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Incomplete revascularization and long-term survival after coronary artery bypass surgery☆

Umberto Benedetto [a,1], Mario Gaudino [b,*,1], Antonino Di Franco [b], Massimo Caputo [a], Lucas B. Ohmes [b], Juan Grau [c], David Glineur [c], Leonard N. Girardi [b], Gianni D. Angelini [a]

[a] *Bristol Heart Institute, University of Bristol, School of Clinical Sciences, Bristol, United Kingdom*
[b] *Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York, USA*
[c] *Division of Cardiac Surgery, Ottawa Heart Institute, Ottawa, Canada*

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ABSTRACT

Background: We sought to investigate the impact of incomplete revascularization (IR) on long-term survival after isolated coronary artery bypass grafting (CABG). The possible interaction between IR and off-pump surgery was also explored.
Methods: A total of 13,701 patients with multivessel disease undergoing CABG were included in the analysis. All patients received left internal thoracic artery (LITA) to the left anterior descending artery (LAD) territory. IR was defined as at least one diseased arterial territory (right coronary artery [RCA] and/or circumflex [CX] artery) incompletely revascularized.
Results: Overall, 3107 (22.7%) patients received IR. After propensity score matching, IR did not increase all-cause death in the overall group (HR 1.09; 95%CI 0.96–1.22; P = 0.17). However, when both RCA and CX artery were incompletely revascularized, late survival was significantly lower (HR 2.15; 95%CI 1.57–2.93). IR was associated with a higher risk of death after off-pump (HR 1.26; 95%CI 1.05–1.49) regardless the extent of IR. After on-pump, IR significantly affected survival only when both RCA and CX artery only were incompletely revascularized (HR 2.32; 95%CI 1.27–4.22).
Conclusions: The present analysis shows that in patients with LITA-LAD graft the impact of IR on survival is marginal when only one coronary territory is left ungrafted. When both the RCA and CX territory remain unrevascularized the survival rate is significantly reduced. IR after off-pump CABG is associated with significantly lower survival and affects long-term outcome even when only one coronary territory is not revascularized.

1. Introduction

Despite complete revascularization (CR) has long been considered the goal of coronary artery bypass graft (CABG) surgery [1], this is not always achieved due to procedural difficulties [2]. The impact of incomplete revascularization (IR) on long term survival remains uncertain [2,3]. No randomized controlled trial has ever tested whether CR is superior to IR and results from observational cohorts are conflicting [2–7]. What remains unclear is whether different degrees of IR can have different effects on survival. Moreover, patients who undergo IR are more likely to present multiple comorbidities and this could bias the data in favour of CR. Finally, several comparisons between IR and CR strategies report mid-term results only [2,3] and longer follow-up might be necessary for IR to show its detrimental effect on survival [4].

We sought to investigate the impact of IR on long-term survival after isolated CABG by analysing 20-year single institution data. The emphasis of this study is large sample size, focus on the extent of IR and long term follow-up.

2. Methods

The study was conducted in accordance with the principles of the Declaration of Helsinki. The local audit committee approved the study, and the requirement for individual patient consent was waived. We retrospectively analysed prospectively collected data from The National Institute for Cardiovascular Outcomes Research (NICOR) registry on 1 June 2015 for all isolated first time CABG procedures performed at the Bristol Heart Institute, Bristol, United Kingdom, from 1996 to April 2015. Reproducible cleaning algorithms were applied to the database, which are regularly updated as required. Briefly, duplicate records and non-adult cardiac surgery entries were removed, transcriptional discrepancies harmonized, and clinical conflicts and extreme values corrected or removed. The data are returned regularly to the local units for validation.

Further details and definition of variables are available at http://www.ucl.ac.uk/nicor/audits/adultcardiac/datasets. During the study period, a total of 15,119 patients underwent

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* Corresponding author at: Department of Cardiothoracic Surgery, Weill Cornell Medicine, 525 E 68th St., New York, NY 10065, USA.
E-mail address: mfg9004@med.cornell.edu (M. Gaudino).

[1] Equal contribution.

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first time isolated CABG; 931 subjects operated for single vessel disease were excluded; information on the use of cardiopulmonary bypass (on-pump vs off-pump) was not available in 487 cases which were excluded. A total of 13,701 subjects were included in the final analysis. All patients received left internal thoracic artery (LITA) to the left anterior descending artery (LAD) territory. IR was defined as at least one diseased arterial territory (right coronary artery [RCA] and/or circumflex [CX] artery) incompletely revascularized. Overall 3107 (22.7%) and 10,594 patients (77.3%) received IR and CR, respectively.

2.1. Pre-treatment variables

The effect of IR on outcomes of interest was adjusted for the following pre-treatment variables including: age, gender, body mass index (BMI), New York Heart Association grade III or IV, previous myocardial infarction (MI), and MI within 30 days, previous percutaneous coronary intervention (PCI), diabetes mellitus (DM) on oral treatment or on insulin, chronic obstructive pulmonary disease (COPD), current smoking, serum creatinine ≥ 200 mmol/l, previous CVA, peripheral vascular disease (PVD), left main disease (LMD), number of vessel diseased, left ventricular ejection fraction (LVEF) between 30% and 49%, LVEF < 30%, non-elective admission, emergent/salvage operation, preoperative IABP, off-pump surgery, use of additional arterial grafts, and eras of surgery.

2.2. Statistical methods

Categorical variables are presented as frequencies and percentages and continuous variables as mean ± standard deviation. Survival curves were constructed using Kaplan-Meier estimates. To reduce the effect of treatment selection bias and potential confounding, we adjusted for differences in baseline characteristics by propensity score (PS) matching [8].

A PS was generated for each patient from a multivariable logistic regression model based on pre-treatment covariates as independent variables with treatment type (IR vs CR) as a binary dependent variable. The resulting PS represented the probability of a patient undergoing IR. Pairs of patients undergoing IR and CR were derived using greedy 1:1 matching with a calliper of width of 0.2 standard deviation of the logit of the PS (nonrandom R package). The quality of the match was assessed by comparing selected pre-treatment variables in PS matched patient using the standardized mean difference (SMD), by which an absolute standardized difference of >10% is suggested to represent meaningful covariate imbalance. Analytic methods that account for the within-pair homogeneity and clustering effect related to individual surgeon were used for the estimation of the treatment effect in the matched sample. Cox proportional hazards regression stratified for PS matched pairs was used to investigate the effect of IR on survival (survival R package). IR of the RCA and the CX artery was investigated separately. Potential effect modifiers (interaction terms) examined were age < 70 vs ≥70 years; female vs male; DM vs no DM; LVEF < 0.50 vs ≥50%; creatinine > 200 mmol/l vs creatinine < 200 mmol/l; off-pump vs on-pump; 3-vessel vs 2-vessel disease; left main disease vs no left main disease; use of multiple arterial conduits vs single arterial revascularization plus saphenous vein grafts. All P-values < 0.05 were considered to indicate statistical significance. The Schoenfeld residuals test was used to test the independence between residuals and time and hence to test the proportional hazards assumption in Cox models (all P values were >0.05). All statistical analyses were performed using R Statistical Software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Overall, 3107 (22.7%) patients received IR. Patients' characteristics before and after PS matching are reported in Table 1. Patients receiving IR were more likely to have three vessel disease and receive off-pump surgery. We also found a trend towards a higher incidence of LVEF < 30% and PVD in the IR group. Patients receiving CR were more likely to receive multiple arterial grafting. The overall number of grafts was significantly lower in the IR group. PS matching selected 3107 matched pairs comparable for all the baseline characteristics. Table 2 summarizes number of grafts performed with relative targets in the CR and IR groups. Before matching survival rates at 5, 10 and 15 years were 86.4 ± 0.6% vs 89.3 ± 0.3%, 69.9 ± 0.9% vs 74.7 ± 0.5% and 51.5 ± 1.4% vs 57.2 ± 0.8% in the IR and CR groups, respectively (HR 1.24; 95%CI 1.15–1.34; P < 0.001). Survival rates at 5, 10 and 15 years in the CR matched group were 88.6 ± 0.6%, 72.3 ± 1.0% and 51.8 ± 1.5% with no significant difference compared to the IR group (HR 1.09; 95%CI 0.96–1.22; P = 0.17; Fig. 1 left). When the analysis was conducted according to the extent of IR, we found that incompletely revascularized RCA only (HR 1.06; 95%CI 0.95–1.19) or incompletely revascularized CX artery only did not increased the risk of death (HR 1.04; 95%CI 0.90–1.19). However, when both RCA and CX artery were incompletely revascularized, late survival was significantly lower (HR 2.15; 95%CI 1.57–2.93; Fig. 1 right).

Table 1
Baseline characteristics before and after matching.

	IR	CR	SMD	CR matched	SMD
	N = 3107	N = 10,594		N = 3107	
Age, mean (sd)	66.55 (9.47)	66.05 (9.27)	0.054	66.73 (8.95)	0.020
Female, n (%)	557 (17.9)	1866 (17.6)	0.008	549 (17.7)	0.007
BMI, mean (SD)	27.91 (4.53)	27.86 (4.42)	0.011	27.86 (4.61)	0.011
NYHA III–IV, n (%)	965 (31.1)	3090 (29.2)	0.041	966 (31.1)	0.001
MI 30 days, n (%)	589 (19.0)	2053 (19.4)	0.011	597 (19.2)	0.007
PCI, n (%)	182 (5.9)	545 (5.1)	0.031	192 (6.2)	0.014
DMO, n (%)	356 (11.5)	1089 (10.3)	0.038	329 (10.6)	0.028
DMI, n (%)	257 (8.3)	761 (7.2)	0.041	253 (8.1)	0.005
Smoking, n (%)	419 (13.5)	1377 (13.0)	0.014	419 (13.5)	<0.001
Cr > 200 mmol/l, n (%)	99 (3.2)	257 (2.4)	0.046	111 (3.6)	0.021
COPD, n (%)	267 (8.6)	795 (7.5)	0.040	273 (8.8)	0.007
CVA, n (%)	128 (4.1)	391 (3.7)	0.022	118 (3.8)	0.017
PVD, n (%)	358 (11.5)	1025 (9.7)	0.060	358 (11.5)	<0.001
LVEF 31–49%, n (%)	731 (23.5)	2290 (21.6)	0.046	731 (23.5)	<0.001
LVEF ≤ 30%, n (%)	198 (6.4)	522 (4.9)	0.063	207 (6.7)	0.012
Non-elective, n (%)	1503 (48.4)	5054 (47.7)	0.013	1504 (48.4)	0.001
Emergent, n (%)	56 (1.8)	165 (1.6)	0.019	56 (1.8)	<0.001
Preop IABP, n (%)	45 (1.4)	155 (1.5)	0.001	44 (1.4)	0.003
NVD, n (%)			0.502		<0.001
2	383 (12.3)	3421 (32.3)		383 (12.3)	
3	2724 (87.7)	7173 (67.7)		2724 (87.7)	
LMD, n (%)	810 (26.1)	2829 (26.7)	0.014	826 (26.6)	0.012
OPCAB, n (%)	1751 (56.4)	4978 (47.0)	0.188	1729 (55.6)	0.014
MAG, n (%)	565 (18.2)	2462 (23.2)	0.125	533 (17.2)	0.027
Eras, mean (SD)	2004.92 (5.12)	2004.92 (5.28)	0.001	2004.98 (5.06)	0.012

BMI, body mass index; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CVA, cardiovascular accident; DMI, diabetes mellitus on insulin; DMO, diabetes mellitus on oral treatment; LMD, left main disease; LVEF, left ventricular ejection fraction; MAG, multiple arterial grafts; MI, myocardial infarction; NVD, number of vessels diseased; NYHA, New York Heart Association; OPCAB, off-pump coronary artery bypass; PCI, percutaneous coronary intervention; Preop IABP, preoperative intra-aortic balloon pump; PVD, peripheral vascular disease.

Subgroup analysis (Fig. 2) showed that IR was associated with a higher risk of death after off-pump (HR 1.26; 95%CI 1.05–1.49) but not on-pump surgery (HR 0.91; 95%CI 0.75–1.1; interaction P = 0.01). In case of off-pump surgery, incompletely revascularized RCA only (HR 1.20; 95%CI 1.02–1.41), incompletely revascularized CX artery only (HR 1.20; 95%CI 1.01–1.44) and concomitant incompletely revascularized RCA and CX artery (HR 2.14; 95%CI 1.48–3.09) were associated with poorer survival. In case of on-pump surgery, when both RCA and CX artery were incompletely revascularized, survival was significantly lower (HR 2.32; 95%CI 1.27–4.22), but IR did not significantly affect survival in case of incompletely revascularized RCA only (HR 0.96; 95%CI 0.82–1.12) or incompletely revascularized CX artery only (HR 0.90;95%CI 0.73–1.10) (Fig. 3).

Table 2
Number of grafts and targets in CR and IR groups.

	CR	IR	P
2-Vessel disease, n	383	383	
N grafts, mean (SD)	2.18 (0.40)	1.56 (0.51)	<0.001
CX artery, n (%)	223 (58.2)	14 (3.7)	<0.001
RCA, n (%)	179 (46.7)	20 (5.2)	<0.001
3-Vessel disease, n	2724	2724	
N grafts, mean (SD)	3.26 (0.47)	2.58 (0.62)	<0.001
CX artery, n (%)	2723 (100.0)	1761 (64.6)	<0.001
RCA, n (%)	2724 (100.0)	911 (33.4)	<0.001

CX, circumflex; RCA, right coronary artery.

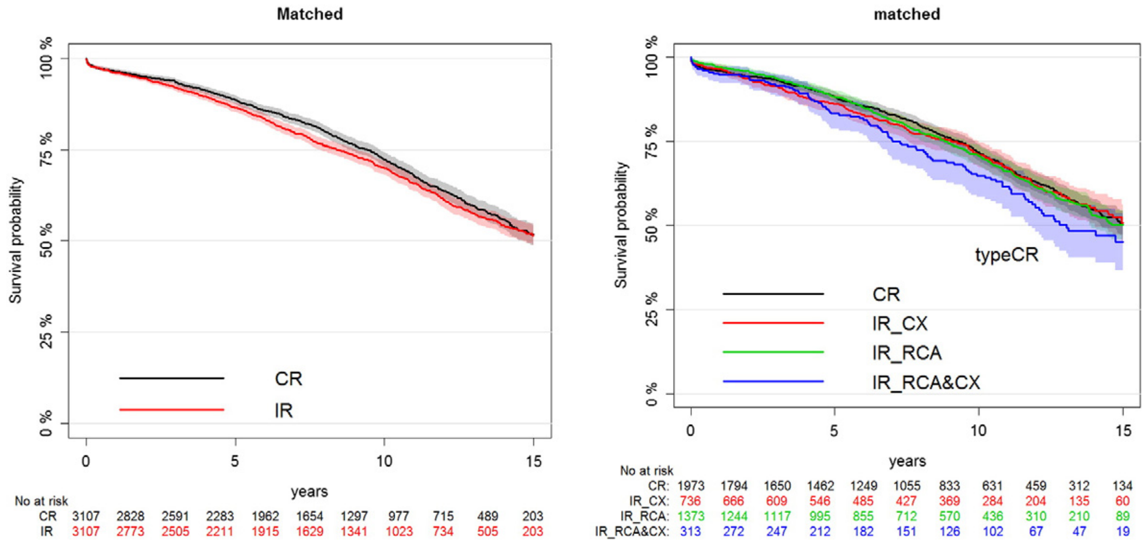

Fig. 1. Survival rates in propensity matched subjects receiving complete revascularization (CR) vs incomplete revascularization (IR) in the overall sample (left) and impact of incomplete revascularization in the right coronary artery (RCA) and circumflex (CX) artery territory (right).

4. Discussion

In the present analysis, we focused on the prognostic impact of IR of CX and RCA territory when performing LITA-to-LAD bypass and we found that, IR does not adversely affect survival unless both the CX and RCA territory are incompletely revascularized. The detrimental effect of IR is more relevant in subjects undergoing off-pump when compared to on-pump surgery. In fact, IR was associated with a higher risk of death after off-pump CABG and in off-pump cases even IR of a single coronary territory affected survival.

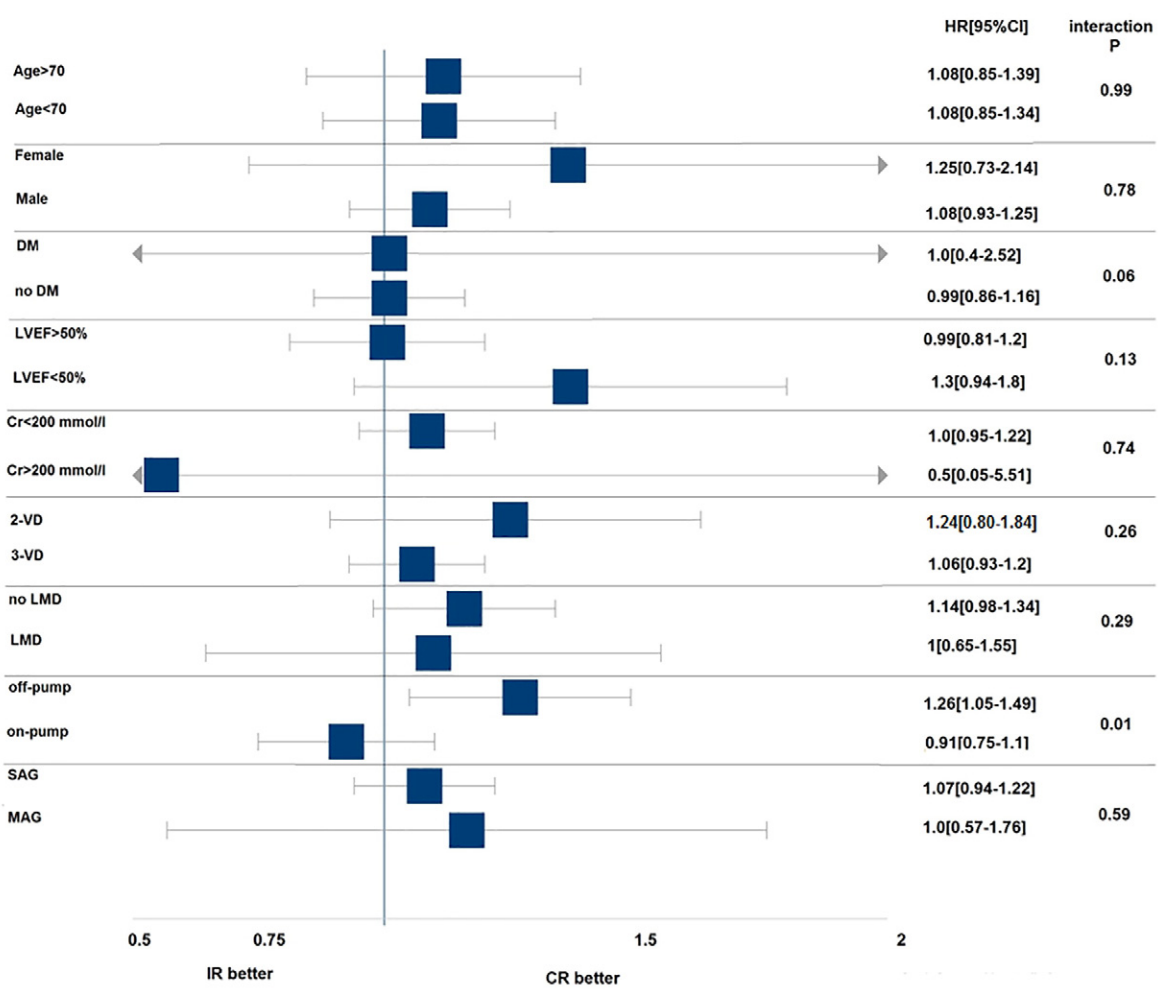

Fig. 2. Subgroup analysis of the effect of incomplete revascularization on mortality.

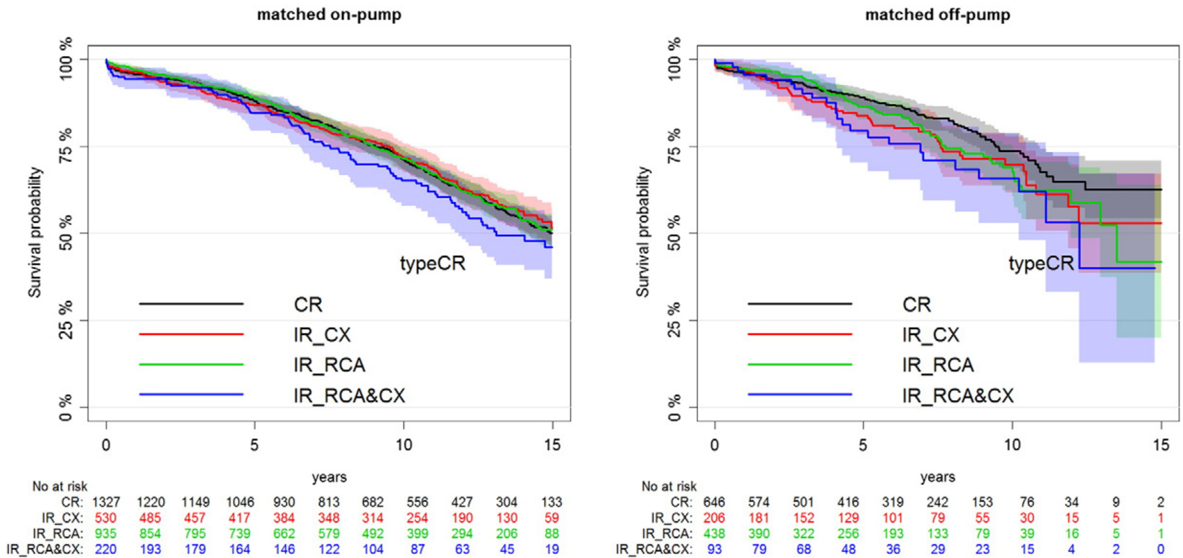

Fig. 3. Impact of incomplete revascularization (IR) in the right coronary artery (RCA) and circumflex artery (CX) territory when compared to complete revascularization (CR) in on-pump and off-pump surgery.

CR is a major goal in CABG based on the dogma that CR leads to better early and long-term survival [1]. The association between CR and lower risk for subsequent cardiovascular events may be causal. CR may improve clinical outcomes by reducing or eliminating myocardial ischemia, which has been linked to worse prognosis, especially when large [9,10]. However, IR may be a surrogate marker for higher burden of comorbidities and more advanced coronary artery disease that is less amenable to revascularization [3]. In the latter case, IR per se might not be particularly relevant on patients' outcome. According to a widely accepted approach, the likelihood of achieving CR with either CABG or PCI, ideally estimated by a heart team approach, should influence the decision to proceed with CABG or PCI [2,11]. With this approach in the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial [2], the rates of IR were 43.3% for PCI and 36.8% for CABG, which compares favourably with historical cohorts [12], while still highlighting the procedural complexity of achieving CR during CABG. Interestingly, in the SYNTAX trial, IR was found to be associated with poorer outcomes in the PCI arm but not in the CABG arm [2]. It has been suggested the detrimental effect of IR in the CABG population might be mitigated by the presence of LITA to LAD graft [3] and the use of additional arterial grafts [13]. On the other hand, off-pump CABG has been consistently associated with a higher incidence of IR and a trend towards poorer survival [14–18]. The present analysis showed that IR is more relevant when occurs in off-pump CABG than on-pump CABG.

Common reasons for IR are based on preoperative assessment (e.g., non-dominant diseased RCA, non-vital myocardium, limited graft material), or unexpected findings during the operation (i.e., small target vessel, severely calcified artery). As in these situations the unrevascularized coronary targets are usually small or severely diseased, these conditions are anticipated to not have a major impact on outcomes.

However, during off-pump CABG, technical factors and operator's experience play a major role in determining the completeness of revascularization. In this scenario, it is possible that vessels of acceptable quality supplying large portion of viable myocardium can remain ungrafted due to surgical and not vessel-related factors [17,18].

There are several possible explanations for our findings. It has been suggested that the lower number of distal anastomoses might be compensated by the higher number of arterial grafts for non-LAD targets in IR patients [13]. However, our analysis was corrected for the number of arterial grafts used. Other possible explanations are the high efficacy of the modern secondary prevention strategies after CABG and the possible development of new collateral flow from the grafted areas. The reduced prognostic impact of the CX and RCA territory once the LAD has been revascularized by a LITA graft must also be taken into account.

4.1. Limitations

There are some limitations in the present study. First, it was subject to all limitations inherent to a non-randomized study, including potential selection bias regarding which patients underwent CR vs IR. This was partially addressed by using PS matching to minimize residual imbalance for measured variables, but we could not account for unmeasured factors and, in particular, for targets quality. The current data lacks a standardized, universal definition of what constitutes an IR procedure [2–4]. Gössl et al. [19] recently proposed a universal definition of IR using coronary angiography and fractional-flow reserve (FFR) data. Based on the previous work by Pijls et al. [20] regarding the excellent long-term outcomes of patients with intermediate stenosis and insignificant FFR and the observation that FFR-guided PCI in patients with multivessel coronary artery disease is superior to angiography-guided PCI, a definition of IR that includes anatomy and physiology seems intuitive. However, FFR was not available for the present analysis.

Finally, it is possible that with further refinement in technology and surgical technique for off-pump CABG and with a higher ability to achieve complete revascularization, the effect of IR among off-pump CABG cases could be different from what we have presented.

5. Conclusion

The present analysis showed that IR of the CX or the RCA does not impact on survival in patients with LIMA-LAD graft. However, when both the CX and the RCA system are not revascularized long term survival is significantly reduced.

The detrimental effect of IR is higher in patients undergoing off-pump CABG. After off-pump procedures even IR of a single coronary territory adversely affects long term outcome.

Taken together these results show that IR does not play a prognostic role when the reason for it is related to the target vessel and not to the surgical technique. In case of off-pump CABG all vessel with adequate diameter and quality should be revascularized.

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Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.08.005.

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