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ORIGINAL ARTICLE

Outcome after coronary artery bypass surgery and percutaneous coronary intervention in patients with atrial fibrillation and oral anticoagulation

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Aim. **This study was planned to compare the clinical characteristics and outcome of patients on warfarin treatment for atrial fibrillation (AF) undergoing coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI).**
Methods. **This is a retrospective analysis of 121 patients who underwent isolated CABG and 301 patients who underwent PCI.**
Results. **PCI patients were older (mean age, 72.9 versus 69.8 years) and more often had prior cardiac surgery (15.9% versus 1.7%) and acute coronary syndrome (53.8% versus 21.5%). CABG patients more often had two- and three-vessel disease (95.0% versus 60.2%) and left main stenosis (32.2% versus 7.0%). The 30-day outcome was similar after PCI and CABG. At 3 years, PCI was associated with lower overall survival (72.0% versus 86.4%, $P = 0.006$), freedom from repeat revascularization (85.3% versus 98.2%, $P < 0.001$), freedom from myocardial infarction (83.4% versus 93.8%, $P = 0.008$), and freedom from major cardiovascular events (57.4% versus 78.9%, $P < 0.001$). Propensity score adjusted analysis showed that PCI was associated with increased risk of all-cause mortality ($P = 0.016$, RR 2.166, CI 1.155–4.060), myocardial infarction ($P = 0.017$, RR 3.161, 95% CI 1.227–8.144), repeat revascularization ($P = 0.001$, RR 13.152, 95% CI 2.799–61.793), and major cardiac and cerebrovascular complications ($P = 0.001$, RR 2.347, 95% CI 1.408–3.914). There was no difference in terms of stroke and bleeding episodes at any time point.**
Conclusion. **In clinical practice, PCI is the preferred revascularization strategy in these frail patients. Patients selected for CABG have a relatively low operative risk and better mid-term outcome in spite of warfarin treatment. The poor prognosis after PCI may mainly reflect frequent co-morbidities in this patient group.**

Key words: Anticoagulation, atrial fibrillation, coronary artery bypass, percutaneous coronary intervention, warfarin

Key messages

- CABG appears to confer better mid-term outcome compared to PCI in coronary patients with atrial fibrillation and long-term oral anticoagulation.
- The high mortality in PCI-treated patients may reflect more common severe co-morbidities.
- Bleeding events are infrequent both after PCI and CABG and should not affect the treatment choice.

Introduction

Approximately 5%–12% of patients undergoing either coronary artery bypass grafting (CABG) (1–10) or percutaneous coronary intervention (PCI) (5,11,12) have preoperative atrial fibrillation. There are only a limited number of observational studies analyzing the long-term outcome after CABG (3,5–9) or PCI (5,12,13) in patients on oral anticoagulation for atrial fibrillation. Based on the existing evidence, preoperative atrial fibrillation has an independent negative prognostic impact on survival and cardiovascular events both after CABG and PCI (1–11). This increased risk seems to be partially explained by frequent co-morbidities and an increased risk of thromboembolism. In patients on oral anticoagulation a number of studies have reported on late survival after CABG (at 3 years, 71% to 85%; at 5 years, 68% to 75%) (3,4,6–9), but to our knowledge only two studies reported on at least 3-year survival after PCI (72% to 88% at 3 years) (12,13). No previous study has compared the long-term outcome after these two treatment methods in this frail patient group. In this observational study, we sought to analyze the long-term outcome and clinical features of warfarin-treated patients with atrial fibrillation referred for PCI and CABG.

Material and methods

This study is part of a wider protocol in progress to assess thrombotic and bleeding complications of cardiac procedures in Western Finland (14–17). The present analysis included a consecutive series of 121 patients on warfarin treatment for atrial fibrillation who underwent CABG at Oulu University Hospital and Turku University Hospital, Finland, between the years 2004 and 2010.

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Data on 301 patients on oral anticoagulation for atrial fibrillation who underwent PCI from 2000 to 2010 were retrieved from Turku University Hospital, Oulu University Hospital, and Satakunta Central Hospital, Finland. Only patients residing in the same catchment areas were included in this study in order to allow complete retrieval of data on late cardiovascular and bleeding events. Follow-up data were retrieved up to June 2011 for all these contributing databases, except for the PCI patients from Oulu University Hospital which provided only 1-year follow-up data on non-fatal events. Follow-up data were complete for all these patients. Hospital records and death certificates from the Central Statistical Office of Finland were used to acquire data on mode and date of death. This study complied with the Declaration of Helsinki. The study protocol was approved by the Ethics Committees of the participating hospitals.

Perioperative antithrombotic treatments in patients undergoing CABG

The main strategy in patients referred for elective surgery was preoperatively to discontinue warfarin two days prior to surgery without heparin bridging (15). Enoxaparin was used preoperatively instead of warfarin only in patients with acute coronary syndromes or mechanical heart valves. Aspirin and/or clopidogrel was discontinued for 5 to 7 days when feasible, i.e. when patients were stable enough to postpone surgery for a few days. Enoxaparin (40–60 mg once a day) was administered postoperatively in all patients since the evening of the operation day. Warfarin was restarted on the first postoperative day unless significant bleeding had occurred. Clopidogrel 75 mg once daily was administered only in patients with recently deployed coronary stents.

Perioperative antithrombotic treatments in patients undergoing PCI

In patients undergoing PCI, the peri-procedural antithrombotic management was also conducted according to the local practices of participating institutions, and patients underwent PCI during uninterrupted oral anticoagulation (16). Perioperative bivalirudin and glycoprotein IIb/IIIa inhibitors were administered at the discretion of the treating physician (16,17). Long-term treatment with aspirin was prescribed to all patients in the absence of contraindications. Clopidogrel was prescribed for 1 to 12 months (mean 2.6 ± 3.1 months) according to the stent type and underlying disease (acute coronary syndrome or stable disease).

Outcome end-points

The main outcome end-points of this study were all-cause mortality, stroke, myocardial infarction, repeat revascularization and major bleeding episodes. Furthermore, we considered combined major adverse cardiac and cerebrovascular events (MACCE), i.e. all-cause mortality, stroke, myocardial infarction and/or repeat revascularization, a main outcome end-point. Stroke was defined as a new neurologic deficit following surgery or PCI lasting >24 hours accompanied by new structural changes in computed tomography or magnetic resonance imaging or otherwise verified by clinical assessment. Myocardial infarction was diagnosed when a rise in the myocardial injury marker level was detected together with symptoms suggestive of acute myocardial ischemia. Repeat revascularization was defined as any CABG or PCI performed during follow-up for target or non-target vessel disease. Major bleeding was defined as cardiac tamponade, intracranial hemorrhage, any bleeding requiring hospital treatment, blood transfusion, and/or operative intervention, and any fatal bleeding. MACCE was defined as all-cause mortality, cerebrovascular event, myocardial infarction, and/or repeat revascularization (PCI and/or CABG).

Statistical analysis

Statistical analysis was performed using SPSS software statistical software (version 18, IBM SPSS Inc., Chicago, IL, USA). Continuous variables are reported as the mean $\pm$ standard deviation. The chi-square test, Fisher exact test, Mann–Whitney test, and Kaplan–Meier test were used for univariate analysis. Multivariate analysis was performed employing the Cox regression method by including clinical variables of relevance. Differences between the study groups were further accounted for by developing a propensity score for the treatment method. Propensity score analysis was used to control for all known patient factors that might be related to the decision to perform PCI or CABG, and thus potentially the outcome of interest. The propensity score was calculated by logistic regression with backward selection by including clinical variables with a $P<0.05$ in univariate analysis. Receiver-operating characteristic (ROC) curve analysis was used to estimate the area under the curve of the model, predicting the probability of being included in the PCI or CABG group. Because of the limited size of the study population, the estimated propensity score was employed only for risk adjusted analysis, i.e. as a covariate in any regression model, for all outcome end-points.

Results

Baseline characteristics and clinical outcome in the overall series

The baseline clinical characteristics of the study population are detailed in Table I. As expected, major baseline differences were observed between the study groups. PCI patients were significantly older (mean age, 72.9 versus 69.8 years) and more often had prior cardiac surgery (15.9% versus 1.7%) and acute coronary syndrome (53.8% versus 21.5%). Primary PCI for ST-elevation myocardial infarction comprised 8.6% of the indications for PCI. On the other hand, CABG patients had more often two- and three-vessel disease (95.0% versus 60.2%) and left main stenosis (32.2% versus 7.0%).

The mean follow-up of these patients was 2.9 ± 1.6 years. Thirty-day postoperative outcome was similar after PCI and CABG (Table II). At 3 years, patients selected for PCI revascularization had significantly lower overall survival as well as freedom from myocardial infarction and repeat revascularization compared to patients undergoing CABG. Patients treated with CABG also had a higher freedom from MACCE (Table II). When comparing PCI patients with incomplete ($n=164$) and complete ($n=137$) revascularization at index hospitalization, the rates of freedom from re-intervention were similar at 3 years on Kaplan–Meier analysis (86.9% and 82.9%, log rank $P=0.927$). A total of 29.7% of re-interventions in the PCI group were non-target vessel procedures, and 88.2% of these were performed after 3 months (not planned staged procedures). Freedom from MACCE at 3 years for PCI patients with incomplete and complete revascularization were 53.2% and 58.0%, respectively (log rank $P=0.626$).

Incidences of stroke and major bleeding episodes were not different between the study groups, and $CHADS_2$ scores were also similar in the study groups. Bleeding events are summarized in Table III. Two patients died in the PCI group (one intracranial and one pulmonary bleeding) and one patient in the CABG group (intracranial bleeding) because of bleeding.

When adjusted for age, gender, previous cardiac surgery, recent myocardial infarction, acute coronary syndrome, left

Table I. Baseline characteristics and operative data on patients with chronic oral anticoagulation for atrial fibrillation who underwent isolated coronary artery bypass surgery and percutaneous coronary intervention.

	CABG group (121 patients)	PCI group (301 patients)	*P* value
Age (years)	69.8 ± 8.5	72.9 ± 7.7	< 0.001
Age ≥ 80 years	11 (9.1%)	58 (19.3%)	< 0.001
Females	19 (15.7%)	79 (26.2%)	0.020
Diabetes	46 (38.0%)	92 (30.6%)	0.140
Hypertension	83 (68.6%)	236 (78.4%)	0.034
Stroke or transient ischemic attack	19 (15.7%)	65 (21.6%)	0.170
Prior percutaneous coronary intervention	18 (14.9%)	51 (16.9%)	0.604
Prior cardiac surgery	2 (1.7%)	48 (15.9%)	< 0.001
Acute coronary syndrome	26 (21.5%)	162 (53.8%)	< 0.001
Two- or three-vessel disease	115 (95.0%)	181 (60.2%)	< 0.001
Left main stenosis	39 (32.2%)	21 (7.0%)	< 0.001
Left ventricular ejection fraction < 30%	6 (5.0%)	14 (4.7%)	1.000
Preoperative INR	1.9 ± 0.6	2.3 ± 0.6	0.067
Off-pump surgery	43 (35.5%)	–	
At least one mammary artery graft	115 (95.0%)	–	
Maze procedure, *n*	10 (8.2%)	–	
Distal anastomoses	3.1 ± 1.0	–	
Vessels treated by PCI, *n*	–	1.1 ± 0.3	
Patients treated with drug-eluting stent	–	73 (24.3%)	
$CHADS_2$ score	2.0 ± 1.2	2.1 ± 1.2	0.613
Drug treatment at discharge:			
Aspirin	59 (49.6%)	275 (91.4%)	< 0.001
Clopidogrel	8 (6.8%)	291 (96.7%)	< 0.001
Statin	88 (73.9%)	262 (89.1%)	< 0.001
β-Blockers	110 (93.2%)	257 (87.4%)	0.088

Continuous variables are reported as mean ± standard deviation. Values in parentheses are percentages.
INR = international normalized ratio.

main stenosis, and multivessel disease, PCI was associated with a higher risk of all-cause mortality ($P = 0.036$, RR 2.035, 95% CI 1.049–3.949), myocardial infarction ($P = 0.010$, RR 3.848, 95% CI 1.378–10.746), repeat revascularization ($P = 0.001$, RR 13.152, 95% CI 2.799–61.793), and MACCE ($P = 0.003$, RR 2.219, 95% CI 1.315–3.747) at 3-year follow-up. Treatment methods had no effect on stroke ($P = 0.826$) and bleeding risk ($P = 0.829$).

Logistic regression (Hosmer–Lemeshow's test: $P = 0.182$) estimated a propensity score with an area under the ROC curve of 0.875 (95% CI 0.840–0.910). When adjusted for propensity score, PCI was associated with an increased risk of all-cause mortality ($P = 0.016$, RR 2.166, 95% CI 1.155–4.060), myocardial infarction ($P = 0.017$, RR 3.161, 95% CI 1.227–8.144), repeat revascularization ($P = 0.002$, RR 11.302, 95% CI 2.430–52.562), and MACCE ($P = 0.001$, RR 2.347, 95% CI 1.408–3.914). No difference was observed between the treatment methods in terms of stroke ($P = 0.554$) or major bleeding ($P = 0.433$). Propensity score adjusted Cox's estimates for survival and freedom from MACCE are shown in Figures 1 and 2, respectively.

Table II. Outcome after coronary artery bypass surgery and percutaneous coronary intervention in patients on chronic oral anticoagulation for atrial fibrillation.

	CABG group (121 patients)	PCI group (301 patients)	*P* value
30-day outcome:			
Mortality	4 (3.3)	7 (2.3)	0.520
Stroke	3 (2.5)	1 (0.7)	0.145
Repeat revascularization	0 (0)	3 (1.0)	0.561
Myocardial infarction	2 (1.7)	5 (1.7)	1.000
Major bleeding	3 (2.5)	12 (4.0)	0.570
3-year outcome:			
Overall survival	86.4%	72.0%	0.006
Freedom from stroke[a]	94.8%	94.9%	0.711
Freedom from myocardial infarction	93.8%	83.4%	0.008
Freedom from repeat revascularization	98.2%	85.3%	< 0.001
Freedom from major bleeding[a,b]	88.7%	89.3%	0.823
Freedom from MACCE	78.9%	57.4%	< 0.001

Values in parentheses are percentages.
[a]Also events before discharge included.
[b]Includes three cases of pericardial tamponade that occurred immediately after CABG and one immediately after PCI.
MACCE = major adverse cardiac and cerebrovascular events defined as all-cause mortality, stroke, myocardial infarction and repeat revascularization (either percutaneous coronary intervention or coronary artery bypass grafting).

Discussion

The present study is the first to compare the clinical characteristics and outcome of patients on long-term warfarin treatment for atrial fibrillation referred for CABG or PCI. As expected, major differences were observed with respect to baseline co-morbidities

Table III. Bleeding episodes after coronary revascularization in patients on warfarin treatment for atrial fibrillation.

	CABG group (121 patients)	PCI group (301 patients)
30-day events:		
Cardiac tamponade, operated	3	1
Access site bleeding, operated	–	4
Intracranial bleeding	–	3
Gastrointestinal bleeding	–	2
Airway bleeding	–	1
Late events:		
Gastrointestinal bleeding	4	8
Airway bleeding	1	2
Intracranial bleeding	4	2
Vitreous bleeding	–	1
Hemarthron	2	–
Urinary tract bleeding	1	2

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

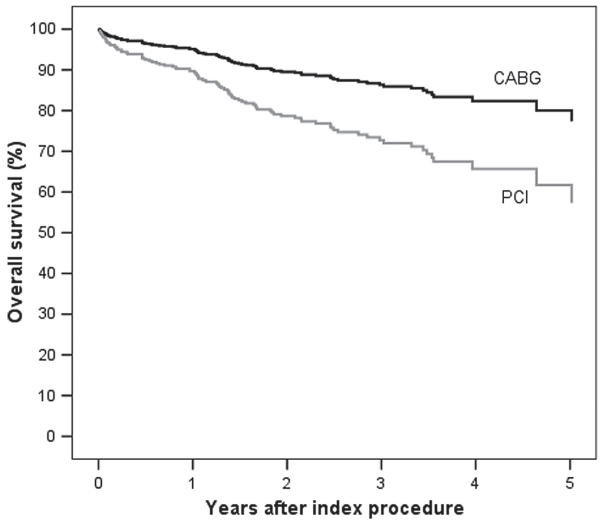

Figure 1. Propensity score adjusted Cox's estimates of overall survival in patients on warfarin treatment for atrial fibrillation after isolated coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI).

and extent of coronary disease which were in accordance with general guidelines and recommendations on choice between PCI and CABG.

The main finding of our study was that the patients selected on clinical grounds for CABG revascularization had a better overall survival than those selected for treatment with PCI both according to conventional Cox regression analysis and propensity score adjusted analysis. The relatively high overall mortality of 13.6% at 3-year follow-up in the CABG group was similar to that previously reported for postoperative atrial fibrillation, although these studies also included patients who were not on warfarin (5–6). Secondly, in line with earlier reports, patients undergoing CABG had a lower overall risk of myocardial infarction, repeat revascularization, and MACCE (8–10,12) than patients treated with PCI. In this respect it is noteworthy that over half of the PCI patients were treated for acute coronary syndromes. In this scenario, typically only the culprit lesion is stented, and the milder stenoses might later give rise to symptoms and lead to a need for

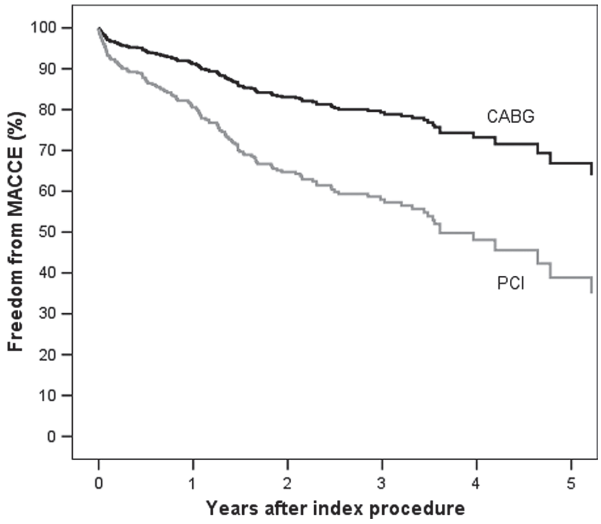

Figure 2. Propensity score adjusted Cox's estimates of freedom from major cardiac and cerebrovascular events (MACCE) in patients on warfarin treatment for atrial fibrillation after isolated coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI).

further revascularization. Secondly, bare-metal stents are recommended and were mainly used for this frail patient group with a high risk of bleeding to shorten the duration of dual antiplatelet treatment together with warfarin (18). Re-stenosis is, however, common with this treatment strategy. With the current treatment strategy, the rate of early and late stent thrombosis seems comparable to patients with no oral anticoagulation undergoing PCI (19,20) and is not a major factor behind the continued need for revascularization.

One major finding of this study was that this complicated patient group seems to be currently mostly referred to PCI when revascularization is needed, and more than half of these patients were treated with incomplete revascularization. This kind of clinical decision-making is understandable when the risks of CABG or additional PCI procedures are deemed unacceptable in frail patients with severe co-morbidities. It is conceivable that some of the patients in the PCI group had serious co-morbidities and clinical characteristics that might contribute to the observed poor outcome, but cannot be accounted for based on patient records. These factors may contribute to the 3-year mortality of 28% which is much higher than generally in PCI-treated populations (12,21). The clinical selection led to obvious major heterogeneity between the patient groups, with clinically significant risk factors distributed unevenly. In fact, on the one hand, patients who underwent PCI were significantly older, they were more frequently females, and with a history of prior cardiac surgery. On the other hand, as recommended in the guidelines, patients who underwent CABG more frequently had two- and three-vessel coronary artery disease and left main stenosis. Clinical selection understandably leads to an over-representation of single-vessel treatment in PCI patients. These factors make comparability of the study groups particularly difficult, and the limited size of the series prevents any analysis in subgroups of patients, although baseline differences were taken into account in multivariate analysis and in propensity score adjusted Cox regression analysis.

The present findings showed that chronic anticoagulation decreases the risk of thromboembolic complications associated with atrial fibrillation (AF) also after revascularization. Remarkably, we observed that at 3 years freedom rates from stroke after CABG and PCI were similar between the two groups at 97% and 96%, respectively, which are similar to the rate observed at 3 years after CABG in patients without preoperative fibrillation (97%, after exclusion of patients who suffered stroke immediately after surgery) (22).

A previous study on PCI in patients with oral anticoagulation demonstrated a relatively low risk of bleeding despite opposing concerns (23). The present study supports the view that the fear of major bleeding episodes seems overemphasized in patients on oral anticoagulation irrespective of the type of revascularization, although it is of note that this study only evaluated severe events requiring hospitalization or leading to disability and death. In fact, serious bleeding events were equally infrequent in patients who had undergone CABG and those who received PCI in the early post-procedural period and later, even taking into account that the majority of PCI patients were on triple therapy including aspirin and clopidogrel. This suggests that such a low risk of bleeding in patients with AF should not affect the treatment choice.

The retrospective nature of this study is by nature a limitation, and adjustment for unmeasured variables (e.g. frailty, severe co-morbidities, SYNTAX score) is impossible. On the other hand, follow-up was complete in all these patients, since the treatment of patients residing in the catchment areas of our institutions is centralized. This allowed us to get information on any major clinical event requiring hospital treatment. Furthermore, data on

late mortality were obtained from the Finnish national registry, Statistics Finland, which ensures the quality of survival data of these patients. The small size of this study is another limitation of this analysis, and therefore these findings should be viewed as hypothesis-generating. However, the prevalence of patients with AF requiring myocardial revascularization is rather low, rendering prospective recruitment of an adequately powered patient population difficult. In accordance with contemporary guidelines, drug-eluting stents were seldom used in these patients and may contribute to the need of re-interventions in the PCI group. Furthermore, the policy of treating only the culprit lesion could have exposed a number of patients to a high risk of re-intervention and residual ischemia. Rates of re-intervention, however, were similar for patients with and without incomplete revascularization at 3 years, and 29.7% of interventions in the PCI group were non-target vessel procedures.

In conclusion, the present results suggest that in clinical practice CABG may be associated with a better mid-term outcome compared with PCI in patients with atrial fibrillation and on warfarin treatment, although this probably reflects a lower co-morbidity burden in patients selected for surgical treatment. Major bleeding events were infrequent after both treatment modalities, suggesting that oral anticoagulation should not affect the choice of revascularization. Further larger, prospective studies are needed to confirm these findings.

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