

Revascularization in patients with heart failure

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ABSTRACT

Background: Although practice guidelines recommend coronary revascularization for patients with heart failure, the evidence to support this recommendation is weak. The objective of our study was to determine the association of coronary revascularization with survival in patients who have had heart failure.

Methods: Data were obtained from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH), a clinical outcome-monitoring initiative that has captured data on all patients undergoing cardiac catheterization in the province of Alberta since 1995. Our study included data from patients with a history of heart failure and with documented coronary artery disease; patients with normal coronary arteries or prior coronary artery bypass grafting (CABG) were excluded. We constructed survival curves and adjusted them by the corrected group prognosis method (incorporating all clinical variables in APPROACH). Propensity scores were used to account for clinical characteristics that could influence the decision to revascularize.

Results: A total of 2538 patients (mean age 68 yr, standard deviation [SD] 11 yr, 31% female) underwent revascularization; 1690 patients (mean age 69 [SD 11] yr, 34% female) did not. Crude 1-year mortality was 11.8% among patients who underwent revascularization, compared with 21.6% among those who did not. Adjusted survival curves diverged early and continued up to 7 years of follow-up (hazard ratio 0.50, 95% confidence interval 0.44–0.57). Propensity scores showed improved survival with revascularization across all quintiles of likelihood of revascularization.

Interpretation: This new evidence lends support to practice guidelines, which recommend revascularization in patients with heart failure and coronary disease.

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important public health problem. In Canada in the year 2000, heart failure accounted for over 106 000 hospital admissions and 1 400 000 inpatient days, which reveals it to be one of the most prevalent acute-care diagnoses.²

Coronary artery disease is the primary etiology in two-thirds of all cases of heart failure.⁴ In addition, uncontrolled coronary ischemia has been identified as a common precipitant of heart-failure exacerbations.⁵⁻⁷ As such, practice guidelines recommend coronary revascularization for patients with heart failure and coronary artery disease.^{3,4}

There is, however, relatively little evidence for a strategy of routine revascularization in patients with heart failure, with the only published literature examining coronary-artery bypass grafting (CABG), either from cohort trials or subgroups from randomized trials.^{8,9} To date, no randomized studies of revascularization have been completed that specifically involve patients with heart failure.

We sought to determine the association of coronary revascularization with survival in patients with heart failure, with use of a population-based registry. Our secondary objective was to determine differences in survival based upon revascularization strategy: CABG versus percutaneous coronary intervention (PCI).

Methods

Data were obtained from a prospective clinical data-collection initiative, the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH), which has captured data on all patients who have undergone cardiac catheterization in the province since 1995.¹⁰ The database contains detailed information including patients' age, sex, left-ventricular ejection fraction, coronary anatomy and comorbidities. It tracks therapeutic interventions such as previous thrombolytic therapy and previous or subsequent revascularization procedures (CABG or PCI). Follow-up mortality is ascertained by means of a semiannual merge with data from the Alberta Bureau of Vital Statistics. This database therefore allows for the study of processes and outcomes of cardiac procedures at the population level.

We included patients with a documented history of heart failure at the time of coronary catheterization. Excluded were patients with normal coronary arteries or nonsignificant coro-

Although the prevalence of cardiovascular disease is generally on the decrease in Western society, that of heart failure is, paradoxically, increasing, owing to improved survival of patients with cardiovascular disease and a generally aging population.¹⁻⁴ Heart failure is associated with very high rates of illness and death, and constitutes an

nary disease (defined as stenoses < 50%) and those with prior CABG, because such patients would be unlikely to be recommended coronary revascularization. Cases were then grouped according to whether the patients had undergone revascularization within the first year after catheterization or not. Survival data were collected over the next 1–7 years of follow-up.

The APPROACH study protocol was approved by the research ethics boards of the Universities of Calgary and Alberta. The requirement for informed consent was waived.

Patient characteristics among the 2 groups were compared with χ^2 tests. Kaplan–Meier plots and log-rank tests were used to determine and compare crude survival rates per age group according to treatment strategy (revascularization or no revascularization). Time to events for survival analyses was measured from the index catheterization.

To address concerns over the prognostic role of clinical factors that simultaneously influence outcomes and the decision to undergo revascularization, we conducted a propensity score analysis as described by Rubin.¹¹ A logistic regression model was constructed that estimated the probability (i.e., the propensity) of being revascularized based on the clinical characteristics captured in the APPROACH study. The overall study population was then subdivided into quintiles according to propensity for being revascularized. Each of these

“propensity groups” contains patients who were and were not revascularized. One-year mortality rates in each of these groups were determined and compared for revascularization versus nonrevascularization subsets.

We constructed survival curves were and adjusted them for risk with the corrected group prognosis method,¹² incorpor-

Table 1: Demographic and medical characteristics of patients with heart failure* who underwent coronary catheterization, 1995 through 2000, in %†

Characteristic or risk factor	All n = 4228	No revasc n = 1690	Revasc n = 2538	p value
Age, yr	68.2	68.9	67.7	0.002
Standard deviation, yr	10.7	10.8	10.7	0.06
Male	67.6	66.0	68.8	0.06
Diabetes mellitus	33.0	35.3	31.6	0.01
Hyperlipidemia	37.9	33.9	40.5	< 0.001
Hypertension	59.5	59.7	59.4	0.83
Present smoker	26.0	25.0	26.7	0.22
Previous smoker	46.5	45.7	47.0	0.38
Prior cardiovascular event				
Myocardial infarction	74.2	69.8	77.1	< 0.001
Thrombolytic therapy	13.0	8.4	16.0	< 0.001
PCI	8.0	6.8	8.8	0.01
Cerebrovascular disease	11.7	11.5	11.9	0.68
Peripheral-arterial disease	12.5	12.7	12.4	0.77
COPD	22.2	23.5	21.4	0.10
Liver or GI disease	6.4	5.9	6.7	0.27
Malignancy	5.6	6.2	5.2	0.16
Renal disease	9.1	8.9	9.3	0.67
Requires dialysis	3.4	3.6	3.2	0.50

Note: revasc = revascularization, PCI = percutaneous coronary intervention, COPD = chronic obstructive pulmonary disease, GI = gastrointestinal.

*Excluding patients with normal anatomy and those who previously underwent coronary-artery bypass grafting.

†Except as indicated for age.

Table 2: Clinical characteristics of patients with heart failure* who underwent coronary catheterization, 1995–2000, in %

Condition or medication	All n = 4228	No revasc n = 1690	Revasc n = 2538	p value
Primary indication for catheterization				< 0.001
Stable angina	10.0	12.1	8.5	
Unstable angina	21.3	20.1	22.1	
Myocardial infarction	47.2	36.5	54.3	
Heart failure	12.3	19.3	7.7	
Other†	9.2	12.0	7.3	
Coronary anatomy				< 0.001
Low risk‡	38.0	40.5	36.4	
High risk‡	45.8	44.3	46.8	
Left main coronary artery	13.2	11.1	16.2	
Data unavailable	2.0	4.1	0.6	
Left-ventricular ejection fraction				< 0.001
> 50%	23.0	17.8	26.5	
35%–50%	30.1	26.9	32.3	
20%–34%	20.7	25.9	17.3	
< 20%	4.4	7.2	2.5	
Could not be calculated	0.3	0.4	0.2	
Not measured	11.1	10.8	11.3	
Datum missing	10.5	11.4	9.9	
Medications in use§				
Aspirin	60.0	54.5	63.8	< 0.001
Ticlopidine/clopidogrel	1.2	0.9	1.3	< 0.001
ACE inhibitors	42.9	46.5	40.5	< 0.001
Beta-blocker	38.2	32.9	41.7	< 0.001
Calcium-channel blockers	12.8	12.3	13.0	0.001
Glyburide	3.3	3.9	3.0	< 0.001
Lipid-lowering agents	13.1	12.1	13.7	< 0.001
Long-acting nitrate	31.3	31.2	31.4	< 0.001
Crude mortality rates (total deaths)				
At 30 days (n = 267)	6.9	8.6	5.7	0.003
At 1 year (n = 613)	15.8	21.6	11.8	< 0.001

Note: revasc = revascularization, ACE = angiotensin-converting enzyme.

*Excluding patients with normal anatomy and those who previously underwent coronary-artery bypass grafting.

†Serious arrhythmia, nonischemic cardiomyopathy, valvular heart disease or congenital heart disease.

‡Adapted from the Duke classification:

- Low risk: single-vessel disease with $\geq 50\%$ stenosis or 2-vessel disease, with or without stenosis (excepting 95% stenosis in the proximal left anterior descending artery).
- High risk: 2-vessel disease with 95% stenosis of the proximal left anterior descending artery or 3-vessel disease with or without stenosis.

§At the time of cardiac catheterization.

ating all clinical variables collected (Table 1 and Table 2), excluding medications (listed in Table 2).

Because our data were hierarchical in nature, with data from 4 hospitals and potential within-hospital clustering of data, we carried out sensitivity analyses with generalized estimating equations (proc GENMOD in SAS) as well as a generalized hierarchical model (GLIMMIX macro in SAS) with a random effect for hospital. These analyses changed neither the statistical significance of any of our findings nor the width of our confidence intervals (CIs) in any notable way. We therefore concluded that there was minimal (or no) clustering in our data and that our proportional hazard models were appropriate.

Results

Of the 6134 patients with heart failure who underwent coronary catheterization from 1995 through 2001, 1353 were excluded because their coronary arteries were normal, and a further 553 because of prior CABG. A total of 4228 patients therefore met the inclusion criteria, with 2538 receiving revascularization and 1690 patients not receiving it. Demographic and clinical characteristics of these patients are shown in Table 1 and Table 2.

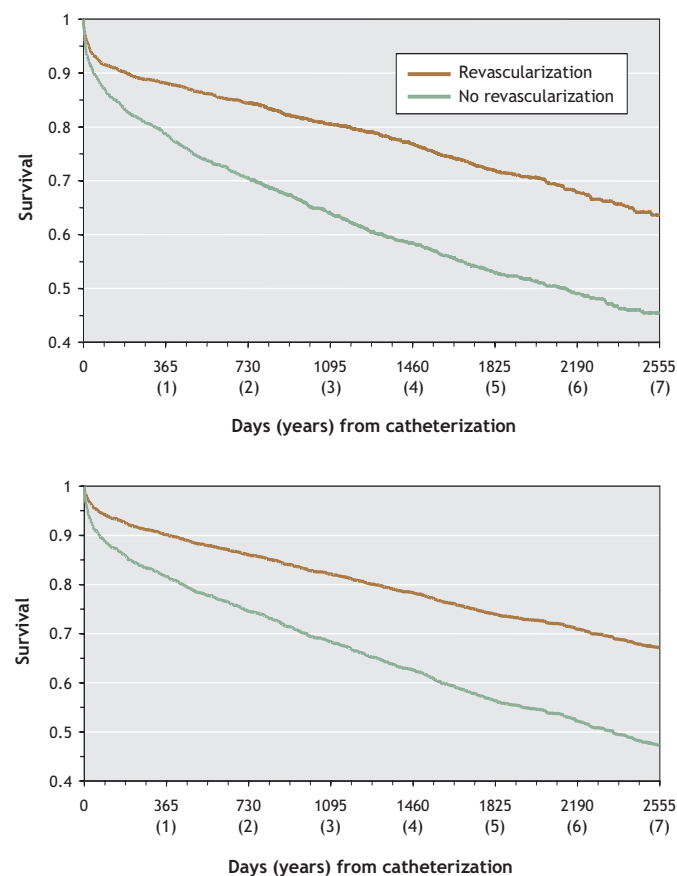


Fig 1: Crude survival of patients with heart failure who underwent revascularization compared to those not revascularized. Upper panel, crude survival; lower panel, risk-adjusted survival.

The average age of the patients studied was 68 years; two-thirds of them were male. Overall, 60% of the patients received revascularization, 52.5% by CABG and 48.5% by PCI. As expected in this patient population, coronary risk factors were common, the most frequent being hypertension, hyperlipidemia, diabetes and current smoking. Three-quarters of the patients had a prior myocardial infarction. Comorbidities, including chronic obstructive pulmonary, peripheral arterial, cerebrovascular and renal disease, were often present.

The main indications for coronary catheterization were myocardial infarction (47%), unstable angina (21%) and heart failure (12%). Most patients had left-ventricular ejection fractions of less than 50%. In general, patients who were revascularized were slightly younger, were more likely to have had a prior myocardial infarction, had a higher ejection fraction, and were more likely to have high-risk coronary anatomy (2-vessel disease with involvement of the proximal left anterior descending artery, 3-vessel disease or left main coronary-artery disease). Medications at the time of catheterization included ASA in 60%, angiotensin-converting enzyme (ACE) inhibitors in 43%, β -blockers in 38%, long-acting nitrates in 31%, calcium-channel blockers in 13% and lipid-lowering agents in 13%.

Crude survival curves for the patients who underwent revascularization and those who did not are shown in the upper panel of Fig. 1. Corresponding mortality rates at 1 year were 11.8% in those who underwent revascularization and 21.6% in those who did not (hazard ratio [HR] 0.52, 95% CI 0.47–0.58). The risk-adjusted 7-year survival curves, meanwhile (Fig. 1, lower panel), diverged early and continued diverging in favour of revascularization for up to 7 years of follow-up (HR 0.50, 95% CI 0.44–0.57). Propensity-adjusted relative survival is shown in Table 3. Within all 5 propensity quintiles of likelihood of revascularization, patients who received revascularization had an improved survival, with a relative risk ranging from 1.79 to 2.86.

Crude and adjusted 7-year survival curves are shown in Fig. 2, comparing patients who underwent PCI or CABG with those who did not. Based upon the crude survival curve (upper panel), CABG and PCI appear to confer similar survival benefits (CABG HR 0.51, 95% CI 0.44–0.59; PCI HR 0.46, 95% CI 0.39–0.54 [each v. no revascularization]). The adjusted curve (Fig. 2, lower panel) shows CABG to be associated

Table 3: Propensity-adjusted relative survival, scored from 1 (least likely to be revascularized) through 5 (most likely)

Score quintile	No. of patients		Survival at 1 year, %		
	No revasc	Revasc	No revasc	Revasc	RR (95% CI)
1	421	230	79.8	89.6	1.92 (1.3-2.9)
2	366	297	80.1	88.8	1.79 (1.2-2.6)
3	260	405	80.0	89.1	1.85 (1.3-2.6)
4	191	454	82.2	90.5	1.89 (1.2-2.9)
5	137	539	79.6	92.8	2.86 (1.8-4.3)

Note: revasc = revascularization, RR = relative risk, CI = confidence interval.

with the best survival (HR 0.44 v. no revascularization, 95% CI 0.38–0.52), with survival for the PCI group of patients (HR 0.58 v. no revascularization, 95% CI 0.49–0.69) lying between that of the CABG and no-revascularization groups.

Interpretation

Coronary artery disease is highly relevant to the management of patients with heart failure, as it represents the single most important cause of heart failure and is a major factor in exacerbations of symptoms.^{1,3–7} Therefore, examination is needed of the role that coronary revascularization plays in the management of patients with heart failure. In our analysis of a large cohort of patients with heart failure who underwent cardiac catheterization, we demonstrated a strong association between revascularization and survival. This finding provides valuable support to the practice guidelines for heart failure.

All recent practice guidelines recommending coronary revascularization in patients with heart failure cite the systematic review conducted by Baker and associates in 1994.⁸ The authors evaluated 8 cohort studies that involved 2695 patients whose heart failure was treated with CABG or medical ther-

apy. The studies' results were not combined for meta-analysis because of a high degree of heterogeneity. No studies of PCI were included, because none were available when that review was conducted. Baker's group concluded that, in patients with heart failure and limiting angina, CABG improved 3-year survival by 30%–50% and physical function by about 1 New York Heart Association Functional class. Although they used quality ratings for cohort studies, the causal inference from such study designs is rather limited. In a systematic review by Yusuf and coworkers⁹ of 2649 patients randomized to CABG or to medical treatment, it was noted that the subgroup of patients with lower ejection fractions had relative benefits of CABG similar to those with ejection fractions in the normal range. However, because of their higher mortality risk, patients with lower ejection fractions had a greater absolute benefit from CABG.

Our study, using a truly population-based cohort of patients with heart failure who were referred for cardiac catheterization, combined with powerful statistical techniques, observed a striking association with improved survival in patients undergoing revascularization. Although these are observational data, with a lower level of causal inference than a randomized trial, this may be the best available evidence to-date for the efficacy of revascularization in patients with heart failure. Our results suggest that all patients with heart failure and clinically significant coronary artery disease amenable to revascularization should be considered for these procedures.

Our secondary objective was to evaluate differences between PCI and CABG in the survival of patients with heart failure. In the adjusted analysis (Fig. 2, lower panel) patients undergoing CABG appeared to have slightly better survival than those who received PCI. The results of these subgroup analyses should be viewed with caution, however: the complexity of clinical decision-making for revascularization is likely not completely accounted for, in our adjustments. In any case, differences in survival by revascularization type are modest compared with those between patients who underwent revascularization and those who did not.

It is also notable that less than half of the patients were receiving ACE inhibitors or β -blockers at the time of their coronary catheterization. Although about a quarter of the patients had preserved systolic function, these observations are consistent with other reports of the underuse of the therapies proven efficacious in heart failure.^{13,14} It can be argued that the survival rate of nonrevascularized patients is perhaps not reflective of what might be seen in a nonrevascularized cohort that receives optimal medical therapy.

The causal inference that can be drawn from an observational study, no matter how well conducted or analyzed, will always be less robust than that drawn from an appropriately powered randomized controlled trial. There may be clinical details that influenced the decision to revascularize that were not captured. Nevertheless, the propensity score analysis indicates that the study findings are robust and consistent across groups of patients with different probabilities for selection for revascularization. Second, the patient population evaluated in our study was confined to those who were referred for cardiac catheterization. We recognized that this

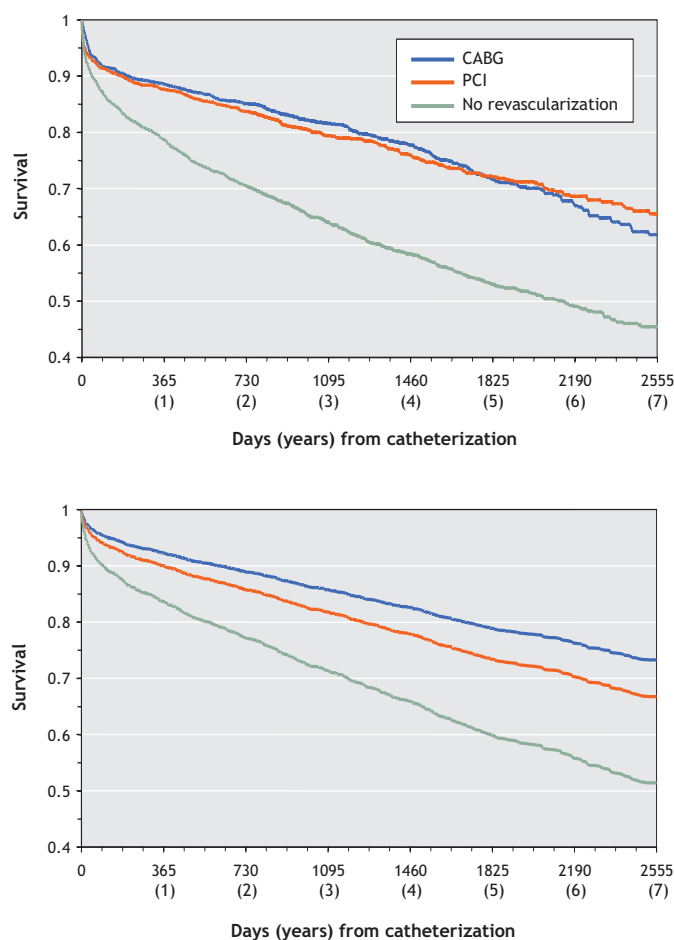


Fig 2: Survival of patients with heart failure, according to revascularization strategy. Upper panel, crude survival; lower panel, risk-adjusted survival.

would not include all patients with heart failure, and that we would therefore be unable to determine if a strategy of routine revascularization would be beneficial to patients with heart failure and asymptomatic or minimally symptomatic coronary artery disease. To protect the internal validity of our study, we excluded patients with normal coronary arteries or coronary disease that would not be clinically significant (i.e., those who would not need revascularization). Third, we did not apply strict diagnostic criteria for heart failure in this population. "Heart failure" was a clinical diagnosis, documented by the referring physicians. Nevertheless, the ejection fraction was low in most patients, suggesting that these assumptions were applicable. Fourth, we did not have information on the use of implantable cardioverter-defibrillator devices. Finally, we only had data on the medications being taken at the time of the procedure. Postprocedure medications may be important covariates, if their use differed between groups.

Given the implications of heart failure for public health, a randomized trial of revascularization for patients with heart failure is needed. Currently, the Surgical Treatment for Ischemic Heart Failure (STICH) randomized multicentre trial is evaluating medical therapy versus CABG surgery for patients with heart failure, an ejection fraction of less than 35% and coronary artery disease suitable for revascularization.¹⁵ The trial, which began in July 2002, aims to enrol 2800 patients at 50 sites in North America and Europe, with follow-up of at least 3 years. In contrast to our study, STICH will exclude patients who are candidates for PCI. This trial is scheduled for completion in 2008; until then, the best available evidence must be drawn from observational studies.

In this analysis of a large cohort of patients with heart failure who underwent catheterization, a strong association was revealed between revascularization and improved survival. This finding supports current recommendations in practice guidelines on heart failure and suggests that revascularization should be considered for all patients with heart failure and coronary artery disease.

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