronary Artery Stenting; FREEDOM: Future Revascularization Evaluation in Patients with Diabetes Mellitus; VA CARDS: Coronary Artery Revascularization in Diabetes; BEST: Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease; PRECOMBAT: Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; EXCEL: Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NOBLE: Nordic-Baltic-British Left Main Revascularization Study; Boudriot: study by Boudriot et al.: J Am Coll Cardiol. 2011; 57: 538-545. Graph obtained using the software Review Manager (RevMan), version 5.3.

Study or Subgroup	Stent Events	Stent Total	CABG Events	CABG Total	Weight	Risk Difference M-H, Fixed, 95% CI
Boudriot et al. 2011	2	100	5	101	4.3%	–0.03 [–0.08, 0.02]
EXCEL 2010	38	948	38	948	40.4%	0.00 [–0.02, 0.02]
LE MANS 2008	1	52	4	52	2.2%	–0.06 [–0.14, 0.02]
NOBLE 2016	9	592	17	592	25.2%	–0.01 [–0.03, 0.00]
PRECOMBAT 2011	6	300	8	300	12.8%	–0.01 [–0.03, 0.02]
SYNTAX LM 2013	15	357	15	348	15.0%	–0.00 [–0.03, 0.03]
Total (95% CI)		**2349**		**2341**	**100.0%**	**–0.01 [–0.02, 0.00]**
Total events	71		87			

Heterogeneity: Chi² = 3.60, df = 5 (p = 0.61); I² = 0%
Test for overall effect: Z = 1.33 (p = 0.18)

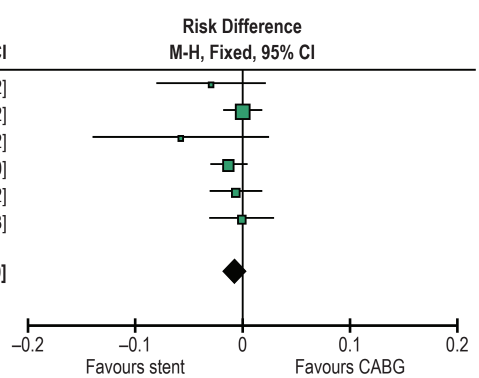

Figure 5 – *Studies including the left main coronary artery. Mortality at 1 year: Stent versus coronary artery bypass grafting.*
The size of the boxes is proportional to the number of patients. The bars represent 95% confidence intervals. The diamond represents the synthesis of the results. Abbreviations: CABG: coronary artery bypass grafting; LE MANS: Left Main Coronary Artery Stenting; SYNTAX LM: left main coronary artery subgroup of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery); PRECOMBAT: Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; EXCEL: Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NOBLE: Nordic-Baltic-British Left Main Revascularization; Boudriot: study by Boudriot et al.: J Am Coll Cardiol. 2011; 57: 538-545. Graph obtained using the software Review Manager (RevMan), version 5.3.

Discussion

Several systematic reviews, collaborative studies, and meta-analyses[13-18] have been published comparing PCI and CABG. The most important ones included studies of the balloon and bare-metal stent era or left out important recent studies.[14-16] The main differential of the present meta-analysis is the large number of included studies and patients and the fact that it is up-to-date and included only trials of the drug-eluting stent era.

Study or Subgroup	Stent Events	Stent Total	CABG Events	CABG Total	Weight	Risk Difference M-H, Fixed, 95% CI
EXCEL 2010	71	913	53	903	41.6%	0.02 [–0.00, 0.04]
LE MANS 2008	11	52	16	53	2.4%	–0.09 [–0.26, 0.08]
NOBLE 2016	36	592	33	592	27.1%	0.01 [–0.02, 0.03]
PRECOMBAT 2011	17	279	23	275	12.7%	–0.02 [–0.07, 0.02]
SYNTAX LM 2013	42	357	50	348	16.2%	–0.03 [–0.08, 0.02]
Total (95% CI)		**2193**		**2171**	**100.0%**	**0.00 [–0.02, 0.02]**
Total events	177		87			

Heterogeneity: $Chi^2 = 5.99$, df = 4 (p = 0.20); $I^2 = 33\%$
Test for overall effect: Z = 0.01 (p = 1.00)

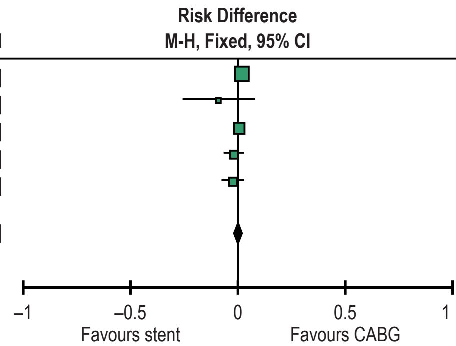

Figure 6 – *Studies including the left main coronary artery. Late mortality: stent versus coronary artery bypass grafting.*
The size of the boxes is proportional to the number of patients in the trial. The bars represent 95% confidence intervals. The diamond represents the synthesis of the results.
Abbreviations: CABG: coronary artery bypass grafting; LE MANS: Left Main Coronary Artery Stenting; SYNTAX LM: left main coronary artery subgroup of SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery); PRECOMBAT: Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; EXCEL - Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NOBLE: Nordic-Baltic-British Left Main Revascularization; Boudriot: study by Boudriot et al.: J Am Coll Cardiol. 2011; 57: 538-545. ***.*** *Graph obtained using the software Review Manager (RevMan), version 5.3.*

In the evaluation of the results, it is important to highlight the superiority of PCI in the mortality at 30 days. This is in line with a prior systematic review[17] and with the New York registry.[19] The difference is obviously not applicable to patients with lesions of high angiographic complexity, as seen in the analysis of the survival curves of aggregated results from SYNTAX LM and PRECOMBAT.[20] A greater incidence of stroke in the surgical group had already been suggested in prior systematic reviews,[14,17] and in the light of the data presented here, this fact becomes indisputable. It is worth mentioning a reduced incidence of stroke in more recent studies, reflecting a greater care taken by surgeons while manipulating the aorta. The similarity of the mortality results at 1 year is aligned with a prior systematic review, which included studies of the era prior to drug-eluting stents.[17] The difference favoring surgery in regards to late mortality is consistent with another meta-analysis[16] and also with a recently published collaborative study.[21] It should be emphasized that the difference found was due to the large number of patients with diabetes in the studies of the drug-eluting stent era, which disappeared in the aggregated results when these studies were excluded. These data confirm those of the collaborative study by Hlatki et al.[15], which demonstrated a lower overall mortality at 5 years with surgery, but no difference among nondiabetic patients. We should emphasize that the study by Hlatki et al.[15] included trials of the balloon era in which two-vessel disease predominated, while in the present review there was a predominance of three-vessel disease and obstruction of the left main coronary artery.

In regards to the results of obstruction of the left main coronary artery, it is important to remember that the group of patients with this type of obstruction comprised for a long time a forbidden territory for angioplasty. LE MANS was the first randomized study that attempted to compare stent and surgery in left main coronary artery obstruction, with results similar or even superior to those with PCI. However, this was a small study (105 patients), which has been criticized for not having used grafting of internal thoracic artery in approximately 25% of the cases. After that, emerged the results of the SYNTAX[12] subgroup with left main coronary artery obstruction and of the PRECOMBAT trial and the study by Boudriot et al.[5], which led to the improvement of the recommendations of PCI in left main artery obstruction. Despite that, the American guidelines only changed the recommendation to IIA in patients with a low SYNTAX score and IIB in patients with intermediate SYNTAX scores.[18] We should emphasize that such recommendations are restricted to patients with a high surgical risk. In the present study, which combined the results of six studies with 4700 patients, the outcomes of PCI with drug-eluting stents were equal or even greater than those with CABG. In light of these evidence and recent results of NOBLE and EXCEL, we believe that the American and Brazilian guidelines[22,23] may be soon modified to improve the classification of PCI with drug-eluting stents, mainly in left main coronary artery obstruction.

In relation to the results in patients with diabetes, it is important to remember that the evidence contrary to PCI in diabetes has its origin in the balloon era, from occasional

Study or Subgroup	Stent Events	Stent Total	CABG Events	CABG Total	Weight	Risk Difference M-H, Fixed, 95% CI
1.7.1 Patients with diabetes						
BEST 2015	34	177	17	186	1.5%	0.10 [0.03, 0.17]
EXCEL 2016	51	256	47	259	2.1%	0.02 [–0.05, 0.09]
FREEDOM 2012	257	953	179	947	7.8%	0.08 [0.04, 0.12]
PRECOMBAT 2011	23	102	15	90	0.8%	0.06 [–0.05, 0.17]
SYNTAX LM 2009	54	226	43	226	1.9%	0.05 [–0.03, 0.12]
Subtotal (95% CI)		**1714**		**1708**	**14.1%**	**0.00 [–0.02, 0.02]**
Total events	419		301			
Heterogeneity: $Chi^2 = 3.63$, df = 4 (p = 0.46); $I^2 = 0\%$						
Test for overall effect: Z = 4.90 (p = 0.00001)						
1.7.2 Patients without diabetes						
BEST 2015	33	261	30	256	2.1%	0.01 [–0.05, 0.07]
EXCEL 2016	86	692	88	707	5.8%	–0.00 [–0.03, 0.03]
PRECOMBAT 2011	29	198	27	210	1.7%	0.02 [–0.05, 0.08]
SYNTAX LM 2009	133	679	107	669	5.6%	0.04 [–0.00, 0.08]
Subtotal (95% CI)		**1830**		**1842**	**14.1%**	**0.02 [–0.01, 0.04]**
Total events	281		252			
Heterogeneity: $Chi^2 = 1.83$, df = 3 (p = 0.61); $I^2 = 0\%$						
Test for overall effect: Z = 1.42 (p = 0.16)						
1.7.3 Elderly						
BEST 2015	41	229	30	252	2.0%	0.06 [–0.00, 0.12]
EXCEL 2016	82	466	67	463	3.8%	0.03 [–0.02, 0.08]
PRECOMBAT 2011	15	129	30	252	1.4%	–0.00 [–0.07, 0.07]
Subtotal (95% CI)		**824**		**967**	**7.2%**	**0.03 [–0.00, 0.07]**
Total events	138		127			
Heterogeneity: $Chi^2 = 1.74$, df = 2 (p = 0.42); $I^2 = 0\%$						
Test for overall effect: Z = 1.91 (p = 0.06)						
1.7.4 Nonelderly						
BEST 2015	26	209	17	190	1.6%	0.03 [–0.03, 0.10]
EXCEL 2016	55	482	68	485	4.0%	–0.03 [–0.07, 0.02]
PRECOMBAT 2011	21	171	10	171	1.4%	0.06 [0.00, 0.12]
Subtotal (95% CI)		**862**		**846**	**7.1%**	**0.01 [–0.02, 0.04]**
Total events	102		95			
Heterogeneity: $Chi^2 = 6.69$, df = 2 (p = 0.04); $I^2 = 70\%$						
Test for overall effect: Z = 0.41 (p = 0.68)						
1.7.5 Male gender						
BEST 2015	45	304	34	325	2.6%	0.04 [–0.01, 0.10]
EXCEL 2016	94	722	107	742	6.0%	–0.01 [–0.05, 0.02]
FREEDOM 2012	188	698	118	658	5.6%	0.09 [0.05, 0.13]
PRECOMBAT 2011	39	228	30	231	1.9%	0.04 [–0.02, 0.11]
Subtotal (95% CI)		**1952**		**1956**	**16.1%**	**0.04 [0.01, 0.06]**
Total events	366		289			
Heterogeneity: $Chi^2 = 13.75$, df = 3 (p = 0.003); $I^2 = 78\%$						
Test for overall effect: Z = 3.20 (p = 0.001)						
1.7.6 Female gender						
BEST 2015	22	134	13	137	1.1%	0.07 [–0.01, 0.15]
EXCEL 2016	43	226	28	215	1.8%	0.06 [–0.01, 0.13]
FREEDOM 2012	67	256	61	289	2.2%	0.05 [–0.02, 0.12]
PRECOMBAT 2011	13	72	12	69	0.6%	0.01 [–0.12, 0.13]
Subtotal (95% CI)		**688**		**710**	**5.8%**	**0.05 [0.01, 0.09]**
Total events	145		114			
Heterogeneity: $Chi^2 = 0.73$, df = 3 (p = 0.87); $I^2 = 0\%$						
Test for overall effect: Z = 2.56 (p = 0.01)						
1.7.7 Reduced ejection fraction						
BEST 2015	7	17	4	17	0.1%	0.18 [–0.13, 0.49]
EXCEL 2016	20	111	20	115	0.9%	0.01 [–0.09, 0.11]
FREEDOM 2012	13	21	3	11	0.1%	0.35 [0.01, 0.68]
Subtotal (95% CI)		**149**		**143**	**1.2%**	**0.06 [–0.03, 0.05]**
Total events	40		27			
Heterogeneity: $Chi^2 = 4.47$, df = 2 (p = 0.11); $I^2 = 55\%$						
Test for overall effect: Z = 1.28 (p = 0.20)						
1.7.8 Non-reduced ejection fraction						
BEST 2015	60	421	43	425	3.5%	0.04 [–0.00, 0.09]
EXCEL 2016	109	782	111	786	6.5%	–0.00 [–0.04, 0.03]
FREEDOM 2012	143	620	115	629	5.2%	0.05 [0.00, 0.09]
Subtotal (95% CI)		**1823**		**1840**	**15.1%**	**0.03 [0.00, 0.05]**
Total events	312		269			
Heterogeneity: $Chi^2 = 3.87$, df = 2 (p = 0.14); $I^2 = 48\%$						
Test for overall effect: Z = 2.09 (p = 0.04)						
1.7.9 SYNTAX lower tertile						
BEST 2015	24	185	23	186	1.5%	0.01 [–0.06, 0.07]
EXCEL 2016	28	294	46	364	2.7%	–0.03 [–0.08, 0.02]
FREEDOM 2012	75	329	58	340	2.8%	0.06 [–0.00, 0.12]
PRECOMBAT 2011	16	128	13	104	0.9%	0.00 [–0.09, 0.09]
SYNTAX LM 2009	64	402	64	401	3.3%	–0.00 [–0.03, 0.12]
Subtotal (95% CI)		**1338**		**1395**	**11.2%**	**0.00 [–0.02, 0.03]**
Total events	207		204			
Heterogeneity: $Chi^2 = 5.24$, df = 4 (p = 0.26); $I^2 = 24\%$						
Test for overall effect: Z = 0.54 (p = 0.59)						
1.7.10 SYNTAX upper tertile						
BEST 2015	13	66	10	79	0.6%	0.07 [–0.05, 0.19]
EXCEL 2016	37	220	30	217	1.8%	0.03 [–0.04, 0.10]
FREEDOM 2012	56	182	41	192	1.5%	0.09 [0.01, 0.18]
PRECOMBAT 2011	14	58	13	68	0.5%	0.05 [–0.09, 0.19]
SYNTAX LM 2009	76	290	54	315	2.5%	0.09 [0.03, 0.16]
Subtotal (95% CI)		**816**		**871**	**7.0%**	**0.07 [0.03, 0.11]**
Total events	196		148			
Heterogeneity: $Chi^2 = 2.11$, df = 4 (p = 0.72); $I^2 = 0\%$						
Test for overall effect: Z = 3.63 (p = 0.0003)						

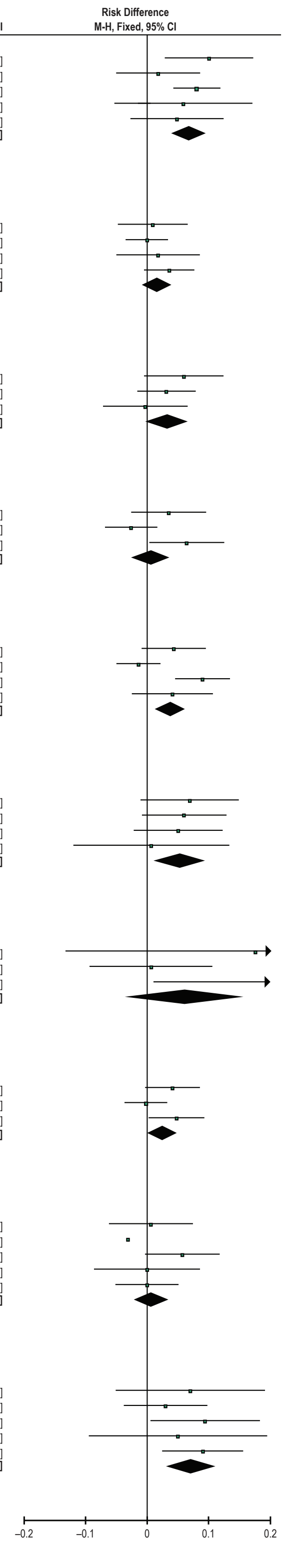

Figure 7 – *Combined adverse events outcomes (major adverse cardiovascular and cerebrovascular disease events, MACCE) in subgroups in five studies. The size of each box is proportional to the number of patients in the subgroup. The bar is equal to the confidence interval. The diamonds represent the synthesis of the results. In the SYNTAX, FREEDOM, and EXCEL, the combined events were death, acute myocardial infarction (AMI), and stroke. In the remaining studies, they were death, AMI, and new revascularization.*

Abbreviations: CABG: coronary artery bypass grafting; SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; FREEDOM: Future Revascularization Evaluation in Patients with Diabetes Mellitus; PRECOMBAT: Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; EXCEL: Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization. Graph obtained using the software Review Manager (RevMan), version 5.3.

Table 1 – Overview of randomized studies comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in the era of drug-eluting stents

Study	Origin	Year of publication	Number of patients	Disease extension	Patients with diabetes(%)	Unstable angina(%)	Mean ejection fraction (%)	Type of stent	Follow-up Maximum
LEMANS[1]	Poland	2008	105	LMCA	25	32	53 ± 11	BMS and DES	10
SYNTAX[2]	International	2009	1800	LMCA and three-vessel disease	35	28	ND ‡	SF	5
CARDia[4]	United Kingdom	2010	510	Two- and three-vessel disease	100	22	59 ± 14	BMS and DES	5
Boudriot et al.[5]	Germany	2011	201	LMCA	30	ND	ND	DES	1
PRECOMBAT[6]	South Korea	2011	600	LMCA	42	45	60 ± 9	DES	5
FREEDOM[8]	International	2012	1900	Two- and three-vessel disease	100	30	65 ± 12	DES	5
Va-Cards[7]	USA	2013	198	Two- and three-vessel disease	100	ND	ND†	DES	2
BEST[9]	South Korea	2015	880	Two- and three-vessel disease	45	42	59 ± 9	DES	5
EXCEL[11]	International	2016	1905	LMCA	25	37	57 ± 10	DES	3
NOBLE[10]	Europe	2016	982	LMCA	18	18	60 ± 10	DES	5

SYNTAX: Synergy between PCI with Taxus and Cardiac Surgery; CARDia: Coronary Artery Revascularization in Diabetes; LE MANS: Left Main Coronary Artery Stenting; FREEDOM: Future Revascularization Evaluation in Patients with Diabetes Mellitus; VA CARDS: Coronary Artery Revascularization in Diabetes; BEST: Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease; PRECOMBAT: Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; EXCEL: Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; NOBLE: Nordic-Baltic-British Left Main Revascularization Study; Boudriot - study by Boudriot et al.: J Am Coll Cardiol. 2011; 57: 538-545; DES: drug-eluting stent; BMS: bare-metal stent; LMCA: left main coronary artery; USA: United States. †: 37% with ejection fraction < 55%; ‡: 3% with ejection fraction < 30%.

findings of the BARI study. The investigators of this study evaluated a subgroup of 343 patients with diabetes and found a late mortality of 34.5% for PCI with balloon and 19.4% for surgery ($p = 0.03$). In the era of conventional stent, studies such as SoS and ARTS have confirmed a trend toward greater mortality with PCI in patients with diabetes, even though it did not reach statistical significance. From there onwards, the presence of diabetes has become a criterion for preferential indication of surgery as a method for myocardial revascularization. There used to be a hypothesis that drug-eluting stents would eliminate the differences in mortality found in these studies, but the results presented here demonstrate that the difference in mortality between PCI and surgery in patients with diabetes continues in the era of drug-eluting stents. However, it should be noted a reduced risk difference compared with previous studies (3.5% risk difference as opposed to 7.3% in the study by Hclatki et al. and 15.1% in BARI). This should raise the hypothesis that it is not the metabolic disorder in itself, but the complexity of the lesions which is the factor leading to a higher mortality of angioplasty in patients with diabetes. This question could perhaps be explained by a meta-analysis of individual patient data involving a large number of studies. In this sense, a recent collaborative study categorizing the results of three studies (SYNTAX, BEST, and PRECOMBAT) corroborated this hypothesis.[24]

The MACCE outcomes in subgroups (Figure 7) in the present study demonstrate that the SYNTAX score in the upper tertile strongly and negatively influenced the PCI outcomes, similarly to the presence of diabetes. The elderly condition and the female gender had a small influence on the results; an ejection fraction < 50% did not negatively influence the PCI outcomes, but an ejection fraction < 35% had a greater impact, even though it had no statistical significance. These results are in agreement with those of the collaborative study by Cavalcante et al.[20] In that study, by aggregating the results of the SYNTAX LEFT MAIN and PRECOMBAT for combined adverse events (death, stroke, AMI, and new revascularization), a high SYNTAX score, like diabetes, had an important role. The female gender, elderly condition, ejection fraction < 50%, and renal insufficiency did not negatively affect the results compared with PCI. This same study showed that the subgroups most significantly affecting PCI-associated mortality outcomes in obstruction of the left main coronary artery were those with two- or three-vessel disease and with a SYNTAX score > 32. Diabetes had a less important role, possibly related to the fact that only patients with left main coronary artery obstruction were evaluated.

Study limitations

This study has important limitations. Because the meta-analysis included published data rather than individual patient data, we were unable to analyze the mortality outcomes in subgroups, except in those with diabetes. Additionally, the percentages had to be processed as absolute numbers, which may deserve criticism. The results apply only to patients in whom revascularization is possible by both methods and without a high surgical risk or history of prior surgical revascularization, and with the procedures carried out in institutions of excellence.

Conclusion

In combined results of randomized studies involving multivessel disease or obstruction of the left main coronary artery, PCI with drug-eluting stent was associated with a lower incidence of stroke, lower mortality at 30 days, and increased late mortality when compared with CABG. There was no difference in early, intermediate, or late mortality in the subgroup with left main coronary obstruction, but there was a difference in favor of PCI in regards to the incidence of stroke. The presence of diabetes and a high SYNTAX score were factors most strongly and negatively impacting PCI outcomes in terms of combined adverse results.

Author contributions

Conception and design of the research: Andrade PJN. Acquisition of data: Andrade PJN, Falcão JLAA, Andrade AT, Falcão BAA. Analysis and interpretation of the data: Andrade PJN, Rocha HAL, Falcão JLAA, Andrade AT. Statistical analysis: Rocha HAL. Writing of the manuscript: Andrade PJN, Rocha HAL, Falcão JLAA, Falcão BAA. Critical revision of the manuscript for intellectual content: Andrade PJN, Falcão BAA. Supervision / as the major investigador: Andrade PJN.

Potential Conflict of Interest

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Study Association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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