Early reports

Rate of heart failure and 1-year survival for older people receiving low-dose β-blocker therapy after myocardial infarction

Paula A Rochon, Jack V Tu, Geoffrey M Anderson, Jerry H Gurwitz, Jocalyn P Clark, Paula Lau, John Paul Szalai, Kathy Sykora, C David Naylor

Summary

Background Many older people do not receive β-blocker therapy after myocardial infarction or receive doses lower than those tested in trials, perhaps because physicians fear that β-blockers may precipitate heart failure. We examined the relation between use of β-blockers, the dose used, and hospital admission for heart failure and 1-year survival in a cohort of all older patients surviving myocardial infarction in Ontario, Canada.

Methods We collected data on a cohort of 13 623 patients aged 66 years or older who were discharged from hospital after a myocardial infarction and who did not receive β-blocker therapy or received low, standard, or high doses. We used Cox's proportional-hazards models to study the association of dose with admission for heart failure and survival with adjustment for factors including age, sex, and comorbidity.

Findings Among 8232 patients with no previous history of heart failure, dispensing of β-blocker therapy was associated with a 43% reduction in subsequent admission for heart failure (adjusted risk ratio 0·57 [95% CI 0·48–0·69]) compared with patients not dispensed this therapy. Among the 4681 patients prescribed β-blockers, the risk of admission was greater in the high-dose than in the low-dose group (1·53 [1·01–2·31]). Among all 13 623 patients in the cohort, 2326 (17·1%) died by 1 year. Compared with those not dispensed β-blocker therapy, the adjusted risk ratio for mortality was lower for all three doses (low 0·40 [0·34–0·47], standard 0·36 [0·31–0·42], high 0·43 [0·33–0·56]).

Interpretation Compared with high-dose β-blocker therapy, low-dose treatment is associated with a lower rate of hospital admission for heart failure and has a similar 1-year survival benefit. Our findings support the need for a randomised controlled trial comparing doses of β-blocker therapy in elderly patients.

Lancet 2000; **356:** 639–44

Kunin-Lunenfeld Applied Research Unit, Baycrest Centre for Geriatric Care (P A Rochon MD, J P Clark MSc)**; Departments of Medicine** (P A Rochon, J V Tu MD, C D Naylor MD)**, Public Health Sciences** (P A Rochon, J V Tu, J P Szalai PhD, C D Naylor)**, and Health Administration** (P A Rochon, J V Tu, G M Anderson MD, J P Szalai, C D Naylor)**, Sunnybrook and Women's College Health Science Centre** (J V Tu, J P Szalai) **and Dean's Office** (C D Naylor)**, Faculty of Medicine, University of Toronto; and Institute for Clinical Evaluative Sciences** (P A Rochon, J V Tu, G M Anderson, J P Szalai, P Lau MSc, K Sykora MSc, C D Naylor)**, Toronto, Ontario, Canada; and Meyers Primary Care Institute, Fallon Healthcare System and University of Massachusetts Medical School, Worcester, MA, USA** (J H Gurwitz MD)

Correspondence to: Dr Paula A Rochon, Kunin-Lunenfeld Applied Research Unit, Baycrest Centre for Geriatric Care, 3560 Bathurst Street, Toronto, Ontario, Canada M6A 2E1

Introduction

Treatment with β-adrenergic-blocking agents lowers mortality among individuals at high risk after myocardial infarction, including elderly people.[1] Furthermore, use of β-blocker therapy is associated with better survival among patients with heart failure.[2] Despite this proven benefit, not all eligible elderly people receive β-blocking drugs after myocardial infarction.[3,4]

Of survivors of myocardial infarction who do receive β-blockers, the treatment is commonly prescribed at doses lower than those investigated in the main randomised controlled trials (RCTs).[5] No RCT[6–10] investigated the minimum effective dose. Although β-blocker therapy is now recommended in the setting of heart failure,[2,11–13] a possible reason why it is not given routinely[4,5] is fear that these drugs may precipitate an acute episode of heart failure. Because older people are frail and prone to heart failure, and because most adverse drug effects are dose-related, identification of the minimum effective dose is particularly important for these patients.

We assessed the association between β-blocker prescription and the dose prescribed, admission for heart failure, and survival in a large population-based cohort of all elderly patients surviving an acute myocardial infarction in Ontario, Canada.

Methods

Patients

We obtained hospital discharge abstracts from the Canadian Institute for Health Information database. These data include all separations (discharges, transfers, or deaths) from general hospitals in Ontario. We linked by unique health-card numbers records for patients discharged alive after myocardial infarction to the Ontario Registered Persons Database to obtain demographic and survival information, and to the Ontario Drug Benefit Plan (ODB) database to find out whether β-blocker therapy was dispensed and the dose given. Electronic safeguards are used to validate the health-card numbers. Multicentre audits have shown high accuracy of myocardial infarction coding (94–100% accurate) in the database.[14–16] These databases have been used to study cardiovascular disease in several studies.[14]

β-blocker	Dose range (mg/day)		
	Low	Standard	High
Atenolol[6]	<50	50 to <100	⩾100*
Metoprolol[7]	<100	100 to <200	⩾200*
Propranolol[9]	<30	30 to <180	⩾180*
Timolol[8]	<10	10 to <20	⩾20*
Acebutolol	<200	200 to <600	⩾600†
Labetalol	<200	200 to <800	⩾800†
Nadolol	<40	40 to <240	⩾240†
Pindolol	<5	5 to <40	⩾40†
Sotalol	<160	160 to <320	⩾320†

*High dose range based on doses equal to or greater than those used in RCTs.
†High dose range based on highest recommended dose for angina.[22]

Table 1: **Classification of low, standard, and high doses of β-blocker therapy**

We identified all people aged 66 years or older living in Ontario who were admitted to an acute-care hospital between April 1, 1993, and March 31, 1995, with a most responsible diagnosis (the diagnosis that describes the most important disorder of a patient, which causes the stay in hospital) of acute myocardial infarction (code 410 from the International Classification of Diseases, 9th revision, Clinical Modification [ICD-9][17]). We included patients of 66 years or older so that we could examine the preceding year of drug use under Ontario's Drug Benefit Plan.

There were 19 970 acute-care hospital discharges for elderly people in which myocardial infarction was the most responsible diagnosis and the patients were discharged alive. Identification of patients for the cohort was done in two stages. In the first stage, 2900 of the 19 970 discharges with a most responsible diagnosis of myocardial infarction were excluded: length of stay was 4 days or less in 2113; 96 patients discharged themselves, which suggests that they had not had a myocardial infarction;[18,19] length of stay was longer than 60 days in 88; 30 had been admitted with a myocardial infarction within the preceding 8 weeks (the discharge coding does not distinguish between a new and a previous myocardial infarction for patients readmitted within 8 weeks); 383 were not residents of Ontario; and 190 were discharged to a chronic-care facility (these patients do not receive treatment from the Ontario Drug Benefit Plan; nursing-home residents were included because they obtain treatment from the plan). In the second stage, 1528 repeat discharges were excluded because the patients were treated for more than one myocardial infarction. Thus, we obtained a cohort of 15 542 elderly patients who were followed up for subsequent use of β-blocker therapy, hospital admissions for heart failure, and survival.

Design and procedures

We found out whether patients were dispensed any oral β-blocker therapy in the 365 days that followed their hospital discharge after myocardial infarction. Because the Ontario Drug Benefit Plan provides information on the quantity of pills dispensed rather than daily dose, we estimated the daily dose based on the first two prescriptions dispensed after discharge. If, for example, a patient was prescribed metoprolol in a dose of 50 mg for 30 days and was given 15 pills, the calculated daily dose would be 25 mg. We rounded the calculated average dose to a clinically plausible dose.[20–22] We have used this method of dose calculation previously.[4,5]

β-blocker dose was classified into one of five mutually exclusive groups: not dispensed, low, standard, or high dose of one oral β-blocker, or uncertain dose. Low-dose therapy was defined as a dose lower than that achievable with the smallest available tablet size; standard-dose therapy as a dose achieved with available tablet sizes but less than the doses used in the RCTs; and high-dose therapy as doses equal to or higher than the dose used in the RCTs for secondary prevention after myocardial infarction (table 1). We excluded 1919 patients classified as receiving an uncertain dose of β-blocker therapy (only

	Total	Not dispensed	Low dose	Standard dose	High dose	p*
Total	13 623	7549	2248	3068	758	· ·
Age (years)						
Mean (SD)	75·6 (6·6)	76·8 (6·9)	74·8 (6·2)	73·6 (5·8)	73·1 (5·5)	0·0001
66–74	6717 (49·3%)	41·7%	53·1%	61·4%	64·5%	0·001
75–84	5445 (40·0%)	43·7%	39·5%	33·3%	31·0%	
⩾85	1461 (10·7%)	14·6%	7·4%	5·2%	4·5%	
Sex						
Male	7469 (55·0%)	53·9%	55·5%	56·8%	57·5%	0·019
Female	6127 (45·0%)	46·1%	44·5%	43·2%	42·5%	
Charison index score						
Mean (SD)	0·9 (1·1)	1·2 (1·2)	0·7 (1·0)	0·6 (0·9)	0·6 (1·0)	0·0001
0–1	10 454 (76·7%)	68·6%	85·1%	88·1%	86·7%	0·001
2	2088 (15·3%)	20·2%	10·0%	8·5%	10·0%	
⩾3	1081 (7·9%)	11·1%	4·9%	3·4%	3·3%	
Contraindications						
Heart failure	5391 (39·6%)	53·0%	27·3%	20·4%	20·4%	0·001
Chronic obstructive pulmonary disease/ asthma	3837 (28·2%)	35·3%	19·9%	18·9%	19·4%	0·001
Diabetes	2864 (21·0%)	24·5%	15·5%	17·5%	16·9%	0·001
Heart block	1019 (7·5%)	9·0%	6·6%	4·9%	5·1%	0·001
Hypotension	315 (2·3%)	2·6%	2·5%	1·5%	2·0%	0·008
Bradycardia	611 (4·5%)	4·8%	4·6%	3·7%	3·6%	0·054
Long-term care						
No	13 205 (96·9%)	95·3%	98·8%	99·2%	99·1%	0·001
Yes	418 (3·1%)	4·7%	1·2%	0·9%	0·9%	
Other drug use						
Aspirin	9916 (72·8%)	64·5%	81·6%	83·6%	85·5%	0·001
ACE inhibitor	6978 (51·2%)	57·8%	46·6%	40·2%	43·8%	0·001
Calcium-channel blocker	6380 (46·8%)	47·2%	42·5%	47·4%	54·2%	0·001

*For group differences on continuous measures, we used ANOVA. Categorical variables were compared by use of the χ^2 test.

Table 2: **Characteristics of 13 623 survivors of myocardial infarction**

one prescription was dispensed; the drug claim information was inconsistent with clinical practice; or the prescription changed to another β-blocker). Patients with prescription intervals of more than 100 days were excluded because this period exceeds the maximum interval for renewals under the Ontario Drug Benefit Plan; thus non-compliance or some intercurrent events or assessments seem likely to have occurred. The final cohort consisted of 13 623 survivors of myocardial infarction.

Contraindications to β-blocker therapy were predefined similarly to the Canadian Consensus Guidelines for the management of patients after myocardial infarction[23] and identified by use of diagnoses from hospital admissions and drug benefit claims in the 365 days before the index admission. Discharge abstracts were reviewed to identify hospital admissions with a primary diagnosis of chronic obstructive pulmonary disease (ICD-9 code 496), asthma (493), heart block (426), hypotension (458), or bradycardia (427.8). We used the Ontario Drug Benefit Plan database to identify patients who were dispensed medications to treat these disorders. For example, patients with asthma or chronic obstructive pulmonary disease were identified by their dispensed claims for bronchodilators and patients with diabetes by their use of insulin therapy.

Patients were classified into three standard age-groups (66–74 years; 75–84 years; and 85 years and older).[24] Comorbidity was measured with the Charlson index[25] adapted by Deyo[26] for computerised databases, by use of diagnostic information on the discharge abstract for the index admission. Three groups of Charlson comorbidity scores were identified (0–1, 2, ⩾3).

We investigated the relation between dose of β-blocker and subsequent admission for heart failure among patients with no previous history of heart failure based on diagnoses obtained from hospital admissions, drug benefit claims, or both, in the 365 days before the index admission. We reviewed discharge abstracts to identify previous admissions with a primary diagnosis of heart failure (ICD-9 code 428) and the Ontario Drug Benefit Plan database to identify patients who were dispensed medications to treat heart failure (furosemide and digoxin, furosemide and an angiotensin-converting-enzyme [ACE] inhibitor, or ACE inhibitor and digoxin). The development of heart failure was defined as any new hospital admission with a primary diagnosis of heart failure (ICD-9 code 428). Among the 4681 patients dispensed β-blocker therapy, the relation between the dose dispensed and subsequent readmission for heart failure was assessed.

We investigated the relation between dose of β-blocker and subsequent mortality among all survivors of myocardial infarction. All deaths in hospital were identified from Canadian Institute of Health Information data. Deaths occurring elsewhere were identified from the Registered Persons database, an approach shown to identify more than 99% of all deaths.[15]

Statistics

Descriptive statistics were used to compare characteristics of older people prescribed various doses of β-blockers.

We used Cox's proportional-hazards models to assess β-blocker exposure by dose dispensed and its relation with time to admission for heart failure in the year after myocardial infarction. We controlled for age, sex, Charlson comorbidity scores, potential contraindications to β-blocker therapy, residence in a long-term care facility, and medications associated with either good (aspirin, ACE inhibitors) or poor outcomes (calcium-channel blockers) after myocardial infarction. For this analysis, we censored for death. Among the 4681 patients who received β-blockers, the Cochran-Armitage trend test[27] was used to look for a dose-related trend between increasing dose and the development of heart failure.

To see whether confounding by age or comorbidity is important in relation to the dose of β-blocker therapy prescribed and the subsequent development of heart failure, we used the approach described by Wen and colleagues.[28] Real differences in doses of β-blocker therapy should be most obvious when they are compared in a healthy, and therefore more homogeneous, subgroup. We identified 2751 patients in the youngest age-group (66–74 years) with the lowest comorbidity scores (0–1), and we used Cox's proportional-hazards models to assess the independent effect of patients' characteristics on the time to admission for heart failure. If age and comorbidity did explain differences in admissions for heart failure, the effect of β-blocker therapy dose should be least in this group.

We used Cox's proportional-hazards models to assess β-blocker exposure by dose dispensed and its relation to time to death in the year after the myocardial infarction, again with control for patients' characteristics. To check for uncontrolled confounding, we again applied increasingly restrictive criteria, on the basis of age and comorbidity, to identify increasingly healthy subgroups of myocardial infarction survivors.

Analyses used SAS Unix (release 6.11) and Windows 95 (release 6.11).

Results

Characteristics of cohort

Of the 13 623 survivors of myocardial infarction for whom β-blocker dosage could be classified, 1800 (13·2%) were admitted to hospital with heart failure and 2326 (17·1%) died during the 1-year follow-up period.

	Total	Heart failure	Adjusted risk ratio (95% CI)*
Total	8232	533 (6·5%)	· ·
β-blocker dispensed			
Not dispensed†	3551	326 (9·2%)	1·00
Low-dose	1635	64 (3·9%)	0·48 (0·37–0·64)
Medium-dose	2443	107 (4·4%)	0·58 (0·46–0·73)
High-dose	603	36 (6·0%)	0·78 (0·55–1·10)
Age (years)			
66–74†	4593	221 (4·8%)	1·00
75–84	2990	230 (7·7%)	1·45 (1·20–1·75)
⩾85	649	82 (12·6%)	2·44 (1·86–3·21)
Sex			
Male†	4820	271 (5·6%)	1·00
Female	3412	262 (7·7%)	1·23 (1·03–1·46)
Charlson index score			
0–1†	7445	457 (6·1%)	1·00
2	584	49 (8·4%)	1·12 (0·83–1·52)
⩾3	203	27 (13·3%)	1·97 (1·32–2·93)

*See methods. †Reference category.

Table 3: **Admission for heart failure in relation to β-blocker dose in 8232 patients with no history of heart failure**

	Total	Mortality	Adjusted risk ratio (95% CI)*
Total	13 623	2326 (17·1%)	· ·
β-blocker dispensed			
Not dispensed†	7549	1874 (24·8%)	1·00
Low-dose	2248	187 (8·3%)	0·40 (0·34–0·47)
Standard-dose	3068	208 (6·8%)	0·36 (0·31–0·42)
High-dose	758	57 (7·5%)	0·43 (0·33–0·56)
Age (years)			
66–74†	6717	798 (11·9%)	1·00
75–84	5445	1063 (19·5%)	1·46 (1·33–1·60)
⩾85	1461	465 (31·8%)	2·16 (1·91–2·44)
Sex			
Male†	7496	1262 (16·8%)	1·00
Female	6127	1064 (17·4%)	0·92 (0·85–1·01)
Charlson index score			
0–1†	10 454	1363 (13·0%)	1·00
2	2088	545 (26·1%)	1·64 (1·48–1·82)
⩾3	1081	418 (38·7%)	2·46 (2·19–2·76)

*See methods. †Reference category.

Table 4: **Mortality in relation to β-blocker dose in 13 623 survivors of myocardial infarction**

The mean age of the group was 75·6 years (SD 6·6); 6127 patients (45·0%) were women. Many patients were frail; 3169 (23·3%) had Charlson comorbidity scores above 2. Overall, 6074 (44·6%) were started on β-blocker therapy. Most were prescribed a β-blocker investigated in a major trial: 3105 (51·1%) metoprolol, 1603 (26·4%) atenolol, 169 (2·8%) propranolol, and 70 (1·2%) timolol.

Of the patients prescribed β-blockers, 2248 (37·0%) received low-dose therapy, 3068 (50·5%) standard-dose therapy, and 758 (12·5%) high-dose therapy. Patients receiving low-dose β-blocker therapy were older (p=0·0001) and frailer with higher comorbidity scores (p=0·04) than those receiving high-dose β-blocker therapy (table 2).

Heart failure

Among the 8232 patients with no previous history of heart failure, admissions for heart failure were more frequent with advancing age and among women compared with men (table 3). After control for several risk factors, prescribing of β-blocker therapy was associated with a 43% reduction in admissions for heart failure compared with patients not dispensed this therapy (adjusted risk ratio 0·57 [95% CI 0·48–0·69]). Among the 4681 older adults dispensed β-blocker therapy, there was a dose-related association between β-blocker therapy and subsequent admission for heart failure (Cochran-Armitage trend test p=0·028). Compared with the group prescribed low-dose therapy, those prescribed high-dose therapy were 53% more likely to be admitted with heart failure (1·53 [1·01–2·31]). Among the 2751 healthiest patients, those prescribed high-dose therapy were more than twice as likely as those prescribed low-dose therapy to be admitted with heart failure (2·24 [1·16–4·33]).

Age over 75 years	Two or more comorbidities	Number of patients	Relative risk (95% CI)	p
Yes	Yes	1700	0·42 (0·32–0·54)	0·0001
Yes	No	5206	0·41 (0·35–0·48)	0·0001
No	Yes	1469	0·49 (0·37–0·65)	0·0001
No	No	5248	0·30 (0·24–0·37)	0·0001

Table 5: **Sensitivity analyses of survival in relation to dispensing of β-blocker therapy**

Survival

Among all 13 623 patients, advanced age, male sex, and high comorbidity scores were each associated with worse survival (table 4). After adjustment for all factors in our model, patients dispensed low-dose therapy had a 60% reduction in the risk of death (0·40 [0·34–0·47]), compared with those not prescribed β-blocker therapy. Similar risk reductions were seen with the use of standard-dose and high-dose therapy (table 4). Sensitivity analyses, including the 1919 patients who received an uncertain dose of β-blocker, did not substantially affect the findings (data not shown).

Among the subgroups the reduction in risk of death associated with use of β-blocker therapy persisted in the healthiest group (table 5). The consistency of our results, even in the healthiest and most homogeneous group of our cohort, suggests that real differences in survival are likely on the basis of the drug therapy and are not explained by uncontrolled confounding.

Discussion

Our findings are consistent with a meta-analysis of the effect of β-blocker therapy in heart failure, which found that the addition of β-blocker therapy to conventional treatment was associated with a 41% reduction in hospital admissions.[2]

Our findings also suggest that dispensing of high-dose rather than low-dose β-blocker therapy was associated with more than a 50% greater risk of admission for heart failure in this cohort. Heart failure is the commonest reason for hospital admission among elderly people[29] and has been associated with the use of β-blocker therapy. Fear of causing heart failure may be one of the reasons why clinicians underprescribe β-blocker therapy to older people. Our findings suggest that use of a low-dose β-blocker may further lower the risk of admission for heart failure among survivors of myocardial infarction.

For survival, we found a strong relation with use of β-blocker therapy at low dose or the higher doses used in RCTs.[6–9] The majority of patients were treated with a β-blocker tested in a clinical trial (atenolol, propranol, metoprolol, or timolol). Our findings are similar to those of Barron and colleagues[30] who documented the benefit of β-blocker therapy in a sample of 1050 survivors of myocardial infarction; patients receiving β-blocker therapy at doses lower than 50% of the tested dose had better survival than those receiving the higher doses.

Our research looked at clinical issues for which existing RCTs do not provide guidance. This research is important for two reasons. First, the results bridge new research evidence promoting the benefit of β-blocker therapy for the management of heart failure[11,12] with the longstanding clinical belief that β-blocker therapy may precipitate heart failure. Consistently with previous trials[11,12] we found an association between use of β-blockers and a lower rate of admissions for heart failure. These trials used titrated doses of β-blocker therapy with the aim of high-dose therapy. Even under the optimum conditions of a clinical trial of patients with heart failure (excluding those with a recent myocardial infarction), about a third of participants were unable to reach the target doses. Neither trial explored the dose-related association between β-blocker therapy and subsequent admission for heart failure. We addressed the more subtle but critical issue of the optimum dose

of β-blocker therapy. Higher doses were associated with a greater risk of admission for heart failure. Consistent with clinical wisdom,[31] our findings support the need to initiate β-blocker therapy, when indicated, in lower doses and to increase the dose gradually as tolerated.

Second, our study provides insight into the benefit of low-dose β-blocker therapy not explored in RCTs. There is a dissociation between trial evidence and clinical practice. Whereas the RCTs used high doses of β-blockers after myocardial infarction, the majority of older adults in clinical practice are prescribed these drugs at much lower doses.[5,30] In the absence of trial data, our results provide some assurance that patients receiving low doses of β-blocker (who are probably unable to tolerate higher doses) should continue their therapy. Furthermore, the potential survival benefit associated with the use of low-dose β-blocker therapy may encourage physicians to use these drugs in frail older people who might otherwise not be prescribed them. Our results do not provide definitive evidence on the best dose, but support a low dose at first and gradual increases as tolerated.

This study has certain limitations. First, development of heart failure after a myocardial infarction may not be an adverse drug effect, but may reflect only the natural course of disease. However, in that case, heart failure should have been most common in the group receiving low-dose rather than high-dose β-blocker therapy because that group included older and frailer patients at increased risk of heart failure. Our results show the opposite.

Second, and most importantly, because our study is observational and relies on administrative data, there may have been residual confounding by indication. We have confidence that our findings are due to a true drug effect. We used statistical techniques to control for key variables that might capture selection biases, including age, sex, and comorbidity. Also, when we restricted the analysis to the healthiest and most homogeneous subgroup, we still found a dose-related response. Finally, in the survival analysis, when we applied increasingly restrictive criteria to identify the healthiest subgroups, the survival benefit associated with the use of β-blocker therapy persisted. These analyses suggest that unmeasured differences in patients' characteristics were unlikely to confound our results.[28]

Obviously, an observational study design cannot replace a well-conducted RCT. However, RCTs have generally excluded patients with multiple comorbidities and included few older adults and women.[32,33] Data obtained from linked administrative databases have allowed us to assess the full range of patients receiving drug therapy in clinical practice. In the future, however, researchers should design clinical trials that more adequately represent older people. Our findings support the need for an RCT comparing dosing and dose-titration strategies for optimum use of β-blockers after acute myocardial infarction.

Contributors

P A Rochon originated the idea for the study and was the principal investigator. J V Tu, G M Anderson, J H Gurwitz, and J P Szalai were coinvestigators and with C D Naylor developed the concept and provided guidance on study design and data interpretation. P Lau, K Sykora, and J P Szalai did the data analysis and statistical evaluation. J P Clark assisted with the study organisation and data interpretation. P A Rochon wrote the report with input from all investigators, particularly C D Naylor.

Acknowledgments

This study is part of the Medications in Ontario for Myocardial Infarction Survivors (MOMIS) program, supported by the Baycrest Centre for Geriatric Care, the Institute for Clinical Evaluative Sciences, and the physicians of Ontario through the P S I Foundation. The Institute for Clinical Evaluative Sciences is supported in part by a block grant from the Ontario Ministry of Health. At the time of this study, CDN was a senior scientist of the Medical Research Council of Canada. JVT is supported as a scholar of the Medical Reseach Council of Canada.

We thank Penelope de Nobrega, Angela M Neglia, and Julie Dergal for their help with preparation of the paper.

References

1 Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998; **339:** 489–97.

2 Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998; **98:** 1184–91.

3 Krumholz HM, Radford MJ, Wang Y, Chen J, Heiat A, Marciniak TA. National use and effectiveness of beta-blockers for the treatment of elderly patients after acute myocardial infarction: National Cooperative Cardiovascular Project. *JAMA* 1998; **280:** 623–29.

4 Rochon PA, Anderson GM, Tu JV, et al. Use of beta-blocker therapy in the elderly following acute myocardial infarction. *Can Med Assoc J* 1999; **161:** 1403–08.

5 Rochon PA, Anderson GM, Tu JV, et al. Age and gender-related use of low dose drug therapy: the need to manufacture low-dose therapy and evaluate the minimum effective dose. *J Am Geriatr Soc* 1999; **47:** 954–59.

6 Wilcox RG, Roland JM, Banks DC, Hampton JR, Mitchell JRA. Randomised trial comparing propranolol with atenolol in immediate treatment of suspected myocardial infarction. *BMJ* 1980; **280:** 885–88.

7 Hjalmarson A, Herlitz J, Holmberg S, Ryden L, Swedberg K. The Goteborg metoprolol trial: effects on mortality and morbidity in acute myocardial infarction. *Circulation* 1983; **67** (suppl I): I-26–I-32.

8 Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981; **304:** 801–07.

9 Beta Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. *JAMA* 1982; **247:** 1707–14.

10 Boissel JP, Leizorovicz A, Pilolet H, Peyrieux JC, for the APSI investigators. Secondary prevention after high-risk acute myocardial infarction with low-dose acebutolol. *Am J Cardiol* 1990; **66:** 251–60.

11 MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; **353:** 2001–07.

12 CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; **353:** 9–13.

13 Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HR). *JAMA* 2000; **283:** 1295–302.

14 Tu J, Naylor CD, Austin P. Temporal changes in the outcomes of acute myocardial infarction in Ontario 1992–1996. *Can Med Assoc J* 1999; **161:** 1257–61.

15 Tu JV, Austin P, Naylor CD, Iron K, Zhang H. Acute myocardial infarction outcomes in Ontario: methods appendix. In: Naylor CD, Slaughter PM, eds. Cardiovascular health and services in Ontario: an ICES Atlas. Toronto: Institute for Clinical Evaluative Sciences, 1999: 25–30.

16 Cox JL, Melady MP, Chen E, Naylor CD. Towards improved coding of acute myocardial infarction in hospital discharge abstracts: a pilot project. *Can J Cardiol* 1997; **13:** 351–58.

17 Commission on Professional and Hospital Activities. International classification of diseases, ninth revision, clinical modification. Ann Arbor: the Commission, 1992.

18 McClellan M, McNeil BJ, Newhouse JP. Does more intensive treatment of acute myocardial infarction in the elderly reduce mortality? Analysis using instrumental variables. *JAMA* 1994; **272:** 859–66.
19 Pashos CL, Newhouse JP, McNeil BJ. Temporal changes in the care and outcomes of elderly patients with acute myocardial infarction, 1987 through 1990. *JAMA* 1993; **270:** 1832–36.
20 Physicians' desk reference. 51st edn. Montvale: Medical Economics Company Inc, 1997.
21 Joint Formulary Committee 1997–98. British national formulary. London: British Medical Association and Pharmaceutical Press, 1997.
22 Canadian Pharmacists Association. Compendium of pharmaceuticals and specialities, 33rd edn. Ottawa: Canadian Pharmacists Association, 1998.
23 Fallen EL, Cairns J, Dafoe W, et al. Management of the postmyocardial infarction patient: a consensus report—revision of 1991 CCS guidelines. *Can J Cardiol* 1995; **11:** 477–86.
24 Rochon PA, Fortin PR, Dear KBG, Minaker KL, TC. Reporting of age data in clinical trials of arthritis: deficiencies and solutions. *Arch Intern Med* 1993; **153:** 243–48.
25 Charlson ME, Pompei PA, Ales KL. MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987; **40:** 373–83.
26 Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; **45:** 613–19.
27 Agresti A. Categorical data analysis. New York: John Wiley and Sons, 1990.
28 Wen SW, Hernandez R, Naylor CD. Pitfalls in nonrandomized outcome studies: the case of incidental appendectomy with open cholecystectomy. *JAMA* 1995; **274:** 1687–91.
29 Schocken DD. Arrieta MI, Leaverton PE, Ross EA. Prevalence and morbidity rate of congestive heart failure in the United States. *J Am Coll Cardiol* 1992; **20:** 301–06.
30 Barron HV, Viskin S, Lundstrom RJ, et al. Beta blocker dosages and mortality after myocardial infarction: data from a large health maintenance organization. *Arch Intern Med* 1998; **158:** 449–53.
31 Sharpe N. Benefit of beta-blockers for heart failure: proven in 1999. *Lancet* 1999; **353:** 1988–99.
32 Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. *JAMA* 1992; **268:** 1417–22.
33 Rochon PA, Clark JP, Binns MA, Patel V, Gurwitz JH. Reporting of gender-related information in clinical trials of drug therapy for myocardial infarction. *Can Med Assoc J* 1998; **159:** 321–27.