Antihypertensive Medication Prescribing in 27,822 Elderly Canadians With Diabetes Over the Past Decade

FINLAY A. MCALISTER, MD, MSC[1,2]
NORMAN R.C. CAMPBELL, MD[3]
MINH DUONG-HUA, BSC[2]
ZHONGLIANG CHEN, MD, BSC, MSC[2]
KAREN TU, MD, MSC[2,4,5]

OBJECTIVE — The purpose of this study was to examine whether prescribing practices for elderly individuals with diabetes and hypertension changed over the past decade.

RESEARCH DESIGN AND METHODS — We linked the Ontario Diabetes Database and four administrative databases in Ontario, Canada, to identify 27,822 patients >65 years of age who had diabetes and were newly treated for hypertension between 1 January 1995 and 31 December 2001. All patients were followed for 2 years after their initial antihypertensive medication prescription.

RESULTS — The 27,822 patients in this study (mean age 72 years, 51% men) were treated with oral hypoglycemic agents alone (n = 17,128 patients, 62%), insulin alone (n = 2,346, 8%), both oral hypoglycemic agents and insulin (n = 2,205, 8%), or diet alone (n = 6,143, 22%). Management within the first 2 years of hypertension diagnosis consisted of antihypertensive monotherapy in 20,183 patients (73%), two antihypertensive drugs in 6,207 (22%), and three or more drugs in 1,432 (5%); the most frequently chosen antihypertensive drugs were ACE inhibitors (68%), thiazides (15%), and calcium channel blockers (9%). Between 1995 and 2001, physician prescribing practices changed: the population-adjusted rates of antihypertensive drug prescribing increased by 46% (95% CI 33–55%), the proportion of initial antihypertensive prescriptions for ACE inhibitors increased from 54 to 76% ($P < 0.0001$), and the use of multiple antihypertensive agents within the first 2 years of diagnosis increased from 21 to 32% ($P < 0.0001$).

CONCLUSIONS — Antihypertensive prescribing patterns in elderly individuals with diabetes changed over the past decade in Ontario in directions consistent with the evolving evidence base.

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Although most patients with diabetes die of atherosclerotic disease (1), practice audits consistently highlight the suboptimal control of atherosclerotic risk in individuals with diabetes. In particular, numerous studies have demonstrated that few patients with diabetes have their blood pressure lowered to currently recommended targets (130/80 mmHg) (2–8), despite the fact that the benefits of aggressive blood pressure lowering may exceed those of aggressive glycemic control and that control of blood pressure has been identified by the Centers for Disease Control and Prevention as the most cost-effective intervention for reducing macrovascular risk in individuals with diabetes (9–11).

From the [1]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; the [2]Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada; the [3]Departments of Medicine and Pharmacology and Therapeutics, University of Calgary, Calgary, Alberta, Canada; the [4]University Health Network, Toronto Western Hospital Family Medicine Centre, Toronto, Ontario, Canada; and the [5]Departments of Family and Community Medicine, Family Healthcare Research Unit, University of Toronto, Toronto, Ontario, Canada.

Address correspondence and reprint requests to Finlay McAlister, 2E3.24 Walter Mackenzie Centre, University of Alberta Hospital, 8440 112 St., Edmonton, Alberta T6G 2R7, Canada. E-mail: finlay.mcalister@ualberta.ca.

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Abbreviations: MICRO-HOPE, Microalbuminuria, Cardiovascular, and Renal Outcomes–Heart Outcomes Prevention Evaluation; ODB, Ontario Drug Benefit.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

However, practice audits are typically small, drawn from highly select samples, frequently rely on patient self-report, are usually cross-sectional, and leave some questions unanswered. In particular, by focusing only on measured blood pressure levels, these audits have been unable to show whether the care gap in hypertensive individuals with diabetes is due to physician factors (such as underprescription of antihypertensive agents and/or failure to initiate treatment with multiple drugs to achieve blood pressure targets), patient factors (for example, noncompliance with medications or failure to seek medical care), or a combination (hypertension surveys consistently demonstrate that less than half of hypertensive individuals are even aware of their diagnosis). Although this care gap is undoubtedly multifactorial, it is important to define the key factors contributing to it to properly direct efforts to reduce the gap.

Thus, we designed this study to explore physician prescribing practices (and trends over the past decade) for patients with diabetes in whom hypertension is newly diagnosed to determine whether practices have changed as evidence has accumulated on the effectiveness of antihypertensive therapy in diabetes (particularly ACE inhibitors and angiotensin receptor blockers) and the frequent need for multiple drugs (for example, in the U.K. Prospective Diabetes Study Group trial, 29% of subjects randomly assigned to tight blood pressure control required three or more antihypertensive drugs) (11). In particular, as proxies for judging the aggressiveness of physicians' approaches to hypertension management, we were interested in exploring *1*) the frequency of new prescriptions for antihypertensive agents, *2*) the frequency with which two or more drugs were prescribed concurrently, and *3*) the frequency of discontinuation of antihypertensive therapy after diagnosis.

RESEARCH DESIGN AND METHODS

— We cross-linked the Ontario Diabetes Database (12) with the Ontario Drug Benefit (ODB) database to identify a cohort of all Ontario residents

aged ≥66 years who had a diagnosis of diabetes and had received a new prescription for an antihypertensive agent between 1 January 1995 and 31 December 2001. To identify incident cases of treated hypertension in our cohort, we prespecified a 1-year washout period (i.e., we excluded any patients with a first ODB claim date for an antihypertensive drug within the first 12 months of the study to exclude prevalent hypertensive patients getting medication refills). Using unique encrypted Ontario health care numbers, we further linked this cohort to the Ontario Health Insurance Plan physician claims database (which records all fee-for-service billings and most responsible diagnoses at each visit), the Canadian Institute for Health Information hospitalization database (which records the primary responsible and up to 15 secondary diagnoses for all discharges from acute care hospitals), and the Registered Persons Database (which records dates of death or emigration from Ontario). Studies have confirmed the comprehensiveness and validity of these administrative databases in Ontario (13).

To ensure that patients in our cohort were given an antihypertensive agent for treatment of hypertension, we excluded those patients who had non–blood pressure–lowering indications for particular antihypertensive drugs. As described in full in our previous publication focusing on antihypertensive medication prescribing in nondiabetic seniors (14), we excluded any patients with *1*) physician outpatient billing claims within 3 years or *2*) hospitalization claims within 4 years, or *3*) prescriptions for marker medications in the ODB within 1 year for any of the following conditions: myocardial infarction or angina, heart failure, arrhythmias, renal disease (including nephropathy), liver disease (including esophageal varices), stroke or transient ischemic attack, hyperthyroidism, or migraines.

In addition to exploring initial antihypertensive medication prescription choices, we followed our cohort of newly treated hypertensive patients with diabetes for 2 years after their initial antihypertensive drug prescription and examined subsequent prescriptions to evaluate rates of discontinuation or concurrent antihypertensive drug use using previously published definitions (14). Thus, we used 100 days as the intended duration of each prescription and checked to see whether a patient was given another prescription for the same drug within 180 days. If no repeat prescription was filled within 180 days and the patient did not die or become hospitalized, then the patient was deemed to have discontinued the drug. We examined rates of discontinuation for all antihypertensive drugs within the first 2 years of treatment, as well as drug-class specific discontinuation rates (for example, if a patient discontinued drug A but started antihypertensive drug B they would be deemed to have discontinued drug class A but not all antihypertensive therapy). Concurrent use was defined as the addition of another antihypertensive drug class within 100 days from the date of the last prescription for another agent. Combination agents that consisted of agents from two different subclasses were separated and counted as one prescription in each respective subclass when concurrent use was assessed (but were aggregated together for any counts of total antihypertensive medication prescriptions). Combination agents that consisted of a potassium-sparing diuretic plus a thiazide diuretic were counted as one prescription in the diuretic subclass.

Prescribing rates were calculated using the Ontario Diabetes Database to determine the denominator (i.e., the number of individuals aged ≥66 years with prevalent diabetes) in each time frame. Kaplan-Meier curves were used to assess rates of discontinuation and concurrent drug use, and χ^2 testing was performed on the discontinuation and concurrent use rates to assess for significant trends with a P value set at 0.05. Time series analyses to examine the impact of presentation of the Microalbuminuria, Cardiovascular, and Renal Outcomes–Heart Outcomes Prevention Evaluation (MICRO-HOPE) study (15) on ACE inhibitor prescribing was done using population-adjusted prescription rates and calculating the annualized prescription increases from the application of time series models to logarithmically transformed prescription numbers. All models included systematic components for periodic calendar variation plus a segmented "switching" linear regression (switching in mid-1999). Residual errors were modeled as autoregressive moving average processes. Graphic inspection of residuals revealed no systematic departures from assumptions. All computations were programmed in the R-project implementation of the S language. To make the clinical significance of the results transparent, we chose to present 95% CIs around the estimates of 1999-related changes in prescribing patterns.

RESULTS — From January 1995 through December 2001, we identified 27,822 elderly individuals (median age 71 years [interquartile range 68–75 years], mean ± SD age 72 ± 5.4 years, and 51% male) with a diagnosis of diabetes who were newly treated with antihypertensive drugs and did not have a non–blood pressure–lowering indication for that medication. Diabetes was managed by oral hypoglycemic drugs alone in 17,128 patients (62%), insulin alone in 2,346 (8%) patients, both oral hypoglycemic drugs and insulin in 2,205 (8%) patients, and diet alone in 6,143 (22%) patients. Statins were prescribed for 9,066 patients (33%).

There was an annual increasing trend in the number of individuals with newly treated hypertension in this cohort of diabetic subjects (Table 1), with a 46% increase in the population-adjusted rate of new antihypertensive prescriptions from the beginning to the end of the study period (95% CI 33–55%, $P < 0.0001$). The population-adjusted incidence of new antihypertensive prescriptions increased by 40% in elderly women with diabetes between 1995 and 2001, whereas initiation of antihypertensive drugs in previously untreated elderly men with diabetes increased by 52% over the same time period (Table 1).

Hypertension management within the first 2 years of diagnosis consisted of monotherapy in 20,183 patients (73%), two drugs in 6,207 (22%) patients, and three or more drugs in 1,432 (5%) patients. We defined a patient as being treated with monotherapy if their first antihypertensive medication prescription was for a single agent and no other antihypertensive agents were added within the first 2 years of diagnosis. The three most frequently prescribed classes of antihypertensive drugs in men and women and in all 9 years of our study were ACE inhibitors (68%), thiazide diuretics (15%), and calcium channel blockers (9%) (Table 1). Between 1995 and 2001, the proportion of all initial prescriptions that were for ACE inhibitors increased from 54 to 76% ($P < 0.0001$), whereas initial prescriptions for thiazide diuretics decreased from 22 to 10% ($P < 0.0001$), and initial prescriptions for calcium channel blockers decreased from 16 to 6% ($P < 0.0001$). β-Blocker prescribing rates remained relatively stable at ~7%. ACE

Table 1—*Population-adjusted rates of initial antihypertensive prescriptions per 1,000 elderly Ontario residents with diabetes and newly treated for hypertension, total and by sex*

	1995	1996	1997	1998	1999	2000	2001
Total							
ACE inhibitors	7.57	8.52	9.72	10.0	12.84	17.01	15.40
Angiotensin II receptor blockers		0.04	0.10	0.17	0.20	0.24	0.35
β-Blockers	0.95	1.14	1.09	1.18	1.20	1.15	1.13
Calcium channel blockers	2.26	2.00	1.67	1.38	1.49	1.32	1.18
Combination agents	0.06	0.03	0.11	0.07	0.12	0.14	0.18
Thiazides	3.07	2.90	2.78	2.68	2.77	2.64	2.08
Any antihypertensive	13.91	14.63	15.47	15.48	18.63	22.50	20.32
Women							
ACE inhibitors	6.77	7.59	8.60	8.71	11.00	14.39	13.50
Angiotensin II receptor blockers		0.03	0.13	0.19	0.19	0.27	0.41
β-Blockers	0.92	1.12	1.06	1.12	1.19	1.06	1.16
Calcium channel blockers	2.25	2.21	1.68	1.33	1.49	1.34	1.20
Combination agents	0.08	0.03	0.14	0.09	0.13	0.13	0.19
Thiazides	3.48	3.46	3.31	2.99	3.19	3.07	2.41
Any antihypertensive	13.49	14.43	14.92	14.43	17.19	20.26	18.87
Men							
ACE inhibitors	8.47	9.55	10.95	11.44	14.85	19.85	17.44
Angiotensin II receptor blockers		0.04	0.07	0.15	0.21	0.22	0.29
β-Blockers	0.98	1.16	1.12	1.24	1.22	1.23	1.09
Calcium channel blockers	2.28	1.76	1.66	1.45	1.49	1.29	1.15
Combination agents	0.04	0.02	0.08	0.06	0.11	0.16	0.17
Thiazides	2.62	2.27	2.19	2.33	2.32	2.18	1.74
Any antihypertensive	14.37	14.82	16.07	16.66	20.21	24.94	21.89

inhibitors were more likely to be prescribed as initial therapy for men than for women (73 vs. 63%, $P < 0.0001$). Time series analyses confirmed that the annualized prescribing rates for ACE inhibitors as initial therapy increased significantly after 1999 (the year that results of the HOPE/MICRO-HOPE study were presented). Even after adjustment for the temporal trends in the pre-1999 data, the annual increase in ACE inhibitor prescriptions was 14.3% per annum (95% CI 9.7–19.0%) after 1999 compared with 6.7% per annum (2.4–11.1%) before 1999.

The number of patients taking more than one antihypertensive drug concurrently within the first 2 years of starting antihypertensive therapy increased steadily over time (from 21% in 1995 to 32% in 2001, $P < 0.0001$) (Fig. 1). Those patients being treated with both oral hypoglycemic drugs and insulin for their diabetes were more likely to be treated with two or more antihypertensive agents concurrently than those being treated with diet or a single hypoglycemic agent (32 vs. 27%, $P < 0.0001$, and 32 vs. 28%, $P = 0.001$). In a similar vein, the 9,066 patients being treated with statins were also more likely to be treated with two or more antihypertensive agents concurrently than those not treated with statins (35 vs. 25%, $P < 0.0001$).

In addition to the increasing population-adjusted rates of antihypertensive prescribing and the increasing proportion of patients for whom two or more antihypertensive drugs were prescribed concurrently, there was a decreasing trend (from 30% in 1995 to 19% in 2001, $P < 0.0001$) (Fig. 2) in the number of patients discontinuing all antihypertensive therapy within 2 years of starting. Discontinuation rates for specific drug classes are reported in Table 2. (Note that these rates are higher than the rates of "discontinuing all antihypertensive therapy" because drug class–specific discontinuation rates include those patients who discontinue all antihypertensive therapy [Fig. 2] plus those patients whose medication was switched from one drug class to another within the study time frame.) Discontinuation rates were high for all drug classes, but the only sex-related difference was in the ACE inhibitor discontinuation rates (women were significantly more likely to discontinue or be switched from ACE inhibitors within the first 2 years of prescription than men: 49 vs. 41%, $P < 0.0001$).

CONCLUSIONS — We found that the proportion of patients treated with an ACE inhibitor as initial therapy increased substantially over time and that ACE inhibitors were the most commonly prescribed drug class in all years. Our data suggest that physicians are being more aggressive in their treatment of hypertensive individuals with diabetes over time as *1*) the population-adjusted rates of antihypertensive prescribing increased by 46% between 1995 and 2001, *2*) patients newly treated in the latter years of our study were substantially more likely to be treated with more than one antihypertensive drug within the first 2 years of diagnosis (32 vs. 21%), and *3*) patients newly treated in the latter years of our study were substantially less likely to have all antihypertensive therapy discontinued than patients treated in the mid-1990s (19 vs. 30%).

Interestingly, our data do not suggest the existence of a "treatment:risk paradox" in diabetes. Thus, although some studies have found that patients at higher risk are less likely to be prescribed efficacious therapies than patients with the same condition but lower baseline risk (16), we found that those patients with more difficult-to-control diabetes (as evi-

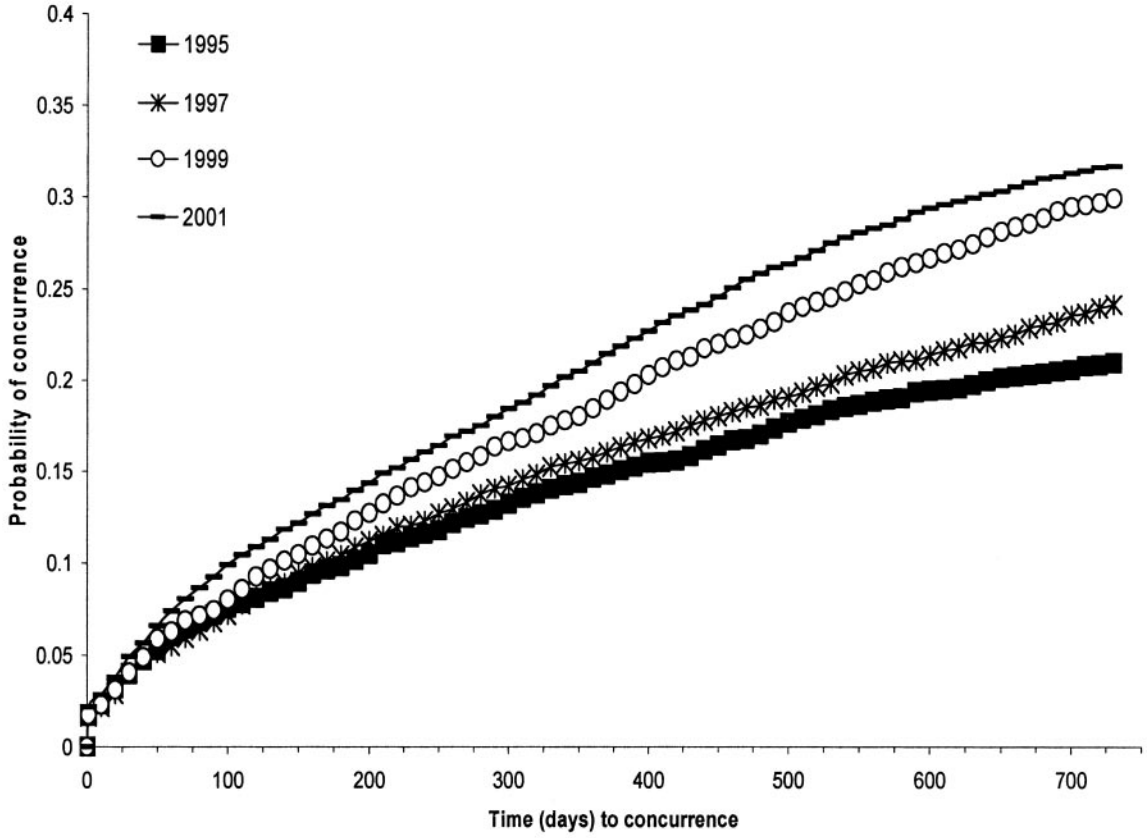

Figure 1—*Probability of use of concurrent antihypertensive drug classes within 2 years of initial treatment in patients with diabetes by year.*

denced by prescriptions for two or more hypoglycemic agents) were significantly more likely to be treated with multiple antihypertensive agents. In a similar vein, those patients receiving statin prescriptions in our cohort were also more likely to be treated with multiple antihypertensive agents than those not prescribed statins.

We found that men were significantly more likely to be prescribed an ACE inhibitor as initial antihypertensive therapy than women (73 vs. 63%), and it is intriguing to speculate whether this is a reflection of physician recognition of increased atherosclerotic risk at baseline in men (and, given the well-publicized results of the HOPE/MICRO-HOPE trial, a desire to intervene with ACE inhibitors earlier) (15) or a reflection of concerns over the greater potential for adverse effects from ACE inhibitors in women. Although the teratogenic risks with ACE inhibitors are well known, this is clearly not a concern in this cohort of elderly patients. However, some authors have raised concerns about the safety of ACE inhibitors in elderly women (17). Indeed, we did find that although women were more likely to continue treatment with other antihypertensive drugs than men, they were significantly more likely to discontinue ACE inhibitor therapy than men (49 vs. 41%), a finding consistent with that in other studies (18–23). Although there is insufficient clinical information in the databases used for this study to explore why women had higher rates of ACE inhibitor discontinuation, reports from clinical trials and registries have consistently documented that women are at higher risk of ACE inhibitor–induced cough than men (21–23). The reasons behind this and the optimal strategy to minimize potential adverse effects with ACE inhibition in women remain active areas of research.

Although our study includes complete prescribing information for a large, representative, and population-based sample of all adults aged >65 years with diabetes with 100% follow-up (thus avoiding problems with small samples, selection bias, and measurement bias that have afflicted previous studies), there are some limitations to our study. First, some may question the use of antihypertensive drug prescriptions to define cases of hypertension as this will miss those patients for whom therapy has not been prescribed; however, data from the National Health and Nutrition Evaluation Survey 1999–2000 in the U.S. and the National Public Health and Community Health Surveys in Canada 2000–2003 have shown that antihypertensive therapy is prescribed for 85% of individuals with diabetes and recognized hypertension (2,24). Second, some may raise concerns that our study was limited to elderly subjects; however, the prevalence of hypertension increases with age, and most hypertensive individuals with diabetes are elderly (25,26). Finally, because administrative databases do not contain information on actual blood pressure measurements, we can only use changes in prescribing frequency and patterns of antihypertensive drug use as proxy measures for changes in detection and control of hypertension. However, this allows us to focus on the physician side of the "diabetes blood pressure care gap"; studies that judge physician management on the basis of patients' blood pressures are confounded by the fact that patient noncompliance with or reduced responsiveness to prescribed therapy will result in the physician's management strategy appearing

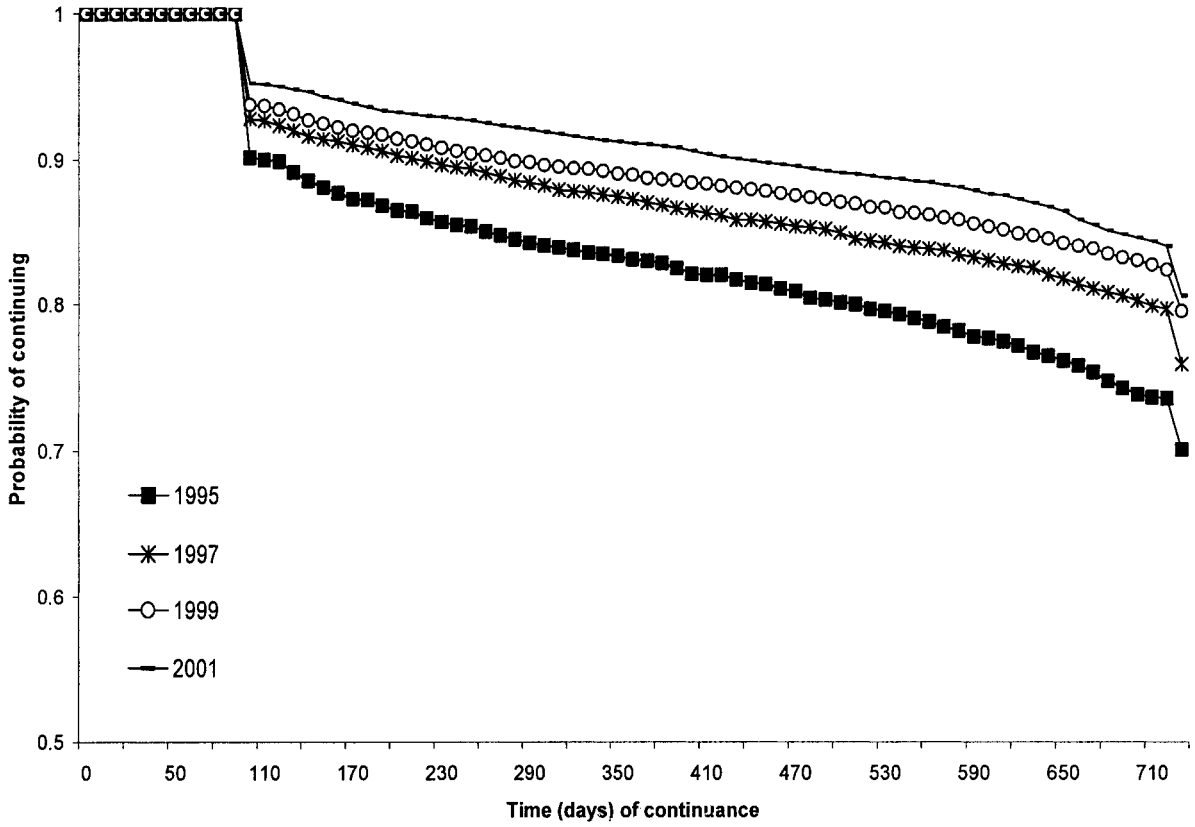

Figure 2—*Probability of continuing antihypertensive therapy within 2 years of initial treatment in patients with diabetes by year.*

less optimal, irrespective of the actual prescribing intent.

In summary, although in previous studies the suboptimal control of blood pressure in individuals with diabetes and the lack of improvement over time has been blamed on physician factors, our data suggest that the prescribing practices of Ontario physicians for their hypertensive elderly patients with diabetes have improved over the past decade. Specifically, we found that, even after adjustments for changes in population demographics, antihypertensive prescribing to patients with diabetes and without other indications for these agents had increased by almost half, discontinuation rates had declined by nearly half, newly treated patients were 52% more likely to be treated with multiple antihypertensive drugs in 2001 than in 1995, and the use of ACE inhibitors as initial therapy increased from 54 to 76% by the end of our study.

Table 2—*Discontinuation of initial prescribed antihypertensive drug class within 2 years of initial prescription, by sex*

Drug class	Drug class–specific discontinuation rates (%)			*P* value for comparison between men and women
	Overall	Women	Men	
ACE inhibitors	44.7	49	41	<0.0001
Angiotensin II receptor blockers	39.4	37	43	0.56
β-Blockers	61.6	61	62	0.72
Calcium channel blockers	53.6	53	55	0.43
Thiazides	70.0	69	71	0.28

Note that drug class–specific discontinuation rates include those patients who discontinued all antihypertensive therapy (as in Fig. 2) plus those patients whose medication was switched from one drug class to another within the study time frame.

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