

# State of the art in coronary revascularization: Everolimus eluting stents versus multiple arterial grafting☆



Umberto Benedetto\*, Massimo Caputo, Hunaid Vohra, Alan Bryan, Gianni D. Angelini

Bristol Heart Institute, University of Bristol, School of Clinical Sciences, United Kingdom

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## ABSTRACT

**Background:** Contemporary comparisons on coronary revascularization should take into account the state of the art percutaneous coronary intervention (PCI) with new generation everolimus-eluting stents (EESs) and coronary artery bypass grafting (CABG) with multiple arterial grafts (MAGs). We aimed to compare early outcomes and late survival after EES versus MAG in patients with multivessel coronary artery disease using a single centre institutional database.

**Methods:** In an observational registry study, we identified 3787 patients with multivessel coronary disease. Of these 696 (18.3%) underwent PCI with EES and 3091 (81.7%) CABG with MAG. With the use of propensity-score matching, we identified 483 pairs for final comparison (C-statistic: 0.91).

**Results:** The two groups were comparable for 30-day mortality (1.6% versus 0.8% in the EES and MAG group respectively,  $P = 0.38$ ). Stroke was not observed in the EES group and it was 0.8% in the MAG group ( $P = 0.13$ ). After a mean follow-up of 3.1 years, PCI with EES was associated with a higher risk of late death (HR 2.2; 95% CI 1.18–4.16;  $P = 0.01$ ).

**Conclusions:** In patients with multivessel coronary disease, CABG with multiple arterial grafts when compared with PCI with new generation drug eluting stent, was associated with significantly improved long-term survival. Further randomized studies are warranted to identify the best revascularization strategies in the current era.

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## 1. Introduction

Coronary-artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are treatment options for patients with multivessel coronary artery disease as they have been shown to provide similar survival rate [1]. Despite studies showing a trend toward a lower mortality after CABG, compared with PCI [2], the routine use of drug-eluting stents has improved outcomes [1,3]. Furthermore, the newer-generation drug-eluting stents, in particular the everolimus-eluting stent (EES), have been shown to reduce the risks of death, myocardial infarction, and stent thrombosis, compared with bare-metal stents or first-generation drug-eluting stents [4]. In contrast, despite compelling evidence supporting a survival advantage from the use of multiple arterial grafting (MAG) over the conventional strategy with single internal thoracic artery [5–7], CABG has changed little over the years. Only 10% of patients undergoing CABG currently receive a second arterial graft in the United States, approximately 4% with bilateral internal thoracic

artery (BITA) and 6% with radial artery (RA) grafts [8]. Contemporary comparisons between PCI and CABG, therefore, should include state of the art strategies: PCI with new generation EES and CABG with MAG. In an observational registry study, we compared the outcomes in patients with multivessel disease who underwent elective CABG with MAG or PCI with the EES.

## 2. Methods

### 2.1. Study design

The study was conducted in accordance with the principles of the Declaration of Helsinki. The local audit committee approved the study, and the requirement for individual patient consent was waived. This study was a registry-based analysis involving patients with multivessel coronary artery disease who underwent elective isolated CABG using at least two arterial conduits and patients who underwent PCI with EES between January 2007 and April 2015, at Bristol Heart Institute, United Kingdom. We retrospectively analysed prospectively collected data from the National Institute for Cardiovascular Outcomes Research (NICOR) registry and the British Cardiovascular Intervention Society (BCIS) registry for audit and quality assessment of PCI in the United Kingdom. Reproducible cleaning algorithms were applied to the

☆ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

\* Corresponding author at: Bristol Heart Institute, University of Bristol, Upper Maudlin St, Bristol BS2 8HW, United Kingdom.

E-mail address: [umberto.benedetto@bristol.ac.uk](mailto:umberto.benedetto@bristol.ac.uk) (U. Benedetto).

database, which are regularly updated as required. Briefly, duplicate records and non-adult cardiac surgery entries were removed; transcriptional discrepancies harmonized; and clinical conflicts and extreme values corrected or removed. The data are returned regularly to the local units for validation. Further details and definition of variables are available at <http://www.ucl.ac.uk/nicor/audits/adultcardiac/datasets>.

## 2.2. Study population

Patients were eligible for inclusion in the study if they had multivessel coronary disease, which was defined as severe stenosis ( $\geq 70\%$ ) in at least two major epicardial arteries including the proximal-mid LAD artery with or without left main coronary disease ( $\geq 50\%$ ), and if they had undergone either PCI with implantation of an EES cobalt–chromium everolimus eluting stents (CoCr-EES, XIENCE V Boston Scientific and Abbott Vascular, Santa Clara, California) or platinum–chromium everolimus-eluting stents (PtCr-EES, PROMUS Element; Boston Scientific, Natick, Massachusetts) or isolated CABG using at least two arterial conduits in the following configuration: bilateral internal thoracic arteries (BITA), left internal thoracic artery and radial artery (RA) and their combination with or without additional saphenous vein grafts (SVG). Exclusion criteria were the following: revascularization within 1 year before the index procedure; previous cardiac surgery (CABG or valve surgery), PCI with a stent other than an EES or with a combination of stents; myocardial infarction within 24 h before the index procedure including primary PCI; and cardiogenic shock.

## 2.3. Outcomes

The primary outcome of the study was all-cause mortality. All-cause mortality is the most robust and unbiased index because no adjudication is required; thus, inaccurate or biased documentation or clinical assessments are avoided [9]. Information about post-discharge mortality tracking was available for all patients (100%) and was obtained by linking the institutional database with the National General Register Office. Secondary outcomes investigated included procedural complications as postoperative stroke, postoperative low output syndrome requiring intra-aortic balloon pump, postoperative dialysis, procedural access complication including arterial bleeding and/or pseudoaneurysm and/or dissection for PCI group and re-exploration for bleeding and/or sternal wound reconstruction for CABG group.

## 2.4. Statistical analysis

Multiple imputation was used to address missing data (<http://www.jstatsoft.org/v45/i07/>). To control for measured potential confounders in the data set, a propensity score (PS) was generated for each patient from a multivariable logistic regression model based on pre-treatment covariates as independent variables with treatment type (MAG versus EES) as a binary dependent variable [10]. Pairs of patients receiving EES and MAG were derived using greedy 1:1 matching with a calliper of width of 0.2 standard deviation of the logit of the PS (<http://CRAN.Rproject.org/package=nonrandom>). The quality of the match was assessed by comparing selected pre-treatment variables in propensity score – matched patients using the standardized mean difference (SMD), by which an absolute standardized difference of greater than 20% is suggested to represent meaningful covariate imbalance [10]. Analytic methods for the estimation of the treatment effect in the matched samples included McNemar's to compare proportions [10]. Time-segmented Cox regression models (within 30 days and beyond 30 days) [11] that stratified on the matched pairs [12] were used to investigate the effect of treatment (MAG versus EES) on early and late mortality. This approach accounts for the within-pair homogeneity by allowing the baseline hazard function to vary across matched sets (<http://CRAN.R-project.org/package=survival>).

Subgroup PS matching analyses were conducted to compare the effect of EES versus BITA and RA separately. Additional subgroup PS matching

was also conducted to compare CoCrEES and PtCrEES separately versus MAG. Finally, the comparison between EES and MAG was repeated in a subgroup PS matching analysis including patients with complete revascularization only to exclude the potential bias related to higher rate of incomplete revascularization in the EES group. As sensitivity analysis, for all the comparisons, we performed Cox analysis on early (within 30 days) and late mortality (beyond 30 days) by regressing the outcome on the treatment assignment and the estimated propensity score [10]. All *p*-values  $< 0.05$  were considered to indicate statistical significance. All statistical analysis was performed using R Statistical Software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

### 3.1. Study population

We identified 3787 patients with multivessel coronary disease who met our inclusion criteria, of these 696 (18.3%) underwent PCI with EES and 3091 (81.7%) CABG with MAG (Table 1).

### 3.2. Procedural data

In the EES group, arterial access was the radial artery in 512 (73%) cases and the femoral artery in the remaining 184 (27%). CoCr-EESs were used in 496 (71%) patients, PtCr-EESs were used in 171 (25%) patients and a combination of both was used in the remaining 29 (4%). Pressure wire for fractional flow reserve was used in 58 (8.3%) cases and intravascular ultrasound (IVUS) in 43 (6.1%) cases. Rotational atherectomy was performed in 29 (4.1%) cases. A total of 60 chronic total occlusions and 20 in-stent restenosis were attempted. A total of  $2.3 \pm 1.1$  stents per patient were used. Mean number of lesions treated per patient was  $2.4 \pm 0.9$ . The average longest stented segment was  $27 \text{ mm} \pm 9 \text{ mm}$  and the average largest stent used was  $3.5 \pm 2.8 \text{ mm}$ . Coronary dissection/perforation occurred in 27 (3.8%) patients, no flow phenomena in 6 (0.8%) patients and side branch occlusion in 7 (1%) patients. Incomplete revascularization defined as at least one diseased primary arterial territory not stented, occurred in 258 (37%) of

**Table 1**

Everolimus-eluting stent (EES) and multiple arterial grafting (MAG) groups characteristics before matching.

	u-EES (n = 696)		u-MAG (n = 3091)		SMD	P
	n	%	n	%		
Age, years (mean, ds)	69	± 12	60	± 9	0.85	<0.001
Female	209	30.0	344	11.1	0.48	<0.001
Body mass index $\geq 30$	235	33.8	923	29.9	0.08	0.07
Angina	291	41.8	1392	45.0	0.06	0.13
Congestive heart failure	185	26.6	689	22.3	0.1	0.02
Prior MI	232	33.3	1361	44.0	0.22	<0.001
Prior PCI	169	24.3	159	5.1	0.56	<0.001
Diabetes: no	552	79.3	2672	86.4	0.15	<0.001
Orally treated	96	13.8	246	8.0		
On insulin	48	6.9	173	5.6		
Hypertension	492	70.7	2026	65.5	0.11	0.01
Smoking	149	21.4	507	16.4	0.13	0.002
Creatinine $\geq 200 \text{ mmol/l}$	32	4.6	29	0.9	0.22	<0.001
Previous stroke	19	2.7	71	2.3	0.03	0.58
Peripheral vascular disease	71	10.2	209	6.8	0.12	0.002
LVEF $\geq 50\%$	441	63.4	2528	81.8	0.48	<0.001
30–49%	179	25.7	505	16.3		
$\leq 30\%$	76	10.9	58	1.9		
Non-elective admission	433	62.2	1289	41.7	0.42	<0.001
3-Vessel disease	128	18.4	2109	68.2	1.16	<0.001
Left main disease	88	12.6	735	23.8	0.29	<0.001
Trainee as operator	327	47.0	1020	33.0	0.28	<0.001

SMD: standardized mean difference; MI: myocardial infarction; PCI: percutaneous coronary intervention; LVEF: left ventricular ejection fraction.

cases. Arterial access complications including dissection and false aneurysm occurred in 7 (1%) patients.

In the MAG group, off-pump coronary surgery was performed in 1828 (59%) cases. BITA only was used in 777 (25%) cases, LITA + RA in 2039 (66%) and a combination of BITA + RA in 275 (89%) cases. Total arterial revascularization was achieved in 1334 (43%) cases and 800 (26%) subjects received off-pump total arterial revascularization. Total number of distal anastomoses were  $2.8 \pm 0.7$ . Incomplete revascularization occurred in 225 (7%) patients. Re-exploration for bleeding occurred in 75 (2.4%) case, sternal wound reconstruction in 14 (0.05%) cases, of which 6 (0.05%) among 1052 patients receiving BITA.

### 3.3. Propensity matching

Before propensity-score matching, there were differences between the two groups in several of the baseline variables (Table 1). Overall, EES group presented a higher burden of comorbidities while MAG group was more likely to have 3 vessel disease and left main disease. With the use of propensity-score matching, 483 patients who underwent PCI with EES were matched with 483 patients who underwent CABG with MAG. The C-statistic for the model was 0.91. After matching, the standardized differences were less than 0.10 for all variables, indicating only small differences between the two groups (Table 2).

### 3.4. Postoperative complications

In the PS-matched sample, low output syndrome occurred in 12 (2.5%) and 12 (2.5%) patients in the EES and MAG groups respectively ( $P = 1$ ). Postoperative dialysis was required in none of EES patients and in 1 (0.2%) patient in the MAG group ( $P = 1$ ). Stroke was not observed in the EES group and was low in the MAG group 4 (0.8%) cases ( $P = 0.13$ ).

### 3.5. Survival

Survival probabilities in the unmatched and PS-matched population are reported in Fig. 1. Treatment effect estimates on survival are the PS-matched cohort summarized in Table 3 and Fig. 2. The two groups were

comparable for 30-day mortality (1.6% versus 0.8% in the EES and MAG group respectively,  $P = 0.38$ ). PCI with EES was associated with a significantly 2 fold increased risk of mortality after a mean follow-up of 3.1 years. For subgroup analysis, we obtained 249 PS-matched pairs of EES versus BITA (Supplementary Table 1) and 442 PS-matched pairs of EES versus RA (Supplementary Table 2) with comparable pre-treatment variable distribution. In the matched EES versus BITA groups, survival probabilities at 1, 3 and 5 years were  $0.95 \pm 0.02$ ,  $0.90 \pm 0.02$  and  $0.90 \pm 0.02$  versus  $0.97 \pm 0.01$ ,  $0.96 \pm 0.01$  and  $0.95 \pm 0.01$  (EES and BITA group respectively) and EES group was significantly associated with 4-fold increased risk of late mortality. In the matched EES versus LITA + RA groups, survival probabilities at 1, 3 and 5 years were  $0.93 \pm 0.01$ ,  $0.87 \pm 0.02$  and  $0.87 \pm 0.02$  versus  $0.98 \pm 0.006$ ,  $0.95 \pm 0.01$  and  $0.911 \pm 0.01$  (EES and LITA + RA group respectively) and EES group remained significantly associated with 2-fold increased risk of late mortality. MAG remained significantly associated with better survival when the analysis was restricted to 360 PS-matched pairs of patients receiving CoCr-EES versus MAG (Supplementary Table 3). We found a non-significant increased risk in late mortality on 139 PS-matched pairs of patients receiving PtCr-EES versus MAG (Supplementary Table 4) although this analysis was largely underpowered to detect difference in survival. When the analysis was restricted to patients with complete revascularization, we obtained 321 matched pairs for comparison (Supplementary Table 5). PCI with EES was confirmed to be associated to significantly increased risk of late mortality when compared to CABG with MAG also among patients receiving complete revascularization. PS-adjusted analyses confirmed the survival advantage from MAG over EES in the overall sample and in subgroup analysis.

## 4. Discussion

In a contemporary cohort of patients with multivessel coronary artery disease, the risk of death associated with PCI with everolimus-eluting stents was higher than with CABG using multiple arterial grafts. The survival benefit from MAG over EES was also present in patients receiving complete revascularization. There was no difference in early mortality (within 30 days) between the two groups. Although no stroke occurred in the EES group, the incidence of stroke in the MAG group was low (0.4%, not significant).

Although CABG leads to a reduced rate of repeat revascularizations [1–3] this is considered a soft end-point by many physicians and patients wishing to avoid cardiac surgery and data on the risk of death will clearly play a larger role in assessing treatment options [2]. Given no clear superiority of surgical treatment with regard to mortality, and the marginal increase in early strokes with CABG [1], PCI is often preferred in patients with multivessel disease [1]. Furthermore, the introduction of new drug-eluting stents has led to improved outcomes including mortality in non-surgically treated patients with multivessel disease, in particular everolimus eluting stents [4]. On the other hand, despite compelling evidence supporting the superiority in terms of survival by using additional arterial grafts, CABG practice has changed little over the years and MAG remains largely underutilized [8]. Current recommendations [13] are based on comparisons between first generation drug eluting stents and CABG where most patients received a single arterial grafts such as the SYNTAX trial (rate of a second arterial conduit 32% only) [1]. Therefore, there is a need for a state of the art comparison between PCI and CABG by including new generation stents and multiple arterial bypass grafting. A recent large observational study on registries of the New York State [14] comparing EES versus CABG found that the two strategies have comparable survival. However, the main limitation of this study is that there was no information on the use of a second arterial graft in the CABG group although multiple arterial grafting in the United States has been recently reported to be below 10%. Therefore, the impact of multiple arterial grafts could not be assessed. Moreover, patients with at least two diseased major epicardial coronary arteries were included regardless of LAD coronary involvement. As a consequence only 27% of EES patients and 53.8%

**Table 2**  
Everolimus-eluting stent (EES) and multiple arterial grafting (MAG) groups characteristics after matching.

	m-EES (n = 483)		m-MAG (n = 483)		SMD	P
	N	%	n	%		
Age, years (mean, ds)	66 ± 12		65 ± 9		0.09	0.10
Female	118	24.4	97	20.1	0.09	0.12
Body mass index ≥ 30	166	34.4	169	35.0	0.04	0.46
Angina	210	43.5	198	41.0	0.05	0.47
Congestive heart failure	128	26.5	124	25.7	0.02	0.82
Prior MI	162	33.5	157	32.5	0.02	0.78
Prior PCI	92	19.0	76	15.7	0.08	0.2
Diabetes: no	391	81.0	402	83.2	0.05	0.45
Orally treated	60	12.4	51	10.6		
On insulin	32	6.6	30	6.2		
Hypertension	332	68.7	336	69.6	0.02	0.83
Smoking	100	20.7	88	18.2	0.06	0.37
Creatinine ≥ 200 mmol/l	17	3.5	16	3.3	0.01	1
Previous stroke	14	2.9	11	2.3	0.04	0.68
Peripheral vascular disease	54	11.2	44	9.1	0.07	0.33
LVEF ≥ 50%	337	69.8	354	73.3	0.09	0.1
30–49%	109	22.6	105	21.7		
≤ 30%	37	7.7	24	5.0		
Non-elective admission	281	58.2	271	56.1	0.04	0.55
3-Vessel disease	119	24.6	119	24.6	0	1
Left main disease	73	15.1	83	17.2	0.05	0.43
Trainee as operator	201	41.6	187	38.7	0.06	0.4

SMD: standardized mean difference; MI: myocardial infarction; PCI: percutaneous coronary intervention; LVEF: left ventricular ejection fraction.

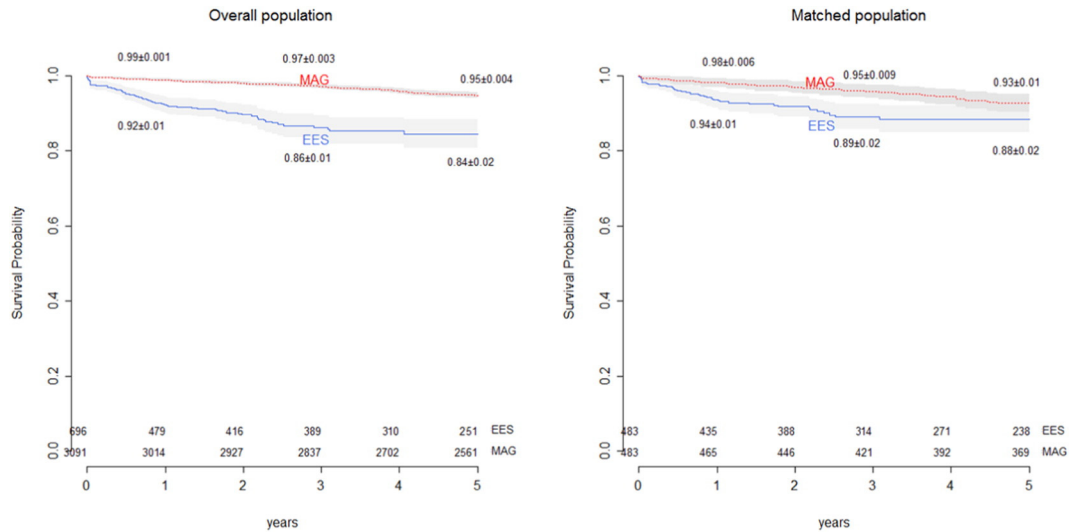


Fig. 1. Survival probabilities for everolimus-eluting stent and multiple arterial grafting groups. Caption: EES: everolimus-eluting stent; MAG: multiple arterial grafting.

of CABG patients presented a significant LAD lesion. It is well recognized that CABG is more likely to improve survival when compared to PCI in case of significant LAD involvement and this aspect might partially account for the equipoise observed between the two strategies [15]. In a prematurely terminated trial recently published [16], EES was found to have comparable survival to CABG at 2 years. It should be noted that while all lesions were attempted to be treated with Everolimus-eluting stents in the PCI group, no information was provided with regard to arterial conduits selection and the rate of multiple arterial grafting in the CABG group. Moreover, patients with two vessel disease were included regardless of LAD involvement and this might partially account for the equipoise in terms of survival between the two groups [15]. In addition this study remained largely underpowered due to premature termination (only 49% of predicted number of patients enrolled) and the relatively high number of crossovers particularly from CABG to PCI, may have introduced a bias. Finally the trial enrolled only patients of Asian race and this could affect the generalizability of the findings.

To the best of our knowledge, this is the first study comparing state of the art in coronary revascularization, including patients receiving PCI with EES or CABG with MAG only. In contrast with previous investigations, we included only patients with significant LAD and/or left main involvement as these two groups represent the vast majority of the

Table 3

Treatment effect estimates for early and late mortality in time segmented Cox model after propensity score matching and propensity score adjustment.

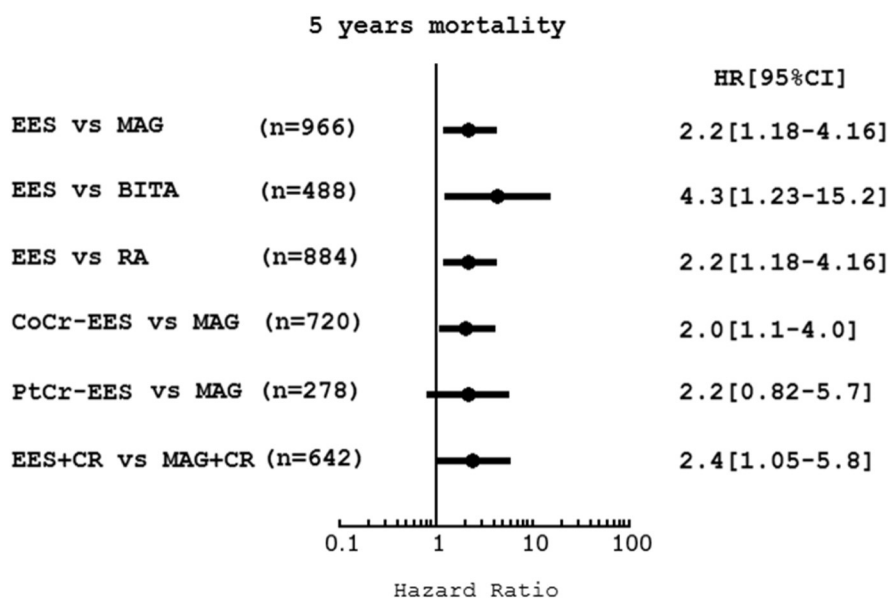
	n	Early mortality		Late mortality	
		HR [95% CI]	P	HR [95% CI]	P
<i>PS-matching</i>					
EES vs MAG	966	2.0 [0.60–6.64]	0.26	2.2 [1.18–4.16]	0.01
EES vs BITA	488	0.8 [0.21–2.97]	0.73	4.3 [1.23–15.2]	0.02
EES vs RA	884	2.33 [0.60–9.02]	0.22	2.2 [1.18–4.16]	0.01
CoCr-EES vs MAG	720	–	0.07	2.0 [1.1–4.0]	0.04
PtCr-EES vs MAG	278	2.0 [0.18–22]	0.57	2.2 [0.82–5.7]	0.1
EES + CR vs MAG + CR	642	1.50 [0.25–8.97]	0.65	2.4 [1.05–5.8]	0.04
<i>PS-adjusted</i>					
EES vs MAG	3787	2.2 [0.79–6.26]	0.13	1.50 [1.08–2.22]	0.03
EES vs BITA	1473	1.02 [0.27–3.80]	0.97	2.11 [1.11–4.0]	0.02
EES vs RA	2735	2.7 [0.85–8.2]	0.11	1.69 [1.13–2.53]	0.01
CoCr-EES vs MAG	3587	2.19 [0.70–6.90]	0.18	1.53 [1.01–2.42]	0.04
PtCr-EES vs MAG	3262	0.91 [0.14–5.93]	0.92	1.35 [0.71–2.56]	0.36
EES + CR vs MAG + CR	3304	0.94 [0.23–3.76]	0.92	1.45 [1.05–2.25]	0.04

EES: everolimus-eluting stent; MAG: multiple arterial grafting; BITA: bilateral internal thoracic artery; RA: radial artery; CoCr-EES: cobalt–chromium everolimus eluting stents; PtCr-EES: platinum–chromium everolimus-eluting stents; CR: complete revascularization.

patients commonly referred for surgery. We found CABG with MAG significantly associated with a superior late survival and not associated with increased risk of early mortality and operative complications including the risk of stroke. It should be noted that in the present series the rate of off-pump CABG was ~60% and it is well recognised that the combination of off-pump technique and use of multiple arterial graft configurations minimizes aortic manipulation and the subsequent risk of stroke [17]. As expected, the rate of incomplete revascularization was higher in the EES than the MAG group (37% versus 7%) although this is far better than those reported by others (~50%) [16]. However, incomplete revascularization is a well-recognized risk factor for late mortality and it could introduce a bias when comparing CABG versus PCI [18,19]. To exclude the effect of incomplete revascularization on the treatment effect difference between EES and MAG, we conducted a subgroup analysis including patients with complete revascularization only and we found that MAG remained associated with a better survival rate. Although we were unable to provide specific causes of death (cardiac vs non-cardiac), myocardial infarction-related death has been shown to be the leading cause of death after coronary revascularization [20]. We can speculate that the superior patency rate of multiple arterial grafts over saphenous vein grafts [7] might partially account for the observed improved survival rate after MAG. Moreover, multiple arterial grafting has been shown to improve long-term survival by preventing progression of atherosclerosis in the native coronary vessels [21]. On the other hand, EES remains associated with a residual increased risk of adverse events mainly related to fracture-related restenosis or thrombosis [22]. Furthermore, prolonged dual antiplatelet therapy after PCI has been associated with increased mortality because of an increased risk of non-cardiovascular mortality not offset by a reduction in cardiac mortality [23] and this can partially contribute to the excess in mortality observed in the EES groups.

#### 4.1. Limitations

Although the data were collected prospectively, the main limitation is the retrospective analysis and the nonspecific design of the data for the comparison between PCI versus CABG. Propensity technique can adjust only for measurable and included variables and we cannot exclude a selection bias based on non-measurable “eye-ball”. Poor surgical candidates may have been more likely to have had PCI, whereas reasonable surgical candidates may have been more likely to be treated with CABG. Finally no follow-up data were available on the cause of death (cardiac versus non-cardiac), recurrence of angina, need for repeat revascularization to compare the two groups.



**Fig. 2.** Forest plot of treatment effect estimates for death at 5 years in propensity score matched cohorts. Caption: EES: everolimus-eluting stent; MAG: multiple arterial grafting; BITA: bilateral internal thoracic artery; RA: radial artery; CoCr-EES: cobalt–chromium everolimus eluting stents; PtCr-EES: platinum–chromium everolimus-eluting stents; CR: complete revascularization.

In conclusion, contemporary comparisons between PCI and CABG should include the use of new generation drug eluting stents and multiple arterial grafts. In a real world clinical practice, CABG with MAG was associated with similar early outcomes and significantly improved long term survival when compared to PCI with EES. If confirmed in other series, these findings have the potential to drastically modify the PCI versus CABG debate. Further randomized studies are warranted.

#### Conflict of interest

No potential conflicts exist for all authors.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2016.06.059>.

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