Evidence of suboptimal management of cardiovascular risk in patients with type 2 diabetes mellitus and symptomatic atherosclerosis

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Abstract

Background: Given that most deaths among patients with diabetes mellitus are due to cardiovascular disease, we sought to determine the extent to which medications proven to reduce cardiovascular mortality are prescribed for patients with type 2 diabetes who have symptomatic atherosclerosis (i.e., coronary artery disease [CAD], cerebrovascular disease [CBVD] or peripheral arterial disease [PAD]).

Methods: Administrative records from Saskatchewan Health were used to evaluate the use of antiplatelet agents, statins and angiotensin-converting enzyme (ACE) inhibitors by people with treated type 2 diabetes with and without symptomatic atherosclerosis. CAD and CBVD were defined by International Classification of Diseases (ninth revision) codes, and PAD was defined on the basis of pentoxifylline use or lower limb amputation. Multivariate logistic regression analysis was used to compare medication use in patients with and without PAD, with adjustments for differences in age, sex and comorbidity.

Results: In this cohort of 12 106 patients with type 2 diabetes (mean age 64 years, 55% male, mean follow-up 5 years), fewer than 25% received an antiplatelet agent or statin, and fewer than 50% received an ACE inhibitor. Although patients with CAD were more likely to receive antiplatelet agents, statins or ACE inhibitors than people without CAD ($p < 0.001$ for all), the overall use of these medications was suboptimal (37%, 29% and 60% respectively among patients with symptomatic CAD). Similar patterns of practice were found for patients with symptomatic CBVD and PAD. All 3 proven efficacious therapies were prescribed for only 11% of patients with CAD, 22% with CBVD and 12% with PAD. Patients with PAD who had undergone lower limb amputation were no more likely to subsequently receive antiplatelet agents or statins than those without an amputation.

Interpretation: Diabetic patients with symptomatic atherosclerotic disease are undertreated with medications known to reduce cardiovascular morbidity and mortality, perhaps because of a "glucocentric" view of diabetes. Programs to improve the quality of cardiovascular risk reduction in these high-risk patients are needed.

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Diabetes mellitus in adults is associated with an annual rate of death of about 5%, approximately double the rate for age- and sex-matched control subjects without diabetes. Most of this excess mortality risk is attributable to macrovascular atherosclerotic disease.[1] Thus, it has been recommended that medical management to decrease cardiovascular risk should start when type 2 diabetes mellitus is diagnosed.[2,3] At the very least, medications proven to reduce cardiovascular risk should be prescribed for patients with diabetes and established atherosclerotic disease.

In addition to smoking cessation and control of blood pressure, strategies proven to reduce cardiovascular risk in patients with diabetes and established atherosclerotic disease include therapy with antiplatelet agents, statins and angiotensin-converting enzyme (ACE) inhibitors.[2] Coronary artery disease (CAD), cerebrovascular disease (CBVD) and peripheral arterial disease (PAD) are all manifestations of established atherosclerosis.[4] Recent epidemiologic studies have suggested that PAD may be present in one-quarter to one-half of all adults with type 2 diabetes and have confirmed that PAD is a powerful predictor of cardiovascular death.[4] In fact, the survival rate for patients with PAD is worse than that for patients with breast cancer (72% v. 85% at 5 years).[4] However, a recently published survey suggested that clinicians were less likely to prescribe antiplatelet therapy for patients with PAD than for patients with CAD.[5]

We sought to evaluate the use of antiplatelet agents, statins and ACE inhibitors among diabetic patients with and without symptomatic atherosclerotic vascular disease. Given the high prevalence of symptomatic PAD among diabetic patients and suggestions that it is often neglected as a marker of atherosclerotic disease, we were particularly interested in examining patterns of care for overall cardiovascular risk reduction in patients with this condition.[4]

Methods

We used linked information on demographic characteristics, prescription medications, outpatient visits and hospital admissions for a cohort of 12 106 consecutive patients with new-onset type 2 diabetes identified between 1991 and 1996 from administrative records obtained from Saskatchewan Health (covering approximately 1 million people) for a previous analysis.[6] The cohort was followed until 2000. Subjects were identified as having diabetes if they had 1 or more dispensation records for an antidiabetic agent (i.e., oral agent or insulin), 2 or more physician service claims for diabetes (International Classification of Diseases,

ninth revision [ICD-9], code 250) within a 2-year period, or 1 or more hospital admissions with a diabetes code as either the primary, secondary or tertiary diagnosis.[6] This case identification algorithm is the basis of the National Diabetes Surveillance System[7] and has been validated for this and other Canadian administrative databases.[8]

We examined utilization rates for antiplatelet agents, statins and ACE inhibitors within the entire cohort, as well as among patients with evidence of CAD, CBVD or PAD. CAD was defined on the basis of a hospital separation ICD-9 code for myocardial infarction or a procedure code for coronary revascularization (i.e., coronary artery bypass grafting or percutaneous transluminal coronary angioplasty). We also used dispensation records for a short-acting nitrate preparation as a marker for established CAD, as this marker has high sensitivity.[9,10] CBVD was defined on the basis of hospital separation ICD-9 codes for stroke or transient ischemic attack. PAD was defined on the basis of a hospital separation code or procedure code for lower limb amputation, with exclusion of traumatic amputations and upper limb amputations from the analyses. Pentoxifylline dispensation records were also used as an indicator of symptomatic PAD, because the only approved indication for pentoxifylline is the symptomatic treatment of patients with chronic occlusive peripheral vascular disease.[11]

We used multivariate logistic regression analyses to compare the use of antiplatelet agents, statins and ACE inhibitors between patients with pentoxifylline use or lower limb amputation, as markers of symptomatic or end-stage PAD, and those without either of these markers. Covariates in the multivariate regression models were age, sex, chronic disease score as an index of comorbidity and nitrate use.[6,12,13] Among those who underwent amputation, we compared medication use before and after amputation.

Results

The mean age of patients in the cohort was 64 (range 30–105) years, 55% were male, and the mean duration of follow-up was 5 (range 0–9) years.

The use of all 3 types of agents proven to reduce cardiovascular risk was low in this cohort of patients with type 2 diabetes (Table 1). Diabetic patients with CAD were significantly more likely than those without CAD to be receiving antiplatelet agents (37% v. 15%, $p < 0.001$), statins (29% v. 15%, $p < 0.001$) and ACE inhibitors (60% v. 43%, $p < 0.001$). Diabetic patients with CBVD were significantly more likely than those without CBVD to be receiving antiplatelet agents (46% v. 20%, $p < 0.001$) and ACE inhibitors (58% v. 47%, $p < 0.001$) but were less likely to be receiving statins (16% v. 20%, $p = 0.001$). Patients with PAD were significantly more likely than those without PAD to be receiving antiplatelet agents (44% v. 23%, $p < 0.001$) and ACE inhibitors (62% v. 49%, $p < 0.001$); however, there was no significant difference in the use of statins (23% v. 20%, $p = 0.12$). All 3 proven efficacious therapies were prescribed for only 11% of diabetic patients with CAD, 22% of those with CBVD and 12% of those with PAD.

After adjustment for age, sex and comorbidities, subjects with dispensation records for pentoxifylline were more likely to have received antiplatelet agents (adjusted odds ratio [OR] 1.5, 95% confidence interval [CI] 1.2–2.0) than those without pentoxifylline prescriptions; the prevalence of statin therapy (adjusted OR 1.1, 95% CI 0.8–1.5) and ACE inhibitor use (adjusted OR 1.0, 95% CI 0.8–1.4) did not differ. Use of the 3 types of medication was low among patients with lower limb amputation and no different than among patients without amputation: adjusted OR 1.0 (95% CI 0.6–1.8) for antiplatelet agents, adjusted OR 1.0 (95% CI 0.6–1.9) for statins and adjusted OR 0.9 (95% CI 0.5–1.4) for ACE inhibitors. Among subjects who had a lower limb amputation because of PAD, prescriptions for ACE inhibitors increased after amputation (from 32% to 42%, $p = 0.008$); marginal increases in the use of statins and antiplatelet agents were observed, but these were not statistically significant (Table 2).

Interpretation

We found that 3 medications proven to reduce cardiovascular risk and mortality (antiplatelet agents,[14] statins[15] and ACE inhibitors[16]) were systematically underused for patients with diabetes, even among those with established atherosclerotic disease (manifest as either CAD, CBVD or

Table 1: Number (and percentage) of subjects with type 2 diabetes mellitus, with and without symptomatic atherosclerotic disease, using cardiovascular medications*

Medication	All patients *n = 12 106*	No CAD, CBVD or PAD *n = 7866*	CAD†		CBVD‡		Symptomatic PAD§	
			Yes *n = 3385*	No *n = 8721*	Yes *n = 1331*	No *n = 10 775*	Yes *n = 281*	No *n = 11 825*
Antiplatelet agent	2847 (24)	886 (11)	1251 (37)	1277 (15)	618 (46)	2110 (20)	125 (44)	2727 (23)
Statin	2405 (20)	1217 (15)	979 (29)	1341 (15)	218 (16)	2161 (20)	66 (23)	2342 (20)
ACE inhibitor	5917 (49)	3253 (41)	2038 (60)	3731 (43)	769 (58)	5096 (47)	174 (62)	5746 (49)
All 3 medications	596 (5)	111 (1)	383 (11)	0 (0)	288 (22)	265 (2)	34 (12)	313 (3)

Note: CAD = coronary artery disease, CBVD = cerebrovascular disease, PAD = peripheral arterial disease, ACE = angiotensin-converting enzyme.
*The totals in the last 3 pairs of columns are not mutually exclusive (i.e., some patients had more than 1 of these conditions).
†Defined as having a history of myocardial infarction, admission to hospital for coronary revascularization (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) or prescription for nitrate.
‡Defined as having a history of stroke or transient ischemic attack.
§Defined as having a lower limb amputation or a prescription for pentoxifylline.

PAD). Although CAD and CBVD are well-recognized manifestations of atherosclerotic disease, PAD is also a powerful indicator of systemic atherosclerotic disease.[4] Patients with PAD have a greater risk of myocardial infarction and stroke and are 6 times more likely to die within 10 years than patients without PAD.[17] Given these statistics, medications proven to decrease the risk of cardiovascular disease should be used extensively for patients with symptomatic PAD. However, very low prescribing rates were seen for patients with symptomatic PAD (manifest by use of pentoxifylline) or end-stage PAD (manifest by lower limb amputation). In fact, there was very little improvement in the use of proven efficacious therapies even after lower limb amputation, an event that would have been expected to highlight the extent and severity of atherosclerotic disease in afflicted patients.

The strengths of this study include the population-based cohort design, the large sample size and the detailed data on medication use. However, as with other studies based solely on administrative databases, several limitations must be recognized. Our figures probably underestimate the prevalence of symptomatic conditions, as patients with mild conditions, who are unlikely to seek treatment or be admitted to hospital, would not be captured in the databases. This would result in an underestimation of care gaps. Further, the Saskatchewan Health databases cover approximately 90% of the Saskatchewan population; excluded from the databases are federal employees and Aboriginal people, who are covered under federal health insurance programs.[18] It is unlikely, however, that the management of these individuals would be systematically better than that of the general population of Saskatchewan; in fact, there is some evidence that the management of global cardiovascular risk among Aboriginal diabetic patients may be even worse than among non-Aboriginal patients.[19]

In addition, use of administrative records of drug dispensations does not ensure complete information on drug use. In particular, rates of antiplatelet use are likely to be underestimated in this population because acetylsalicylic acid can be obtained without a prescription. However, in Saskatchewan anyone with a prescription is eligible for medication reimbursement by the provincial drug plan, so we suspect that the underestimation was not large and was certainly unlikely to be systematically different for patients with CAD, CBVD or PAD than for those without manifest atherosclerotic disease. Further, the rate of antiplatelet use that we observed is similar to rates of use in large American trials, such as ALLHAT (published in 2002),[20] as well as a recent prospective cohort study in a neighbouring Canadian province.[19]

The underutilization of medications that reduce cardiovascular risk among patients with type 2 diabetes, particularly those with symptomatic atherosclerotic disease, is an alarming care gap that needs to be addressed. We identified a cohort of people who were all receiving treatment for their diabetes with either insulin or oral hypoglycemic agents. Having diabetes puts these patients at high risk of cardiovascular events, yet we found very low use of therapies of proven benefit in the prevention of cardiovascular events (antiplatelet agents, statins and ACE inhibitors), even among subjects with symptomatic or end-stage PAD. We think that these data demonstrate substantial treatment gaps, whereby elevated cardiovascular risk is unattended even though glucose control has been initiated; such treatment gaps imply a "glucocentric view" in the overall management of these patients. We hypothesize that an overemphasis on glycemic control in patients with diabetes deflects attention away from cardiovascular risk management. This is worrisome, given that the primary cause of death in patients with type 2 diabetes remains cardiovascular disease.[2,21]

We join the members of the Prevention of Atherothrombotic Disease Network[4] in advocating increased screening of patients with type 2 diabetes for symptoms suggestive of CAD, CBVD and PAD, and suggest that diabetic patients with any of these conditions should receive prescriptions for antiplatelet agents, statins and ACE inhibitors unless they have specific contraindications.[4] As recently pointed out by others, all 3 of these medication types have complementary actions and additive benefits, so "there is much to gain and little to lose by the widespread use of these drugs."[22]

Table 2: Use of cardiovascular medications before and after PAD-associated amputation of a lower limb

Drug use before amputation	Drug use after amputation; no. (%) of patients			*p* value*
	Yes	No	Total	
Antiplatelet agents				0.06
Yes	12	0	12 (16)	
No	5	59	64 (84)	
Total	17 (22)	59 (78)	76	
Statins				0.12
Yes	7	0	7 (9)	
No	4	65	69 (91)	
Total	11 (14)	65 (86)	76	
ACE inhibitors				0.008
Yes	24	0	24 (32)	
No	8	44	52 (68)	
Total	32 (42)	44 (58)	76	
All medications				0.50
Yes	2	0	2 (3)	
No	2	72	74 (97)	
Total	4 (5)	72 (95)	76	

*McNemar's test.

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