Coronary artery bypass grafting vs percutaneous coronary intervention in a ‘real-world’ setting: a comparative effectiveness study based on propensity score-matched cohorts†

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OBJECTIVES: Most studies comparing coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCI) showed that fewer patients who had undergone CABG required repeat revascularizations, but no difference in survival, with the exception of some subgroups of patients. However, long-term real-world evidence on patients in whom both procedures are technically feasible is yet not available. The aim of this study was to compare 5-year rates of death, myocardial infarction (MI), target vessel revascularization (TVR) and stroke in a large cohort of patients with left main coronary artery (LMCA) or multivessel disease, treated with CABG or PCI (with or without DES) or PCI with DES only.

METHODS: Two propensity score (PS)-matched cohorts of patients undergoing revascularization procedures at the regional public and private centres of Emilia-Romagna over the period July 2002–December 2008 were used to compare long-term outcomes of PCI (6246 patients) and CABG (5504 patients).

RESULTS: PCI was associated with higher risk of death (HR = 1.6; 95% CI 1.4–1.8, P < 0.0001), MI (HR = 3.3; 95% CI 2.7–4.0, P < 0.0001) and TVR (HR = 4.5; 95% CI 3.8–5.2, P < 0.0001) at 5 years. No significant difference was shown for stroke (HR = 1.1; 95% CI 0.9–1.4, P = 0.43). CABG benefit was more evident in the risk of death in patients with two-vessel disease plus LMCA and in those with three-vessel disease, LVEF <35%, congestive heart failure and diabetes. Adjusted comparison with PS between PCI with DES only and CABG confirmed significant differences in favour of CABG for mortality, MI and TVR rates. Competing risk analysis showed that the difference in the mortality rate was due to higher rate of MI in PCI.

CONCLUSIONS: In the ‘real-world’ setting of this study, CABG was associated with significantly lower rates of death, MI and TVR in patients with LMCA or multivessel disease, so it remains the standard of care, particularly for patients with more extensive coronary disease and diabetes.

Keywords: Cardiac surgery • Coronary artery bypass grafting • Percutaneous coronary angioplasty

INTRODUCTION

Although technological innovation (i.e. drug-eluting stents, DES) has led clinical practice to favour percutaneous coronary intervention (PCI) over coronary artery bypass grafting (CABG) [1], in terms of available evidence, the management of patients to be referred to revascularization procedures is much more controversial.

Similar mortality or morbidity rates for CABG and PCI with DES have been shown in several observational studies [2–4]. Other registry studies have found a higher mortality rate after PCI [5–7]; however, length of follow-up in those studies was never longer than 3 years. Randomized, controlled trials comparing these two treatment strategies had longer follow-up, but most of them preceded the introduction of DES [8–10]. In the post-DES era, the results of the SYNTAX trial confirmed better
outcomes, in terms of major adverse cardiac and cerebrovascular events, of CABG at 3 years, in the treatment of most patients with three-vessel and left main coronary artery (LMCA) disease, particularly in cases of severe artery disease [11]. However, long-term real-world evidence on patients in whom both procedures are technically feasible is not yet available.

This study was aimed at investigating the comparative effectiveness of CABG and PCI or DES only, on large cohorts of patients with similar probability of treatment assignment. The main purpose of the study was to assess 5-year outcomes (death, myocardial infarction (MI), target vessel revascularization (TVR) and stroke); the second goal was to identify those subgroups of patients, eligible for both procedures, who present crucial risk factors for death.

**MATERIALS AND METHODS**

Emilia-Romagna (ER) is an Italian region with about 4 million inhabitants, where six hospitals (two public and four private) perform both cardiac surgery and interventional cardiology and 10 hospitals (six public and four private) perform only interventional cardiology.

Two databases were primarily used for this study: the Regional Registry of Coronary Angioplasties (REAL) and the Regional Registry of Cardiac Surgery (RERIC), both administered by the regional Agency for Health and Social Care. Both databases prospectively include all the patients undergoing revascularization procedures and were described elsewhere [12, 13].

Further information on events following hospital discharge was obtained by matching the patients from the above registries with their corresponding records in two other regional data sources: the Mortality Registry and the Database of Hospital Admissions. The latter was also used to complement and cross-check some information from REAL and RERIC.

**Study population**

The study includes all patients affected by LMCA or at least two other coronary vessels treated with PCI or CABG from 1 July 2002 to 31 December 2008. Patients were excluded from the analysis if they had associated valve disease, previously undergone coronary revascularization, had a recent (<24 h) STEMI, or were in shock. Additional exclusion criteria were patients not resident in the ER (administrative follow-up not feasible) and the presence of incomplete information about baseline and procedural characteristics (Fig. 1). The remaining 11,750 patients, 6,246 receiving PCI and 5,504 undergoing CABG, were followed through December 2010.

**Procedures**

Decisions about the type of treatment were taken according to local practices, and there were no standard regional protocols. The choice between bare metal stents (BMS) or DES and type of DES (i.e. sirolimus-eluting or paclitaxel-eluting stents) was left to the cardiologist’s discretion. All patients undergoing PCI were prescribed aspirin plus clopidogrel (loading dose, 300 or 600 mg) before or during the coronary intervention. After the procedure, aspirin was continued indefinitely. Clopidogrel was prescribed for patients treated with DES for at least 6 months, regardless of DES type. Clopidogrel treatment beyond this duration was at the discretion of the physician. The choice of CABG technique, performed with the use of extracorporeal circulation or off-pump, was left to the surgeon’s discretion. Whenever possible, the left internal thoracic artery was used preferentially for revascularization of the left anterior descending artery (LAD). Complete revascularization was performed with other arterial conduits or saphenous vein grafts.

Follow-up angiography was not performed routinely in either group of patients.

**Outcomes**

Outcomes considered were death (during the index hospital admission or thereafter), acute MI, stroke and repeat revascularization (PCI or CABG). Information on the occurrence of these events was retrieved through the regional mortality registry, the regional hospital admission database and the regional CABG and PCI registries. Death included mortality from all causes. Acute MI was defined as any hospital admission occurring after the index procedure with a principal diagnosis of MI. Stroke included complications at the index admission and further hospital admissions with stroke as the principal diagnosis. Repeat revascularization included CABG or PCI on the targeted vessel occurring during follow-up. In order to account for staged PCI in multivessel patients, we evaluated only repeat PCI occurring after 45 days from the index procedure.

**Statistical analysis**

Prevalence of risk factors and demographic and clinical features of the patients in both groups were compared by the χ² test and Fisher’s exact test.

Propensity score (PS) matching was used to reduce the effect of treatment-selection bias. PS, which is the probability of treatment assignment conditional on observed baseline characteristics, was estimated by multivariate logistic regression analysis [14] with a binary dependent variable representing PCI vs CABG. Independent variables included demographics, the available clinical potential risk factors and year of procedure. Each missing value for three variables (smoking, family history of coronary artery disease, hypertension) was treated as an additional category. Patients were matched on the logit of the PS using a caliper of width equal to 0.25 standard deviations of the logit of PS.

Appropriateness of the specification of the PS was assessed by examining the degree to which matching on the estimated PS resulted in a matched sample in which the distribution of measured baseline covariates was similar between the two types of treatment [15].

To detect imbalances in baseline covariates, standardized differences were used. Standardized differences represent the difference in means between the two groups in units of standard deviation, do not depend on the unit of measurement and are not influenced by sample size. Standardized differences of <0.10 (10%) are likely to indicate a negligible imbalance between the two groups [16, 17].

Kaplan–Meier estimates were used to plot the rates of the four long-term adverse events, and differences between risk curves were assessed using the Klein–Moeschberger test for matched pairs [18]. For each adverse outcome, the hazard ratio of PCI vs
CABG was estimated through Cox proportional hazard models with robust standard errors, to account for clustering in matched pairs.

Furthermore, to take into account the effect of ‘competing risk’, the cumulative incidence function of death and of TVR was estimated, considering the risk of postoperative acute MI as competing risk. The significance of their differences was evaluated by the Pepe and Mori test [19, 20].

To compare the long-term mortality in subgroups, a PS-matched sample was calculated for each subgroup, and Cox proportional hazard models with robust standard errors were performed to estimate hazard ratio of PCI vs CABG. The consistency of treatment effects in prespecified subgroups (age <61 years, age 61–75 years, age >75 years, female, male, only LMCA, two-vessel disease without LMCA, two-vessel disease with LMCA, three-vessel disease without LMCA, three-vessel disease with LMCA, LVEF ≥35%, LVEF <35%, previous MI, congestive heart failure, unstable angina or NSTEMI, familiarity for CAD, diabetes, hypertension, smoking, cerebrovascular disease, peripheral vascular disease, renal failure, chronic obstructive pulmonary disease, malignancy, ulcer) was assessed using Cox regression models.

All the analyses were performed with SAS version 9.1

RESULTS

Overall, 11,750 patients were included, 6246 and 5504 undergoing PCI and CABG, respectively. CABG patients were on average older, although the proportion of patients with age >75 years was higher in the PCI group. PCI patients were more frequently female and had a higher clinical risk profile than CABG patients. In the CABG group, the proportion of patients with LMCA disease, with or without additional diseased vessels, was higher, and patients with the most severe angiographic risk profile (three-vessel and LMCA disease) were 1772 (32.2%) and 162 (2.6%) for CABG and PCI, respectively (Table 1).

Among PCI patients, 3120 (50%) received BMS only and 3126 (50%) were treated with DES. Particularly, 1584 (25.4%) patients underwent multivessel coronary revascularization with DES only. In the group of patients treated with DES, 1776 (53.6%) patients received sirolimus-eluting stents and 1450 (46.4%), paclitaxel-eluting stents. The mean number of stents used was 2.6 ± 1.24. In the CABG group, 276 (5%) patients underwent off-pump surgery and 5162 (93.8%) received one internal thoracic artery that was used in the revascularization of the LAD artery. The mean number of bypass grafts was 3.2 ± 0.97 per patient.

All the initially observed differences balanced out in the two groups after matching: standardized differences were lower than 0.10 (see Table 1). Matching on estimated PS made available a matched cohort of 5524 patients, 2762 for each group, with similar demographic, clinical and angiographic risk profiles. Moreover, the PS analysis allowed us to pull out a cohort of 1216 patients from the subgroup of 1584 patients treated with DES only, matched with 1216 CABG patients with similar demographic, clinical and angiographic risk profiles.

Follow-up and outcomes

Follow-up times ranged from 24 to 108 months. The mean follow-up was 1827 ± 617 days for all cases and 1822 ± 601 days for the matched sample (1736 ± 525 days in the PCI group and 1904 ± 655 days in the CABG group). There were no significant differences between the two groups in the crude rates of 30-day mortality (1.9% for PCI and 1.5% for CABG, P = 0.07).

During the entire study period, 1662 patients died (999 in the PCI group and 663 in the CABG group), and 958 MIs (731 PCI patients and 227 CABG patients) and 485 strokes (243 in the PCI group and
The Kaplan–Meier risk curves at 5 years are reported in Figure 2. The cumulative incidence curves of death in the two cohorts proved similar during the follow-up period (P = 0.92) (Fig. 3). Moreover, separating the risk of TVR from the risk of MI, TVR rates estimated at 5 years were lower than the corresponding Kaplan–Meier estimates, but remained significantly different between the two treatments (Fig. 3).

Subgroup analyses

In the PS-matched cohort of patients treated with DES, the Kaplan–Meier risk curves at 5 years confirmed significant differences between PCI and CABG in the rates of mortality for all causes, MI and TVR and no significant difference for stroke (Fig. 2). Furthermore, considering death and MI as competing risks, in this cohort, the risk of death in the two arms also proved similar during the follow-up period (P = 0.41) (Fig. 3).
Figure 4 shows the hazard ratios for death for PCI vs CABG in the PS-matched subgroups of patients identified by their demographic and clinical characteristics. In every subgroup, the risk of death for PCI was significantly higher than for CABG, excluding the subgroups of malignancy and patients with LMCA plus one-vessel disease or two-vessel disease without LMCA. The

Figure 2: Kaplan–Meier risk curves between CABG and PCI.
subgroups in which CABG more clearly reduced the risk of death were two- or three-vessel disease plus LMCA, LVEF <35%, congestive heart failure and diabetes.

**DISCUSSION**

In this study, patients treated with CABG reported significantly lower 5-year rates of death, MI and TVR than those undergoing PCI. CABG benefit was more evident in reducing the risk of death in patients with two-vessel disease plus LMCA, three-vessel disease associated or not with LMCA, LVEF <35%, congestive heart failure and diabetes.

In the anatomical subgroups of patients with LMCA plus one-vessel disease or two-vessel disease without LMCA, differences in mortality rates between both treatment groups showed a trend towards better outcome with CABG, although statistical significance was not reached. Finally, PS matching between patients treated with DES only and similar patients treated with CABG confirmed significant differences in favour of CABG in rates of mortality for all causes, MI and TVR. No significant difference was found for stroke.

Patients with LMCA or multivessel disease constitute a challenging treatment group, often with significant comorbidities that increase the risk of mortality and healthcare costs. The New York State registry study [5] found that CABG is associated with lower rates of death or MI and repeat revascularization than PCI with DES. This advantage was also clear among patients with two-vessel disease, either with or without involvement of the proximal LAD artery. However, no information was provided in that study about the LMCA treatment, those patients being excluded from the study. In the same study, many of the repeat revascularizations for the patients treated with DES were performed in the first 60 days after the index procedure, suggesting that most of these events were staged interventions and not real target-vessel failure. In our study, in order to account for staged PCI in multivessel patients, we evaluated only repeat PCI occurring after 45 days from the index procedure, and reported that PCI with or without DES was associated with a significantly higher TVR rate. Moreover, separating the risk of TVR from that of acute MI as a competing risk, our study found that the TVR rate remained significantly higher in the PCI group, depending on the native coronary disease progression and recurrence of angina, well described in the long-term follow-up after PCI [21]. The higher MI rate reported in the PCI group probably influenced the occurrence of death. To verify this hypothesis, we separated the risk of death from that of MI, considering them as competing risks. The cumulative incidence curves of death in the two cohorts were the same during the follow-up period. This could mean that the higher mortality rate estimated for the PCI group is related to the higher MI rate.

Recently, the 3-year follow-up data of the SYNTAX Trial were published [11]. Similar to the 1-year outcomes [22], the MACCE rate in CABG patients proved significantly lower, mostly due to the higher cumulative rate of repeat revascularization for PCI in comparison with CABG. In contrast to the 1-year outcomes, at 3-year follow-up, the differences in cerebrovascular events between treatments were no longer significant. In subgroup analyses, PCI demonstrated unsatisfactory results for patients with isolated three-vessel disease, with an evident survival benefit of surgery demonstrated for the first time. The study showed no significant major differences in mortality or MI rates between PCI and CABG, either in the treatment of LMCA alone or associated with one- or two-vessel disease, and a higher incidence of stroke in the CABG subgroup.

Safety outcomes reported in our study are substantially in agreement with the 3-year results of the SYNTAX Trial. Stroke remains an event that negatively influences the long-term outcome of patients after coronary artery revascularization. During the entire study period, 259 strokes occurred in the PCI...
group and 296 occurred in the CABG group, without statistical significance. These findings underline the necessity of improving perioperative management in order to reduce the occurrence of this adverse event after surgery in the future [23].

Recently, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease Trial results have been published [24, 25], confirming the benefit of CABG in multivessel, diabetic patients. This randomized trial was designed with the aim of comparing PCI with DES and CABG in diabetic patients affected by multivessel coronary artery disease. The primary outcome measure was a composite of death from any cause, non-fatal MI or non-fatal stroke. It resulted less frequently in the CABG group, and related to the significant differences in rates of both MI and death from any cause reported between two arms of the study. However, stroke remained more frequent in the surgical group.

The results from the EXCEL (Evaluation of Xience Prime vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization), and BEST (Bypass Surgery Versus Everolimus-Eluting Stent Implantation for Multivessel Coronary Artery Disease) trials will provide important insights for the optimal treatment of LMCA and multivessel patients. The impact of a new generation of stents and the continued improvements in PCI techniques will be evaluated in these studies.

The limitations of a retrospective registry study should be noted. Hidden biases are often claimed as an explanation for the apparent superiority of CABG over PCI. According to this claim, clinicians allocate ‘frailer’ patients to PCI while the measured covariates do not capture this frailty. Factors precluding CABG include coexisting conditions that are linked to poor prognosis, like malignancy, whereas factors that contraindicate PCI are often ‘lesion based’, like chronic vessel occlusion, and may have a
smaller effect on long-term outcome after CABG. Moreover, our Registry also included patients treated by BMS because they are still widely used at the clinicians’ discretion and are part of the current alternative options to CABG. Finally, the definition of some endpoints like MI or stroke was based on the main diagnosis entered in the databases of hospital admissions and not on an adjudication process founded on objective criteria. This limitation is related to the specific design of a registry observational study, and it could explain the different results reported with respect to randomized trials in which strong predefined criteria are used.

In conclusion, this is very large registry series of patients with long-term follow-up. At 5 years, CABG was associated with significantly lower rates of mortality, MI and TVR in patients with LMCA or multivessel disease than PCI, and it remains the standard of care, particularly for patients with more complex anatomy. PS matching was used to reduce the effect of treatment-selection bias and potential confounding. The large cohorts of patients derived from PS-matching guarantee a broad reliability of our results, in the analysis of both the overall population and the subgroup of patients treated with DES. The competing risk analysis yielded the important new result of identifying MI as the true cause of higher adverse events associated with PCI. The results obtained in the analysis of the demographic, anatomic and clinical subgroups of patients were detailed enough to allow closer evaluation of the effects of both PCI and CABG.

The SYNTAX trial set up an interdisciplinary heart team for the first time. Our findings also support the view that collaboration between cardiologists and cardiac surgeons is essential at scientific conferences, but particularly in routine care, in order to identify the optimal revascularization strategy for individual patients.

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REFERENCES

APPENDIX. CONFERENCE DISCUSSION

**Dr T. Graham (Birmingham, UK):** Dr Nicolini and his colleagues have presented a real-world study looking at CABG against percutaneous coronary intervention on behalf of both the REAL and the RERIC investigators. The aim of this study was to compare five-year rates of death, myocardial infarction, target vessel revascularization and stroke. There is an impressive number of patients, 11,750, from whom two propensity scored matched cohorts, each consisting of 2,800 patients, were studied.

PCI was associated with a higher risk of death and, interestingly, this risk analysis has shown that the difference in the mortality rate was due to a higher rate of myocardial infarction in the PCI group. I have three questions or themes that I would like Dr Nicolini to consider, and will take these in order. First of all, studies like this are very dependent upon having validated data. So how confident were you about the long-term data which you received from the two registries and how was this data validated?

**Dr Nicolini:** This is a retrospective registry analysis. Obviously this paper and this type of statistical analysis have a severe limitation related to the design of the study. I think that the key points of this study are the large number of patients and the long-term follow-up, as you say. It is important that the results of this study have been obtained by a neutral statistical institution, that is the Regional Agency for Health and Social Care. I think this is the most important point for the validation of this study.

**Dr Graham:** The next point I would just like to explore with you is your description of this as a “real-world” study. If you look at the CABG subgroup, was it possible to identify any different outcomes, for example in patients who had total arterial revascularization or off-pump surgery, and has this study influenced a change in local cardiological practice in relation to PCI?

**Dr Nicolini:** Unfortunately I do not have complete data at the moment on these subsets of patients that you would like to consider. I have no data from the comparison of specific subgroups of patients, namely, patients treated with total arterial revascularization or off-pump surgery, with respect to PCI, because this would be the next step in our analysis. Obviously I agree with you that the next stage in the near future will be to compare these modern techniques of coronary surgery with the results of ongoing clinical trials involving the second generation of drug-eluting stents in order to define the future indications, but I have no data at the moment for this.

**Dr Graham:** Finally, and importantly, one of the best things that has come out of the SYNTAX study in our practice in the UK has been the development of heart teams or multidisciplinary teams to try and come up with the best management plan for individual patients. So I am interested to know whether undertaking this study, and the subsequent results that have come from it, has influenced or affected the development and the organization of your local and your regional heart teams in a multidisciplinary fashion?

**Dr Nicolini:** We know that the SYNTAX trial set up an interdisciplinary heart team for the first time. We acknowledge (and agree with) the necessity to have frequent heart team conferences in every heart centre. But as we said before, in our region there are a lot of institutions without cardiac surgery units. In all the situations where there is a cardiologist and surgeon, we have adopted the heart team concept, but in all the other institutions where there are only interventional cardiologists, mainly in the past obviously, the decision-making has sometimes been undertaken by the cardiologist alone at the time of patient admission and without any dialogue with the surgeon. I think this was not the best way to decide the optimal strategy for the patient. Obviously, the absence of uniformity in the decision-making for these patients was a limitation of this study, but this is the “real world”.

**Dr G. Laufer (Vienna, Austria):** I think this study also confirms the result from the ASSERT study (also a propensity score matched analysis) from the United States which was presented yesterday and which came to the same conclusion. I have only a brief question. Did you look at, or have any opportunity to look at, the completeness of revascularization in the surgical set? Because in the SYNTAX trial, for example, there was a surprisingly low rate of completeness of revascularization, a little above 60%.

**Dr Nicolini:** I am sorry, but I do not have complete data on the percentage of complete revascularization in both study groups. I have only one, I think, important consideration derived from this study with respect to SYNTAX trial results. I remember that the mean number of stents used in the PCI group of SYNTAX was 4.4. In our real-world population it was 2.6 and probably this is an explanation for the lower completeness of revascularization, and it accounted for the worse results in our PCI group. In fact we know that incomplete revascularization is an important factor determining the outcome of the patients at mid- and long-term follow-up.