Prior Percutaneous Coronary Intervention and Mortality among Adults Undergoing Surgical Myocardial Revascularization: Results from the European Multicenter Study on Coronary Artery Bypass Grafting (E-CABG) with a Systematic Review and Meta-analysis

Short title

Mariscalco et al., Prior PCI in patients undergoing CABG

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Abstract

Background **–** The clinical impact of prior percutaneous coronary intervention (PCI) in patient requiring coronary artery bypass grafting (CABG) remains unsettled**.** We sought to determine whether prior PCI is associated with adverse outcome after surgical myocardial revascularization.

Methods **-** Data from the European Multicenter Study on Coronary Artery Bypass Grafting (E-CABG) conducted between January 2015 and March 2016 at 16 European centres were analysed. A parallel systematic review and meta-analysis (MEDLINE, Embase, SCOPUS, Cochrane Library) through December 2016 was also accomplished. In the E-CABG study, propensity weighted methodology was adopted for correcting for confounding.

Results **-** A total of 3641 adult patients in the E-CABG study were obtained, including 685 (19%) patients with a history of PCI. At multivariable level, prior PCI was not associated with an increased hospital mortality in both unweighted and weighted patient groups (OR, 0.73; 95%CI 0.29-1.38; p=0.3279, and OR, 0.90; 95%CI 0.39-2.08; p=0.8142, respectively). Sub-group analyses confirmed that prior PCI had no impact on hospital mortality and morbidity, including re-exploration for bleeding/tamponade, blood transfusion, hospital resource use, neurological, renal and cardiac complications. The systematic review provided a total of 71 366 individuals and confirmed that prior PCI was not associated with higher in-hospital/30-day mortality (adjusted OR, 0.26; 95% CI, -0.01–0.53; I^2=43.1%) nor with re-exploration for bleeding/tamponade (OR, 1.30; 95% CI, 0.89-1.91 , stroke(OR, 1.04; 95% CI, 0.82-1.31), renal failure (OR, 1.20; 95% CI, 0.90-1.60), postoperative atrial fibrillation (OR, 1.01; 95% CI, 0.90-1.14), and longer in-hospital stay (mean difference, 0.18; 95%CI, -0.03-0.40). Adjustments for important confounders did not alter our results.

Conclusions **–** Prior PCI is not associated with an increased risk of mortality and other adverse outcomes in patients undergoing subsequent CABG.

Abstract word count: 278**Key words:** percutaneous coronary intervention ● CABG ● cardiac surgery ● mortality ● adult

Introduction

Percutaneous coronary intervention (PCI) has been proven to constitute a valid option for myocardial revascularization also in high risk patients with a severe comorbidity profile, including diabetes, left main stem and triple vessel coronary artery diseases (CAD).[1-4] As a result, an increased number of patients undergoing coronary artery bypass grafting (CABG) present a history of prior PCI, because of coronary stent failure and/or progression of the native coronary disease.[5,6] Although several studies attempted to analyse early and late outcomes in this patient population, the prognostic impact of prior PCI in patients requiring surgical myocardial revascularization is still debated. Some studies reported worse outcomes in patients with prior PCI, while others failed to demonstrate an association between hospital mortality and prior PCI.[5-19] Plausible explanations for these controversial results include the retrospective nature of observational studies in capturing detailed data on coronary catheterization, extent of CAD, causes of coronary stent failure, and impact of time interval between PCI and CABG.[10,11] We report the results of two related studies in patients with prior PCI undergoing CABG: the prospective European Coronary Artery Bypass Grafting (E-CABG) multicenter study,[20] and a systematic review with meta-analysis of this and other similar studies which considered the relationship between prior PCI and early outcome after CABG.

Methods

Observational Study Cohort

The E-CABG registry is a prospective, multicenter study enrolling patients undergoing isolated CABG at 16 European centers of cardiac surgery from Finland, France, Italy, Germany, Sweden and United Kingdom. The present study is registered in Clinicaltrials.gov (Identifier: NCT02319083), and its detailed protocol with definition criteria have been previously published.[20] Data were collected prospectively and underwent robust validation and checking procedures to maintain data quality. Data submissions are constantly verified with regular data quality reports, with review of administrative and medical chart audits in order to correct clinical and temporal conflicts and/or discrepancies.[20]

This study was approved by the Institutional Review Board (IRB) of the participating centers, and it was not financially supported. Informed consent was collected in Institutions where it was specifically required by the internal IRB, otherwise it was waived. The study complies with the Strengthening the Reporting of Observational Studies in Epidemiology reporting requirements for observational studies (supplemental Table 1).[21]

Study Design and Outcome measures

Patients undergoing first-time isolated CABG with history of prior PCI and those without prior PCI constituted the two study groups. Patients who had a prior PCI within 30 days from surgery were excluded from the analysis in order to control for any acute PCI-related complication, which subsequently might have jeopardized the outcome of surgical revascularization. For each patient, more than 200 variables were recorded, including demographic, clinical, perioperative and early and late postoperative data. Antiplatelet therapy, type and site of coronary stents, number of received PCI procedures, and time interval between PCI and CABG were rigorously registered.[20] Bypass grafting and cardiopulmonary bypass (CPB) strategies were at discretion of the individual surgeon, and antiplatelet drugs were administered according to the recommendations of the European Society of Cardiology guidelines for acute coronary syndromes (ACS).[22,23]

All study end-points of the present study were pre-specified. The primary end-point was hospital mortality, defined as death within 30-days after the index surgical procedure. Secondary end-points included the hemodynamic support of intra-aortic balloon pump (IABP) and/or extra-corporeal membrane oxygenation (ECMO), re-exploration for bleeding/tamponade, the use of blood products, postoperative neurological, renal, cardiac and gastric complications, length of stay in the intensive care unit (ICU), and sternal wound infections. Length of in-hospital stay as an outcome measure was not considered since the timing of patient discharge could have been influenced by the availability of beds in rehabilitation clinics.

Systematic Review and Meta-Analysis

The review protocol with complete details, including electronic search strategy, objectives, criteria for study selection, eligibility, and data collection were published online and registered in International Registry of Systematic Reviews PROSPERO (CRD42017062314).[24] The review adhered to MOOSE (MetaAnalysis of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Reviews and MetaAnalyses) guidelines (supplemental Tables 2 and 3).[25,26] Briefly, literature searches were systematically performed with electronic databases (MEDLINE [PubMed and Ovid], Embase, SCOPUS, and Cochrane Library) without date or language restriction from inception to the end of December 2016. Key words and MeSH terms pertinent to the exposure of interest were used in relevant combinations, including "coronary artery bypass grafting", "surgical revascularization", "CABG", "percutaneous coronary intervention", "PCI", "coronary stenting", and "coronary stent", "adult", "cardiac surgery", "mortality", and "morbidity", and "patient outcome". References of all eligible studies and review articles were also screened to identify relevant resources that were not previously identified. Only studies reporting on comparative analysis of patients undergoing CABG who had prior PCI or those without it were considered. Studies including patient undergoing CABG having had PCI during the same hospital admission or those without specification of the time interval between PCI and subsequent CABG were excluded. The primary outcome of interest was all-cause mortality in hospital or within 30 days from the index surgical procedure. Inclusion and exclusion criteria for qualitative/quantitative analyses were summarized according to the PICOS (population, intervention, comparator, outcomes, and study design) approach (supplemental Table 4). Year of publication, study design, country, sample size, recruitment period, number of patients in each treatment group, inclusion and exclusion criteria, measured outcomes, baseline patient demographics, cardiac status, comorbidities, and outcomes among relevant subgroups of patients were extracted.

Statistical Analysis

In the prospective E-CABG study, statistical analyses were performed using the SAS statistical package, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria).[27] Covariates and outcomes were reported as counts and

percentages, and as mean and standard deviation, or median and 25th-75th percentiles. The normal distribution of continuous parameters was tested with the Kolmogorov-Smirnov test and t-test was used to compare means among groups, if applicable. Variables with a skewed distribution were compared with the use of Wilcoxon rank sum tests. Chi-square or Fisher exact tests were used to compare frequencies among groups, as appropriate. The propensity score model was developed implementing a generalized boosted regression methodology with a non-parsimonious approach. The following clinical baseline variables were included in the regression model: age, gender, body mass index, hemoglobin, potent antiplatelet drugs discontinued within 5 days from the operation, clopidogrel, ticagrelor, warfarin, prior stroke, poor mobility, extracardiac arteriopathy, hypertension, dialysis, pulmonary disease, diabetes mellitus, recent myocardial infarction, ACS, atrial fibrillation (AF), emergency operation, critical preoperative status, prior cardiac surgery, Syntax score, number of diseased vessels, left main stem stenosis, left ventricular ejection fraction (LVEF) and classes of chronic kidney disease. Generalized boosted regression model is a machine learning technique that use a flexible estimation method of propensity score through an iterative process based on the analysis of multiple regression tree results. This method allows to capture complex and nonlinear relationships between treatment assignment and the pretreatment covariates without over-fitting the data.[28] To estimate the propensity score were used 100,000 iterations and a shrinkage parameter of 0.001. The iteration-stopping rule was based on the minimization of the Kolmogorov-Smirnov statistics mean. The balance of covariates between the groups was evaluated by plotting the absolute standardized difference before and after weighting and with a Q-Q plot comparing the quantiles of the observed Kolmogorov-Smirnov statistic p-values before and after weighting. Propensity score estimates for each patient were finally used to obtain proportional weights that were entered as a weighting factor in adjusted analyses. Average treatment effects on the treated (ATT) weights were set at 1 for patients with prior PCI and calculated as propensity score/(1-propensity score) for patients without prior PCI. All tests performed were two-tailed and a p-value <0.05 was considered statistically significant.
The meta-analysis was performed with R version 3.3.2. Treatment effect on operative outcomes is reported as odds ratio (OR) with a 95% confidence interval (CI). Yates correction was implemented if a cell contained a zero in the 2×2 contingency table.[29] Individual ORs and variance were computed

using number of events and sample size and pooled by using Mantel-Haenszel method and random-effects model.[30] A fixedeffects model was also computed as sensitivity analysis. Detailed subgroup analyses according to the secondary end-points was also performed. Finally, to account for inherent patient selection bias related with an observational study design, individual riskadjusted ORs for the primary endpoint were obtained when reported, and pooled adjusted risk estimates were computed by using log transformation and a generic inverse variance weighting method. I^2 statistic was used to estimate the percentage of total variation across studies attributed to heterogeneity rather than chance.[31] Suggested thresholds for heterogeneity were used, with I^2 values of 25% to 49%, 50% to 74%, and ≥75%, indicative of low, moderate, and high heterogeneity. Publication bias was evaluated using visual inspection of funnel plot asymmetry and by Egger's test.[32] $P<0.05$ was used as the level of significance and 95% CIs were reported where appropriate.

Results

E-CABG study

Of the 3788 patients enrolled in the E-CABG study between January 2015 and March 2016, 3641 (96%) were included in the final analysis (supplemental Figure 1). The cohort presented a median age of 68 years (25^{th}–75^{th} percentile, 61-75 years), and 17% were women. Characteristics of the enrolled patient population are detailed in Table 1. A total of 685 (19%) patients had a prior PCI, and the mean time elapsed between last PCI and CABG was 46 months (25^{th}–75^{th} percentile, 8-110 months). Indication for surgical revascularization included progression of native coronary disease in 88% of the patients, in-stent restenosis in 40%, and thrombosis in 5%. Left main trunk was stented in 5% of the individuals, while left anterior descending artery, circumflex and right coronary arteries in 51%, 38%, and 52%, respectively (supplemental Table 5). Compared with non-weighted CABG patients with no prior PCI, those with prior PCI exhibited different demographic, clinical, and comorbidity characteristics. Patients with prior PCI were younger (66.4 ± 9.4 *vs* 67.6 ± 9.3 years, p=0.0025), and presented a lower Syntax score (26.5 ± 10.4 *vs* 28.6 ± 10.9, p=0.0001). No clinical differences were observed between patients with prior PCI and propensity weighted score patients with no prior PCI

(Table 1, supplemental Figure 2). Operative and postoperative data are summarized in Tables 1 and 2. At multivariable level, no differences were observed both in unweighted and weighted patient groups regarding hospital mortality (OR, 0.73; 95%CI 0.29-1.38; p=0.3279, and OR, 0.90; 95%CI 0.39-2.08; p=0.8142, respectively). Sensitivity analyses and variable interactions that considered gender, age classes, syntax score categories, LVEF classes, eGFR classes (≤ 60 ml/min/1.73m^2), and presence of diabetes mellitus confirmed that prior PCI had no impact on hospital mortality (Figure 1, and supplemental Table 6). Prior PCI was also not associated with an increased risk of postoperative need of IABP and/ECMO support, re-exploration for bleeding/tamponade, ICU stay, blood transfusion, and occurrence of stroke, acute kidney injury, atrial fibrillation, and gastro-intestinal complications in both unweighted and weighted patient groups (Table 2).

At multivariable logistic regression, number of prior PCIs (1 PCI: 1.4%; 2 PCIs: 1.1%; ≥ 3 PCIs: 3.8%) did not affect the hospital mortality (1/2 PCI: OR, 0.82; 95%CI, 0.35 to 1.70, and ≥3 PCIs: OR, 2.17; 95%CI, 0.50 to 6.42) as well as the number of treated vessels (1 vessel: 1.4%; 2 vessels: 1.0%; ≥3 vessels: 4.8%) did not also affect the hospital mortality (≥ 1 vessel: OR, 0.85; 95%CI, 0.31 to 1.91, and ≥2 vessels: OR, 1.28; 95%CI, 0.42 to 3.11). No patients with prior PCI of the left main trunk died after CABG.

Systematic Review and Meta-analysis

Literature search yielded a total of 50 292 records, and 8 eligible studies (3 retrospective single center, 3 retrospective multicenter, 2 national registry), which were published between 2005 and 2016 and were included in the meta-analysis (supplemental Figure 3).[6-13] Region of origin of participants included Europe (n=3), North America (n=3), Australia (n=1), and South America (n=1). Study characteristics and collected outcomes for patients with and without prior PCI are summarized in the supplemental Tables 7-10. When the data from the E-CABG study were included, the final meta-analysis population comprised 71 366 patients.

Pooled unadjusted ORs showed that patients with prior PCI had a higher in-hospital/30-day mortality when compared with patients with no prior PCI (unadjusted OR, 1.33; 95% CI, 1.07–1.66; supplemental figure 4). A moderate heterogeneity among studies (I^2 =43.1%) was observed, and

funnel plot revealed no evidence of publication bias (p=0.8071; supplemental Figure 7). Overall, 9 studies reported on adjusted effect size of prior PCI on mortality (supplemental Table 10). Pooled estimates of individual log adjusted ORs confirmed that prior PCI was not independently associated with higher in-hospital/30-day mortality (adjusted OR, 0.26; 95% CI, -0.01–0.53; I^2=43.1%; Figure 2, top). Similarly, pooled estimates of individual log adjusted ORs obtained from propensity score analyses confirmed no effects of prior PCI on in-hospital/30-day mortality (adjusted OR, 0.60; 95% CI, -0.05–1.25; I^2=65.8%; Figure 2, bottom). Pooled estimates did not reveal any significant effect of prior PCI with reference to re-exploration for bleeding/tamponade (OR, 1.30; 95% CI, 0.89-1.91; I^2=53.7%), postoperative stroke (OR, 1.04; 95% CI, 0.82-1.31; I^2=0%), renal failure (OR, 1.20; 95% CI, 0.90-1.60; I^2=37.8), atrial fibrillation (OR, 1.01; 95% CI, 0.90-1.14; I^2=37.8%), and length of in-hospital stay (mean difference, 0.18; 95%CI, -0.03-0.40; I^2 =0%) (Table 3, supplemental Figures 4-6).

Discussion

In the prospective E-CABG study we demonstrated that patients undergoing CABG with a history of PCI do not have higher early mortality compared with patients without such history. In addition, prior PCI does not confer any additional risk in terms of postoperative morbidity, including low cardiac output, blood transfusion requirement, pulmonary, renal, and cardiac complications. In a systematic review of 9 studies that included patients from 20 countries we observed consonant results, and sensitivity analyses substantiated these observations also in young patients, in those with severe coronary artery disease, heart failure, and diabetes mellitus.

The above results are not negligible in light of the widespread use of PCI even in patients affected by complex coronary disease and severe comorbidities.[1-4] The number of patients undergoing CABG with a history of PCI has steadily increased, from 8% in 2004 to over 20% in 2008,[6] and 10% to 30% of patients with prior PCI, requires surgical myocardial revascularization within 10 years.[33] In this context, the prognostic impact of prior PCI is relevant, especially because some studies suggest that incomplete revascularization strategies or procrastination of surgical revascularization are associated

with worse outcomes.[13,17] However, the cumulative evidence on the clinical relevance of prior PCI in patients requiring CABG is largely controversial. In 1996, Jones et al.[34] firstly documented a negative impact of prior PCI, by an extensive review of large databases that included 172 184 patients undergoing CABG. Similar data were subsequently observed in other experiences. Hassan et al.[8] identified prior PCI as an independent predictor of in-hospital mortality (3.6% *vs* 2.3%) in a retrospective cohort of 6 504 patients undergoing first-time isolated CABG. In the study of Bonaros and colleagues,[17] prior PCI also emerged as predictor of an increase in-hospital mortality (4.4% *vs* 2.4%) and major adverse cardiac events (7.9% *vs* 4.3%). The negative prognostic impact of prior PCI was observed also in specific patient populations, including patients with diabetes mellitus and triple-vessel coronary artery disease.[9,15] Conversely, other studies failed to demonstrate the negative PCI role. Metha et al.[6] analysing a total of 34 316 isolated CABG patients at 16 different state-wide institutions, observed similar mortality rates between patients with and without prior PCI (2.3% *vs* 1.9%), although major complications and longer hospitalization were recorded in the PCI group only. In the Massachusetts Adult Cardiac Surgery Database, 12 591 CABG patients were considered for analysis, and prior PCI (≥14 days) did not affect early and late survivals.[11]

There is a number of plausible explanations for these controversial data. The design of these studies was retrospective with its well-known limitations, notably the likelihood that unmeasured confounders could have introduced unknown bias.[5-19] This represents the inherited inability of retrospective observational analyses in proving causality. Some studies did not consider the impact of the time interval between PCI and the subsequent CABG, pooling all patients with a PCI history together,[5,15-19] and the possible bias related to any uncontrollable acute PCI-related complication has been demonstrated having a dramatic impact on early mortality and morbidity.[11,13] Stevens et al.[11] characterized the outcomes after isolated CABG in patients with history of remote (≥14 days) and recent (<14 days) PCI. While hospital mortality did not differ between patients with and without a PCI history in the remote cohort, recent PCI was associated with higher hospital mortality and morbidity (4.1% vs 1.9%, and 58% vs 43%, respectively).[11] An important source of bias is the comparison among different patient groups. Some studies specifically addressed the prognostic impact of prior PCI

comparing patients with and without such history,[5-13,15-19] whereas others analysed the impact of PCI in CABG patients only.[14,19] Finally, data on cardiac catheterization procedures, which could have hampered the assessment of coronary lesions and the completeness of percutaneous coronary revascularization, were not recorded in these retrospective analyses nor considered in the final multivariable models.[5-19]

The E-CABG study was design to specifically address the prognostic impact of prior PCI in patients undergoing CABG.[20] All study end-points were pre-specified, and all cardiac catheterization data fully recorded and imputed in our statistical models. The E-CABG study also used high quality prospectively collected data, with robust and constant validation processes and harmonization of transcriptional discrepancies.[20] In addition, to substantiate our analyses, we performed a qualitative and quantitative systematic review, using a comprehensive search strategy and contemporary assessments of study quality. The results of our meta-analysis confirmed that in patients undergoing CABG, prior PCI was not associated with higher mortality (in-hospital/30-day), major postoperative complications, or greater use of hospital resources. Our two studies confirm that CABG can be safely deferred in favour of PCI, and that hybrid revascularization strategy of PCI first and CABG later can be safely performed. In addition, patients with prior PCI, who subsequently develop recurrent angina, are potentially good candidate for surgical revascularization. Finally, the common belief that prior PCI is a marker of sicker/more ill patients is not sustained by our data along our systematic literature review. As a consequence, the inclusion of "prior PCI" in risk model stratification (i.e. EuroSCORE) is not supported by the present analyses.[13]

Our study has a number of limitations. First, although the present data are from a prospective multicentre registry, and the study protocol and aims were planned before data collection,[20] bias inherent to its observational nature are still possible. Second, we analysed the prognostic impact of prior PCI in the early postoperative period only. The presence of coronary stents is a recognized cause for distal bypass grafting, which involves smaller target vessels with less favourable run-off, and for a potential reduced long-term graft patency. However, several studies consistently failed to show any significant impact of prior PCI on long-term mortality following CABG procedures.[7,10,11] Third, the

present results are conditional to survival after PCI and our data does not allow an assessment of the outcome after PCI. The meta-analysis also had limitations. Principally, we were able to include a limited number of studies focusing in this topic among those effectively screened. Severe methodological flaws, unclear inclusion/exclusion criteria, and different patient group comparisons prevent us from a large study analysis.[5,14-19]

In conclusion, prior PCI was not associated with an increased risk of mortality following surgical revascularization. No associations between prior PCI and other postoperative outcomes, including organ failures, hospital resource use, and blood transfusion were also observed.

Appendix

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Biancari, Mariscalco, Rosato, Serraino had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest

None.

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Table 1. Preoperative and intraoperative characteristics of the patient population. Weighted and unweighted patient groups are presented

Variable*	Unweighted						Propensity Score Weighted		
	No PCI		Prior PCI		*P*-value		No PCI		*P*-value†
	n = 2956		n = 685				n = 651		
	N	%	N	%			N	%	
Demographics									
Age, y	67.6 ± 9.3		66.4 ± 9.4		0.0025		66.7 ± 4.4		0.4095
BMI, Kg/m^2	27.5 ± 4.2		27.6 ± 4.3		0.6033		27.6 ± 2.0		0.9978
Female	511	(17.3)	107	(15.6)	0.2952		112	(17.1)	0.4528
Presentation									
ACS type									
Unstable angina	493	(16.7)	130	(19)	0.0168		127	(19.5)	0.5903
NSTEMI	706	(23.9)	126	(18.4)			137	(21.1)	
STEMI	187	(6.3)	49	(7.2)			46	(7.1)	
Emergency	131	(4.4)	20	(2.9)	0.0737		25	(3.8)	0.3637
Critical preop state	111	(3.8)	18	(2.6)	0.1504		20	(3.1)	0.6055
Prior cardiac surgery	21	(0.7)	11	(1.6)	0.0237		5	(0.8)	0.1594
Recent MI	893	(30.2)	175	(25.5)	0.0157		184	(28.2)	0.2751
Left main stenosis	1074	(36.3)	246	(35.9)	0.8366		226	(34.7)	0.6441
EF class									
>50%	2114	(71.6)	486	(71.2)	0.0116		467	(71.8)	0.9170
31-50%	690	(23.4)	173	(25.3)			163	(25)	
21-30%	137	(4.6)	17	(2.5)			16	(2.5)	
≤20%	12	(0.4)	7	(1)			4	(0.7)	
Syntax score	28.6 ± 10.9		26.5 ± 10.4		0.0000		26.8 ± 5.0		0.5419
Diseased coronaries, n	2.7 ± 0.6		2.6 ± 0.6		0.0001		2.6 ± 0.3		0.0699
Comorbidities									
EuroSCORE 2, n	2.6 ± 3.9		2.4 ± 3.8		0.2774		2.4 ± 1.6		0.9386
Hypertension	2335	(79)	561	(81.9)	0.0894		517	(79.3)	0.2324
Diabetes mellitus									
Type I (insulin)	531	(18)	144	(21)	0.0635		126	(19.3)	0.7254
Type II	398	(13.5)	103	(15)			97	(14.9)	
Pulmonary disease	281	(9.5)	62	(9.1)	0.7134		63	(9.6)	0.7125
Extracardiac arteriopathy	609	(20.6)	159	(23.2)	0.1314		136	(20.9)	0.3140
Prior stroke	117	(4)	29	(4.2)	0.7405		31	(4.8)	0.6465
Prior AF	224	(7.6)	56	(8.2)	0.5732		49	(7.5)	0.6293
Poor mobility	76	(2.6)	9	(1.3)	0.0496		14	(2.1)	0.2715
Anaemia	668	(22.6)	159	(23.2)	0.7190		151	(23.2)	0.9743
Hb, mg/dl	136.3 ± 16.3		135.8 ± 17.3		0.5046		136.0 ± 7.9		0.7901
Dialysis	34	(1.2)	10	(1.5)	0.5039		8	(1.3)	0.7981
eGFR, ml/min/1.73m^2	75.5 ± 20.6		75.8 ± 21.2		0.6598		75.9 ± 9.9		0.9333
Medication									
Anti-platelet within 5 days	335	(11.3)	135	(19.7)	0.0000		113	(17.4)	0.2811
Clopidogrel	469	(15.9)	209	(30.5)	0.0000		179	(27.5)	0.2197
Ticagrelor	352	(11.9)	120	(17.5)	0.0001		99	(15.3)	0.2682
Warfarin	68	(2.3)	18	(2.6)	0.6112		15	(2.4)	0.7647

Intraoperative									
CPB time, min	57.5 ± 26.0		56.0 ± 28.7		0.2636		56.4 ± 12.2		0.7624
ACC time, min	83.7 ± 36.1		79.0 ± 34.9		0.0061		82.4 ± 16.6		0.0474
Operation time, min	227.6 ± 84.3		218.8 ± 88.0		0.0259		226.3 ± 38.1		0.0586
OPCAB	587	(19.9)	140	(20.4)	0.7322		131	(20.1)	0.8696
Maze proc	9	(0.3)	2	(0.3)	0.9572		2	(0.3)	0.9624
Epiaortic ultrasound	275	(9.3)	60	(8.8)	0.6572		54	(8.3)	0.7588
Diseased ascending aorta	85	(2.9)	17	(2.5)	0.5736		19	(2.9)	0.6398
N. of grafts, n	2.7 ± 0.9		2.5 ± 0.9		0.0000		2.7 ± 0.4		0.0000
LITA graft	2886	(97.6)	663	(96.8)	0.2049		635	(97.5)	0.4403
RITA graft	1129	(38.2)	285	(41.6)	0.0987		244	(37.5)	0.1249
BITA graft	1106	(37.4)	279	(40.7)	0.1074		239	(36.6)	0.1241
SVG graft	1933	(65.4)	397	(58)	0.0003		418	(64.2)	0.0199
Radial artery graft	39	(1.3)	12	(1.8)	0.3855		8	(1.3)	0.4929

*Continuous variables are reported as mean and standard deviation. Categorical variables are reported as absolute number and percentages. †Comparison between patients with no prior PCI versus propensity score weighted patients with no PCI.

Abbreviations: ACC, aortic cross clamp; ACS, acute coronary syndrome; AF, atrial fibrillation; BITA, bilateral internal thoracic artery; BMI, body mass index; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; Hb, haemoglobin; LITA, left internal mammary artery; NSTEMI, non ST-elevation myocardial infarction; OPCAB, off-pump coronary artery bypass; RITA, right internal thoracic artery; STEMI, ST-elevation myocardial infarction; SVG, saphenous vein graft.

Table 2. Multivariable adjusted primary and secondary end-points of study population, for weighted and unweighted patient groups

Variable*	Unweighted							Propensity weighted score			
	No PCI		Prior PCI		OR (95% CI)	P-value		No PCI		OR (95% CI)	P-value
	N	%	N	%				N	%		
Primary end-point											
Hospital mortality	65	(2.2)	11	(1.6)	0.73 (0.29-1.38)	0.3279		12	(1.8)	0.90 (0.39-2.08)	0.8142
Secondary end-points											
ITU stay, day	2.8 ± 4.5		2.7 ± 3.5		-	0.3141		2.8 ± 1.8		-	0.5686
IABP/ECMO support	155	(5.2)	24	(3.5)	0.66 (0.42-1.02)	0.0577		622	(4.4)	0.78 (0.45-1.36)	0.3825
Re-exploration for bleeding/tamponade	89	(3.0)	14	(2.0)	0.67 (0.38-1.19)	0.1690		19	(2.9)	0.69 (0.34-1.38)	0.2937
Stroke	39	(1.3)	13	(1.9)	1.45 (0.77-2.72)	0.2516		8	(1.2)	1.61 (0.66-3.95)	0.2940
Acute kidney injury (AKI)	736	(25.2)	147	(21.6)	0.82 (0.67-1.00)	0.0508		164	(25.5)	0.81 (0.62-10.4)	0.0979
Atrial fibrillation (AF)	791	(26.9)	166	(24.3)	0.87 (0.71-10.5)	0.1535		171	(26.5)	0.89 (0.70-1.41)	0.3599
Gastro-intestinal bleeding/ischemia	9	(0.3)	2	(0.3)	0.96 (0.21-4.45)	0.9572		1	(0.2)	1.55 (0.16-14.66)	0.7013
RBC Unit, n	1.1 ± 2.2		1.1 ± 2.0		-	0.9691		1.1 ± 1.2		-	0.7125
Other outcomes											
In-hospital mortality	58	(2.0)	8	(1.2)	0.59 (0.28-1.24)	0.1603		10	(1.5)	0.77 (0.30-1.96)	0.5767
Prolonged inotropic support	843	(28.5)	185	(27.0)	0.93 (0.77-1.12)	0.4286		170	(26.2)	1.04 (0.82-1.33)	0.7240
Postoperative PCI requirement	34	(1.2)	6	(0.9)	0.76 (0.32-1.82)	0.5349		7	(1.1)	0.82 (0.27-2.46)	0.7244
Sternal wound infections	161	(5.4)	36	(5.3)	0.96 (0.66-1.40)	0.8421		37	(5.7)	0.92 (0.57-1.38)	0.7320
Use of antibiotics	419	(14.2)	88	(12.8)	0.89 (0.70-1.14)	0.3657		96	(14.8)	0.85 (0.62-1-16)	0.3103

*Continuous variables are reported as mean and standard deviation. Categorical variables are reported as absolute number and percentages. Abbreviations: CI, confidence interval; ECMO, extra-corporeal membrane oxygenation, IABP, intra-aortic balloon pump; ICU, intensive care unit; OR, odds ration; PCI, percutaneous coronary intervention.

Table 3. Systematic review outcomes of patients undergoing CABG with and without prior PCI

Postoperative Outcomes	No. of studies	No. of patients	Prior PCI*	No PCI*	Effect estimate (95%CI)	I^2	P-value
Primary							
Unadjusted in-hospital/30-day mortality	9	71366	3.8 (1.1 to 9.3)	2.4 (1.5 to 5.1)	1.33 (1.07 to 1.66)	43.1%	0.0103
Adjusted in-hospital/30-day mortality	8	63511	-	-	0.26 (-0.01 to 0.53)	43.1%	0.0631
Adjusted PS in-hospital/30-day mortality	5	26528	-	-	0.60 (-0.05 to 1.25)	65.8%	0.0701
Secondary							
Re-exploration for bleeding/tamponade	5	43196	3.0 (1.8 to 6.3)	2.0 (1.2 to 3.0)	1.30 (0.89 to 1.91)	53.7%	0.1766
Stoke	5	43196	3.8 (1.7 to 8.8)	3.0 (1.2 to 5.8)	1.04 (0.82 to 1.31)	0%	0.7383
Renal failure (dialysis)	4	42447	1.6 (0.8 to 2.7)	1.6 (1.3 to 1.9)	1.20 (0.90 to 1.60)	34.6%	0.2189
Postoperative AF	4	41942	20.1 (16.4 to 24.2)	19.9 (13.7 to 26.8)	1.01 (0.90 to 1.14)	37.8%	0.8289
In-hospital stay	3	38806	8.4 (7.1 to 10)	8.4 (6.9 to 10)	0.18 [-0.03 to 0.40)	0%	0.0989

*Expressed as mean (min to max). Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; PS, propensity score.

Figure legends

Figure 1. Sub-group analysis with reference to hospital mortality. CI, indicates confidence interval; IR, ; OR odds ratio.

Figure 2. Forest plot with adjusted risk estimates for in-hospital/30-day based on multivariate logistic regression in unmatched (top) and matched patient groups (bottom). CI indicates confidence interval, OR odds ratio.

ONLINE-ONLY SUPPLEMENTAL MATERIAL

Mariscalco G, Rosato S, Serraino GF, Maselli D, Dalén M Airakisen JKE, Reichart D, Zanobini M, Onorati F, De Feo M, Gherli R, Santarpino G, Rubino A, Gatti G, Nicolini F, Santini F, Perrotti A, Bruno VD, Ruggeri VG, Biancari F, on behalf of the E-CABG Investigators

Prior Percutaneous Coronary Intervention and Mortality among Adults Undergoing Surgical Myocardial Revascularization: Results from the European Multicenter Study on Coronary Artery Bypass Grafting (E-CABG) with a Systematic Review and Meta-analysis

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplemental Tables

Table 1. The RECORD statement – checklist of items, extended from the STROBE statement

	Item No	Recommendation	Reported on Page N.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3,4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3,4
Bias	9	Describe any efforts to address potential sources of bias	3,5, and 6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5,6
		(*b*) Describe any methods used to examine subgroups and interactions	5,6
		(*c*) Explain how missing data were addressed	na
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	na
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7,8
		(b) Give reasons for non-participation at each stage	7,8

		(c) Consider use of a flow diagram	Appendix
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Appendix
Outcome data	15*	Report numbers of outcome events or summary measures	8 Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8
		(*b*) Report category boundaries when continuous variables were categorized	7,8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8 Table 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8 Suppl Table 6
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11,12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10,11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

Table 2. MOOSE Checklist for Meta-analyses of Observational Studies[2]

Item N.	Recommendation	Reported on Page N.
Reporting of background should include		
1	Problem definition	5, Appendix
2	Hypothesis statement	5, Appendix
3	Description of study outcome(s)	5, Appendix
4	Type of exposure or intervention used	5, Appendix
5	Type of study designs used	5, Appendix
6	Study population	5, Appendix
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5, Appendix
8	Search strategy, including time period included in the synthesis and key words	5, Appendix
9	Effort to include all available studies, including contact with authors	5, Appendix
10	Databases and registries searched	5, Appendix
11	Search software used, name and version, including special features used (eg, explosion)	5, Appendix
12	Use of hand searching (eg, reference lists of obtained articles)	5, Appendix
13	List of citations located and those excluded, including justification	5, Appendix
14	Method of addressing articles published in languages other than English	Appendix
15	Method of handling abstracts and unpublished studies	Appendix
16	Description of any contact with authors	Appendix
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5, Appendix
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	na
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	na
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	6, Appendix
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Appendix
22	Assessment of heterogeneity	6, Appendix
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6, Appendix
24	Provision of appropriate tables and graphics	Appendix
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2, Suppl Figures 4-6

26	Table giving descriptive information for each study included	Suppl Table 7-10
27	Results of sensitivity testing (eg, subgroup analysis)	8,9 Table 3
28	Indication of statistical uncertainty of findings	Table 3
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Appendix
30	Justification for exclusion (eg, exclusion of non-English language citations)	Appendix
31	Assessment of quality of included studies	Appendix
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	9
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	10
34	Guidelines for future research	9,10, and 11 Appendix
35	Disclosure of funding source	14

Table 3. PRISMA checklist of Items to Include when Reporting a Systematic Review or Meta-analysis[3]

Section/topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3, Appendix
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3, Appendix
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Ref. 24
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Suppl Table 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, Appendix
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5, Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5, Appendix
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5, Appendix Suppl Figure 3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5, Appendix
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5, Appendix
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6, Appendix

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6, Appendix
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6, Appendix
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6, Appendix
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Appendix Suppl Figure 3
Study characteristics	18	For each study, present characteristics for which data were extracted and provide the citations.	Suppl Table 7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Suppl Table 9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8,9 Suppl Fig. 4-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8,9 Suppl Fig. 4-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Suppl Figure 7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8,9 Table 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10,11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

Table 4. PICOS criteria for inclusion and exclusion of studies into meta-analysis

Parameter	Inclusion criteria	Exclusion criteria
Patients	Adult patients affected by CAD, requiring CABG	Other cardiac diseases other than CAD
Intervention*	Patients undergoing CABG	Patients not necessitating surgical revascularization
Comparator	Presence of prior PCI	No comparison between patients with and without PCI
Outcomes	Primary: in-hospital/30-day mortality (all cause) Secondary: postoperative stroke; re-exploration for bleeding/tamponade; postoperative dialysis/renal failure; occurrence of postoperative AF; in-hospital stay (days)	-
Study design	Clinical randomised trials Controlled before-and-after studies Prospective and retrospective cohort studies Cross-sectional studies Case-control studies	Repeat publications of the same analysis or dataset Conference abstracts Editorials & opinion pieces Books or grey literature

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Table 5. Detailed stent data and indications for surgery

Variable	Data available*	n	%	Median	25th-75th percentile
Baseline PCI data					
N. of prior PCI	683			1	1-2
Prior PCI ≥ 2	683	258	38		
Time last PCI to CABG, months	685			46	8-110
Site of PCI					
LMS stenting	684	37	5.4		
LAD stenting	684	347	50.7		
CX Stenting	684	260	38.0		
RCA stenting	684	357	52.2		
Type of stenting					
BMS	658	226	34.3		
DES	658	412	62.6		
BAP	658	82	12.5		
Indication for surgery					
Stent thrombosis	652	30	4.6		
Stent re-stenosis	652	260	39.9		
Disease progression	651	570	87.6		

*Data not available from patient medical history or medical notes at the time of current admission are excluded.
Abbreviations: BAP, balloon angioplasty (without stent); BMS, bare metal stent; CX, circumflex coronary artery; DES, drug eluting stentstent; LAD, left anterior descending; LMS, left main stem; RCA, right coronary artery.

Table 6. Sub-group analysis considering the effect of age and syntax score classes on hospital mortality

Variable	No PCI		Prior PCI		OR (95% CI)	*P* interaction
	n	IR	n	IR		
Age Classes (yrs)						
≤70	3	(0.9)	7	(1.7)	1.03 (0.66-1.63)	0.1971
>70	7	(2.6)	4	(1.6)	0.77 (0.41-1.44)	
Age Classes (yrs)						
≤62	1	(0.8)	4	(1.9)	1.23 (0.49-3.07)	0.4146
62-70	2	(1.0)	3	(1.5)	1.32 (0.27-6.34)	
>70	7	(2.6)	4	(1.6)	1.63 (0.15-13.61)	
Syntax Score Classes						
≤23	2	(0.8)	1	(0.4)	1.26 (0.61-2.61)	0.7058
23-32	3	(1.5)	5	(2.4)	1.66 (0.45-6.08)	
≥32	5	(2.7)	5	(2.7)	2.19 (0.32-15.07)	

Abbreviations: CI, confidence interval; IR, PCI, percutaneous coronary intervention; OR, odds ratio. ischemic heart disease; OR, odds ratio.

Table 7. Characteristics of the studies included in the systematic review

Study (Author, Year)	Design	Country	Study period	Population (n)	PCI (n, %)	Inclusion criteria	Exclusion criteria	Outcomes
Lisboa et al,[4] 2012	Retrospective, single-center	Brazil	2007-2009	1099	161 (16.6%)	Elective, urgent or emergency CABG surgery	Combined, off-pump and reoperation surgery, PCI and CABG during the same hospitalization	In-hospital mortality
Mannacio et al,[5] 2012	Retrospective, multicenter	Italy	2000-2005	7855	1021 (13%)	First time isolated CABG	recent myocardial infarction, reoperation or conbined surgery. CABG during the same hospitalization	30-day mortality, MACE, 3-yr and 5-yr mortality
Mehta et al,[6] 2012	Retrospective, multicenter	USA	2001-2008	34.316	4346, (12.7%)	Isolated CABG	conbined surgery. CABG during the same hospitalization	In-hospital mortality, Re-exploration, perioperative MI, Stroke, AKI, Dialysis, POAF, DSWI, Limb ischemia, MOF, LOS, GI bleeding, heart block, Readmission 30-days
Stevens et al,[7] 2010	Retrospective, multicenter	USA	2002-2004	9642	823 (8.5%)	Isolated CABG	primary PCI for acute MI, PCI-CABG interval 5 years or unknown, out-of-state patients	30-day mortality, Re-exploration, perioperative MI, Stroke, Renal failure, POAF, Transfusion, prolonged ventilation, pneumonia, LOS, Readmission 30-days, 5-yr mortality
Yap et al,[8] 2009	Retrospective, multicenter	Australia	2001-2008	13184	1457 (11%)	First time isolated CABG	conbined surgery. CABG during the same hospitalization	In-hospital mortality, MACE, 6-yr mortality
Thielmann et al,[9] 2006	Retrospective, single-center	Germany	2000-2006	621	128 (20.6%)	First time isolated CABG (triple-vessel coronary artery disease) with a history of diabetes	1- or 2-vessel disease at the time of recent PCI or before CABG surgery , nondiabetic patients, left	In-hospital mortality, Re-exploration, perioperative MI, MACE, Stroke, LCOS,

						mellitus	main disease, emergency status, acute coronary syndromes	Dialysis, CPR, POAF, ITU stay, LOS,
Hassan et al,[10] 2005	Retrospective, multicenter	Canada	1996-2000	6032	919 (15.2%)	First time isolated CABG	CABG during the same hospitalization	In-hospital mortality
van den Brule et al,[11] 2005	Retrospective, single-center	Netherlands	1999-2001	1254	113 (9%)	First time isolated CABG	Failed PCI	In-hospital mortality, Reintervention, perioperative MI, Stroke, Renal complications, Pulmonary complications, Arrhythmias, LOS

Abbreviations: AKI, acute kidney injury, CABG, coronary artery bypass grafting; CPR, cardiopulmonary resuscitation; DSWI, deep sternal wound infection; ITU, intensive care unit; LCOS, low cardiac output syndrome; LOS, length of stay (in-hospital stay); MACE, major adverse cardiac evenets; MI, myocardial infarction; MOF, multiple organ failure; PCI, percutaneous coronary intervention; POAF, postoperative atrial fibrillation.

Table 8. Study characteristics in patients who underwent coronary artery bypass grafting (CABG) with prior percutaneous coronary intervention (PCI), stratified by Author.

Study (Author, Year)	Age, yrs (mean ± SD)		Female (n, %)		Emergency (n, %)		Diabetes Mellitus (n, %)		Left main stem (n, %)		N. distal anastomosis (mean ± DS)	
	PCI	No PCI	PCI	No PCI	PCI	No PCI	PCI	No PCI	PCI	No PCI	PCI	No PCI
Lisboa et al,[4] 2012	63 (56-69)[a]	62 (56-70)[a]	36 (22%)	254 (27%)	6 (4%)	26 (3%)	71 (44%)	449 (48%)	24, (15%)	188 (20%)	-	-
Mannacio et al,[5] 2012	-	-	286 (28%)	1708 (25%)*	-	-	2597 (38%)	347 (34%)*	1572 (23%)	214 (21%)	2.7 ± 0.5	2.5 ± 0.6*
Mehta et al,[6] 2012	62.8 ± 10.7	64.1 ± 10.7**	1078 (25%)	7942 (27%)*	248 (6%)	929 (3%)**	1786 (41%)	11238 (38%)**	1199, (28%)	8362 (28%)	-	-
Stevens et al,[7] 2010	63 ± 11	67 ± 11**	255 (31%)	2305 (26%)*	14 (2%)	256 (3%)	355 (43%)	3297 (37%)*	216 (26%)	3132 (36%)**	3.1 ± 1.0	3.3 ± 1.0**
Yap et al,[8] 2009	63.3 ± 10.5	66.0 ± 10.2**	296 (20%)	2674 (23%)*	48 (3%)	480 (4%)*	474 (33%)	3776 (32%)	270 (19%)	3026 (26%)**	3.0 ± 1.1	3.3 ± 1.0**
Thielmann et al,[9] 2006	66 ± 9	67 ± 9	33 (26%)	165 (27%)	0	0	100%	100%	0	0	3.5 ± 1.3	3.6 ± 1.2
Hassan et al,[10] 2005	-	-	212 (23%)	1237 (24%)	60 (7%)	271 (5%)	254 (28%)	1576 (31%)	-	-	3.0	3.3**
van den Brule et al,[11] 2005	61.5 ± 10.9	64.2 ± 10.6*	24 (21%)	305 (27%)	0	0	10 (9%)	69 (6%)	8 (7%)	200 (18%)*	2.2 ± 0.9	3.2 ± 1.3*

Abbreviations: PCI, percutaneous coronary intervention; SD, standard deviation.
*and** significant unadjusted differences ($p<0.05$ and $p<0.001$, respectively) between patients with PCI compared with those with no PCI.

Table 9. Study outcomes in patients who underwent coronary artery bypass grafting (CABG) with prior percutaneous coronary intervention (PCI), stratified by Author.

Study (Author, Year)	In-hospital/30-day mortality (n, %)		Re-exploration for bleeding/tamponade (n, %)		Stroke (n, %)		Dialysis (n, %)		POAF (n, %)		LOS (mean ± SD) or median (range)	
	PCI	No PCI	PCI	No PCI	PCI	No PCI	PCI	No PCI	PCI	No PCI	PCI	No PCI
Lisboa et al,[4] 2012	15 (9%)	48 (5%)*	-	-	-	-	-	-	-	-	-	-
Mannacio et al,[5] 2012	31 (3%)	130 (2%)*	-	-	-	-	-	-	-	-	-	-
Mehta et al,[6] 2012	100 (2%)	569 (2%)	100 (2%)	539 (2%)*	56 (1%)	390 (1%)	74 (2%)	360 (1%)*	730 (16%)	4705 (17%)	7.10 ± 7.4	6.88 ± 7.7
Stevens et al,[7] 2010	9 (1%)	36 (2%)	20 (3%)	39 (2%)	12 (2%)	38 (2%)	20 (3%)	61 (3%)	-	-	10 ± 7	10 ± 7
Yap et al,[8] 2009	24 (2%)	184 (2%)	-	-	-	-	-	-	-	-	-	-
Thielmann et al,[9] 2006	10 (8%)	18 (3%)	8 (6%)	14 (2%)*	1 (1%)	12 (2%)	-	-	21 (16%)	85 (14%)	8 (7-12)	9 (7-13)
Hassan et al,[10] 2005	33 (4%)	118 (2%)*	-	-	-	-	-	-	-	-	-	-
van den Brule et al,[11] 2005	4 (4%)	24 (2%)	2 (2%)	14 (1%)	3 (3%)	29 (3%)	10 (9%)	66 (6%)	-	-	8.2 ± 9.0	8.3 ± 9.4

Abbreviations: LOS, length of hospital stay; POAF, postoperative atrial fibrillation; SD, standard deviation.
*and** significant unadjusted differences ($p<0.05$ and $p<0.001$, respectively) between patients with PCI compared with those with no PCI.

Table 10. List of variables included in the final multivariable logistic models with or without propensity score use; in-hospital/30-day mortality assessed.

Study (Author, Year)	Adjustement performed		Variables included in the final model	Multivariate Logistic Regression	Propensity Score Analysis
	Multivariate Logistic Regression	Propensity Score Analysis		Adjusted OR (95% CI) *P*-value	Adjusted OR (95% CI) *P*-value
Lisboa et al,[4] 2012	Performed	Performed (1:1)	Age, Female sex, EF, LMS > 50%, CHF, Unstable angina, Recent MI, MI with < 48hs, Cardiogenic shock, Preoperative IABP, Diabetes, Hypertension, Morbid obesity, Renal insufficiency, Dialysis, COPD, Pulmonary hypertension, Emergency, Previous PCI	OR 1.94 (95% CI, 1.02-3.68) p = 0.044	OR 3.46 (95%CI, 1.1-10.93) p = 0.034
Mannacio et al,[5] 2012	-	Performed (1:1)	Age ≥ 70 yrs Female sex, BMI ≥ 30,Hypertension Hypercholesterolemia, Diabetes mellitus, PVD, Respiratory disease, Renal disease, History of MI, EF ≤ 40%, NYHA ≥ class III, EuroSCORE ≥ 7, Multivessel coronary disease, LMS ≥ 50%, Single previous PCI, Multiple previous PCI, OPCABG, On-pump CABG, Prior PCI	na	OR 3.5 (95%CI, 1.1-10.6) p = 0.03
Mehta et al,[6] 2012	Performed	-	Society of Thoracic Surgeons Predicted Risk of Mortality-STS PROM, Operative year, Number of arterial and venous bypass grafts, CPB time, Prior PCI	OR 1.17 (95% CI, 0.91-1.51) p = 0.23	-
Stevens et al,[7] 2010	Performed	Performed (1:3)	na	OR 0.82 (95%CI, 0.34-2.02) p = 0.672	na
Yap et al,[8] 2009	Performed	Performed (1:1)	Age, Female sex, Diabtes, Hypertension, Hypercholesterolemia, Cerebrovascular disease, PVD, Renal failure, Respiratory disease, MI within 21 days, CHF, Unstable angina, NYHA classes, LMS > 50%, EF classes, Urgency status, Prior PCI	OR 1.26 (95%CI, 0.77-2.08) p = 0.35	OR 1.22 (95%CI, 0.76-1.99) p = 0.41
Thielmann et al,[9] 2006	Performed	Performed (1:1)	Age, Female sex, BMI > 30, EF, PVD, COPD, Hypertension Hyperlipidemia, Angina class III-IV, Previous MI, Renal disease, Prior PCI	OR 2.5 (95%CI, 1.3-5.8) p = 0.03	OR 2.97 (95%CI, 1.12-7.86) p = 0.028
Hassan et al,[10] 2005	Performed	Performed (1:1)	Age, Female sex, Smoking history, Diabetes, Renal insufficiency, Hypertension, PVD, Cerebrovascular disease, History of MI, CHF, Unstable angina, CCS classes,	OR 1.93 (95%CI, 1.26-2.96) p = 0.003	na

			Cardiogenic shock, Preoperative IABP, Urgency status, 3-Vessel/LMS, Surgical center, Prior PCI		
van den Brule et al,[11] 2005	Performed	-	Age, Gender, Diabetes, Hypertension, Hyperlipidemia, PVD, Neurological disease, Renal disease, Pulmonary disease, Preoperative MI, Arrhythmia, Diseased vessels, LMS, NYHA, EF, Postoperative arrhythmia, Reintervention, Renal complications, Stroke, Pulmonary complications, Prior PCI	OR 1.02 (95%CI, 0.68-1.54) p = 0.41	-

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Class (angina); CHF, congestive herat failure, CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; EF, ejection fraction; IABP, intra-aortic balloon pump; LMS, left main stem; MI, myocardial infarction; na, not available; NYHA, New York Heart Association; OPCABG, off-pump coronary artery bypass grafting; OR, Odds ratio; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease;

Supplemental Figures

Figure 1. Flow diagram for considered patient groups. CABG indicates coronary artery bypass grafting; PCI, percutaneous coronary intervention.

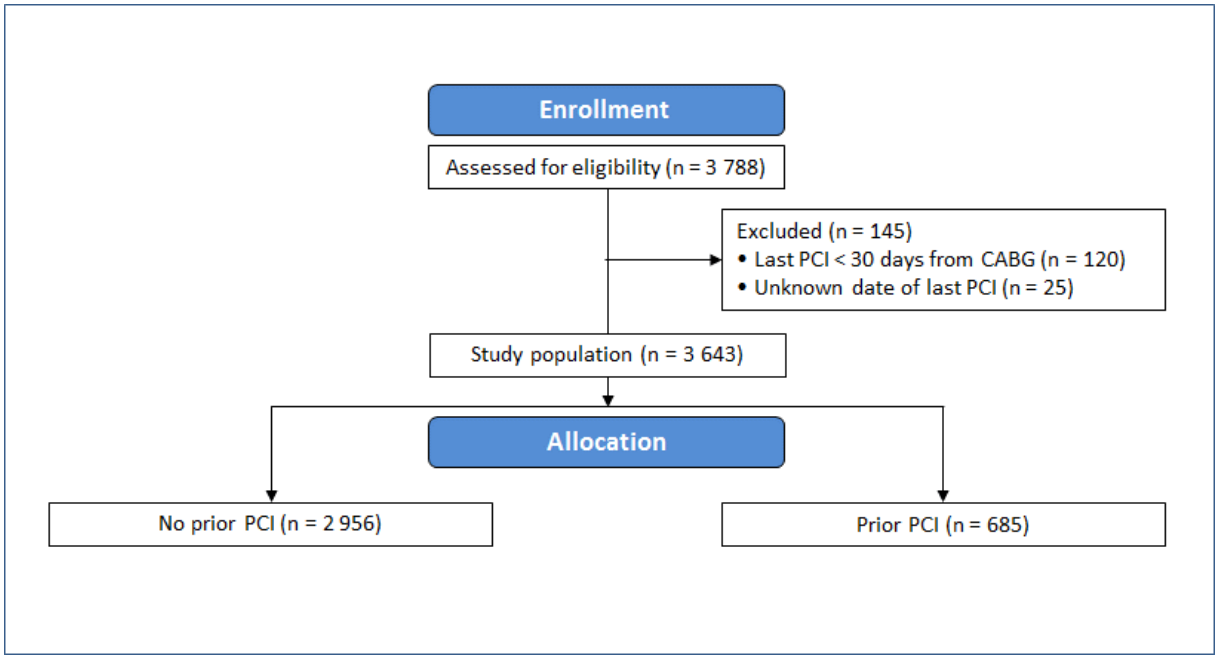


Figure 2. Relative influence of the covariates on the estimated propensity score (panel A), rank of p-value for pretreatment variables (hollow is weighted, solid is unweighted - panel B), absolute standardized differences before and after weighting (closed circles represent variables with statistically significant difference – panel C), balance of subgroups as function of iterations' number of GBM (panel D).

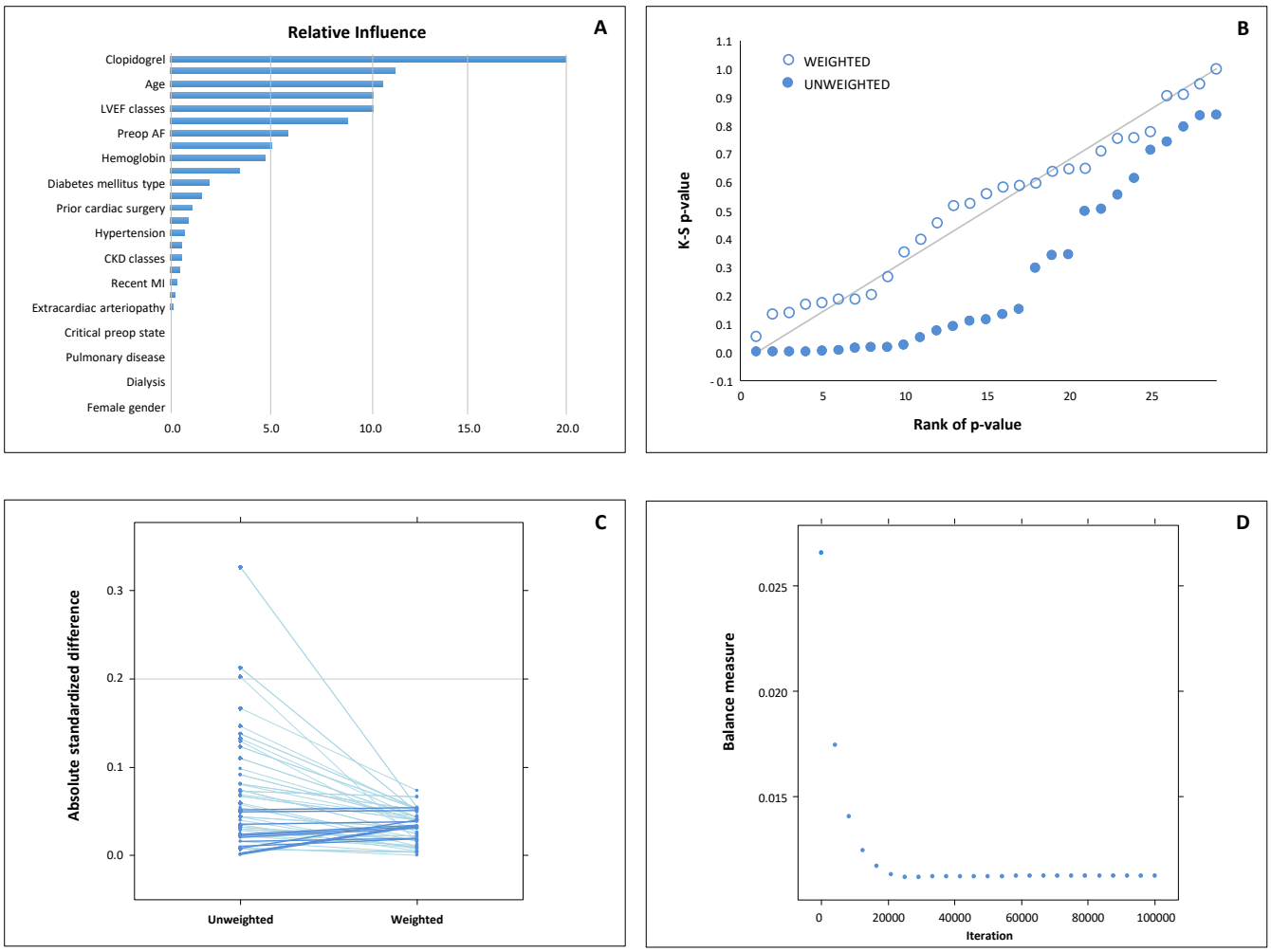


Figure 3. PRISMA flow chart of search strategy[3]

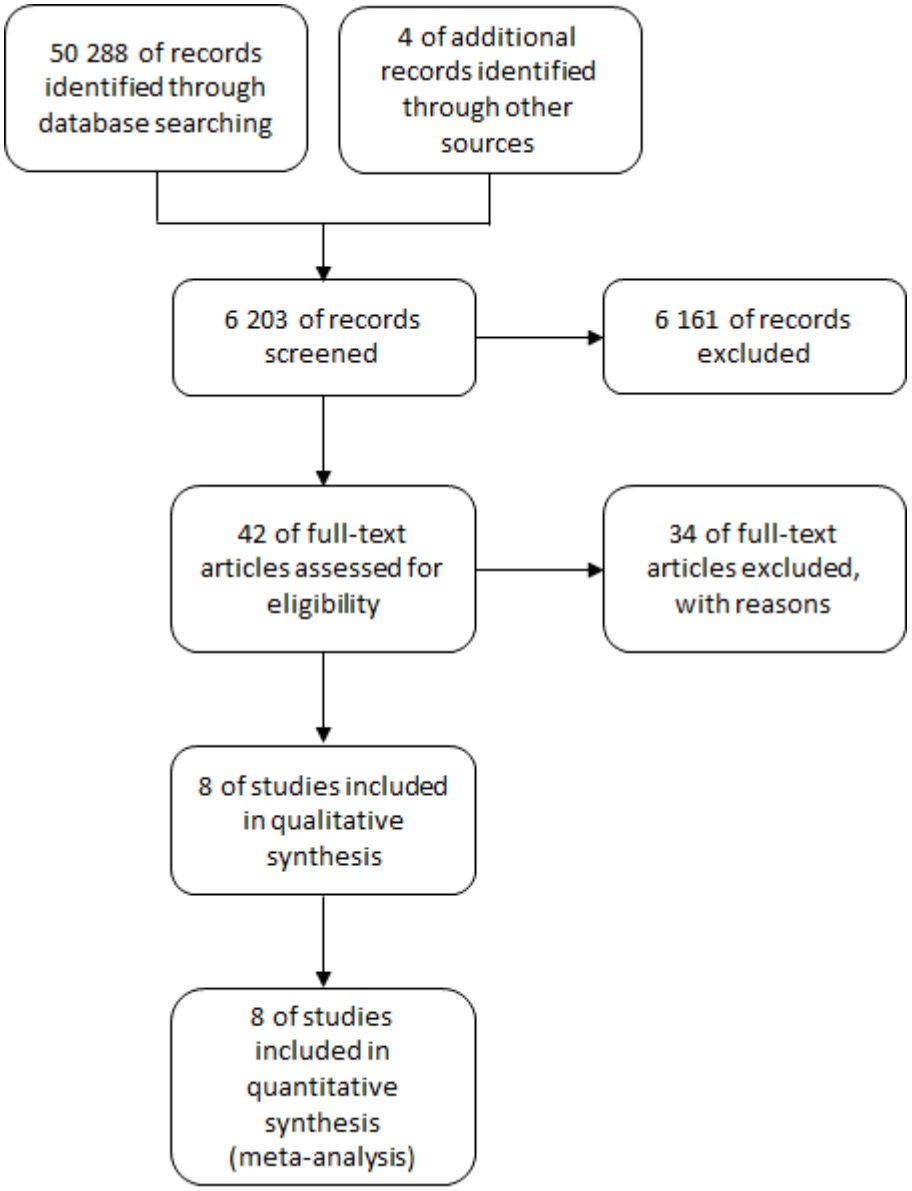
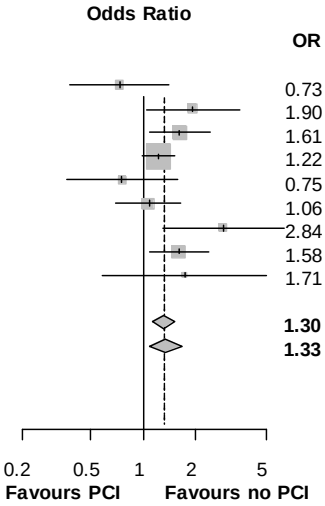


Figure 4. Forest plot with unadjusted risk estimates for in-hospital/30-day mortality (top) and re-exploration for bleeding/tamponade (bottom) in patients who underwent coronary artery bypass grafting (CABG) with prior percutaneous coronary intervention (PCI). CI, indicates confidence interval; OR, odds ratio.

MORTALITY

Study	PCI Events	PCI Total	No PCI Events	No PCI Total	OR	95%CI	W(fixed)	W(random)
E-CABG Study, 2017	11	685	65	2956	0.73	[0.38; 1.38]	4.9%	8.2%
Lisboa et al. 2012[4]	15	161	48	938	1.90	[1.04; 3.49]	5.5%	9.0%
Mannacio et al. 2012[5]	31	1021	130	6834	1.61	[1.09; 2.40]	12.8%	14.9%
Mehta et al.2012[6]	100	4346	569	29970	1.22	[0.98; 1.51]	43.9%	22.8%
Stevens et al. 2010[7]	9	809	36	2427	0.75	[0.36; 1.56]	3.8%	6.8%
Yap et al. 2009[8]	24	1457	182	11727	1.06	[0.69; 1.63]	11.0%	13.7%
Thielmann et al. 2006[9]	10	128	18	621	2.84	[1.28; 6.30]	3.2%	6.0%
Hassan et al. 2005[10]	33	919	118	5113	1.58	[1.06; 2.33]	13.2%	15.0%
Van den Brule et al. 2005[11]	4	113	24	1141	1.71	[0.58; 5.01]	1.7%	3.6%
Fixed effect model		**9639**		**61727**	**1.30**	**[1.13; 1.50]**	**100%**	**--**
Random effects model					**1.33**	**[1.07; 1.66]**	**--**	**100%**

Heterogeneity: I^2=43.1%
Test for overall effect (fixed effect): p=0.0003
Test for overall effect (random effects): p=0.0103



RE-EXPLORATION FOR BLEEDING/TAMPONADE

Study	PCI Events	PCI Total	No PCI Events	No PCI Total	OR	95%CI	W(fixed)	W(random)
E-CABG Study, 2017	14	685	89	2956	0.67	[0.38; 1.19]	10.4%	21.8%
Mehta et al. 2012[6]	100	4346	539	29970	1.29	[1.04; 1.60]	72.5%	37.1%
Stevens et al. 2010[7]	20	809	39	2427	1.55	[0.90; 2.68]	11.4%	22.7%
Thielmann et al. 2006[9]	8	128	14	621	2.89	[1.19; 7.04]	4.3%	12.8%
Van den Brule et al. 2005[11]	2	113	14	1141	1.45	[0.33; 6.46]	1.5%	5.7%
Fixed effect model		**6081**		**37115**	**1.27**	**[1.06; 1.53]**	**100%**	**--**
Random effects model					**1.30**	**[0.89; 1.91]**	**--**	**100%**

Heterogeneity: I^2=53.7%
Test for overall effect (fixed effect): p=0.0099
Test for overall effect (random effects): p=0.1766

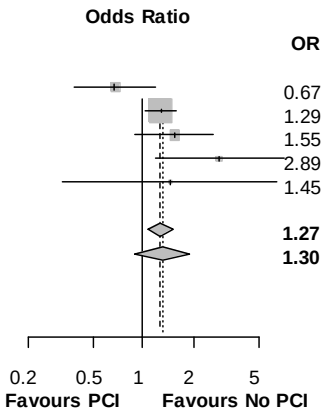
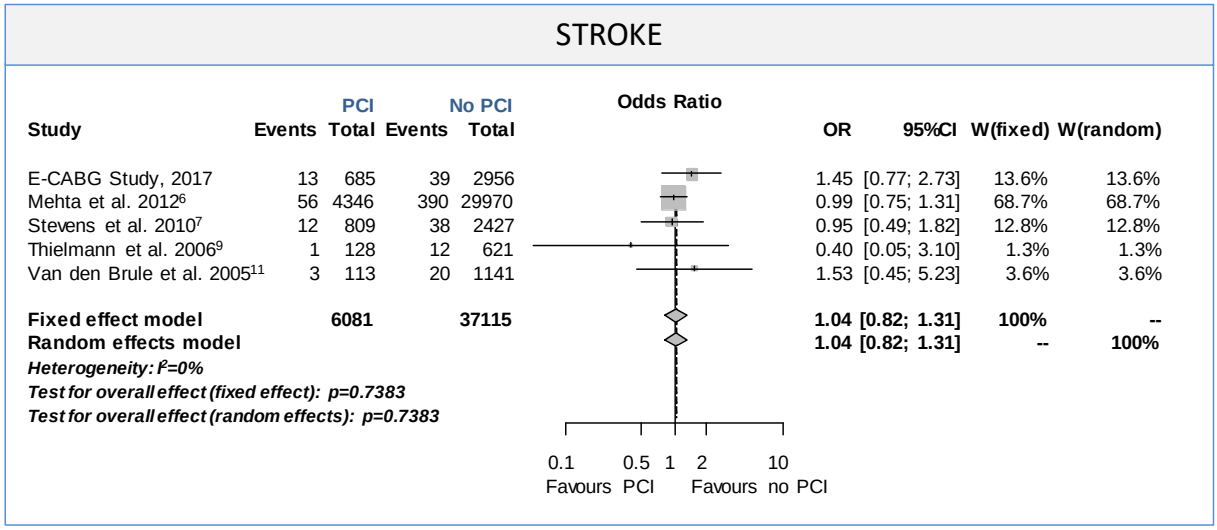


Figure 5. Forest plot with unadjusted risk estimates for stroke (top) and renal failure (bottom) who underwent coronary artery bypass grafting (CABG) with prior percutaneous coronary intervention (PCI). CI, indicates confidence interval; OR, odds ratio.



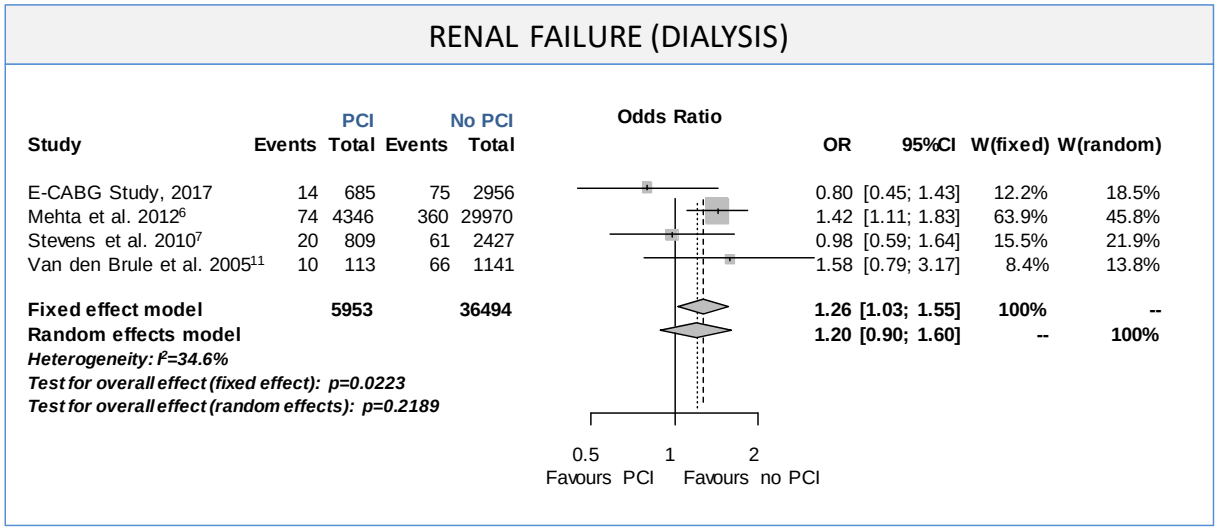
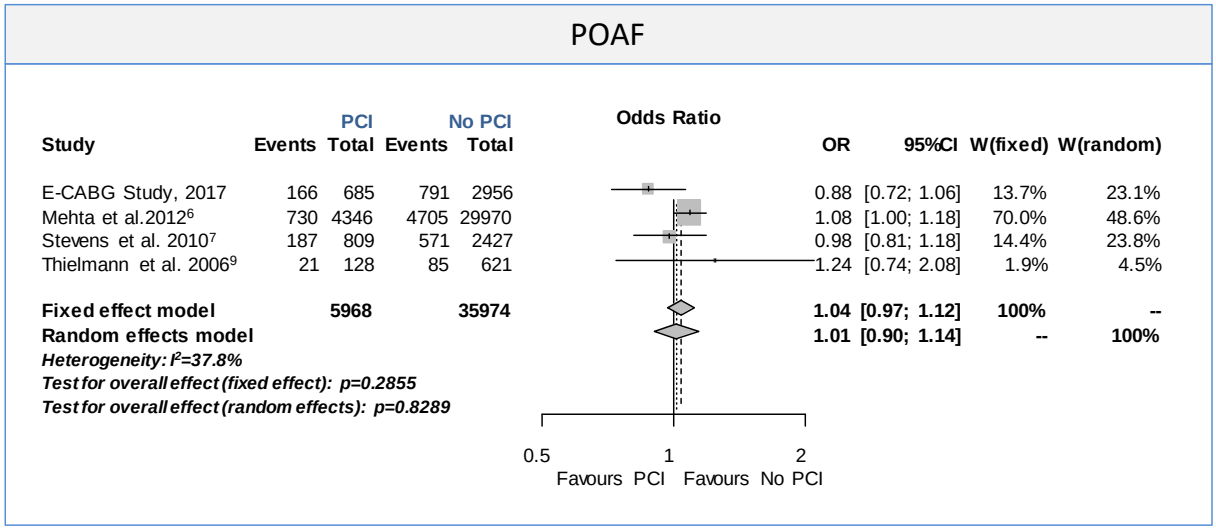


Figure 6. Forest plot with unadjusted risk estimates for postoperative atrial fribrillation (top) and in-hospita stay expressed in days (bottom) who underwent coronary artery bypass grafting (CABG) with prior percutaneous coronary intervention (PCI). CI, indicates confidence interval; OR, odds ratio; POAF, postoperative atrial fibrillation.



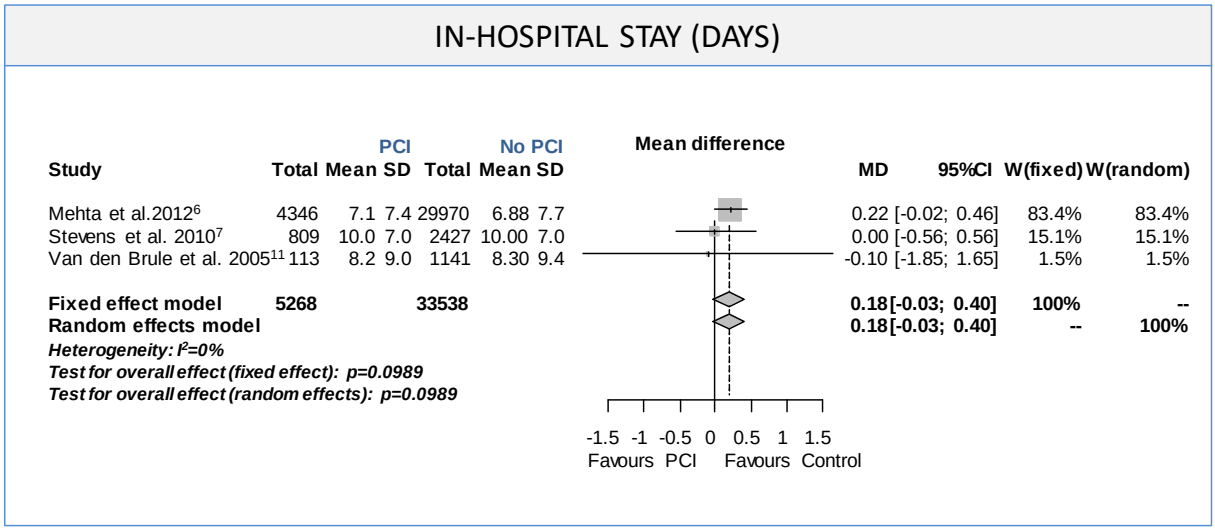
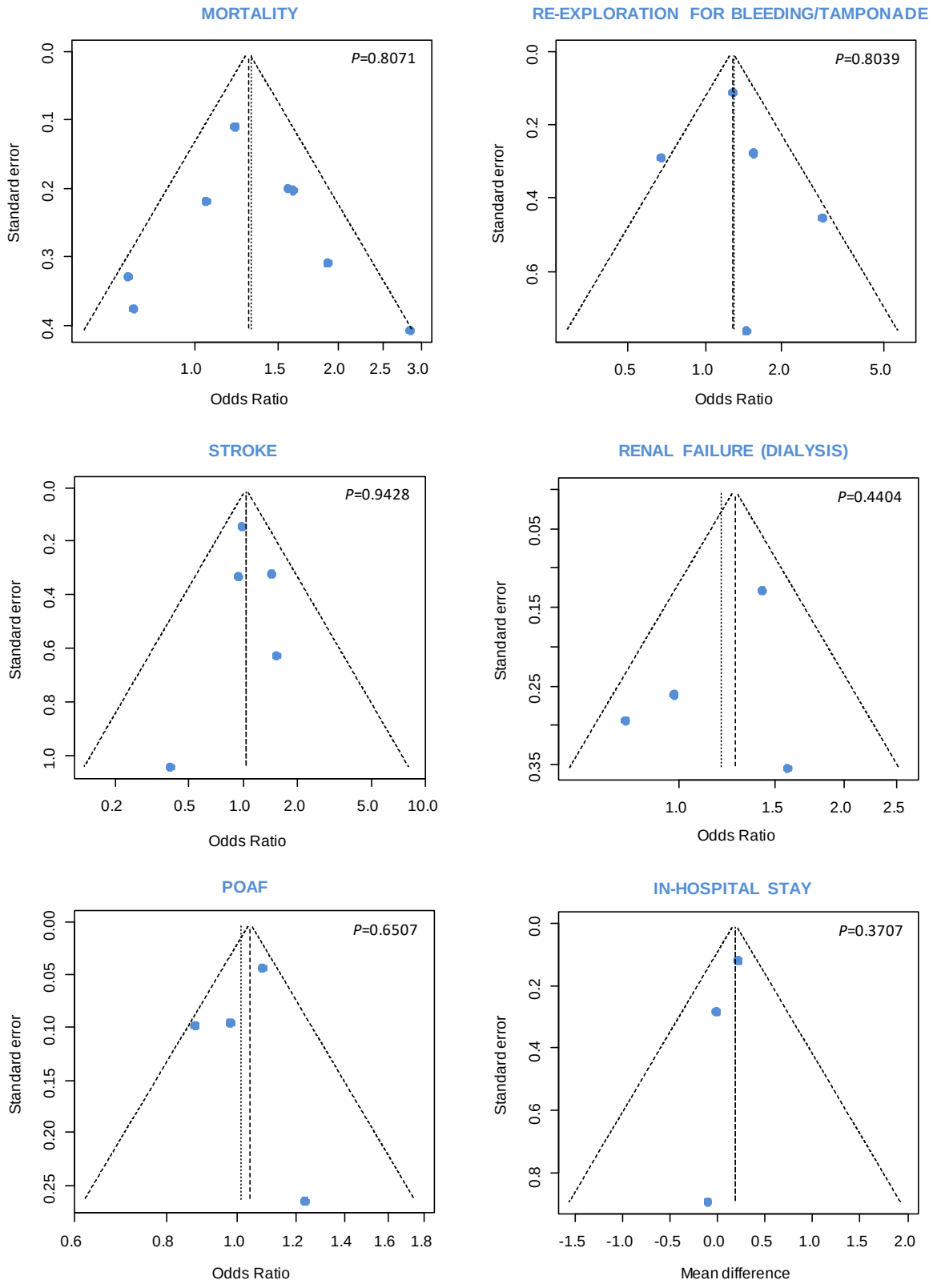


Figure 7. Funnel plots showing the absence of publication bias in primary and secondary outcomes.



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The effects of prior percutaneous coronary intervention outcomes after coronary artery bypass grafting: systematic review and meta-analysis

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1.2. Conflict of interest

None

1.3. Founding Sources/Sponsor

University of Leicester

1.4. Dates

- Start date: 01 February 20157
- Anticipated completion date: 31 May 2017

1.5. Type of review

Epidemiologic; Intervention

1.6. Language

English

1.7. Country

United Kingdom

1.8. Keywords

Systematic review; meta-analysis; Percutaneous coronary intervention; Coronary artery bypass grafting; Cardiac surgery; Coronary artery disease; Treatment outcome; Hospital mortality.

1.9. Registration on PROSPERO

Registration number: **CRD42017062314**

1.10. Hypothesis

Coronary artery bypass grafting in patients with prior percutaneous coronary intervention results in worse peri- and postoperative outcomes.

2. ABSTRACT

Background: Worldwide the number of percutaneous coronary interventions (PCI) prior to coronary artery bypass grafting (CABG) increased drastically during the last decades. Results from medical literature comparing PCI and CABG have shown that initial PCI may possibly lead to significantly higher perioperative and long-term mortality and morbidity than CABG without prior PCI.

Objectives: Our primary objective is to establish whether *coronary artery bypass grafting in patients with prior percutaneous coronary intervention may results in* higher mortality and morbidity.

Search methods: We will conduct the search between February-May 2017. Potentially eligible study will be identified by searching electronic databases (MEDLINE [PubMed and Ovid], Embase, SCOPUS, and Cochrane Library).

Selection Criteria: Two review authors will independently select references for further assessment by going through all titles and abstracts. Further selection will be based on review of full-text articles for selected references.

Data Collection and Analysis: Two review authors will independently extract study data. We will perform meta-analysis when possible, when I^2 is less than or equal to 80% using a fixed-effect or random-effects model, using R software (version 4.3-2). The range of point estimates for individual studies will be presented when $I^2 < 80\%$. Heterogenity will be explored using subgroup analyses. Sensitivity analyses will explore the robustness of our primary analysis to exclusion of studies at high risk of bias.

3. BACKGROUND

The number of percutaneous coronary interventions (PCI) has been continuously increasing during the last years.[1] PCI represents the main revascularization strategy in acute myocardial infarction and interventionalists have gained significant experience in treating coronary artery disease (CAD) even in high-risk patients.[2] Althought the use of drug-eluting stents is associated with a reduced risk of repeat revascularization compared with previous stents,[3] still a significant number of patients initially treated by PCI may require subsequent coronary artery bypass grafting (CABG). Hence, cardiac surgeons are costantly faced with a rapidly increasing number of patients who initially managed with PCI are finally referred to CABG.

3.1 Why is it important to do this review

The outcome of CABG in patients with previous PCI still remains unexplored. Initial results demonstrated that previous PCI had no influence on perioperative outcome after CABG, demonstrating that PCI was successful and no residual stenosis was left. Several randomized trials and registries comparing CABG and PCI have shown that patients with prior PCI have higher rates of symptom recurrence and repeat revascularization than patients undergoing CABG alone. However, some studies reported that a history of previous PCI was not associated with increased mortality and morbidity after CABG.[4-8] This discordance between studies is an important issue to be confronted in establishing a treatment strategy for patients requiring repeat coronary revascularization.
To resolve this uncertainty we propose to undertake a systematic review and meta-analysis of the available evidence from literature to assess the clinical evidence of coronary artery bypass grafting in patients with prior percutaneous coronary intervention, identify knowledge gaps in the exisiting evidence and provide reccomendations for further research.

4. OBJECTIVES

To establish whether the *coronary artery bypass grafting in patients with prior percutaneous coronary intervention may results in* reductions in mortality, major morbidity, bleeding and resource use.

5. METHODS

5.1. Types of Studies

Studies with quantitative, qualitative and mixed-methods approaches in order to obtain a comprehensive overview of the existing literature will be included (clinical randomized trials, observational prospective and retrospective cohort studies, case control studies, and cross sectional studies).

5.1.2. Study inclusion criteria

1) All the observational studies irrespective of blinding, language, publication status, date of publication and sample size will be considered.
2) Only studies reporting on comparative analysis between patients undergoing CABG with prior PCI and those undergoing CABG with no PCI will be included in the present systematic review and meta-analysis.
3) Studies including failures immediately after PCI or CABG during the same hospitalization (or < 14 days) will be excluded.

5.1.2. Study exclusion criteria

Exclusion criteria will include:

- Conference abstracts;
- Editorials & opinion pieces;
- Books or grey literature.

5.2. Types of Participants

Patients to be included will be:

1) patients undergoing coronary bypass surgery (CABG) for acquired coronary artery disease;
2) patients undergoing isolated CABG.

No age restriction will be applied.

5.3. Types of Interventions

Intervention: *coronary artery bypass grafting in patients with prior percutaneous coronary intervention*.
Comparator/control: *coronary artery bypass grafting alone (without prior percutaneous coronary intervention)*

5.4. Types of Outcome Measure

5.4.1. Primary outcomes

Mortality: 30 day or hospital all-cause mortality.

5.4.2 Secondary outcomes

1. Acute brain injury: stroke as defined by study authors.
2. Acute kidney Injury requiring haemofiltration as defined by study authors.
3. Reoperation for bleeding/tamponade
4. Resource Use: hospital LOS as defined by study authors.

5.5. Search methods for identification of studies

5.2.1. Electronic searches

The following databases (from inception to 31st December 2015) were explored:

- Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2015).
- MEDLINE (OvidSP, 1946 to December 2015).
- Embase (OvidSP, 1974 to December 2015).
- PubMed (e-publications only: searched December 2015).
- SCOPUS (1960 to December 2015)

No language restriction will be applied. We also anticipate that articles not in English will be translated using Google Translate® which is a free, Web-based program with a reputation for accurate, natural translation.[9,10]

5.2.2. Searching other resources

The references of all identified trials, relevant review articles, and current treatment guidelines for further literature were also considered. These searches will be limited to the 'first generation' reference lists.

5.6. Selection of Studies

Two reviewers (G.F.S. and G.M.) will identify trials for inclusion independently of each other. Exluded studies and the reason for exclusion will be recorded.

5.7. Data extraction (selection and coding)

Two authors (G.F.S. and G.M.) will independently screen the search output to identify records of potentially eligible trials examining the outcomes, the full texts of which will be retrieved and assessed for inclusion.
A standardised form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include:

- Year and language of publication
- Country of Participant recruitment
- Year of conduct of the trial
- Study setting; university teaching hospital, non universityteaching hospital
- Study population; inclusion and exlusion criteria
- Sample size
- Participant demographics
- Baseline characteristics
- Outcomes and times of measurement

Two review authors (G.F.S. and G.M.) will extract data independently, discrepancies will be identified and resolved through discussion (with a third author where necessary, F.B.). Missing data will be requested from study authors. If there is doubt as to whether trials share participiants completely or partially (with common authors and centres) we will contact the study authors to ascertain whether the studty report has been duplicated.

5.8. Measures of treatment effect

For dichotomous variables, we will calculate the risk ratio (RR) with 95% confidence interval (CI). For continuous variables, we will calculate the mean difference (MD) with 95% CI for outcomes such as hospital stay, and standardised mean difference (SMD) with 95% CI for quality of life (when different scales were used).

5.9. Dealing with missing data

For dichotomous data presented only as percentages we will estimate frequencies using reported sample sizes for this outcome. For continuous outcomes if the mean and the standard deviation were not available from the trial report, we will seek this information from the trial authors. If this information is still not available, we will calculate the mean and standard deviation from median (interquartile ranges) using the software available in Review Manager Version 5.

5.10. Data synthesis and assessment of Heterogeineity[11-17]

A narrative synthesis of the included studies will be provided, focusing on the impact of prior PCI to the hospital outcomes. Detailed tables of the findings from the included studies will be provided, with reference to the type of study (i.e. randomized, cohort studies, case control studies...), the study period, the inclusion/exclusion criteria, type of analysed outcomes, the percetange of PCI in the study population. In addition, additional tables will be provided listing salient characteristics of each study, with reference to population age, gender proportions (male vs. female), comorbidity proportions (i.e. diabetes), number of treatment or control subjects, proportions of postoperative complications (i.e. stroke, reexploration for bleeding, renal dysfunction, perioperative myocardial infarction, respiratory failure…), and length of hospital stay. We will provide summaries of intervention effects for each study by calculating odds ratios (for dichotomous outcomes) or standardised mean differences (for continuous outcomes). Pooled adjusted odds ratios (OR) and (95% confidence interval) will be estimated using both fixed-effects and random effects models. Separate analyses for observational studies and/or randomized controlled trials will be conducted if applicable. Subgroup analyses will performed by study design and type of outcomes. Heterogeneity will be assess by Cochrane *Q* statistic, which will give a qualitative value and will be considered statistically significant for heterogeneity if a *P* value of less than 0.10 is obtained,

and the I^2 statistic, which gives a quantitative measurement; I^2 values higher than 75% will be considered a reflection of severe heterogeneity. Sensitivity analyses will be conducted to explore the robustness of our results. Results obtained with a fixed-effects model will be compared with those obtained with a random effects model. Finally, to account for inherent patient selection bias related with an observational study design, individual risk-adjusted ORs for the primary endpoint were obtained when reported, and pooled adjusted risk estimates were computed by using log transformation and a generic inverse-variance weighting method. Publication bias was evaluated using visual inspection of funnel plot asymmetry and by Egger's test. P<0.05 was used as the level of significance and 95% CIs were reported where appropriate. Statistical analysis was conducted using meta package for R (version 4.3-2; R Foundation for Statistical Computing, Vienna, Austria).

6. COMPETING INTERESTS

The authors declare that they have no competing interests.

7. AUTHORS' CONTRIBUTIONS

G.F.S., G.M. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: G.F.S., G.M., F.B.
Acquisition of data: G.F.S., G.M.
Analysis and interpretation of data: G.F.S., G.M., V.D.B.
Drafting of the manuscript: G.F.S., G.M.
Statistical analysis: V.D.B.
Study supervision: F.B.

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