The Effectiveness of $\beta$-Blockers After Myocardial Infarction in Patients With Type 2 Diabetes

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OBJECTIVE — $\beta$-Blocker therapy has been proven to reduce mortality and reinfarction after myocardial infarction (MI), but the impact of $\beta$-blockers on cardiac outcomes in patients with type 2 diabetes in routine practice is not clear. The purpose of this study was to determine the effectiveness of $\beta$-blockers after MI in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Using the Saskatchewan Health Databases, 12,272 patients with newly treated diabetes were identified between 1991 and 1996; 625 patients were subsequently admitted for MI. $\beta$-Blocker exposure within 30 days of discharge was identified in 298 patients, and all were followed until death, coverage termination, or 31 December 1999. Multivariate proportional hazards models were used to assess differences in all-cause mortality, recurrent MI, and 30-day all-cause rehospitalization (the latter a proxy measure for drug safety).

RESULTS — Patients were aged 69 ± 11 years old, 66% were male, and mean follow-up was 2.7 ± 2.1 years. Overall, $\beta$-blockers were prescribed for 48% of patients. There were fewer deaths in the $\beta$-blocker group versus control subjects (55 of 298 [18.5%] vs. 126 of 327 [38.5%], respectively, $P < 0.001$). However, $\beta$-blockers were not associated with improved survival in multivariate analyses (hazard ratio [HR] 0.89 [95% CI 0.63–1.25]). There were no differences in rates of recurrent MI (adjusted HR 1.35 [0.93–1.95]) or rehospitalizations (adjusted odds ratio 1.40 [0.83–2.37]) between the groups.

CONCLUSIONS — $\beta$-Blocker therapy post-MI was not associated with reduced mortality or fewer recurrent events in people with type 2 diabetes in routine practice, although these medications were safe in this population.

Cardiovascular disease is a major cause of morbidity and mortality in people with type 2 diabetes (1). Intensive modification of cardiovascular risk factors, including hypertension and hyperlipidemia, and therapy with antiplatelet agents and ACE inhibitors significantly reduces myocardial infarction (MI) and other cardiovascular events in patients with diabetes (2).

Randomized trials have established that $\beta$-blocker therapy after MI reduces mortality and reinfarction by up to 20% (3,4). These studies were conducted before the benefits of multifactorial risk-factor intervention were recognized and at a time when most people with diabetes were excluded from trials because $\beta$-blockers were considered to be “contra-indicated” (5,6). Post hoc subgroup analyses of subjects with diabetes enrolled in these trials suggested statistically nonsignificant reductions in mortality of 35–60% (7–11).

There are also observational data that $\beta$-blockade reduces mortality and reinfarction in subjects with diabetes (12–15). For example, mortality was reduced by 36% in patients with diabetes who received $\beta$-blockers after MI in the Cooperative Cardiovascular Project (14). These studies, conducted in the mid-1980s and early 1990s, tended to exclude subjects with congestive heart failure, previous coronary artery disease, or relative contraindications to $\beta$-blockers and tended not to adjust for proven effective interventions such as ACE inhibitors, aspirin, or lipid-lowering therapies (12–15). Thus, the effectiveness of $\beta$-blockers on cardiovascular outcomes after MI in people with diabetes under conditions of contemporary clinical practice is unclear. Therefore, the purpose of our study was to evaluate the effectiveness (all-cause mortality, reinfarction) and safety (30-day all-cause rehospitalization) of $\beta$-blockers after MI in patients with newly recognized type 2 diabetes in the current era of evidence-based multifactorial risk management.

RESEARCH DESIGN AND METHODS — A population-based, retrospective cohort study was conducted using the computerized databases of Saskatchewan Health.

Saskatchewan Health Databases include information on most residents (99%) of the province of Saskatchewan (population ~1 million). Individuals not covered by Saskatchewan Health include those with federally funded health care,
such as members of the Royal Canadian Mounted Police and Canadian Forces (16). About 90% of the covered population is eligible for prescription drug benefits. Those ineligible include registered Indians who receive prescription benefits through a federal program. Saskatchewan residents who were eligible for prescription drug benefits were ≥30 years of age, and those who had coverage in the provincial health plan for at least 1 year earlier were eligible for inclusion.

An inception cohort of 12,272 subjects with newly treated type 2 diabetes was identified based on a new outpatient prescription for a sulfonylurea or metformin between 1 January 1991 and 31 December 1996 (17). During this time, these agents comprised the main categories of antihyperglycemic agents available in Canada. Patients for whom insulin was subsequently prescribed were retained. From this cohort, 625 subjects who were discharged with a diagnosis of MI that occurred after the initiation of diabetes treatment were identified by ICD-9 codes (online appendix [available at http://care.diabetesjournals.org]) from hospital separations (18).

**Exposure**

Exposure to β-blockers was based on an outpatient prescription claim for any β-blocker (online appendix) within 30 days after the discharge date of the index MI. The control cohort, by study definition, had no evidence of β-blocker use within this period. For the rehospitalization analysis, the exposed cohort only consisted of subjects who received their first prescription for a β-blocker within 30 days of discharge (i.e., had no evidence of prior β-blocker use before the index MI); the control cohort consisted of subjects who never received a prescription for a β-blocker during the follow-up period (i.e., no exposure).

### Outcomes

Subjects were followed prospectively from the date of the first nonfatal MI until death, termination of coverage, or 31 December 1999, providing a maximum follow-up of 9 years. The primary outcome was all-cause mortality. Secondary end points included recurrent MI and all-cause rehospitalization within 30 days. Admissions for nonfatal and fatal MI were identified through ICD-9 codes in the hospital services file. Previous validation studies have demonstrated excellent agreement between hospital discharge diagnostic codes used in the hospital files of the Saskatchewan Database and diagnoses from charts for ischemic heart disease, with agreement of 97% for acute MI (18). Rehospitalization within 30 days of discharge was included as a surrogate measure of safety based on our expectation that serious adverse events associated with the new initiation of β-blockers in this population would lead to hospitalization relatively soon after initial discharge, if these agents were indeed associated with harms in this population.

### Statistical analysis

Multivariate time-to-event analysis was conducted using Cox proportional hazards regression models. Proportional hazards assumptions were tested and met. Hazard ratios (HRs) and 95% CIs were estimated for the relationship of β-blocker exposure to time-to-all-cause mortality and time-to-recurrent fatal or nonfatal MI, while controlling for potential confounding factors such as age, sex, and comorbidity (Table 1). For comorbidity, we used the Chronic Disease Score, updated to include contemporary agents. The Chronic Disease Score is a validated index that identifies specific drug therapies during the follow-up period and has been shown to predict risk of mortality, hospitalization, and health care resource use (19). In addition, conditions and medications known to affect cardiovascular outcomes in patients with type 2 diabetes were included in the models. Congestive heart failure before or following the index MI and previous coronary artery disease were identified based on hospital separations (online appendix) or by prescription claims for loop diuretics or nitrates, respectively (20–22). Medications known to reduce the risk for cardiovascular events were identified based on outpatient prescription drug claims (Table 1). Because so few people used insulin during follow-up, we did not include it in our models. Lastly, we included revascularization procedures that occurred following the index MI (percutaneous coronary angioplasty and coronary artery bypass grafting), identified through the hospital services file by Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures codes (online appendix).

Prespecified, potentially clinically important first-order interactions were examined; no significant ($P$ value < 0.1) interaction terms were identified, and these terms were excluded from all models. Similar modeling strategies using multiple logistic regression were used to analyze the relationship of β-blocker exposure to all-cause rehospitalization within 30 days.

### RESULTS

The characteristics of the cohort are shown in Table 1. The mean age
The mean duration of follow-up was 2.7 ± 2.1 years. Overall, β-blockers were prescribed for 48% of patients, of whom 95% received at least one repeat prescription. In the control cohort, 15% of patients received a β-blocker prescription outside the exposure window. Patients who used β-blockers were younger, more likely to be male, had fewer comorbidities, and less congestive heart failure than control subjects (P < 0.001) (Table 1).

Patients receiving β-blockers after MI were significantly more likely to have received β-blockers before the index MI (P < 0.001) (Table 1); they also had significantly more prescription claims for antiplatelet agents, lipid-lowering agents, metformin, and sulfonylureas. The unadjusted HR (95% CI) for time-to-all-cause mortality (β-blocker group relative to control subjects) was 0.49 (0.36–0.67) (Table 2). Univariate analysis demonstrated that increasing age, congestive heart failure, and previous coronary artery disease were significantly and positively associated with increased mortality; β-blockers, antiplatelet agents, lipid-lowering agents, metformin, and revascularization were significantly associated with decreased mortality. The association between β-blocker exposure and mortality was not significant after controlling for the prespecified covariates (adjusted HR 0.89 [0.63–1.25]). Older age, congestive heart failure, and previous coronary artery disease were independently associated with increased mortality while antiplatelet agents, lipid-lowering therapies, and revascularization were associated with decreased mortality (Fig. 1).

### Mortality

There were 55 (18.5%) deaths in the β-blocker group and 126 (38.5%) in the control group (P < 0.001) (Table 2). There were 211 (69%) male subjects, and 66% of the subjects were male. The mean duration of follow-up was 2.7 ± 2.1 years. Overall, β-blockers were prescribed for 48% of patients, of whom 95% received at least one repeat prescription. In the control cohort, 15% of patients received a β-blocker prescription outside the exposure window. Patients who used β-blockers were younger, more likely to be male, had fewer comorbidities, and less congestive heart failure than control subjects (P < 0.001) (Table 1). Insulin was prescribed for only 16% of subjects over the course of follow-up.

### Table 2—Primary and secondary outcomes for β-blocker and control groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cohort</th>
<th>HR (95% CI) Unadjusted</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>55 (18.5)†</td>
<td>0.49 (0.36–0.67)†</td>
<td>0.89 (0.63–1.25)</td>
</tr>
<tr>
<td>Fatal or nonfatal</td>
<td>65 (21.8)</td>
<td>1.04 (0.74–1.46)</td>
<td>1.35 (0.93–1.95)</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>42 (23.3)</td>
<td>0.95 (0.60–1.49)</td>
<td>1.40 (0.83–2.37)</td>
</tr>
</tbody>
</table>

Data are n (%), HR (95% CI), or odds ratio (OR) (95% CI). *Adjusted for age, sex, Chronic Disease Score, previous coronary artery disease, congestive heart failure, revascularization, previous β-blocker use, antiplatelet agents, ACE inhibitors, lipid-lowering agents, metformin, and sulfonylureas. †P < 0.001 for comparisons of β-blocker vs. control cohorts.

**Figure 1**—Adjusted HRs (95% CIs) for all-cause mortality.
the control group (P = 0.98). The adjusted HR (95% CI) for β-blocker exposure and time-to-recurrent fatal or nonfatal MI was 1.35 (0.93–1.95) (Table 2). The only variable that was independently associated with recurrent MI in our models was congestive heart failure 1.83 (1.16–2.90).

Rehospitalization within 30 days of MI
In the subset of 419 subjects with no prior β-blocker exposure, there were 180 subjects in the exposed cohort and 239 control subjects. There were 42 (23.3%) rehospitalizations in the β-blocker group and 58 (24.3%) in the control group (Table 2). The adjusted OR (95% CI) for β-blocker exposure and rehospitalization was 1.40 (0.83–2.37).

CONCLUSIONS — In this large cohort of patients with newly treated type 2 diabetes studied under effectiveness (“real-world”) conditions, β-blocker therapy post-MI appeared to be associated with reduced all-cause mortality. However, after carefully adjusting for clinical characteristics and use of drugs with proven cardiovascular efficacy, this association was markedly attenuated and not statistically significant. Similarly, use of β-blockers was not independently associated with reduced risk for recurrent MI. Importantly, however, the rate of rehospitalization within 30 days of starting a β-blocker was not increased, suggesting that the use of these agents is not associated with major adverse effects in people with type 2 diabetes.

In randomized trials, β-blockers reduced mortality and reinfarction in patients after MI by up to 20% (3,4). No trials identified subjects with diabetes as an a priori subgroup of interest. However, subgroup analyses of subjects with diabetes included in randomized trials demonstrated relative reductions in mortality between 35 and 63% (7,9,11). The magnitude of risk reduction in those trials was similar to our unadjusted risk estimate but much greater than the reduction we observed after adjusting for various markers of adherence to evidence-based guidelines for contemporary clinical practice. It should be noted that ACE inhibitors and lipid-lowering agents were not standard therapies when the original β-blocker trials were conducted, and the most widely used revascularization procedure at the time was coronary artery bypass grafting. Congestive heart failure, insulin use, and even a diagnosis of diabetes were frequent exclusion criteria in previous randomized trials. In routine clinical practice, the absolute and relative benefits of drug therapies may be less than those demonstrated in a structured research setting. Thus, in the current era of multiple interventions of proven efficacy, it may be that the benefits of β-blockers are much less than has been suggested by systematic reviews (3,4), prior randomized trials (8,9,11), and older observational studies (12–15).

The strengths of our study include the use of the Saskatchewan Databases, which are comprehensive, cover a large representative population, provide a long and consistent duration of follow-up, and contain high-quality data (16). These databases have been validated and used extensively in previously published studies (17,23,24). Another strength is the incorporation of data about other proven, effective, evidence-based therapies. Previous observational studies were conducted before availability of evidence regarding adjunctive therapies or did not fully account for other therapies such as antithrombotic agents, statins, ACE inhibitors, early revascularization, or even different types of oral hypoglycemic agents and thus may have been subject to residual confounding.

There are several limitations that we need to acknowledge. First, akin to most large database studies, was the inability to control for potential clinical confounders such as smoking status, lipid levels, glycemic control, and blood pressure measurements. Second, our results cannot necessarily be generalized to diet-controlled or thiazolidinedione-treated people with diabetes. Third, our study may have lacked sufficient power to detect a clinically important reduction in mortality, even though it was population based. Thus, while the observed mortality reduction in this study was 11%, our CIs include a 37% reduction as well as a 12.5% increase in mortality with β-blocker exposure. Further, we recognize that simple bivariate analyses of the use of β-blockers and overall mortality is clearly confounded, as we observed a change in the mortality risk reduction estimate from 51% (unadjusted) to 11% (adjusted).

We believe, however, that the most likely explanation for this somewhat counterintuitive finding is that the quality of background interventions for secondary prevention of MI was such that potential benefits of β-blockers may have been reduced or attenuated. Subjects who received β-blockers were more likely to receive a greater number of other evidence-based therapies, suggesting that the clinical care they received may have been more “comprehensive.” In this study, however, those patients with the worst prognoses were the least likely to receive β-blockers, another example of the well-documented treatment-risk paradox (25). If the effectiveness of β-blockers in people with type 2 diabetes in the real world is less than has been suggested by clinical trials, and if those who might derive the most benefit are still left untreated, the result could be a much-less-than-expected difference in mortality between treated and untreated groups, exactly as we observed in our study.

The aforementioned limitations aside, perhaps the most unanticipated and striking observation of this study is the number of very-high-risk and vulnerable diabetic patients who did not receive antithrombotic agents, lipid-lowering therapy, ACE inhibitors, or even β-blockers (notwithstanding our actual findings). This undertreatment represents important achievable benefits that are not being realized. Although large trials are currently underway to assess the effects of intensive multifactorial cardiovascular risk factor modification in patients with diabetes, it is clear that strategies aimed at improving prescribing practices of physicians caring for patients with diabetes and cardiovascular disease need to be developed and studied to reduce cardiovascular death in this population (26).

In conclusion, our study suggests that the putative benefits of β-blockers in diabetic subjects may be much less than previously reported, particularly when combined with other proven effective treatments. Should these results alter current practice? Given the limitations of our nonexperimental design, these results should not necessarily alter current prescribing practices, although our findings may help physicians in dealing with the overarching issue of polypharmacy and deciding how many and which medications should be prescribed for their patients after a MI, and it is unlikely that randomized trials will ever be conducted to answer this question. Early rehospitalization rates were not increased in pa-
patients who received β-blockers in this study, suggesting that these agents do not result in any increase in clinically important adverse effects. This finding should, at least, reinforce the view that these agents are safe to prescribe for patients with diabetes, assuring many clinicians’ reservations about their use in this population.

Acknowledgments — This study was funded in part by grants from the Alberta Heritage Foundation for Medical Research (AHFMR) and the Institute of Health Economics. This work was also supported by a New Emerging Team (NET) grant to the Alliance for Canadian Health Outcomes Research in Diabetes (ACHORD). The ACHORD NET grant is sponsored by the Canadian Diabetes Association, the Heart and Stroke Foundation of Canada; The Kidney Foundation of Canada; the Canadian Institutes of Health Research (CIHR), Institute of Nutrition, Metabolism and Diabetes; and the CIHR, Institute of Circulatory and Respiratory Health. S.R.M. holds a Population Health Investigator Award through the AHFMR and is a New Investigator of the CIHR. J.A.J. is a health scholar with the AHFMR and holds a Canada Research Chair in Diabetes Health Outcomes.

The results of this study are based in part on nonidentifiable data provided by the Saskatchewan Department of Health. The interpretations and conclusions herein are the authors’ and do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health. The authors thank Dr. Mary Rose Stang (Saskatchewan Health) for comments on an earlier draft and Dr. Scot Simpson (University of Alberta) for his assistance with the datasets.

References