Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data

Evidence

Études

J. Jaime Caro,*† MD, CM; Jeanne L. Speckman,* MSc; Maribel Salas,* MS, MD; Gabriel Raggio,* ScD; Joseph D. Jackson,‡ PhD

From *Caro Research, Concord, Mass., †the Division of General Internal Medicine, Royal Victoria Hospital, McGill University, Montreal, Que., and ‡the Pharmaceutical Research Institute, Bristol–Myers Squibb, Princeton, NJ

This article has been peer reviewed.

CMAJ 1999;160:41-6

See related articles pages 31 and 64

Abstract

Background: Rational medical decisions should be based on the best possible evidence. Clinical trial results, however, may not reflect conditions in actual practice. In hypertension, for example, trials indicate equivalent antihypertensive efficacy and safety for many medications, yet blood pressure frequently remains uncontrolled, perhaps owing to poor compliance. This paper examines the effect of initial choice of treatment on persistence with therapy in actual practice.

Methods: The authors examined all outpatient prescriptions for antihypertensive medications filled in Saskatchewan between 1989 and 1994 by over 22 000 patients with newly diagnosed hypertension whose initial treatment was with a diuretic, β-blocker, calcium-channel blocker or angiotensin-converting-enzyme (ACE) inhibitor. Rates of persistence over the first year of treatment were compared.

Results: After 6 months, persistence with therapy was poor and differed according to the class of initial therapeutic agent: 80% for diuretics, 85% for β-blockers, 86% for calcium-channel blockers and 89% for ACE inhibitors ($p < 0.001$). These differences remained significant when age, sex and health status in the previous year were controlled for. Changes in the therapeutic regimen were also associated with lack of persistence.

Interpretation: A relation not seen in clinical trials — between persistence with treatment and initial antihypertensive medication prescribed — was found in actual practice. This relation also indicates the importance of real-world studies for evidence-based medicine.

Résumé

Contexte : Les décisions médicales rationnelles doivent reposer sur les meilleures données probantes possibles. Il se peut toutefois que les résultats d'études cliniques ne reflètent pas la réalité. Dans le cas de l'hypertension, par exemple, les études indiquent que de nombreux médicaments ont une efficacité antihypertensive et une sûreté équivalentes, mais la tension artérielle demeure souvent non contrôlée peut-être parce que les patients suivent mal le traitement. Dans ce document, on examine l'effet du choix initial du traitement sur la persévérance dans la réalité.

Méthodes : Les auteurs ont examiné toutes les ordonnances de médicaments antihypertenseurs remplies pour des patients en service externe en Saskatchewan entre 1989 et 1994, et présentées par plus de 22 000 patients chez lesquels on venait de diagnostiquer une hypertension traitée au début au moyen d'un diurétique, d'un β-bloquant, d'un inhibiteur calcique ou d'un inhibiteur de l'enzyme de conversion de l'angiotensine (ECA). On a comparé les taux de persévérance au cours de la première année du traitement.

Résultats : Après six mois, la persévérance face au traitement était médiocre et différait selon la catégorie de l'agent thérapeutique initial : elle atteignait 80 % dans le cas des diurétiques, 85 % dans celui des β-bloquants, 86 % dans celui des inhibiteurs calciques et 89 % dans celui des inhibiteurs de l'ECA ($p <$ 0,001). Ces différences sont demeurées significatives lorsqu'on a tenu compte de l'âge, du sexe et de l'état de santé au cours de l'année précédente. On a aussi établi un lien entre des changements apportés au régime de traitement et le manque de persévérance.

Interprétation : On a constaté dans la réalité un lien qui n'existait pas dans le contexte des études cliniques entre la persévérance face au traitement et le premier médicament antihypertenseur prescrit. Ce lien indique aussi l'importance, pour la médecine fondée sur les données probantes, des études réalisées dans le monde réel.

That clinical decisions should be rational and based on the best evidence possible is the keystone of modern scientific medicine. Finding reality wanting, however, opinion leaders have increasingly called for a more determined effort to ensure that actual practice meets this standard.[1,2] Indeed, the pursuit of evidence-based medicine is now the subject of several journals (e.g., *Evidence-Based Medicine* and *Evidence Based Cardiovascular Medicine*), and criteria for the selection of studies that can provide such evidence have been proposed.[3] Prominent among these criteria is that studies of medical interventions be randomized trials. It has even been suggested that "the ultimate test of the *usefulness* of a drug [is] ideally in randomized, controlled clinical trials"[4] (emphasis ours).

A physician faced with a common — and very well-studied — condition such as hypertension would thus be expected to turn to randomized trials (or corresponding meta-analyses) for guidance regarding the choice of initial treatment. On the basis of this evidence, where trials regularly find similar efficacy in lowering blood pressure and safety among available agents,[5] the physician might be tempted to follow the recommendation of various guidelines to start with the least expensive drugs with proven ability to reduce rates of sickness and death from cardiovascular disease.

Yet, as shown in our accompanying paper[6] (see page 31 of this issue), and elsewhere,[7] results obtained in actual medical practice — even the best, most evidence-based ones — may differ substantially from those of randomized clinical trials. In hypertension, surveys of actual practice have revealed that blood pressure remains uncontrolled in many patients.[8–11] One reason for this appears to be lack of persistence with therapy.[12–14] Whether the type of drug chosen for initial treatment helps determine persistence (perhaps through its tolerability) should therefore be a consideration when making rational decisions about antihypertensive treatment.

Unfortunately, this effect, observable in actual practice, cannot be studied properly in traditional randomized clinical trials because the limitations imposed to increase the validity of efficacy comparisons (e.g., lead-in periods, mandatory close follow-up and informed consent) tend to eliminate the conditions of interest. Moreover, randomized trials tend to be of short duration and to involve relatively small numbers of highly selected patients.

One alternative is to analyse a database that already contains the required information from actual practice. To examine the relation of persistence with treatment to the class of antihypertensive drug chosen initially, we used the databases maintained by Saskatchewan Health, a government department that funds the health care system for this Canadian province.[15]

Methods

The database and methods used to infer the therapeutic regimen are described in our accompanying paper (page 31 of this issue). Of the 79 591 hypertensive patients identified, 22 918 had newly diagnosed hypertension (i.e., they had not received any antihypertensive drug in the previous 10 months), were observed in the database for at least 6 months and received as initial pharmacologic antihypertensive treatment a single drug from 1 of 4 drug classes: diuretic, β-blocker, calcium-channel blocker (CCB) or angiotensin-converting-enzyme (ACE) inhibitor.

For the 22 918 patients, we analysed the antihypertensive prescriptions filled between Nov. 1, 1989, and the date of death or of emigration from the province or Dec. 31, 1994, whichever came first. We determined the therapeutic course for each patient using a specially designed computer program that processes each dispensing record to establish whether a change in regimen occurred: namely, addition of a new drug, deletion of 1 or more drugs, or a switch to 1 or more other drugs.

A patient was classified as persisting with therapy if the last prescription filled during the study period provided sufficient medication to cover the period until the end of observation. In addition, hospitalization data were cross- checked to determine whether lack of persistence was explained by admission to hospital.

Statistical analysis

We performed all statistical analyses using SAS-Windows (version 6.12, SAS Institute, Inc., Cary, NC). Comparisons were tested with Fisher's exact test, the χ^2 test, Wilcoxon's rank-sum test, the Kruskal–Wallis test and analysis of variance, where appropriate. Since patients began treatment at different times during the study period and thus were followed for differing lengths of time, we used Kaplan–Meier failure time analyses[16] to estimate the cumulative persistence rate, with patients being censored at the end of their observation time if they persisted with therapy. Differences in persistence rates were assessed with the log-rank test. In analyses where only persistence over a defined period was considered, we used logistic regression analysis to compare pairs of drug classes, controlling for other determinants that could confound the relation with initial drug class. These potential confounders included age, sex and health status in the year before beginning antihypertensive therapy. We used 3 measures of health status: the number of physician visits, the number of hospital admissions and the number of prescriptions for drugs other than antihypertensive agents. All continuous factors were modelled with the use of indicator variables.

Results

Of the 22 918 patients, 9659 (42%) received a diuretic as the index drug, 7241 (32%) an ACE inhibitor , 3305 (14%) a calcium-channel blocker and 2713 (12%) a β-blocker. Patients initially prescribed a diuretic were more frequently older and female (Table 1). Those starting with a calcium-channel blocker or diuretic had more physician visits, hospital admissions and prescriptions for medications other than antihypertensive agents in the preceding year. The study observation time, which by definition ranged from 6 months to 5 years, was similar across the index drug classes.

In general, persistence with antihypertensive therapy was poor: 6 months after starting treatment 84% of the patients persisted. This picture differed according to the index drug class (Fig. 1). In addition, 17% to 19% of the patients persisted with treatment regimens that were somewhat or completely different from the index drug. If the status of each patient at the end of their observation time is considered, only 58% were persistent, and in each class more than two-thirds of patients who persisted with therapy were not receiving their original class of drug.

These crude proportions may be misleading, however, because they do not take varying observation times into account. Fig. 2 shows the cumulative persistence according to index drug class. Patients initially prescribed diuret-

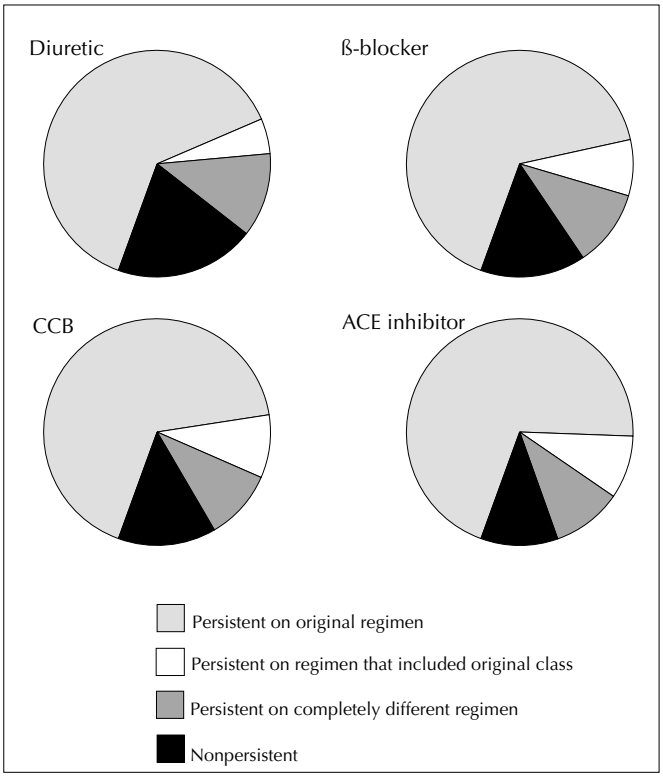


Fig. 1: Distribution of antihypertensive regimens by class of index drug after 6 months of therapy for patients with newly diagnosed hypertension in Saskatchewan in 1989–1994. CCB = calcium-channel blocker, ACE inhibitor = angiotensin-converting-enzyme inhibitor.

Table 1: Characteristics of patients with newly diagnosed hypertension in Saskatchewan in 1984–1994 by initial drug class

	Initial drug class				
Characteristic	Overall *n = 22 918*	Diuretic *n = 9 659*	β-blocker *n = 2 713*	CCB *n = 3 305*	ACE inhibitor *n = 7 241*
Median age at diagnosis, yr	63	65	58	64	61
% males	43	35	46	49	50
Median no. of physician visits in previous year	7	7	6	7	6
Mean no. of hospital admissions in previous year per 100 patients (and SD)	30 (74)	33 (79)	26 (74)	35 (77)	25 (64)
Mean no. of prescriptions other than antihypertensive agents in previous yr per 10 patients (and SD)	39 (37)	42 (37)	36 (36)	40 (38)	36 (36)
Mean length of follow-up (and SD), d	1 077 (501)	1 099 (513)	1 145 (507)	1 079 (488)	1 021 (484)

Note: CCB = calcium-channel blocker, ACE = angiotensin-converting enzyme, SD = standard deviation.

ics exhibited the lowest persistence over the first 6 months (80% [95% confidence interval (CI) 79% to 81%]). The values for those initially prescribed β-blockers, calcium-channel blockers and ACE inhibitors were 85% (95% CI 84% to 86%), 86% (95% CI 84% to 87%) and 89% (95% CI 88% to 90%) respectively. By 4.5 years of observation, only 40% of patients initially prescribed diuretics persisted, as compared with 49% of those prescribed β-blockers, 47% of those prescribed calcium-channel blockers and 53% of those prescribed ACE inhibitors. The persistence curves were significantly different ($p < 0.001$).

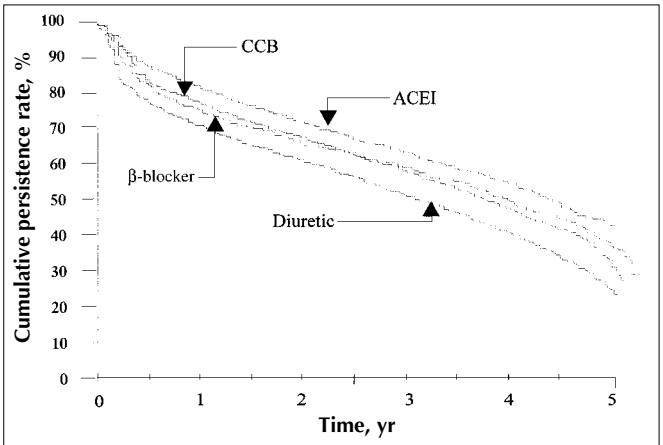
To explore possible confounding by imbalances in patient characteristics among index drug classes, we performed a logistic regression analysis addressing persistence during the first year among the 20 531 patients observed at least 1 year (Table 2). The initial drug class remained significantly associated with the likelihood of persistence after adjustment for age, sex, and the number of physician visits, hospital admissions and prescriptions of medications other than antihypertensive agents in the year before beginning antihypertensive therapy.

Given the rapid early decrease in the proportion of patients who persisted with treatment, we examined the period of the first 3 antihypertensive prescriptions. Of the patients whose index drug was a diuretic, 27% did not persist beyond 3 prescriptions (Fig. 3), accounting for more than half of the lack of persistence. The corresponding values for β-blockers, calcium-channel blockers and ACE inhibitors were 20%, 16% and 13%. In logistic regression analysis in which we included the same factors as previously, ACE inhibitors remained significantly different from all other classes.

When the data for patients who stopped treatment early on were excluded from analysis, substantial nonpersistence remained: 29% of those who filled at least 4 prescriptions eventually stopped taking antihypertensive agents. Although the differences between drug classes diminished, they did not disappear: patients beginning with an ACE inhibitor remained most likely to persist ($p < 0.001$).

We next examined the possibility that turbulence in the therapeutic regimen decreased persistence. Therapeutic turbulence was expressed as the number of changes (i.e., addition of a new drug, dropping of 1 or more drugs or a switch to 1 or more other drugs) occurring in 6-month intervals from the time of the index prescription. Patients with therapeutic turbulence consistently exhibited a lower level of persistence. For example, the risk of not persisting in the second 6 months was higher among patients with 1 change in the first 6 months (risk ratio 1.07 [95% CI 0.94 to 1.22]) than among those with no change. For patients with 2 or more changes in the first 6 months the likelihood of not persisting was still higher (risk ratio 1.25 [95% CI 1.12 to 1.37]); this difference was statistically significant ($p < 0.05$) and remained so throughout the first 3 years of observation but not consistently thereafter.

Patients who are not persistent at the end of observation may still return to treatment. The longer the period of nonpersistence, the more likely it is that the patient has stopped treatment. Conversely, a short gap between prescriptions may mean simply that the patient has temporarily run out of medication. We found that the mean duration of nonpersistence was 550 days, which suggests that most of these patients had truly stopped treatment.



ACEI				
Not persistent	1182	560	361	243
n	5498	3964	2357	1239
CCB				
Not persistent	634	262	214	151
n	2463	1842	1230	627
ß-blocker				
Not persistent	595	133	126	126
n	1962	1497	1073	600
Diuretic				
Not persistent	2474	787	618	519
n	6618	4884	3460	1852

Fig. 2: Cumulative rate of persistence with antihypertensive therapy by index drug class. The table shows the number of patients who stopped persisting each year and the number of patients observed at least that long. Patients who persisted with therapy to the end of their observation time were censored on the last day of their follow-up.

Table 2: Odds ratio of persistence with antihypertensive therapy through the first year compared with patients who initially received diuretics

	Odds ratio (and 95% confidence interval)	
Initial drug class	Crude	Adjusted*
β-blocker	1.18 (1.06–1.31)	1.25 (1.12–1.39)
CCB	1.45 (1.30–1.61)	1.51 (1.36–1.69)
ACE inhibitor	1.82 (1.67–1.98)	1.92 (1.76–2.09)

*Adjusted for age (< 60 yr, or ≥ 60 yr), sex and, in the previous year, the number of physician visits (< 8, or ≥ 8), hospital admissions (none, or ≥ 1) and prescriptions for medications other than antihypertensive agents (< 4, or ≥ 4).

Exclusion of the 7% who lapsed for less than 14 days did not alter the results.

Interpretation

We examined comprehensive dispensing and long-term follow-up data for a stable North American population. Two main findings emerged. First, a remarkably high proportion of patients with newly diagnosed hypertension stopped taking their antihypertensive medication within a relatively short time. Second, whether a patient stopped treatment seemed to depend on the class of antihypertensive drug prescribed initially: patients beginning with a diuretic were the least persistent, and those starting with an ACE inhibitor were the most persistent. Moreover, persistence was inversely related to therapeutic turbulence. These findings in actual clinical practice appear to challenge the recommendations, emerging from clinical trial evidence,[17–19] that diuretics and β-blockers should be prescribed first and that subsequent changes be made if patients experience difficulty with the initial choice of medication (i.e., the stepped-care approach).

It is unclear why patients do not persist in taking their medication and why there are differences in persistence among drug classes. One possible explanation for the latter may be class-related side effects. Thus, the higher persistence rates observed with ACE inhibitors may reflect their reported good tolerability.[20]

Alternatively, our findings may be the result of imbalances in other determinants of outcome (confounders). Although both age and sex differed among the drug classes, the relation of persistence to initial drug class remained significant when these variables were controlled for. Another potential confounder is the occurrence of "white-coat hypertension."[21,22] For this factor to explain the differential persistence among drug classes, however, one would have to assume that physicians who suspect it, and thus are prone to stop treatment early on, preferentially prescribe diuretics or β-blockers. It seems unlikely that this mechanism would entirely explain the large observed differences between the drug classes. Coexisting illnesses or health status may also influence the relation between persistence and drug class. We used the number of physician visits, hospital admissions and prescriptions for medications other than antihypertensive agents in the year preceding antihypertensive therapy as a proxy for health status, and controlling for these variables did not remove or even attenuate the significance of the relation.

Differences in drug costs are often assumed to affect compliance. In our study, however, the less expensive medications, the diuretics, were associated with the lowest levels of persistence, and the generally more expensive medications, calcium-channel blockers and ACE inhibitors, were associated with the highest levels of persistence. These findings suggest that cost does not explain the relation observed.

No blood pressure data were available to confirm the diagnosis of hypertension. In their place, we used the physician's recorded diagnosis, confirmed by the recorded dispensing of at least 1 antihypertensive drug. Although not specific to hypertension, there has been extensive reported validation of the Saskatchewan health care database.[15,23,24] Therefore, it is unlikely that large numbers of patients would be misclassified as having hypertension.

Although therapeutic efficacy could not be directly addressed, it is assumed that discontinuation of antihypertensive treatment is a negative event because these patients are likely to remain with uncontrolled hypertension and thus be at greater risk for cardiovascular disease.

Many studies of compliance with antihypertensive therapy have been performed; however, few investigators have studied the actual practice setting with an unrestricted choice of medication. None of the studies is directly comparable to our study, for several reasons. Most important, they were not limited to patients with newly diagnosed disease. Other reasons include short follow-up, small sample or failure to exclude patients with coexisting conditions that may have affected treatment decisions.[25–30] A recent study involving patients with newly diagnosed hypertension gave results similar to ours but was limited to an elderly population.[31]

Despite the potential limitations of our study, the results provide cause for concern. First, it seems that the desired goal of keeping hypertensive patients on treatment is not being achieved adequately in actual practice. Second, the results suggest that recommendations to begin treatment with diuretics or β-blockers may result in less persis-

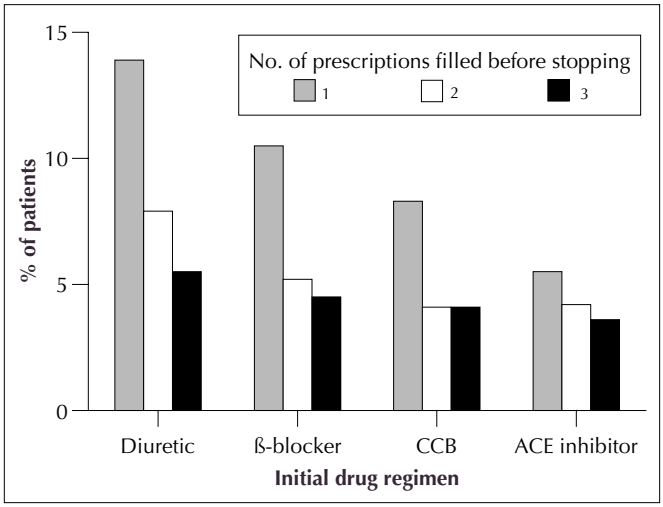


Fig. 3: Proportion of patients who stopped antihypertensive treatment before filling 4 prescriptions, by index drug class.

tence with therapy, despite the demonstrated efficacy of these drugs in clinical trials. Perhaps patients are less forgiving of therapeutic trial and error, particularly in the setting of a largely asymptomatic condition. Our findings suggest that to maximize the likelihood of achieving blood pressure control and, therefore, long-term reduction in cardiovascular risk, a physician might consider selecting an ACE inhibitor as initial therapy. The choice of other drug classes may carry greater potential for loss of effectiveness over time. It remains to be seen whether newer agents with yet greater tolerability will fulfil their promise to increase effectiveness further.

The randomized controlled clinical trial is the cornerstone of the scientific method for determining whether an intervention can work to improve health. However, the relations seen in our examination of real-world data may not be evident in the clinical trial environment. Nevertheless, data such as ours are vital in order to make rational medical decisions in the less-controlled world of actual practice. Additional evidence of this kind, gathered through investigation of real-world conditions, may meaningfully inform guideline development and perhaps decisions in the actual practice setting.

We thank Winanne Downey, BSP, and Scott Livingstone, BSP, of Saskatchewan Health, for help in defining the dataset. We also thank Ralph Kent, MD, Kenneth Flegel, MD, Pablo LaPuerta, MD, Gilbert L'Italien, PhD, M. McGregor, MD, and M. Osbakken, MD, for their comments on the paper.

This work was supported in part by grants from Bristol–Myers Squibb Pharmaceutical Research Institute and Sanofi Pharmaceutical Inc. This study is based in part on data provided by Saskatchewan Health. The interpretation and conclusions contained herein do not necessarily represent those of the government of Saskatchewan or Saskatchewan Health.

Competing interests: Dr. Caro, Ms. Speckman and Dr. Raggio have received grants from pharmaceutical companies for conducting research in this area. Dr. Salas declared no competing interests. Dr. Jackson is employed by Bristol–Myers Squibb Pharmaceutical Research Institute.

References

1. Hiatt H, Goldman L. Making medicine more scientific. *Nature* 1994;371:100.
2. Gibaldi M. Evidence based medicine and cost effectiveness. *Univ Wash Pharm Outcomes Res Policy Program Rep* 1997;3:1-3.
3. Purpose and procedure. *Evidence Based Med* 1996;1:98-9.
4. Sobel B, Furberg C. Surrogates, semantics, and sensible public policy. *Circulation* 1997;95:1661-3.
5. Neaton JD, Grimm RH, Prineas RJ, Stamier J, Grandits GA, Elmer PJ, et al. Treatment of mild hypertension study. Final results. *JAMA* 1993;270:713-24. [Leanne looked this ref up for Myers; 4th author is Stamler; also "Treatment of Mild Hypertension Study" is a formal name, and MEDLINE lists "Treatment of Mild Hypertension Study Research Group" at the end of the title]
6. Caro JJ, Salas M, Speckman JL, Raggio GD, Jackson JD. Persistence with treatment for hypertension in actual practice. *CMAJ* 1999;160:31-7
7. Andrade SE, Walker AM, Gottlieb LK, Hollenberg NK, Testa MA, Saperia GM, et al. Discontinuation of antihyperlipidemic drugs — Do rates reported in clinical trials reflect rates in primary care settings? *N Engl J Med* 1995;332:1125-31.
8. Mancia G, Sega R, Milesi C, Cesana G, Zanchetti A. Blood pressure control in the hypertensive population. *Lancet* 1997;349:454-7.
9. Marques-Vidal P, Tuomilehto J. Hypertension awareness, treatment and control in the community: Is the "rule of halves" still valid? *J Hum Hypertens* 1997;11:213-20.
10. Goldstein AO, Carey TS, Levis D, Madson S, Bernstein J. Variations in hypertension control in indigent rural primary care clinics in North Carolina. *Arch Fam Med* 1994;3:514-19.
11. Stockwell DH, Madhavan S, Cohen H, Gibson G, Alderman MH. The determinants of hypertension awareness, treatment and control in an insured population. *Am J Public Health* 1994;84:1768-74.
12. Black DM, Brand RJ, Greenlick M, Hughes G, Smith J, for the SHEP Pilot Research Group. Compliance to treatment for hypertension in elderly patients: the SHEP pilot study. *J Gerontol* 1987;42:552-7.
13. Hershey JC, Morton BG, Davis JB, Reichgott MJ. Patient compliance with antihypertensive medication. *Am J Public Health* 1980;70:1081-9.
14. Nelson EC, Stason WB, Neutra RR, Solomons HS. Identification of the noncompliant hypertensive patient. *Prev Med* 1980;9:504-17.
15. Malcolm E, Downey W, Stand LM, McNutt M, West R. Saskatchewan Health's linkable data bases and pharmacoepidemiology. *Post Mark Surveillance* 1993;6:175-264.
16. Kalbfleisch JD, Prentice RL. *The statistical analysis of failure time data*. New York: John Wiley & Sons; 1980. p. 10-9.
17. Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. The fifth report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC-V). *Arch Intern Med* 1993;153:154-83.
18. Ogilvie RI, Burgess ED, Cusson JR, Feldman RD, Leiter LA, Myers MG. Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of essential hypertension. *CMAJ* 1993;149:575-84.
19. National High Blood Pressure Education Program Working Group. National High Blood Pressure Education Program Working Group Report on hypertension in the elderly. *Hypertension* 1994;23:275-85.
20. Williams GH. Hypertensive vascular disease. In: Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fanci AS, Kasper DL, et al, editors. *Harrison's principles of internal medicine*. New York: McGraw-Hill; 1994.
21. Reeves RA. Does this patient have hypertension? How to measure blood pressure. *JAMA* 1995;273:1211-8.
22. Pierdomenico SD, Mezzetti A, Lapenna D, Guglielmi MD, Mancini M, Salvatori I, et al. "White-coat" hypertension in patients with newly diagnosed hypertension: evaluation of prevalence by ambulatory monitoring and impact on cost of health care. *Eur Heart J* 1995;16:692-7.
23. Rawson NS, Malcolm E. Validity of the recording of ischaemic heart disease and chronic obstructive pulmonary disease in the Saskatchewan health care datafiles. *Stat Med* 1995;14:2627-43.
24. Rawson NS, Malcolm E, D'Arcy C. Reliability of the recording of schizophrenia and depressive disorder in the Saskatchewan health care datafiles. *Soc Psychiatry Psychiatr Epidemiol* 1997;32:191-9.
25. Jones JK, Gorkin L, Lian JF, Staffa JA, Fletcher AP. Discontinuation of and changes in treatment after start of new courses of antihypertensive drugs: a study of a United Kingdom population. *BMJ* 1995;311:293-5.
26. Hamilton RA, Briceland LL. Use of prescription-refill records to assess patient compliance. *Am J Hosp Pharm* 1992;49:1691-6.
27. Elliott WJ. Discontinuation rates for ACE inhibitors and calcium antagonists in a tertiary hypertension clinic [abstract]. *Am J Hypertens* 1993;6:94A.
28. Shea S, Misra D, Ehrlich MG, Field L, Francis CK. Correlates of nonadherence to hypertension treatment in an inner-city minority population. *Am J Public Health* 1992;82:1607-12.
29. Sharkness CM, Snow DA. The patient's view of hypertension and compliance. *Am J Prev Med* 1992;8:141-6.
30. Cooper JK, Love DW, Raffoul PR. Intentional prescription nonadherence (noncompliance) by the elderly. *J Am Geriatr Soc* 1982;30:329-33.
31. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J. The effects of initial drug choice and comorbidity on antihypertensive therapy compliance: results from a population-based study in the elderly. *Am J Hypertens* 1997;10(7 pt 1):697-704.

Reprint requests to: *Dr. J. Jaime Caro, 336 Baker Ave., Concord MA 01742, USA; fax 978 371-2445; jcaro@caroresearch.com*