Long-term survival in 11,661 patients with multivessel coronary artery disease in the era of stenting: A report from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators

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Background Studies of survival of patients with multivessel coronary artery disease (MVD) in the prestent era suggested that outcomes after coronary artery bypass surgery (CABG) are similar to those after percutaneous coronary intervention (PCI) in subsets of coronary severity. The purpose of this study of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) was to examine the association between treatment and survival up to 5 years in patients with MVD enrolled from 1995 through 1998.

Methods and Results Data on patient characteristics were obtained at the time of the initial coronary angiography. Survival was determined through data linkage to the provincial Bureau of Vital Statistics. Risk-adjusted hazard ratios were calculated to compare different treatments. In the 11,661 patients with MVD, CABG was the initial therapy in 3782, PCI in 3540, and medical therapy in 4339. Cumulative 5-year survival was 91.4% with CABG, 91.9% with PCI, and 82.9% with medical therapy (P < .001). Hazard ratios were CABG: medical 0.53 (95% confidence interval [CI] 0.46-0.71), PCI: medical 0.65 (95% CI 0.56-0.74), and CABG: PCI 0.81 (95% CI 0.68-0.96). Analysis across coronary severity groups revealed a benefit of CABG compared with PCI only in the group with severe left main CAD: 0.30 (95% CI 0.17-0.54).

Conclusions In a multicenter clinical setting, MVD patients treated with revascularization have significantly higher 5-year survival rate than those treated medically. Risk-adjusted comparison reveals PCI treatment to be associated with long-term survival similar to treatment with CABG in all coronary severity subgroups except the group with severe left main coronary artery disease. Patient selection factors are likely to be contributing to these findings. (Am Heart J 2001;142:119-26.)

Percutaneous coronary intervention (PCI) is now widely used in the treatment of patients with multivessel coronary artery disease (CAD). Trials conducted before routine use of stents suggested similar survival after PCI compared with coronary artery bypass grafting (CABG). A large prospective registry from Duke University on a cohort also enrolled before the advent of stenting in fact suggested better survival with CABG in those with 3-vessel CAD and equivalent survival rates with CABG, percutaneous transluminal coronary angioplasty (PTCA), and medical therapy in patients with 2-vessel CAD. Few data are available on long-term survival of patients with multivessel CAD (MVD) in the current era of stenting. The main aim of the current study was to examine cumulative survival to 5 years in patients with MVD managed with medical therapy, PCI, or CABG who were prospectively enrolled in the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) from January 1995 to December 1998 and to determine risk-adjusted hazard ratios for mortality for each interventional treatment modality compared with medical therapy.

Methods APPROACH is a province-wide inception cohort database of all patients undergoing cardiac catheterization with the primary clinical diagnosis of CAD in Alberta, a Canadian province.
with a population of 2.75 million people. Patients with a pri-
mary diagnosis of valvular or congenital heart disease were
excluded. The project, which began enrolling patients in
1995, is approved annually by the Ethics Review Board of
each participating center. Patients signed informed consent to
allow clinical follow-up. Demographic and clinical data of
enrolled patients were prospectively collected at the time of
the initial diagnostic procedure in the catheterization labora-
tories of the Foothills Hospital and Holy Cross Hospital in Cal-
gary as well as the University of Alberta Hospital and the Royal
Alexandra Hospital in Edmonton, Alberta, Canada. Coronary
angiographic data were recorded with use of Heartview soft-
ware (Duke Medical Center, Durham, NC). Left ventricular
ejection fraction (LVEF) was measured in each center by com-
puterized edge detection methods at the time of the diagnos-
tic angiographic procedure. In the event that measurement
was not done (31% of cases), the operator performing the
diagnostic procedure made a visual estimate of the LVEF.
Other incomplete clinical data were supplemented by corre-
sponding International Classification of Disease, 9th Revision,
Clinical Modification coded diagnoses from the administrative
databases of the 4 centers with use of a validated data
enhancement method.6 Data were transmitted from participat-
ing centers by a secure encrypted internet link to the data
center at the University of Alberta Hospital. Vital status was
determined semiannually from the Province of Alberta Depart-
ment of Vital Statistics.

Definitions

Two-vessel and 3-vessel disease was defined as presence of 2
or 3 major epicardial coronary arteries with ≥70% diameter
stenosis, determined visually by the cardiologist performing
the first diagnostic catheterization procedure during the study
period 1995-1998. Left main disease was defined as ≥50% diam-
eter stenosis in the left main coronary artery. Patients were cat-
egorized into treatment groups according to the first treatment
type within the first year after enrollment. This definition was
instituted as a result of waiting periods for revascularization
procedures in the province. The medical therapy group was
therefore defined as patients with no coronary revasculariza-
tion procedure within 1 year of the index angiographic pro-
cedure. Revascularized patients were included in the PCI or
CABG groups if they had one of these procedures as the first
intervention within 1 year of the index angiographic pro-
cedure. Events were assigned for any given treatment modality
received at the time and not for intention to treat.

Statistical analysis

Baseline comparisons of clinical characteristics across treat-
ment groups were made by χ² tests for categorical variables
and analysis of variance for continuous variables. Kaplan-
Meier analysis was used to present unadjusted 5-year survival
for each of the treatment groups. Cox proportional hazards
models were then used to determine risk-adjusted survival for
clinical characteristic and comorbidity and for each of the
treatment groups. These included age, sex, history of diabetes
mellitus, hyperlipidemia, hypertension, liver or gastrointesti-
nal disease, malignancy, chronic obstructive pulmonary dis-
case, serum creatinine level >200 mmol/L, cerebrovascular
disease, peripheral vascular disease, congestive heart failure,
prior myocardial infarction, prior coronary revascularization
procedures, coronary anatomy severity, and LVEF. Comorbid
conditions were deemed to be present if they were identified
as such by the referring cardiologist or in the hospital record.
The indication for the catheterization procedure (acute or
recent myocardial infarction, unstable angina, stable angina,
or other) was also included. Risk-adjusted hazard ratios were
calculated for the following treatment comparisons:
CABG/medical, PCI/medical, and CABG/PCI. Risk-adjusted
treatment comparisons were also made within each level of
coronary anatomy. The Duke coronary severity system was
used in all risk-adjustment procedures. All analyses were con-
ducted with use of SPSS version 10.0 (SPSS, Chicago, Ill).

Results

Clinical characteristics

Of the 23,877 patients who underwent coronary
angiography for presumed CAD in the province of
Alberta in 1995-1998, 22,690 were Alberta residents,
and of these 11,661 (51%) had MVD. Mean time from
catheterization to CABG was 70 ± 82 days and to PCI
22 ± 48 days. Mean follow-up was 2.7 ± 1.3 years
(median 2.7 years). Patients selected for medical ther-
apy were older. The group treated with CABG con-
tained the lowest proportion of women. Patients in the
CABG group were also less likely to have had a previ-
ous myocardial infarction (MI) than any other group
and were less likely to have had previous CABG or PCI.
Type 2 diabetes, hypertension, and renal dysfunction
were observed least frequently in the PCI group. How-
ever, PCI was the treatment performed most frequently
in the setting of acute or recent MI and least frequently
in the setting of stable angina (Table I). Thirty percent
of PCI patients received at least 1 stent.

Analysis of coronary anatomy and LV function (Table
II) indicated that among patients treated with a revascu-
larization procedure 2-vessel CAD was more prevalent
in the PCI group, whereas CABG patients had a higher
incidence of left main and 3-vessel CAD with proximal
left anterior descending (LAD) stenosis. Medically
treated patients were more likely to have severe LV dys-
function.

Coronary anatomy, treatment, and 5-year survival
(Figure 1)

Cumulative 5-year survival ranged from 91.4% in
the group with 2-vessel CAD to 87.9% in those with
3-vessel CAD and 82.8% in patients with left main dis-
ease. Unadjusted survival was similar in the CABG
(91.4%) and PCI (91.9%) groups but was significantly
lower in the group selected for medical therapy
(82.9%, P < .0001). Survival for patients with 2-vessel
CAD was CABG 91.6%, PCI 93.6%, and medical 88.5%
(P < .0001). In those with 3-vessel CAD survival was
CABG 92.1%, PCI 91.0%, and medical 82.8% (P <
.0001). Finally, in those with left main CAD survival
was 89.5% with CABG, 80.5% with PCI, and 69.5% with medical therapy \( (P < .0001) \).

**Clinical characteristics and survival (Figure 2)**

Women were at higher risk than men. Diabetes, malignancy, chronic obstructive pulmonary disease, peripheral vascular disease, MI, and congestive heart failure were independent predictors of worse outcome. The hazard also increased with increasing Duke coronary severity and decreasing left ventricular function. An indication for the procedure of acute or recent MI was also an independent predictor of increased risk.
Outcome comparison of revascularization versus medical therapy

Risk-adjusted hazard ratio analysis comparing cumulative 5-year mortality of patients treated with PCI, CABG, and medical therapy indicate significantly lower hazard ratio for 5-year mortality for treatment with CABG (hazard ratio 0.53, 95% confidence interval [CI] 0.46-0.61; \( P < .001 \)) as well as PCI (hazard ratio 0.65, 95% CI 0.56-0.74; \( P < .001 \)) compared with medical therapy in the overall MVD cohort. A more complex picture emerges with comparison of treatment strategies in the broad coronary anatomy groups and Duke subgroups.

In the entire group with 2-vessel disease, an association between treatment and survival was found only for PCI-treated patients. PCI treatment appeared to have a similar impact in the overall group with 3-vessel CAD (PCI vs medical hazard ratio 0.61, 95% CI 0.51-0.74; \( P < .001 \)). A similar association was observed with CABG compared with medical therapy in the 3-vessel CAD patients (CABG vs medical hazard ratio 0.55, 95% CI 0.46-0.66). In the presence of left main disease, only treatment with CABG was associated with a lower risk compared with medical therapy (\( P < .001 \)).

Detailed treatment comparison of revascularization versus medical therapy by Duke coronary severity groups (Figure 3) reveals an association between CABG and survival in patients with left main CAD and all sub-
sets with 3-vessel CAD. An association in all 3-vessel CAD subgroups is also observed for PCI treatment, an association that extends to those with 2-vessel CAD with severe (95%) proximal LAD disease.

**Outcome comparison of revascularization strategies**

Risk-adjusted comparison reveals a lower risk of mortality up to 5 years for treatment with CABG compared with PCI for the entire group (hazard ratio 0.81, 95% CI 0.68-0.96; \( P = .019 \)). As Figure 3 indicates, this overall advantage favoring CABG is largely related to the low hazard ratio for CABG in the subgroup with severe left main disease.

Cumulative 5-year survival was 82.9% in the 2654 patients with MVD who had diabetes mellitus. By treatment group, survival was as follows: medical therapy 76.6%, PCI 87.3%, and CABG 87.4%.

**Discussion**

This study examines survival in patients with MVD in a large multicenter regional setting in a transitional period of increasing stent utilization.\(^5\) An association is observed between treatment with CABG as well as PCI and favorable cumulative survival up to 5 years compared with medical therapy alone, after adjustment for important risk factors and comorbid conditions.
Outcome after CABG

Early registries demonstrated a higher survival rate in patients treated with CABG compared with those treated medically, with survival in patients with 3-vessel CAD being linked to completeness of revascularization.9,11 Randomized trials comparing CABG and medical therapy showed mixed results.12,13 Long-term survival was improved by surgery only in those with 3-vessel CAD and impaired LV function or 2-vessel CAD with a severe proximal LAD stenosis.14-18 Our cumulative 5-year survival observations are in accordance with these findings. Although surgically treated patients with 3-vessel and left main CAD clearly have a lower risk-adjusted mortality than do similar patients treated medically, there appears to be no significant survival benefit to initial treatment with CABG compared with medical therapy in those with 2-vessel CAD even in the presence of severe proximal LAD disease.

These findings are also similar to those of a Duke Medical Center Registry of 9263 patients treated between 1984 and 1990, which revealed a significant 5-year survival benefit of CABG over medical therapy in patients with 3-vessel CAD, as well as a small survival advantage in those with 2-vessel CAD.19 At 10-year follow-up, treatment with CABG was associated with a significant survival advantage over medical therapy in MVD patients in all Duke coronary severity subgroups except those without at least one 95% stenosis.20 The lack of an adjusted survival difference in the current study between CABG and medical therapy, in 2-vessel CAD patients, including those with severe proximal LAD stenosis, may be related to advances in medical therapy that have occurred since completion of the Duke study.21,22

Outcome after PCI

Uncontrolled studies demonstrated sustained clinical improvement in long-term outcome with multivessel PCI,23,24 especially when complete revascularization could be achieved.25,26 Randomized data comparing long-term survival after PCI and medical therapy are sparse. Small sample size in the Veterans Affairs Angioplasty Compared to Medicine (ACME) trial precluded the possibility of a survival comparison.27 The Atorvastatin Versus Revascularization Treatments (AVERT) trial, which reported a lower incidence of ischemic events with high-dose atorvastatin compared with PCI, enrolled just 148 patients with 2-vessel CAD and excluded those with 3-vessel CAD.

Our observations with respect to the risk with PCI compared with medical treatment confirm those of the earlier Duke Registry with respect to survival differences favoring PCI in all coronary severity groups up to 3-vessel CAD.19 However, our data indicate an extension of risk reduction with PCI to those with 3-vessel disease, including those with proximal LAD (including 95% stenosis) disease. This extension of apparent benefit is likely related to introduction of stents to the field of interventional cardiology, which has markedly reduced the rates of restenosis and abrupt closure,28-31 advances in balloons and guide wires, as well as refinement in patient selection and interventional strategies stemming from an added 10 years of cumulative operator experience. The lack of a difference in patients with less severe 2-vessel CAD parallels the comparison between CABG and medical therapy, and may, again, be related to advances in medical therapy that may have favorably influenced survival in the medically treated group.

CABG versus PCI

Early randomized trials of CABG versus percutaneous transluminal coronary angioplasty, reporting similar outcome with surgery and PCI, were all underpowered to detect differences in survival.1,2,32 Three larger trials, with a combined sample size of 3894 patients, confirmed the survival equivalence of the 2 treatment strategies.3,4,33 A recently reported study of 450 patients randomized to PCI versus CABG in the stent era revealed significantly higher survival in the group assigned to PCI (96.9% vs 92.5%, P < .017) at 18-month follow-up.34 The only finding suggestive of worse outcome with PTCA was in the Bypass Angioplasty Revascularization Investigation (BARI), in which diabetic patients assigned to percutaneous transluminal coronary angioplasty had significantly lower survival at 5 years than did those randomized to CABG. Interestingly, our data with respect to the diabetic population with MVD indicate similar survival rates in those treated with PCI and CABG, suggesting that appropriate case selection to a PCI strategy can result in excellent long-term survival in diabetic patients.

The applicability of knowledge gained from these trials to current treatment of unselected patients with MVD in clinical practice is limited by highly selected study populations. All trials excluded patients with previous revascularization procedures, whereas some excluded any patients with total coronary occlusions.1,2 All but one were conducted before the current era of stenting.

The concern of generalizability was addressed by the Duke Registry studies reporting on an unselected population and more recently by the BARI Registry, which showed equivalent survival up to 7 years in patients treated with PCI and CABG, findings attributed to appropriate case selection for PCI, with patients undergoing PCI having more favorable coronary anatomy, resulting in higher procedural success and thus better outcome.35

The current study extends knowledge regarding long-term survival in patients with MVD to reflect implementation of current technical and procedural advances. The high survival observed with PCI in the stent era is
quite likely a function of reduction in major cardiac events, especially the need for repeat target vessel revascularization, recently observed with a temporal increase in the utilization of stents in another large Canadian prospective registry.\textsuperscript{36}

The hazard ratio favoring CABG compared with PCI is almost entirely a function of benefit in the severe left main disease group. The suggested equivalence of CABG and PCI in the setting of 2-vessel and 3-vessel disease is compelling. Admittedly, we cannot rule out an effect of clinical selection, whereby patients with the most favorable anatomy are selected for PCI, with the remaining patients suitable for revascularization being referred for CABG and those with most untoward anatomy being treated medically.

**Study limitations**

The major limitation of this study lies in its non-randomized nature and the inherent patient selection that operates in clinical practice. It is probable that those with the least favorable clinical or anatomic characteristics are selected for medical therapy and those with the best characteristics are selected for revascularization. Although our risk adjustment deals with this problem to some extent, important characteristics such as diffuseness of CAD are missing from the model. We thus strongly caution against drawing inferences on treatment efficacy from these data. Rather, these results from a population-based study demonstrate the prognosis associated with treatment received.

Furthermore, with a waiting list for revascularization, the most unstable patients waiting may have died, rendering the revascularization group to be less unstable and to have a lower mortality rate. Risk adjustment would have corrected for this at least in part. This phenomenon raises the possibility that revascularization in the province should be considered earlier and more broadly. Finally, with incomplete data on concomitant medical therapies and lipids, we are uncertain of secondary prevention therapy utilization in the 3 treatment groups.

**Conclusions**

Capturing the entire spectrum of clinical practice in a geographic region, this prospective registry of patients undergoing cardiac catheterization and found to have MVD demonstrates an association with favorable survival to 5 years with CABG and PCI compared with medical therapy. Risk-adjusted survival is also similar in patients with 2- and 3-vessel CAD selected for PCI compared with CABG. These observations likely represent a combination of appropriate patient selection factors as well as possible true differences in the efficacy of the treatment strategies. The findings must therefore be corroborated by long-term follow-up from randomized trials comparing PCI and adjunctive contemporary antiplatelet therapy with CABG as well as with current optimal medical therapy.

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