ORIGINAL RESEARCH

Long-Term Clinical Outcomes Following Revascularization in High-Risk Coronary Anatomy Patients With Stable Ischemic Heart Disease

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BACKGROUND: The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial failed to show a reduction in hard clinical end points with an early invasive strategy in stable ischemic heart disease (SIHD). However, the influence of left main disease and high-risk coronary anatomy was left unaddressed. In a large angiographic disease-based registry, we examined the modulating effect of revascularization on long-term outcomes in anatomically high-risk SIHD.

METHODS AND RESULTS: 9016 patients with SIHD with high-risk coronary anatomy (3 vessel disease with ≥70% stenosis in all 3 epicardial vessels or left main disease ≥50% stenosis [isolated or in combination with other disease]) were selected for study from April 1, 2002 to March 31, 2016. The primary composite of all-cause death or myocardial infarction (MI) was compared between revascularization versus conservative management. A total of 5487 (61.0%) patients received revascularization with either coronary artery bypass graft surgery (n=3312) or percutaneous coronary intervention (n=2175), while 3529 (39.0%) patients were managed conservatively. Selection for coronary revascularization was associated with improved all-cause death/ MI as well as longer survival compared with selection for conservative management (Inverse Probability Weighted hazard ratio [IPW-HR] 0.62; 95% CI 0.58 to 0.66; $P<0.001$; IPW-HR 0.57; 95% CI 0.53–0.61; $P<0.001$, respectively). Similar risk reduction was noted with percutaneous coronary intervention (IPW-HR 0.64, 95% CI 0.59–0.70, $P<0.001$) and coronary artery bypass graft surgery (IPW-HR 0.61; 95% CI 0.57–0.66; $P<0.001$).

CONCLUSIONS: Revascularization in patients with SIHD with high-risk coronary anatomy was associated with improved long-term outcome compared with conservative therapy. As such, coronary anatomical profile should be considered when contemplating treatment for SIHD.

Key Words: coronary anatomy ■ revascularization ■ stable ischemic heart disease

See Editorial by Bergmark and Morrow

In patients with stable ischemic heart disease (SIHD), randomized studies suggest similar outcomes with coronary revascularization compared to optimal medical therapy (OMT).[1,2] However, selection bias based on coronary anatomy may have precluded enrollment of higher risk patients. Moreover, it was unclear whether outcomes could be modulated by the degree of jeopardized myocardium.[3] In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) nuclear sub-study,

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CLINICAL PERSPECTIVE

What Is New?

- In an observational study of stable ischemic heart disease patients with high-risk coronary anatomy (including left main disease), revascularization compared with conservative management was associated with improved clinical outcome (all-cause death or myocardial infarction), which appeared early and continued long-term, irrespective of type of revascularization (coronary artery bypass graft or percutaneous coronary intervention).

What Are the Clinical Implications?

- Given the results of the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, our data challenges these findings in patients with high-risk coronary anatomy and should be considered when contemplating revascularization.

Nonstandard Abbreviations and Acronyms

ISCHEMIA	International Study of Comparative Health Effectiveness with Medical and Invasive Approaches
LM	left main
OMT	optimal medical therapy
SIHD	stable ischemic heart disease
VD	vessel disease

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patients with at least moderate ischemia at baseline (≥10%) demonstrated improved clinical outcomes (death or myocardial infarction [MI]) when the degree of ischemia was reduced—which was demonstrated to a greater extent with percutaneous coronary intervention (PCI).[4] In a subsequent large single center observational study, revascularization of patients with ≥10% inducible ischemia was associated with improved survival long-term (≈9 year follow-up).[5]

Given these findings, the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial randomized subjects with SIHD *prior* to coronary angiography with moderate or severe ischemia and found no difference in clinical events (including hard clinical end points) with a routine invasive strategy (in addition to OMT) of cardiac catheterization and revascularization (when feasible) compared with an initial conservative strategy of OMT alone (with catheterization and revascularization reserved for failure of medical therapy).[6]

While the ISCHEMIA trial has undoubtedly contributed to our understanding of SIHD management, the influence of coronary anatomy complexity on outcomes with revascularization remains unclear—particularly considering left main (LM) disease was an exclusion. Moreover, angiographic disease complexity may be a better predictor of adverse clinical outcome compared with non-invasive metrics of ischemic burden.[7,8] Accordingly, we examined whether an association exists between revascularization and clinical outcomes in patients with SIHD with high-risk coronary anatomy using a large angiographic disease-based registry.

METHODS

Data Source and Linkage

The data that support the findings of this study are available from the corresponding author on reasonable request. The Alberta Ministry of Health databases used for the study, linked using a unique patient identifier, have been previously described.[9] In brief, these include: (1) the Discharge Abstract Database (DAD), which contains diagnostic and treatment information, length of stay, and discharge status for patients admitted to any acute care hospital in Alberta; (2) the Alberta Health Care Insurance Registry database, which tracks the vital status of all residents of Alberta; (3) the National Ambulatory Care Reporting System (NACRS) database, which records all outpatient clinic visits (including emergency department visits); (4) the Physician Claims Database, which includes all physician claims for outpatient services; and (5) the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) database, which includes detailed demographic, clinical, and anatomical data for all patients who undergo cardiac catheterization in the province of Alberta (total 3 cardiac catheterization sites). As Alberta has a government-funded single-payer healthcare system with universal access, these data sets capture all patient interactions with the healthcare system. Ethics approval for the study was obtained from the Health Research Ethics Board of the University of Alberta. Since data were collected from heath databases, the need for informed consent from participants was waived.

Patient Selection

Using the APPROACH registry, we identified a contemporary population of 9016 patients with SIHD and high-risk coronary anatomy. Entry criteria included those patients with angiographically significant 3 vessel disease (VD) (≥70% stenosis in all 3 epicardial vessels) or LM disease (≥50% stenosis) (isolated or in combination with other disease) from April 1, 2002 to March 31, 2016. Subgroups of interest for

angiographic risk were: 3 VD with 1 vessel stenosis ≥95%, 3 VD with proximal left anterior descending coronary artery (pLAD) ≥70% stenosis, 3 VD with pLAD ≥95% stenosis, LM ≥50% stenosis, and severe LM ≥70% stenosis. Patients receiving revascularization during the index catheterization (ie, with ad hoc multivessel PCI) or outpatients receiving coronary artery bypass graft (CABG) or PCI up to 3 months from index catheterization were included as 'revascularization'. In Alberta, outpatient revascularization can occur as far as 3 months from referral (particularly CABG). Patients without revascularization within the first 3 months following index catheterization were identified as receiving 'conservative management'. Patients who died within 3 months of index catheterization were excluded from the survival analysis to avoid bias of those patients who may have died prior to revascularization.

Evidence-Based Medication Use

The Pharmaceutical Information Network (PIN) database of pharmaceutical claims was available as of January 1, 2008. We examined their pharmaceutical claims in the 6-month post-discharge period from coronary angiography to identify prescription of the following cardiovascular specific drugs: angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta-blockers, calcium-channel blockers, lipid modifying agents, spironolactone, and P2Y12 receptor antagonists (acknowledging that acetylsalicylic acid usage cannot be quantified due its non-prescription usage).

Clinical Outcomes

The primary clinical outcome of interest was a composite of all-cause death or MI during the entire follow-up. Secondary outcomes of interest included all-cause death, MI, or revascularization during the entire follow-up. Clinical events were obtained via the Alberta Strategy for Patient Oriented Research (SPOR) Support Unit, a jointly funded program by Alberta Innovates and the Canadian Institutes of Health Research to support patient-oriented research, using the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes in provincial health databases and follow-up status from the AHCIP (Alberta Health Care Insurance Plan) registry.

Statistical Analysis

Median and interquartile range (IQR) for continuous data, and frequency (%) for categorical data were determined and compared between patient groups (revascularized versus medically managed) using the Mann-Whitney U rank sum test and the Pearson χ^2 test, respectively. The Cox proportional hazard (PH)

regression model was used to evaluate the association of the primary and secondary clinical outcomes with revascularization relative to conservative management, which was reported as hazard ratio (HR) and 95% CI. Since the event of (or repeat of) revascularization after 3 months will highly influence the probability of experiencing the main clinical outcomes, it was considered as a competing risk. We specifically modeled the cause-specific hazard of the primary end point of death/MI and treated the competing event of repeat revascularization post 3-months as a censored observation at the time of revascularization if it happened before occurrence of MI or death. For the secondary end point of death/MI/revascularization, the post 3-months revascularization was part of the composite and, therefore, the Standard Cox-PH model was applied. To account for treatment selection bias, the above-mentioned analyses were adjusted applying the inverse probability weighted (IPW) approach. A multivariable logistic regression model was applied to estimate the probability (propensity) of a patient to undergo revascularization versus conservative management, given a set of measured covariates that would be predictive of the binary outcome (Table S1). The predictor variables that were identified with stepwise backward selection (with significance level of 0.3 to stay) in the logistic regression model include age, sex, hyperlipidemia, diabetes mellitus, present and past smoking status, prior MI, heart failure, elevated creatinine, dialysis, peripheral vascular disease, cerebrovascular disease, and the ejection fraction. Since significance is not a necessary condition for inclusion of covariates in propensity modeling,[10] more covariates were used than in conventional regression approach, through less stringent choice of level of significance to stay set at 0.3. Modeling assumptions of linearity of continuously measured predictor variables were assessed using the restricted cubic spline.[11] Flexible modeling with piece-wise linear regression was applied when observed to be non-linear. Overlap of propensity scores between these comparator groups and whether there were extreme scores that could result in instability caused by large weights were evaluated using histograms (Figure S1). Then, the estimated propensity score was used as a weight function in the cause-specific hazard Cox-PH regression of the clinical outcome on the patient treatment group. Since the confounding effect of the covariates is summarized through the propensity score, the IPW model contained the treatment group binary variable as the only predictor. Validity of the proportionality assumption of the hazards was tested through including time dependent covariate in the model. The cause-specific event rates were estimated using the IPW weighted Kaplan-Meier method,[12] and

Table 1.   **Baseline Characteristics**

	Conservative Management (N=3529)	Revascularization (N=5487)		P Value*
		CABG (N=3312)	PCI (N=2175)	
Age (y), median (IQR)	68 (61, 75)	67 (60, 74)	65 (58, 73)	<0.001
Age ≥75 y	918 (26.0)	718 (21.7)	419 (19.3)	<0.001
Women (%)	643 (18.2)	477 (14.4)	402 (18.5)	0.0065
BMI (kg/m^2), median (IQR)	28 (25, 32)	28 (26, 32)	29 (26, 32)	0.0017
Cardiac risk factors				
Hypertension (%)	2854 (80.9)	2627 (79.3)	1717 (78.9)	0.049
Hyperlipidemia (%)	2737 (77.6)	2715 (82.0)	1703 (78.3)	<0.001
Diabetes mellitus (%)	1402 (39.7)	1081 (32.6)	676 (31.1)	<0.001
Current smoker (%)	537 (15.2)	449 (13.6)	258 (11.9)	0.0017
Ex-smoker (%)	1179 (33.4)	1117 (33.7)	625 (28.7)	0.10
Previous MI (%)	694 (19.7)	500 (15.1)	284 (13.1)	<0.001
CHF (%)	413 (11.7)	211 (6.4)	127 (5.8)	<0.001
Other comorbidities				
Creatinine >200 mmol/L (%)	151 (4.3)	79 (2.4)	59 (2.7)	<0.001
Dialysis (%)	52 (1.5)	20 (0.6)	12 (0.6)	<0.001
COPD (%)	463 (13.1)	399 (12.0)	245 (11.3)	0.051
PAD (%)	375 (10.6)	291 (8.8)	116 (5.3)	<0.001
CVD (%)	306 (8.7)	253 (7.6)	98 (4.5)	<0.001
Ejection fraction (%)				<0.001
>50	1636 (46.4)	1626 (49.1)	1086 (49.9)	
35–50	521 (14.8)	474 (14.3)	218 (10.0)	
20–35	174 (4.9)	128 (3.9)	46 (2.1)	
<20	464 (13.1)	280 (8.5)	213 (9.8)	
Not done-instability	75 (2.1)	49 (1.5)	54 (2.5)	
Not available	231 (6.5)	190 (5.7)	105 (4.8)	

BMI indicates body mass index; CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; IQR, interquartile range; MI, myocardial infarction; PAD, peripheral artery disease; and PCI, percutaneous coronary intervention.

*P values are for test of difference between revascularization group (PCI+CABG combined) vs conservatively managed.

graphically depicted the event free survival over the long-term follow-up. To further illustrate the impact of ignoring the competing risk event of post 3-months revascularization, the "standard" (IPW adjusted but does not censor post 3-month revascularization as a competing risk event) Cox-PH regression analysis was performed and results were compared against those of the cause-specific Cox-PH regression. The standard errors of the HRs from the IPW adjusted Cox-PH models are based on the robust sandwich variance estimator.[13] An explorative sensitivity analysis involving evaluable patients with medication status at 6 months was performed to assess whether the relative benefit of revascularization remains after adjusting for the use of preventive therapies. This was done in a landmark analysis at 6 months, applying the IPW and including cardiovascular medication use at 6 months as covariates in the PH-Cox regression model. To evaluate whether the association of revascularization varies according to specific patient coronary anatomy, subgroup analyses with formal tests of interactions were performed. The anatomy subgroups considered were: 3 VD with 1 vessel stenosis ≥95%, 3 VD with pLAD ≥70% stenosis, 3 VD with pLAD ≥95% stenosis, LM ≥50% stenosis, and severe LM ≥70% stenosis. A two-sided test with $P<0.05$ was regarded as significant and no multiple testing corrections were applied. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Between April 1, 2002 to March 31, 2016, there were 9016 patients selected with high-risk coronary anatomy for study. Of these, 61.0% (n=5487) of patients were treated with revascularization within 3 months following the index coronary angiogram with either CABG surgery (n=3312) or PCI (n=2175), while the remaining 3529 (39%) were managed conservatively.

Table 2. Long-Term Clinical Outcomes With Revascularization Relative to Conservative Management

	Unadjusted HR (95% CI)	Standard IPW-HR* (95% CI)	Cause-Specific IPW-HR† (95% CI)	P Value	Event Rates at 1-y, % (95% CI) Median Event Free Survival, y	
					Revascularization (N=5487)	Conservative Management (N=3529)
Primary end point						
Death/MI	0.64 (0.59–0.70)	0.80 (0.73–0.87)	0.62 (0.56–0.69)	<0.001	2.9% (2.5%–3.4%) 13.9 y	5.7% (4.8%–6.7%) 12.1 y
Secondary end points						
Death/MI/revascularization	0.21 (0.20–0.23)	0.24 (0.22–0.26)	...	<0.001	4.4% (3.8%–4.9%) 12.8 y	45.9% (44.2%–47.6%) 1.6 y
All-cause death	0.60 (0.55–0.66)	0.77 (0.70–0.85)	0.60 (0.54–0.67)	<0.001	1.3% (1.0%–1.6%) 14.0	3.7% (3.0%–4.6%) 13.3 y
MI	0.64 (0.55–0.75)	0.74 (0.63–0.87)	0.77 (0.62–0.96)	0.023	1.4% (1.1%–1.7%) Not reached	1.4% (1.0%–2.0%) Not reached
Revascularization	0.08 (0.07–0.09)	0.07 (0.07–0.08)	...	<0.001	1.7% (1.4%–2.1%) Not reached	43.9% (41.4%–44.9%) 3.3 y
Cardiovascular death	0.44 (0.36–0.54)	0.62 (0.50–0.77)	0.41 (0.32–0.52)	<0.001	0.2% (0.08%–0.3%) Not reached	0.9% (0.6%–1.4%) Not reached

HR indicates hazard ratio; IPW, inverse probability weighted; and MI, myocardial infarction.

*Without censoring repeat revascularization as a competing risk event.

†Subsequent revascularization is a competing risk event.
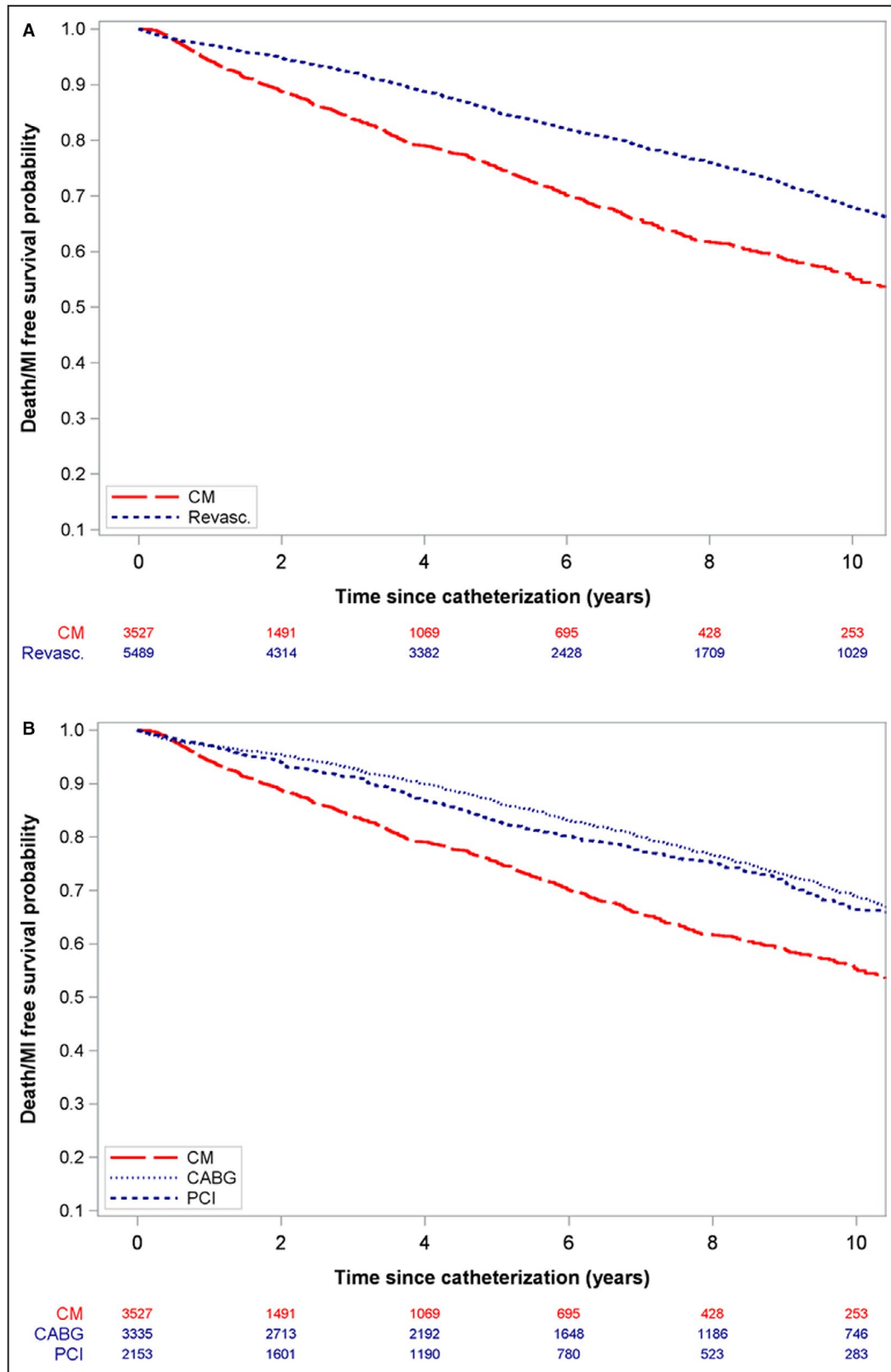
Figure 1.   Long-term all-cause death or myocardial infarction free survival for patients with stable ischemic heart disease.
(**A**) Kaplan-Meier Curves Comparing Revascularization and Conservative Management; (**B**) Kaplan Meier Curves Comparing Mode of Revascularization (CABG or PCI) and Conservative Management. CABG indicates coronary artery bypass grafting; CM, conservative management; PCI, percutaneous coronary intervention; and Revasc, revascularization.

Median (IQR) follow-up time was 6.2 (3.1, 9.9) years. In the total population, post 3-month revascularization rates were 23.9% (n=2158) over the entire follow-up (1543 within the first year) with CABG being most used (76.7%).

Baseline Characteristics

Table 1 provides key baseline patient characteristics according to revascularization status. As compared with patients treated conservatively, revascularization patients were younger, less commonly female, and had a slightly higher body mass index. Hyperlipidemia was more common but smoking and diabetes mellitus were less frequent. Prior MI and congestive heart failure were less common and impaired ejection fraction was less likely. Comorbid conditions were also less likely in patients receiving revascularization.

Revascularization Characteristics

In the revascularization cohort (n=5487), the median time (IQR) to revascularization within 3 months was 15 days (1–44 days) (CABG 29 days [9–56 days], and PCI 0.6 days [0.5–17 days]). Repeat revascularization rates in this cohort were 6.2% (n=339) over the entire

follow-up (93 within the first year) with PCI being used the most (61.1%). Among the 3529 managed medically, revascularization rates (post 3-months) were 51.5% (n=1819) over the entire follow-up (1450 within the first year) with CABG being used the most (83.7%).

Medications Within 6 Months

In 4974 patients with medication status at 6 months following discharge, a high use of cardiovascular preventative therapies was noted in both groups. However, in those receiving revascularization, a slightly higher use of P2Y12 receptor antagonists (mainly due to PCI), beta blockers, and lipid modifying agents were observed (Table S2).

Long-Term Clinical Outcomes According to Revascularization Status

Long-term clinical outcomes according to revascularization status and Kaplan-Meier estimates of 1-year event rates are summarized in Table 2. As seen in Figure 1, the long-term primary clinical composite end point of all-cause death or MI was lower with revascularization compared with conservative management (Figure 1A). Similar results were seen for left main
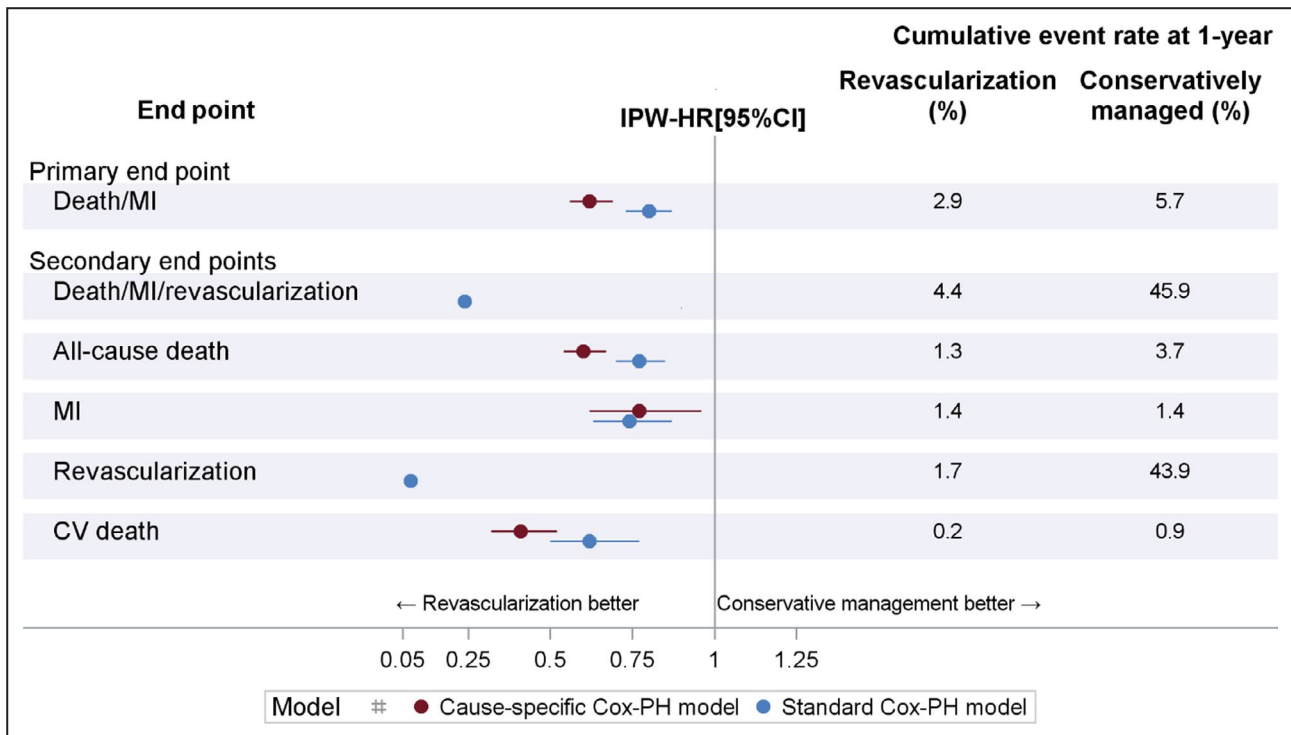
Figure 2. Adjusted hazard ratios for clinical end points in high risk anatomy patients with stable ischemic heart disease undergoing revascularization and conservative management.
Cox-PH indicates Cox—proportional hazard; CV, cardiovascular; IPW-HR, inverse probability weighted—hazard ratio; and MI, myocardial infarction.

Table 3. Subgroup Analysis by Anatomy for the Primary End point of Death/Myocardial Infarction

Subgroups*	Cause-Specific IPW-HR† (95% CI)	P Value	Death/MI Rates at 1-y, % (95% CI) Median Event Free Survival, y	
			Revascularization (N=5487)	Conservative Management (N=3529)
Overall	0.62 (0.56–0.69)	<0.001	2.9% (2.5%–3.4%) 13.9 y	5.7% (4.8%–6.7%) 12.1 y
	CABG: 0.61 (0.55–0.68)			
	PCI: 0.64 (0.56–0.73)			
3VD with pLAD ≥70% stenosis (n=1299)	0.87 (0.68–1.11)	0.25	2.8% (1.8%–4.5%) 12.7 y	3.6% (2.3%–5.8%) 12.3 y
	CABG: 0.86 (0.64–1.15)			
	PCI: 0.87 (0.65–1.18)			
3VD with 1VD ≥95% stenosis (n=3321)	0.66 (0.56–0.77)	<0.001	2.8% (2.1%–3.7%) Not reached	4.6% (3.5%–6.1%) 12.6 y
	CABG: 0.65 (0.53–0.80)			
	PCI: 0.66 (0.55–0.79)			
3VD with pLAD ≥95% stenosis (n=2151)	0.42 (0.33–0.54)	<0.001	2.8% (2.0%–3.8%) Not reached	9.5% (6.9%–13.2%) 8.9 y
	CABG: 0.38 (0.30–0.49)			
	PCI: 0.51 (0.38–0.68)			
Left main ≥50% stenosis (n=1126)	0.49 (0.37–0.66)	<0.001	3.5% (2.3%–5.2%) Not reached	7.8% (4.9%–12.3%) 9.0 y
	CABG: 0.49 (0.37–0.65)			
	PCI: 0.57 (0.29–1.12)			
Severe left main ≥70% stenosis (n=1119)	0.29 (0.19–0.45)	<0.001	3.0% (2.1%–4.4%) 12.7 y	11.8% (6.3%–21.6%) 3.8 y
	CABG: 0.29 (0.19–0.44)			
	PCI: 0.54 (0.24–1.22)			

CABG indicates coronary artery bypass grafting; HR, hazard ratio; IPW, inverse probability weighted; MI, myocardial infarction; PCI, percutaneous coronary intervention; pLAD, proximal left anterior descending; and VD, vessel disease.

*Significant interaction effect (P<0.001) suggesting the relative risk reduction of revascularization varies depending on the anatomy subgroup.

†Subsequent revascularization is a competing risk event.

disease alone and 3 VD alone (Figure S2). Evaluation by the specific type of revascularization showed similar reduction for the primary end point in PCI and CABG (Figure 1B). As seen in Figure 2, following adjustment, selection for revascularization was associated with a lower risk of all-cause death or MI compared with a conservative approach (IPW-HR 0.62; 95% CI, 0.58–0.66; P<0.001). The 1-year event rate was 2.7% versus 6.8%, respectively. Similar relative benefit for the primary end point was noted with PCI (IPW-HR 0.64; 95% CI, 0.59–0.70; P<0.001; rate at 1-year 2.7%) and CABG (IPW-HR 0.61; 95% CI, 0.57–0.66; P<0.001; rate at 1-year 2.8%). The relative risk reduction without consideration of the competing risk event of subsequent revascularization was still significant (standard Cox-PH regression IPW-HR 0.80; 95% CI, 0.75–0.84) (Figure 2). No statistically significant difference in treatment effect was observed according to left ventricular ejection fraction subsets (P-interaction 0.62).

For the secondary clinical composite end point of all-cause death, MI, and revascularization, significantly lower risk was observed for those selected for revascularization compared with conservative management following adjustment (IPW-HR 0.24; 95% CI, 0.23–0.25; P<0.001; event rates at 1-year: 4.2% versus 45.4%) (Figure 2).

Similar patterns were observed for MI (IPW-HR 0.53; 95% CI ,0.47–0.60; P<0.001; event rates at 1-year: 1.7% versus 3.2%) and subsequent revascularization (IPW-HR 0.07; 95% CI, 0.07–0.08; P<0.001; event rates at 1-year: 1.7% versus 41.9%) (Figure 2).

We observed a reduction in all-cause mortality with those selected for revascularization compared with conservative management following adjustment (IPW-HR 0.57; 95% CI, 0.53–0.61; P<0.001; mortality rate at 1-year of 1.1% versus 4.6%). Similar results were demonstrated with cardiovascular-specific mortality (IPW-HR 0.62; 95% CI, 0.51–0.71; P<0.001; cardiovascular mortality at 1-year 0.1% versus 1.1%).

As a sensitivity analysis adjusting for covariates in a Cox regression model, similar associations of revascularization were observed with clinical outcomes (Table S3).

Among the 4974 evaluable patients with medication status at 6 months, the use of preventative therapies was slightly higher among revascularized patients. However, in an explorative analysis adjusted for medication use at 6 months, a similar estimate of the relative effect measure for the primary end point was obtained in favor of revascularization (IPW-HR 0.62; 95% CI, 0.53–0.72; P<0.001).

Subsets of Complex Coronary Artery Disease

Death and MI according to subtypes of high-risk coronary anatomy with and without revascularization are presented in Table 3. With the exception of 1 anatomical category (strong trend), selection for revascularization was associated with improved outcomes compared with conservative management. Test of interaction effect of the treatment group was statistically significant ($P<0.001$), suggesting that the relative risk reduction benefit of revascularization varies according to the subtypes of coronary anatomy (ie, the estimated HR showed that relative benefit was even higher among those with more severe disease).

DISCUSSION

In this large prospective angiographic registry of patients with SIHD with high-risk coronary anatomy, several novel findings were demonstrated. Patients selected to receive revascularization (compared with those with conservative management) were associated with improved clinical outcomes long-term (including hard clinical end points). This association appears congruent with either mode of revascularization (CABG or PCI) and was observed regardless of the high-risk anatomical profile defined in our study. Our results support the selection of revascularization as the mode of therapy for anatomically complex SIHD, but deserves confirmation, ideally in a large clinical trial of patients whose high-risk coronary anatomy is known.

The ISCHEMIA trial randomized 5179 patients with SIHD and moderate to severe ischemia to routine invasive therapy with OMT versus OMT alone. Patients were allocated to an assigned strategy without knowledge of anatomy with coronary angiography. However, patients with LM disease were excluded with a blinded coronary computed tomography angiography prior to randomization. The primary outcome of CV death, MI, resuscitated cardiac arrest, or hospitalization for unstable angina was no different between groups. Moreover, an invasive strategy failed to show a reduction in the composite of CV death or MI, as well as all-cause mortality at a median of 3.3 years.[6] While this study supports a conservative strategy for SIHD patients, the effects of revascularization on those with LM disease and/or high-risk coronary anatomy remain speculative. In the ISCHEMIA trial, there was no heterogeneity in treatment effect based on coronary disease severity (1 VD, 2 VD, ≥3 VD)[6]; however, this was based on 50% stenosis. Similar findings were reported for those with proximal LAD involvement with ≥50% stenosis.[6] In our study, we included LM disease and

used a ≥70% cut off to define significant disease with further stratification based on 95% epicardial stenoses. Based on our defined high-risk criteria, we demonstrated a reduction in the composite of all-cause mortality or MI as well as all-cause mortality (and CV mortality) with revascularization, regardless of high-risk angiographic subset. It is of interest to note the incremental risk reduction with revascularization according to the spectrum of disease severity within this high-risk angiographic cohort demonstrated in our study. Moreover, we report a median follow-up of 6.2 years, which is almost twice the median follow-up in the ISCHEMIA trial. This is particularly important given the divergence of curves at 2 years, which appears to start favoring an invasive strategy in the ISCHEMIA trial.[14]

Within revascularization modalities, we have demonstrated improved clinical outcomes with both CABG and PCI. It is of interest to note most guideline recommendations for CABG are based on historic randomized studies (VA Cooperative Study, European Study, Coronary Artery Surgery Study, etc) for SIHD. In a meta-analysis performed by the CABG Surgery Trialists Collaboration of 2649 patients (1972–1984), CABG compared with medical therapy reduced all-cause mortality at 10-years with benefits being most pronounced in higher-risk categories (LM and 3 vessel coronary artery disease).[15] However, it is important to note these benefits were seen in a small subgroup of patients (150 patients with LM, 1300 patients with 3 VD) in a total patient population of predominantly negative pooled trials.[15] Our data (1996–2017) of 4566 selected patients with CABG with high-risk coronary anatomy confirm these findings in an "all-comer" patient population, which provides reassurance to guideline-based recommendations for myocardial revascularization with CABG.[16,17]

With PCI, the data to support myocardial revascularization in SIHD is less clear. In a 2006 meta-analysis of 2950 patients with SIHD, PCI compared with medical therapy did not improve survival.[18] More recently, an updated 2013 meta-analysis of 8070 patients again found no difference in all-cause or cardiovascular mortality with PCI.[19] However, in a smaller meta-analysis (n=1557) of patients with objective evidence of ischemia (including patients with moderate-severe ischemia from COURAGE), revascularization with PCI was associated with lower all-cause mortality at 3 years.[20] The current analysis of 2175 patients with SIHD selected for PCI supports long-term survival in this high-risk anatomical cohort. This becomes particularly relevant given the 2011 American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Intervention guidelines on PCI do not account

for angiographic or ischemic burden of disease, and recommend PCI only be performed to improve symptoms of stable angina if refractory to guideline-directed medical therapy.[21] In contrast, the 2018 European Society of Cardiology and the European Association for Cardio-Thoracic Surgery Guidelines on Myocardial Revascularization recommend revascularization (CABG or PCI) with a large ischemic burden (>10% of myocardium) or proximal LAD stenosis in SIHD.[22]

In a high-risk anatomical cohort of patients with multivessel disease selected for revascularization, roughly 40% received PCI (as opposed to CABG). As it is sometimes difficult to ascertain the best mode of revascularization, a recent meta-analysis of randomized trials for unprotected left main disease found no significant difference in all-cause death, MI, or stoke between drug-eluting stents and CABG surgery.[23] While the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial, comparing CABG versus first-generation DES with left main or 3-vessel coronary disease, found a higher risk of all-cause death, MI, stroke, or repeat revascularization with PCI at 12-months, these results were mainly driven by more frequent revascularization (considered a "soft" outcome) with no significant difference in the rate of death, MI, or stroke with PCI.[24] At 3 and 5 years, similar outcomes were demonstrated.[25,26] Hence, PCI is still considered a reasonable approach—recognizing that over one-half of our cohort selected for revascularization still received CABG.

We did observe a substantial crossover towards revascularization in patients managed conservatively. Over one-half of patients received subsequent revascularization during the entire follow-up with a vast number of cases occurring within the first year (but after 3 months from index coronary angiogram). In part, this may be due to recurrent symptoms despite conservative management, which may be more apparent in patients with high-risk coronary anatomy. Although speculative, the differences in outcome observed in our study may be more pronounced in the conservatively treated patients who did not undergo subsequent revascularization.

We do recognize that patients being managed conservatively may be due to patient comorbidities or complex coronary anatomy. Given our findings, this represents an underserved and vulnerable population at risk. With the advances in PCI, revascularization can now be performed safely to achieve revascularization in those where CABG is precluded. Our data would support revascularization programs, such as the Complete Revascularization for Higher-risk Indicated Patients (CHIP), which provides the skillset to perform PCI safely in these patients.[27] Currently, the OPTIMUM (Outcomes of Percutaneous Revascularization for Management of Surgically Ineligible Multivessel or Left Main Coronary Artery Disease) prospective registry (NCT02996877) is underway, which will compare 30-day survival following high-risk percutaneous coronary revascularization versus guideline-directed medical therapy.

Limitations

While our prospective observational study is based on a robust, large, population-based cohort of patients with SIHD with systematic angiographic data collection, we cannot exclude unmeasured variables as potential confounders in our analysis. We have not accounted for patients with high-risk coronary artery disease who were unable to receive coronary angiography. While our results are impressive for long-term survival with revascularization, our survival analysis excluded patients who expired within 3-months of index cardiac catheterization to avoid bias of those patients who may have died prior to revascularization. We did not collect ischemic risk (ie, non-invasive stress tests) prior to angiography, as our focus was based on the prognostic value of high-risk angiographic anatomy in SIHD. We do acknowledge the limited number of patients with pharmaceutical claims at 6 months which does not reflect the chronicity of optimal medical therapy. Clinical rationale for revascularization (and the choice of CABG versus PCI) could not be collected. In this context, it should be recognized that the members of the revascularization group were younger with less comorbid risk. Outcomes were adjusted accordingly (using an inverse probability weighted approach) but may not fully account for treatment selection bias. The subgroup with 3 VD and 70% proximal LAD did not show a significant reduction in the primary end point with revascularization and this may be a function of the anatomic degree of ischemia. We did not perform a direct comparison of outcomes between CABG and PCI, as this was not the primary intent of our study. However, it is interesting to note the incremental difference in outcome with CABG (over PCI) when compared with conservative management amongst the high spectrum of angiographic risk. Finally, our analysis of patients with SIHD was performed in a provincial, government-funded single-payer healthcare system and our results may not be generalizable to other healthcare systems internationally.

CONCLUSIONS

In a large registry of patients with SIHD with coronary angiography, patients with high-risk coronary anatomy appear to survive longer and have a lower risk of MI with revascularization based on the associations

demonstrated in our study. Accordingly, we believe that the coronary anatomical profile should be considered when revascularization selection is contemplated in SIHD.

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coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. *Eur Heart J*. 2011;32:2125–2134.

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Supplemental Material

Table S1. Results of multivariable logistic regression model to estimate of probability of revascularization.

Covariate	Regression coefficient	Wald χ2	P-value
Intercept	-1.067	20.7	<.0001
Age*			
<=70	0.067	3.4	0.0638
>70	0.630	31.6	<.0001
Age ≥ 75	-0.324	8.3	0.004
Sex: Female	0.072	1.5	0.2271
Hyperlipidemia	-0.198	12.8	0.0004
Diabetes mellitus	0.349	56.1	<.0001
Current smoker	0.252	13.5	0.0002
Ex-smoker	0.082	2.7	0.1011
Previous MI	0.265	19.5	<.0001
CHF	0.503	37.4	<.0001
Creatinine >200mmol/L	0.275	4.1	0.0422
Dialysis	0.683	7.6	0.006
PAD	0.227	8.2	0.0041
CVD	0.1945	5.2	0.022
Ejection Fraction %			
>50	-0.0742	2.6	0.109
35-50	0.00732	0.01	0.9052
20-35	0.1116	1.3	0.2582
<20	0.3144	23.3	<.0001
Not done-instability	0.0451	0.1	0.7351
Not available	ref		

* Linearity assumption was not met thus piece-wise linear effects below and above 70- years of age
Global χ2 was 384 with 19 degrees of freedom (P <0.0001; C-stat 0.62)

**Table S2. Medications at 6 months after discharge (N=4,974).**

	Revascularization N=3086	Conservative management N=1888	Total N=4974	P-value
Claim for any within 6 months after Cath.	2822 (91.4)	1687 (89.4)	4509 (90.7)	0.0139
P2Y12 receptor antagonists	1374 (44.5)	282 (14.9)	1656 (33.3)	<.0001
Clopidogrel	1219 (39.5)	269 (14.2)	1488 (29.9)	<.0001
Prasugrel	5 (0.2)	0 (0.0)	5 (0.1)	0.0801
Ticagrelor	179 (5.8)	14 (0.7)	193 (3.9)	<.0001
B-Blocker	2462 (79.8)	1364 (72.2)	3826 (76.9)	<.0001
ACEI & ARB	2184 (70.8)	1379 (73.0)	3563 (71.6)	0.0849
Lipid modifying agents	2698 (87.4)	1525 (80.8)	4223 (84.9)	<.0001

Table S3. Results of multivariable cause-specific Cox regression model for the association of revascularization with clinical outcomes.

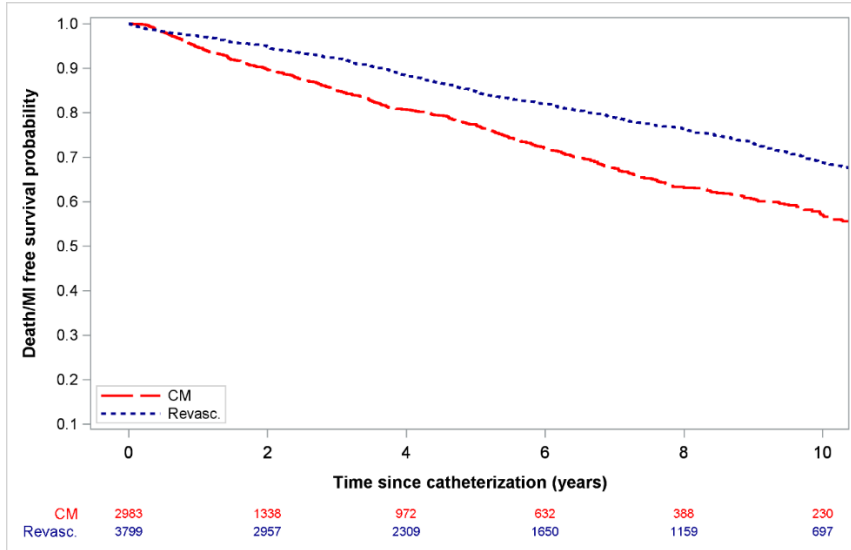|	HR† (95% CI)	P-value
Primary endpoint		
Death/ MI	0.65 (0.59-0.72)	<.001
Secondary Endpoints		
Death/ MI/ revascularization	0.23 (0.21-0.24)	<.001
All cause death	0.65 (0.59-0.73)	<.001
MI	0.81 (0.65-1.00)	0.05
Revascularization	0.07 (0.06-0.08)	<.001
Cardiovascular death	0.45 (0.35-0.57)	<.001

Figure S1. Distribution of propensity score.
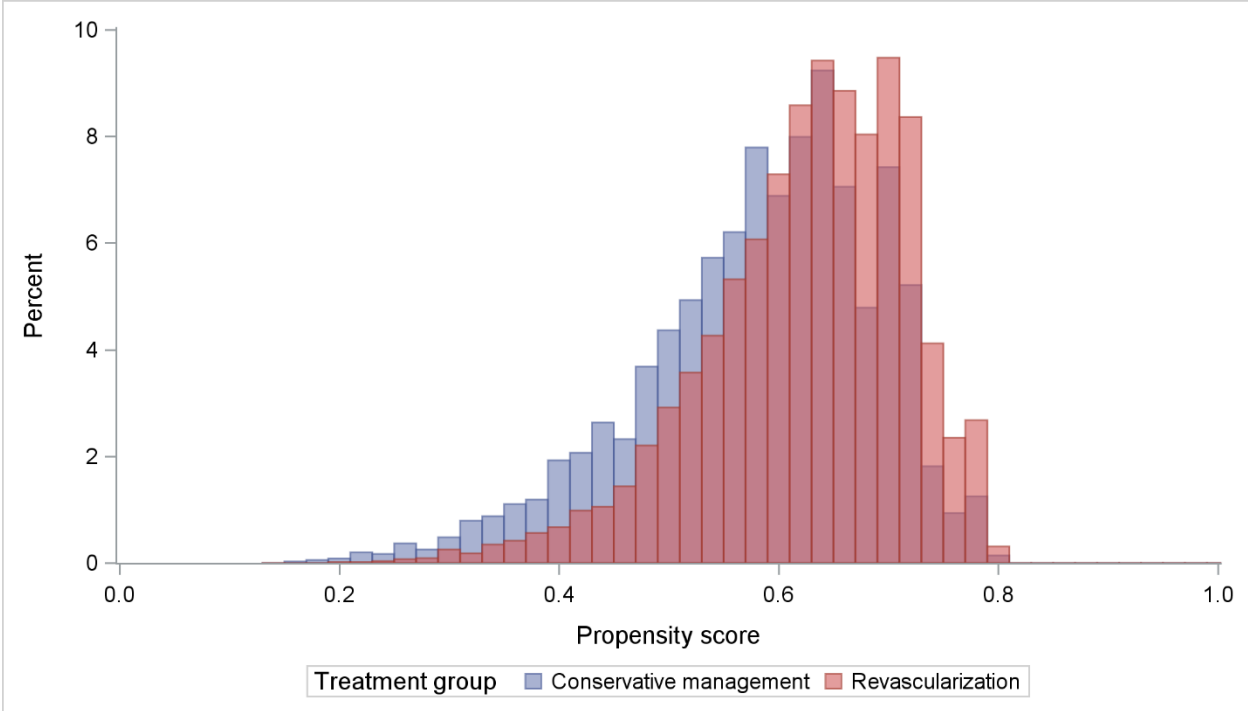
The range for the corresponding inverse probability weights was 1.2 to 5.0 indicating no extreme weight.

Figure S2. Long-term all-cause death or myocardial Infarction free survival comparing revascularization (Revasc) and conservative management (CM) among: (A) three vessel disease subgroup alone; (B) left main disease subgroup alone.

(A)

(B)