Incidence and Prognostic Impact of Incomplete Revascularization Documented by Coronary Angiography 1 Year After Coronary Artery Bypass Grafting

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Complete revascularization (CR) at the time of coronary artery bypass graft (CABG) surgery improves long-term cardiac outcomes. No studies have previously reported angiographically confirmed CR rates post-CABG. This study's aim was to assess the impact upon long-term outcomes of CR versus incomplete revascularization (IR), confirmed by coronary angiography 1 year after CABG. Randomized On/Off Bypass Study patients who returned for protocol-specified 1-year post-CABG coronary angiograms were included. Patients with a widely patent graft supplying the major diseased artery within each diseased coronary territory were considered to have CR. Outcomes were all-cause mortality and major adverse cardiovascular events (MACE; all-cause mortality, nonfatal myocardial infarction, repeat revascularization) over the 4 years after angiography. Of the 1,276 patients, 756 (59%) had CR and 520 (41%) had IR. MACE was 13% CR versus 26% IR, p <0.001. This difference was driven by fewer repeat revascularizations (5% CR vs 18% IR; p <0.001). There were no differences in mortality (7.1% CR vs 8.1% IR, p = 0.13) or myocardial infarction (4% in both). Adjusted multivariable models confirmed CR was associated with reduced MACE (odds ratio 0.44, 95% confidence interval 0.33 to 0.58, p <0.01), but had no impact on mortality. In conclusion, CR confirmed by post-CABG angiography was associated with improved MACE but not mortality. Repeat revascularization of patients with IR, driven by knowledge of the research angiography results, may have ameliorated potential mortality differences. **(Am J Cardiol 2020;131:7−11)**

The Department of Veterans Affairs (VA) "Randomized On/Off Bypass (ROOBY) Trial" was designed to compare the relative efficacy of off-pump versus on-pump coronary artery bypass grafting (CABG).[1] The results based upon the randomized allocation of the trial have been reported, including that patients receiving on-pump CABG had better graft patency rates than patients in the off-pump arm. Overall graft patency was 85% and about 33% of patients had at least one occluded graft.[1] Using the subjects who had protocol-driven 1-year post-CABG coronary angiograms, the objective of this substudy was to determine the impact of angiographically apparent incomplete revascularization (IR) versus complete revascularization (CR) upon clinical outcomes over the 4 years after the post-CABG coronary angiogram.

Methods

The ROOBY trial was a single-blinded, controlled, multicenter study conducted at 18 VA medical centers from February 2002 to May 2008 with prospective patient follow-up to 1 year after CABG.[1] Each VA medical center's Institutional Review Board, the VA Cooperative Studies Program Human Rights Committee, and VA Clinical Merit

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Review Board provided ROOBY trial approvals. A ROOBY follow-up study (ROOBY-FS) was separately funded by the VA Cooperative Studies Program and received Institutional Review Board approvals from the Northport VA Medical Center, the Rocky Mountain Regional VA, and the Palo Alto Health Economics Resource Center.[2] The ROOBY-FS assessed 5-year outcomes of ROOBY patients. This study was a prespecified secondary objective of ROOBY-FS and was approved by the ROOBY-FS Executive Committee during the planning phase. The full trial protocol (Clinical Trial Registration: NCT01924442) has been published.[2] As this report was a prospective cohort analysis, the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for cohort studies were followed. Detailed methods and results of both ROOBY and ROOBY-FS have been published.[1,2] Clinical outcome assessments were completed for all randomized patients.[2] Using VA and non-VA database merges, the Palo Alto VA Health Economics Resource Center team documented all the post-CABG primary and secondary clinical endpoints over the 4 years after the post-CABG coronary angiogram. National nurse reviewers conducted in-depth medical chart reviews centrally. An endpoints committee adjudicated all major adverse cardiovascular event (MACE) endpoints, and any differences between medical chart review and database abstracts were reconciled.

The study population consisted of ROOBY patients who returned for the study's 1-year post-CABG coronary angiogram. Patients who had an interim repeat revascularization procedure prior to 1-year coronary angiography were excluded due to a higher risk of subsequent repeat revascularizations. For purposes of the generalizability of the results, patients were asked to self-report their race. Five-year post-CABG vital status was complete for all patients. There were 3 patients who were not documented to have been seen clinically within 180 days of the 5-year post-CABG time point, and these patients were thus considered lost to follow-up for the MACE endpoint.[2]

Details of the methods of the angiographic core lab assessments have been published.[3] Briefly, all study patients were asked to return for a 1-year post-CABG follow-up coronary artery angiogram unless contraindicated. All baseline and 1-year coronary angiograms were scored by a core lab, which was blinded to treatment assignment. Percent stenosis was calculated by comparing the narrowest diameter of a lesion in any view to the most normal proximal or distal reference segment in the same frame. An artery with a reference diameter ≥1.5 mm and a ≥50% diameter narrowing of a diseased segment was considered to have a clinically significant stenosis. At 1-year coronary angiography, bypass grafts were evaluated for patency. The 3 primary coronary regions, consisting of the left anterior descending (LAD), circumflex, and right coronary arteries, were evaluated using prespecified criteria. Each coronary region was assessed for CR versus IR. A coronary region was defined as having CR when a patent graft with no significant lesions was supplying the major diseased artery within the region, the graft was appropriately anastomosed distal to the primary stenosis, and there were no new significant distal coronary lesions within 1 cm of the graft anastomosis. If all 3 coronary regions had CR, then the patient had CR. Otherwise the patient was considered to have IR, which included patients with graft occlusions to significantly diseased arteries and those with diseased coronary regions which were never bypassed.

As this study required patients to survive and return for the 1-year post-CABG coronary angiogram, the focus was placed upon events over the 4 years after the angiogram (i.e., the 1- to 5-year post-CABG events). The primary outcomes were all-cause death and MACE (composite of all-cause death, repeat revascularization, or nonfatal myocardial infarction). Secondary endpoints included the individual MACE subcomponents and cardiac death. Study site investigators were advised to refrain from interventions during the study-driven angiograms. Subsequent decisions regarding the need for revascularization were left to the local treating physicians, and the specific clinical indications for revascularization were not captured.

Baseline variables were compared between CR and IR groups using chi-square tests and Fisher exact tests (categorical endpoints) or Wilcoxon Rank Sum and *t*-test analyses (continuous variables) depending on normality. For time-to-event endpoints, Kaplan-Meier curves with likelihood ratio tests compared CR versus IR associations. Two multivariable adjusted logistic regression analyses were performed to evaluate which demographic, clinical, operative, and 1-year angiographic variables were independently associated with mortality and with MACE. Variables included in both models were age, ethnicity, education level, diabetes, peripheral vascular disease (PVD), chronic obstructive pulmonary disease, atrial fibrillation, stroke, serum creatinine >1.5 mg/dl (to convert to μmol/l multiply by 88.4), left ventricular ejection fraction <35%, 3-vessel coronary artery disease, left main disease ≥50%, off-pump CABG, endoscopic vein harvest, use of internal mammary artery conduit, urgent procedure, perioperative complications, and CR.

Per the ROOBY-FS protocol, primary hypotheses were evaluated for statistical significance using a p value of ≤0.01 to avoid type I errors arising from multiple comparisons; however, all p values have been reported permitting independent interpretation and assessment for potential type II errors.[2] Adjusting for baseline characteristics, multivariable logistic regression analyses used a pre-established p ≤0.05 to validate bivariate study-related findings.

Both the Perry Point VA Coordinating Center and the Palo Alto VA Health Economics Resource Center teams coordinated major components of the database programming and analyses to support this ROOBY-FS 1- to 5-year follow-up analysis. SAS version 9.4 (SAS Institute, Cary, NC) was used for the analyses performed.

Results

Of the 2,203 patients randomized in the ROOBY study, 1,276 returned for 1-year (range 10 to 14 months) post-CABG coronary artery angiography and were included in this substudy. The primary reason for not having a post-CABG coronary angiogram was that the patient declined the procedure (n = 711). Other reasons included patient death prior to 1 year, repeat revascularization prior to

1 year, or a contraindication to angiography such as an elevated serum creatinine >2.0 mg/dl. Compared with the study group, excluded patients had more comorbidities including previous stroke (9.6%), PVD (19%), diabetes (47%), and hypertension (89%). The vital status was known for all 1,276 study patients. Only 3 patients (1 CR and 2 IR) were not seen for a clinical visit within 180 days of the 5-year post-CABG date and were considered lost to follow-up for the MACE and MACE subcomponent endpoints.

Of the 1,276 study patients, 520 (41%) had IR and 756 (59%) had CR documented by coronary angiography. Within the IR group, approximately 47% had IR of the circumflex territory, 53% had IR of the RCA territory, and 22% had IR of the LAD territory (a patient could have 1 or more territories with IR). Significant graft stenoses and/or occlusions were found in 413 (79%) of the IR group and 79 (15%) had less grafts completed than planned during the initial CABG. Others had progression of disease or postanastomotic lesions.

Comparison of baseline variables between the 2 groups found the IR group was more likely to have 3-vessel coronary artery disease and to have had an off-pump procedure (Table 1). The rates of aspirin, beta-blocker, and lipid lowering medication use were ≥90% for each medication at discharge and the 1-year visit, with no difference between groups.

There was no difference between groups in 1- to 5-year all-cause mortality (7% CR, 8% IR; Table 2). The MACE rates were 26% IR and 13% CR, p <0.001. The difference in the MACE composite outcome was primarily driven by more repeat revascularizations in the IR group, and there were no differences in mortality, nonfatal myocardial infarction, or cardiac mortality. Comparison of patients with LAD IR (n = 115) versus LAD CR (n = 1,153) found similar outcomes with a difference in MACE (30% LAD IR vs 17% LAD CR, p = 0.002), but not mortality (5% LAD IR vs 8% LAD CR, p = 0.46). Also, when a lesion severity of ≥70% (rather than 50%) was used to define IR, the mortality rate was still 8%.

Table 2
Primary and secondary clinical outcomes in the 4 years after post-CABG coronary angiography

Variable	CR (n = 756)	IR (n = 520)	p value
Death	54 (7%)	42 (8%)	0.53
MACE	100 (13%)	134 (26%)	<0.001
Nonfatal MI	30 (4%)	21 (4%)	0.95
Repeat revascularization	41 (5%)	93 (18%)	<0.001
Repeat PCI	41 (5%)	86 (17%)	<0.001
Repeat CABG	0	7 (1%)	0.001
Cardiac death	15 (2%)	16 (3%)	0.21

CABG = coronary artery bypass graft surgery; CR = complete revascularization; IR = incomplete revascularization; MACE = major adverse cardiovascular event; MI = myocardial infarction; PCI = percutaneous coronary intervention.

The mortality endpoints were complete for all 1,276 patients. For the other endpoints, n = 755 for CR and n = 518 for IR. Percentages are rounded to nearest whole number.

Multivariable modeling was used to assess whether IR was independently associated with 5-year mortality or MACE. Variables included in the model were off-pump versus on-pump CABG, age, ethnicity, education level, diabetes, PVD, chronic obstructive pulmonary disease, atrial fibrillation, stroke, serum creatinine >1.5 mg/dl, left ventricular ejection fraction <35%, 3-vessel coronary artery disease, left main disease >50%, endoscopic vein harvesting, use of internal mammary artery conduit, urgent procedure, and perioperative complications. In the mortality model, IR was not independently associated with death (p = 0.83). The variables significantly associated with 5-year mortality were age (odds ratio 1.04, 95% confidence interval 1.01 to 1.07), PVD (2.38, 1.40 to 4.04), and depressed left ventricular ejection fraction (5.55, 2.67 to 11.54; Table 3). Although there was no association with mortality, CR was significantly associated with freedom from MACE (0.44, 0.33 to 0.58, p <0.001). Variables independently associated with worse MACE were PVD (1.90, 1.28 to 2.81), left main coronary artery disease (1.66, 1.14 to 2.41), and major perioperative complication within 30 days of the initial CABG (5.94, 3.92 to 8.98; Table 3). The c-statistics were 0.74 for the mortality model and 0.72 for the MACE model. Kaplan-Meier freedom from MACE analysis showed the IR group had significantly more MACE events in the first few months after the coronary angiogram, and the curves continued to separate over time (Figure 1).

Table 1
Baseline demographic, clinical, and operative variables

Variable	CR (n = 756)	IR (n = 520)	p value
Age (years, mean ± SD)	61.9 ± 8.2	62.4 ± 8.2	0.26
Men	752 (99%)	517 (99%)	0.91
White	656 (87%)	445 (86%)	0.54
Serum creatinine >1.5 mg/dl	31 (4%)	28 (5%)	0.28
COPD	146 (19%)	107 (21%)	0.58
Peripheral vascular disease	99 (13%)	73 (14%)	0.63
Previous stroke	48 (6%)	36 (7%)	0.68
Diabetes mellitus	317 (42%)	214 (41%)	0.78
Hypertension	640 (85%)	434 (83%)	0.57
Current smoker	237 (31%)	173 (33%)	0.50
3-vessel disease	477 (63%)	367 (71%)	0.006
Left main disease ≥50%	176 (23%)	126 (24%)	0.69
Ejection fraction <55%	238/711 (34%)	167/463 (36%)	0.38
SAQ-AF score (mean ± SD)	63.7 ± 27	64.2 ± 27	0.72
Internal mammary artery conduit	729 (96%)	498 (96%)	0.55
Radial artery conduit	53 (7%)	51 (10%)	0.07
Endoscopic vein harvesting	175/509 (34%)	138/324 (43%)	0.02
Off-pump CABG	334 (44%)	290 (56%)	<0.001

CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; CR = complete revascularization; IR = incomplete revascularization; SAQ-AF = Seattle Angina Questionnaire Angina Frequency; SD = standard deviation.

Percentages are rounded to nearest whole number.

Discussion

This study found IR was present in 41% of patients who underwent prespecified coronary angiography 1 year after CABG. In comparison to patients with CR, patients with IR

Table 3
Variables associated with Mortality and MACE in the 4 years after post-CABG angiography

Mortality model (c-statistic 0.74)		
Variable	Odds ratio (95% CI)	p value
Age	1.04 (1.01, 1.07)	0.008
Peripheral vascular disease	2.38 (1.40, 4.04)	0.001
LVEF <35%	5.55 (2.67, 11.54)	<0.001
MACE model (c-statistic 0.72)		
Peripheral vascular disease	1.90 (1.28, 2.81)	0.001
Left main stenosis ≥50%	1.66 (1.14, 2.41)	0.008
30-day perioperative complication	5.94 (3.92, 8.98)	<0.001
Complete revascularization	0.44 (0.33, 0.58)	<0.001

CABG = coronary artery bypass graft surgery; CI = 95% confidence interval; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular event.

had more MACE over the 4 years after angiography, primarily due to repeat revascularizations. There was no difference in mortality between groups.

This is the only study to date with protocol-specified coronary angiography after CABG to report subsequent long-term outcomes based upon the angiographic finding of IR versus CR. Investigators of the Project of Ex-vivo Vein graft Engineering through Transfection IV trial, which also included a protocol-specified angiogram 12 to 18 months after CABG, reported 42% of 1,829 patients had failure of at least one graft.[4] They reported outcomes based upon the finding of graft failure and found that patients with vein graft failure had more repeat revascularization, but no difference in myocardial infarction or mortality.[5] Similar to our study, they also found that left internal mammary artery graft failure was associated with more repeat revascularizations, but not with worse mortality.[6] Another retrospective analysis of a large series of patients who underwent clinically indicated, as opposed to routine study-driven, coronary angiograms between 1 and 18 months after CABG found that long-term MACE outcomes were worse in patients with significantly diseased or occluded vein grafts.[7]

Up to 30% of saphenous vein grafts will occlude within 1 year after CABG.[8-10] Commonly contributing causes include poor quality and/or size of either the conduit vessel or the coronary target, technical issues arising during graft construction, or factors related to secondary prevention.[4,11,12] As the graft occlusion rate can be a source of alarm to patients and their families during their preoperative CABG counseling or postoperative debriefing, it is not surprising that most are relieved to understand that, in the majority of cases, such occurrences are more of an incidental finding than a cause of clinical events.[13]

The degree and impact of CR versus IR continues to be of interest in cardiologists and cardiac surgeons. Most studies suggest a survival benefit with CR at the time of surgery, defined as placement of 1 graft to each diseased territory, however, the detriment of subsequent graft occlusions appears less certain.[14-17] Our study found that IR documented by 1-year post-CABG angiography was associated with subsequent MACE, but not mortality. Although the reason mortality was not impacted is not clear and warrants additional study, one possibility might be that identification of high-grade lesions on catheterization prompted a more careful discussion of symptoms, further stress testing, subsequent interventions and an emphasis on medication adherence; any of which may have improved mortality in these patients.[12]

The study has several limitations. Patients were predominantly male veterans (99%) with complex comorbid diseases, so the results may not be applicable to women or nonveterans. Not all randomized patients underwent the 1-year post-CABG study angiogram, and there was a selection bias toward healthier patients returning for angiography. However, there was no difference in Seattle Angina

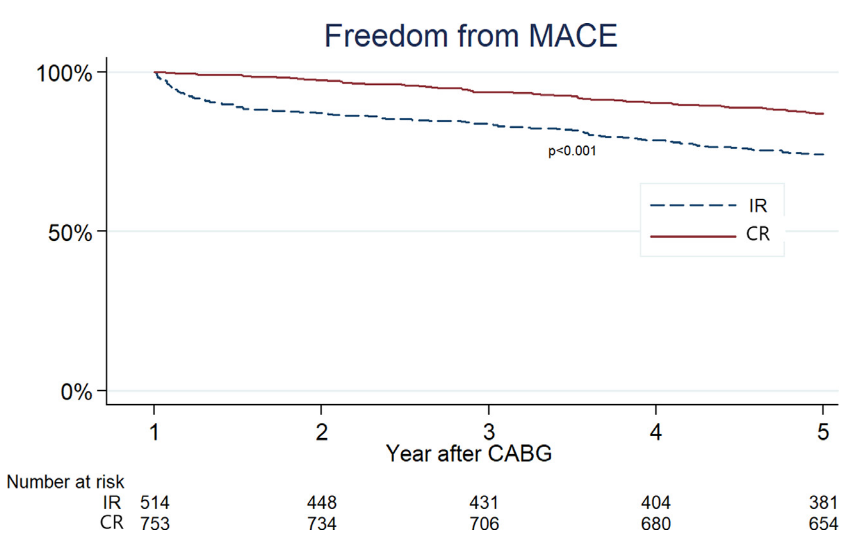

Figure 1. Freedom from MACE. Freedom from MACE curves comparing patients with CR versus those with IR documented by 1-year post-CABG coronary angiography. MACE endpoints were assessed over the 4 years following 1-year post-CABG coronary angiography (i.e., beginning at year 1 and continuing to year 5 after CABG). CABG = coronary artery bypass graft surgery; CR = complete revascularization; IR = incomplete revascularization; MACE = major adverse cardiac events.

Questionnaire Angina Frequency scores between patients who did and did not return for angiography (average scores were 89.9 and 91.0, respectively, $p = 0.22$), arguing that symptomatic patients were not more likely to return for follow-up.[18] The study's site investigators were discouraged from intervening during the 1-year post-CABG study angiogram. All subsequent intervention decisions over the 4 years after the angiogram were left to the discretion of local cardiologists. As indicated by the Kaplan-Meier freedom from MACE curves, repeat revascularizations in the IR group were more frequent in the first year after the study angiogram, indicating the angiographic findings may have influenced clinical follow-up.

In conclusion, this study provided an opportunity to evaluate long-term outcomes based upon systematic, routine, 1-year post-CABG angiographic findings. Although angiographic IR was frequent and was associated with higher reintervention rates, survival was not adversely affected. Additional investigation appears warranted to determine if routine post-CABG assessments for IR could improve long-term MACE.

Authors' Contributions

Brack Hattler: Conceptualization, Methodology, Investigation, Writing − original draft, review and editing; Frederick L. Grover: Conceptualization, Methodology, Writing − review and editing; Todd Wagner: Validation, Formal Analysis, Writing − review and editing; Robert B. Hawkins: Writing − original draft, review and editing; Jacquelyn A. Quin: Writing − original draft, review and editing; Joseph F. Collins: Methodology, Validation, Formal Analysis; Muath Bishawi: Writing − review and editing; G. Hossein Almassi MD: Writing − review and editing; A. Laurie Shroyer: Conceptualization, Methodology, Writing − original draft, review and editing.

Disclosures

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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