Does Prior Percutaneous Coronary Intervention Adversely Affect Early and Mid-Term Survival After Coronary Artery Surgery?

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Objectives To determine the association between previous percutaneous coronary intervention (PCI) and results after coronary artery bypass graft surgery (CABG).

Background Increasing numbers of patients undergoing CABG have previously undergone PCI.

Methods We analyzed consecutive first-time isolated CABG procedures within the Australasian Society of Cardiac and Thoracic Surgeons Database from June 2001 to May 2008. Logistic regression and propensity score analyses were used to assess the risk-adjusted impact of prior PCI on in-hospital mortality and major adverse cardiac events. Cox regression model was used to assess the effect of prior PCI on mid-term survival.

Results Of 13,184 patients who underwent CABG, 11,727 had no prior PCI and 1,457 had prior PCI. Mean follow-up was 3.3 ± 2.1 years. Patients without prior PCI had a higher EuroSCORE value (4.4 ± 3.3 vs. 3.6 ± 3.0, p < 0.001), were older, and more likely to have left main stem stenosis and recent myocardial infarction. There was no difference in unadjusted in-hospital mortality (1.65% vs. 1.55%, p = 0.78) or major adverse cardiac events (3.0% vs. 3.0%, p = 0.99) between patients with or without prior PCI. After adjustment, prior PCI was not a predictor of in-hospital (odds ratio: 1.22, 95% confidence interval [CI]: 0.76 to 2.0, p = 0.41) or mid-term mortality at 6-year follow-up (hazard ratio: 0.94, 95% CI: 0.75 to 1.18, p = 0.62).

Conclusions In this large registry study, prior PCI was not associated with increased short- or mid-term mortality after CABG. Good outcomes can be obtained in the group of patients undergoing CABG who have had previous PCI. (J Am Coll Cardiol Intv 2009;2:758–64) © 2009 by the American College of Cardiology Foundation

Percutaneous coronary intervention (PCI) is emerging as the main treatment option for coronary artery disease and the number of PCI procedures are rapidly increasing worldwide (1–4). The widespread use of PCI has resulted in an increasing number of patients being referred for coronary artery bypass graft surgery (CABG) who have undergone prior PCI. Patients with a history of prior PCI undergo subsequent CABG either because of failure of the original PCI (10% to 30% of patients develop in-stent restenosis after PCI with stent implantation) or more commonly because of progression of native disease (5). The timing of

subsequent CABG after prior PCI is usually around 12 months (6). One of the reasons accounting for the rapid increase in PCI use is the perception that if PCI fails, patients can safely be referred to surgery without adverse consequences. However, there are very little data on early and long-term outcomes in patients undergoing CABG with a history of prior PCI in the stenting era. Historical data in patients undergoing CABG having had previous percutaneous transluminal balloon angioplasty suggested worse early mortality in this group (7). Moreover, several reports have demonstrated worse outcomes in patients who have had prior PCI undergoing noncardiac surgery (8). In this large multicenter registry report, we aim to assess the association between prior PCI and short- and mid-term mortality after subsequent revascularization by CABG.

Methods

Study population. The study population comprised of 13,184 consecutive patients who underwent first-time, isolated CABG surgery in the ASCTS (Australasian Society of Cardiac and Thoracic Surgeons) Cardiac Surgery Database between June 2001 and May 2008. Patients with prior PCI (PCI group) were compared with patients without prior PCI (non-PCI group). Patients who underwent PCI during the same admission as their CABG were excluded from the analysis. This was to exclude those patients who may have had an unsuccessful PCI necessitating CABG on an urgent or emergent basis. Isolated CABG refers to the performance of CABG only; those patients requiring concomitant valve or other cardiac, such as atrial fibrillation surgery, or aortic procedures were thus excluded from this study.

All 6 Victorian public hospitals that perform adult cardiac surgery—The Royal Melbourne Hospital, The Alfred Hospital, Monash Medical Centre, The Geelong Hospital, Austin Hospital, and St Vincent's Hospital Melbourne—were involved in the prospective data collection for the ASCTS database during the entire study period. Additionally, 8 cardiac surgical units from South Australia, New South Wales, and Queensland joined the database in the

last 12 months of the study period and contributed a total of 13.4% of the total patient numbers. The ASCTS database contained detailed information on patient demographics, pre-operative risk factors, operative details, post-operative hospital course, and morbidity and mortality outcomes. These data were collected prospectively using an agreed dataset and definitions as part of clinical care by surgeons, perfusionists, hospital medical officers, and database managers. Data collection and audit methods have been previously described (9–11). In the state of Victoria, the collection and reporting of cardiac surgery data is compulsory and mandated by the Victorian state government; hence it is all-inclusive. The data are subject to external audit measures with an overall data accuracy of 97.4% recently reported (11). The institutional review board of each participating hospital had approved the use of these databases for research; hence, the need for individual patient consent was waived for this study.

The study end points were in-hospital death and major adverse cardiac events (MACE) and mid-term survival after CABG. We defined MACE as a composite end point of in-hospital death, myocardial infarction (MI), or stroke. Cause of in-hospital death was defined as cardiac or noncardiac. Mid-term survival status of patients was obtained from the Australian National Death Index. The closing date was June 30, 2008.

Pre-operative data analyzed were age; sex; the presence of diabetes mellitus, hypercholesterolemia, hypertension, cerebrovascular disease, peripheral vascular disease, renal failure, and respiratory disease; recent MI, congestive heart failure, or unstable angina; New York Heart Association functional class; presence of left main coronary artery stenosis >50%; degree of left ventricular impairment; and operation urgency and EuroSCORE value (additive). Hypercholesterolemia was defined as a history of fasting cholesterol >5.0 mmol/l or treatment of high cholesterol. Hypertension was blood pressure exceeding 140/90 mm Hg or a history of high blood pressure, or the need for antihypertensive medications. Cerebrovascular disease was any prior unresponsive coma >24 h, stroke or transient ischemic attack, or carotid stenosis >75%. Peripheral vascular disease was defined as any of the following: claudication, amputation for arterial insufficiency, aorto-iliac occlusive disease reconstruction or peripheral vascular surgery, or documented abdominal aortic aneurysm. Renal failure was defined as last pre-operative serum creatinine level >200 μmol/l or pre-operative dialysis-dependence. The most recent assessment of left ventricular function by nuclear imaging, echocardiography, or left ventricular angiography before surgery was used. Left

Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery

MACE = major adverse cardiac events

MI = myocardial infarction

PCI = percutaneous coronary intervention

ventricular ejection fraction was expressed as normal (>60%) or reduced: mildly (45% to 60%), moderately (30% to 44%), or severely (<30%). Recent MI is defined as the occurrence of an MI within 21 days of CABG. Urgency status is defined as elective, urgent (needing inpatient surgery), and emergent (needing surgery within 24 h).

Bypass grafting strategy, perioperative management of antiplatelet therapy, and the choice of using cardiopulmonary bypass were at the discretion of the individual surgeon. **Statistical methods.** Continuous variables are presented as mean ± 1 SD. Fisher exact test and Mann-Whitney *U* test were used to compare categorical and discrete variables, respectively. Differences in in-hospital mortality and MACE between the PCI and non-PCI groups were assessed using multiple variable logistic regression and propensity score methods to account for differences in patient characteristics. In the former, the 17 variables listed in Table

1 were forced into a multiple logistic regression model with in-hospital mortality and MACE as the outcomes to obtain the adjusted odds ratio (OR) for the prior PCI variable. In the propensity score method, the 17 variables were entered into a stepwise logistic regression model to obtain the propensity score with prior PCI as the outcome variable. The propensity score model was assessed by checking for balance of each variable between the PCI and non-PCI groups across quartiles of risk. The propensity score and the prior PCI variable were then forced into a logistic regression model with in-hospital mortality and MACE as the outcome to obtain the adjusted odds ratio for the prior PCI variable.

Kaplan-Meier analysis was used to estimate mid-term survival. Differences in mid-term survival were assessed by the log-rank test. A Cox proportional hazards model using the 17 variables in Table 1 was constructed to assess the

Table 1. Pre-Operative Characteristics of Patients Undergoing Isolated CABG

Variable	Prior PCI (n = 1,457)	No Prior PCI (n = 11,727)	p Value
Age, yrs, mean ± SD	63.3 ± 10.5	66.0 ± 10.2	<0.001
<60, %	37.3	27.5	
60–69, %	33.5	33.0	
70–79, %	24.8	33.5	
≥80, %	4.5	6.0	
Female sex, %	20.3	22.8	0.03
Diabetes, %	32.5	32.2	0.79
Hypercholesterolemia, %	87.2	80.2	<0.001
Hypertension, %	78.6	75.2	0.005
Cerebrovascular disease, %	9.5	11.3	0.044
Peripheral vascular disease, %	11.8	12.8	0.28
Renal failure, %*	2.8	2.7	0.74
Respiratory disease, %	12.3	12.5	0.86
Myocardial infarction within 21 days, %	15.6	24.0	<0.001
History of congestive heart failure, %	16.6	17.7	0.27
Unstable angina, %†	8.3	9.9	0.06
NYHA functional class, %			0.38
I	35.1	36.4	
II	37.3	36.8	
III	21.1	19.5	
IV	6.6	7.3	
Left main stenosis >50%, %	18.5	25.8	<0.001
LV function, %			0.41
Normal or mild LV impairment (EF >45%)	70.1	68.6	
Moderate impairment (EF 30%–45%)	25.8	26.8	
Severe impairment (EF <30%)	4.1	4.7	
Urgency status, %			0.002
Elective	61.8	57.0	
Urgent	34.9	38.8	
Emergent	3.3	4.1	

*Defined as serum creatinine >0.20 mmol/l. †Defined as need for intravenous nitrates until arrival in the operating theater.

CABG = coronary artery bypass graft surgery; EF = ejection fraction; LV = left ventricular; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

effect of prior PCI on mid-term survival. Tests were 2-sided, and $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 16.0 for Windows (SPSS Inc., Chicago, Illinois).

Results

BASELINE CHARACTERISTICS. Of 13,184 consecutive patients undergoing first-time isolated CABG, 1,457 (11.1%) had previously undergone PCI and 11,727 (88.9%) had no previous PCI (Table 1). Patients with previous PCI were younger (63.3 ± 10.5 years vs. 66.0 ± 10.2 years, $p <$ 0.001); less likely to be female (20.3% vs. 22.8%, $p = 0.03$), have cerebrovascular disease (9.5% vs. 11.3%, $p < 0.05$), left main coronary artery stenosis (18.5% vs. 25.8%, $p < 0.001$), or recent MI (15.6% vs. 24.0%, $p < 0.001$); or undergo urgent CABG (34.9% vs. 38.8%, $p = 0.004$). The lower

surgical risk profile of the patients who have had prior PCI is reflected in a lower EuroSCORE value (3.6 ± 3.0 vs. 4.4 ± 3.3, $p < 0.001$).

Operative characteristics. Intraoperatively, patients with a prior PCI had, on average, fewer distal coronary anastomoses performed (3.0 ± 1.1 vs. 3.3 ± 1.0, $p < 0.001$), shorter cross-clamp times (61.5 ± 34.8 min vs. 68.0 ± 35.7 min, $p < 0.001$), and shorter bypass times (83.6 ± 43.4 vs. 91.7 ± 42.6 min, $p < 0.001$). Use of the internal mammary artery graft was slightly lower in the PCI group (95.3% vs. 97.3%, $p < 0.001$), as was the use of off-pump CABG (8.2% vs. 11.3%, $p < 0.001$).

CLINICAL OUTCOMES. There was no difference in unadjusted in-hospital mortality between patients with or without previous PCI (1.65% vs. 1.55%, $p = 0.78$). There was no preponderance of cardiac death in either group (49% vs. 56%, $p = 0.67$). In-hospital MACE rates were 3.0% in both

Table 2. Multiple Variable Logistic Regression Analysis of Variables Associated With In-Hospital Mortality and MACE

Variable	In-Hospital Mortality Odds Ratio (95% CI)	p Value	In-Hospital MACE Odds Ratio (95% CI)	p Value
Age, yrs				
<60	1.00	—	1.00	—
60–69	1.11 (0.66–1.89)	0.69	1.14 (0.82–1.60)	0.43
70–79	2.35 (1.46–3.77)	<0.001	1.81 (1.33–2.48)	<0.001
≥80	5.19 (2.99–9.02)	<0.001	2.87 (1.90–4.29)	<0.001
Female sex	1.40 (1.01–1.93)	0.04	1.09 (0.85–1.39)	0.50
Diabetes	1.23 (0.89–1.68)	0.20	1.13 (0.90–1.42)	0.29
Hypercholesterolemia	0.83 (0.58–1.19)	0.32	0.83 (0.64–1.08)	0.17
Hypertension	1.15 (0.76–1.71)	0.51	1.04 (0.79–1.36)	0.79
Cerebrovascular disease	1.33 (0.91–1.94)	0.14	1.64 (1.25–2.16)	<0.001
Peripheral vascular disease	1.70 (1.19–2.42)	0.003	1.44 (1.10–1.89)	0.008
Renal failure*	2.32 (1.33–4.04)	0.003	1.83 (1.16–2.91)	0.01
Respiratory disease	1.09 (0.74–1.62)	0.66	0.96 (0.71–1.30)	0.80
Myocardial infarction within 21 days	1.41 (0.98–2.02)	0.06	1.36 (1.04–1.79)	0.02
History of congestive heart failure	2.26 (1.59–3.20)	<0.001	1.55 (1.19–2.00)	0.001
Unstable angina†	1.62 (1.11–2.37)	0.01	1.49 (1.10–2.01)	0.009
NYHA functional class				
I	1.00	—	1.00	—
II	0.91 (0.58–1.42)	0.69	1.19 (0.88–1.59)	0.25
III	1.24 (0.77–1.97)	0.37	1.35 (0.98–1.88)	0.07
IV	1.54 (0.93–2.55)	0.09	1.49 (1.02–2.18)	0.04
Left main stenosis >50%	1.32 (0.96–1.82)	0.08	1.16 (0.92–1.47)	0.22
Left ventricular function				
Normal or mild LV impairment (EF >45%)	1.00	—	1.00	—
Moderate impairment (EF 30%–45%)	1.20 (0.84–1.71)	0.32	1.24 (0.84–2.8)	0.61
Severe impairment (EF <30%)	2.89 (1.87–4.47)	<0.001	2.89 (1.19–6.99)	0.02
Urgency status				
Elective	1.00	—	1.00	—
Urgent	1.82 (1.22–2.71)	0.003	1.33 (1.02–1.75)	0.04
Emergency	4.07 (2.28–7.24)	<0.001	2.86 (1.85–4.42)	<0.001
Prior PCI	1.26 (0.77–2.08)	0.35	1.19 (0.83–1.68)	0.34

*Defined as serum creatinine >0.20 mmol/l. †Defined as need for intravenous nitrates until arrival in the operating theater.

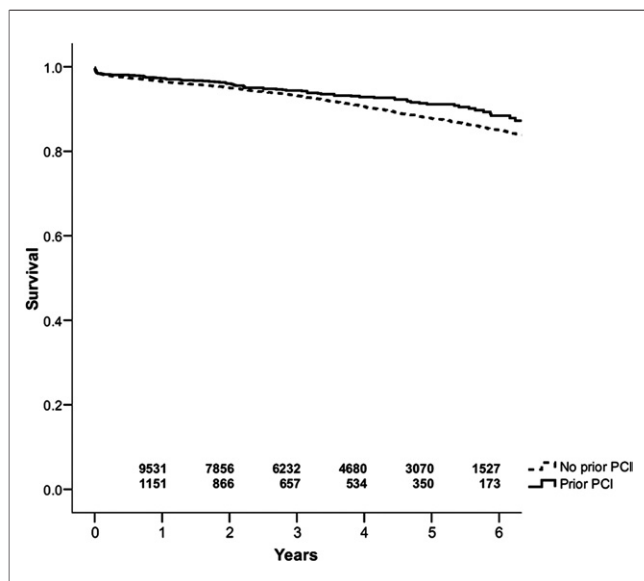CI = confidence interval; MACE = major adverse cardiac events; other abbreviations as in Table 1.

groups (p = 0.99). After adjusting for patient characteristics by logistic regression, prior PCI was not an independent predictor of in-hospital mortality (OR: 1.26, 95% confidence interval [CI]: 0.77 to 2.08, p = 0.35) or MACE (OR: 1.19, 95% CI: 0.83 to 1.68, p = 0.34) (Table 2). The propensity score model was well-balanced (63 of 64 variables assessed were balanced between PCI groups). Similar results were obtained after adjustment with propensity score; prior PCI was not associated with in-hospital mortality (OR: 1.22, 95% CI: 0.76 to 1.99, p = 0.41) or MACE (OR: 1.15, 95% CI: 0.72 to 1.84, p = 0.56).

Mean patient follow-up was 3.3 ± 2.1 years (median: 3.2 years, range 0 to 7 years). Survival at 1, 3, and 5 years was higher in the PCI group compared with the non-PCI group (97.3% vs. 96.5%, 94.4% vs. 93.2%, and 91.1% vs. 87.7%; log-rank test: p = 0.013) (Fig. 1). After adjusting for patient characteristics, prior PCI was not an independent predictor of mid-term mortality (hazard ratio: 0.94, 95% CI: 0.75 to 1.18, p = 0.62) (Fig. 2).
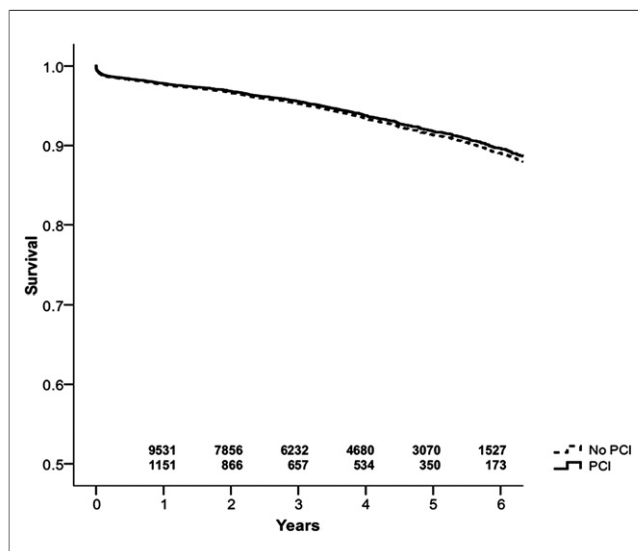
Discussion

There are several possible mechanisms by which prior PCI may affect the outcome of subsequent CABG. The recent increase in the number of patients undergoing PCI has stimulated interest in the effect of prior PCI in these patients.

First, prior PCI may limit the number of distal anastomoses, which are performed during subsequent CABG. In

Figure 2. Adjusted Survival Post-CABG With and Without Prior PCI

After adjusting for patient characteristics, prior PCI was not an independent predictor of mid-term mortality (hazard ratio: 0.94, 95% CI: 0.75 to 1.18, p = 0.62). Abbreviations as in Figure 1.

Figure 1. Unadjusted Survival Post-CABG With and Without Prior PCI

At a mean patient follow-up of 3.3 ± 2.1 years, survival was higher in the PCI group than in the non-PCI group (1 year: 97.3% vs. 96.5%, 3 years: 94.4% vs. 93.2%, and 5 years: 91.1% vs. 87.7%; log-rank test: p = 0.013). CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

patients with an occluded stent, it may be technically difficult to graft the coronary artery distal to a stent if the stent has been positioned in the distal portion of the vessel. Moreover, vessels with patent stents are usually not grafted because graft patency rates, especially of arterial grafts, are significantly reduced in the absence of significant coronary stenosis. However, leaving vessels with patent stents ungrafted may lead to post-operative MI should the stent occlude given the post-operative prothrombotic state of patients and the perioperative cessation of antiplatelet agents. A possible solution here would be to place vein grafts on all coronary vessels with patent stents. We do not have data on whether patent stented vessels were grafted in this study.

Second, prior PCI may reduce the patency of coronary artery bypass grafts. This is because the distal run-off from the graft may be compromised by multiple overlapping stents compromising collateral blood flow or because the surgeon is forced to graft more distal parts of the coronary artery due to a proximally placed stent.

Third, it has become increasingly clear that stents in general and drug-eluting stents in particular may affect coronary artery endothelial function (12,13).

Fourth, patients undergoing initial PCI may represent a cohort of patients who may have been assessed as likely to have suboptimal outcomes from CABG, due to being poor targets or debility out of proportion to age for instance. Such factors are not adjusted for as they are not measured, thus confounding subsequent analysis of CABG outcomes.

Finally, patients who have PCI and subsequently present for CABG may represent a cohort of patients with more aggressive atherosclerosis (14).

For these reasons, there have been concerns in the cardiac surgical community about the effect of prior PCI after subsequent CABG. These concerns have been supported by a number of reports suggesting worse outcomes after CABG in patients with prior PCI. The earliest and largest report was in 6,032 patients, 15% of whom had undergone PCI prior to subsequent CABG between 1996 and 2000 from 2 Canadian centers (15). In that study, patients with prior PCI had greater in-hospital mortality (OR: 1.93, p = 0.003) despite less comorbidity. The main limitation of that report was the historical nature of the data. For example, there were no patients with drug-eluting stents. Thielmann et al. have published 2 articles on the subject. The first compared 2,626 patients with no prior PCI with 679 patients with prior PCI undergoing subsequent CABG (16). The second article, a subset analysis of the first, compared the impact of prior PCI on 621 diabetic patients with triple vessel disease (17). In both these articles, Thielmann et al. reported significantly worse early mortality and adverse clinical events in patients with prior PCI. In the most recent report from the IMAGINE (Ischemia Management with Accupril Post-Bypass Graft via Inhibition of the Converting Enzyme) study, 430 patients with prior PCI were compared to 2,059 patients referred to CABG without prior PCI (18). Interestingly, that was the first article to report no difference in early mortality although they did report an increase in unstable angina requiring hospitalization and increased coronary revascularization in the prior PCI group. The main limitation of that study, however, remains that it is a reanalysis of data from a study not specifically designed to answer this question (19).

The principal finding of this analysis of a large Australian registry is that prior PCI was not a predictor of operative mortality or MACE, defined as a composite end point of in-hospital death, MI, or stroke after CABG. Similarly, prior PCI does not negatively affect survival at a mean follow-up of 3.3 years after subsequent CABG. Our study has several strengths. It is a large study with over 13,000 patients; it reports mid-term data; and because it is mandatory, all-inclusive, registry data from multiple cardiac surgery units it is likely to reflect real-world practice. In our opinion, these are the principal reasons why our results differ from those published previously.

Study limitations. Notwithstanding these advantages, our study has certain limitations. The lack of cardiac catheterization data precluded the identification of target vessels for prior PCI and the target vessels for subsequent CABG, thus preventing the determination of the mode of failure of PCI (i.e., restenosis vs. de novo development of occlusive lesions at remote sites). In addition, the lack of available cardiac catheterization data at the time of initial PCI did not allow

us to determine whether PCI was performed in the setting of single-vessel or multivessel disease or whether balloon angioplasty alone was performed or in combination with stent placement. Data are lacking concerning the interval between PCI and subsequent CABG or on the volume of stents in place at time of CABG. Both of these variables may be important determinants of outcome after CABG. Finally, this study does not assess the potential for cardiac death or MI in the interval between initial PCI and subsequent surgery. Large registry studies have shown that in the setting of multivessel disease managed with an initial strategy of PCI, 4% to 9% of patients die within 12 months (20–22). Hence, our study does not allow us to draw conclusions on the safety or effectiveness of a strategy of PCI first and CABG later.

Conclusions

There was no association between prior PCI and short- and mid-term mortality after CABG. Good outcomes can be obtained in the group of patients undergoing CABG who have had previous PCI.

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Key Words: coronary disease ■ surgery ■ revascularization ■ angioplasty ■ stents.

▷ **APPENDIX**