ORIGINAL RESEARCH

Prognostic Impact of Multiple Prior Percutaneous Coronary Interventions in Patients Undergoing Coronary Artery Bypass Grafting

Fausto Biancari, MD, PhD; Magnus Dalén, MD, PhD; Vito G. Ruggieri, MD, PhD; Till Demal, MD; Giuseppe Gatti, MD; Francesco Onorati, MD, PhD; Giuseppe Faggian, MD; Antonino S. Rubino, MD, PhD; Daniele Maselli, MD; Riccardo Gherli, MD; Antonio Salsano, MD; Matteo Saccocci, MD; Giuseppe Santarpino, MD, PhD; Francesco Nicolini, MD, PhD; Tuomas Tauriainen, MD, PhD; Marisa De Feo, MD, PhD; Juhani Airaksinen, MD, PhD; Stefano Rosato, MSc; Andrea Perrotti, MD, PhD; Giovanni Mariscalco, MD, PhD

***Background*—**Multiple percutaneous coronary interventions (PCIs) are considered determinant of poor outcome in patients undergoing coronary artery bypass grafting (CABG), but scarce data exist to substantiate this.

***Methods and Results*—**Patients who underwent CABG without history of prior PCI or with PCI performed >30 days before surgery were selected for the present analysis from the prospective, multicenter E-CABG (European Multicenter Study on Coronary Artery Bypass Grafting) registry. Out of 6563 patients with data on preoperative SYNTAX (Synergy between PCI With Taxus and Cardiac Surgery) score, 1181 patients (18.0%) had undergone PCI >30 days before CABG. Of these, 11.6% underwent a single PCI, 4.4% 2 PCIs, and 2.1% ≥3 PCIs. PCI of a single main coronary vessel was performed in 11.3%, of 2 main vessels in 4.9%, and of 3 main vessels in 1.6% of patients. Multivariable analysis showed that differences in early mortality and other outcomes were not significantly different in the study cohorts. The adjusted hospital/30-day mortality rate was 1.8% in patients without history of prior PCI, 1.9% in those with a history of 1 PCI, 1.4% after 2 PCIs, and 2.5% after ≥3 PCIs (adjusted P=0.8). The adjusted hospital/30-day mortality rate was 2.0% in those who had undergone PCI of 1 main coronary vessel, 1.3% after PCI of 2 main vessels, and 3.1% after PCI of 3 main coronary vessels (adjusted P=0.6).

***Conclusions*—**Multiple prior PCIs are not associated with increased risk of early adverse events in patients undergoing isolated CABG. The present results are conditional to survival after PCI and should not be viewed as a support for a policy of multiple PCI as opposed to earlier CABG.

***Clinical Trial Registration*—**URL: http://www.Clinicaltrials.gov. Unique identifier: NCT02319083. **(*J Am Heart Assoc*. 2018;7: e010089. DOI: 10.1161/JAHA.118.010089.)**

Key Words: coronary artery bypass grafting • percutaneous coronary intervention • previous PCI • prior PCI

Currently, an increasing number of patients undergoing coronary artery bypass grafting (CABG) have previously been treated with percutaneous coronary intervention (PCI). A recent study from the Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Database showed that 28.9% of patients who underwent isolated CABG had a prior PCI, which was performed before the index hospitalization in 25% of patients.[1] This figure has increased as compared with the previous decade, when the

From the Department of Surgery, Oulu University Hospital and University of Oulu, Finland (F.B., T.T.); Heart Center, Turku University Hospital and University of Turku, Finland (F.B., J.A.); Department of Molecular Medicine and Surgery, Department of Cardiac Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden (M.D.); Division of Cardiothoracic and Vascular Surgery, Robert Debré University Hospital, Reims, France (V.G.R.); Hamburg University Heart Center, Hamburg, Germany (T.D.); Division of Cardiac Surgery, Ospedali Riuniti, Trieste, Italy (G.G.); Division of Cardiovascular Surgery, Verona University Hospital, Verona, Italy (F.O., G.F.); Centro Clinico-Diagnostico "G.B. Morgagni," Centro Cuore, Pedara, Italy (A.S.R.); Department of Cardiac Surgery, St. Anna Hospital, Catanzaro, Italy (D.M.); Cardiac Surgery Unit, Department of Cardiovascular Sciences, S. Camillo-Forlanini Hospital, Rome, Italy (R.G.); Division of Cardiac Surgery, University of Genoa, Italy (A.S.); Department of Cardiac Surgery, Centro Cardiologico - Fondazione Monzino IRCCS, University of Milan, Italy (M.S.); Cardiovascular Center, Paracelsus Medical University, Nuremberg, Germany (G.S.); Città di Lecce Hospital GVM Care & Research, Lecce, Italy (G.S.); Division of Cardiac Surgery, University of Parma, Italy (F.N.); Department of Cardiothoracic and Respiratory Sciences, University of Campania, Napoli, Italy (M.D.F.); National Center of Global Health, Istituto Superiore di Sanità, Rome, Italy (S.R.); Department of Thoracic and Cardio-Vascular Surgery, University Hospital Jean Minjoz, Besançon, France (A.P.); Department of Cardiovascular Sciences, Clinical Sciences Wing, Glenfield Hospital, University of Leicester, United Kingdom (G.M.).

Correspondence to: Fausto Biancari, MD, PhD, Heart Center, Turku University Hospital, PO Box 52, 20521 Turku, Finland. E-mail: faustobiancari@yahoo.it

Received June 15, 2018; accepted August 6, 2018.

Clinical Perspective

What Is New?

- Multiple prior percutaneous coronary interventions do not increase the risk of early adverse events after isolated coronary artery bypass grafting.

What Are the Clinical Implications?

- Although the present results are conditional to survival after percutaneous coronary intervention, a policy of multiple percutaneous coronary interventions does not compromise the early outcome of an eventual isolated coronary artery bypass grafting.

overall prevalence of prior PCI in the Society of Thoracic Surgeons 2008 Adult Cardiac Surgery Database was 21.3%.[2] Analysis of patients who had surgery in 2015 from the E-CABG registry (European Multicenter Study on Coronary Artery Bypass Grafting), showed that 21.9% of patients had a history of prior PCI and 18.8% underwent isolated CABG >30 days after PCI.[3] This study showed that prior PCI was not associated with worse early outcome.[3] However, the accompanying meta-analysis including 71 366 patients from 8 studies showed a trend toward higher in-hospital/30-day mortality (adjusted odds ratio [OR], 1.30; 95% confidence interval [CI], 0.99–1.70) in patients with prior PCI. However, some of the available studies were potentially biased by the lack of adequate adjustment for important confounders. Multiple prior PCI procedures and multiple treated vessels could hypothetically be associated with worse outcome, but scarce data exist to substantiate this.[4] We sought to investigate this issue in patients who had surgery from 2015 to 2017 from the E-CABG registry.

Methods

The E-CABG registry is a prospective, multicenter study that enrolled patients undergoing isolated CABG at 16 European centers of cardiac surgery in Finland, France, Italy, Germany, Sweden, and the United Kingdom. The study is registered in Clinicaltrials.gov (Identifier: NCT02319083). The detailed protocol and definition criteria have been previously published.[5] This study was approved by the Institutional Review Board of the participating centers. Informed consent was obtained when required by the Institutional Review Board; otherwise, it was waived. Because of restrictions in sharing patient information, the data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

This registry included 7352 consecutive patients who underwent isolated CABG at the participating hospitals from January 2015 to May 2017. Patients who underwent any other concomitant procedure on the heart valves, ascending aorta, and ventricular wall were not included in this registry. Data were collected prospectively and underwent checking of its quality. For the purpose of this study, only patients with complete data on the timing and number of PCIs and vessels treated and on the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score were included in this analysis. Patients who underwent PCI ≤30 days from CABG were excluded from this study because indication for surgical revascularization might be related to acute complication of PCI or severe ischemia not successfully treated by PCI.

Outcomes

Hospital/30-day death was the primary outcome of this study. Secondary outcomes were 1-year all-cause mortality, length of stay in the intensive care unit, stroke, postoperative use of intra-aortic balloon pump and/or extracorporeal membrane oxygenation, acute kidney injury, renal replacement therapy, and E-CABG bleeding grades 2 to 3. Postoperative acute kidney injury was defined according to the KDIGO (Kidney Disease: Improving Global Outcomes) criteria.[6] E-CABG bleeding grades 2 to 3 was defined as bleeding requiring reoperation or transfusion of >4 units of red blood cells.[5] The definition criteria of the other outcomes were previously published.[5]

Statistical Analysis

Statistical analyses were performed using SPSS version 24.0 (IBM Corporation, New York, USA) and Stata version 14.2 (StataCorp LLC, TX, USA) statistical software. The Mantel-Haenszel, Kruskal-Wallis, and Kaplan-Meier tests were used for univariate analysis of baseline and operative data as well as outcomes of the study cohorts. Logistic, linear, and Cox proportional hazard regression analyses were performed to evaluate the impact on the outcomes of increasing numbers of prior PCIs as well as main coronary vessels treated by PCI. Regression models assessing the outcomes in patients with increasing number of PCIs were adjusted by the following baseline risk factors, which significantly differed between subgroups of patients: age, body mass index, dialysis, anemia, pause of P2Y12 receptor inhibitors <5 days before surgery, diabetes mellitus, prior cardiac surgery, urgency of the procedure, SYNTAX score, off-pump surgery, and number of distal anastomoses. Similarly, regression models assessing the outcomes in patients with an increasing number of main coronary vessels treated by PCI were adjusted by the following baseline risk factors, which significantly differed between subgroups of patients with increasing number of prior PCIs: age, female sex, dialysis, pause of P2Y12 receptor

inhibitors <5 days before surgery, diabetes mellitus, prior cardiac surgery, urgency of the procedure, SYNTAX score, off-pump surgery, and number of distal anastomoses. The observed number of events was divided by the risk-adjusted expected number of events to produce observed-to-expected ratios. The risk-adjusted expected number of events was estimated by logistic regression with backward modality. Early adjusted mortality rates for each subgroup was estimated by multiplying the observed-to-expected ratio by the mean outcome rate. All tests were 2-sided, and $P<0.05$ was set for statistical significance.

Results

The flow chart of patient selection of this study is depicted in the Figure. Of 7352 patients operated from January 2015 to May 2017 and included in the E-CABG registry, 1540 (20.9%) had a prior PCI, and 1524 patients (99.0%) had complete data on the date of last PCI and the number of PCIs performed. Two-hundred thirty-five patients (15.4% of patients with prior PCI) underwent CABG within 30 days of prior PCI and were excluded from the analysis. These patients had a higher risk of in-hospital/30-day death than those with prior PCI performed >30 days from surgery (3.8% versus 1.8%; unadjusted $P=0.044$), a difference that was not statistically significant when adjusted for EuroSCORE (European System for Cardiac Operative Risk Evaluation) II (OR, 1.553; 95% CI, 0.658–3.666).

Among 5812 patients without prior PCI, 5382 patients had data on preoperative SYNTAX score (92.6%). Among 1309 patients who underwent CABG >30 days after PCI, 1181 patients (90.2%) had complete data on the timing and number of PCIs as well as on preoperative SYNTAX score (Figure).

When adjusted for baseline covariates listed in Table 1 along with surgical technique, bilateral internal mammary artery grafting and number of distal anastomoses, patients undergoing CABG after any prior PCI did not have an increased risk of hospital/30-day (1.7% versus 1.9%; adjusted $P=0.8$), intermediate mortality (1-year mortality, 3.6% versus 3.5%; adjusted $P=0.9$), stroke (1.0% versus 1.2%; adjusted $P=1.0$), length of intensive care unit stay (mean 2.8±3.6 versus 2.9±4.5 days; adjusted $P=1.0$), postoperative insertion of intra-aortic balloon pump and/or extracorporeal membrane oxygenation (3.3% versus 4.9%; adjusted $P=0.1$), KDIGO acute kidney injury (21.3% versus 22.8%; adjusted $P=0.2$) and dialysis (1.8% versus 1.8%; adjusted $P=0.8$), but they showed a trend toward increased risk of severe/massive bleeding (7.8% versus 6.4%; adjusted $P=0.06$; OR 1.284, 95% CI, 0.989–1.667).

Number of Prior PCIs and Outcome After CABG

A single PCI was performed in 759 patients (11.6%), 2 PCIs in 287 patients (4.4%), and ≥3 PCIs in 135 patients (2.1%) (Table 1). The operative risk was higher, particularly in

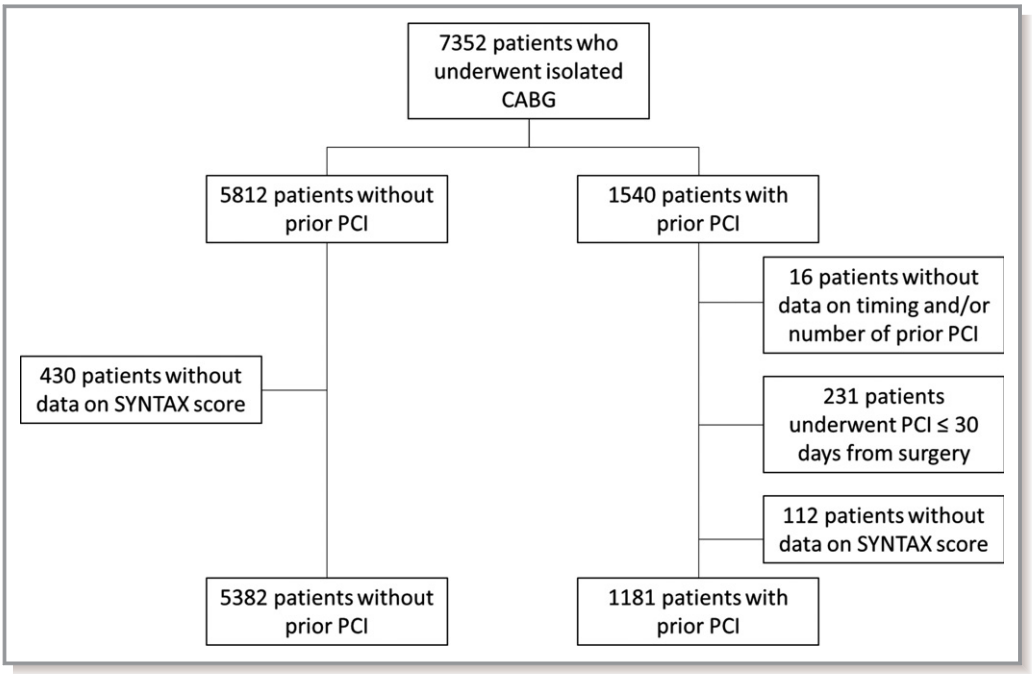

Figure. Flow chart of patient selection for the present analysis. CABG indicates coronary artery bypass grafting; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery.

Table 1. Baseline Characteristics and Operative Data According to the Number of Prior PCIs

Covariates	No Prior PCI (5382 Pts)	1 Prior PCI (759 Pts)	2 Prior PCIs (287 Pts)	≥3 Prior PCIs (135 Pts)	*P* Value
Baseline risk factors					
Age, y	67.8±9.3	66.2±9.6	66.7±9.2	67.7±8.8	<0.0001
Female	915 (17.0)	109 (14.4)	41 (14.3)	20 (14.8)	0.058
Body mass index	27.5±4.1	27.5±4.2	28.1±4.3	26.7±4.0	0.016
eGFR, mL/min per 1.73 m^2	76±20	76±20	74±22	73±24	0.627
Dialysis	54 (1.0)	11 (1.4)	4 (1.4)	6 (4.4)	0.002
Anemia	1202 (22.4)	151 (19.9)	75 (26.1)	49 (36.3)	<0.0001
Diabetes mellitus	1632 (30.3)	246 (32.4)	109 (38.0)	62 (45.9)	<0.0001
Acute coronary syndrome	2630 (48.9)	344 (45.3)	127 (44.3)	74 (54.8)	0.420
Recent STEMI	293 (5.4)	57 (7.5)	13 (4.5)	6 (4.4)	0.782
Prior stroke/TIA	319 (5.9)	47 (6.2)	23 (8.0)	7 (5.2)	0.457
Atrial fibrillation	442 (8.2)	46 (6.1)	33 (11.5)	19 (14.1)	0.067
Pulmonary disease	529 (9.8)	75 (9.9)	30 (10.5)	13 (9.6)	0.863
Extracardiac arteriopathy	1207 (22.4)	178 (23.5)	77 (26.8)	36 (26.7)	0.046
Prior cardiac surgery	20 (0.4)	6 (0.8)	5 (1.7)	4 (3.0)	<0.0001
Left ventricular ejection fraction ≤50%	1517 (28.2)	206 (27.1)	86 (30.0)	45 (33.6)	0.327
Critical preoperative state	359 (6.7)	34 (4.5)	19 (6.6)	6 (4.4)	0.101
Urgency of the procedure					0.001
Urgent	2253 (41.9)	251 (33.1)	102 (35.5)	57 (42.5)	
Emergency	259 (4.8)	17 (2.2)	11 (3.8)	9 (6.7)	
P2Y12 receptor inhibitors pause <5 d	663 (12.3)	150 (19.8)	66 (23.0)	38 (28.1)	<0.0001
Indication for surgery					
In-stent restenosis	…	218 (28.8)	130 (45.3)	92 (68.7)	<0.0001
Stent thrombosis	…	44 (5.8)	23 (8.0)	14 (10.4)	<0.0001
Coronary artery disease progression	…	567 (74.8)	226 (78.7)	107 (79.3)	<0.0001
Left main coronary artery PCI	…	33 (4.3)	12 (4.2)	19 (14.1)	<0.0001
Any drug-eluting stent	…	384 (51.8)	180 (63.2)	107 (81.7)	<0.0001
Delay from last PCI, y	…	6.2±6.2	5.6±4.9	3.6±4.2	0.001
SYNTAX score	29±12	26±12	27±12	28±12	<0.0001
EuroSCORE II, %	2.8±4.1	2.3±3.7	2.9±4.1	3.7±6.1	<0.0001
Operative data					
No. of distal anastomoses	2.8±0.9	2.5±0.9	2.5±0.9	2.4±0.9	<0.0001
Cardiopulmonary bypass time, min	86±36	79±31	84±34	83±34	0.670
Aortic clamping time, min	58±26	55±23	56±27	58±28	0.067
Off-pump surgery	1024 (19.0)	181 (23.8)	75 (26.1)	43 (31.9)	<0.0001
Bilateral internal mammary artery grafts	2022 (37.6)	319 (42.0)	103 (35.9)	40 (29.6)	0.609

Continuous variables are reported as the mean±standard deviation. Categorical variables are reported as counts and percentages. Anemia is defined as baseline hemoglobin concentration <12.0 g/L in women and <13.0 g/L in men. Clinical variables are according to the EuroSCORE II definition criteria. eGFR indicates estimated glomerular filtration rate according to the Modification of Diet in Renal Disease equation; EuroSCORE, European System for Cardiac Operative Risk Evaluation; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery; TIA, transient ischemic attack.

patients who underwent ≥3 PCIs. The crude hospital/30-day mortality rates in these study cohorts were 1.9%, 1.6%, 1.4%, and 3.0%, respectively (Table 2). Early mortality and other outcomes were not significantly different in the study cohorts either in univariate and multivariable analyses (Table 2).

Table 2. Outcomes According to the Number of Prior PCIs

	No Prior PCI (5382 Pts)	1 Prior PCI (759 pts)	2 Prior PCIs (287 Pts)	≥3 Prior PCIs (135 Pts)	Univariate/Multivariate Analysis *P* Value
Hospital/30-d death	103 (1.9)	12 (1.6)	4 (1.4)	4 (3.0)	0.935
Adjusted risk estimates	Reference	1.09, 0.59 to 2.03	0.75, 0.27 to 2.13	1.12, 0.38 to 3.30	0.933
1-y mortality, %	3.5	3.2	3.9	4.8	0.857
Adjusted risk estimates	Reference	1.00, 0.66 to 1.52	0.92, 0.50 to 1.70	0.79, 0.34 to 1.77	0.937
Intensive care unit stay, d	2.9±4.5	2.7±3.7	3.0±3.2	3.0±3.8	0.309
Adjusted risk estimates	Reference	−0.02, −0.35 to 0.31	0.14, −0.38 to 0.65	−0.09, −0.83 to 0.66	0.853
Stroke	62 (1.2)	7 (0.7)	4 (1.4)	1 (0.7)	0.769
Adjusted risk estimates	Reference	0.95, 0.43 to 2.11	1.42, 0.51 to 3.99	0.64, 0.08 to 4.75	0.874
Postoperative IABP or ECMO	263 (4.9)	26 (3.4)	8 (2.8)	5 (3.7)	0.034
Adjusted risk estimates	Reference	0.82, 0.53 to 1.26	0.60, 0.29 to 1.25	0.59, 0.22 to 1.54	0.314
KDIGO acute kidney injury*	1204 (22.8)	165 (22.1)	60 (21.3)	21 (16.4)	0.122
Adjusted risk estimates	Reference	1.01, 0.83 to 1.22	0.85, 0.63 to 1.15	0.59, 0.36 to 0.97	0.143
Renal replacement therapy*	95 (1.8)	12 (1.6)	5 (1.8)	4 (3.1)	0.597
Adjusted risk estimates	Reference	1.04, 0.56 to 1.94	0.95, 0.38 to 2.39	1.53, 0.53 to 4.41	0.884
E-CABG bleeding grades 2–3	344 (6.4)	60 (7.9)	18 (6.3)	14 (10.4)	0.080
Adjusted risk estimates	Reference	1.42, 1.05 to 1.92	0.93, 0.55 to 1.55	1.17, 0.63 to 2.17	0.133

Continuous variables are reported as the mean±standard deviation. Categorical variables are reported as counts and percentages. Estimates are odds ratios and hazard rates with 95% confidence interval (CI). ECMO indicates extracorporeal membrane oxygenation; E-CABG, European Multicenter Study on Coronary Artery Bypass Grafting; IABP, intra-aortic balloon pump; KDIGO, Kidney Disease Improving Global Outcomes; PCI, percutaneous coronary intervention.
*Patients with chronic kidney disease class 5 excluded from the analysis.

Number of Coronary Vessels Previously Treated by PCI and Outcome After CABG

For the purpose of this study, the coronary system was divided into 3 main coronary vessels: the left anterior descending coronary artery, the circumflex coronary artery, and the right coronary artery. PCI was considered multiple when performed in >1 of these main coronary vessels. For the sake of simplicity and because of the small number of such cases (64 patients, 1.0%), PCI of the left main coronary artery was considered as a procedure involving 2 main coronary vessels. PCI of a single main coronary vessel was performed in 741 patients (11.3%), of 2 main vessels in 320 patients (4.9%), and of 3 main vessels in 106 patients (1.6%) (Table 3). The crude hospital/30-day mortality rates in these study cohorts were 1.9%, 1.6%, 1.3%, and 3.8%, respectively (Table 4). Despite an increased Euro-SCORE II, particularly in patients who had undergone PCI of all 3 coronary vessels, differences in early mortality and other outcomes were not significantly different in the study cohorts in univariate and multivariable analyses (Table 4).

Adjusted Rates of Hospital/30-Day Mortality

Logistic regression identified age ($P<0.001$), female sex ($P=0.001$), urgency of the procedure ($P<0.0001$), the SYNTAX score ($P=0.003$), left ventricular ejection fraction ≤50% ($P<0.0001$), critical preoperative state ($P=0.005$), ST-elevation myocardial infarction ($P<0.0001$), and estimated glomerular filtration rate ($P<0.0001$) as independent predictors of hospital/30-day mortality. When outcome was adjusted by these independent risk factors, the adjusted hospital/30-day mortality rate was 1.8% in patients without a history of prior PCI, 1.9% in those who underwent 1 PCI, 1.4% after 2 PCIs, and 2.5% after ≥3 PCIs (adjusted $P=0.8$). The adjusted hospital/30-day mortality rate was 1.8% in patients without a history of prior PCI, 2.0% in those who underwent PCI of 1 main coronary vessel, 1.3% after PCI of 2 main vessels, and 3.1% after PCI of 3 main vessels (adjusted $P=0.6$).

Outcomes in Patients With Recent Exposure to P2Y12 Receptor Inhibitors

In view of the increased prevalence of exposure to potent antiplatelets in patients with prior PCI (Tables 1 and 3), a pause of P2Y12 receptor inhibitors less than 5 days before surgery was included in all adjusted analyses of this study. When adjusted for the number of prior PCIs and all risk factors listed in the Statistical Analysis section, a pause of P2Y12 receptor inhibitors <5 days before surgery was not associated with increased risk of early death ($P=0.5$),

Table 3. Baseline Characteristics and Operative Data According to the Number of Main Coronary Vessels Treated by PCI

Covariates	No Prior PCI (5382 Pts)	Prior PCI on 1 Main Coronary Vessel (741 Pts)	Prior PCI on 2 Main Coronary Vessels (320 Pts)	Prior PCI on 3 Main Coronary Vessels (106 Pts)	*P* Value
Baseline risk factors					
Age, y	67.8±9.3	66.2±9.7	67.1±8.9	66.4±9.0	<0.0001
Female	915 (17.0)	114 (15.4)	40 (12.5)	16 (15.1)	0.035
Body mass index	27.5±4.1	27.5±4.2	28.0±4.4	27.0±4.3	0.185
eGFR, mL/min per 1.73 m^2	76±20	77±20	74±22	73±23	0.248
Dialysis	54 (1.0)	9 (1.2)	7 (2.2)	4 (3.8)	0.003
Anemia	1202 (22.4)	156 (21.1)	85 (26.6)	32 (30.2)	0.064
Diabetes mellitus	1632 (30.3)	249 (33.6)	123 (38.4)	42 (39.6)	<0.0001
Acute coronary syndrome	2630 (48.9)	341 (46.0)	141 (44.1)	57 (53.8)	0.264
Recent STEMI	293 (5.4)	55 (7.4)	13 (4.1)	7 (6.6)	0.573
Prior stroke/TIA	319 (5.9)	42 (5.7)	25 (7.8)	9 (8.5)	0.168
Atrial fibrillation	442 (8.2)	50 (6.7)	29 (9.1)	16 (15.1)	0.228
Pulmonary disease	529 (9.8)	72 (9.7)	35 (10.9)	8 (7.5)	0.943
Extracardiac arteriopathy	1207 (22.4)	172 (23.2)	91 (28.4)	23 (21.7)	0.092
Prior cardiac surgery	20 (0.4)	8 (1.1)	4 (1.3)	3 (2.8)	<0.0001
Left ventricular ejection fraction ≤50%	1517 (28.2)	202 (27.3)	98 (30.6)	32 (30.5)	0.507
Critical preoperative state	359 (6.7)	34 (4.6)	17 (5.3)	7 (6.6)	0.119
Urgency of the procedure					<0.0001
Urgent	2253 (41.9)	250 (33.7)	110 (34.4)	46 (43.8)	
Emergency	259 (4.8)	19 (2.6)	12 (3.8)	5 (4.8)	
P2Y12 receptor inhibitors pause <5 d	66.3 (12.3)	154 (20.8)	67 (20.9)	26 (24.5)	<0.0001
Indication for surgery					
In-stent restenosis	…	221 (29.8)	149 (46.9)	69 (65.1)	<0.0001
Stent thrombosis	…	43 (5.8)	31 (9.7)	7 (6.6)	<0.0001
Coronary artery disease progression	…	545 (73.5)	267 (83.7)	86 (81.1)	<0.0001
Left main coronary artery PCI	…	10 (1.3)	20 (6.3)	33 (31.1)	<0.0001
Any drug-eluting stent	…	378 (52.4)	206 (65.0)	86 (81.9)	<0.0001
Delay from last PCI, y	…	5.9±6.0	5.7±5.3	3.7±4.3	0.003
SYNTAX score	29±12	26±11	28±12	27±13	<0.0001
EuroSCORE II, %	2.8±4.1	2.5±4.0	2.8±4.4	3.2±4.2	<0.0001
Operative data					
No. of distal anastomoses	2.8±0.9	2.5±0.9	2.6±0.9	2.4±0.9	<0.0001
Cardiopulmonary bypass time, min	86±36	79±32	82±31	83±39	0.066
Aortic clamping time, minute	58±26	55±25	56±24	58±28	<0.0001
Off-pump surgery	1024 (19.0)	182 (24.6)	82 (25.6)	29 (27.4)	<0.0001
Bilateral internal mammary artery grafts	2022 (37.6)	306 (41.3)	121 (37.8)	29 (27.4)	0.747

Continuous variables are reported as the mean±standard deviation. Categorical variables are reported as counts and percentages. Anemia is defined as baseline hemoglobin concentration <12.0 g/L in women and <13.0 g/L in men. Clinical variables are according to the EuroSCORE II definition criteria. eGFR indicates estimated glomerular filtration rate according to the Modification of Diet in Renal Disease equation; EuroSCORE, European System for Cardiac Operative Risk Evaluation; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery; TIA, transient ischemic attack.

intermediate death (*P*=0.6), stroke (*P*=0.6), length of intensive care unit stay (*P*=1.0), and postoperative insertion of intra-aortic balloon pump and/or extracorporeal membrane oxygenation (*P*=0.07). However, a pause of P2Y12 receptor inhibitors <5 days before surgery was an independent predictor of severe/massive bleeding (*P*<0.0001; OR, 1.933,

Table 4. Outcomes According to the Number of Main Coronary Vessels Treated by PCI

	No Prior PCI (5382 Pts)	Prior PCI on 1 Main Coronary Vessel (741 Pts)	Prior PCI on 2 Main Coronary Vessels (320 Pts)	Prior PCI on 3 Main Coronary Vessels (106 Pts)	Univariate/Multivariate Analysis *P* Value
Hospital/30-d death	103 (1.9)	12 (1.6)	4 (1.3)	4 (3.8)	0.989
Adjusted risk estimates	Reference	1.10, 0.59 to 2.05	0.70, 0.25 to 2.00	1.94, 0.65 to 5.78	0.559
1-y mortality, %	3.5	2.7	4.9	6.1	0.284
Adjusted risk estimates	Reference	0.81, 0.52 to 1.28	1.19, 0.70 to 2.02	1.38, 0.61 to 3.15	0.581
Intensive care unit stay, d	2.9±4.5	2.7±3.2	3.1±4.8	2.4±1.9	0.678
Adjusted risk estimates	Reference	−0.03, −0.37 to 0.31	0.26, −0.23 to 0.75	0.51, −1.35 to 0.33	0.984
Stroke	62 (1.2)	7 (0.9)	3 (0.9)	2 (1.9)	0.970
Adjusted risk estimates	Reference	0.98, 0.44 to 2.16	0.89, 0.28 to 2.88	1.64, 0.38 to 7.05	0.919
Postoperative IABP or ECMO	263 (4.9)	23 (3.1)	10 (3.1)	5 (4.7)	0.057
Adjusted risk estimates	Reference	0.75, 0.48 to 1.18	0.69, 0.36 to 1.34	0.86, 0.33 to 2.25	0.457
KDIGO acute kidney injury*	1204 (22.8)	158 (21.6)	68 (21.9)	15 (14.9)	0.113
Adjusted risk estimates	Reference	0.97, 0.80 to 1.18	0.92, 0.70 to 1.22	0.57, 0.33 to 1.00	0.248
Renal replacement therapy*	95 (1.8)	10 (1.4)	6 (1.9)	4 (3.9)	0.504
Adjusted risk estimates	Reference	0.88, 0.45 to 1.71	1.11, 0.47 to 2.58	2.34, 0.82 to 6.68	0.416
E-CABG bleeding grades 2 to 3	344 (6.4)	54 (7.3)	25 (7.8)	11 (10.4)	0.052
Adjusted risk estimates	Reference	1.29, 0.94 to 1.76	1.28, 0.82 to 1.98	1.49, 0.73 to 2.86	0.243

Continuous variables are reported as the mean±standard deviation. Categorical variables are reported as counts and percentages. Estimates are odds ratios and hazard rates with their related 95% confidence interval (CI). E-CABG indicates European Multicenter Study on Coronary Artery Bypass Grafting; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; KDIGO, Kidney Disease Improving Global Outcomes; PCI, percutaneous coronary intervention.
*Patients with chronic kidney disease class 5 excluded from the analysis.

95% CI, 1.524–2.452) and KDIGO acute kidney injury (*P*=0.001; OR, 1.319, 95% CI, 1.116–1.559), and it showed a trend toward increased risk of postoperative dialysis (*P*=0.052; OR, 1.569, 95% CI, 0.998–2.428).

Discussion

The E-CABG registry is a prospective, multicenter study, which was designed to specifically address the impact of prior PCI on the outcome after CABG by collecting data on the timing, type, and number of PCIs, along with the severity of coronary artery disease quantified by the SYNTAX score. This analysis showed that early outcomes of patients undergoing isolated CABG are not jeopardized by multiple prior PCIs. Although we decided to exclude patients undergoing CABG soon after PCI, analysis of this larger series adjusted for EuroSCORE II also showed that CABG performed soon after PCI can be performed without increased risk of death. Overall, these findings have important clinical implications, as CABG is performed in a large number of patients with prior PCI[7] and seems to be a valid revascularization strategy even after failure of multiple stents and/or progression of coronary artery disease. Importantly, patients who had a history of ≥3 prior PCIs or in whom PCI was performed in all 3 main coronary arteries had a significantly higher estimated operative risk compared with patients without a history of prior PCI and to those with a history of 1 or 2 prior PCIs (Tables 1 and 3). Despite their incremental estimated operative risk, the rates of adverse events in these patients was numerically higher than those of the other study cohorts, but the difference did not reach statistical significance (Tables 2 and 4).

Data on the prognostic impact of multiple PCIs are scant. Thielmann et al[8] showed that multiple prior PCIs increased the risk of early mortality and major cardiac and cardiovascular events in a single center series. The same authors evaluated the impact of multiple prior PCIs in patients undergoing CABG from a large multicenter series.[4] The authors demonstrated that ≥2 prior PCIs were associated with significantly increased risk of in-hospital mortality (adjusted OR, 2.02; 95% CI, 1.36–2.99) and major cardiac and cardiovascular events (adjusted OR, 1.51; 95% CI, 1.17–1.93) after CABG. Similar findings were observed in propensity score matching analysis, even if the authors did not report the characteristics of the matched populations. However, this study most likely also included patients who underwent CABG early after PCI, and this might introduce a bias related to the characteristics of patients with early PCI failure. Importantly,

patients were operated on from 2000 to 2005, and PCIs were performed with previous generations' stent technology and secondary prevention strategy. Furthermore, that study was retrospective and the outcome of patients was not adjusted for the extent of coronary artery disease. Indeed, the present study showed that SYNTAX score was an independent predictor of hospital/30-day death and therefore is a confounding factor in the analysis of the outcome of these patients.

A few studies showed that multiple prior PCIs do not have an impact on early mortality. Mannacio et al[9] showed that multiple PCI was not associated with increased risk of hospital death, but it increased the risk of major cardiac and cardiovascular events. However, the authors reported an increased risk of 5-year mortality and 3-year cardiac mortality in patients with multiple prior PCIs.[9] In the study by Stevens et al,[10] 30-day mortality after CABG was no different in patients with 1 versus multiple PCIs (1.2% versus 0.9%; P=0.8).

In this study, we observed that patients with an increasing number of prior PCIs and branches treated had an increased prevalence of pause of P2Y12 receptor inhibitors <5 days before CABG, which did not affect the early and intermediate survival, but significantly increased the risk of postoperative acute kidney injury and severe bleeding. Indeed, a trend toward increased risk of severe/massive bleeding was also observed in patients with any prior PCI compared with those without a history of PCI (7.8% versus 6.4%; adjusted P=0.06; OR 1.284, 95% CI, 0.989–1.667). Such complications may in turn unfavorably impact the late outcome of these patients.

The present study has several limitations. First, despite the fact that this is a large multicenter study, it is not powered to detect differences in the outcome of patients who previously underwent >1 PCI or in whom PCI was performed in 2 or 3 main coronary arteries. Second, we do not have any information on the length of stented vessels, which might have an impact on the feasibility of surgical revascularization as well as on the choice of grafts and site of anastomosis. Third, these outcomes were adjusted for the SYNTAX score, but most likely this angiographic score may not define to what extent the side branches and collateral circulation was affected by PCI. Fourth, these findings may not apply to patients undergoing CABG combined with heart valve and/or aortic procedures. In fact, exclusion of side branches and collateral circulation during PCI may have clinical significance in terms of myocardial protection in patients undergoing combined surgical procedures and requiring prolonged aortic cross-clamp time. Still, occlusion of side branches occurring after PCI is often clinically silent and occluded branches can be found patent at later angiography.[11] Fifth, the short follow-up of this series does not allow an analysis of the long-term impact of multiple prior PCIs in these patients. Finally, the present results are conditional to survival after PCI and should not be viewed as a support for a policy of multiple PCIs as opposed to earlier CABG.

In conclusion, this prospective, multicenter study specifically addressed the impact of prior PCIs and showed that having undergone multiple prior PCIs is not associated with poorer early outcome in patients undergoing isolated CABG.

Disclosures

None.

References

1. O'Brien SM, Feng L, He X, Xian Y, Jacobs JP, Badhwar V, Kurlansky PA, Furnary AP, Cleveland JC Jr, Lobdell KW, Vassileva C, Wyler von Ballmoos MC, Thourani VH, Rankin JS, Edgerton JR, D'Agostino RS, Desai ND, Edwards FH, Shahian DM. The Society of Thoracic Surgeons 2018 adult cardiac surgery risk models: part 2—statistical methods and results. *Ann Thorac Surg*. 2018;105:1419–1428.
2. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP; Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1—coronary artery bypass grafting surgery. *Ann Thorac Surg*. 2009;88(1 suppl):S2–S22.
3. Mariscalco G, Rosato S, Serraino GF, Maselli D, Dalén M, Airaksinen JKE, Reichart D, Zanobini M, Onorati F, De Feo M, Gherli R, Santarpino G, Rubino AS, Gatti G, Nicolini F, Santini F, Perrotti A, Bruno VD, Ruggieri VG, Biancari F. Prior percutaneous coronary intervention and mortality in patients undergoing surgical myocardial revascularization: results from the E-CABG (European Multicenter Study on Coronary Artery Bypass Grafting) with a systematic review and meta-analysis. *Circ Cardiovasc Interv*. 2018;11:e005650.
4. Massoudy P, Thielmann M, Lehmann N, Marr A, Kleikamp G, Maleszka A, Zittermann A, Körfer R, Radu M, Krian A, Litmathe J, Gams E, Sezer O, Scheld H, Schiller W, Welz A, Dohmen G, Autschbach R, Slottosch I, Wahlers T, Neuhäuser M, Jöckel KH, Jakob H. Impact of prior percutaneous coronary intervention on the outcome of coronary artery bypass surgery: a multicenter analysis. *J Thorac Cardiovasc Surg*. 2009;137:840–845.
5. Biancari F, Ruggieri VG, Perrotti A, Svenarud P, Dalén M, Onorati F, Faggian G, Santarpino G, Maselli D, Dominici C, Nardella S, Musumeci F, Gherli R, Mariscalco G, Masala N, Rubino AS, Mignosa C, De Feo M, Della Corte A, Bancone C, Chocron S, Gatti G, Gherli T, Kinnunen EM, Juvonen T. European multicenter study on coronary artery bypass grafting (E-CABG registry): study protocol for a prospective clinical registry and proposal of classification of postoperative complications. *J Cardiothorac Surg*. 2015;10:90.
6. Acute Kidney Injury Work Group. Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for acute kidney injury. *Kidney Int*. 2012;2:1–138.
7. Gardner TJ, Garratt KN. Percutaneous catheter interventions followed by coronary artery bypass grafting: primum non nocere. *Circ Cardiovasc Interv*. 2018;11:e006398.
8. Thielmann M, Leyh R, Massoudy P, Neuhäuser M, Aleksic I, Kamler M, Herold U, Piotrowski J, Jakob H. Prognostic significance of multiple previous percutaneous coronary interventions in patients undergoing elective coronary artery bypass surgery. *Circulation*. 2006;114(1 suppl):I441–I447.
9. Mannacio V, Di Tommaso L, De Amicis V, Lucchetti V, Pepino P, Musumeci F, Vosa C. Previous percutaneous coronary interventions increase mortality and morbidity after coronary surgery. *Ann Thorac Surg*. 2012;93:1956–1962.
10. Stevens LM, Khairy P, Agnihotri AK. Coronary artery bypass grafting after recent or remote percutaneous coronary intervention in the Commonwealth of Massachusetts. *Circ Cardiovasc Interv*. 2010;3:460–467.
11. Alfonso F, Hernández C, Pérez-Vizcayno MJ, Hernández R, Fernández-Ortíz A, Escaned J, Bañuelos C, Sabaté M, Sanmartín M, Fernández C, Macaya C. Fate of stent-related side branches after coronary intervention in patients with in-stent restenosis. *J Am Coll Cardiol*. 2000;36:1549–1556.