# **ORIGINAL ARTICLE**

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

Pedro José Negreiros de Andrade,<sup>1,2</sup> Hermano Alexandre Lima Rocha,<sup>1,3</sup> João Luiz de Alencar Araripe Falcão,<sup>1,2</sup> Antonio Thomaz de Andrade,<sup>1</sup> Breno de Alencar Araripe Falcão<sup>1,4</sup>

Hospital Dr. Carlos Alberto Studart Gomes, Messejana,<sup>1</sup> Universidade Federal do Ceará (UFC),<sup>2</sup> Centro Universitário Christus,<sup>3</sup> Universidade Estadual do Ceará (UECE),<sup>4</sup> Fortaleza, CE – Brazil

## 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.<sup>1-12</sup> 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

Mailing address: Pedro José Negreiros de Andrade

Francisco Holanda, 992, Ap.: 1101. Postal Code 60130-040, Dionisio Torres, Fortaleza, CE – Brazil. E-mail: pedroneg@gmail.com; pedroneg@gmail.com

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<sup>1,4</sup> 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,<sup>1</sup> SYNTAX,<sup>2-3</sup> CARDia,<sup>4</sup> Boudriot et al.,<sup>5</sup> PRECOMBAT,<sup>6</sup> VA CARDS,<sup>7</sup> FREEDOM,<sup>8</sup> BEST,<sup>9</sup> NOBLE,<sup>10</sup> and EXCEL.<sup>11</sup> 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.<sup>2,4,7</sup> 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<sup>2</sup> and one for 10 years.<sup>1</sup> We were unable to obtain this information from two studies.<sup>5,7</sup> 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,<sup>2</sup> 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.<sup>24,6,8,9</sup> Combined MACCE comprised death, AMI, and new revascularization in two of these trials,<sup>6,9</sup> 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 154

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<sup>1</sup> 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<sup>4</sup> used initially bare-metal stents and only assessed patients with diabetes and multivessel disease; SYNTAX<sup>2</sup> evaluated left main coronary artery obstruction and multivessel disease and used first-generation drug-eluting stents (TAXUS); FREEDOM<sup>8</sup> and VA CARDS<sup>7</sup> exclusively

assessed patients with diabetes and multivessel disease; BEST<sup>9</sup> evaluated patients with multivessel disease and used only everolimus-eluting stents; the study by Boudriot et al.<sup>5</sup> evaluated left main coronary artery obstruction and used only sirolimus-eluting stents; EXCEL<sup>11</sup> evaluated left main coronary artery obstruction and used only everolimuseluting stents; NOBLE<sup>10</sup> 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,<sup>2</sup> FREEDOM,<sup>8</sup> BEST,<sup>9</sup> and CARDIa<sup>4</sup>), 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,<sup>1</sup> SYNTAX LEFT MAIN,<sup>12</sup> PRECOMBAT,<sup>6</sup> EXCEL,<sup>11</sup> NOBLE,<sup>10</sup> and the study by Boudriot et al.<sup>5</sup>) 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).

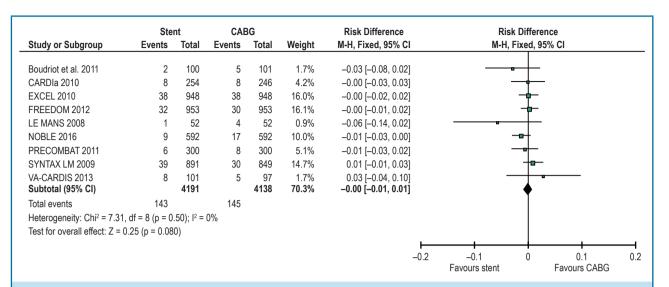
Four studies reported late mortality in patients with diabetes (SYNTAX,<sup>3</sup> CARDIa,<sup>4</sup> FREEDOM,<sup>8</sup> and BEST<sup>9</sup>). In the combined results (n = 3223), mortality up to 5 years was 12.5% in the stent group *versus* 9.7% in the surgery group (p < 0.0001).

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

	Ste	nt	CAE	3G		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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]	-0-
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]	-8-
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 <sup>2</sup> = 3.6	5, df = 6 (p = 0	.72); I <sup>2</sup> =	0%				
Test for overall effect: Z =	2.83 (p = 0.00	5)					
						<u> </u>	
						-0.2	-0.1 0 0.1 0

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.



#### 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 Everolinus-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.

	Ste	nt	CAE	BG		Risk Difference	Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
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]	<b>←</b>	
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 Subtotal (95% CI)	123	871 <b>4292</b>	92	805 <b>4175</b>	14.0% <b>70.9%</b>	0.03 [–0.00, 0.06] <b>0.02 [0.00, 0.03]</b>	•	
Total events	435		353					
Heterogeneity: Chi <sup>2</sup> = 6.8	5, df = 7 (p = 0	.44); I <sup>2</sup> =	0%					
Test for overall effect: Z =	2.58 (p = 0.01	0)						
							F F F	
						-	-0.2 -0.1 0 0.1	

#### 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.

	Ste	nt	CAE	3G		Risk Difference	Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
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]	<b>u</b>	
EXCEL 2010	5	948	12	948	15.9%	-0.01 [-0.02, 0.00]	-8-	
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]	<u>_</u>	
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]	-0-	
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: Chi <sup>2</sup> = 7.5	3, df = 8 (p = 0	.48); l <sup>2</sup> =	0%					
Test for overall effect: Z =	= 5.37 (p = 0.00	001)						
						H		
						-0.2	-0.1 0 0.1	0.
							Favours stent Favours CABG	

#### 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.

	Ste	Stent		CABG		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	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]	a
NOBLE 2016	9	592	17	592	25.2%	-0.01 [-0.03, 0.00]	-8+
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: Chi <sup>2</sup> = 3.6	0, df = 5 (p = 0	.61); I <sup>2</sup> =	0%			Ļ.	
Test for overall effect: Z =	1.33 (p = 0.18	3)				-0.2	–0.1 0 0.1 0 Favours stent Favours CABG

**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<sup>13-18</sup> 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.<sup>14-16</sup> 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.

s		nt	CABG			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
EXCEL 2010	71	913	53	903	41.6%	0.02 [-0.00, 0.04]	Þ
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]	ф –
PRECOMBAT 2011	17	279	23	275	12.7%	-0.02 [-0.07, 0.02]	4
SYNTAX LM 2013	42	357	50	348	16.2%	-0.03 [-0.08, 0.02]	-8-
Total (95% CI)		2193		2171	100.0%	0.00 [-0.02, 0.02]	•
Total events	177		87				
Heterogeneity: Chi <sup>2</sup> = 5.9	9, df = 4 (p = 0	.20); I <sup>2</sup> =	33%				
Test for overall effect: Z =	0.01 (p = 1.00	)				-	-1 -0.5 0 0.5 1 Favours stent Favours CABG

**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 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<sup>17</sup> and with the New York registry.<sup>19</sup> 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.<sup>20</sup> A greater incidence of stroke in the surgical group had already been suggested in prior systematic reviews,<sup>14,17</sup> 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.<sup>17</sup> The difference favoring surgery in regards to late mortality is consistent with another meta-analysis<sup>16</sup> and also with a recently published collaborative study.<sup>21</sup> It should be emphasized that the difference found was due to the large number of patients with diabetes in the studies of the drugeluting 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.<sup>15</sup>, 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.<sup>15</sup> 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<sup>12</sup> 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<sup>22,23</sup> 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

REEDCUART 2012 22 9 83 179 67 756 0.06 [0.0.07] 122 42 42 224 42 226 197 20 0.06 [-0.0.07] 122 42 42 224 42 226 197 20 0.06 [-0.0.07] 122 42 42 197 20 170 42 197 20 170 42 197 20 170 42 197 20 170 20 10 10 0.07] 123 42 4 40 - 200 1 - 200 1 - 200 1 - 200 0 - 200 1 - 200 0 0.07] 123 42 4 40 - 201 1 - 20 - 201 1 - 200 1 - 200 0 - 201 - 200 0 0.07] 123 42 4 40 - 201 1 - 20 - 201 1 - 200 1 - 200 0 - 201 - 200 0 0.07] 123 42 4 4 - 20 - 201 1 - 200 - 201 - 200 0 - 200 - 200 0										
7.1 Protection with adducts         7.2 Protection with adducts         SXE2_206       8       9       7.5       0.00	Study or Column					M-1-1 -				
EST 2015       34       77       17       196       105       0.010 (0.01.17)         FEEDUAL (0.11)       17       176       186       0.010 (0.01.17)         FEEDUAL (0.11)       178       1.05       0.010 (0.01.17)         FEEDUAL (0.11)       178       0.010 (0.01.17)       0.010 (0.01.17)         FEEDUAL (0.11)       178       0.010 (0.01.17) <t< td=""><td></td><td></td><td>Total</td><td>Events</td><td>Total</td><td>Weight</td><td>M-H, Fixed, 95% CI</td><td>M-H, Fixed, 95% Cl</td></t<>			Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl		
SXE2.206       S<			177	17	186	1.5%	0 10 0 03 0 171	<b>_</b>		
SECOLATION         20         000         0.00	EXCEL 2016									
VNLIVLAURDE       4       228       4       228       196       001       000       001         Understand       250.20       301       301       301       301       301       301         22.0       100 </td <td>FREEDOM 2012</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	FREEDOM 2012									
At 17.4         17.4         17.4         17.4         17.6         44.15         0.00 [-0.02, 0.07]           17. Protect at the 2 = 4.90 (p = 0.0001)         17.5         18.6         2.7.8         0.01 (-0.02, 0.07)           17. Protect at the 2 = 4.90 (p = 0.0001)         19.8         2.7.9         0.01 (-0.02, 0.07)           17. Protect at the 2 = 4.90 (p = 0.0001)         19.8         2.7.8         0.01 (-0.02, 0.07)           17. Protect at the 2 = 4.90 (p = 0.0001)         19.8         2.7.8         0.01 (-0.02, 0.07)           17. Protect at the 2 = 1.40 (p = 1.0001)         19.82         2.7.8         0.01 (-0.02, 0.07)           17. State for an at the 2 = 1.40 (p = 1.0001)         19.82         14.15         0.01 (-0.02, 0.07)           17. State for an at the 2 = 1.40 (p = 1.0001)         17.7         0.01 (-0.02, 0.07)         0.01 (-0.02, 0.07)           17. State for an at the 2 = 1.00 (p = 1.0001)         17.7         0.01 (-0.02, 0.07)         0.01 (-0.02, 0.07)           17. State for an at the 2 = 1.00 (p = 1.0001)         17.7         18.4         0.01 (-0.02, 0.07)           17. State for an at the 2 = 1.00 (p = 1.0001)         17.7         18.4         0.01 (-0.02, 0.07)           17. State for an at the 2 = 1.00 (p = 1.0001)         17.7         18.4         0.01 (-0.0, 0.07)           18.1 State (p = 0.							0.06 [-0.05, 0.17]			
bit de norm         419         90           et de normal dinez 2 + 4 20 p = 0.0001; 00         27           27 Partiest Worksomer         80         26         2.1%         0.01 [-0.05, 0.07]           EST 2015         31         0.21         37         0.25         0.01 [-0.05, 0.07]           FECURATIONI         189         77         55         0.01 [-0.05, 0.07]         0.01 [-0.05, 0.07]           FECURATIONI         189         77         55         0.01 [-0.05, 0.07]         0.01 [-0.05, 0.07]           FECURATIONI         189         72         20         1.44         0.01 [-0.05, 0.07]           FECURATIONI         189         72         20         0.00 [-0.05, 0.07]         0.01 [-0.05, 0.07]           FECURATIONI         189         72         20         0.00 [-0.05, 0.07]         0.01 [-0.05, 0.07]           FECURATIONI         189         72         20         0.01 [-0.05, 0.07]         0.01 [-0.05, 0.07]           FECURATIONI         189         72         20         0.01 [-0.05, 0.07]         0.01 [-0.05, 0.07]           FECURATIONI         189         70         55         0.05 [-0.05, 0.07]         0.01 [-0.05, 0.07]           FECURATIONI         19         20         20		54		43			0.05 [-0.03, 0.12]	•		
able overall field, 27 4 40 p = 0.0001)         257 2016       251 40 p = 0.0001)         257 2016       251 40 p = 0.0001         258 2016       252 16 h = 0.0001         258 2016       252 16 h = 0.0001         258 2016       258 40 p = 0.0001         258 2016       250 h = 0.0001         258 2016       251 40 p = 0.0001     <	Total events	419		301				-		
2.1 Protection whether districts         SPEE_COMMAT 2011       0				0%						
BST 2015       3.0       2.01       0.0       2.01       0.00       0.00       0.00         BST 2015       0.0       0.00       1.75       0.00       0.00       0.00       0.00         BST 2015       1.90       0.00       0.00       0.00       0.00       0.00       0.00         BST 2015       1.90       0.00<	Test for overall effect: Z = 4.9	90 (p = 0.00	001)							
BST 2015       3.0       2.01       0.0       2.01       0.00       0.00       0.00         BST 2015       0.0       0.00       1.75       0.00       0.00       0.00       0.00         BST 2015       1.90       0.00       0.00       0.00       0.00       0.00       0.00         BST 2015       1.90       0.00<	1.7.2 Patients without diab	etes								
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	BEST 2015		261	30	256	2.1%	0.01 [-0.05, 0.07]			
NNRVAL N200       13       67       107       68       5.56       0.04 [= 0.00, 0.05]         State vector       21       22       14.55       0.04 [= 0.00, 0.05]         State vector       23       22       2.56       0.06 [= 0.00, 0.05]         State vector       23       22       2.56       0.06 [= 0.00, 0.12]         State vector       13       127       2.56       0.06 [= 0.00, 0.12]         State vector       13       127       2.56       0.06 [= 0.00, 0.12]         State vector       13       127       2.56       0.06 [= 0.00, 0.12]         State vector       13       127       2.56       0.06 [= 0.00, 0.12]         State vector       13       127       2.56       0.04 [= 0.02, 0.12]         State vector       13       127       2.56       0.04 [= 0.02, 0.12]         State vector       13       127       145       0.04 [= 0.02, 0.12]         State vector       13       127       15       0.04 [= 0.02, 0.12]         State vector       13       127       15       0.04 [= 0.02, 0.12]         State vector       13       127       15       0.04 [= 0.02, 0.12]         State vector       13       <	EXCEL 2016						-0.00 [-0.03, 0.03]	<b>_</b>		
Name         133         132         142         14.15         0.02 [-0.01, 0.02]           Stempore         22         22         22         22         22         22           Stempore         23         24         25         22         24         25           Stempore         24         25         25         25         25         25         25           Stempore         24         46         67         43         35         0.01 [-0.02, 0.02]         0.01 [-0.02, 0.02]           Stempore         24         24         27         27         20         24.24         0.01 [-0.02, 0.02]           Stempore         1.1         25         25         1.1         0.01 [-0.02, 0.02]         0.01 [-0.02, 0.02]           2.1         Nonelistic         2.1         17         10         1.1         0.01 [-0.02, 0.02]         0.01 [-0.02, 0.02]           2.1         Nonelistic         2.2         1.1         1.1         0.01 [-0.02, 0.02]         0.01 [-0.02, 0.02]           2.1         Nonelistic         2.2         1.1         1.1         0.01 [-0.02, 0.02]         0.01 [-0.02, 0.02]         0.01 [-0.02, 0.02]         0.01 [-0.02, 0.02]         0.01 [-0.02, 0.02]         0.01 [-0							0.02 [-0.05, 0.08]			
Dig A work         Dial         Dial         Dial         Dial           State for our all mick 2 = 14.2 (p = 0.1 (k)         22         20.6         0.06 (-0.0.0.12)           State for our all mick 2 = 14.2 (p = 0.1 (k)         22         20.6         0.06 (-0.0.0.12)           State for our all mick 2 = 14.2 (p = 0.0 (k)         22         20.6         0.06 (-0.0.0.12)           State for our all mick 2 = 14.2 (p = 0.0 (k)         22         21.4         0.02 (-0.0.0.01)           State for our all mick 2 = 14.2 (p = 0.0 (k)         20         22         14.4         0.02 (-0.0.0.01)           State for our all mick 2 = 14.2 (p = 0.0 (k)         70         100         116         0.03 (-0.0.0.01)           State for our all mick 2 = 14.2 (p = 0.0 (k)         70         164         0.03 (-0.0.0.01)         0.04 (0.0.0.01)           State for our all mick 2 = 0.0 (k)         70         164         0.04 (-0.0.0.01)         0.04 (-0.0.0.01)           State for our all mick 2 = 0.0 (k)         70         164         0.04 (-0.0.0.01)         0.04 (-0.0.0.01)           State for our all mick 2 = 0.0 (k)         70         164         0.04 (-0.0.0.01)         0.04 (-0.0.0.01)           State for our all mick 2 = 0.0 (k)         70         165         0.04 (-0.0.0.01)         0.04 (-0.0.0.01)           <		133		107						
Heangenery, Dr <sup>2</sup> + 13, d + 3,	Total events	281	1000	252	1012	14.174	0.02 [ 0.01, 0.04]	•		
1.3 Elseny         EST 2015       1       1       22       0       25       2.05       0.05 (-0.00, 0.07)         EST 2015       1       1       2       9       7       7.25       8.8 (-0.00, 0.07)         Webbal (PS C)       1       3       1       1       1       1       1         State vebs       13       1		df = 3 (p = 0.								
EST 2015       41       228       30       222       2.0%       0.06 (= 0.00, 0.12)         PECCUART 2011       15       129       30       222       1.4%       -0.00 (= 0.07, 0.07)         Determine 1       13, 42       129       127       -0.00 (= 0.07, 0.07)       -0.01 (= 0.07, 0.07)         Determine 1       13, 42       127       -0.01 (= 0.07, 0.07)       -0.01 (= 0.07, 0.07)         Determine 1       13, 42       127       -0.01 (= 0.07, 0.07)       -0.01 (= 0.07, 0.07)         Determine 1       15, 42       2.02 (= 0.07, 0.07)       -0.01 (= 0.02, 0.07)       -0.01 (= 0.02, 0.07)         Determine 1       25       26       -0.01 (= 0.02, 0.07)       -0.01 (= 0.02, 0.07)       -0.01 (= 0.02, 0.07)         Determine 1       26       26       -0.01 (= 0.02, 0.07)       -0.01 (= 0.02, 0.07)       -0.01 (= 0.02, 0.07)         Determine 1       55       34       325       2.6%       -0.04 (= 0.02, 0.07)       -0.01 (= 0.02, 0.07)         Determine 1       56       29       126       156       -0.01 (= 0.05, 0.02)       -0.01 (= 0.05, 0.02)         Determine 1       56       26       26       26       26       26       -0.01 (= 0.02, 0.01)         Table period       16	Test for overall effect: Z = 1.4	42 (p = 0.16)	)							
EST 2015       41       228       30       222       2.0%       0.06 (= 0.00, 0.12)         PECCUART 2011       15       129       30       222       1.4%       -0.00 (= 0.07, 0.07)         Determine 1       13, 42       129       127       -0.00 (= 0.07, 0.07)       -0.01 (= 0.07, 0.07)         Determine 1       13, 42       127       -0.01 (= 0.07, 0.07)       -0.01 (= 0.07, 0.07)         Determine 1       13, 42       127       -0.01 (= 0.07, 0.07)       -0.01 (= 0.07, 0.07)         Determine 1       15, 42       2.02 (= 0.07, 0.07)       -0.01 (= 0.02, 0.07)       -0.01 (= 0.02, 0.07)         Determine 1       25       26       -0.01 (= 0.02, 0.07)       -0.01 (= 0.02, 0.07)       -0.01 (= 0.02, 0.07)         Determine 1       26       26       -0.01 (= 0.02, 0.07)       -0.01 (= 0.02, 0.07)       -0.01 (= 0.02, 0.07)         Determine 1       55       34       325       2.6%       -0.04 (= 0.02, 0.07)       -0.01 (= 0.02, 0.07)         Determine 1       56       29       126       156       -0.01 (= 0.05, 0.02)       -0.01 (= 0.05, 0.02)         Determine 1       56       26       26       26       26       26       -0.01 (= 0.02, 0.01)         Table period       16	173 Fiderly									
XCRL 2016       8       466       67       453       325       0.03 (-0.02, 0.05)         Visibility       13       127         Stebal (87 C)       824       987       7.25       0.03 (-0.02, 0.05)         Visibility       987       7.25       0.03 (-0.02, 0.05)         7.4       0.05 (-0.01, 0.17)       0.03 (-0.02, 0.01)         7.4       0.05 (-0.01, 0.17)       0.03 (-0.02, 0.01)         7.4       0.05 (-0.01, 0.10)       0.03 (-0.02, 0.01)         7.4       0.05 (-0.01, 0.01)       0.03 (-0.02, 0.01)         7.4       0.05 (-0.01, 0.01)       0.03 (-0.02, 0.01)         7.4       0.05 (-0.01, 0.02)       0.03 (-0.02, 0.01)         7.5       0.05 (-0.01, 0.02)       0.03 (-0.02, 0.01)         7.5       0.05 (-0.01, 0.02)       0.03 (-0.02, 0.01)         7.5       0.05 (-0.01, 0.02)       0.05 (-0.02, 0.03)         7.5       0.05 (-0.01, 0.02)       0.05 (-0.02, 0.03)         7.5       0.05 (-0.01, 0.03)       0.05 (-0.02, 0.03)         7.6       0.05 (-0.01, 0.03)       0.05 (-0.02, 0.03)         7.6       0.05 (-0.01, 0.03)       0.05 (-0.02, 0.03)         7.6       0.05 (-0.01, 0.03)       0.05 (-0.01, 0.03)       0.05 (-0.01, 0.03)       0.05 (	BEST 2015	41	229	30	252	2.0%	0.06 [-0.00, 0.12]			
BECOMBAT 2011       15       129       39       32       22       1.4%       -0.00 [-0.07, 0.07]         Other works       13       127       72X       0.00 [-0.07, 0.07]       0.01 [-0.00, 0.07]         State for works whether 2 + 15 (p - 0.00);       72X       0.01 [-0.00, 0.07]       0.01 [-0.00, 0.07]         State for works whether 2 + 15 (p - 0.00);       72X       0.01 [-0.00, 0.07]       0.01 [-0.00, 0.07]         State for works whether 2 + 15 (p - 0.00);       72X       0.03 [-0.00, 0.02]       0.03 [-0.00, 0.02]         State for works whether 2 + 15 (p - 0.00);       72X       0.04 [-0.00, 0.01]       0.04 [-0.00, 0.02]         State for works whether 2 + 0.01 [-0.01]       15X       0.04 [-0.01, 0.02]       0.04 [-0.01, 0.02]         State for works whether 2 + 0.01 [-0.01]       12       13X       0.04 [-0.01, 0.02]       0.04 [-0.01, 0.02]         State for works whether 2 + 0.01 [-0.02]       15X       0.04 [-0.01, 0.02]       0.04 [-0.01, 0.02]       0.04 [-0.01, 0.02]         State for works whether 2 + 0.01 [-0.02]       15X       0.04 [-0.01, 0.02]       0.04 [-0.01, 0.02]       0.04 [-0.01, 0.02]         State for works whether 2 + 0.03 [-0.01]       14       14       15X       0.04 [-0.01, 0.02]       0.04 [-0.01, 0.02]       0.04 [-0.01, 0.02]       0.04 [-0.01, 0.02]       0.04 [-0.01, 0	EXCEL 2016	82	466	67	463			+		
bill events       13       107         table overall effect Z = 151 (p = 0.06)       22       100       151       400       0.03 (0.00,010)         ZA Monotaline       25       200       10       151       400       0.03 (0.00,010)         State for averall effect Z = 151 (p = 0.06)       24       0.01 (0.02, 0.00)       0.01 (0.02, 0.00)       0.01 (0.02, 0.00)         State for averall effect Z = 0.41 (p = 0.68)       22       200       0.01 (0.02, 0.00)       0.01 (0.02, 0.00)         ZAM and gender       20       0.01 (0.02, 0.00)       0.01 (0.02, 0.00)       0.01 (0.02, 0.00)         State for averall effect Z = 0.41 (p = 0.68)       22.00       107       24.00       0.01 (0.02, 0.00)         ZAME and effect Z = 0.41 (p = 0.68)       22.00       107       24.00       0.01 (0.02, 0.00)         ZAME and effect Z = 0.20 (p = 0.00)       1952       28.00       0.04 (p.01, 0.16)       0.01 (p.02, 0.02)         ZAME and effect Z = 0.20 (p = 0.00)       1952       28.00       0.05 (p.01, 0.16)       0.05 (p.01, 0.16)         ZAME and effect Z = 0.20 (p = 0.00)       1952       28.00       0.05 (p.01, 0.16)       0.01 (p.02, 0.10)         ZAME and effect Z = 0.20 (p = 0.01)       114       0.01 (p.02, 0.10)       0.01 (p.02, 0.10)       0.01 (p.02, 0.01)	PRECOMBAT 2011	15		30			-0.00 [-0.07, 0.07]			
belanguage (Dr <sup>2</sup> = 1.7, 4 = 2 (p - 0.2); F = 20%           L7 Accordory           EST 2015         25         209         17         190         1.5%         0.03 (-0.03, 0.10)           SC22_21016         25         42.0         44.4         4.0%         -0.03 (-0.03, 0.10)           SC22_21016         25         42.0         44.4         4.0%         -0.03 (-0.03, 0.10)           SC22_21016         107         45.6         43.4         4.0%         -0.03 (-0.03, 0.10)           SC2_21016         107         45.7         107         45.6         0.04 (-0.01, 0.10)           State sends         107         95.7         107         42.6         0.04 (-0.01, 0.10)           SC2E_21016         107         107         42.6         0.04 (-0.01, 0.10)         0.04 (-0.01, 0.10)           State sends         108         98.8         118         668         65%         0.09 (0.05, 0.02)           State sends         108         107         107         10.7         0.01 (-0.05, 0.02)           State sends sends         118         0.04 (-0.01, 0.16)         0.01 (-0.05, 0.02)           State sends sends         118         0.05 (-0.01, 0.05)         0.01 (-0.05, 0.02)           State sends sends </td <td></td> <td>400</td> <td>824</td> <td>407</td> <td>967</td> <td>1.2%</td> <td>0.03 [-0.00, 0.07]</td> <td>-</td>		400	824	407	967	1.2%	0.03 [-0.00, 0.07]	-		
ist for overall effect Z = 137 (p = 0.06)         IZA Nonsider/ ESI 2015       20       17       190       1.6%       0.03 (= 0.03, 0.01)         SUCE, 2016       25       442       64       45       4.0%       -0.03 (= 0.0, 0.01)         SUCE, 2016       26       45       4.0%       -0.03 (= 0.0, 0.01)       0.03 (= 0.0, 0.01)         SUCE, 2016       26       45       4.0%       -0.03 (= 0.0, 0.01)       0.03 (= 0.0, 0.01)         State works       45       204       46       44       -0.06 (= 0.0, 0.02)       0.03 (= 0.0, 0.02)         State works       45       304       32       25       2.6%       0.04 (= 0.0, 0.02)         State works       13       22       14       13       15%       0.04 (= 0.0, 0.02)         State works       32       32       32       15%       0.04 (= 0.0, 0.02)         State works       32       32       32       15%       0.04 (= 0.0, 0.02)         State works       13       72       26       60       205       0.01 (= 0.0, 0.02)         State works       0.01       0.03 (= 0.0, 0.03)       0.05 (= 0.0, 0.03)       0.05 (= 0.0, 0.03)       0.05 (= 0.0, 0.03)         State works       0.01       0			42): 12 = 1							
If A localistic P         EST 2015       2       2       0       1.6%       0.03 (-0.03, -0.01, 0)         PRECOMPARY 2011       2       2         data works       -0.03 (-0.01, 0)         10       0.04 (-0.00, 0)         data works       -0.04 (-0.00, 0)         -0.04 (-0.00, 0)         -0.04 (-0.00, 0)         -0.04 (-0.00, 0)         -0.04 (-0.00, 0)         -0.05 (-0.00, 0)         -0.05 (-0.00, 0)         -0.05 (-0.00, 0)         -0.05 (-0.00, 0)         -0.05 (-0.00, 0)         -0.05 (-0.00, 0)         -0.05 (-0.00, 0)         -0.05 (-0.00, 0)         -0.05 (-0.00, 0)         -0.05 (-0.00, 0)         -0.05 (-0.00, 0)         -0.05 (-0.00, 0)         -0.04 (-0.00, 0) <th< td=""><td>Test for overall effect: Z = 1.9</td><td>91 (p = 0.06)</td><td>) )</td><td>- /*</td><td></td><td></td><td></td><td></td></th<>	Test for overall effect: Z = 1.9	91 (p = 0.06)	) )	- /*						
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$										
$\begin{aligned} & \text{XCEL 2016} & \text{55} & \text{462} & \text{86} & \text{465} & \text{40\%} & -0.03 \pm 0.07, 0.23 \\ & \text{404 both (S^{-1} C)^{-1} & \text{56}, \text{47} & \text{2} (p = 0.4),  ^{-1} = 70\% \\ & \text{466 rowshift diffed: } 2 = 0.41,  ^{-1} = 70\% \\ & \text{467 rowshift diffed: } 2 = 0.41,  ^{-1} = 70\% \\ & \text{467 rowshift diffed: } 2 = 0.41,  ^{-1} = 70\% \\ & \text{467 rowshift diffed: } 2 = 0.41,  ^{-1} = 70\% \\ & \text{467 rowshift diffed: } 2 = 0.41,  ^{-1} = 70\% \\ & \text{467 rowshift diffed: } 2 = 0.41,  ^{-1} = 70\% \\ & \text{467 rowshift diffed: } 2 = 0.41,  ^{-1} = 70\% \\ & \text{467 rowshift diffed: } 2 = 0.41,  ^{-1} = 70\% \\ & \text{467 rowshift diffed: } 2 = 0.41,  ^{-1} = 70\% \\ & \text{467 rowshift diffed: } 2 = 0.41,  ^{-1} = 70\% \\ & \text{467 rowshift diffed: } 2 = 0.41,  ^{-1} = 70\% \\ & \text{467 rowshift diffed: } 2 = 0.41,  ^{-1} = 70\% \\ & \text{467 rowshift diffed: } 2 = 0.20,  ^{-1} = 70\% \\ & \text{468 rowshift } 1 = 0.51,  ^{-1} = 0.40,  ^{-1} = 70\% \\ & \text{468 rowshift } 1 = 0.51,  ^{-1} = 0.41,  ^{-1} = 0.55,  ^{-1} = 0.51,  ^{-1} = 0$		~~	000		100	4.004	0.001.000.00			
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$										
Auboha (95% C)         662         546         7.1%         0.01 [-0.02, 0.04]           deterogeneric, Ch <sup>2+</sup> 6.05, d=*2 (0 = 0.04, F* 70%)         55         56         0.04 [-0.01, 0.10]           7.3 Male gender         EST 2015         45         504         325         2.6%         0.04 [-0.02, 0.10]           7.3 Male gender         EST 2015         45         504         34         225         2.6%         0.04 [-0.02, 0.10]           7.15%         0.04 [-0.01, 0.15]         36         1.9%         0.04 [-0.02, 0.10]         0.04 [-0.02, 0.10]           VEREDUM X12:         1.88         688         118         605         0.04 [-0.02, 0.10]           Valuation with         36         2.29         0.221         1.9%         0.04 [-0.02, 0.10]           VICE 2016         2.43         12.5         1.8%         0.04 [-0.02, 0.10]         0.16 [-0.10, 0.15]           VICE 2016         13         7.17         4         17         0.18 [-0.10, 0.16]         0.05 [0.01, 0.69]           VICE 2016         7.18         0.05 [-0.02, 0.12]         0.05 [0.01, 0.69]         0.05 [0.01, 0.69]         0.05 [0.01, 0.69]           VICE 2016         7.17         4         17         0.18         0.35 [0.0, 0.69]         0.01 [-0.00, 0.07] <td>PRECOMBAT 2011</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	PRECOMBAT 2011									
$ \begin{array}{c} \mbox{there} Chi ^{-1} \in 0.9, \ dr \geq 0.01; \ l^{-1} = 705; \\ tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.41 \ (p = 0.85); \\ \mbox{tel for ownall effect $2$ = 0.22 \ (p = 0.01); \\ \mbox{tel for ownall effect $2$ = 0.25 \ (p = 0.01); \\ \mbox{tel for ownall effect $2$ = 0.25 \ (p = 0.01); \\ \mbox{tel for ownall effect $2$ = 0.25 \ (p = 0.01); \\ \mbox{tel for ownall effect $2$ = 0.25 \ (p = 0.01); \\ \mbox{tel for ownall effect $2$ = 0.25 \ (p = 0.01); \\ \mbox{tel for ownall effect $2$ = 0.25 \ (p = 0.01); \\ \mbox{tel for ownall effect $2$ = 0.26 \ (p = 0.55); \\ \mbox{tel for ownall effect $2$ = 0.26 \ (p = 0.55); \\ \mbox{tel for ownall effect $2$ = 0.26 \ (p = 0.55); \\ \mbox{tel for ownall effect $2$ = 0.26 \ (p = 0.55); \\ \mbox{tel for ownall effect $2$ = 0.26 \ (p = 0.25); \\ \mbox{tel for ownall effect $2$ = 0.26 \ (p = 0.25); \\ \mbox{tel for ownall effect $2$ = 0.26 \ (p = 0.25); \\ \mbox{tel for ownall effect $2$ = 0.26 \ (p = 0.25); \\ \mbox{tel for ownall effect $2$ = 0.26 \ (p = 0.25); \\ \mbox{tel for ownall effect $2$ = 0.26 \ (p = 0.25); \\ \mbox{tel for ownall effect $2$ = 0.26 \ (p = 0.25); \\ \mbox{tel for ownall effect $2$ = 0.26 \ (p = 0.25); \\ \mbox{tel for ownall effect $2$ = 0.26 \ (p = 0.25);$	Subtotal (95% CI)							+		
Test for overall effect $Z = 0.41 (p = 0.68)$ T.7 Mag gender EST 2015 45 304 34 225 2.6% 0.04 (-0.01, 0.10) SIXCEL 2016 94 722 107 742 6.0% -0.01 (-0.5, 0.02) RECOM 2012 188 668 118 655 55% 0.004 (-0.02, 0.11) 0.04 (-0.02, 0.11) BEST 2015 22 134 13 137 1.1% 0.07 (-0.01, 0.15) SIXCEL 2016 23 2.0 (p = 0.001) T.7 Formal effect $Z = 3.20 (p = 0.001)$ T.7 Formal effect $Z = 2.5 (p = 0.01)$ T.7 Formal effect $Z = 2.5 (p = 0.01)$ T.7 Record ejection fraction EST 2015 20 11 20 115 0.5% 0.04 (-0.00, 0.05) EST 2015 20 11 20 111 20 115 0.5% 0.04 (-0.00, 0.05) SIXCEL 2016 109 732 2 EST 2015 20 11 20 115 0.5% 0.04 (-0.00, 0.05) T.7 Record ejection fraction EST 2015 60 421 43 425 5.5% 0.04 (-0.00, 0.05) T.7 Norwall effect $Z = 2.6 (p = 0.01)$ T.7 Record ejection fraction EST 2015 60 421 43 625 5.5% 0.04 (-0.00, 0.05) T.7 Strend ejection fraction EST 2015 60 421 43 625 5.5% 0.04 (-0.00, 0.05) T.7 Norwall effect $Z = 2.0 (p = 0.04)$ T.7 Strend ejection fraction EST 2015 60 42 111 76 65 5% 0.004 (-0.00, 0.05) T.7 Strend ejection fraction EST 2015 60 42 124 52 2.99 Heterogeneity, Ch <sup>2</sup> = 4.27, d = 2.10 (p = 0.34) T.7 Strend effect $Z = 2.0 (p = 0.04)$ T.7 Strend ejection fraction EST 2015 60 42 2.2% 0.05 (0.00, 0.05) T.7 Strend effect $Z = 2.0 (p = 0.04)$ T.7 Strend effect $Z = 2.0 (p = 0.04)$ T.7 Strend $Z = 2.5 (p = 0.04)$ T.7 Strend $Z = 2.5 (p = 0.04)$ T.7 Strend $Z = 2.5 (p = 0.05)$ T.7 Strend $Z = 2$	Total events									
7.5 Male gender         EST 2015       45       304       34       325       2.5%       0.04 [-0.01, 0.10]         CSEL 2016       94       7.22       107       7.42       6.0%       -0.01 [-0.05, 0.02]         REEDOM 2012       188       668       118       658       5.5%       0.06 [-0.01, 0.15]         Subbotal (6% C0)       1952       1955       15.1%       0.04 [-0.01, 0.15]         Subbotal (6% C0)       1952       12       14       13       17.1%       0.07 [-0.01, 0.15]         SUEL 2016       42       22       134       13       17.1%       0.06 [-0.01, 0.15]         SUEL 2016       42       25.6       1.29       0.05       0.01 [-0.02, 0.17]       0.05         SUEL 2016       43       22.6       0.6%       0.01 [-0.02, 0.17]       0.35 [0.21, 0.68]         SUEL 2016       20       112       20       110       0.5%       0.05 [-0.00, 0.16]         SUEL 2016       21.41       12       118       0.5%       0.04 [-0.00, 0.05]         SUEL 2016       10       12       111       0.5%       0.05 [-0.00, 0.05]         SUEL 2016       10       12       112       111       0.5% <t< td=""><td></td><td></td><td></td><td>70%</td><td></td><td></td><td></td><td></td></t<>				70%						
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	iest for overall effect: Z = 0.4	+ i (p = 0.68)	,							
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1.7.5 Male gender									
REEDOM 2012 188 698 119 658 5.5% 0.06 [0.05, 0.13] whole a left $232$ 30 $22$ 30 $21$ 1.9% 0.04 [0.02, 0.14] whole worth 366 289 test for overall effect $2-320$ ( $p=0.001$ ); $P=78\%$ test for overall effect $2-320$ ( $p=0.01$ ); $P=25\%$ test for overall effect $2-320$ ( $p=0.001$ ); $P=25\%$ test for overall effect $2-320$ ( $p=0.001$ ); $P=25\%$ test for overall effect $2-320$ ( $p=0.0001$ ); $P=2$	BEST 2015							+		
$\begin{aligned} & \text{PRECOMBAT2011} & 39 & 228 & 30 & 231 & 1.9 \\ & \text{Markovski } (35, 0) & 1522 & 1956 & 16.1\% & 0.04 [0.01, 0.06] \\ & \text{Markovski } (35, 0) & 1576 & 32 \\ & \text{Markovski } (35, 0) & 1776 & 366 & 228 \\ & \text{Markovski } (35, 0) & 1776 & 366 & 328 & 225 \\ & \text{Markovski } (35, 0) & 1776 & 328 & 225 & 328 & 225 & 365 & 005 [-0.02, 0.15] \\ & \text{Markovski } (35, 0) & 1676 & 328 & 225 & 0.055 [-0.02, 0.12] \\ & \text{Markovski } (25, 0) & 1676 & 328 & 225 & 0.055 [-0.02, 0.12] \\ & \text{Markovski } (25, 0) & 688 & 710 & 588 & 0.05 [-0.02, 0.12] \\ & \text{Markovski } (25, 0) & 688 & 710 & 588 & 0.05 [-0.02, 0.12] \\ & \text{Markovski } (25, 0) & 168 & 171 & 20 & 115 & 0.055 \\ & \text{Markovski } (25, 0) & 171 & 20 & 115 & 0.055 \\ & \text{Markovski } (25, 0) & 111 & 20 & 115 & 0.056 & 0.01 [-0.02, 0.01] \\ & \text{Markovski } (25, 0) & 1622 & 111 & 20 & 115 & 0.056 & 0.01 [-0.02, 0.01] \\ & \text{Markovski } (25, 0) & 1623 & 115 & 0.058 & 0.04 [-0.03, 0.05] \\ & \text{Markovski } (25, 0) & 1623 & 115 & 0.055 & 0.05 [0.00, 0.06] \\ & \text{Markovski } (25, 0) & 1623 & 156 & 0.55 & 0.05 [0.00, 0.06] \\ & \text{Markovski } (25, 0) & 1623 & 156 & 0.55 & 0.05 [0.00, 0.06] \\ & \text{Markovski } (25, 0) & 1623 & 156 & 0.55 & 0.05 [0.00, 0.06] \\ & \text{Markovski } (25, 0) & 1623 & 156 & 0.55 & 0.05 [0.00, 0.06] \\ & \text{Markovski } (25, 0) & 1623 & 156 & 0.55 & 0.05 [0.00, 0.06] \\ & \text{Markovski } (25, 0) & 1623 & 156 & 0.55 & 0.05 [0.00, 0.06] \\ & \text{Markovski } (25, 0) & 1623 & 156 & 0.55 & 0.05 [0.00, 0.06] \\ & \text{Markovski } (25, 0) & 1623 & 156 & 0.55 & 0.06 [-0.00, 0.12] \\ & \text{Markovski } (25, 0) & 1623 & 156 & 0.55 & 0.06 [-0.02, 0.02] \\ & \text{Markovski } (25, 0) & 1623 & 156 & 0.55 & 0.06 [-0.00, 0.12] \\ & \text{Markovski } (25, 0) & 162 & 116 & 151 & 100 & 0.05 & 0.00 [-0.02, 0.02] \\ & \text{Markovski } (25, 0) & 162 & 116 & 157 & 0.05 [0.00, 0.16] \\ & \text{Markovski } (25, 0) & 198 & 118$	EXCEL 2016							-• <u>+</u>		
Subtack (95% CI)       1922       1956       16.1%       0.04 [0.01, 0.06]         Value vents       366       229       205       16.1%       0.04 [0.01, 0.15]         Value vents       22       134       13       137       1.1%       0.07 [-0.01, 0.15]         Value vents       22       134       13       137       1.1%       0.07 [-0.01, 0.15]         Value vents       43       228       225       0.06 [-0.02, 0.12]       14         Vencome vents       145       114       145       14         Vencome vents       145       124       135       0.05 [0.01, 0.06]         Value vents       40       27       0.05%       0.05 [0.01, 0.06]         Value vents       41       143       1.25%       0.06 [-0.03, 0.05]         Value vents       40       27       15       0.5%       0.05 [0.00, 0.06]         Value vents       40       27       135       0.04 [-0.00, 0.06]       149         Value vents       40       27       0.05       0.05 [0.00, 0.06]       140         Value vents       40       27       0.05       0.06 [-0.02, 0.07]       140         Value vents       207       204								<b>.</b>		
bal wents 366 229 weighting only: $P^{-1}$ 235, $d = 3$ 0 003); $P^{-1}$ 278% test for overall effect: Z = 3.20 (p = 0.001) <b>1.75 Female gender</b> test 72 101 22 134 13 137 1.1% 0.07 [-0.01, 0.15] SZEL 2016 43 226 28 215 1.2% 0.05 [-0.02, 0.12] SZEL 2016 43 226 29 22% 0.05 [-0.02, 0.12] SZEL 2016 43 226 29 22% 0.05 [-0.02, 0.12] SZEL 2016 51 145 114 telterogeneity: Ch <sup>2</sup> = 0.73, d = 3 (p = 0.87); P = 0% test for overall effect: Z = 2.56 (p = 0.01) <b>1.77 Reduced ejection fraction</b> test 7 vore 1 effect: Z = 2.56 (p = 0.01); <b>1.73 Non-reduced ejection fraction</b> test 7 vore 1 effect: Z = 1.28 (p = 0.07); P = 0% test for overall effect: Z = 2.56 (p = 0.01); <b>1.74 Non-reduced ejection fraction</b> test 7 vore 1 effect: Z = 1.28 (p = 0.07); P = 0% test for overall effect: Z = 2.56 (p = 0.01); P = 55%, test for overall effect: Z = 1.28 (p = 0.01); P = 55%, test for overall effect: Z = 2.56 (p = 0.04); P = 45%, test for overall effect: Z = 2.59 (p = 0.04); P = 45%, test for overall effect: Z = 2.59 (p = 0.04); P = 45%, test for overall effect: Z = 2.59 (p = 0.04); P = 45%, test for overall effect: Z = 2.59 (p = 0.04); P = 45%, test for overall effect: Z = 2.59 (p = 0.04); P = 45%, test for overall effect: Z = 2.59 (p = 0.04); P = 45%, test for overall effect: Z = 0.59 (p = 0.04); P = 45%, test for overall effect: Z = 0.59 (p = 0.04); P = 45%, test for overall effect: Z = 0.59 (p = 0.04); P = 45%, test for overall effect: Z = 0.59 (p = 0.04); P = 45%, test for overall effect: Z = 0.59 (p = 0.04); P = 45%, test for overall effect: Z = 0.59 (p = 0.04); P = 45%, test for overall effect: Z = 0.59 (p = 0.03); P = 0.56 (p = 0.06) 0.17] <b>1.70 SYMX Loper tertile</b> Heterogeneity; Ch <sup>2</sup> = 5.24 (p = 0.52); P = 0.56 SYMTA Loper tertile Heterogeneity; Ch <sup>2</sup> = 2.11, d = 4 (p = 0.72); P = 0.56 test for overall effect: Z = 0.53 (p = 0.003); P = 0.50 (p	Subtotal (95% CI)	23		JU						
detengenery: Ch <sup>2</sup> = 1375, df = 3 (p = 0.001); h <sup>2</sup> = 78%, site for overall effect Z = 320 (p = 0.001); Z = 780, site for overall effect Z = 230 (p = 0.001); Z = 780, site for overall effect Z = 230 (p = 0.01); Z = 780, site for overall effect Z = 250 (p = 0.02); Z = 780, site for overall effect Z = 250 (p = 0.02); Z = 780, site for overall effect Z = 0.010, site for o	Total events							-		
7.5 Formula gender         EEST 2015       22       134       137       114         MEELOM 2012       67       256       61       28       215       1.9%       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.01       0.05       0.05       0.05       0.05       0.05       0.05       0.05       0.05       0.05       0.05       0.05       0.05       0.05       0.05 <th <="" colspan="2" td=""><td>Heterogeneity: Chi<sup>2</sup> = 13.75,</td><td>df = 3 (p = 0</td><td>0.003); I<sup>2</sup></td><td>= 78%</td><td></td><td></td><td></td><td></td></th>	<td>Heterogeneity: Chi<sup>2</sup> = 13.75,</td> <td>df = 3 (p = 0</td> <td>0.003); I<sup>2</sup></td> <td>= 78%</td> <td></td> <td></td> <td></td> <td></td>		Heterogeneity: Chi <sup>2</sup> = 13.75,	df = 3 (p = 0	0.003); I <sup>2</sup>	= 78%				
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Test for overall effect: Z = 3.2	20 (p = 0.00	1)							
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1.7.6 Female gender									
$\begin{aligned} & \text{XCEL2016} & 43 & 226 & 22 & 215 & 1.8\% & 0.06[-0.01, 0.13] \\ & \text{REEDOM 2012} & 67 & 226 & 61 & 29 & 2.2\% & 0.05[-0.02 0.12] \\ & \text{REEDOM 2012} & 67 & 273, d = 3 & (-0.57), F = 0\% \\ & \text{sign for warell effect } 2-2.56 & (-0.03), F = 0\% \\ & \text{sign for warell effect } 2-2.56 & (-0.03), F = 0\% \\ & \text{sign for warell effect } 2-2.56 & (-0.03), F = 0\% \\ & \text{sign for warell effect } 2-2.56 & (-0.03), F = 0\% \\ & \text{sign for warell effect } 2-2.56 & (-0.01) \\ & \text{TREEOM 2012} & 31 & 21 & 3 & 11 & 0.1\% & 0.35 & [0.01, 0.08] \\ & \text{subtolal (95\% CI)} & 149 & 143 & 1.2\% & 0.06 & [-0.03, 0.05] \\ & \text{subtolal (95\% CI)} & 149 & 143 & 1.2\% & 0.06 & [-0.03, 0.05] \\ & \text{subtolal (95\% CI)} & 149 & 143 & 1.2\% & 0.06 & [-0.03, 0.05] \\ & \text{subtolal (95\% CI)} & 1822 & 115 & 6.95 & 5.2\% & 0.04 & [-0.00, 0.09] \\ & \text{subtolal (95\% CI)} & 1822 & 115 & 6.95 & 5.2\% & 0.05 & [0.00, 0.06] \\ & \text{subtolal (95\% CI)} & 1822 & 115 & 6.95 & 5.2\% & 0.05 & [0.00, 0.06] \\ & \text{subtolal (95\% CI)} & 1822 & 156 & 1.5\% & 0.01 & [-0.06, 0.07] \\ & \text{TREEOM 2012} & 75 & 328 & 58 & 340 & 2.8\% & 0.06 & [-0.00, 0.12] \\ & \text{TREEOM 2012} & 75 & 328 & 58 & 340 & 2.8\% & 0.06 & [-0.00, 0.12] \\ & \text{TREEOM 2012} & 75 & 328 & 58 & 340 & 2.8\% & 0.06 & [-0.00, 0.12] \\ & \text{TREEOM 2012} & 75 & 328 & 58 & 340 & 2.8\% & 0.06 & [-0.00, 0.12] \\ & \text{TREEOM 2012} & 75 & 328 & 58 & 340 & 2.8\% & 0.06 & [-0.00, 0.12] \\ & \text{TREEOM 2012} & 75 & 328 & 58 & 340 & 2.8\% & 0.06 & [-0.00, 0.12] \\ & \text{TREEOM 2012} & 75 & 328 & 58 & 340 & 2.8\% & 0.06 & [-0.00, 0.12] \\ & \text{TREEOM 2012} & 75 & 328 & 58 & 340 & 2.8\% & 0.06 & [-0.00, 0.12] \\ & \text{TREEOM 2012} & 75 & 328 & 58 & 340 & 2.8\% & 0.06 & [-0.00, 0.12] \\ & \text{TREEOM 2012} & 51 & 3 & 66 & 10 & 79 & 0.6\% & 0.07 & [-0.50, 0.19] \\ & \text{TAT IX LOR09 for the 18} \\ & \text{EST 2015} & 13 & 66 & 10 & 79 & 0.6\% & 0.07 & [-0.50, 0.19] \\ & \text{TAT IX 1206} & 72 & 20.0 & 51 & 2.5\% & 0.07 & [-0.50, 0.19] \\ & \text{TAT IX 1206} & 72 & 20.0 & 51 & 2.5\% & 0.07 & [-0.50, 0.19] \\ & \text{TAT IX 1206} & 72 & 0.0 & 51 & 2.5\% & 0.07 & [-0.50, 0.19] \\ & \text{TAT IX 1206} & $	BEST 2015									
$\begin{aligned} & \text{PRECOMMAT 2011} & 13 & 72 & 12 & 69 & 0.6\% & 0.01 [-0.12 & 0.13] \\ & \text{bitotal} (95% C) & 688 & 710 & 5.8\% & 0.05 [0.01, 0.09] \\ & \text{bitotal} (95% C) & 145 & 114 \\ & \text{tetro great effect 2 - 25.6 (p = 0.57); } P = 0\% \\ & \text{tetro recall effect 2 - 25.6 (p = 0.01)} \\ & \text{I.7.7 Reduced ejection fraction} \\ & \text{EST 2015} & 7 & 17 & 4 & 17 & 0.1\% & 0.18 [-0.13, 0.49] \\ & \text{CXELE 2016} & 20 & 111 & 20 & 115 & 0.9\% & 0.01 [-0.08, 0.11] \\ & \text{REEDOM 2012} & 13 & 21 & 3 & 11 & 0.1\% & 0.35 [0.01 & 0.68] \\ & \text{subtotal} (95% C) & 149 & 143 & 1.2\% & 0.06 [-0.03, 0.05] \\ & \text{otal events} & 40 & 27 \\ & \text{tetro great effect 2 - 12.8 (p = 0.11); } P = 55\% \\ & \text{tetro rougel effect 1 - 12.6 (p = 0.12); } P = 25\% \\ & \text{tetro rougel effect 1 - 12.6 (p = 0.12); } P = 25\% \\ & \text{tetro rougel effect 1 - 12.6 (p = 0.12); } P = 25\% \\ & \text{tetro rougel effect 1 - 12.6 (p = 0.12); } P = 24\% \\ & \text{tetro rougel effect 1 - 12.6 (p = 0.14); } P = 45\% \\ & \text{tetro rougel effect 2 - 2.09 (p = 0.04)} \\ & \textbf{.7.9 SYNTAX lower tertile} \\ & \text{EET 2015} & 24 & 185 & 23 & 186 & 1.5\% & 0.01 [-0.06, 0.07] \\ & \text{REEDOM 2012} & 75 & 329 & 58 & 340 & 2.8\% & 0.06 [-0.00, 0.12] \\ & \text{reactor rougel effect 2 - 2.09 (p = 0.04)} \\ & \textbf{.7.9 SYNTAX lower tertile} \\ & \text{EET 2015} & 24 & 40 = 0.26); P = 24\% \\ & \text{tetro rougel effect 2 - 13.6 (p = 0.59); } \\ & \textbf{.7.0 SYNTAX upper tertile} \\ & \text{EET 2015} & 13 & 66 & 10 & 79 & 0.6\% & 0.07 [-0.05, 0.19] \\ & \text{reactor rougel effect 2 - 0.54 (p = 0.59); } \\ & \textbf{.7.0 SYNTAX upper tertile} \\ & \text{EST 2015} & 13 & 66 & 10 & 79 & 0.6\% & 0.07 [-0.05, 0.19] \\ & \text{reactor rougel effect 2 - 0.54 (p = 0.59); } \\ & \textbf{.7.0 SYNTAX upper tertile} \\ & \text{EST 2015} & 13 & 66 & 10 & 79 & 0.6\% & 0.07 [-0.05, 0.19] \\ & \text{reactor rougel effect 2 - 0.54 (p = 0.59); } \\ & \textbf{.7.0 SYNTAX upper tertile} \\ & \text{EST 2015} & 13 & 66 & 10 & 79 & 0.6\% & 0.07 [-0.05, 0.19] \\ & \text{reactor rougel effect 2 - 0.54 (p = 0.59); } \\ & \textbf{.7.0 SYNTAX upper tertile} \\ & \text{tetro rougel effect 2 - 0.54 (p = 0.59); } \\ & \textbf{.7.0 SYNTAX upper tertile} \\ & tet$	EXCEL 2016		226	28	215	1.8%	0.06 [-0.01, 0.13]			
bubble (9% Ct) 688 710 5.8% 0.05 [0.01, 0.09] bubble (9% Ct) 612 0.03 [0.01, 0.09] bubble (9% Ct) 0.13 0 = 0.87); F = 0% set for overall effect Z = 2.56 ( $p = 0.01$ ) 1.7.7 Reduced ejection fraction EST 2015 7 17 4 17 0.1% 0.18 [-013, 0.49] XXCEL 2016 20 111 20 115 0.9% 0.01 [-0.09, 0.11] EXXCEL 2016 20 111 21 31 10 0.1% 0.35 [0.01, 0.08] bubble (9% Ct) 149 143 1.2% 0.06 [-0.03, 0.05] bubble (9% Ct) 149 143 1.2% 0.06 [-0.03, 0.05] bubble (9% Ct) 1823 114 776 6 6.5% -0.00 [-0.04, 0.03] XXCEL 2016 109 782 111 766 6.5% -0.00 [-0.04, 0.03] XXCEL 2016 109 782 111 766 6.5% -0.00 [-0.04, 0.03] EST 2015 60 421 43 425 3.5% bubble (9% Ct) 1823 1840 15.1% 0.03 [0.00, 0.05] bubble (9% Ct) 1823 1940 15.1% 0.03 [0.00, 0.05] bubble (9% Ct) 1823 1940 15.1% 0.03 [0.00, 0.05] bubble (9% Ct) 1823 1940 15.1% 0.01 [-0.06, 0.07] XXCEL 2016 22 294 46 364 2.7% -0.03 [-0.00, 0.02] FRECOMAD12 11 16 128 13 104 0.9% 0.006 [-0.00, 0.12] FRECOM212 17 339 68 340 2.8% 0.006 [-0.00, 0.12] FRECOM212 11 16 128 13 104 0.9% 0.007 [-0.06, 0.07] XXCEL 2016 29 524 dt 40 = 0.59) 1.7.0 SYNTAX Lower tertile EST 2015 24 10 = 0.59) 1.7.0 SYNTAX Lower tertile EST 2015 13 66 10 79 0.6% 0.07 [-0.06, 0.07] XXCEL 2016 133 61 0.79 0.6% 0.07 [-0.06, 0.07] XXCEL 2016 37 220 30 217 1.1% 0.03 [-0.04, 0.10] TXOE VITAX Lower tertile EST 2015 37 200 54 (12 336 63 0.5% 0.05 [-0.09, 0.17] XXCEL 2016 37 220 30 217 1.1% 0.03 [-0.04, 0.10] XXCEL 2016 37 220 30 217 1.1% 0.03 [-0.04, 0.10] XXCEL 2016 37 220 30 217 1.1% 0.03 [-0.04, 0.10] XXCEL 2016 37 220 30 217 1.1% 0.03 [-0.04, 0.10] XXCEL 2016 37 220 30 217 1.1% 0.03 [-0.04, 0.10] XXCEL 2016 37 220 30 217 1.1% 0.03 [-0.04, 0.10] XXCEL 2016 37 220 30 217 1.1% 0.03 [-0.04, 0.10] XXCEL 2016 37 220 30 217 1.1% 0.03 [-0.04, 0.10] XXCEL 2016 37 220 30 217 1.1% 0.03 [0.01, 0.10] XXCEL 2016 37 220 30 217 1.1% 0.03 [0.01, 0.10] XXCEL 2016 37 220 30 217 1.1% 0.03 [0.01, 0.10] XXCEL 2016 37 220 0.53 1.2% 0.06 [0.03, 0.10] XXCEL 2016 37 220 54 1.2% 0.06 [0.03, 0.10] XXCEL 2016 37 2.20 54 0										
bal events $145$ 114 telerogeneity: Ch <sup>2</sup> = 0.73, df = 3 (p = 0.87); P = 0% est for vorall effect Z = 2.26 (p = 0.01) <b>1.77 Reduced ejection fraction</b> EST 2015 7 17 4 17 0.1% 0.18 (= 0.13, 0.49) CXEL 2016 20 111 20 115 0.0% 0.01 (= 0.08, 0.01) EST 2015 7 17 4 13 12% 0.06 (= 0.03, 0.05) telerogeneity: Ch <sup>2</sup> = 4.47, df = 2 (p = 0.11); P = 55% est for vorall effect Z = 1.26 (p = 0.20) <b>1.78 Non-reduced ejection fraction</b> EST 2015 60 421 43 425 3.5% 0.04 (= 0.00, 0.09) Subtal (95% Ct) 1823 1840 15.1% 0.03 (0.00, 0.05) Subtal (95% Ct) 1823 1840 15.1% 0.03 (0.00, 0.05) Subtal (95% Ct) 1823 1840 15.1% 0.03 (0.00, 0.05) Subtal (95% Ct) 338 df = 2.3% 634 2.2% 0.06 (= 0.00, 0.02) <b>1.78 SYNTAX lower tertile</b> EST 2015 24 df 40 (= 0.26); P = 24% est for overall effect Z = 2.09 (p = 0.59); P = 24% est for overall effect Z = 0.54 (p = 0.59); P = 24% est for overall effect Z = 0.54 (p = 0.59); P = 24% est for overall effect Z = 0.54 (p = 0.59); P = 24% est for overall effect Z = 0.54 (p = 0.59); P = 24% est for overall effect Z = 0.54 (p = 0.59); P = 24% est for overall effect Z = 0.54 (p = 0.59); P = 24% est for overall effect Z = 0.54 (p = 0.59); P = 24% est for overall effect Z = 0.54 (p = 0.59); P = 24% est for overall effect Z = 0.54 (p = 0.59); P = 24% est for overall effect Z = 0.54 (p = 0.59); P = 24% est for overall effect Z = 0.54 (p = 0.59); P = 0.64 est for overall effect Z = 0.54 (p = 0.003); P = 0.64 P = 0.0000 (0.000); P = 0.04) <b>1.0</b>	Subtotal (95% CI)	13		12		0.5% 5.8%	0.01 [-0.12, 0.13] 0.05 [0.01, 0.09]			
$ \begin{array}{c} \text{deterogeneity}, \ Ch^2 = 0.73, \ d = 30, \ c = 0.87); \ l^2 = 0\% \\ \text{eat for overall effect $2 = 256 (p = 0.01) \\ \hline $1.7$ Reduced ejection fraction \\ \text{ESI 2015 } 201 11 20 115 0.9\% & 0.01 [= 0.03, 0.49] \\ \text{XCEL 2016 } 20 111 20 115 0.9\% & 0.01 [= 0.04, 0.11] \\ \text{XCEL 2016 } 20 111 20 115 0.9\% & 0.06 [= 0.03, 0.05] \\ \text{Subtact of eyerall effect $2 = 1.26 (p = 0.11); \ l^2 = 55\% \\ \text{test for overall effect $2 = 1.26 (p = 0.11); \ l^2 = 55\% \\ \text{test for overall effect $2 = 1.26 (p = 0.11); \ l^2 = 55\% \\ \text{test for overall effect $2 = 1.26 (p = 0.12); \ l^2 = 55\% \\ \text{test for overall effect $2 = 1.26 (p = 0.14); \ l^2 = 45\% \\ \text{test for overall effect $2 = 2.09 (p = 0.04) \\ \hline $1.27 \text{ Non-reduced ejection fraction} \\ \text{VCEL 2016 } 103 \ 722 & 111 \ 766 \ 6.5\% & -0.00 (= 0.04, 0.03) \\ \text{VCEL 2016 } 103 \ 722 & 1164 \ 15.1\% \ 0.03 [0.00, 0.05] \\ \text{Subtact of eyerall effect $2 = 2.09 (p = 0.04) \\ \hline $1.73 \text{ SWTAX lower tertile} \\ \text{UST 2015 } 24 \ 125 \ 23 \ 166 \ 15.5\% \ 0.00 [= 0.06, 0.01] \\ \text{VCRL 2016 } 73 \ 226 \ 30 \ 2.77 \ 1.3\% \ 0.03 [= 0.00 (-0.03, 0.02] \\ \text{VATA LW poor tertile} \\ \text{EST 2015 } 13 \ 66 \ 10 \ 79 \ 0.6\% \ 0.007 [= 0.06, 0.01] \\ \text{VATA LW poor tertile} \\ \text{EST 2015 } 13 \ 66 \ 10 \ 79 \ 0.6\% \ 0.007 [= 0.02, 0.03] \\ \text{VATA LW poor tertile} \\ \text{EST 2015 } 37 \ 220 \ 30 \ 2.77 \ 1.3\% \ 0.35 \ 0.05 [= 0.00, 0.12] \\ \text{VATA LW poor tertile} \\ \text{EST 2015 } 37 \ 60 \ 79 \ 0.6\% \ 0.007 [= 0.05, 0.19] \\ \text{VATA LW poor tertile} \\ \text{EST 2015 } 37 \ 220 \ 30 \ 2.77 \ 1.3\% \ 0.35 \ 0.05 \ 0.006 \ 0.000 \ 0.101 \\ \text{VATA LW poor tertile} \\ \text{EST 2015 } 37 \ 220 \ 30 \ 2.77 \ 1.3\% \ 0.35 \ 0.05 \ 0.000 \ 0.000 \ 0.010 \ 0.000 \ 0.000 \ 0.010 \ 0.000 \ 0$	Total events	145		114				-		
7.7 Reduced ejection fraction         EST 2015       7       17       4       17       0.1%       0.18 [-0.13, 0.49]         EXCEL 2016       20       111       20       115       0.9%       0.01 [-0.69, 0.01]         EXEDDM 2012       13       21       3       11       0.1%       0.35 [0.01, 0.68]         Subtotal (95% Ct)       149       143       1.2%       0.06 [-0.03, 0.05]         Z telenogenety: Chi" = 4.47, d = 2 (p = 0.11); P = 55%       55%       0.04 [-0.00, 0.09]         EST 2015       60       421       43       425       5.5%       0.04 [-0.00, 0.09]         XCEL 2016       109       782       111       76       5.5%       -0.00 [-0.04, 0.03]       1.5%         VEED 20121       143       620       115       629       5.2%       0.05 [0.00, 0.09]       1.5%         Vibitotal (95% Ct)       1823       1840       1.5%       0.01 [-0.06, 0.07]       1.5%       0.02 [-0.08, 0.02]       1.5%         X2CEL 2016       28       294       46       342       2.5%       0.00 [-0.00, 0.12]       1.5%       0.00 [-0.00, 0.12]       1.5%       0.00 [-0.00, 0.12]       1.5%       0.00 [-0.00, 0.12]       1.5%       0.00 [-0.00, 0.12]       1.5%	Heterogeneity: Chi <sup>2</sup> = 0.73, d			0%						
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Test for overall effect: Z = 2.5	56 (p = 0.01)	)							
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1.7.7 Reduced election frac	ction								
$\begin{aligned} & \text{XCEL 2016} & 20 & 111 & 20 & 115 & 0.9\% & 0.01[-0.09, 0.11] \\ & \text{Matchal (95% CI)} & 149 & 143 & 1.2\% & 0.06[-0.03, 0.05] \\ & \text{Subtoal (95% CI)} & 149 & 143 & 1.2\% & 0.06[-0.03, 0.05] \\ & \text{Subtoal (95% CI)} & 149 & 143 & 1.2\% & 0.06[-0.03, 0.05] \\ & \text{Stat for avail effect Z = 1.28 (p = 0.11); P = 55\% \\ & \text{set for avail effect Z = 1.28 (p = 0.20)} \\ & \text{XCEL 2016} & 109 & 782 & 111 & 786 & 6.5\% & -0.00 - 0.04, 0.03] \\ & \text{KZEL 2016} & 109 & 782 & 111 & 786 & 6.5\% & -0.00 - 0.04, 0.03] \\ & \text{KZEL 2016} & 109 & 782 & 111 & 786 & 6.5\% & -0.00 - 0.04, 0.03] \\ & \text{Subtoal (95% CI)} & 1823 & 1840 & 15.1\% & 0.03 [0.00, 0.05] \\ & \text{Idelargeneity: Ch2 = 3.87, df = 2 (p = 0.14); P = 48\% \\ & \text{Stat for avail effect Z = 2.09 (p = 0.04)} \\ & \text{KZEL 2016} & 28 & 224 & 46 & 364 & 2.7\% & -0.03 - 0.06, 0.02] \\ & \text{RECOM AD12 IT 75 } 29 & 58 & 304 & 2.8\% & 0.06 [-0.00, 0.12] \\ & \text{VitTAX LM 2009 Tertile} \\ & \text{Set To oreal effect Z = 0.59); \\ & \text{KZEL 2016} & 27 & 204 \\ & \text{Hatrogeneity: Ch2 = 5.24, df = 4 (p = 0.26); P = 24\% \\ & \text{Stat oreal effect Z = 0.56 (p = 0.59); } \\ & \text{KZEL 2016} & 37 & 220 & 30 & 217 & 1.8\% & 0.03 [-0.09, 0.09] \\ & \text{VitTAX LM 2009 Tertile} \\ & \text{Set To oreal effect Z = 0.56 (p = 0.59); } \\ & \text{KZEL 2016} & 37 & 220 & 30 & 217 & 1.8\% & 0.07 [-0.05, 0.19] \\ & \text{KZCEL 2016} & 37 & 220 & 30 & 217 & 1.8\% & 0.07 [-0.05, 0.19] \\ & \text{KZCEL 2016} & 37 & 220 & 30 & 217 & 1.8\% & 0.07 [-0.05, 0.19] \\ & \text{KZCEL 2016} & 37 & 220 & 30 & 217 & 1.8\% & 0.06 [-0.00, 0.10] \\ & \text{KZCEL 2016} & 37 & 220 & 30 & 217 & 1.8\% & 0.07 [-0.05, 0.19] \\ & \text{KZCEL 2016} & 37 & 220 & 30 & 217 & 1.8\% & 0.07 [-0.05, 0.19] \\ & \text{KZCEL 2016} & 37 & 220 & 30 & 217 & 1.8\% & 0.07 [-0.05, 0.19] \\ & \text{KZCEL 2016} & 37 & 220 & 30 & 217 & 1.8\% & 0.07 [0.03, 0.11] \\ & Matrogeneity: Ch2 = 2.11, df = 4 (p = 0.72); F = 0\% \\ & \text{Store and effect Z = 0.58) \\ & \text{Hatrogeneity: Ch2 = 2.11, df = 4 (p = 0.72); F = 0\% \\ & \text{Store and effect Z = 3.83 (p = 0.0003) \\ & \text{Hatrogeneity: Ch2 = 2.11, df = 4 (p = 0.203); Hat \\ & \text{Hatrogene$	BEST 2015		17	4	17		0.18 [-0.13, 0.49]			
Subtobil (95% Ct)       149       143       1.2%       0.06 [-0.03, 0.05]         Viablate vents       40       27         telarogeneity: Chi <sup>+</sup> = 4.47, di= 2 (p = 0.11); l <sup>+</sup> = 55%,       27         telarogeneity: Chi <sup>+</sup> = 4.47, di= 2 (p = 0.11); l <sup>+</sup> = 55%,       55%,       0.04 [-0.00, 0.09]         17.8 Non-reduced ejection fraction       ESET 2015       60       421       43       425       3.5%,       0.04 [-0.00, 0.09]         XXCEL 2016       109       782       111       766       6.5%,       -0.00 [-0.04, 0.03]         Viablatel (95% Ct)       1823       1840       15.1%,       0.03 [0.00, 0.05]         staterogeneity: Chi <sup>+</sup> = 387, df = 2 (p = 0.14); l <sup>+</sup> = 48%,       east for overall effect 2 = 2.00 (0.01)          7.3 SYNTAX lower tertile       ESET 2015       24       185       23       186       1.5%,       0.01 [-0.06, 0.07]         XXCEL 2016       28       284       440       284       0.06 [-0.00, 0.12]          YNTAX LM 2004       11       15       1385       112%,       0.00 [-0.02, 0.03]          Viablatel (95% Ct)       1338       1395       112%,       0.00 [-0.02, 0.03]           XNTAL X MOPE tertile       EST 2015 <t< td=""><td>EXCEL 2016</td><td></td><td></td><td></td><td></td><td>0.9%</td><td>0.01 [-0.09, 0.11]</td><td></td></t<>	EXCEL 2016					0.9%	0.01 [-0.09, 0.11]			
$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	FREEDOM 2012	13		3						
$ \frac{1}{48} \operatorname{trogenety} Ch^2 = 4.47, d = 2 (p = 0.11); l^2 = 55\% \\ \operatorname{isch} for overall effect Z = 1.28 (p = 0.20) \\ \begin{array}{ccccccccccccccccccccccccccccccccccc$		40	149	97	143	1.2%	0.00 [-0.03, 0.05]			
test for overall effect 2 = 1.28 (p = 0.20) 7.8 Non-reduced ejection fraction EST 2015 60 421 43 425 3.5% 0.04 (-0.00, 0.09) EST 2015 60 421 43 620 115 629 5.2% 0.05 [0.00, 0.03] EST 2015 123 620 115 629 5.2% 0.05 [0.00, 0.09] Subtolal (95% C1) 1822 1840 15.1% 0.01 (-0.06, 0.07] 7.9 SYNTAX lower tertile EST 2015 24 185 23 186 1.5% 0.01 (-0.06, 0.07] FRECOMADI2 175 3.87, df = 2 (p = 0.4); f = 48% EST 2015 24 185 23 186 1.5% 0.01 (-0.06, 0.07] 7.9 SYNTAX lower tertile EST 2015 24 40 384 2.7% -0.03 (-0.06, 0.02] FRECOMADI2 175 329 58 340 2.8% 0.06 (-0.00, 0.12] FRECOMADI2 175 329 58 340 2.8% 0.06 (-0.02, 0.03] Subtolal (95% C1) 1338 1395 11.2% 0.00 (-0.92, 0.03] State avents 207 204 Heterogeneity: Chi <sup>+</sup> = 2.41, df = 4 (p = 0.26); F = 2.4% EST 2015 37 220 30 217 1.8% 0.03 (-0.04, 0.10] FRECOMADI2 15 56 182 44 113 158 0.05% 0.06 (-0.03, 0.16] StXCEL 2016 37 220 30 217 1.8% 0.08 (0.01, 0.18] FRECOMADI2 11 14 58 13 68 0.5% 0.06 (-0.00, 0.19] StXCEL 2016 37 220 30 217 1.8% 0.08 (0.01, 0.18] FRECOMADI2 11 14 58 13 68 0.5% 0.06 (0.03, 0.16] StXCEL 2016 37 220 54 152 2.5% EST 2015 737 2.00 540 6 100 79 0.6% 0.07 (-0.05, 0.19] StXCEL 2016 73 7 2.00 54 152 2.5% EST 2015 737 2.00 54 152 2.5% EST 2015 737 2.00 54 152 2.5% EST 2015 737 2.00 540 6 100 79 0.06 (0.03, 0.11] StXCEL 2016 73 7 2.00 54 152 2.5% EST 2015 737 2.00 54 152 2.5% EST 2015 737 2.00 54 152 2.5% EST 2015 737 2.00 540 6 100 79 0.06 (0.01, 0.108] StXCEL 2016 73 7 2.00 54 152 2.5% EST 2015 737 2.00 540 6 100 79 0.00 (0.01, 0.07 (0.03, 0.11] 2.70 2.70 0 0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1			.11) <sup>,</sup> l <sup>2</sup> = f							
7.8 Non-reduced ejection fraction         EST 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]         EXCEL 2016       109       782       111       786       6.5%       -0.00 [-0.04, 0.03]         Wibboal (9%) C1)       1823       1840       15.1%       0.05 [0.00, 0.05]         Vibboal (9%) C1)       1823       1840       15.1%       0.03 [0.00, 0.05]         Vibboal (9%) C1)       1823       186       1.5%       0.01 [-0.06, 0.07]         XCEL 2016       28       294       46       364       2.7%       -0.03 [-0.08, 0.02]         YTAX LM 2004 Tertile       EST 2015       24       402       64       2.5%       0.00 [-0.00, 0.12]         YWTAX LM 2005       64       40.2       64       0.3%       0.00 [-0.00, 0.12]       •         Vibbobal (9% C1)       133       66       10       79       0.6%       0.00 [-0.02, 0.03]       •         Vibbobal (9% C1)       133       66       10       79       0.6%       0.07 [-0.05, 0.19]       •         XCEL 2016       37       220       3	Test for overall effect: Z = 1.2	28 (p = 0.20)	)							
$\begin{array}{cccccccccccccccccccccccccccccccccccc$										
$\begin{aligned} & XCEL 2016 & 109 & 782 & 111 & 766 & 6.5\% & -0.00 [-0.44, 0.03] \\ & FEECOM 2012 & 143 & 620 & 115 & 63 & 5.2\% \\ & FEECOM 2012 & 143 & 620 & 115 & 63 & 5.2\% \\ & Statusal (85\% C1) & 1823 & 1840 & 15.1\% & 0.03 [0.00, 0.05] \\ & Statusal (85\% C1) & 1823 & 128 & 986 \\ & Statusal (85\% C1) & 1823 & 195 & 23 & 186 & 1.5\% \\ & Statusal (85\% C1) & 1823 & 195 & 23 & 186 & 1.5\% \\ & Statusal (85\% C1) & 1823 & 1384 & 0.9\% & 0.001 [-0.06, 0.07] \\ & FEECOM 2012 & 75 & 329 & 58 & 304 & 2.8\% \\ & Statusal (85\% C1) & 1338 & 1385 & 11.2\% & 0.001 [-0.06, 0.01] \\ & Statusal (85\% C1) & 1338 & 1385 & 11.2\% & 0.00 [-0.02, 0.03] \\ & Statusal (85\% C1) & 133 & 66 & 10 & 79 & 0.5\% \\ & Statusal (85\% C1) & 133 & 66 & 10 & 79 & 0.5\% \\ & Statusal (85\% C1) & 13 & 66 & 10 & 79 & 0.5\% \\ & Statusal (85\% C1) & 13 & 66 & 10 & 79 & 0.5\% \\ & Statusal (85\% C1) & 13 & 66 & 10 & 79 & 0.5\% \\ & Statusal (85\% C1) & 13 & 66 & 10 & 79 & 0.5\% \\ & Statusal (85\% C1) & 13 & 66 & 10 & 79 & 0.5\% \\ & Statusal (85\% C1) & 13 & 66 & 10 & 79 & 0.5\% \\ & Statusal (85\% C1) & 13 & 66 & 10 & 79 & 0.5\% \\ & Statusal (85\% C1) & 13 & 66 & 10 & 79 & 0.5\% \\ & Statusal (85\% C1) & 13 & 66 & 10 & 79 & 0.5\% \\ & Statusal (85\% C1) & 816 & 871 & 7.0\% \\ & Statusal (85\% C1) & 816 & 871 & 7.0\% \\ & Statusal (85\% C1) & 816 & 871 & 7.0\% \\ & Statusal (85\% C1) & 816 & 871 & 7.0\% \\ & Statusal (11 & 14 & 58 & 13 & 68 & 0.5\% & 0.05 [-0.00, 0.19] \\ & Statusal (11 & 14 & 158 & 13 & 56 & 0.5\% & 0.05 [0.01, 18] \\ & Statusal (11 & 14 & 14 & 158 & 13 & 56 & 0.5\% & 0.05 [0.01, 18] \\ & Statusal (11 & 14 & 158 & 13 & 55 & 0.05 [0.00, 108] \\ & Statusal (11 & 14 & 158 & 13 & 55 & 0.05 [-0.00, 0.19] \\ & Statusal (11 & 14 & 158 & 13 & 55 & 0.05 [0.00, 108] \\ & Statusal (11 & 14 & 158 & 13 & 55 & 0.05 [0.00, 108] \\ & Statusal (11 & 14 & 158 & 13 & 55 & 0.05 [0.00, 108] \\ & Statusal (11 & 14 & 158 & 13 & 55 & 0.05 [0.00, 108] \\ & Statusal (11 & 14 & 158 & 13 & 55 & 0.05 [0.00, 108] \\ & Statusal (11 & 158 & 0.05 [0.00, 108] \\ & Statusal (11 & 158 & 0.05 [0.00, 108] \\ & Statusal (11 & 158 & 0.05 [0.00, 108] \\ & S$						a		_		
$\begin{aligned} & \text{REEDOM 2012} & 143 & 620 & 115 & 629 & 5.2\% & 0.05 [0.00, 0.09] \\ & \text{subtank} (65\% \text{ CI}) & 1823 & 11840 & 15.1\% & 0.03 [0.00, 0.05] \\ & \text{teterogeneity}, Chi^2 = 3.87, df = 2 (p = 0.14); h^2 = 48\% \\ & \text{teterogeneity}, Chi^2 = 3.87, df = 2 (p = 0.14); h^2 = 48\% \\ & \text{teterogeneity}, Chi^2 = 2.39 (p = 0.04) \\ & \textbf{.7.9 SYNTAX lower tertile} \\ & \text{EST 2015} & 24 & 185 & 23 & 186 & 1.5\% & 0.01 [-0.06, 0.07] \\ & \text{REEDOM 2012} & 75 & 329 & 58 & 340 & 2.2\% & 0.06 [-0.00, 0.12] \\ & \text{REEDOM 2012} & 75 & 329 & 58 & 340 & 2.2\% & 0.06 [-0.00, 0.09] \\ & \text{REEDOM 2012} & 75 & 329 & 58 & 340 & 2.2\% & 0.06 [-0.00, 0.02] \\ & \text{REEDOM 2012} & 75 & 329 & 58 & 340 & 2.2\% & 0.06 [-0.00, 0.02] \\ & \text{REEDOM 2012} & 75 & 329 & 58 & 340 & 2.2\% & 0.06 [-0.00, 0.02] \\ & \text{REEDOM 2012} & 75 & 329 & 58 & 340 & 2.2\% & 0.00 [-0.02, 0.03] \\ & \text{teterogeneity}, Chi^2 = 52.4, df = 4 (p = 0.25); h^2 = 24\% \\ & \text{tetrogeneity}, Chi^2 = 52.4, df = 4 (p = 0.25); h^2 = 24\% \\ & \text{tetrogeneity}, Chi^2 = 52.4, df = 4 (p = 0.25); h^2 = 24\% \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.25); h^2 = 24\% \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.72); h^2 = 0\% \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.72); h^2 = 0\% \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.72); h^2 = 0\% \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.72); h^2 = 0\% \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.72); h^2 = 0\% \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.72); h^2 = 0\% \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.72); h^2 = 0\% \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.72); h^2 = 0\% \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.72); h^2 = 0\% \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.72); h^2 = 0\% \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.72); h^2 = 0\% \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.0003) \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.0003) \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.0003) \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p = 0.0003) \\ & \text{tetrogeneity}, Chi^2 = 2.14, df = 4 (p$							0.04 [-0.00, 0.09]			
Subtochal (95% Ct) 1823 1840 15.1% 0.03 (0.00, 0.05) delarogeneity: Ch <sup>2</sup> = 3.87, df = 2 (p = 0.14); P = 48% set for overall effect Z = 2.59 (p = 0.04); P = 48% Set To rowerall effect Z = 2.59 (p = 0.04); P = 48% Set To rowerall effect Z = 2.59 (p = 0.04); P = 48% Set To rowerall effect Z = 2.59 (p = 0.04); P = 48% Set To rowerall effect Z = 2.59 (p = 0.04); P = 48% Set To rowerall effect Z = 0.59 (p = 0.04); P = 48% Set To rowerall effect Z = 0.59 (p = 0.06); P = 24% Set To rowerall effect Z = 0.59 (p = 0.59); P = 24% Set To rowerall effect Z = 0.56 (p = 0.59); P = 24% Set To rowerall effect Z = 0.56 (p = 0.59); P = 24% Set To rowerall effect Z = 0.56 (p = 0.59); P = 24% Set To rowerall effect Z = 0.56 (p = 0.59); P = 24% Set To rowerall effect Z = 0.56 (p = 0.59); P = 24% Set To rowerall effect Z = 0.56 (p = 0.59); P = 24% Set To rowerall effect Z = 0.56 (p = 0.59); P = 24% Set To rowerall effect Z = 0.56 (p = 0.59); P = 24% Set To rowerall effect Z = 0.56 (p = 0.59); P = 24% Set To rowerall effect Z = 0.56 (p = 0.59); P = 24% Set To rowerall effect Z = 0.56 (p = 0.59); P = 24% Set To rowerall effect Z = 0.56 (p = 0.59); P = 24% Set To rowerall effect Z = 0.56 (p = 0.000); P = 0.56 (p = 0.57); P = 0.57 (p = 0.57); P = 0.56 (p = 0.57); P = 0.57 (p = 0.57); P = 0.57 (p = 0.57); P = 0.56 (p = 0.57); P = 0.57 (p = 0.57); P = 0.56 (p = 0.57); P = 0.57 (p = 0.57); P = 0.57 (p = 0.57); P = 0.56 (p = 0.57); P = 0.57 (p = 0.57); P = 0.56 (p = 0.57); P = 0.56 (p = 0.57); P = 0.57 (p = 0.57); P = 0.56 (p = 0.57); P = 0.57 (p = 0.57); P = 0.56 (p = 0.57); P = 0.57 (p = 0.57); P = 0.56	FREEDOM 2012							Ĩ		
Value venits 3 12 269 telanogeneity: $Ch^2 = 337$ , $d = 2$ ( $p = 0.4$ ); $P = 48\%$ set for overall effect $Z = 2.09$ ( $p = 0.4$ ); $P = 48\%$ LT 3 SYNTAX lower tertile EST 2015 24 185 23 186 1.5% 0.01 ( $= 0.06$ , 0.07) CXEL 2016 28 294 46 364 2.7% $= -0.03 = -0.08$ , 0.02] REEDOM 2012 75 329 58 340 2.8% 0.06 ( $= -0.00$ , 0.12] REECOMBA 2012 11 16 128 13 140 0.9% 0.000 ( $= -0.08$ , 0.09] WITAX LIM 2009 64 402 4401 3.3% $= -0.00 = -0.03$ , 0.01 ( $= 0.03$ , 0.0	Subtotal (95% CI)							◆		
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Total events									
isd for overall effect. $Z = 2.09$ (p = 0.04)         :7.9 SYNTAX lower tertile         EST 2015       24       185       23       186       1.5%, 0.01 [-0.06, 0.07]         :XCEL 2016       28       294       46       364       2.7%, -0.03 [-0.06, 0.02]         REED/012       75       329       56       340       2.8%, 0.06 [-0.00, 0.12]         YNTAX LV02012       75       329       58       340       2.8%, 0.001 [-0.03, 0.02]         YNTAX M2009       64       402       64       401       3.3%, -0.00 [-0.03, 0.12]         Vihital (95%) C1       1338       1335       11.2%, 0.00 [-0.02, 0.03]         Vihital (95%) C1       1338       1335       11.2%, 0.00 [-0.02, 0.03]         Vital versite       207       204       telerogeneity: Ch <sup>2</sup> = 5.24, df = 4 (p = 0.26); P = 24%         Vital versite       203       207       1.2%, 0.03 [-0.04, 0.10]         Vital versite       37       20.302       1.12%, 0.05 [0.01, 0.18]         Vital versite       37       20.302       1.12%, 0.06 [0.01, 0.18]         Vital versite       37       20.30       0.01 [0.03, 0.11]         Vital versite       37       20.30       0.06 [0.03, 0.10]         Vital versite       36 </td <td>Heterogeneity: Chi<sup>2</sup> = 3.87, d</td> <td>df = 2 (p = 0.</td> <td>14); I<sup>2</sup> = 4</td> <td>48%</td> <td></td> <td></td> <td></td> <td></td>	Heterogeneity: Chi <sup>2</sup> = 3.87, d	df = 2 (p = 0.	14); I <sup>2</sup> = 4	48%						
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	test for overall effect: Z = 2.0	U9 (p = 0.04)	)							
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1.7.9 SYNTAX lower tertile									
$\begin{aligned} & \text{XXELE 2016} & 28 & 294 & 46 & 364 & 2.7\% & -0.03 (-0.08, 0.02] \\ & \text{REEDOM 2012} & 75 & 329 & 58 & 340 & 2.8\% & 0.06 (-0.00, 0.12] \\ & \text{RECOMBAT 2011} & 16 & 128 & 13 & 104 & 0.9\% & 0.00 (-0.00, 0.09] \\ & \text{YNTAK M 2009} & 64 & 402 & 64 & 401 & 3.3\% & -0.00 (-0.03, 0.12] \\ & \text{subtable} (95% C1) & 1338 & 1395 & 11.2\% & 0.00 (-0.02, 0.03] \\ & \text{talevensh} & 207 & 204 \\ & \text{telerogeneity} C-524 & \text{d} = 4 (0 - 2.6); \text{P} = 24\% \\ & \text{test for overall effect } \text{Z} = 0.54 (p = 0.25); \text{P} = 24\% \\ & \text{telerogeneity} C-524 & \text{d} = 4 (0 - 2.5); \text{P} = 24\% \\ & \text{telerogeneity} C-524 & \text{d} = 4 (0 - 2.5); \text{P} = 24\% \\ & \text{telerogeneity} C-524 & \text{d} = 4 (0 - 2.5); \text{P} = 24\% \\ & \text{telerogeneity} C-524 & \text{d} = 1 (9 - 2.5); \text{P} = 24\% \\ & \text{telerogeneity} C-524 & \text{d} = 1 (1 - 2.5); \text{P} = 24\% \\ & \text{telerogeneity} C-524 & \text{d} = 1 (1 - 2.5); \text{P} = 24\% \\ & \text{telerogeneity} C-524 & \text{d} = 1 (1 - 2.5); \text{P} = 24\% \\ & \text{telerogeneity} C-524 & \text{d} = 1 (1 - 2.5); \text{P} = 24\% \\ & \text{telerogeneity} C-524 & \text{d} = 1 (1 - 2.5); \text{P} = 25\% \\ & \text{telerogeneity} C-524 & \text{d} = 1 (1 - 2.5); \text{P} = 25\% \\ & \text{telerogeneity} C-524 & \text{d} = 1 (2 - 0.72); \text{P} = 0\% \\ & \text{telerogeneity} C-524 & \text{d} = 1 (1 - 2.72); \text{P} = 0\% \\ & \text{telerogeneity} C-524 & \text{d} = 1 (1 - 2.72); \text{P} = 0\% \\ & \text{telerogeneity} C-524 & \text{d} = 0.0003) \\ & \text{deterogeneity} C-524 & \text{d} = 0.0003 \\ & \text{deterogeneity} C-524 & \text{d} = 0.0003 \\ & deteroge$	BEST 2015		185	23	186	1.5%	0.01 [-0.06, 0.071			
$eq:rescaled_$	EXCEL 2016				364	2.7%	-0.03 [-0.08, 0.02]	•		
SYNTAX. W 2009     64     402     64     401     3.3%     -0.00 [-0.03, 0.12]       subtable (95% CI)     1338     11.2%     0.00 [-0.02, 0.03]       telerogeneity: Ch <sup>2</sup> = 5.24, df = (1 p = 2.65); J <sup>2</sup> = 24%       stof roweral left: 2 - 0.54 (p = 0.59); <b>1.7.10 SYNTAX upper tertile</b> BEST 2015     13     66     10     79     0.6%     0.07 [-0.05, 0.19]       XCEL 2016     37     220     30     217     1.5%     0.03 [-0.04, 0.10]       REECDOM 2012     56     182     41     192     1.5%     0.06 [0.00; 0.19]       VITAX LW 009     76     290     54     52     5.00 [0.00; 0.10]       Subtable (95% CI)     816     871     7.0%     0.07 [0.03, 0.11]       dial events     196     148     14     28     0.05 [0.00; 0.16]       subtable (95% CI)     816     871     7.0%     0.07 [0.03, 0.11]       dial events     196     148     14     14     15       est for overall effect Z = 3.63 (p = 0.0003)     -0.2     -0.1     0     0.1     0	FREEDOM 2012									
Subtotal (95% CI)         1338         1395         11.2%         0.00 [-0.02, 0.03]           deterogeneity: Ch <sup>2</sup> = 524, df 4 (p = 0.26); P = 24%         set for overall effect Z = 0.54 (p = 0.26); P = 24%         set for overall effect Z = 0.54 (p = 0.26); P = 24%           17.10 SYNTAX upper tertile         EST 2015         13         66         10         79         0.6%         0.07 [-0.05, 0.19]           XCEL 2016         37         220         30         217         1.8%         0.03 [-0.04, 0.10]           XREED0M 2012         56         182         41         122         1.5%         0.06 [-0.00, 0.19]           VPTTAX LM 2009         76         200         54         15         2.5%         0.05 [-0.09, 0.19]           VPTTAX LM 2009         76         200         54         15         2.5%         0.06 [0.03, 0.16]           ublotal (95% CI)         816         871         7.0%         0.07 [0.03, 0.11]         4           detaregeneity: Ch <sup>2</sup> = 2.11, df = 4 (p = 0.72); h <sup>2</sup> = 0%, et al.003)         -0.2         -0.1         0         0.1         0.1								<u>i</u>		
Val events 207 204 delarogneity: Ch <sup>2</sup> = 524, df = 4 (p = 0.26); P = 24% set for verall effect Z = 0.54 (p = 0.59) <b>.7.10 SYNTAX upper tertile</b> ESET 2015 13 66 10 79 0.6% 0.07 [-0.05, 0.19] XCEL 2016 37 220 30 217 1.8% 0.03 [-0.04, 0.10] REECDM 2012 56 182 41 192 1.5% 0.09 [0.01, 0.18] RECCMART 2011 14 58 13 68 0.5% 0.05 [-0.09, 0.19] VITAX LUX 009 76 280 54 315 2.5% 0.09 [0.01, 0.18] VITAX LUX 009 76 280 54 315 2.5% 0.09 [0.03, 0.11] Old events 196 148 Heterogeneity: Ch <sup>2</sup> = 2.11, df = 4 (p = 0.72); P = 0% iest for overall effect Z = 3.63 (p = 0.0003)	SYNTAX LM 2009 Subtotal (95% CI)	64		64		3.3% 11.2%	-0.00 [-0.03, 0.12] 0.00 [-0.02, 0.031	<b></b>		
Idelangeneity: Chi" = 524, df - 4 (p = 0.26); l" = 24%           test for overall effect: Z = 0.54 (p = 0.59);           7.09 SYITAX upper tertile           EST 2015         13         66         10         79         0.6%,         0.07 [-0.05, 0.19]           EST 2016         37         220         30         217         1.3%,         0.037 [-0.06, 0.19]           ERECOM 2012         56         162         41         122         1.5%,         0.09 [0.01, 0.18]           FRECOMM2012         56         162         41         122         1.5%,         0.09 [0.01, 0.18]           VITAX LM 2009         76         290         54         515         2.5%,         0.06 [0.03, 0.16]           Jubtatel (95% Ct)         816         871         7.0%,         0.097 [0.03, 0.11]         4           Heterogeneity: Chi" = 2.11, df = 4 (p = 0.72); l" = 0%;         est for overall effect: Z = 3.63 (p = 0.0003)         -0.2         -0.1         0         0.1         0	Total events	207		204				T		
I.7.10 SYNTAX upper tertile         EEST 2015       13       66       10       79       0.5%       0.07 ( $-0.05$ , 0.19]         XXCEL 2016       37       220       30       217       1.8%       0.03 ( $-0.04$ , 0.10]         EXECL 2016       37       220       30       217       1.8%       0.03 ( $-0.04$ , 0.10]         FRECOM 2012       56       182       41       192       1.5%       0.08 [0.03, 0.19]         VITAX LM 2009       76       290       54       55       2.5%       0.05 [0.03, 0.16]         Subtotal (95% Ct)       816       871       7.0%       0.07 [0.03, 0.11]       14         teterogeneity: Chi" = 2.11, df = 4 ( $p = 0.72$ ); h <sup>2</sup> = 0%;       est for overall effect Z = 3.63 ( $p = 0.0003$ )       -0.2       -0.1       0       0.1       0	Heterogeneity: Chi2 = 5.24, d	df = 4 (p = 0.								
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Test for overall effect: Z = 0.5	54 (p = 0.59)	)							
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1.7.10 SYNTAX unner tertile									
$\begin{aligned} & \text{XCEL2016} & 37 & 220 & 30 & 217 & 1.8\% & 0.03 [-0.44, 0.10] \\ & \text{REEDOM 2012} & 56 & 182 & 41 & 192 & 1.5\% & 0.09 [0.01, 0.18] \\ & \text{RECOMBAT 2011} & 14 & 58 & 13 & 68 & 0.5\% & 0.05 [-0.90, 0.19] \\ & \text{YNTAX III 2009} & 76 & 290 & 54 & 315 & 2.5\% & 0.09 [0.3, 0.16] \\ & \text{Solubal}(95\%\text{CC}) & 816 & 871 & 7.0\% & 0.07 [0.33, 0.11] \\ & \text{cal events} & 196 & 148 \\ & \text{telerogeneity}(\text{Chi}^2 = 2.11, df = 4 (p = 0.72); f^2 = 0\% \\ & \text{set for overall effect } Z = 3.63 (p = 0.0003) \end{aligned}$			66	10	79	0.6%	0.07 [-0.05 0.19]	•		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	EXCEL 2016					1.8%	0.03 [-0.04, 0.10]			
YNTAX LW 2009         76         290         54         315         2.5%         0.09 [0.0.3, 0.16]           witchal (95% Cl)         816         871         7.0%         0.07 [0.03, 0.11]           ictal events         196         148         0.07 [0.03, 0.11]           ictal events         196         140           set for overall effect: Z = 3.63 (p = 0.0003)         -0.2         -0.1         0         0.1         0	FREEDOM 2012	56	182	41	192	1.5%	0.09 [0.01, 0.18]			
Subtotal (95% Ct)         816         871         7.0%         0.07 [0.03, 0.11]           deterogeneity: Ch <sup>2</sup> = 2.11, df = 4 (p = 0.72); f <sup>2</sup> = 0%         148           sets for overall effect: Z = 3.63 (p = 0.0003)         -0.2         -0.1         0         0.1         0	PRECOMBAT 2011									
total events 196 148 teterogeneity: Chi <sup>2</sup> = 2.11, df = 4 (p = 0.72); l <sup>2</sup> = 0% est for overall effect: Z = 3.63 (p = 0.0003) −0.2 −0.1 0 0.1 0		76		54		2.5% 7.0%	0.09 (0.03, 0.16) 0.07 (0.03, 0.11)			
Heterogeneity, Chi <sup>+</sup> = 2.11, df = 4 (p = 0.72); l <sup>+</sup> = 0% šest for overall effect: Z = 3.63 (p = 0.0003) -0.2 -0.1 0 0.1 0	Total events	196		148	5					
Test for overall effect Z = 3.63 (p = 0.0003)         -0.2         -0.1         0         0.1         0	Heterogeneity: Chi <sup>2</sup> = 2.11, d	if = 4 (p = 0.	72); I <sup>2</sup> = (							
	Test for overall effect: Z = 3.6	63 (p = 0.00	03)							

**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 <sup>1</sup>	Poland	2008	105	LMCA	25	32	$53 \pm 11$	BMS and DES	10
SYNTAX <sup>2</sup>	International	2009	1800	LMCA and three-vessel disease	35	28	ND ‡	SF	5
CARDia <sup>4</sup>	United Kingdom	2010	510	Two- and three-vessel disease	100	22	$59\pm14$	BMS and DES	5
Boudriot et al. <sup>5</sup>	Germany	2011	201	LMCA	30	ND	ND	DES	1
PRECOMBAT <sup>6</sup>	South Korea	2011	600	LMCA	42	45	$60\pm9$	DES	5
FREEDOM <sup>8</sup>	International	2012	1900	Two- and three-vessel disease	100	30	$65\pm12$	DES	5
Va-Cards <sup>7</sup>	USA	2013	198	Two- and three-vessel disease	100	ND	ND†	DES	2
BEST <sup>9</sup>	South Korea	2015	880	Two- and three-vessel disease	45	42	$59\pm9$	DES	5
EXCEL <sup>11</sup>	International	2016	1905	LMCA	25	37	$57 \pm 10$	DES	3
NOBLE <sup>10</sup>	Europe	2016	982	LMCA	18	18	$60 \pm 10$	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.<sup>24</sup> 160

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.<sup>20</sup> 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**

No potential conflict of interest relevant to this article was reported.

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#### **Study Association**

This study is not associated with any thesis or dissertation work.

#### 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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