ORIGINAL ARTICLE

Description of a methodological approach to verify the outcome-optimization of tailored therapeutic choices and test application to PCI vs. CABG

Stefano Di Bartolomeo[1], Paolo Guastaroba[2], Daniela Fortuna[2], Rossana De Palma[2], Roberto Grilli[2]

1. Regional Agency for Health and Social Care of Emilia-Romagna/Azienda Ospedaliero-Universitaria di Udine, Bologna, Italy. 2. Regional Agency for Health and Social Care of Emilia-Romagna, Italy

Correspondence: Stefano Di Bartolomeo. Address: Regional Agency for Health and Social Care of Emilia-Romagna/Azienda Ospedaliero-Universitaria di Udine, Viale Aldo Moro 21, 40127 Bologna, Italy. E-mail: stefano.dibartolomeo@uniud.it

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Abstract

Background: The scientific evidence guiding the choice between Percutaneous Coronary Intervention (PCI) and Bypass Graft Surgery (CABG) is inconclusive. Yet, tailoring the choice to the patients' characteristics is generally considered important to optimize outcomes.

Objectives: To verify the supposed outcome benefits of tailoring the choice of the revascularization procedure.

Methods: We calculated a propensity score (PS) - i.e. the probability, given the patients' characteristics, of undergoing one of the two alternative procedures - for the 11,750 patients with severe coronary disease who underwent coronary revascularization between 2002 and 2008 in an Italian region. Then we investigated the effect-modification of the PS on the Hazard Ratios (HR) of PCI vs. CABG for death, myocardial infarction, stroke and repeat revascularization with a likelihood ratio test and by visual inspection.

Results: Only the least important outcome (repeat revascularization) significantly differed across deciles of PS (p=0.05) and its graphical trend supported a favorable effect of the decision process.

Conclusions: In agreement with the current scientific uncertainty, but contrary to common opinion, the medical decision process between PCI and CABG based on demographic and clinical factors is marginally capable of optimizing the post-procedural outcomes. The study relies on the assumption that the variables considered by clinicians were among those included in the PS.

Key words

Outcome and process assessment (health care), Coronary disease, Coronary artery bypass, Angioplasty, Patient selection, Propensity score

1 Introduction

When two therapeutic options are alternative, it is important to know whether their outcomes are uniform across all types of patients or change in subgroups having some characteristics. These characteristics then receive careful consideration by the clinicians who decide the indication. In statistical terms, the former condition is called uniformity of effects, while, in the latter, a so-called interaction (or effect-modification) must be present between any of the patient characteristics and the outcome of the therapeutic procedures.

In the case of severe Coronary Artery Disease (CAD) (left main or multivessel involvement) - the scientific evidence [1-9] supporting the interventional choice between Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Graft (CABG) is inconclusive. Uncertainty surrounds not only the ‘best’ technique in absolute terms (i.e. better for all or most patients), but also, more importantly, the effect-modifier factors that could make either technique preferable in the specific patient. For example, in diabetic patients CABG was preferable according to some studies [10], but not to others [11].

Notwithstanding this, tailoring the choice to the patient’s characteristics is often advocated as important for outcome optimization [4], as if the clinicians’ judgment could attain what the literature has not yet demonstrated.

The objective of this study is therefore to verify retrospectively if tailoring the interventional choice to the patient’s characteristics had an actual impact on the outcome of coronary revascularization.

2 Materials and methods

2.1 Setting and sources

Emilia-Romagna is an Italian region with about $4.5*10^6$ inhabitants where six hospitals perform cardiac surgery and interventional cardiology and ten hospitals perform only interventional cardiology and have defined referral policies to one cardiac-surgery facility.

The main data sources for this study were the Regional Registry of Coronary Angioplasties and the Regional Registry of Cardiac Surgery Procedures. The former, established in 2002, collects demographic and clinical data on the procedures performed in all the interventional-cardiology centers of the region and currently contains about 95,000 records. The latter, also established in 2002, gathers similar data from the regional centers of cardiac surgery and currently contains about 36,000 records. More information about these registries is available from previous publications [12, 13].

We obtained further information 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. A regional unique patient identifier facilitated the matching.

2.2 Patient selection

All patients whose left main or at least two other coronary vessels were treated for CAD with PCI or CABG in Emilia Romagna from July/1/2002 to December/31/2008 were eligible.

The exclusion criteria were: missing information on the number of treated vessels, concomitant valvular disease treatment, patient not resident in Emilia Romagna, previous coronary revascularization, recent (<24 hours) ST-elevation myocardial infarction, and moderate to severe valvulopathy or shock. The follow-up extended through December 2010.

Given the observational design of the study and the anonymity of the databases available for analysis, the approval of the ethical committee was not necessary.

2.3 Procedures

The definition of diseased vessel was a stenosis >50%.

Table 1. Distribution of baseline covariates and standardized differences

	PCI N=6246 (N=5593)*	CABG N=5504 (N=4208)*	Standardized Difference*†
Age (%)			
<61 yr	24.3 (24.8)	20.1 (20.4)	10.0 (10.4)
61 to 75 yr	46.7 (47.5)	58.0 (56.6)	-22.5 (-18.2)
>75 yr	28.9 (27.6)	21.9 (22.9)	16.2 (10.9)
Gender (%)			
Male	73.7 (74.7)	80.4 (79.3)	-15.9 (-10.94)
Year of admission (%)			
2002	3.3 (3.1)	8.4 (6.0)	-21.8 (-13.8)
2003	12.0 (12.7)	20.5 (21.7)	-23.2 (-24.1)
2004	15.9 (16.4)	18.4 (18.9)	-6.6 (-6.6)
2005	17.6 (17.4)	14.7 (15.0)	8.0 (6.5)
2006	16.9 (16.5)	13.2 (13.0)	10.4 (9.7)
2007	17.6 (17.7)	13.5 (13.8)	11.2 (10.7)
2008	16.7 (16.2)	11.2 (11.5)	15.6 (13.5)
Hospital (%)			
A	5.3 (5.6)	5.1 (5.2)	0.9 (1.7)
B	2.0 (1.5)	6.2 (1.5)	-21.3 (0.38)
C	5.1 (5.3)	8.8 (9.4)	-14.7 (-15.7)
D	18.0 (18.1)	8.1 (10.4)	29.6 (22.2)
E	3.7 (3.7)	7.4 (5.0)	-16.1 (-6.3)
F	8.7 (7.4)	5.9 (7.6)	10.7 (-0.8)
G	2.3 (2.3)	2.3 (2.8)	0.3 (-2.7)
H	7.1 (7.5)	11.6 (12.4)	15.5 (-16.1)
I	9.7 (9.9)	7.8 (9.6)	7.0 (0.9)
L	6.9 (6.3)	6.7 (6.6)	0.65 (-1.2)
M	15.7 (16.4)	5.0 (6.4)	35.7 (31.9)
N	4.7 (4.9)	7.2 (7.8)	-10.4 (-12.1)
P+Q	2.5 (2.1)	9.6 (6.6)	-30.2 (-22.0)
R+S	8.3 (8.9)	8.4 (8.8)	-0.31 (0.5)
Number and type of diseased vessels (%)			
1, only LMCA	1.71 (0)	0.16 (0)	16.1 (N/A)
2, without LMCA	2.58 (1.8)	1.6 (1.8)	6.6 (-0.1)
2, with LMCA	55.6 (54.3)	13.1 (15.7)	99.9 (88.5)
3, without LMCA	4.9 (5.3)	13.8 (11.5)	-31.0 (-22.6)
3, with LMCA	32.7 (35.8)	39.1 (46.4)	-13.4 (-21.7)
4	2.6 (2.8)	32.2 (24.6)	-84.8 (-66.6)
Ejec. fraction < 35% (%)	6.1 (5.3)	5.3 (5.9)	3.7 (-2.6)
Previous myocardial infarction (%)	19.5 (20.2)	37.1 (37.2)	-39.7 (-38.2)
Congestive heart failure(%)	19.0 (18.2)	19.2 (20.2)	-0.5 (-5.0)
Unstable angina or non-ST-elevation MI (%)	55.8 (54.8)	49.7 (50.2)	12.2 (9.4)
Familiarity of CAD (% of non-missing)	21.6	28.2 (28.5)	N/A
Missing data	10.6 (7.9)	21.2 (14.6)	-29.4 (-19.2)
Diabetes (%)	22.7 (23.2)	26.6 (27.1)	-9.1 (-9.0)
Hypertension (% of non-missing)	76.9 (77.5)	80.7 (81.0)	N/A
Missing data	2.1 (0.8)	2.0 (1.1)	0.3 (-3.4)
Smoking (% of non-missing)	24.1 (22.4)	20.4 (20.0)	N/A
Missing data	4.6 (3.4)	11.0 (7.0)	-24.3 (-16.2)
Cerebrovascular disease (%)	10.9 (10.6)	15.2 (14.5)	-12.7 (-11.8)
Peripheral vascular disease (%)	7.7 (7.3)	12.1 (11.1)	-14.8 (-13.1)
Renal failure (%)	6.3 (5.4)	5.1 (4.8)	5.4 (2.9)
Chronic obstructive pulmonary disease (%)	8.5 (7.7)	9.5 (9.3)	-3.3 (-5.6)
Malignancy diagnosed ≤ 2 yr (%)	5.9 (4.6)	3.4 (3.3)	11.7 (6.4)
Gastric ulcer (%)	1.4 (1.2)	1.0 (1.1)	3.1 (0.7)

* In round brackets the values of cases and percentages within the common support of propensity score (see methods for details); †100(pT1 − pT2)/[pT1*(1 − pT1) + pT2*(1 − pT2)], where pT = proportion of PCI cases and pT2= proportion of CABG cases. A standardized difference greater than 10 per cent represents meaningful imbalance in a given covariate. PCI=Percutaneous coronary intervention, CABG=Coronary artery bypass grafting, LMCA=Left main coronary artery, MI=Myocardial infarction, CAD=Coronary artery disease

All types of stents (i.e. bare metal or sirolimus-eluting or paclitaxel-eluting stent) were used, according to the interventionist's preference.

Standard bypass techniques were used for CABG operations. Whenever possible, the LAD was revascularized with the left internal thoracic artery. Multiple revascularizations were performed when possible with other arterial conduits or saphenous vein grafts.

Neither group of patients underwent routine follow-up angiography.

Repeat revascularization included target vessel revascularization only. In order not to spuriously include staged procedures, we considered only PCIs repeated ⩾45 days from the index one.

2.4 Statistical analysis

The classic definition of propensity score (PS) is the probability that an individual would have received a certain treatment (PCI in this case) based on that individual's observed pretreatment variables [14]. Usually, the PS is applied by various techniques in observational studies to balance covariates and thus control confounding [15] when estimating the effect of the treatment relative to an alternative (e.g. no treatment or another treatment). Propensity models generally assume that this effect is the same for all subjects. However, if the treatment effect depends on patient-specific factors, then its estimate will vary across subgroups with different distributions of these factors [16]. This should be the case of PCI relative to CABG if tailoring the choice to demographic and clinical characteristics could actually optimize the outcomes. More specifically, the outcomes of one procedure relative to the other should improve when the propensity to receive that procedure is higher and, vice versa, worsen with decreasing propensity.

The PS was calculated by a logistic regression model whose binary dependent variable was PCI versus CABG and the independent variables were the demographic and clinical variables shown in Table 1 plus indicator variables for the year of admission and for the centre of the first, diagnostic angiogram. All main effects and first level interactions with stable estimates were included. The final model included 704 terms. The C statistics of this model was 0.912.

Common support was then applied, i.e. the patients of either treatment-group with a PS outside the range of the counterfactual group were excluded. The PS was then recalculated on the remaining cases.

The effects on mortality, MI, repeat revascularization and stroke of PCI vs. CABG across the spectrum of patients' characteristics were assessed by Cox regression. The proportional hazard assumption was verified by examination of the log [-log (survival)] curves and by testing of partial (Schoenfeld) residuals.

The Hazard Ratios (HR) of the various outcomes were calculated in each of the deciles of PS. We then assessed the significance of any difference across these strata with a Likelihood Ratio (LR) test with nine degrees of freedom between a model comprising of treatment (PCI vs. CABG) and PS deciles (nine indicator variables) and another model including also indicator variables for the products (interactions) between treatment and PS deciles. When the absences of events in one treatment group made the estimation impossible, deciles were grouped (deciles 1 and 2 and deciles 9 and 10 for MI, deciles 9 and 10 for revascularization) and the degrees of freedom reduced accordingly.

Missing data were managed by simple imputation (i.e. assigning another level for missing variables) when needed (hypertension, familiarity, smoke history).

3 Results

The characteristics of the whole population (N= 11,750) are shown in Table 1. In the PCI group, more patients were in the extreme classes of age (>75 yr and < 61 yr) and suffered from unstable angina or malignancy. In the CABG group, more patients were in the intermediate (61 to 75 yr) class of age, the number of diseased vessels was larger, more patients had had a previous MI, were males, had cerebral or peripheral vascular disease. Strong differences concerning the year and hospital of admission were also present.

Table 2. Proportion of patients experiencing the various outcomes in each PS decile and by treatment group

PS Decile*	No. of events/total cases							
	Mortality		Myocardial infarction		Repeat revascularization		Stroke	
	PCI	CABG	PCI	CABG	PCI	CABG	PCI	CABG
1	5/17	106/964	0/17	44/964	6/17	79/964	1/17	46/964
2	15/71	118/909	9/71	38/909	26/71	51/909	3/71	34/909
3	31/168	92/812	28/168	33/812	58/168	47/812	8/168	42/812
4	67/371	83/609	44/371	36/609	96/371	42/609	15/371	26/609
5	112/594	65/386	68/594	15/386	133/594	26/386	27/594	20/386
6	135/764	18/216	98/764	7/216	173/764	12/216	36/764	9/216
7	119/835	16/145	114/835	5/145	210/835	8/145	32/835	4/145
8	113/884	6/96	100/884	6/96	184/884	5/96	33/884	2/96
9	129/928	7/53	90/928	5/53	197/928	7/53	33/928	1/53
10	130/961	1/18	102/961	0/18	185/961	0/18	31/961	1/18
Total	856/ 5593	512/ 4208	653/ 5593	189/ 4208	1268/ 5593	277/ 4208	219/ 5593	185/ 4208

PS=Propensity Score, PCI=Percutaneous coronary intervention, CABG=Coronary artery bypass grafting; *Decile 1 is most likely to receive CABG and decile 10 is most likely to receive PCI

Six hundred fifty three patients of the PCI group had a PS higher than the maximum value (0.9906251) of the CABG group and 1,296 patients of the CABG group had a PS lower than the minimum value (0.0028794) of the PCI group. These cases (16.6%) should approximate the patients for whom an alternative treatment was not feasible, represent the equivalent of those judged non-randomizable in RCTs and were excluded, leaving 9,801 cases for further analysis.

The follow up ranged from to 24 to 90 months. The mean follow-up for survivors was 1,666 days. The proportional hazard assumption was confirmed in all models.

Table 2 displays the proportion of patients experiencing the various outcomes in each PS decile and by treatment group.

Table 3. Propensity-decile-specific Hazard Ratios of PCI vs. CABG for the various outcomes

Decile of PS*	Mortality	Myocardial infarction HR (95%CI)	Repeat revascularization	Stroke
1	3.11 (1.27-7.63)	n/a	6.31 (2.75-14.50)	1.50 (0.21-10.86)
2	1.74 (0.99-3.03)	2.96 (1.38-6.34)	9.38 (5.80-15.16)	0.86 (0.21-3.62)
3	1.61 (1.06-2.43)	4.43 (2.67-7.34)	7.79 (5.30-11.46)	0.91 (0.41-2.04)
4	1.40 (1.01-1.93)	2.03 (1.30-3.17)	4.34 (3.01-6.24)	0.91 (0.46-1.78)
5	1.12 (0.82-1.53)	2.94 (1.68-5.14)	3.68 (2.41-5.61)	0.93 (0.51-1.71)
6	2.14 (1.32-3.46)	4.19 (1.94-9.03)	4.67 (2.60-8.40)	1.06 (0.50-2.22)
7	1.26 (0.75-2.13)	4.07 (1.66-9.96)	5.12 (2.50-10.4)	1.37 (0.48-3.88)
8	2.14 (0.94-4.86)	1.86 (0.81-4.24)	4.47 (1.84-10.87)	1.79 (0.43-7.49
9	1.07 (0.50-2.30)	1.01 (0.41-2.51)	1.73 (0.81-3.68)	1.79 (0.24-13.11)
10	2.55 (0.35-18.29)	n/a	n/a	0.64 (0.08-4.70)
Overall†	1.48 (1.27-1.73)	2.82(2.25-3.54)	5.25 (4.37-6.32)	1.03 (0.77-1.38)
P value for differences	0.31	0.19	0.05	0.99

PCI=Percutaneous coronary intervention, CABG=Coronary artery bypass grafting PS=Propensity Score, HR=Hazard Ratio, CI= Confidence Interval;*Decile 1 is most likely to receive CABG and decile 10 is most likely to receive PCI;† Adjusted for deciles of propensity score

Table 3 shows the HRs of the various outcomes of PCI vs. CABG across the deciles of PS and the p values of the LR test that assessed the homogeneity of these HRs. The outcomes are generally better with CABG, though this is not the focus of this study. More importantly, there is a substantial homogeneity across the ten categories, except for revascularization.

Figure 1 shows the behavior of the HRs across the PS deciles. If tailoring had had the expected impact, one would expect the risks of adverse events to decrease with the propensity to receive either treatment (i.e. a decreasing trend in the figure, where PCI is the numerator of the HR and PCI-propensity increases left to right on the x axis). No meaningful pattern is instead visible, except an irregular decrease for repeat revascularization.

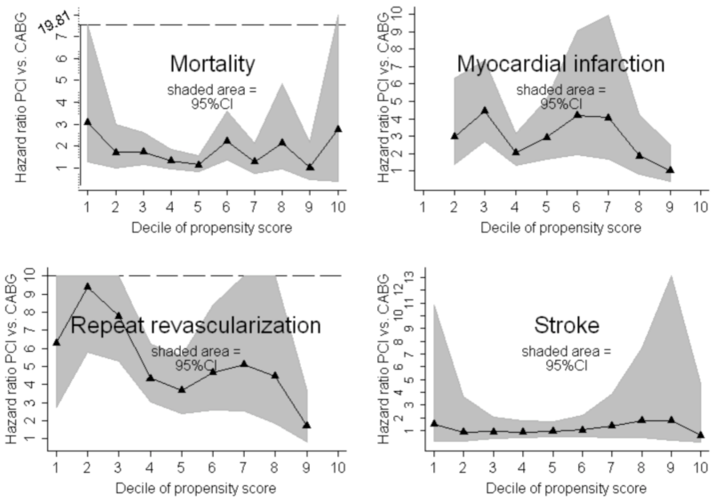

Figure 1. Trends of the Hazard Ratios of the various outcomes across the deciles of propensity score.
Decile 1 is most likely to receive CABG and decile 10 is most likely to receive PCI.

4 Discussion

In a regional population of revascularized CAD patients we found that the complex of characteristics that on average determined the choice between PCI and CABG had a minimal influence on the outcome of the procedures.

On one hand this may not appear surprising, given that it is the in-vivo confirmation of the scientific uncertainty presently surrounding this therapeutic choice. On the other hand, it contradicts the common belief that, despite scientific uncertainty, a careful and personalized formulation of the best revascularization strategy guided by clinical judgment can still lead to optimized outcomes.

Few studies before this one investigated the effect-modification of clinical and demographic characteristics not as single factors, but in combination, resembling the process of clinical judgment. The findings of these studies are consistent with ours because the relative outcomes associated with the two procedures were similar across quartiles [1] or quintiles [17] of PS or terciles of EuroSCORE and SYNTAX Score [4]. The categorization adopted in these studies may, however, have been too broad to unveil the heterogeneity of treatment-effect estimates [18, 19], while the one adopted here should yield stronger evidence.

A diminished importance of the tailoring process may have some positive consequences for the patients: their empowerment to the decision should increase. For example, if the overall survival advantage of CABG over PCI [17] and absence of effect-modification is confirmed, most patients will be able take their own decision, provided they are well informed on the trade-off between a shorter, less stressful and cheaper hospital course with PCI and a lower long-term mortality with CABG. The latest clinical guidelines seem to be already following this tendency, as they recommend

'Awareness that other factors such as sex, race, availability, technical skills, local results, referral patterns, and patient preference […] may have an impact on the decision making process, independently of clinical findings…' [20] The results of this study can contribute to the acceptance and diffusion of these principles.

In order to measure its impact on outcome, we have attempted to objectivize the process of clinical judgment, which is quite subtle and elusive. We adopted a methodology based on established statistical principles and recent research [16, 21, 22], but there are some limitations. Most important is the assumption that the factors considered by clinicians were included in the PS calculation. We made every effort to ensure this by including in the PS all of the available variables. However, hidden confounding cannot be excluded, as usual in observational research. If any characteristic had been considered by clinicians but not recorded in the registries, the PS would have been less representative of the actual clinical judgment and some effect-modification might have been missed. It so, such information should become part the registries for further research.

Another possible limitation is that the propensity we calculated was an average over several institutions and many more clinicians. Because case-mix alone hardly justifies the large between-hospital variation in the procedures' frequency (Table 1), different attitudes or policies are also likely to exist. Therefore, the stronger effect-modification occurring in some hospitals might have gone undetected because of averaging.

A further limitation is that the number of cases in some categories was small. We cannot exclude that some characteristics scarcely represented in this population (e.g. isolated left main disease) may have caused important effect-modification.

Finally, although we believe that the pursuit of outcome optimization was predominant, some clinicians might have allowed other considerations (e.g. patient preference) to enter the decision-making, lowering the chances of this study to detect the real effect modification of the measured factors.

Conflict of interests

The authors declare that they have no conflict of interests.

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