

## Brief Report

# Underuse of Aspirin in Type 2 Diabetes Mellitus: Prevalence and Correlates of Therapy in Rural Canada

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### ABSTRACT

**Background:** Patients with type 2 diabetes mellitus (DM) have a markedly increased risk of cardiovascular morbidity and mortality. Guidelines of both the American and Canadian Diabetes Associations recommend the use of aspirin as antiplatelet therapy for all adults with type 2 DM.

**Objectives:** The aims of this study were to assess the rate of adherence to guidelines for aspirin use in DM patients in rural Canadian communities and to describe the independent correlates of aspirin use in this population.

**Methods:** We collected information from a cohort of patients with type 2 DM living in 2 rural regions of northern Alberta, Canada, at the time of their enrollment in a multidisciplinary outreach program designed to improve their quality of care. Our primary outcome was self-reported use of antiplatelet therapy (aspirin or others). We used multivariate logistic regression analyses to examine the independent association between sociodemographic and clinical characteristics and self-reported use of antiplatelet agents.

**Results:** Among 342 patients included in the study (who were typical of rural Canadian patients with type 2 DM), the mean age was 62.9 years; 149 (44%) were men, 84 (25%) were of indigenous origin, and the median time since diagnosis of DM was 8 years. Despite guideline recommendations, only 23% of the cohort (78 patients) were regularly taking aspirin alone or in combination with a thienopyridine ( $n = 74$  and  $n = 2$ , respectively) or a thienopyridine alone ( $n = 2$ ). The results of the multivariate analyses showed that the only factors independently associated with the use of antiplatelet therapy were symptomatic coronary artery disease (adjusted odds ratio [AOR], 3.1; 95% CI, 1.1–8.7;  $P = 0.033$ ); older age (AOR, 2.0 per 10-year interval; 95% CI, 1.7–2.2;  $P < 0.001$ ); and male sex (AOR, 1.9; 95% CI, 1.1–3.5;  $P = 0.026$ ).

**Conclusions:** Aspirin is a safe, inexpensive, and readily available therapy that is effective for preventing cardiovascular disease, and patients with type 2 DM are particularly likely to benefit from such preventive therapy. However, we found significant underuse of aspirin therapy among our study population. Aspirin should be included and better promoted as a factor in high-quality, evidence-based DM management. (*Clin Ther.* 2004;26:439–446) Copyright © 2004 Excerpta Medica, Inc.

**Key words:** type 2 diabetes mellitus, aspirin therapy, prevention, guideline adherence, underuse.

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## INTRODUCTION

Macrovascular events, such as myocardial infarction or stroke, are the most common cause of morbidity and mortality in type 2 diabetes mellitus (DM).<sup>1,2</sup> The overall risk of cardiovascular death is 2 to 4 times higher<sup>1-3</sup> and the incidence of cardiovascular disease is 2 to 3 times greater in patients with type 2 DM than in those without the disease.<sup>4</sup> A 1998 cohort study<sup>5</sup> found that DM patients without a previous myocardial infarction have as high a risk of a cardiovascular event occurring as non-DM patients with a previous myocardial infarction. As such, DM is considered to be a coronary disease equivalent that necessitates aggressive risk-factor management.

Intensive lifestyle modification and pharmacotherapy that targets hypertension, dyslipidemia, and hyperglycemia have been shown to lower the risk of cardiovascular disease in type 2 DM.<sup>6</sup> The use of aspirin may be equally important because it is a safe, inexpensive, and effective therapy for the primary and secondary prevention of cardiovascular events. The Antithrombotic Trialists' Collaboration meta-analysis<sup>7</sup> concluded that antiplatelet therapy reduces the relative risk of any serious vascular event by ~25% in patients at high risk of a cardiovascular event. Therefore, based on the available evidence, current guidelines from the American and Canadian Diabetes Associations<sup>8,9</sup> recommend the routine use of aspirin for primary and secondary prevention of cardiovascular and cerebrovascular events in those with type 2 DM aged  $\geq 30$  years. Nevertheless, it has been observed that the adherence to many guideline recommendations for patients with type 2 DM is less than optimal.<sup>10-12</sup>

The objectives of the present study were as follows: (1) to assess the rate of adherence to guidelines for aspirin use in DM patients in rural Canadian communities, and (2) to describe the independent correlates of aspirin use in this population.

## PATIENTS AND METHODS

### *Subjects and Setting*

We collected information from a cohort of patients with type 2 DM living in 2 rural regions of northern Alberta, Canada. These 2 regions and their DM populations are considered to be typical and representative of isolated rural regions of Canada.<sup>10</sup>

Sociodemographic and clinical data were collected at the time of patient enrollment into the Diabetes

Outreach Van Enhancement (DOVE) Study in 2000.<sup>10</sup> The DOVE Study was a controlled trial that assessed the effectiveness of a multidisciplinary outreach service that was designed to improve quality of care for patients with type 2 DM. The study design and recruitment procedures have been described in detail elsewhere.<sup>10</sup> In summary, patients living in 2 rural regions were potentially eligible for the study if they met the following criteria: verified type 2 DM, English literacy sufficient for answering questionnaires, willingness to return for follow-up visits, and provision of written informed consent. Patients were recruited by primary care physicians, nurses, DM educators, dietitians, and pharmacists.<sup>10</sup> The data for the current analysis were collected at the time of study entry. The DOVE Study was approved by the Health Research Ethics Board of the University of Alberta, Alberta, Canada, and all patients provided written informed consent.

### *Measurements*

Baseline data were collected from April through October 2000. Trained study coordinators conducted in-person interviews and collected detailed information from the patients.<sup>10</sup> Complete medical histories, including medication use, were compiled with use of patient self-reporting and pharmacy records. Standardized physical assessments were completed, and measurements of body weight, height, and blood pressure were recorded. Generic health-related quality of life was assessed with use of the Medical Outcomes Study 12-Item Short-Form.<sup>13</sup> Samples were obtained for measurement of fasting blood glucose, glycosylated hemoglobin (HbA<sub>1c</sub>), fasting lipids, and random urine albumin/creatinine ratio.

### *Analysis*

Our primary outcome was self-reported use of antiplatelet therapy. We classified patients into 2 groups, based on their regular use of any antiplatelet agent. Patients were included in the antiplatelet group if they reported regularly using  $\geq 1$  of the following medications: aspirin, clopidogrel, ticlopidine, or dipyridamole. Chi-square and Student *t* tests, as appropriate, were used to determine differences in demographic and clinical variables between patients who were taking antiplatelet therapy and those who

were not. Age, sex, and any candidate variable associated with antiplatelet use (at a significance level of  $P \leq 0.10$  in univariate analysis) were included in our multivariate models. We used multivariate logistic regression models to examine the independent association between sociodemographic and clinical characteristics and self-reported use of antiplatelet agents. To assess the goodness of fit of our final model, we used the Hosmer-Lemeshow goodness-of-fit test and determined the  $C$  statistic for the logistic model.<sup>14</sup> We considered  $P \leq 0.05$  to be statistically significant. We also determined unadjusted and adjusted odds ratios (AORs) and their 95% CIs.

## RESULTS

We consecutively recruited and enrolled people until we reached our goal of 400 people for the study, or about 20% of the entire population with DM in the study region.<sup>10</sup> Our final study sample included 394 volunteer subjects who were cared for by 39 fee-for-service primary care physicians. Agreement between patient self-reporting and pharmacy records was excellent in our study sample; for example, for antihypertensive drugs,  $\kappa = 0.83$ ; for hypoglycemic agents,  $\kappa = 0.93$ ; and for lipid-lowering drugs,  $\kappa = 0.78$ .<sup>15</sup>

Of the initial 394 individuals enrolled in the DOVE Study, we excluded 29 patients (7%) with incomplete or missing data. In addition, we excluded 23 patients (6%) who were taking warfarin because the effects of combining antiplatelet therapy with warfarin-based anticoagulation are not well defined. The sociodemographic and clinical characteristics of the 342 study subjects were typical of rural Canadian patients with type 2 DM<sup>10</sup> and are presented in **Table I**. The mean age was 62.9 years; 149 (44%) were men, and 84 (25%) were of indigenous origin. The median time since diagnosis of type 2 DM was 8 years, and 197 patients (58% of the cohort) had previously attended a DM education clinic. In about half of the patients, individual targets for risk factor management had been met: 167 (49%) had HbA<sub>1c</sub> <7%, 158 (46%) had systolic blood pressure (SBP) <130 mm Hg, and 118 (35%) had low-density lipoprotein (LDL) cholesterol <2.5 mmol/L. The median total number of prescription medications taken was 4.

Only 78 of 342 patients (23%) reported regularly using any antiplatelet therapy. Of the 78 patients

**Table I. Sociodemographic and clinical characteristics of 342 patients with type 2 diabetes mellitus (DM) in 2 rural regions in Alberta, Canada, who were enrolled in the Diabetes Outreach Van Enhancement Study<sup>10</sup> in 2000.**

Characteristic	Value
Age, y	
Mean (SD)	62.9 (12.5)
Range	28–86
Sex, no. (%)	
Women	193 (56)
Men	149 (44)
Married or common-law, no. (%)	229 (67)
Annual household income below Can \$20,000, no. (%)	134 (39)
Retired, no. (%)	141 (41)
Indigenous,* no. (%)	84 (25)
English as first language, no. (%)	241 (70)
SF-12 score, mean (SD)	52.0 (25.3)
Time since diagnosis of DM, mean (SD), y	8.2 (8.6)
Previously attended DM education clinic, no. (%)	197 (58)
Nonsmoker, no. (%)	280 (82)
Prescription medications per patient	
Median	4
Interquartile range	1–8
Symptomatic CAD,† no. (%)	22 (6)
Antiplatelet agent use,‡ no. (%)	78 (23)
Body mass index, kg/m <sup>2</sup>	
Median	32
Interquartile range	28–36
Clinical and laboratory parameters, no. (%)	
HbA <sub>1c</sub> <7%	167 (49)
SBP <130 mm Hg	158 (46)
LDL-C <2.5 mmol/L	118 (35)

SF-12 = Medical Outcomes Study 12-Item Short-Form<sup>13</sup> (12 items were added and the mean was determined, then standardized to the Alberta population, which has a mean [SD] score of 50 [10]; higher scores represent better physical and mental health); CAD = coronary artery disease; HbA<sub>1c</sub> = glycosylated hemoglobin; SBP = systolic blood pressure; LDL-C = low-density lipoprotein cholesterol.

\*First Nation, Aboriginal, or Métis.

†Based on the use of nitrates.

‡Aspirin, clopidogrel, ticlopidine, or dipyridamole.

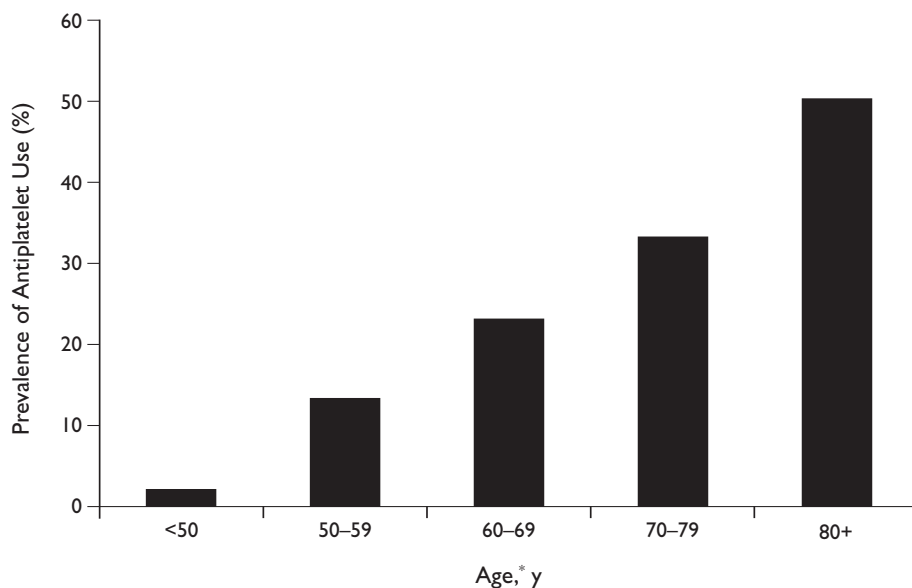
using antiplatelet agents, 74 patients were taking aspirin alone, 2 patients were taking a thienopyridine (clopidogrel or ticlopidine) alone, and 2 patients were taking a thienopyridine in combination with aspirin. The use of antiplatelet agents was lowest among patients aged <50 years (2%) but increased steadily with age, reaching 50% among those aged  $\geq 80$  years ( $P < 0.001$ ; **Figure**). **Table II** presents sociodemographic and clinical characteristics of patients according to their antiplatelet agent use. Of note, 42 of 149 men (28%) were taking antiplatelet agents compared with 36 of 193 women (19%;  $P = 0.037$ ). Symptomatic coronary artery disease (CAD [defined by the use of nitroglycerin preparations]), smoking status, and total number of medications excluding antiplatelet agents were also significantly associated with the use of antiplatelet agents ( $P < 0.001$ ,  $P = 0.018$ , and  $P < 0.001$ , respectively). However, the achievement of optimal levels of any of the individual cardiovascular risk factors (eg,  $HbA_{1c} < 7\%$ , SBP <130 mm Hg, or LDL <2.5 mmol/L) was not associated with a greater likelihood of use of antiplatelet agents.

According to the results of the multivariate analyses (**Table III**), patients with symptomatic CAD were

more likely to report taking antiplatelet agents than those without symptomatic CAD (AOR, 3.1; 95% CI, 1.1–8.7;  $P = 0.033$ ). Older patients were significantly more likely to regularly use antiplatelet agents than were younger patients (AOR, 2.0 per 10-year interval; 95% CI, 1.7–2.2;  $P < 0.001$ ), and men were more likely to use them than women (AOR, 1.9; 95% CI, 1.1–3.5;  $P = 0.026$ ). Overall, this final multivariate logistic regression model had an acceptable fit,<sup>14</sup> with a Hosmer-Lemeshow goodness-of-fit test statistic of 6.69 ( $P = 0.57$ ) and a *C* statistic of 0.79 for the final model.

## DISCUSSION

Studies have shown that aspirin therapy is effective for both primary and secondary prevention of cardiovascular and cerebrovascular events.<sup>7,15–17</sup> Subgroup analyses in these studies have shown similar, if not greater, benefits of aspirin use in those with DM.<sup>17,18</sup> By 1998, both the American and Canadian Diabetes Association guidelines recommended the use of aspirin in all patients with type 2 DM aged  $\geq 30$  years.<sup>9,19</sup> Our study sample consisted of older patients (mean age, 62.9 years) with long-standing DM and a high risk of cardiovascular or cerebrovas-



**Figure.** Association between use of antiplatelet agents and age among 342 patients with type 2 diabetes mellitus in 2 rural regions in Alberta, Canada, who were enrolled in the Diabetes Outreach Van Enhancement Study<sup>10</sup> in 2000. \* $P < 0.001$  for trend.

**Table II. Univariate analysis of correlates of self-reported use of antiplatelet therapy among 342 patients with type 2 diabetes mellitus (DM) in 2 rural regions in Alberta, Canada, who were enrolled in the Diabetes Outreach Van Enhancement Study<sup>10</sup> in 2000.**

Variable	Antiplatelet Therapy (n = 78)	No Antiplatelet Therapy (n = 264)	P
Age, mean (SD), y	70.4 (9.7)	60.7 (12.3)	<0.001
Sex, no. (%)			0.037
Men	42 (54)	107 (41)	
Women	36 (46)	157 (59)	
Married or common-law, no. (%)	54 (69)	175 (66)	0.66
Annual household income below Can \$20,000, no. (%)	34 (44)	100 (38)	0.20
Indigenous,* no. (%)	19 (24)	65 (25)	0.93
SF-12 score, mean (SD)	50.2 (25.5)	52.6 (25.3)	0.46
Time since diagnosis of DM, mean (SD), y	9.4 (8.0)	7.8 (8.8)	0.18
Attended DM education clinic, no. (%)	51 (65)	146 (55)	0.12
Nonsmoker, no. (%)	69 (88)	211 (80)	0.018
Prescription medications per patient, mean (SD) <sup>†</sup>	5.5 (2.1)	4.2 (2.8)	<0.001
Symptomatic CAD, <sup>‡</sup> no. (%)	14 (18)	8 (3)	<0.001
Body mass index, mean (SD), kg/m <sup>2</sup>	32.1 (7.3)	33.2 (7.1)	0.22
Clinical and laboratory parameters, no. (%)			
HbA <sub>1c</sub> <7%	39 (50)	128 (48)	0.81
SBP <130 mm Hg	40 (51)	118 (45)	0.31
LDL-C <2.5 mmol/L	26 (33)	92 (35)	0.53
All 3 targets achieved	9 (12)	21 (8)	0.42

SF-12 = Medical Outcomes Study 12-Item Short-Form<sup>13</sup> (12 items were added and the mean was determined, then standardized to the Alberta population, which has a mean [SD] score of 50 [10]; higher scores represent better physical and mental health); CAD = coronary artery disease; HbA<sub>1c</sub> = glycosylated hemoglobin; SBP = systolic blood pressure; LDL-C = low-density lipoprotein cholesterol.

\*First Nation, Aboriginal, or Métis.

<sup>†</sup>Excludes antiplatelet agents.

<sup>‡</sup>Based on the use of nitrates.

**Table III. Multivariate logistic regression analysis of the independent correlates of self-reported use of antiplatelet therapy among 342 patients with type 2 diabetes mellitus in 2 rural regions in Alberta, Canada, who were enrolled in the Diabetes Outreach Van Enhancement Study<sup>10</sup> in 2000.\***

Variable	Adjusted Odds Ratio (95% CI)	P
Symptomatic CAD <sup>†</sup>	3.1 (1.1–8.7)	0.033
Age, per 10-year interval	2.0 (1.7–2.2)	<0.001
Sex, men vs women	1.9 (1.1–3.5)	0.026
Nonsmoker	1.5 (0.6–3.8)	0.36
Prescription medications, per drug <sup>‡</sup>	1.1 (1.0–1.2)	0.088

CAD = coronary artery disease.

\*Hosmer-Lemeshow goodness-of-fit test = 6.69 ( $P = 0.57$ ) with a C statistic of 0.79 for final model.

<sup>†</sup>Based on the use of nitrates.

<sup>‡</sup>Excluding antiplatelet agents.

cular events. The majority of patients were obese (median body mass index, 32 kg/m<sup>2</sup>), hypertensive, or dyslipidemic. Only 2 of the 342 study patients were aged <30 years. Therefore, the vast majority of our study patients were candidates for aspirin therapy according to current American and Canadian guidelines, assuming no allergies or absolute contraindications to aspirin.

We found that only 78 patients in our study sample (23%) were using an antiplatelet agent, usually aspirin (76/78 [97%]). The use of aspirin was meticulously documented by pharmacy records and by direct interviewing of patients. The use of patient self-reporting is a strength of this study because patients may buy aspirin over the counter, and because aspirin use tends not to be well documented in medical charts or well captured in administrative databases. We previously reported substantial agreement between patient self-reporting and pharmacy records for prescription drugs in this population,<sup>15</sup> further suggesting that patient self-reporting of aspirin use should be considered reliable.

Through multivariate analyses, we found that male sex and older age were significantly associated with the use of antiplatelet agents. Only 19% of women (compared with 28% of men) were using an antiplatelet agent on a regular basis. Although antiplatelet agents were underused by all of the patients in our study, these results suggest that there may be a bias toward underestimating the risk of cardiovascular disease in women with DM. Perhaps as interesting was the association between older age and increased use of antiplatelet agents. Unlike many (if not most) therapies, for which undertreatment in the elderly is common,<sup>20</sup> we found that use of antiplatelet agents increased with increasing age. Half of the patients aged ≥80 years (14/28 [50%]) were taking an antiplatelet agent, which suggests that cardiovascular risk may also be commonly underestimated in younger patients with DM.

Our study has several limitations. First, it was a cross-sectional study of patients in rural Alberta, Canada. As such, our results may not be generalizable to other rural regions or to more urban or tertiary care settings. That said, it is unlikely that rates of aspirin use are much greater in other settings—previous reports have documented rates between 20% and 66%.<sup>21–23</sup> The latter value, the highest in the litera-

ture, was drawn from an elderly population of male veterans with DM in the United States, ~50% of whom had established cardiovascular disease.<sup>22</sup> For the subset of our patients with similar characteristics (ie, age, sex, and presence of cardiovascular disease), the rate of use was 59% (13/22). Second, our data were gathered from patients who had consented to be involved in a research study. This may have led to selection bias, resulting in a sample more likely to be adherent with medical advice and, therefore, more likely to be taking aspirin compared with the entire population of patients with type 2 DM. Thus, our results may actually be an overestimate of the actual prevalence of aspirin use in rural Canadian patients with type 2 DM.

A major limitation of our study was the lack of prescription data specific to primary care physicians and the lack of access to the medical charts of their patients. By agreement with the participating study regions, we did not attempt in any way to profile the activities of the 39 physicians caring for these patients. Perhaps this is not as great a limitation as one might believe, given that study participants had a median time since diagnosis of DM of 8 years and had likely seen a number of specialists (eg, internists, endocrinologists, cardiologists). There would have been many opportunities over the years for a health professional to counsel the use of aspirin, and we cannot know whether patients had been advised to take aspirin but declined. For the same reasons, we could not ascertain whether patients had ever previously tried aspirin therapy or had absolute contraindications to aspirin. Indeed, it may be that many of the patients in our sample had previously attempted aspirin therapy, but we suspect that this is unlikely given the low rate of use of aspirin alternatives reported in our study. Finally, the lack of access to complete medical records included a lack of access to hospital discharge data. Thus, we had little information regarding past clinical events, such as previous myocardial infarction or stroke. Although this information might have been useful in understanding the issues related to primary versus secondary prevention and cardiovascular risk stratification in a study of patients without DM, our entire study sample was already eligible for aspirin therapy regardless of their history of cardiovascular events.

Faragon et al<sup>23</sup> recently examined a group of patients very similar to the ones in the current study.

They identified DM patients within a rural primary care clinic and screened their medical records for documentation of aspirin use as well as for any allergies, adverse events, or contraindications. The investigators then instituted a simple pharmacist-directed intervention. Patients with DM and without contraindications for aspirin use were advised, either during routine clinic visits or via structured telephone interviews, to begin aspirin therapy. Only 9% of patients were found to have a contraindication for aspirin use, and preintervention rates of use were 33% among those who were eligible. The pharmacist-directed intervention was associated with a 49% absolute increase in aspirin use, and serves as one potential model for the improvement of adherence with antiplatelet therapy in patients at high risk of cardiovascular and cerebrovascular events.<sup>23</sup>

## CONCLUSIONS

Aspirin is a safe, inexpensive, and readily available therapy that is effective for both primary and secondary prevention of cardiovascular disease. Patients with established DM are likely to derive much greater cardiovascular benefits from aspirin therapy than more average-risk patients without DM. However, we found significant underuse of aspirin therapy among the patients with type 2 DM who made up our study population. Much emphasis has been placed on the control of blood pressure, dyslipidemia, and hyperglycemia for optimal DM care. We believe that aspirin should be included and better promoted as a factor in high-quality, evidence-based DM management.

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