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Clinical and Angiographic Outcomes in Coronary Artery Bypass Surgery with Multiple versus Single Distal Target Grafts

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ABSTRACT

Background: Coronary artery bypass grafting (CABG) with multiple distal target (MDT) grafts requires less graft material and reduces cardiopulmonary bypass time; however, there may be a higher incidence of graft failure. A real-world analysis reporting long-term outcomes associated with MDT grafts is lacking.

Material and Methods: In 6262 consecutive patients who underwent an isolated first CABG from 2004-2012, patients with MDTs were propensity matched to those with single distal target (SDT) grafts. Logistic regression adjusted for traditional, anatomical, and functional definitions of complete revascularization (CR). Outcomes included 30-day, 1-year, and long-term mortality (median 6.29 years).

Results: A total of 549 (8.8%) CABG patients had a MDT graft. CR defined using traditional (96.1% versus 92.0%, $P = .005$), anatomical (89.0% versus 80.20%, $P < .001$), and functional (90.7% versus 82.6, $P < .001$) definitions was more frequent in MDT patients. No significant differences in mortality were observed at 30 days (2% versus 3.3%, $P = .18$), 1-year (3.8% versus 4.9%, $P = .37$), or through end of follow-up (18.0% versus 16.6% $P = .52$) between the MDT and SDT groups, respectively. Similarly, no differences were observed after adjustment for all definitions of CR. Graft failure in MDT and SDT patients was 37.8% and 27.6%, respectively ($P = .18$).

Conclusion: In a contemporary population-based cohort, no differences in mortality were observed between CABG patients with MDT and SDT grafts. Our findings support the safety of MDT grafts to facilitate CR in patients and when graft material is limited.

INTRODUCTION

Coronary artery bypass grafting (CABG) improves outcomes in patients with multivessel coronary artery disease. The use of bypass grafts with multiple distal target (MDT) is an attractive alternative to grafts with a single distal target (SDT), as these require less graft material, are associated with shorter cardiopulmonary bypass time, and may help facilitate complete revascularization when graft material is limited [Bartley 1972; Flemma 1971].

Previous investigations and a systematic review have reported improved patency of MDT grafts [Farask 2003; Gao 2010; Kim 2011a; Li 2011; Oz 2006; Vural 2001]. These studies, however, were limited by small sample sizes, lack of clinical endpoints, and/or preceded the current era of secondary prevention pharmacotherapy. A secondary analysis of a multi-center study reported a higher incidence of graft failure and worse clinical outcomes using MDT grafts; however, the ex-vivo graft handling, study exclusion criteria, and lack of adjustment for complete revascularization may limit the generalizability of the results [Mehta 2011]. Therefore, in a large contemporary unselected real-world analysis, we sought to describe the clinical and angiographic outcomes in CABG patients with and without MDT grafts.

MATERIALS AND METHODS

Data Source

This study, and a waiver of patient consent in this prospectively collected data registry, was approved by the University of Alberta Health Research Ethics Board (Pro00042805). In this retrospective single center study, data were derived from The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) registry, which prospectively captures demographic, medical, cardiac catheterization, and cardiac surgery information on all patients in the province of Alberta, Canada [Ghali 2000; Norris 2000; van Diepen 2014]. Trained personnel in the cardiac catheterization lab and operating room staff enter demographic, medical, and procedural information at the time of each procedure. Mortality is tracked through an Alberta Bureau of Vital Statistics data linkage [Norris 2000].

Study Population

All patients ≥18 years old that underwent a first isolated CABG at the University of Alberta Hospital between January 1, 2004 and December 30, 2012 were considered. All

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Table 1. Baseline Characteristics in Patients Undergoing CABG with Multiple and Single Distal Targets in the Unmatched and Propensity Matched Cohorts

	Unmatched Cohort			Propensity Matched Cohort		
	MDTs n = 549	SDTs n = 5713	*P*	MDTs n = 549	SDTs n = 549	*P*
Age, y mean (SD)	66 (10.3)	65.5 (10)	.55	66 (10.3)	66 (9.6)	.72
Female, n (%)	94 (17.1)	997 (17.5)	.85	94 (17.1)	96 (17.5)	.87
Medical history, n (%)						
Hypertension	473 (86.2)	4865 (85.2)	.53	473 (86.2)	469 (85.4)	.73
Diabetes	231 (42.1)	2132 (37.3)	.03	231 (42.1)	220 (40.1)	.5
Dyslipidemia	539 (98.2)	5583 (97.7)	.5	539 (98.2)	540 (98.4)	.81
Current smoking History	154 (28.1)	1571 (27.5)	.93	154 (28.1)	163 (29.7)	.54
Prior myocardial infarction	351 (63.9)	3540 (62)	.6	351 (63.9)	367 (66.8)	.31
Prior PCI	83 (15.1)	1086 (19)	.07	83 (15.1)	85 (15.5)	.86
Heart failure	65 (11.8)	454 (7.9)	.003	65 (11.8)	64 (11.7)	.92
Cerebrovascular disease	62 (11.3)	699 (12.2)	.8	62 (11.3)	62 (11.3)	1.00
Peripheral vascular disease	55 (10)	468 (8.2)	.3	55 (10)	68 (12.4)	.21
Chronic lung disease	164 (29.9)	1631 (28.5)	.5	164 (29.9)	147 (26.8)	.25
Chronic liver disease	3 (0.5)	55 (1)	.009	3 (0.5)	2 (0.4)	.65
Preoperative dialysis	19 (3.5)	136 (2.4)	.03	10 (1.8)	12 (2.2)	.67
Previous malignancy	10 (1.8)	78 (1.4)	.4	31 (5.6)	35 (6.4)	.61
Preoperative investigations, n (%)						
Number of coronary stenosis (≥70%)			<.001			.65
1-2 vessel disease	19 (3.5)	424 (7.4)		19 (3.5)	22 (4)	
3 vessel disease	345 (62.8)	3150 (55.1)		345 (62.8)	326 (59.4)	
Left main	165 (30.1)	1894 (33.2)		165 (30.1)	182 (33.1)	
Unavailable	20 (3.6)	245 (4.3)		20 (3.6)	19 (3.5)	
Left ventricular EF, %			.02			.57
>50%	234 (42.6)	2236 (39.1)		234 (42.6)	212 (38.6)	
35-50%	125 (22.8)	1186 (20.8)		125 (22.8)	129 (23.5)	
20-34%	35 (6.4)	277 (4.8)		35 (6.4)	34 (6.2)	
<20%	8 (1.5)	69 (1.2)		8 (1.4)	15 (2.7)	
EF not available	147 (26.8)	1945 (34.1)		147 (26.8)	159 (29)	

MDTs indicates multiple distal targets; PCI, percutaneous coronary intervention; SDTs, single distal targets; EF, ejection fraction.

patients were followed for a minimum of 1 year. Exclusion criteria were prior CABG, cardiac transplant, or concomitant valve, aortic or left ventricular remodeling surgery. The APPROACH registry codes for the total number of aortic and coronary anastomoses for all internal mammary, radial, and saphenous vein grafts. MDT grafts were defined as any graft with >1 coronary distal anastomosis. This included T, Y, sequential and all types of MDT grafts. The surgical operative reports of all MDT patients identified in the APPROACH registry were independently reviewed by a physician (AA) to confirm that MDT cohort only included patients with MDT bypasses.

To mitigate potential confounding associated with complete revascularization (CR), 3 published definitions of CR were evaluated in all patients [Christenson 1998; Ouzounian 2010]. Complete traditional revascularization (CTR) was defined as at least 1 bypass graft performed in each major arterial territory (left anterior descending [LAD], left circumflex [LCx], and right coronary artery [RCA]) with a ≥70% angiographic stenosis (or ≥50% left main [LM] stenosis with LAD and LCx territory grafts) [Caputo 2005; Rastan 2009]. Complete anatomical revascularization (CAR) was defined as at least 1 bypass graft performed in all coronary arteries >1.5 mm in diameter and ≥70% angiographic stenosis (or ≥50% LM with LAD and LCx territory grafts) [Kim 2011b; Gossl 2012; Zimarino 2005]. Complete functional revascularization (CFR) was defined using CAR criteria unless one of the following exceptions applied: (1) nonviable myocardium in the vascular territory; (2) fractional flow reserve (FFR) documented a non flow limiting lesion; or (3) the target vessel was not graftable intraoperatively due to technical factors (example: no lumen found or vessel too small) [Gossl 2012; Zimarino 2005; Alexander 2005]. CR definitions were adjudicated with a focused review (AA, JS, MA, SA) of the angiographic diagrams, operative notes, and the viability studies preceding CABG.

Angiographic Sub-Analysis

In an exploratory secondary analysis limited to patients who underwent coronary angiography within the province of Alberta after the index CABG were included in the angiographic analysis. Angiography was not protocolized and patients were included if they underwent any clinically driven angiogram during the follow-up period. If more than one angiogram was performed, only the last angiogram was included in the analysis. Graft failure in MDT and SDT grafts was defined as ≥75% angiographic stenosis [Alexander 2005; Hwang 2010; Kim 2014].

Clinical and Angiographic Outcomes

The primary analysis compared propensity matched outcomes in patients with and without MDT grafts. Clinical outcomes of interest were 30-day, 1-year, and overall mortality. The angiographic outcome of interest was the per-graft incidence of graft failure.

Statistical Analysis

Baseline categorical variables were compared between the 2 groups using the chi-square test for categorical data. All continuous variables had parametric distributions and were compared with t tests. As in all nonrandomized studies, the direct comparisons of distinct groups may be misleading because the groups generally differ systematically. To obtain a comparable distribution of demographic, comorbidities, and clinical variables among patients with MDT grafts compared to patients with SDT grafts, we used the Rosenbaum and Rubin propensity-score matching technique. The propensity score was calculated as the probability of having had MDT grafts conditional on the observed baseline and surgical characteristics. This technique allows for a high number of confounding variables and has been used to create a stratum of subjects who can be matched on the propensity score whereby exposure (MDT grafting) is not confounded with measured baseline covariates. The propensity score was calculated using logistic regression. The following variables were included in the model: age, sex pulmonary disease, cerebrovascular disease, renal disease, heart failure, diabetes, malignancy, peripheral vascular disease, liver disease, surgical priority, pump time, prior MI, prior PCI, and ejection fraction <20% or 20-34%. Greedy matching techniques were applied to match patients with MDT grafts to patients whose CABG included SDT grafts only by matching the participants with the nearest propensity score, ie, within 2 decimal places of the propensity score for each case. Overlap of propensity scores between MDT and SDT patients were evaluated using histograms, and χ^2 values and probability values. Differences in baseline factors between groups were calculated before and after propensity adjustment to assess balance. Following the match, Kaplan-Meier curves and log rank tests were used to determine if there was a statistically significant survival differences between MDT and SDT patients. Similarly, Cox regression analysis was used to test whether there were statistically significant differences in survival between MDT and SDT patients following adjustment for all clinical and comorbid variables. Clinical outcomes were further assessed using logistic regression to adjust for complete revascularization (using the 3 categories of CR) in the propensity matched patients with and without MDT grafts. Data analyses were performed using the SPSS (Statistical Package for the Social Sciences; IBM, Armonk, NY, USA) data management system, version 23.

RESULTS

Between 2004 and 2012, 8005 patients underwent CABG surgery. A total of 1743 patients had a prior CABG, cardiac transplant, concomitant valve, aortic or left ventricular remodeling surgery. The propensity matched study population included 1098 patients and was followed for a median of 6.29 years (range 1 day-10.9 years). In this cohort, 549 (8.8%) patients had at least one MDT graft. The baseline clinical characteristics of patients with and without a MDT graft in the overall and propensity matched cohorts are presented in Table 1. In the unmatched cohort, patients with MDT grafts were more likely to have preoperative diabetes, heart failure, renal failure, triple vessel disease, or reduced left ventricular systolic function. In the propensity matched cohort, the clinical characteristics were well balanced in the MDT and SDT cohorts.

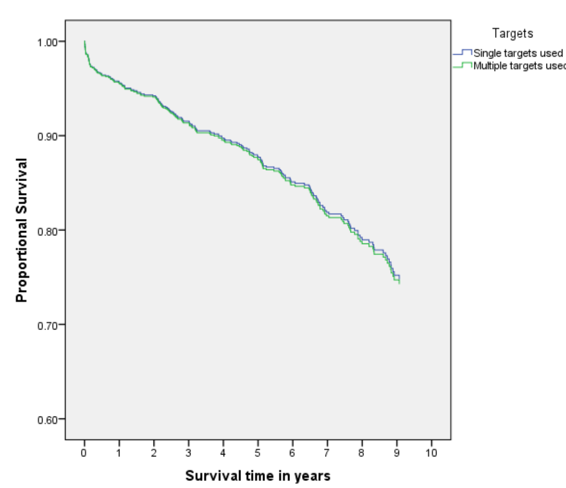

Figure 1. Kaplan-Meier curves of patients with multiple and single distal targets through end of follow-up.

Table 2. Operative Variables in Patients Undergoing CABG with Multiple and Single Distal Targets Unmatched and Propensity Matched Cohorts

	Unmatched Cohort			Propensity Matched Cohort		
	MDTs n = 549	SDTs n = 5713	*P*	MDTs n = 549	SDTs n = 549	*P*
Surgical priority, n (%)						
Emergent	11 (2)	194 (3.4)	.15	11 (2)	23 (4.2)	.06
Emergent salvage	1 (0.2)	3 (0.05)		1 (0.2)	0 (0)	
Urgent in-hospital	292 (53.2)	2883 (50.4)		292 (53.2)	267 (48.6)	
Urgent out-of-hospital	210 (38.2)	2290 (40.1)		210 (38.2)	232 (42.3)	
Elective	35 (6.4)	343 (6)		35 (6.4)	27 (4.9)	
Intraoperative variables						
Cardiopulmonary bypass time, min, mean (SD)	130 (30)	99.7 (33)	<.001	130 (30)	129 (31)	.53
Aortic cross-clamp time, min, mean (SD)	95 (25)	64.2 (30)	<.001	95 (25)	88 (51)	.003
Graft variables						
Distal anastomoses, total (mean per patient)	2607 (4.7)	19,116 (3.3)	<.001	2607 (4.75)	2097 (3.82)	<.001
Type of graft, n (%)						
Saphenous vein grafts	1996 (71.8)	12,675 (65.9)	<.001	1996 (71.8)	1497 (72)	.28
LIMA	525 (26.8)	5,386 (28)	.004	525 (26.8)	511 (24.5)	.02
RIMA	11 (0.5)	153 (0.8)	.23	11 (0.5)	10 (0.6)	.83
Radial	36 (0.9)	536 (2.8)	.19	36 (0.9)	62 (2.9)	.005

LIMA indicates left internal mammary artery; MDTs, multiple distal targets; RIMA, right internal mammary artery; SDTs, single distal targets.

Operative characteristics in patients with and without MDT grafts before and after propensity matching are provided in Table 2. Patients with MDT and SDT grafts had similar surgical priorities and cardiopulmonary bypass time. Aortic cross clamp time and the number of distal anastomoses were significantly higher in the MDT cohort. A total of 440 (98.4%) of MDT grafts were venous and only 9 (1.6%) were arterial mammary MDT grafts.

Complete Revascularization

Complete revascularization data was available for 1077 (98.1%) patients (537 MDT and 540 SDT patients). CTR was achieved in 1013 (94%) of patients (96.1% MDT and 92.0% SDT, P = .005); CAR was achieved in 911 (84.6%) of patients (89.0% MDT and 80.20% SDT, $P < .001$); CFR was achieved in 933 (86.6%) of patients (90.7% MDT and 82.6% SDT, $P < .001$).

Clinical Outcomes

In the propensity matched cohorts, no statistically significant differences in all-cause mortality were observed at 30 days (2% versus 3.3%, P = .18), 1 year (3.8% versus 4.9%, P = .37) or through end of follow up (18.0% versus 16.6%, P = .52) among MDT and SDT patients, respectively (Figure 1). After adjusting for the three definitions of CR, the association remained nonsignificant (Table 3; Figure 2).

Angiographic Outcomes

A total of 357 patients (5.7 %) underwent angiography a median of 3.2 years after CABG. The baseline characteristics of patients who had, and did not have, a follow-up angiogram in the overall (non-propensity matched) cohort are presented in Appendix 1. Patients with a post-CABG angiogram were more frequently younger, had a previous myocardial infarction, percutaneous coronary intervention, and preoperative 3 vessel coronary artery disease. The total number of grafts in this secondary analysis was 1172 including 37 MDT grafts and 1135 SDT grafts. The per-graft incidence of graft failure in patients with MDT and SDT grafts was 37.8% and 27.6% (P = .18), respectively.

DISCUSSION

In this large unselected contemporary population-based cohort of patients undergoing isolated first CABG surgery, several important findings emerge. First, we observed that MDT grafts use was 8.8%. Second, MDT grafts use was associated with higher rate of CR; however, MDT grafts use was not associated with change in mortality in the propensity matched analysis or after adjusting for CR. Finally, no difference in the incidence of graft failure was observed among patients who underwent an angiogram after the index CABG.

Table 3. Propensity Matched Clinical Outcomes for Multiple Versus Single Distal Targets Adjusted for 3 Definitions of Complete Revascularization

	Complete Revascularization Definition					
Outcome	Traditional OR (95% CI)*	*P*	Anatomical OR (95% CI)*	*P*	Functional OR (95% CI)*	*P*
30-day mortality	0.63 (0.29-1.37)	.25	0.63 (0.29-1.37)	.25	0.61 (0.28-1.33)	.21
1-year mortality	0.79 (0.44-1.43)	.45	0.8 (0.44-1.44)	.45	0.78 (0.43-1.42)	.43
Mortality to end of follow-up	1.03 (0.77-1.37)	.81	1.02 (0.76-1.36)	.87	1.02 (0.76-1.36)	.89

*Reference group is a propensity matched patient with single distal targets after adjusting for complete revascularization according to each complete revascularization definition.

The reported frequency of MDT grafts ranges from 20-53% [Farsak 2003; Kim 2011a; Vural 2001; Mehta 2011; Ouzounian 2010]. In this analysis, we observed that MDT grafts were used somewhat less frequently than previously described. We hypothesize the difference may be due to local practice patterns or a high internal mammary artery graft use in this contemporary population which may potentially decrease the need for graft material to achieve complete revascularization. In addition, we observed that MDT grafts were more frequently used in patients with comorbidities that portend a higher perioperative risk such as diabetes, triple vessel disease, reduced left ventricular ejection fractions, and renal failure. Moreover, MDT patients had a mean of nearly 5 distal anastomoses and longer cardiopulmonary bypass times. Although causality cannot be inferred, our findings suggest that MDT grafts are being used in a higher risk group of patients to potentially help facilitate complete revascularization or to shorten cardiopulmonary bypass times. Additionally, MDTs use may reflect individual surgeon or institutional preferences. These findings and the reasons underpinning MDT versus SDT grafting decisions are directions for future research.

Most previous MDT graft studies were designed to evaluate graft patency and few evaluated clinical outcomes [Farsak 2003; Gao 2010; Kim 2011a; Li 2011; Oz 2006; Vural 2001]. The studies that have reported clinical outcomes have disparate results. Christenson et al found that MDT grafts were associated with reduced in-hospital mortality, while a retrospective analysis by Ouzounian et al reported that MDT grafts were not independently associated with in-hospital or long-term mortality [Christenson 1998; Ouzounian 2010]. This analysis did not propensity match patient samples, raising the possibility of residual indication bias, and the incidence of MDT grafts in this study was over 50%, which may suggest a more liberal use of MDT grafts beyond achieving complete revascularization when graft material is limited. The most recent evidence comes from a secondary analysis by Mehta et al. from the Project of Ex-Vivo Vein Graft Engineering via Transfection (PREVENT IV) trial, which showed that MDT grafts were associated with a higher incidence of a 5 year composite of death, MI or revascularization; an observation driven principally by perioperative MI [Mehta 2011]. This raised concerns regarding the safety of MDT grafts, but these results may not be generalizable to all CABG patients given the ex-vivo graft handling mandated by the trial. In this real world analysis, we observed no difference in short-term, 1-year, or overall mortality between propensity matched patients with and without MDT grafts.

In an exploratory angiographic analysis, we observed no differences in the incidence of graft failure. This finding differs with those of Mehta et al who reported reduced 1-year patency rates of MDT saphenous vein grafts [Mehta 2011]. The potential causes for decreased durability include decreased flow and increased intimal proliferation, especially distal to the graft branching. Prospective human studies have reported both higher and lower blood flow rates in MDT grafts [Kim 2011a; Forcillo 2014; Jung 2012; Manncio 2015; O'Neill 1981]. Importantly, in animal studies, lower graft flow rates have been associated with intimal proliferation [Faulkner 1975; Rittgers 1978]. We acknowledge the limitations of the small and selected angiographic cohort in this analysis; however, these results provide a structural correlation to the primary clinical endpoints in this analysis. Future

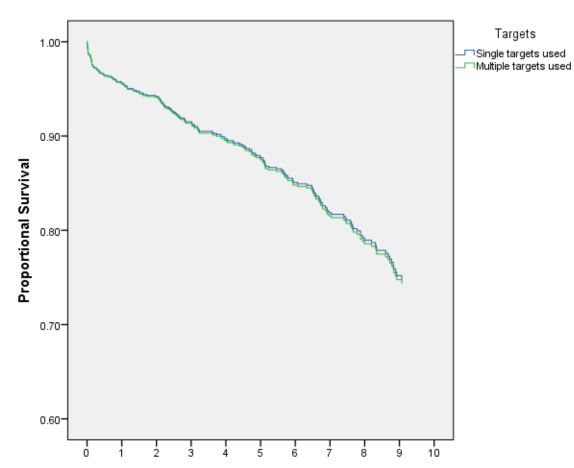

Figure 2. Kaplan-Meier survival curves for multiple and single distal targets after adjusting for 3 definitions of complete revascularization: traditional; anatomical; functional.

research should be directed at confirming our finding in a large unselected CABG cohort and elucidating the pathophysiologic link between MDT grafts and potential graft failure. Taken together, our analysis suggests that CABG surgery with SDT grafts may be more durable and should be used preferentially over MDT grafts under ideal surgical conditions. However, the lack of an observed mortality difference, coupled with similar findings in other studies, suggests the potential safety of MDTs to facilitate complete revascularization when graft material is limited [Mehta 2011; Christenson 1998; Ouzounian 2010].

Study Limitations

The limitations of this study merit consideration. First, this was a retrospective cohort analysis and the results should be considered hypothesis generating; however, it is the largest contemporary population based analysis to date. Secondly, the angiographic analysis was limited to patients undergoing repeat catheterization and thus the results may be subject to a selection bias. Third, the database did not contain information of target vessel or graft quality. Finally, medications at the time of hospital discharge were not available in this dataset, but recently published results of pharmacy chart audits in this population have reported the adherence to aspirin, B-blockers, and statins at the time of hospital discharge were 95%, 84%, and 84%, respectively [Barry 2014].

Conclusion

In a large contemporary population-based propensity matched cohort, no differences in mortality were observed between coronary bypass patients with MDT and SDT grafts. Our findings support the safety of MDT grafts to facilitate complete revascularization for patients at higher risk and when graft material is limited.

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