Clinical and Angiographic Outcomes Associated with Surgical Revascularization of Angiographically Borderline 50-69% Coronary Artery Stenoses

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

in
Translational Medicine

Department of Medicine
University of Alberta

Abstract

Objectives: Coronary artery bypass grafting improves outcomes in patients with multi-vessel coronary artery disease. Bypass of angiographically significant lesions ≥70% is recommended, yet little is known about the incidence/outcomes with bypasses of 50-69% angiographically borderline lesions without fractional flow reserve testing. The objective of this study was to investigate the incidence and outcomes of bypass of 50-69% angiographically borderline lesions.

Methods: Between 2007 and 2013, 3,195 patients underwent isolated first multi-vessel coronary artery bypass grafting at the Mazankowski Alberta Heart Institute. Patients with an isolated angiographically borderline lesion of a major epicardial vessel were included. The primary analysis compared clinical and angiographic outcomes between patients with and without coronary bypasses of angiographically borderline lesions. Outcomes of interest included time to all-cause mortality, 30 day, and 1 year mortality.

Results: Among 350 patients with an angiographically borderline lesion, 268 (76.6%) had the vessel containing the angiographically borderline lesion bypassed while 82 (23.4%) did not. Mean follow-up was 4.2 years. Patients with a bypassed angiographically borderline lesion were older (66.1 vs 62.5 mean years, p=0.006) but otherwise similar in sex, comorbidities, diabetes, ejection fraction, and number of coronary stenoses. Cardiopulmonary bypass time was longer in patients with bypassed angiographically borderline lesions (104.2 versus 90.4 minutes, mean, p<0.001). Unadjusted overall mortality through end of follow-up was higher among patients with bypassed angiographically borderline lesions (11.6% versus 3.7%, p=0.034). After multi-variable adjustment, the association between angiographically borderline lesion bypass and mortality was attenuated (hazard ratio 2.84: 95% confidence interval, 0.87 – 9.23, p=0.080). No differences were observed in unadjusted 30-day (1.1% versus 0.0%, p=0.336) or 1-year mortality (4.1% versus 0.0%, p=0.062). Repeat revascularization of patients with bypassed angiographically borderline lesions was numerically higher (4.1% versus 0.0%, p = 0.107).

Conclusions: In an unselected cohort of patients with angiographically borderline lesions, bypass of borderline 50-69% lesions is frequently performed and not associated with improved long-term survival. Our findings suggest that the routine surgical revascularization of 50-69% angiographically borderline lesions may not be warranted.

Preface

The research project, of which this thesis is a part, received research ethics approval from the Human Research Ethics Board of the Research Ethics Office of the University of Alberta - Pro00045160, March 7, 2014.

Some of the research conducted for this thesis forms part of a national research collaboration, led by Dr. Sean Van Diepen at the University of Alberta. Chapters 2,3, and 4 of this thesis were published as Senaratne J., Norris C., Graham M., Nagendran J., Freed D., Afilalo J., Van Diepen S. (2016) *Clinical and angiographic outcomes associated with surgical revascularization of angiographically borderline 50-69% coronary artery stenosis.* European Journal of Cardiothoracic Surgery. 49:e112-e118. I was responsible for the initial study proposal, data collection, analysis, and manuscript composition. C. Norris assisted with data collection, statistical analysis, and manuscript composition. M. Graham assisted with the study proposal, data collection, and contributed to the manuscript edits. J. Nagendran assisted with the study proposal, and surgical data as well as manuscript edits. D. Freed assisted with the study proposal, surgical data, and manuscript edits. J. Afilalo assisted with the study proposal and manuscript edits. S. Van Diepen was the supervisory author and was involved with conception of the study, statistical analysis, manuscript composition, and manuscript editing. All authors approved the final work and agreed to be accountable for the data presented herewith.

Dedications

This thesis is dedicated to my wife, Dilmini, and to my parents who went through a lot of hardship in helping me achieve this goal.

Acknowledgements

I would like to acknowledge Dr. Sean Van Diepen as my supervisor for this project who has provided great guidance and mentorship over the past two years. I would also like to acknowledge Dr. Michelle Graham and Dr. Craig Butler as members of my supervisory committee.

I would like to acknowledge the following for their provision of funding for this project:

Faculty of Medicine and Dentistry, University of Alberta

Faculty of Graduate Studies and Research, University of Alberta

Government of Alberta

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List of Abbreviations

ABL	Angiographically borderline 50-69% lesions
APPROACH	Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease
CABG	Coronary artery bypass grafting
FFR	Fractional flow reserve
IQR	Interquartile ranges
LAD	Left anterior descending artery
LCx	Left circumflex artery
PCI	Percutaneous coronary intervention
RCA	Right coronary artery
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences

Introduction

Coronary artery bypass grafting (CABG) improves outcomes of patients with multi vessel coronary artery disease. [1-3] The historical criterion for a clinically significant coronary artery lesion requiring percutaneous or surgical revascularization has been defined as a ≥ 70% reduction of the angiographic coronary luminal diameter. [1,4,5] The recent introduction of fractional flow reserve (FFR) to identify the functional significance of a coronary stenosis in percutaneous coronary interventions (PCI) has reduced the number of PCIs and improved patient outcomes. [6] It has also led to the recognition that approximately 35% of angiographically borderline 50-69% lesions (ABLs) were functionally significant. [7] Comparatively little, however, is known about the potential risks and benefits of routine non-FFR guided surgical revascularization of these ABLs. In an environment where FFR is not routinely employed to evaluate the functional significance of ABLs in patients with significant stenoses of other major epicardial vessels suitable for surgical bypass, it remains unclear whether the routine bypass of ABLs in higher risk angiographic territories improves clinical outcomes.

Using a contemporary comprehensive provincial surgical registry of patients undergoing multi-vessel CABG, we sought to evaluate the incidence and outcomes associated with the grafting of isolated 50-69% angiographic stenoses of major epicardial vessels.

Methods

Data Source

The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) registry, as previously described, prospectively collects detailed information on all patients undergoing cardiac catheterization and cardiac surgery in the province of Alberta, Canada. [8,9] Individual patient demographic, medical, angiographic, surgical, and postoperative information is collected and entered into a database by trained cardiac catheterization laboratory and dedicated health information specialists at the time of all angiograms and cardiac surgeries. Mortality is tracked through a data linkage to the Alberta Bureau of Vital Statistics. [10] Approval for this study was given by the Human Research Ethics Board of the Research Ethics Office of the University of Alberta (Pro00045160).

Study Population

All patients who underwent an isolated first multivessel CABG between January 1, 2007 and December 31, 2013 at the Mazankowski Alberta Heart Institute with an isolated ABL on pre-operative angiogram were included in the study. An ABL was defined as an isolated 50-69% angiographic stenosis of a major epicardial vessel reported by the cardiologist performing the pre-operative angiogram. In order to minimize potential surgical selection bias associated with small territories at risk, only ABLs of the proximal or middle segment of the left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA), or a proximal stenosis of a major side branch were included. Epicardial segments were angiographically defined using previously published definitions (Table 1). [11] All 50-69% stenoses of the left main coronary artery or non-dominant RCAs were excluded. LAD or LCx 50-69% lesions in patients with ≥ 50% left main stenosis were also not considered as ABLs in this framework. Patients with an angiographic stenosis ≥70% in the same epicardial vessel as the ABL were excluded. The primary analysis compared clinical and angiographic outcomes between patients with and without coronary bypasses of ABLs.

Subsequently, a review of all angiographic reports of patients in the APPROACH registry with an ABL meeting study inclusion criteria was conducted to verify the patients identified by the ABL definition framework used in this study. During the study period, 3,195 patients underwent multi-vessel isolated CABG. Computerized selection of cases based on inputted catheterization and surgical variables identified 465 ABLs selected for individual chart review. Of these, 350 (75.3%) patients were accurately identified by the initial computerized selection. The remaining 115 (24.7%) were excluded. In addition, a chart review of all operative notes for the 350 patients with an ABL who underwent a CABG was conducted to validate whether the ABL was bypassed. FFR was not performed on any of the identified ABLs during the pre-operative angiogram.

Table 1: Angiographic Definitions

Vessel Location	Angiographic definition
LAD	
Proximal	From the LAD ostium to and including first major septal perforator branch
Middle	From the first major septal perforator branch to half of the distance from the first major septal perforator and the terminal end of the LAD
Proximal major side branch	Initial 1/3 of any large diagonal or ramus branch
LCx	
Proximal	From the LCx ostium to and including the first obtuse marginal branch
Middle	From the first obtuse marginal branch to and including the last obtuse marginal branch
Proximal major side branch	Initial 1/3 of any large obtuse marginal branch
RCA	
Proximal	From the RCA ostium to 1/2 of the distance to the acute margin of the heart
Middle	From 1/2 of the distance to the acute margin of the heart to the acute margin
Proximal major side branch	Initial 1/3 of any posterior descending artery branch

Abbreviations: LAD, Left anterior descending artery; LCx, Left circumflex artery; RCA, Right coronary artery

Missing Data

Missing data within the APPROACH database is inputted from Alberta Population health datasets maintained by Alberta Data Integration Management and Reporting. This data is linked using the hospital identification number as well as the provincial personal health numbers and are coded using the *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM). This data is pulled every 6 months and converted to the variables used in the primary APPROACH database for all missing datapoints using a pre-defined coding algorithm. [11]

Angiographic Subgroup Analysis

All patients who underwent a post-CABG angiogram during the study period were included in the angiographic analysis. If patients had more than one procedure, only the results of the last procedure were included. A chart review of all angiographic reports, produced by the performing cardiologist, was conducted to evaluate native epicardial disease progression and bypass graft patency.

Outcomes

In comparing patients with and without coronary bypasses of ABLs, the primary clinical outcome of interest was time to all-cause mortality from the time of surgery. Secondary clinical outcomes included death through end of follow up, death within 30 days and one year of CABG, length of intensive care unit stay, duration of mechanical ventilation, length of hospitalization, need for repeat revascularization (during total follow-up period), and peri-operative Type 5 myocardial infarction. In a pre-specified sensitivity analysis designed to select for patients with potentially a higher Duke Jeopardy Score and therefore a larger myocardial territory at risk, the primary outcome was evaluated in patients with ABLs of the proximal LAD, LCx, or RCA. [12]

In the subgroup of patients who underwent repeat angiography, the primary angiographic outcome was graft failure defined as graft occlusion, $\geq$ 80% stenosis, or string sign. [13] Secondary outcomes of interest included native disease progression defined as either a new $\geq$ 50% lesion in an arterial segment that was previously normal or a $\geq$ 20% progression in a previous lesion. [13]

Statistical Analysis

Categorical variables were summarized as percentages. Discrete variables were tested with the χ^2 test and Fisher's exact test was used when cell counts were <5. Continuous variables with parametric distributions were tested with the Student's *t*-test and summarized with means and standard deviations. Continuous variables with non-parametric distributions were tested with the Mann-Whitney U-test and reported as medians and interquartile ranges (IQR). A p-value of $\leq$ 0.050 was considered significant for all analyses. An analysis for subgroup effect using a p-interaction was carried out looking at whether the specific surgeon had a measurable effect on operative characteristics and clinical outcomes. Given that the primary outcome was time to all-cause mortality from the time of surgery and all data was right-censored with varying individual patient follow-up, the unadjusted survival distributions of the two groups were displayed using a Kaplan-Meier estimator. The log-rank test was used to compare the survival between cohorts. To adjust for baseline differences the Cox proportional hazard regression model was used to test for the difference in adjusted survival using hazard ratios. To ensure that the model was not overfitted, only 3 variables with a known association in CABG outcomes (age, diabetes, and current smoker) were included in the final model. To test the proportional hazards assumption of the Cox model, a test for correlation between the partial residuals (i.e. the residuals or error coefficients from the model adjusting for confounders) was used that indicated that the effect of using an ABL was not dependent on time. Data analysis was performed using the SPSS (Statistical Package for the Social Sciences; IBM Corp., Armonk, NY, USA) data management system version 23.

Results

Baseline Characteristics

Between January 1, 2007 and December 31, 2013, 3,195 patients underwent multivessel CABG surgery. A total of 350 patients had an isolated ABL of which 14.6% were in the LAD territory, 41.1% in the LCx, and 44.3% in the RCA territory. A bypass of the ABL vessel was performed in 268 (76.6%) patients. In the other 82 (23.4%) patients, the ABL was not bypassed with only severe lesions being bypassed. Follow-up in this cohort was 100%, the mean follow-up time was 4.2 (SD = 1.7) years with a final life status check in August of 2014. The maximum follow-up was 7.8 years.

The baseline characteristics are provided in Table 2. Patients with a bypassed ABL were older (66.1 versus 62.5 years, p=0.006) but were otherwise well balanced by sex, comorbidities, ejection fraction, and number of coronary stenoses.

Table 2. Baseline characteristics of patients with and without a bypass of angiographically borderline lesions

Baseline characteristic	Bypass of borderline lesions Yes n = 268	No n = 82	p-value
Demographics			
Age, mean (SD), years	66.1 (9.7)	62.5 (11.0)	0.006
Male, n (%)	225 (84.0)	67 (81.7)	0.632
Body mass index, mean (SD), kg/m^2	28.8 (4.7)	29.9 (5.2)	0.087
Medical history, n (%)			
Hypertension	229 (85.4)	73 (89.0)	0.410
Dyslipidemia	229 (85.4)	69 (84.1)	0.772
Type 1 Diabetes	11 (4.1)	3 (3.7)	0.857
Type 2 Diabetes	94 (35.1)	27 (32.9)	0.720
Prior myocardial infarction	65 (24.3)	25 (30.5)	0.258
Prior percutaneous coronary intervention	58 (21.6)	19 (23.2)	0.770
Congestive heart failure	17 (6.3)	4 (4.9)	0.625
Canadian Cardiovascular Society Class			
Class 0	10 (3.7)	10 (12.2)	
Class I	6 (2.2)	5 (6.1)	
Class II	74 (27.6)	28 (34.1)	0.005
Class III	54 (20.1)	9 (11.0)	
Class IV	115 (42.9)	29 (35.3)	
Not available	9 (3.4)	1 (1.2)	
Cerebrovascular disease	16 (6.0)	4 (4.9)	0.709
Chronic obstructive pulmonary disease	36 (13.4)	8 (9.8)	0.380
Current smoker	97 (36.2)	22 (26.8)	0.117
Ex-smoker	102 (38.1)	32 (37.8)	0.967
Peripheral vascular disease	24 (9.0)	8 (9.8)	0.826
Pre-operative dialysis	4 (1.5)	1 (1.2)	0.855

Pre-operative Investigations			
Left ventricular ejection fraction, n (%)			
>50%	90 (33.6)	33 (40.2)	
>34-50%	45 (16.8)	16 (19.5)	
>20-34%	9 (3.4)	1 (1.2)	0.428
<20%	2 (0.7)	2 (2.4)	
Not done due to emergency surgery	28 (10.4)	6 (7.3)	
Not available	94 (35.1)	24 (29.3)	
Creatinine, median (IQR), µmol/L	91 (26)	85 (26)	0.055
Pre-operative angiographic findings, n (%)			
No. of ≥ 50% left main stenoses*	51 (19.0)	23 (28.0)	0.080
No. of LAD stenoses			
≥ 70%	201 (75.0)	58 (74.4)	0.909
50-69%	161 (60.1)	42 (53.8)	0.326
No. of LCx stenoses			
≥ 70%	116 (43.3)	34 (43.6)	0.962
50-69%	155 (57.8)	43 (55.1)	0.671
No. of RCA stenoses			
≥ 70%	137 (51.1)	32 (41.0)	0.117
50-69%	168 (62.7)	52 (66.7)	0.520

* Limited to patients with 50-69% stenosis of the right coronary artery as per the inclusion criteria outlined in the methods section

Abbreviations: LAD, Left anterior descending artery; LCx, Left circumflex artery; RCA, Right coronary artery

Operative Characteristics

The operative variables stratified by ABL revascularization are listed in Table 3. The mean cardiopulmonary bypass time (104 versus 90 minutes, $p<0.001$) and aortic cross-clamp time (68 versus 60 minutes, $p=0.019$) were longer in patients with ABL bypass. The mean total per-patient number of coronary bypasses (3.51 versus 2.78, $p < 0.001$) and saphenous vein grafts (2.46 versus 1.96, $p < 0.001$) were higher in the ABL bypass group. The mean number of internal mammary artery bypasses was similar (1.03 versus 1.04, $p=0.530$). The cohorts were otherwise well balanced for surgical priority and operative transfusion requirements. The majority of patients with a bypassed ABL of the LAD received a left internal mammary artery graft while the majority of patients with a bypassed ABL of the LCx or RCA territory received a reverse saphenous vein graft (Table 3). An analysis for subgroup effect examining the interaction between individual surgeons and both operative characteristics and outcomes revealed significant differences in ABL bypass rates (p interaction=0.040), cardiopulmonary bypass times (p interaction=0.001), and aortic cross-clamp times (p interaction=0.001), but no significant interaction for all-cause mortality through follow-up (p interaction=0.190) between the different surgeons.

Table 3. Operative characteristics of patients with and without bypass of angiographically borderline lesions

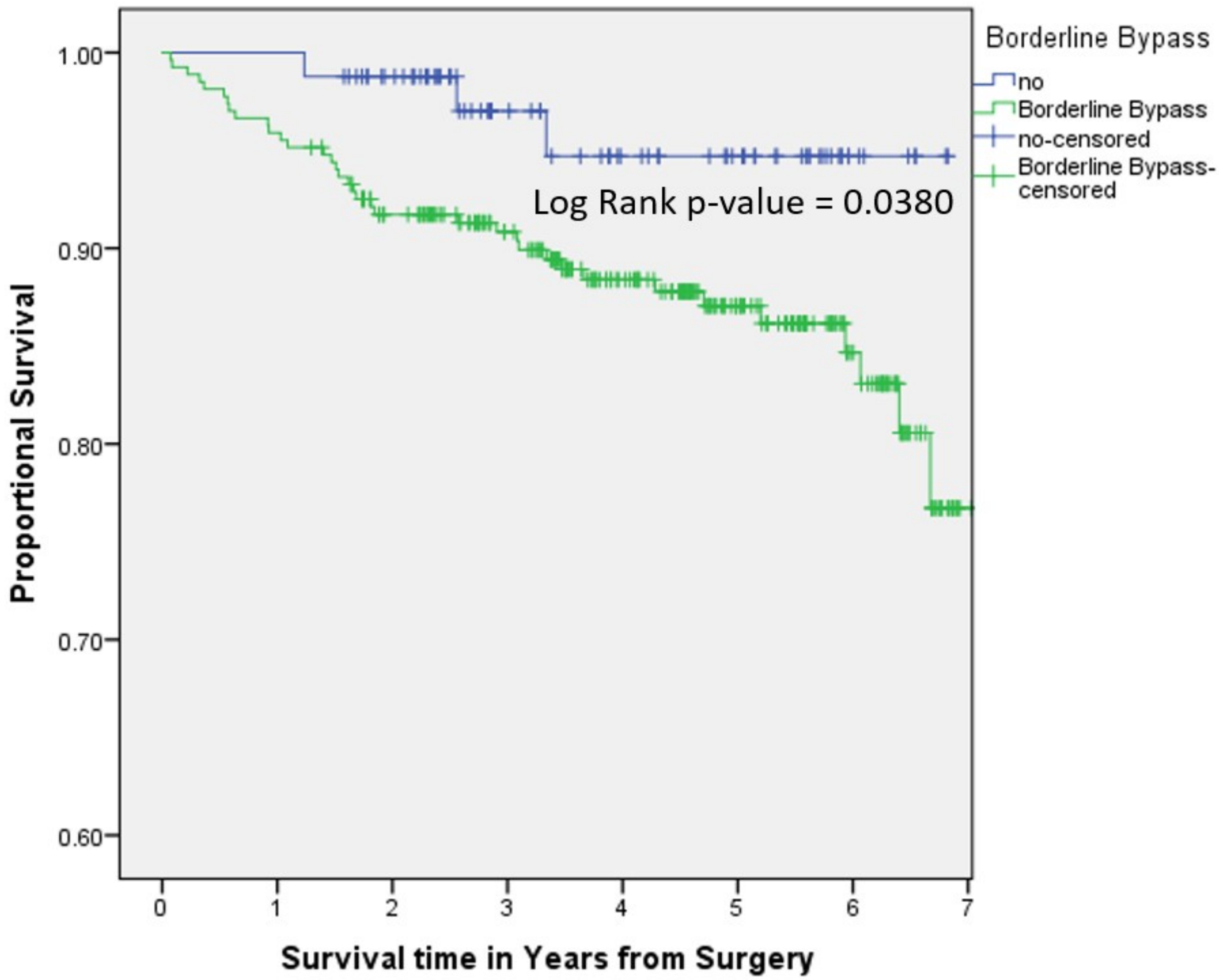
Operative characteristic	Bypass of borderline lesions		p-value
	Yes n = 268	No n = 82	
Surgical Priority, n (%)			
Emergent	6 (2.2)	2 (2.4)	0.865
Emergent salvage	1 (0.4)	1 (1.2)	
Urgent in-hospital	132 (49.3)	37 (45.1)	
Urgent out of hospital	119 (33.4)	38 (46.3)	
Non-urgent out of hospital	10 (3.7)	4 (4.9)	
Operative Characteristics			
Cardiopulmonary bypass time, mean (SD), min	104.2 (28.6)	90.4 (31.4)	<0.001
Aortic cross-clamp time, mean (SD), min	68.1 (25.2)	60.4 (28.0)	0.019
Intra-operative transfusions, median (IQR), units			
Red blood cells	0 (0)	0 (0)	0.303
Fresh frozen plasma	0 (0)	0 (0)	0.528
Bypass Graft Characteristics Per Patient			
Total bypasses, mean (SD)	3.51 (0.70)	2.78 (0.89)	<0.001
Total bypasses minus ABLs, mean (SD)	2.39 (0.78)	2.78 (0.89)	<0.001
Two or more ABLs, %	9.7	10.3	0.89
Internal mammary artery, mean (SD)	1.03 (0.16)	1.04 (0.20)	0.530
Reverse saphenous vein graft, mean (SD)	2.46 (0.75)	1.96 (0.83)	<0.001
Bypass Graft Characteristics of Borderline Lesions, n (%)			
Left anterior descending artery			
Left internal mammary artery graft	38 (84.4)	N/A	N/A
Reverse saphenous vein graft	7 (15.6)	N/A	N/A
Left circumflex artery			
Left internal mammary artery graft	4 (3.6%)	N/A	N/A
Reverse saphenous vein graft	108 (96.4%)	N/A	N/A
Right coronary artery			
Left internal mammary artery graft	4 (3.6%)	N/A	N/A
Reverse saphenous vein graft	107 (96.4%)	N/A	N/A

Clinical Outcomes

The unadjusted clinical outcome of all-cause mortality over a mean follow-up of 4.2 years was significantly higher in patients with ABL bypass (11.6% versus 3.7%, p=0.034; hazard ratio (HR) 3.25, 95% confidence interval [CI]: 1.0-10.6, Table 4). Figure 1 shows the time to all-cause mortality from surgery. Both unadjusted 30 day and 1 year mortality were numerically higher in the ABL bypass cohort, but did not reach statistical significance. In addition, no differences were observed in the incidence of repeat revascularization, hospital length of stay, intensive care unit length of stay, or duration of mechanical ventilation.

Table 4. Unadjusted primary and secondary clinical outcomes

Clinical outcome	Bypass of borderline lesions Yes n = 268	No n = 82	p-value
Mortality, n (%)	30 (11.6)	3 (3.7)	0.034
Death within 30 days, n (%)	3 (1.1)	0 (0.0)	0.336
Death within 1 year, n (%)	11 (4.1)	0 (0.0)	0.062
Intensive care unit stay, median (IQR), days	1.6 (2.0)	1.2 (1.9)	0.832
Duration of mechanical ventilation, median (IQR), hours	8.8 (7.6)	9.0 (7.3)	0.754
Length of hospitalization, median (IQR), days	6.0 (2.0)	6.0 (2.0)	0.650
Reoperation within 30 days, n (%)	14 (5.2)	2 (2.4)	0.291
Repeat revascularization, n (%)	12 (4.5)	1 (1.2)	0.172
Perioperative myocardial infarction, n (%)	5 (1.9)	1 (1.2)	0.667



Number at risk by year	0	1	2	3	4	5	6	7
No Borderline Bypass	82	82	73	46	34	26	7	7
Borderline bypass	268	257	230	196	154	104	54	2

Figure 1. Kaplan-Meier curve of unadjusted mortality of patients with and without a bypass of angiographically borderline lesions

Post-hoc analysis

In a post-hoc analysis, no differences in complications during the index intensive care unit stay were observed (Table 5). A review of all patient deaths was undertaken to ascertain the cause of death. There was no significant difference in cardiac arrest, and the majority of deaths in both groups were from non-cardiac causes (Table 6).

Table 5. Types of complications from surgery.

Complication Type, n (%)	Bypass of borderline lesions Yes n = 268	No n = 82	p-value
Any complications	119 (44.4)	37 (45.1)	0.909
Complications within 30 days	117 (43.7)	36 (43.9)	0.969
Post-operative Bleeding	2 (0.7)	2 (2.4)	0.207
Infectious complications	19 (7.1)	7 (8.5)	0.662
Neurologic complications	14 (5.2)	3 (3.7)	0.564
Pulmonary complications	35 (13.1)	10 (12.2)	0.838
Prolonged Ventilation > 24 hours	21 (8.6)	6 (7.5)	0.763
Renal complications	9 (3.5)	1 (1.2)	0.289
Dialysis	3 (1.2)	0 (0.0)	0.327
Complete heart block	2 (0.8)	0 (0.0)	0.424
Cardiac arrest	1 (0.4)	3 (3.7)	0.170
Cardiac tamponade	1 (0.4)	1 (1.2)	0.391
Perioperative myocardial infarction	5 (1.9)	1 (1.2)	0.667
Post-operative atrial fibrillation	70 (27.1)	24 (29.3)	0.706
Gastrointestinal complications	8 (3.1)	1 (1.2)	0.355
Gastrointestinal Bleeding	5 (1.9)	0 (0.0)	0.204
Mesenteric Ischemia	1 (0.4)	0 (0.0)	0.572
Intensive care unit readmission	7 (2.6)	1 (1.2)	0.460

Table 6. Cause of death.

Cause of death, n (%)	Bypass of borderline lesions Yes n = 268	No n = 82	p-value
Aortoenteric fistula	1 (0.4)	0 (0.0)	0.576
Brain cancer	1 (0.4)	0 (0.0)	
Cardiac arrest	3 (1.1)	0 (0.0)	
Congestive heart failure	1 (0.4)	0 (0.0)	
Cirrhosis	0 (0.0)	2 (2.4)	
Colon cancer	1 (0.4)	0 (0.0)	
Cerebrovascular accident	4 (1.5)	1 (1.2)	
End stage renal disease	1 (0.4)	0 (0.0)	
Hip fracture	1 (0.4)	0 (0.0)	
Lung cancer	7 (2.6)	0 (0.0)	
Mediastinal bleed from surgery	1 (0.4)	0 (0.0)	
Mesenteric ischemia	1 (0.4)	0 (0.0)	
Phrenic nerve injury from surgery	1 (0.4)	0 (0.0)	
Pneumonia	3 (1.1)	0 (0.0)	
Prostate cancer	2 (0.7)	0 (0.0)	
Saphenous vein graft site abscess	1 (0.4)	0 (0.0)	
Unknown	1 (0.4)	0 (0.0)	

Multi-variable regression analysis

After multi-variable adjustment, the association between ABL bypass and mortality was attenuated (HR 2.84: 95% CI, 0.87 – 9.23, p=0.080). This model adjusted for the variables age, diabetes, and current smoker. The pre-specified sensitivity analysis based on location of ABL suggested no significant differences in mortality based on the location of the ABL (Table 7), although confidence intervals were wide.

Table 7. Unadjusted and adjusted mortality by location of borderline lesion

Location of lesion	Bypass of borderline lesions Yes	No	Unadjusted hazard ratio (95% confidence interval)	Adjusted hazard ratio# (95% confidence interval)	p-value
All, n (%)	268 (76.6%)	82 (23.4%)	3.25 (1.00, 10.58)	2.84* (0.87, 9.23)	0.080
LAD, n (%)	45 (88.2%)	6 (11.8%)	0.70 (0.09, 5.75)	0.26† (0.03, 3.78)	0.27
LCx, n (%)	112 (77.8%)	32 (22.8%)	‡	‡	N/A
RCA, n (%)	111 (71.6%)	44 (28.4%)	2.66 (0.61, 11.67)	2.34† (0.53, 10.37)	0.26

* Adjusted for: Age at surgery, diabetes mellitus, and current smoker
† Adjusted for: Age at surgery
‡ There were no deaths in the group of patients with an angiographically borderline lesion of the left circumflex territory who did not have it bypassed
# Variables adjusted in model with associated individual hazard ratios (HR), 95% confidence intervals (CI), and p-values: Borderline lesion bypassed: HR=2.84, CI:0.87-9.23, p=0.071; Age at surgery: HR=1.06, CI:1.02-1.10, p=0.014; Diabetes mellitus: HR=1.21, CI:0.64-2.30, p=0.526; Current smoker: HR=1.81, CI:0.93-3.53, p=0.084
Abbreviations: LAD, Left anterior descending artery; LCx, Left circumflex artery; RCA, Right coronary artery

Angiographic substudy

During the follow-up period, of the 350 study patients, 46 patients (13.1%) underwent repeat angiography: 7 (8.5%) patients from the non-bypassed ABL group and 39 (14.6%) from the group that did have ABLs bypassed. The baseline characteristics of this subgroup were similar to the other 304 patients (86.9%) who did not undergo repeat angiography except for a higher incidence of cerebrovascular disease (13.0% versus 4.6%) in the group that had repeat angiography (Table 8). The incidence of native disease progression (48.7% versus 28.6%, p=0.324), graft failure (64.1% versus 42.9%, p=0.289), and repeat revascularization (30.8% versus 14.3%, p=0.372) in bypassed ABLs were all numerically, but not significantly higher in this small subset of patients.

Table 8. Angiographic substudy - Baseline characteristics of patients who underwent repeat angiography versus those that did not.

Baseline characteristic	Repeat Angiography Yes n = 46	Repeat Angiography No n = 304	p-value
Demographics			
Age, mean (SD), years	63.8 (10.7)	64.6 (9.98)	0.321
Male, n (%)	39 (84.8)	253 (83.2)	0.791
Body mass index, mean (SD), kg/m^2	29.6 (5.0)	28.9 (4.8)	0.394
Medical history, n (%)			
Hypertension	264 (86.8)	38 (82.6)	0.437
Dyslipidemia	41 (89.1)	257 (84.5)	0.415
Type 1 Diabetes	13 (4.3)	1 (2.2)	0.498
Type 2 Diabetes	107 (35.2)	14 (30.4)	0.527
Prior myocardial infarction	17 (37.0)	73(24.0)	0.061
Prior percutaneous coronary intervention	15 (32.6)	62 (20.4)	0.062
Congestive heart failure	4 (8.7)	17 (5.6)	0.409
Cerebrovascular disease	6 (13.0)	14(4.6)	0.022
Chronic obstructive pulmonary disease	7 (15.2)	37 (12.2)	0.561
Current smoker	18 (39.1)	101(33.2)	0.431
Ex-smoker	20 (43.5)	113(37.2)	0.411
Peripheral vascular disease	4 (8.7)	28 (9.2)	0.569
Pre-operative dialysis	0 (0.0)	5 (1.6)	N/A

Discussion

In an analysis of the largest registry-based cohort of patients with ABL undergoing CABG performed to date, several important and novel findings emerge. First, ABLs of major epicardial vessels are bypassed in more than 75% of surgical cases. Second, bypass of ABLs was associated with increased unadjusted long term mortality; however, after multivariable adjustment the association was attenuated. Third, in a limited subset of our study cohort that underwent repeat angiography post-CABG, graft failure, repeat revascularization, as well as native disease progression were all numerically higher in patients who had ABLs bypassed.

The current American College of Cardiology Foundation/American Heart Association CABG guidelines recommends that non-left main coronary artery lesions with < 70% reduction in angiographic luminal diameter should not be bypassed. [14] In contrast, the current European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines recommend complete revascularization of 50-89% lesions with an FFR≤0.8. [15] FFR has led to the recognition that only approximately 35% of ABLs are flow limiting. [7] In a clinical practice environment where FFR is not routinely used to evaluate the functional significance of ABLs in patients with documented surgical coronary artery disease in other major vessels, we observed that over 75% of all patients with ABLs in major epicardial vessels had bypass grafting. This rate is in keeping with other smaller contemporary studies which have reported a 55-84% bypass rate for ABLs. [16-19] Although the reasons underpinning the surgical decisions remain unknown, we hypothesize that the theoretical risk of leaving higher risk territories with potentially flow limiting lesions or the desire to facilitate complete revascularization at the time of surgery may be potential variables that influence surgical decisions. Given that the incidence of routine non-FFR guided bypass of ABLs is much higher than the reported 35% that FFR reclassifies as flow limiting lesions, our results suggest a systematic overuse of bypass grafts in these ABLs that is not supported by current clinical practice guidelines. [7,14] In addition, ABL bypass was associated with a significant increase in surgical resource utilization with longer cardiopulmonary bypass times and aortic cross-clamp times. These findings present an opportunity for future appropriate use quality improvement initiatives and highlights the potential role for multi-disciplinary Heart Team meetings to review and plan pre-operative revascularization strategies by consensus.

Previous studies have described high ABL bypass rates, but the reported associated outcomes have been limited to the incidence of postoperative graft failure. [20,21] No studies have examined clinical outcomes associated with ABL bypass. In this analysis, ABL bypass was not independently associated with mortality, though the hazard ratio point estimate suggested potential harm. The findings from this cohort study, although not powered for mortality, suggest that the bypass of ABLs does not improve survival while increasing the length of surgery and thus supports clinical practice guidelines that recommend that routine non-FFR guided bypass of ABLs is not warranted. Future studies in larger multi-center registries should be directed to confirm the potential harm signal observed in this dataset.

In our pre-specified subgroup analysis of all patients who underwent repeat angiography, the incidence of graft failure, repeat revascularization and native disease progression were all higher in bypasses of ABLs, though we acknowledge the small sample size in this subgroup. Although our results were not statistically significant, they are in keeping with previous studies that have shown that bypassing ABLs is associated with native coronary artery disease progression and graft occlusion. [16-19] Competitive flow is thought to be the putative mechanism underpinning these changes when hemodynamically non-significant lesions are bypassed. [21-23] Taken together, the findings of our study suggest that the routine non-FFR guided bypass of ABLs is not clinically warranted and that native disease progression and graft loss may be possible pathophysiologic mechanisms. We acknowledge, however, that further study is required to confirm these findings.

Limitations

The results of the study should be considered in the context of the limitations. First, FFR was not used to guide bypass grafting. Although FFR has been shown to reclassify 35% of ABL into significant lesions, there are only a few studies that have looked at FFR to guide bypass grafting, with no large randomized data showing a benefit in clinical outcomes. [24-25] FFR is costly and many centres do not use it routinely in patients with documented surgical coronary artery disease. Secondly, the angiographic subgroup analysis was limited to patients who underwent repeat angiography; thus a selection bias is possible. Thirdly, the angiographic interpretation of ABLs was based on the angiographer's interpretations. Although inter-observer variability is possible, the methods used reflect common clinical practice patterns. Lastly, EuroSCOREs were not available in this dataset

Conclusions

In the largest population based analysis examining outcomes associated with the bypass of 50-69% ABLs to date, we observed that approximately >75% of ABLS were bypassed despite guidelines currently recommending against the practice. Although mortality was numerically higher in the ABLs bypass cohort, an independent association with mortality was not observed.

Finally, graft failure, repeat revascularization, and native disease progression were numerically higher in bypassed ABLs. Our findings support clinical practice guidelines and suggest that the routine non-FFR guided surgical revascularization of borderline 50-69% lesions should not be performed and is potentially associated with a long term risk of graft failure.

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