Characteristics and Outcomes of Patients Undergoing Percutaneous Coronary Intervention within 1-year of Coronary Artery Bypass

Graft Surgery

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Abstract

Objectives: The aim of this study was to examine the clinical and procedural outcomes of patients undergoing Percutaneous Coronary Intervention (PCI) within 1 year of Coronary Artery Bypass Graft surgery (CABG).

Background: CABG is the preferred revascularisation strategy for patients with complex coronary artery disease due to a lower rate of repeat revascularization. Despite advances in surgical technique and medical therapy, > 5% of patients require repeat revascularization within 1 year of CABG.

Methods and Results: Patients who underwent PCI within 1 year of CABG were identified from a prospective registry with data on over 20,000 PCI procedures (April 2000 - June 2011). 203 post CABG patients underwent 228 PCI procedures on 390 lesions during this period. 45% of patients had elective PCI while 55% had PCI on an urgent basis. 81% of PCI was performed in native coronary arteries, usually following graft failure in a previously grafted vessel (60%) or in an ungrafted native vessel (21%).

Conclusions: Patients who required PCI within 1 year of CABG were more likely to present on an urgent basis and have PCI performed in grafted native coronary vessels. However, nearly third of the patients had PCI to an ungrafted native vessel or to a lesion in the native vessel where the graft was still patent. Further studies are needed to determine whether the use of hybrid revascularization strategies (combination CABG and planned PCI) in appropriate patients could reduce the need for urgent PCI within the first year after CABG.

Abbreviations

CABG	Coronary artery bypass grafting
PCI	Percutaneous coronary intervention
QCA	Quantitative coronary angiography
CAD	Coronary artery disease
ACS	Acute coronary syndrome
LITA	Left internal thoracic artery
SVG	Saphenous vein graft
QCA	Quantitative Coronary analysis

INTRODUCTION

Coronary artery bypass graft surgery (CABG) remains the preferred strategy for revascularization of patients with complex left main and / or 3-vessel coronary artery disease (1,2). The long term success of CABG is dependent on graft patency after the surgery. Despite advances in surgical technique and medical therapy, early vein graft failure (VGF) remains one of the leading causes of poor outcome after CABG (3).

Almost 10% to 15% of venous grafts occlude within 1 year and almost half of venous grafts fail at 10 years(3-9).

Vein graft failure contributes to considerable morbidity through recurrent angina, myocardial infarction (MI), repeat revascularisation and increased mortality(10,11)

Previous studies have mainly evaluated the predictors of late graft patency (12,13).

Early occlusion (before hospital discharge) has been found to occur in 7 to 10% coronary grafts(14). Optimal blood glucose control and pump time < 2 hours was noted to predict graft patency within first week after successful CABG surgery(15).

Early (within 2 years) graft failure affects long-term mortality.(10) The longevity of the graft conduit depends on many factors, including the quality, size, and diameter of the saphenous vein; the size and diameter of the target vessel; surgical skills; intraoperative handling of vein graft, clamp and perfusion times (15-17). The rate of repeat revascularization in the first year was 2% in a large US registry(18) and 5.8% in the SYNTAX trial(1).

The objectives of the present study were twofold: (1) to examine the clinical and procedural characteristics of patients who undergo PCI within 1 year of CABG (i.e. those patients who experience clinical failure post CABG) and (2) to identify predictors of graft failure in this cohort of patients.

MATERIALS AND METHODS

Patient population

All patients undergoing percutaneous coronary intervention (PCI) at the Peter Munk Cardiac Centre, University Health Network (Toronto, Canada) are enrolled into a dedicated prospective registry(19). This database was used to identify all patients who underwent PCI within 1 year of CABG at Toronto General Hospital, between April 1, 2000 and June 30, 2011. Patients who had CABG more than 1 year from index PCI procedure were excluded. We also excluded patients who had planned PCI as a part hybrid procedure after CABG. Data were abstracted from the registry, as well as from review of patient charts and coronary angiograms. The angiographic graft patency was graded as- fully patent with good antegrade flow (TIMI 3), patent with stenosis or compromised flow (TIMI 1-2) or occluded (TIMI 0 flow). Quantitative coronary angiography (QCA) was used to identify predictors of graft failure in a subset of 113 patients (314 grafts). Local research ethics board approval was obtained for this study.

Indications for PCI were defined as emergent PCI if it included primary, facilitated, or rescue PCI; urgent PCI referred to any procedure for non ST-elevation acute coronary syndromes or > 48 hours after ST-elevation MI; salvage PCI referred to PCI performed when there was no surgical revascularization option and elective PCI if patient presented with stable angina symptoms and positive functional or imaging non-invasive test for inducible ischemia.

QCA Substudy

In the QCA substudy, we assessed the patency of all grafts in each patient at the time of presentation for PCI. We also evaluated a number of angiographic variables

relating to the bypass graft and the native vessel, which we considered important in maintaining graft patency based on our review of the literature and clinical experience. These variables were compared between patent grafts and occluded grafts in order to identify significant differences. The specific variables studied included proximal graft diameter (measured at the ostium), distal graft diameter (measured 10 mm before the distal anastomosis), native coronary artery diameter (measured 10 mm after the anastomosis), the ratio of graft diameter to native coronary artery diameter, and the distal runoff (the distance from the graft insertion to the end of the most distal branch of that vessel). We also measured the severity of the stenoses in the native coronary artery both proximal and distal to the anastomosis. The degree of the most severe stenosis within each segment was visually estimated as a percentage diameter stenosis in relation to an appropriate adjacent reference diameter.

The diameters of graft and native vessels were measured using QAngio XA version 7.3.64.0-x86 (Medis Medical Imaging Systems Inc. Leiden, The Netherlands) QCA software. The measurements were calibrated by convention using the diameter of the contrast-filled straight section of the distal portion of the diagnostic catheter. The measurements were performed by two cardiologists independently. 284 grafts were present in 203 patients.

Procedural parameters

Procedural success was defined as <20% residual stenosis with TIMI 3 flow in the target vessel. Major adverse cardiac and cerebrovascular event (MACCE) was defined as the composite of in-hospital mortality, myocardial infarction (MI) and stroke. Peri-procedural MI was defined as rise in cardiac biomarkers (CK) >3 times of upper limit of normal (ULN). A rise in creatinine of >25% 3- days after procedure was defined as

acute renal failure and a drop in haemoglobin >5g with or without hemodynamic instability or requiring blood transfusion was defined as major bleeding.

Statistical analysis

Continuous data are presented as mean $\pm$ standard deviation (20) or median (Inter Quartile Range {IQR}), and categorical data are presented as percentages.

Differences between groups were assessed using Chi-square test or Fisher's Exact test, as appropriate. Differences in angiographic parameters (continuous variables) of patent and occluded grafts were assessed by the Mann-Whitney-u test. A p-value < 0.05 was considered to be statistically significant.

Missing variables were not replaced and excluded from the analysis. Angiographic predictors of an occluded graft were assessed by forward stepwise logistic regression modelling. Variables included were graft proximal diameter, graft distal diameter, length of run off and native vessel proximal diameter. Continuous variables with non-normal distribution were log transformed prior to inclusion in the regression model.

In addition, Receiver Operating Curves (ROC) were computed to assess the discriminatory power of the native artery proximal diameter, graft proximal diameter, graft distal diameter and length of run off to predict occluded versus patent grafts.

RESULTS

Baseline Characteristics

A total of 20,058 PCI procedures were performed at our institution during the study period. Of these, 203 patients underwent 228 procedures on 390 lesions within 1-year of having CABG surgery. The baseline characteristics of the study population are

outlined in Table 1. Median age was 63 years (range 55.5-70 years) and 28.1% were female (57/203).

Forty-one percent of patients had diabetes mellitus. The surgical details of these patients are summarized in Table 2. This was a contemporary cohort of surgical patients with 1 in 3 patients having left main disease, 96% underwent multivessel CABG and over 80% received a left internal thoracic artery (21) (21) bypass graft.

Procedural characteristics

Fifty-five percent of patients had PCI on an urgent basis, 3% with STEMI and 1% in cardiogenic shock. The remainder had elective PCI, usually for recurrence of symptoms. Two patients had elective PCI as part of a planned hybrid revascularization strategy who were excluded from the analysis. The rate of PCI per month was equally distributed throughout the first year after CABG (Figure 1), although there were more patients with urgent unplanned PCI in the early months.

The median number of days between bypass surgery and the index PCI procedure was 162 days. The PCI details are outlined in Table 3. Many of the procedures involved multiple lesions (average 1.7 lesions/procedure) and 95% of lesions were treated with stents (5% balloon angioplasty only). Only 52% of patients were treated with drug-eluting stents (DES), although this increased over the course of the study (data not shown). The majority of cases (80%) were performed via femoral access.

The majority (64%) of PCI procedures in this cohort were secondary to graft failure. We found that 45% of patients had PCI on a previously grafted native vessel due to failure of the graft and 19% of patients had PCI on a failed bypass graft. Fifteen percent of patients had PCI on a grafted native vessel where the graft was still patent

(e.g. a lesion distal to the insertion site) and 21% of patients had PCI on an ungrafted native vessel. Of those who had PCI to ungrafted native vessels, the lesions were already considered significant but the vessels were not grafted due to size or location. Nearly 90% of the graft interventions were due to anastomotic lesions: 31% at the proximal anastomosis and 57% at the distal anastomosis. Only 12% of graft interventions were in the body of a graft.

Procedural outcomes

The procedural outcomes are summarized in Table 4. The procedural success rate was 97% with a low-rate of major adverse cardiac events (0.4% MI, 0.4% CVA, 1.3% mortality). The rate of major bleeding was 3.1%

Angiographic Predictors of graft failure

Grafts were classified into two groups: patent (176/284, 61.97%) and occluded (109/284, 38.38%). Median native artery length was greater in the patent grafts (2.0 mm { 1.69-2.32}) compared to the occluded grafts (1.65 mm {1.42-1.90}, z score= 6.0, $p<0.05$) as was median length of run off (patent graft 65.6 mm {55-79.1} versus occluded graft 55 mm {44.9-67.3}, z score= 5.15, $p<0.05$) (table 5).

Forward stepwise logistic regression analysis demonstrated that graft distal diameter was a significant predictor of an occluded graft (OR 2.54, 95% CI 1.62-3.98, $p<0.0001$).

ROC analysis of a total of 284 grafts demonstrated significant accuracy of the native artery proximal diameter to predict graft patency with an Area Under the Curve (AUC) of 0.712 (95% CI 0.655-0.764, $p<0.0001$) as shown in figure 2. A native

artery diameter of >1.8 had a sensitivity of 60.2% and a specificity of 71.3% (Youden Index $J=0.315$) in predicting graft patency at a median time of 162 days (5.4 months).

Graft proximal diameter, graft distal diameter and length of run off were significant but modest predictors of graft patency (Table 6). Grafts were more likely to be occluded beyond 6 months post CABG.

DISCUSSION

There are several key findings from this study. Firstly, patients requiring PCI within 1 year of CABG were more likely to present on an urgent basis. Secondly, the majority of these patients underwent PCI because of graft failure and almost 90% of graft interventions were due to anastomotic lesions. Thirdly, significant predictors of graft failure include small graft size, small native artery size, poor distal run-off and distal disease. Fourthly, third of the patients had PCI to an ungrafted native vessel or to a lesion in the native vessel where the graft was still patent (eg. lesion distal to the insertion site).

Predictors of early graft failure

Patient characteristics

In this study, 41% of patients who had PCI within 1 year of CABG had diabetes mellitus. The prevalence of diabetes mellitus in our study population is similar to previous longitudinal angiographic studies by Sabik and colleagues(22), who examined 10,000 venous and internal artery bypass grafts. However, the effect of diabetes on graft patency was not consistent. In the follow-up studies by Shah and colleagues(23) and Bypass Angioplasty Revascularisation Investigation(24), the

presence of diabetes was not a significant factor for saphenous graft attrition in follow-up.

Angiographic predictors of graft failure

Size of target vessel

The size of the distal vessel diameter was a significant independent predictor of graft patency in this study. In published literature, vessel diameter has an important impact on graft patency with smaller vessel diameter being associated with a lower patency rate in saphenous vein grafts(12). Several factors may lead to diminished patency in conduits grafted to smaller target vessels. Size mismatch, particularly when larger (3.5- to 4-mm) saphenous veins are grafted to small targets, may predispose to impaired nonlaminar flow patterns, which result in stimulus for endothelial dysfunction, early intimal hyperplasia or graft occlusion and flow from collateral vessels (25). Small distal targets may be more technically difficult to graft and may have significant disease at or adjacent to the anastomotic site itself. In contrast, larger-calibre target vessels would be expected to have better distal run-off. Our findings are consistent with a recent study that showed a significantly lower patency rate of 79% in vessels with a diameter less than 2.0 mm, and 96.1% in vessels with a diameter exceeding 2.0mm (p=0.0001)(26).

Distal anastomotic lesion

A large proportion of graft failure were related to the presence of distal anastomotic lesions. Angiographic studies have shown occlusive disease at the anastomotic site or in the graft itself in <one-third of patients in the 10 years after surgery (27,28) with distal anastomotic lesions being the most common reason for venous graft failure

(29). Symptoms that recur within days after surgery are usually due to venous graft thrombosis, but may be due to failure of the surgical techniques at the site of the anastomosis (30). Distal anastomotic lesions that occur during the first year are thought to be due to fibrointimal hyperplasia. Thereafter, atherosclerosis begins to contribute to the pathogenesis becoming the predominant cause after 3 years (31-33).

Percutaneous revascularisation

Selecting the most appropriate revascularisation strategy can be difficult in the patient post-CABG; re-operation is technically more difficult and carries a three-fold risk of mortality and non-fatal myocardial infarction as compared to the first operation (34). Therefore, redo-CABG surgery is used as last resort.

In our cohort of patients, almost all PCI which were performed within the a month of CABG surgery were urgent procedures for ACS. Not surprisingly, in this group of patients, most lesions were at the distal anastomosis or were caused by venous graft thrombosis.

Procedural and clinical outcomes

We had a high procedural success (97.4%) of intervention in these patients with a majority of the procedures performed via femoral approach. The reasons for this were likely because of the need for urgent cardiac catheterisation, and also due to need to access LITA graft in these cases as majority of our cases had a LITA graft (81%). Ninety-five percent of patients had PCI with stent deployment and only a small number of patients had balloon angioplasty only. This is in keeping with the notion that percutaneous transluminal coronary angioplasty (PTCA) alone proved to be inadequate therapy with unacceptably high rates of restenosis and MACE (31,35,36).

More than half of these patients underwent drug-eluting stent deployment with the rate of DES use increasing over the course of the study. Data from observational studies comparing DES with BMS favor DES for SVG PCI because of associated reduction in TLR and death.(37,38) However, data from randomized prospective studies comparing BMS to DES in SVG PCI are less conclusive because of the small number of studies available and their small sample sizes (39,40). A recent meta-analyses have shown that the use of DES was associated with lower rates of TVR and TLR in the observational studies, but this was not confirmed in the randomized studies (41,42). A majority of PCI is performed in native vessels and there is published data to support better outcomes in in post CABG patients who undergo native vessel PCI as compared to graft vessel PCI.(43)

We found a favourable in-hospital outcome in these patients undergoing intervention for graft failure that compares favourably with previously published outcomes (38). In a recent study, there was no significant difference between DES and BMS in in-hospital death (0.8% vs. 1.5%, p value 0.33) or in-hospital MI (2.0% vs. 4.1%, p value 0.16).

What can we do to ameliorate unplanned early PCI post CABG?

Many of the grafts that failed in the present study were small in diameter, grafted onto small vessels or vessels with poor distal runoff. In some of these cases, graft failure could have been predicted. In the patients whom PCI was done on an ungrafted native artery, review of the chart revealed that the surgeon often knew that the lesion was significant but could not be revascularized surgically. A heart team approach and greater utilization of hybrid revascularization might be helpful in these situations.(44)

In a recent study, Zhao et al(45) highlights the potential advantages of routine intraoperative graft imaging in detecting early graft failure. They also became more selective regarding the significance of apparently minor kinks in the vein grafts, the effects of (reversed) vein valves on antegrade flow, and the effect of conduit target mismatch. The authors suggested that routine completion of graft imaging should eventually become the standard of care and highlighted the benefits of team approach, combining traditional surgery and PCI.

What can we do to decrease graft failure?

As one of the predictors of graft failure was a graft that was placed on vessel with a lesion that was not hemodynamically significant, one strategy that could help surgeons identify vessels with non-critical stenosis would be to evaluate all intermediate lesions with fractional flow reserve (FFR) prior to CABG. A Belgian study found that patients undergoing FFR-guided CABG, when compared to CABG based on traditional angiographic criteria, had fewer grafts, fewer anastomoses, less on-pump surgery and less angina, with no difference in major adverse cardiac events at 36 month (46). Another study demonstrated that 1-year graft patency was significantly higher when grafts were placed on functionally significant vs. functionally nonsignificant lesions (90.1% vs. 78.6%, $p < 0.0001$)(26). In both studies, FFR-guided revascularization did not increase angina and did not increase revascularization, suggesting that the grafts that were avoided were unnecessary in the first place. Although this type of strategy would reduce unnecessary grafts and therefore procedure complexity and pump time, it would not have an impact on the patient population of the present study (i.e. those patients experiencing clinical failure after CABG).

Limitations

This is a single-centre, retrospective observational study. Given the single center nature of our study, our results may not be generalizable to other centres. There are likely confounders related to the study sample because not all patients who had CABG at our institution underwent PCI at our institution. As such, we were unable to determine precisely the percentage of patients undergoing CABG who came back for PCI within 1-year. Furthermore, because some patients had their CABG elsewhere, we did not have access to some of the pre-operative coronary angiograms. Post CABG coronary angiograms were not performed routinely in all patients and the relationship of graft patency and vessel size/distribution is unknown in a large number of patients who did not have PCI. We also did not include target artery quality as a predictor. We had to rely on the angiogram done at the time of PCI for the QCA. It is also possible that some of the failed grafts might have become atretic after failing and therefore the diameter pre-surgery would have likely been different. We did not have clinical data including clinical outcomes, rate of further interventions for this patient cohort.

CONCLUSION

Patients requiring PCI within 1 year of CABG were more likely to present on an urgent basis and have PCI performed in native coronary vessels that were originally grafted. Predictors of graft failure include small graft size, small native artery size, poor distal runoff and distal disease in the native artery. Nearly third of the patients had PCI to an ungrafted native vessel or to a lesion in the native vessel where the graft was still patent.

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Figure Legends

Figure 1: Time to first PCI in patients with CABG

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Figure 2: AUC for native artery diameter and graft patency

Accepted Article

Table 1. Baseline characteristics of the patients included in the study**Surgical Details****Baseline Characteristics**

Mean Age	63 years
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Male	72%
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Hypertension	78%
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Dyslipidemia	86%
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Family history	47%
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Diabetes	41%
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Smoking Status:

Current:	13%
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Former:	48%
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Non-smoker:	39%
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LVEF* < 40%	16%
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Chronic Renal Failure	13%
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Previous CVA	3%
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Acute coronary syndrome	52.2%
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ST-elevation MI	3.1%
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Stable angina	44.7%
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LVEF*: Left Ventricular Ejection Fraction

Table 2. Details of the CABG procedure that patients had prior to presenting for PCI.

Surgical Details

Left Main:	31%
Number of Vessels:	
1:	4%
2:	23%
3:	74%
Redo Surgery:	5%
#Grafts/Patient	2.9
% with LITA*	81%
% with RITA**	8%
% with Radial	5%
#SVG/Patient:	2.1

LITA*: Left Internal Thoracic Artery; RITA**: Right Internal Thoracic Artery

Table 3. Procedural characteristics for PCI in the study population**Procedural Characteristics**

Total Lesions:	390
# Lesions/Procedure:	1.7
# Stents/Lesion:	1.2
DES [*] :	52%
BMS ^{**} :	48%
Balloon Only:	4.9%
Access:	
Femoral:	80%
Radial:	19%
Brachial:	1%

DES^{*}: Drug Eluting Stent; BMS^{**}: Bare Metal Stent

Table 4. Procedural outcomes for PCI

Procedural Outcomes	Percentage
Procedural Success	97.4%
In-Hospital MACE*	1.8%
MI**	0.4%
CVA***	0.4%
Mortality	1.3%
Acute Renal Failure	0.4%
Major Bleeding	3.1%

MACE*: Major Adverse Cardiac Events; MI**: Myocardial Infarction; CVA***: CerebroVascular Accident

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Table 5. Angiographic parameters in patent and occluded grafts

Variable	Patent Graft	Failed Graft	p-Value (Mann Whitney U Test)
Median Proximal Graft Diameter* (mm)** (± Range)	3.02 (2.6-3.6)	2.79 (2.27-3.4)	0.02 (z=2.26)
Median Distal Graft Diameter* (mm)** (± Range)	2.72 (2.16-3.75)	2.31 (1.59-3.02)	0.0001 (z=3.87)
Median Native Artery Diameter* (mm)** (± Range)	2.0 (1.69-2.32)	1.65 (1.42-1.9)	p<0.05 (z=6.0)
Median length of run-off* (mm)* (±Range)	65.6 (55-79.1)	55 (44.88-67.27)	p<0.05 (z=5.15)
Graft/Native Ratio	1.49	1.36	0.232

* Missing values not replaced; ** mm: millimeters

Table 6. AUC for angiographic parameters versus graft patency

Variable	AUC	95% CI	Significance
Native artery diameter	0.71	0.66-0.77	p<0.0001
Graft Proximal Diameter	0.60	0.53-0.67	p=0.027
Graft Distal Diameter	0.67	0.60-0.73	P<0.0001
Length of run off	0.68	0.62-0.74	P<0.0001

Figure 1: Time to first PCI in patients with CABG

Figure 1

159x119mm (96 x 96 DPI)

Accep

Figure 2: AUC for native artery diameter and graft patency
Figure 2
108x60mm (300 x 300 DPI)

Accepted

Characteristics and Outcomes of Patients Undergoing Percutaneous Coronary Intervention within 1-year of Coronary Artery Bypass Graft Surgery

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Abstract

Objectives: The aim of this study was to examine the clinical and procedural outcomes of patients undergoing Percutaneous Coronary Intervention (PCI) within 1 year of Coronary Artery Bypass Graft surgery (CABG).

Background: CABG is the preferred revascularisation strategy for patients with complex coronary artery disease due to a lower rate of repeat revascularization. Despite advances in surgical technique and medical therapy, > 5% of patients require repeat revascularization within 1 year of CABG.

Methods and Results: Patients who underwent PCI within 1 year of CABG were identified from a prospective registry with data on over 20,000 PCI procedures (April 2000 - June 2011). 203 post CABG patients underwent 228 PCI procedures on 390 lesions during this period. 45% of patients had elective PCI while 55% had PCI on an urgent basis. 81% of PCI was performed in native coronary arteries, usually following graft failure in a previously grafted vessel (60%) or in an ungrafted native vessel (21%).

Conclusions: Patients who required PCI within 1 year of CABG were more likely to present on an urgent basis and have PCI performed in grafted native coronary vessels. However, nearly third of the patients had PCI to an ungrafted native vessel or to a lesion in the native vessel where the graft was still patent. Further studies are needed to determine whether the use of hybrid revascularization strategies (combination CABG and planned PCI) in appropriate patients could reduce the need for urgent PCI within the first year after CABG.

Abbreviations

CABG	Coronary artery bypass grafting
PCI	Percutaneous coronary intervention
QCA	Quantitative coronary angiography
CAD	Coronary artery disease
ACS	Acute coronary syndrome
LITA	Left internal thoracic artery
SVG	Saphenous vein graft
QCA	Quantitative Coronary analysis

INTRODUCTION

Coronary artery bypass graft surgery (CABG) remains the preferred strategy for revascularization of patients with complex left main and / or 3-vessel coronary artery disease (1,2). The long term success of CABG is dependent on graft patency after the surgery. Despite advances in surgical technique and medical therapy, early vein graft failure (VGF) remains one of the leading causes of poor outcome after CABG (3).

Almost 10% to 15% of venous grafts occlude within 1 year and almost half of venous grafts fail at 10 years(3-9).

Vein graft failure contributes to considerable morbidity through recurrent angina, myocardial infarction (MI), repeat revascularisation and increased mortality(10,11)

Previous studies have mainly evaluated the predictors of late graft patency (12,13).

Early occlusion (before hospital discharge) has been found to occur in 7 to 10% coronary grafts(14). Optimal blood glucose control and pump time < 2 hours was noted to predict graft patency within first week after successful CABG surgery(15).

Early (within 2 years) graft failure affects long-term mortality.(10) The longevity of the graft conduit depends on many factors, including the quality, size, and diameter of the saphenous vein; the size and diameter of the target vessel; surgical skills; intraoperative handling of vein graft, clamp and perfusion times (15-17). The rate of repeat revascularization in the first year was 2% in a large US registry(18) and 5.8% in the SYNTAX trial(1).

The objectives of the present study were twofold: (1) to examine the clinical and procedural characteristics of patients who undergo PCI within 1 year of CABG (i.e. those patients who experience clinical failure post CABG) and (2) to identify predictors of graft failure in this cohort of patients.

MATERIALS AND METHODS

Patient population

All patients undergoing percutaneous coronary intervention (PCI) at the Peter Munk Cardiac Centre, University Health Network (Toronto, Canada) are enrolled into a dedicated prospective registry(19). This database was used to identify all patients who underwent PCI within 1 year of CABG at Toronto General Hospital, between April 1, 2000 and June 30, 2011. Patients who had CABG more than 1 year from index PCI procedure were excluded. We also excluded patients who had planned PCI as a part hybrid procedure after CABG. Data were abstracted from the registry, as well as from review of patient charts and coronary angiograms. The angiographic graft patency was graded as- fully patent with good antegrade flow (TIMI 3), patent with stenosis or compromised flow (TIMI 1-2) or occluded (TIMI 0 flow). Quantitative coronary angiography (QCA) was used to identify predictors of graft failure in a subset of 113 patients (314 grafts). Local research ethics board approval was obtained for this study.

Indications for PCI were defined as emergent PCI if it included primary, facilitated, or rescue PCI; urgent PCI referred to any procedure for non ST-elevation acute coronary syndromes or > 48 hours after ST-elevation MI; salvage PCI referred to PCI performed when there was no surgical revascularization option and elective PCI if patient presented with stable angina symptoms and positive functional or imaging non-invasive test for inducible ischemia.

QCA Substudy

In the QCA substudy, we assessed the patency of all grafts in each patient at the time of presentation for PCI. We also evaluated a number of angiographic variables

relating to the bypass graft and the native vessel, which we considered important in maintaining graft patency based on our review of the literature and clinical experience. These variables were compared between patent grafts and occluded grafts in order to identify significant differences. The specific variables studied included proximal graft diameter (measured at the ostium), distal graft diameter (measured 10 mm before the distal anastomosis), native coronary artery diameter (measured 10 mm after the anastomosis), the ratio of graft diameter to native coronary artery diameter, and the distal runoff (the distance from the graft insertion to the end of the most distal branch of that vessel). We also measured the severity of the stenoses in the native coronary artery both proximal and distal to the anastomosis. The degree of the most severe stenosis within each segment was visually estimated as a percentage diameter stenosis in relation to an appropriate adjacent reference diameter.

The diameters of graft and native vessels were measured using QAngio XA version 7.3.64.0-x86 (Medis Medical Imaging Systems Inc. Leiden, The Netherlands) QCA software. The measurements were calibrated by convention using the diameter of the contrast-filled straight section of the distal portion of the diagnostic catheter. The measurements were performed by two cardiologists independently. 284 grafts were present in 203 patients.

Procedural parameters

Procedural success was defined as <20% residual stenosis with TIMI 3 flow in the target vessel. Major adverse cardiac and cerebrovascular event (MACCE) was defined as the composite of in-hospital mortality, myocardial infarction (MI) and stroke. Peri-procedural MI was defined as rise in cardiac biomarkers (CK) >3 times of upper limit of normal (ULN). A rise in creatinine of >25% 3- days after procedure was defined as

acute renal failure and a drop in haemoglobin $>5\text{g}$ with or without hemodynamic instability or requiring blood transfusion was defined as major bleeding.

Statistical analysis

Continuous data are presented as mean $\pm$ standard deviation (20) or median (Inter Quartile Range {IQR}), and categorical data are presented as percentages.

Differences between groups were assessed using Chi-square test or Fisher's Exact test, as appropriate. Differences in angiographic parameters (continuous variables) of patent and occluded grafts were assessed by the Mann-Whitney-u test. A p-value < 0.05 was considered to be statistically significant.

Missing variables were not replaced and excluded from the analysis. Angiographic predictors of an occluded graft were assessed by forward stepwise logistic regression modelling. Variables included were graft proximal diameter, graft distal diameter, length of run off and native vessel proximal diameter. Continuous variables with non-normal distribution were log transformed prior to inclusion in the regression model. In addition, Receiver Operating Curves (ROC) were computed to assess the discriminatory power of the native artery proximal diameter, graft proximal diameter, graft distal diameter and length of run off to predict occluded versus patent grafts.

RESULTS

Baseline Characteristics

A total of 20,058 PCI procedures were performed at our institution during the study period. Of these, 203 patients underwent 228 procedures on 390 lesions within 1-year of having CABG surgery. The baseline characteristics of the study population are

outlined in Table 1. Median age was 63 years (range 55.5-70 years) and 28.1% were female (57/203).

Forty-one percent of patients had diabetes mellitus. The surgical details of these patients are summarized in Table 2. This was a contemporary cohort of surgical patients with 1 in 3 patients having left main disease, 96% underwent multivessel CABG and over 80% received a left internal thoracic artery (21) (21) bypass graft.

Procedural characteristics

Fifty-five percent of patients had PCI on an urgent basis, 3% with STEMI and 1% in cardiogenic shock. The remainder had elective PCI, usually for recurrence of symptoms. Two patients had elective PCI as part of a planned hybrid revascularization strategy who were excluded from the analysis. The rate of PCI per month was equally distributed throughout the first year after CABG (Figure 1), although there were more patients with urgent unplanned PCI in the early months. The median number of days between bypass surgery and the index PCI procedure was 162 days. The PCI details are outlined in Table 3. Many of the procedures involved multiple lesions (average 1.7 lesions/procedure) and 95% of lesions were treated with stents (5% balloon angioplasty only). Only 52% of patients were treated with drug-eluting stents (DES), although this increased over the course of the study (data not shown). The majority of cases (80%) were performed via femoral access. The majority (64%) of PCI procedures in this cohort were secondary to graft failure. We found that 45% of patients had PCI on a previously grafted native vessel due to failure of the graft and 19% of patients had PCI on a failed bypass graft. Fifteen percent of patients had PCI on a grafted native vessel where the graft was still patent

(e.g. a lesion distal to the insertion site) and 21% of patients had PCI on an ungrafted native vessel. Of those who had PCI to ungrafted native vessels, the lesions were already considered significant but the vessels were not grafted due to size or location. Nearly 90% of the graft interventions were due to anastomotic lesions: 31% at the proximal anastomosis and 57% at the distal anastomosis. Only 12% of graft interventions were in the body of a graft.

Procedural outcomes

The procedural outcomes are summarized in Table 4. The procedural success rate was 97% with a low-rate of major adverse cardiac events (0.4% MI, 0.4% CVA, 1.3% mortality). The rate of major bleeding was 3.1%

Angiographic Predictors of graft failure

Grafts were classified into two groups: patent (176/284, 61.97%) and occluded (109/284, 38.38%). Median native artery length was greater in the patent grafts (2.0 mm { 1.69-2.32}) compared to the occluded grafts (1.65 mm{1.42-1.90}, z score= 6.0, $p<0.05$) as was median length of run off (patent graft 65.6 mm{55-79.1} versus occluded graft 55 mm {44.9-67.3}, z score= 5.15, $p<0.05$) (table 5).

Forward stepwise logistic regression analysis demonstrated that graft distal diameter was a significant predictor of an occluded graft (OR 2.54, 95% CI 1.62-3.98, $p<0.0001$).

ROC analysis of a total of 284 grafts demonstrated significant accuracy of the native artery proximal diameter to predict graft patency with an Area Under the Curve (AUC) of 0.712 (95% CI 0.655-0.764, $p<0.0001$) as shown in figure 2. A native

artery diameter of >1.8 had a sensitivity of 60.2% and a specificity of 71.3% (Youden Index $J=0.315$) in predicting graft patency at a median time of 162 days (5.4 months). Graft proximal diameter, graft distal diameter and length of run off were significant but modest predictors of graft patency (Table 6). Grafts were more likely to be occluded beyond 6 months post CABG.

DISCUSSION

There are several key findings from this study. Firstly, patients requiring PCI within 1 year of CABG were more likely to present on an urgent basis. Secondly, the majority of these patients underwent PCI because of graft failure and almost 90% of graft interventions were due to anastomotic lesions. Thirdly, significant predictors of graft failure include small graft size, small native artery size, poor distal run-off and distal disease. Fourthly, third of the patients had PCI to an ungrafted native vessel or to a lesion in the native vessel where the graft was still patent (eg. lesion distal to the insertion site).

Predictors of early graft failure

Patient characteristics

In this study, 41% of patients who had PCI within 1 year of CABG had diabetes mellitus. The prevalence of diabetes mellitus in our study population is similar to previous longitudinal angiographic studies by Sabik and colleagues(22), who examined 10,000 venous and internal artery bypass grafts. However, the effect of diabetes on graft patency was not consistent. In the follow-up studies by Shah and colleagues(23) and Bypass Angioplasty Revascularisation Investigation(24), the

presence of diabetes was not a significant factor for saphenous graft attrition in follow-up.

Angiographic predictors of graft failure

Size of target vessel

The size of the distal vessel diameter was a significant independent predictor of graft patency in this study. In published literature, vessel diameter has an important impact on graft patency with smaller vessel diameter being associated with a lower patency rate in saphenous vein grafts(12). Several factors may lead to diminished patency in conduits grafted to smaller target vessels. Size mismatch, particularly when larger (3.5- to 4-mm) saphenous veins are grafted to small targets, may predispose to impaired nonlaminar flow patterns, which result in stimulus for endothelial dysfunction, early intimal hyperplasia or graft occlusion and flow from collateral vessels (25). Small distal targets may be more technically difficult to graft and may have significant disease at or adjacent to the anastomotic site itself. In contrast, larger-calibre target vessels would be expected to have better distal run-off. Our findings are consistent with a recent study that showed a significantly lower patency rate of 79% in vessels with a diameter less than 2.0 mm, and 96.1% in vessels with a diameter exceeding 2.0mm (p=0.0001)(26).

Distal anastomotic lesion

A large proportion of graft failure were related to the presence of distal anastomotic lesions. Angiographic studies have shown occlusive disease at the anastomotic site or in the graft itself in <one-third of patients in the 10 years after surgery (27,28) with distal anastomotic lesions being the most common reason for venous graft failure

(29). Symptoms that recur within days after surgery are usually due to venous graft thrombosis, but may be due to failure of the surgical techniques at the site of the anastomosis (30). Distal anastomotic lesions that occur during the first year are thought to be due to fibrointimal hyperplasia. Thereafter, atherosclerosis begins to contribute to the pathogenesis becoming the predominant cause after 3 years (31-33).

Percutaneous revascularisation

Selecting the most appropriate revascularisation strategy can be difficult in the patient post-CABG; re-operation is technically more difficult and carries a three-fold risk of mortality and non-fatal myocardial infarction as compared to the first operation (34).

Therefore, redo-CABG surgery is used as last resort.

In our cohort of patients, almost all PCI which were performed within the a month of CABG surgery were urgent procedures for ACS. Not surprisingly, in this group of patients, most lesions were at the distal anastomosis or were caused by venous graft thrombosis.

Procedural and clinical outcomes

We had a high procedural success (97.4%) of intervention in these patients with a majority of the procedures performed via femoral approach. The reasons for this were likely because of the need for urgent cardiac catheterisation, and also due to need to access LITA graft in these cases as majority of our cases had a LITA graft (81%). Ninety-five percent of patients had PCI with stent deployment and only a small number of patients had balloon angioplasty only. This is in keeping with the notion that percutaneous transluminal coronary angioplasty (PTCA) alone proved to be inadequate therapy with unacceptably high rates of restenosis and MACE (31,35,36).

More than half of these patients underwent drug-eluting stent deployment with the rate of DES use increasing over the course of the study. Data from observational studies comparing DES with BMS favor DES for SVG PCI because of associated reduction in TLR and death.(37,38) However, data from randomized prospective studies comparing BMS to DES in SVG PCI are less conclusive because of the small number of studies available and their small sample sizes (39,40). A recent meta-analyses have shown that the use of DES was associated with lower rates of TVR and TLR in the observational studies, but this was not confirmed in the randomized studies (41,42). A majority of PCI is performed in native vessels and there is published data to support better outcomes in in post CABG patients who undergo native vessel PCI as compared to graft vessel PCI.(43)

We found a favourable in-hospital outcome in these patients undergoing intervention for graft failure that compares favourably with previously published outcomes (38). In a recent study, there was no significant difference between DES and BMS in in-hospital death (0.8% vs. 1.5%, p value 0.33) or in-hospital MI (2.0% vs. 4.1%, p value 0.16).

What can we do to ameliorate unplanned early PCI post CABG?

Many of the grafts that failed in the present study were small in diameter, grafted onto small vessels or vessels with poor distal runoff. In some of these cases, graft failure could have been predicted. In the patients whom PCI was done on an ungrafted native artery, review of the chart revealed that the surgeon often knew that the lesion was significant but could not be revascularized surgically. A heart team approach and greater utilization of hybrid revascularization might be helpful in these situations.(44)

[In a recent study, Zhao et al\(45\) highlights the potential advantages of routine intraoperative graft imaging in detecting early graft failure. They also became more selective regarding the significance of apparently minor kinks in the vein grafts, the effects of \(reversed\) vein valves on antegrade flow, and the effect of conduit target mismatch. The authors suggested that routine completion of graft imaging should eventually become the standard of care and highlighted the benefits of team approach, combining traditional surgery and PCI.](#)

What can we do to decrease graft failure?

As one of the predictors of graft failure was a graft that was placed on vessel with a lesion that was not hemodynamically significant, one strategy that could help surgeons identify vessels with non-critical stenosis would be to evaluate all intermediate lesions with fractional flow reserve (FFR) prior to CABG. A Belgian study found that patients undergoing FFR-guided CABG, when compared to CABG based on traditional angiographic criteria, had fewer grafts, fewer anastomoses, less on-pump surgery and less angina, with no difference in major adverse cardiac events at 36 month (46). Another study demonstrated that 1-year graft patency was significantly higher when grafts were placed on functionally significant vs. functionally nonsignificant lesions (90.1% vs. 78.6%, $p < 0.0001$)(26). In both studies, FFR-guided revascularization did not increase angina and did not increase revascularization, suggesting that the grafts that were avoided were unnecessary in the first place. Although this type of strategy would reduce unnecessary grafts and therefore procedure complexity and pump time, it would not have an impact on the patient population of the present study (i.e. those patients experiencing clinical failure after CABG).

Limitations

This is a single-centre, retrospective observational study. Given the single center nature of our study, our results may not be generalizable to other centres. There are likely confounders related to the study sample because not all patients who had CABG at our institution underwent PCI at our institution. As such, we were unable to determine precisely the percentage of patients undergoing CABG who came back for PCI within 1-year. Furthermore, because some patients had their CABG elsewhere, we did not have access to some of the pre-operative coronary angiograms. Post CABG coronary angiograms were not performed routinely in all patients and the relationship of graft patency and vessel size/distribution is unknown in a large number of patients who did not have PCI. We also did not include target artery quality as a predictor. Moreover, post CABG coronary angiograms were not performed as routinely in these patients. We had to rely on the angiogram done at the time of PCI for the QCA. It is also possible that some of the failed grafts might have become atretic after failing and therefore the diameter pre-surgery would have likely been different. We did not have clinical data including clinical outcomes, rate of further interventions for this patient cohort.

CONCLUSION

Patients requiring PCI within 1 year of CABG were more likely to present on an urgent basis and have PCI performed in native coronary vessels that were originally grafted. Predictors of graft failure include small graft size, small native artery size, poor distal runoff and distal disease in the native artery. Nearly third of the patients had PCI to an ungrafted native vessel or to a lesion in the native vessel where the graft was still patent.

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Figure Legends

Accepted Article

Figure 1: Time to first PCI in patients with CABG

Figure 2: AUC for native artery diameter and graft patency

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24th September 2016

To,
Editor-in-Chief
Catheterization and Cardiovascular Interventions
1100 17th Street NW, Suite 330,
Washington, DC 20036

Dear Editor-in-Chief,

Re: Reply to reviewers' comments on Manuscript # CCI-16-0386

We are grateful for the opportunity to respond once more to the review of our paper and to modify it accordingly. We hope that you now find it acceptable for publication in your journal. We confirm that this is original manuscript and has not been previously published or submitted to another journal.

We thank the reviewers for their invaluable comments. Please find our reply and changes in the manuscript below:

Referee(s)' Comments to Author:

Reviewer #1:

The variables examined in terms of predicting graft failure related to graft size and target size, severity of the lesion being bypass, and distance from the anastomosis to the end of the most distal branch of that vessel. Other important parameters such as diffuse disease in the subtended vessel or calcification are not presented. I do not see a specific assessment of graft-target mismatch in terms of size. This is mentioned in the discussion but not presented in the data from this particular study that I can see. Was a graft to target diameter ratio used as a variable in the multivariable analysis? I do not see a table of the multi-variable analysis determining predictors of graft failure.

Authors' reply to Reviewer 1:

The authors agree with the reviewer's comments that diffuse disease in the subtended vessel is an important parameter. Target artery quality is a known predictor of graft failure (*Coronary Artery Bypass Graft Failure After On-Pump and Off-Pump Coronary Artery Bypass: Findings From PREVENT I*. Magee, Mitchell J. et al. *The Annals of Thoracic Surgery*, Volume 85, Issue 2, 494 – 500).

However, we did not include quality of the target artery as a parameter. Graft to target diameter ratio was also not included in multivariate analysis. We acknowledge this in the "Limitations" section on page 15.

Reviewer #2:

This study provided an unique aspect in CABG population. The findings are interesting and significant. It is particularly valuable to demonstrate the potential mechanism for repeated revascularization status post CABG. Their results reinforced the previous published data that technical failure may account for earlier graft failure. The finding that significant % of post-CABG PCI were on non-grafted native vessel is thought-provoking and provides evidence for more individualized revascularization strategies. Their analysis on predictors (vessel size and distribution) of early CABG occlusion is interesting. However, its implication is very limited as the relationship of graft patency and vessel size/distribution is unknown in a large number of patients who did not have PCI or subsequent cath. Authors should acknowledge the limitation and reconsider their conclusion to reflect the limitation. I think the authors should include the following reference (Routine Intraoperative Completion Angiography After Coronary Artery Bypass Grafting and 1-Stop Hybrid Revascularization, J Am Coll Cardiol. 2009;53(3):232-241) in their discussion to address strategies to reduce technical failure as potential cause for early graft failure.

Authors' reply to Reviewer 2:

We appreciate the reviewer's comments and acknowledge the comments regarding patients who did not have subsequent cardiac catheterization. We have alluded to this limitation in our study (page 15, "Limitations" section) and have also included the said reference (page 19, "References" section, reference 45).

Regards

V Sharma

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Title:

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