

The effect of prior percutaneous coronary intervention on the immediate and late outcome after coronary artery bypass grafting: systematic review and meta-analysis

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ABSTRACT

Introduction: A number of studies reported on a possible increased risk of morbidity and mortality after coronary artery bypass grafting in patients with prior percutaneous coronary intervention.

Methods: A systematic review and meta-analysis of studies comparing the outcome of patients undergoing coronary surgery with or without prior percutaneous coronary intervention was performed. Only studies reporting results of adjusted analysis and excluding acute percutaneous coronary intervention failures were included in this meta-analysis.

Results: Literature search yielded nine studies reporting on 68,645 patients who underwent coronary surgery. Of them, 8,358 (12.2%) had a prior percutaneous coronary intervention. Patients without prior percutaneous coronary intervention were significantly older ($p = 0.002$), had significantly higher prevalence of left main stenosis ($p = 0.005$) and three-vessel disease ($p < 0.0001$). Prior percutaneous coronary intervention was associated with higher risk of re-sternotomy for bleeding ($p = 0.04$) and dialysis ($p = 0.003$). Thirty-day/in-hospital mortality was significantly higher in patients with prior percutaneous coronary intervention (pooled rate: 2.7% vs 2.0%, risk ratio 1.39, 95% confidence interval 1.06-1.84, $p = 0.02$) as confirmed also by generic inverse variance analysis (risk ratio 1.47, 95% confidence interval 1.12-1.93, $p = 0.005$). Prior percutaneous coronary intervention did not affect late outcome (five studies included, risk ratio 1.07, 95% confidence interval 0.90-1.28, $p = 0.43$).

Conclusions: Prior percutaneous coronary intervention seems to be associated with an increased risk of immediate postoperative morbidity and mortality after coronary surgery, but does not affect late mortality. These results are not conclusive and need to be confirmed by studies of better quality evaluating the impact of indication, timing, type of stents, amount of treated vessels and number of previous percutaneous coronary interventions.

Keywords: percutaneous coronary intervention, coronary artery bypass, prior, previous, meta-analysis.

INTRODUCTION

Its minimally invasive nature and advances in stent technology have led to a widespread use of percutaneous coronary intervention (PCI) also in patients with complex coronary artery disease. Although

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gh the use of drug-eluting stents is associated with a reduced risk of repeat revascularization compared with bare metal stents (1), still a significant number of patients initially treated by PCI may require coronary artery bypass grafting (CABG) (2). Since a number of studies have reported on an increased risk of morbidity and mortality after CABG in patients with prior PCI (3), there is concern on whether the latter may compromise the results of surgical revascularization. This issue has been investigated in the present meta-analysis.

METHODS

A literature review was performed through PubMed, Scopus and Science Direct up to September 2013 for any study evaluating the outcome of CABG in patients with or without prior PCI.

The words employed in the search were: “coronary artery bypass”, “surgical revascularization”, “CABG”, “PCI”, “coronary”, “percutaneous coronary intervention”, “coronary stent”, “coronary stenting”, “prior” and “previous”. Reference lists of obtained articles were searched as well. This study was not financially supported.

Inclusion criteria. Prospective and retrospective observational studies published in English language and reporting on the outcome of CABG in patients with or without prior PCI were included in the present analysis.

Only studies reporting on comparative analysis of these two study groups were considered for the present analysis. Studies were considered for this analysis only if it was stated that patients who underwent PCI during the same hospital admission were not included in their comparative analyses. Since significant heterogeneity between the study groups were expected, only studies reporting results of

multivariate analysis for adjustment of the impact of other comorbidities on the immediate and late mortality were included in the present analysis.

Exclusion criteria. Data reported only in abstract were not included in this analysis. Studies which did not perform a formal comparative analysis of these two study cohorts were not considered in this meta-analysis. Therefore, studies including prior PCI as a variable in multivariate analysis assessing the immediate and late outcome of these patients were not considered for this analysis. Studies including failures immediately after PCI were excluded. This was done to avoid any negative impact of acute failure of PCI and any PCI-related complications on postoperative outcome after CABG.

Data collection and assessment of data quality. Five investigators (F.B., G.V., F.O., G.M., A.R.) identified the articles potentially dealing with this topic, abstracted data from all eligible studies using a standardized Excel file, retrieved data on study design, study size, patient demographics, types of intervention and outcome.

Data were retrieved only from the articles and no attempt to get missing or unclear data from the authors was made. Since only retrospective, observational studies were expected to be included in this analysis, the assessment of data quality was limited to verify whether the study group were adjusted for baseline variables or matched for any baseline variables or propensity score. We applied the guidelines for Meta-analysis of Observational Studies in Epidemiology (MOOSE) (4).

Outcomes of interest. The main outcome end-points of this study were any immediate and late mortality. Secondary outcome endpoints were re-exploration for excessive bleeding, stroke, dialysis and length of postoperative in-hospital stay.

Statistical analysis. Statistical analysis

was performed using Review Manager 5.2 software (5) and Open Meta-analyst (6). Baseline, operative and outcome data was summarized as untransformed proportions with 95% confidence interval (95% CI) and weighted means and 95% CI. The natural logarithm of odds and hazard ratios and their standard error of were entered in to Review Manager to estimate hazard ratios by generic inverse variance analysis. The pooled risk of adverse event was expressed as risk ratio (RR) and hazard ratio (HR) with 95% CI. Because heterogeneity was anticipated in these observational studies, it was assessed *a priori*

by a random effects model (DerSimonian-Laird). Heterogeneity across studies was evaluated using the I^2 test, assuming that $< 40\%$ indicates a non significant heterogeneity. Sensitivity analysis and meta-regression were not performed because of the limited number of retrieved studies. A $p < 0.05$ was considered statistically significant.

RESULTS

A literature search was performed on August 19, 2013 and yielded 422 articles of

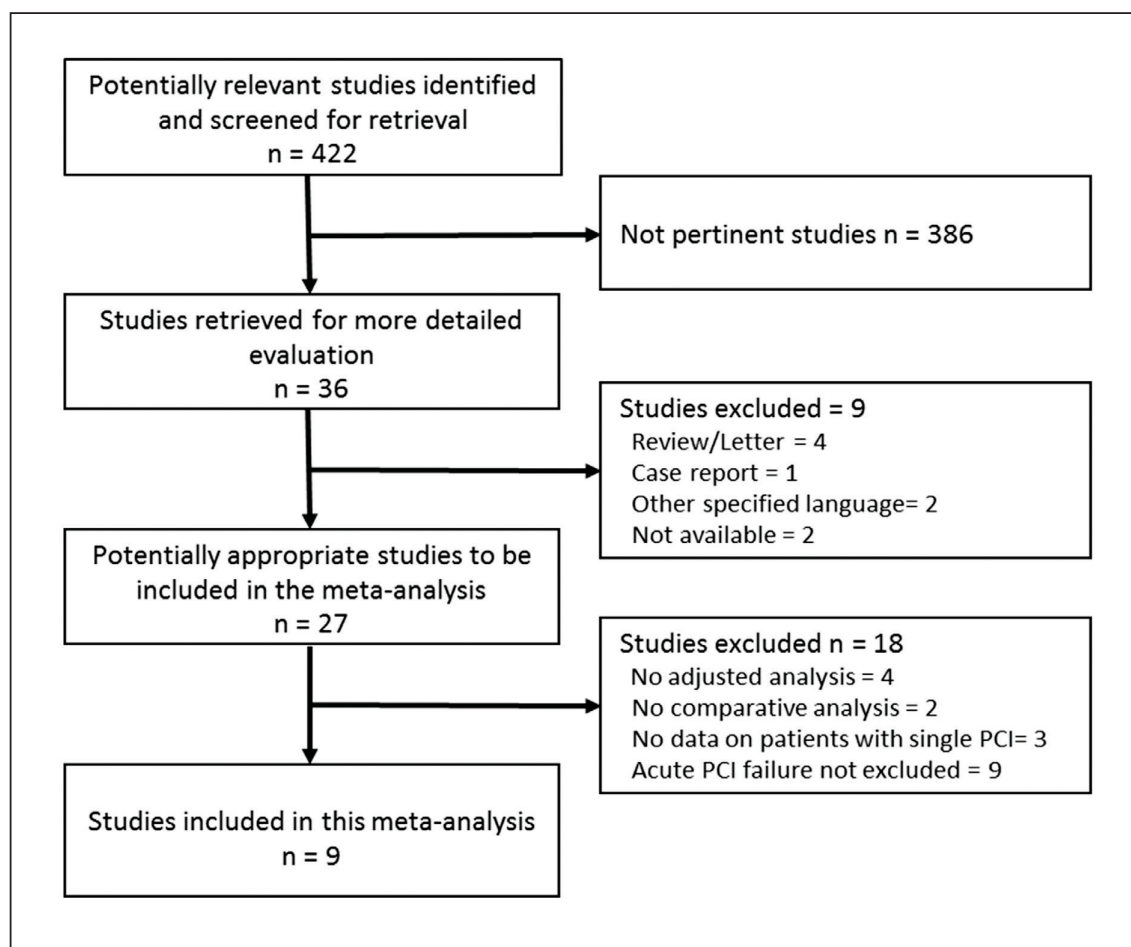


Figure 1 - Literature search flow-chart. PCI = percutaneous coronary intervention .

Table 1 - Characteristics of observational studies evaluating the outcome after coronary artery bypass grafting in patients with or without prior percutaneous coronary intervention.

Author	Year	Country	Study design	No prior PCI	Prior PCI	Stenting	Mean delay to CABG (days)	Follow-up
Hassan	2005	International	R	5113	919	-	-	In-hospital
van den Brule	2005	The Netherlands	R	1141	113	-	-	12 months
Gürbüz	2006	Turkey	R	421	190	78.4%	512 ± 128	45 months
Thielmann	2007	Germany	P	621	128	100 %	244 ± 336	In-hospital
Tran	2009	USA	R	1537	221	100 %	418 ± 221	24 months
Yap	2009	Australia	P	11727	1457	-	-	72 months
Stevens	2010	USA	R	8819	823	-	236 ± 461	60 months
Lisboa	2012	Brasil	P	938	161	100 %	-	In-hospital
Mehta	2012	USA	P	29970	4346	-	-	30-day/in-hospital

R = retrospective; P = prospective; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting.

which 27 were considered as potentially appropriate for inclusion in this meta-analysis (*Figure 1*). After evaluation of the reported data and statistical methods, four studies were excluded because of lack of data on adjusted analysis, two because of lack of comparative analysis, three because failing to report data or perform analysis on patients with single PCI. Furthermore, nine

studies were excluded because they failed to exclude or state about exclusion of acute failures of PCI. Nine studies (7-15) reported on data fulfilling the inclusion criteria and were included in this meta-analysis. Among these studies, one reported only on late mortality in operative survivors (15). These nine studies reported on 68,645 patients who underwent CABG and of them, 8,358 (12.2%) had history of prior PCI.

Table 2 - Characteristics of patients undergoing coronary artery bypass grafting with or without prior percutaneous coronary intervention.

Variables	No. of studies	No. of patients	Prior PCI	No prior PCI	Effect estimate (95% CI)	I ²	P-value
Age (years)	8	62613	63.3 (62.3-64.3)	65.0 (63.9-66.1)	-1.72 (-2.81- -0.63)	91%	0.002
Females	9	68645	26.2 (22.7-29.7)	26.9 (25.2-28.6)	0.96 (0.85-1.08)	64%	0.49
Pulmonary disease	6	26539	11.2 (6.4-16.0)	10.2 (6.2-14.3)	1.02 (0.91-1.15)	0%	0.72
Diabetes	9	68645	45.4 (22.7-68.0)	46.0 (29.4-62.6)	1.00 (0.86-1.17)	82%	1.00
Peripheral vascular disease	8	67546	13.5 (11.9-15.2)	14.0 (12.5-15.5)	0.95 (0.86-1.05)	31%	0.28
Renal failure	8	66887	5.1 (3.4-6.8)	5.4 (4.1-6.7)	1.07 (0.86-1.32)	57%	0.55
Emergency	7	66780	3.1 (0.1-5.2)	2.6 (0.1-4.1)	1.10 (0.69-1.74)	90%	0.69
Left main stenosis	7	62002	16.0 (5.0-27.0)	21.1 (7.2-35.2)	0.70 (0.55-0.90)	90%	0.005
Three-vessel disease	5	52497	76.2 (60.8-91.6)	84.9 (72.7-97.1)	0.56 (0.39-0.78)	95%	< 0.0001
No. distal anastomoses	6	24076	3.0 (2.8-3.2)	3.3 (3.3-3.4)	-0.37 (-0.53- -0.20)	92%	< 0.0001

PCI = percutaneous coronary intervention; dichotomous variable are reported as proportion and 95% confidence interval (95% CI); continuous variables are reported as means and 95% CI; effect estimates are odds ratio and 95% CI for dichotomous variables and mean differences with 95% CI for continuous variables.

Table 3 - Outcome of patients undergoing coronary artery bypass grafting with or without prior percutaneous coronary intervention (PCI).

Outcome end-points	No. of studies	No. of patients	Prior PCI	No prior PCI	Effect estimate (95 % CI)	I ²	P-value
Resternotomy for bleeding	4	38077	2.2 (1.2-3.2)	1.7 (1.3-2.0)	1.39 (1.02-1.89)	10 %	0.04
Stroke	4	38077	1.3 (1.0-1.6)	1.4 (1.2-1.6)	0.99 (0.76-1.29)	0 %	0.92
Dialysis	3	36823	3.1 (0.7-5.5)	2.7 (1.2-4.1)	1.42 (1.13, 1.78)	0 %	0.003
In-hospital stay (days)	3	36319	7.4 (6.7-8.1)	8.0 (7.6-8.8)	0.09 (-0.37-0.55)	15 %	0.71
30-day/in-hospital mortality	8	68034	2.7 (1.8-3.6)	2.0 (1.6-2.4)	1.39 (1.06-1.84)	56 %	0.02
Adjusted 30-day/in-hospital mortality	8	68034	-	-	1.47 (1.12-1.93)	53 %	0.005
Adjusted late mortality	5	26449	-	-	1.07 (0.90-1.28)	63 %	0.43

Dichotomous variables are reported as proportion and 95 % confidence interval (95 % CI); continuous variables are reported as means and 95 % CI; effect estimates are odds ratio and 95 % CI for dichotomous variables and mean differences with 95 % CI for continuous variables.

Table 1 summarizes the main characteristics of these studies.

Only four studies reported on the mean delay between the last PCI and CABG, which ranged from 236 to 512 days. Similarly, only four studies reported on the proportion of stenting, which was 78 % in one study and 100 % in the other three studies. Scarce data were available on the type of stent used and the indication for surgical revascularization. Table 2 summarizes the main characteristics of the study cohorts. Patients without history of prior

PCI were significantly older (p = 0.002), had significantly higher prevalence of left main stenosis (p = 0.005) and three-vessel disease (p < 0.0001).

These patients received a significantly higher number of distal anastomoses (p < 0.0001) (Table 3).

Patients with history of prior PCI had a significantly higher risk of resternotomy for bleeding (p = 0.04) and dialysis (p = 0.003) with a non significant heterogeneity between studies.

Unadjusted 30-day/in-hospital mortality

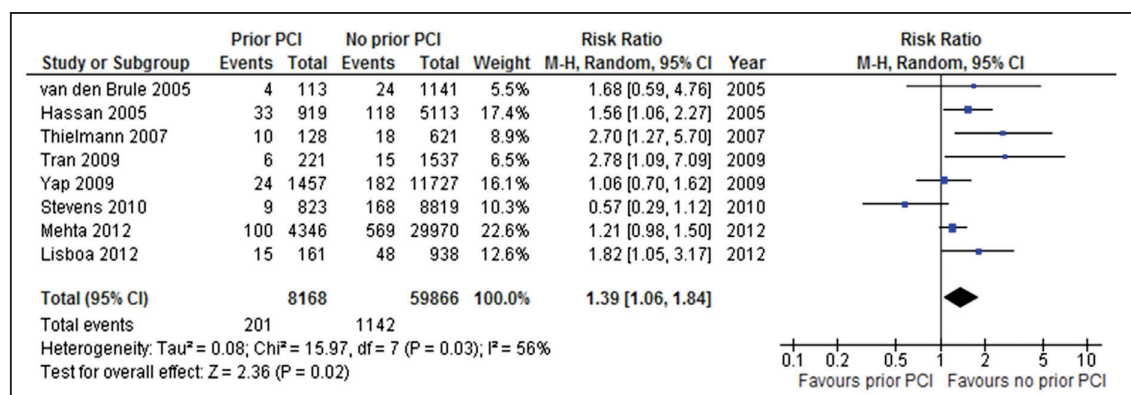


Figure 2 - Forest plot for unadjusted 30-day/in-hospital mortality in patients who underwent coronary artery bypass surgery with and without prior percutaneous coronary intervention. PCI = percutaneous coronary intervention; CI = confidence interval.

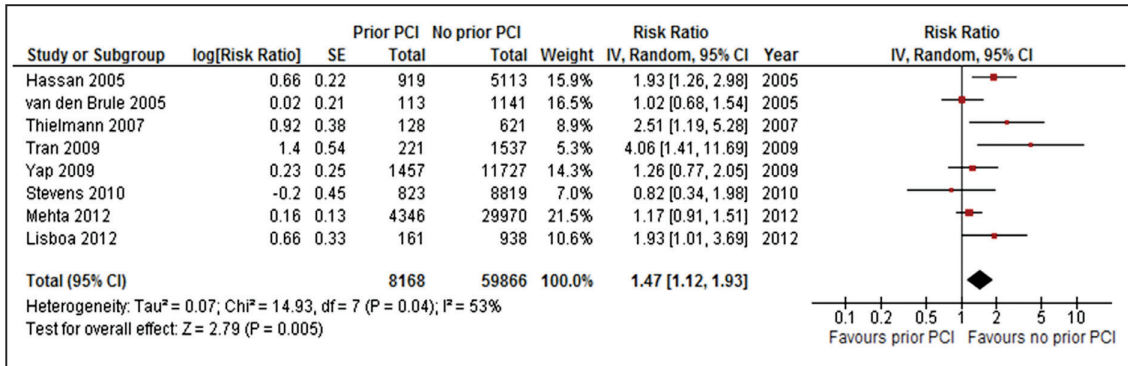


Figure 3 - Forest plot for adjusted 30-day/in-hospital mortality in patients who underwent coronary artery bypass surgery with and without prior percutaneous coronary intervention. PCI = percutaneous coronary intervention; CI = confidence interval.

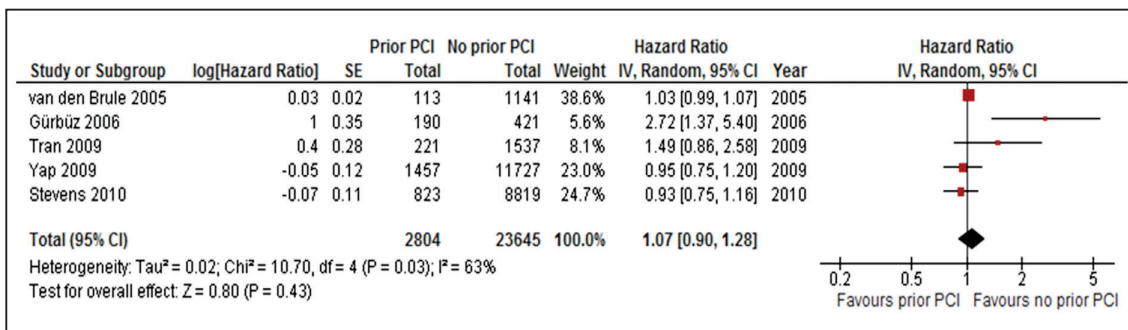


Figure 4 - Forest plot for adjusted later mortality in patients who underwent coronary artery bypass surgery with and without prior percutaneous coronary intervention. PCI = percutaneous coronary intervention; CI = confidence interval.

was significantly higher after CABG in patients with prior PCI ($p = 0.02$, Figure 2). This finding was confirmed in generic inverse variance analysis which showed a significantly higher immediate mortality in patients with prior PCI (RR 1.47, 95% CI 1.12-1.93, $p = 0.005$), but with a significant heterogeneity between studies ($I^2 = 53\%$). Six out of eight studies showed a trend toward increased mortality rate in patients with history of prior PCI (Figure 3).

Generic inverse variance failed to show any significant impact of prior PCI on late outcome after CABG (RR 1.07, 95% CI 0.90-1.28, $p = 0.433$) (Figure 4).

DISCUSSION

The advent of drug-eluting stents has resulted in higher utilization of PCI in patients with class I indications to CABG (16). Although recent randomized studies indicated CABG as the treatment of choice in complex coronary artery disease, PCI arose as first line treatment strategy because of the referral pattern of patients with coronary artery disease and the less invasive nature of this treatment. Preference of PCI is based also on the assumption that PCI failures can still be successfully treated by CABG (14). This policy together with the increasing number of patients

undergoing PCI for ST elevation myocardial infarction or other clinical manifestations of acute coronary syndromes has led to a dramatic increase in the prevalence of prior PCI among patients undergoing CABG (14). A number of early studies (6, 7) showed that the results of surgical revascularization are associated with worse outcome in patients with prior PCI compared with those undergoing CABG as a primary procedure. This negative effect seems to be more evident in patients with history of multiple PCIs (3, 17, 18).

The present meta-analysis showed that patients with history of prior PCI and requiring CABG for repeat revascularization are at slightly higher risk of mortality immediately after surgical revascularization. Although the limited availability of data prevented a throughout analysis of important immediate outcome end-points, herein we were able to observe also an increased risk of re-exploration for excessive bleeding and renal replacement therapy in patients undergoing CABG with prior PCI. On the other hand, prior PCI seems to not jeopardize the late survival of these patients.

Our observations cannot provide explanations for the worse immediate outcome after CABG in patients with prior PCI, although the significant differences in the baseline clinical characteristics may contribute to the worse outcome even after the present adjustments. The use of potent antiplatelet drugs to prevent stent thrombosis is the most probable background for the increased risk of bleeding and may also contribute to the worse prognosis of these patients (19, 20). Secondly, the temporary prothrombotic state occurring after CABG may predispose to stent thrombosis early after coronary stenting, especially when the first-generation drug-eluting stents were used (21). Furthermore, Gaudino et al. (22) has showed that bypass to vessels

with in-stent restenosis is associated with a higher risk of vein graft failure. Prior PCI may also compromise surgical revascularization when long segments or vessel bifurcations are stented (14).

The scarce data on the late outcome of these patients may affect the validity of these present findings and this issue should be addressed in further studies. Herein we may speculate that complete surgical revascularization may provide good late results also after prior PCI. However, any comparative analysis of patients undergoing CABG with or without prior PCI is based on the baseline characteristics and clinical status before CABG and do not take into account any change occurred during the time elapsed from PCI to CABG.

It is worth noting that we have identified 27 studies focusing on this topic, but we were able to include in this analysis only very few of them. In fact, most of these studies showed severe methodological weaknesses, which prompted their exclusion from the present study. A rather large number of studies failed to clearly state the exclusion criteria or even included patients with acute failure of PCI. This might have introduced a major bias in the analysis of the real impact of PCI in these patients. Indeed, the risks associated with acute failure of a properly indicated PCI can be accepted. On the contrary, late failure of PCI in patients with severe and diffuse coronary artery disease must be viewed critically in the light of evidence on the durable results of CABG in these patients. In this respect it is worth noting that 76 % of the herein included prior PCI patients had three-vessel disease at the time CABG (although we do not have data on the extent of coronary artery disease at the time of PCI). Three studies identified multiple prior PCIs as a major determinant of mortality after CABG (3, 17, 18). However, we were not able to include the-

se studies in our analysis as the authors failed to report the results of adjusted analysis for those patients who had any, either single or multiple, prior PCI. Exclusion of these studies has led to a reduced effect estimate of the variable “prior PCI”. On the other hand, we may expect that the characteristics and outcome of patients with prior multiple PCIs may differ from those with a single prior PCI. The lack of data on the outcome of patients with single and those with multiple PCI prevented a specific analysis of the outcome of these two cohorts of patients.

The results of the present analysis may be potentially flawed by a number of limitations which must be acknowledged. The studies herein included are mostly of retrospective nature and the quality of data and methods of data analysis might have varied significantly.

The lack of data on the PCI indication, type and number of stents, number of vessel treated and timing of prior PCI is an important limitation of this meta-analysis. In fact, sensitivity analyses or meta-regression taking into account these variables would have identified those patients with a higher risk of adverse outcome at the time of CABG.

CONCLUSION

In conclusion, prior PCI seems to be associated with an increased risk of immediate postoperative mortality after CABG, but seems not to affect late mortality. These results are not conclusive and need to be confirmed by studies of better quality evaluating the impact of indication, timing, type of stents, amount of treated vessels and number of previous PCIs. Among the outcome end-points, more detailed information on the need of blood transfusion are needed in this patient population so of-

ten exposed to potent antiplatelet drugs. A longer follow-up is required to assess the impact of prior PCI on late outcome after CABG.

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