

Stroke

American Stroke
AssociationSM

JOURNAL OF THE AMERICAN HEART ASSOCIATION

A Division of American
Heart Association



Applying the Evidence: Do Patients With Stroke, Coronary Artery Disease, or Both Achieve Similar Treatment Goals?

Gustavo Saposnik, Shaun G. Goodman, Lawrence A. Leiter, Raymond T. Yan, David H. Fitchett, Neville H. Bayer, Amparo Casanova, Anatoly Langer, Andrew T. Yan, for the Vascular Protection (VP), Guidelines-Oriented Approach to Lipid-Lowering (GOALL) Registries Investigators and on behalf of the Stroke Outcome Research Canada (SORCan) Working Group

Stroke 2009;40;1417-1424; originally published online Feb 12, 2009;

DOI: 10.1161/STROKEAHA.108.533018

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214
Copyright © 2009 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online
ISSN: 1524-4628

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://stroke.ahajournals.org/cgi/content/full/40/4/1417>

Subscriptions: Information about subscribing to Stroke is online at
<http://stroke.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters
Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax:
410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Applying the Evidence

Do Patients With Stroke, Coronary Artery Disease, or Both Achieve Similar Treatment Goals?

Gustavo Saposnik, MD, MSc, FAHA; Shaun G. Goodman, MD, MSc; Lawrence A. Leiter, MD; Raymond T. Yan, MD; David H. Fitchett, MD; Neville H. Bayer, MD; Amparo Casanova, MD, PhD; Anatoly Langer, MD, MSc; Andrew T. Yan, MD; for the Vascular Protection (VP),* Guidelines-Oriented Approach to Lipid-Lowering (GOALL) Registries Investigators,* and on behalf of the Stroke Outcome Research Canada (SORCan) Working Group

Background and Purpose—The importance of early and aggressive initiation of secondary prevention strategies for patients with both coronary artery disease (CAD) and cerebrovascular disease (CVD) is emphasized by multiple guidelines. However, limited information is available on cardiovascular protection and stroke prevention in an outpatient setting from community-based populations. We sought to evaluate and compare differences in treatment patterns and the attainment of current guideline-recommended targets in unselected high-risk ambulatory patients with CAD, CVD, or both.

Methods—This multicenter, prospective, cohort study was conducted from December 2001 to December 2004 among ambulatory patients in a primary care setting. The prospective Vascular Protection and Guidelines-Oriented Approach to Lipid-Lowering Registries recruited 4933 outpatients with established CAD, CVD, or both. All patients had a complete fasting lipid profile measured within 6 months before enrollment. The primary outcome measure was the achievement of blood pressure (BP) <140/90 mm Hg (or <130/80 mm Hg for patients with diabetes) and LDL cholesterol <2.5 mmol/L (<97 mg/dL) according to the Canadian guidelines in place at that time (similar to the National Cholesterol Education Program's value of 100 mg/dL). Secondary outcomes include use of antithrombotic, antihypertensive, and lipid-modifying therapies.

Results—Of the 4933 patients, 3817 (77%) had CAD only; 647 (13%) had CVD only; and 469 (10%) had both CAD and CVD. Mean±SD age was 67±10 years, and 3466 (71%) were male. Mean systolic and diastolic BPs were 130±16 and 75±9 mm Hg, respectively. Minor but significant differences were observed on baseline BP, total cholesterol, and LDL cholesterol measurements among the 3 groups. Overall, 83% of patients were taking a statin and 93% were receiving antithrombotic therapy (antiplatelet and/or anticoagulant agents). Compared with patients with CAD, those with CVD only were less likely to achieve the recommended BP (45.3% vs 57.3%, respectively; $P<0.001$) and lipid (19.4% vs 30.5%, respectively; $P<0.001$) targets. Among patients with CVD only, women were less likely to achieve the recommended BP and lipid targets compared with their male counterparts (for LDL cholesterol <2.5 mmol/L, 18.7% vs 23.8%, respectively; $P=0.048$). In multivariable analysis, patients with CVD alone were less likely to achieve treatment success (BP or lipid targets) after adjusting for age, sex, diabetes, and use of pharmacologic therapy.

Conclusions—Despite the proven benefits of available antihypertensive and lipid-lowering therapies, current management of hypertension and dyslipidemia continues to be suboptimal. A considerable proportion of patients failed to achieve guideline-recommended targets, and this apparent treatment gap was more pronounced among patients with CVD and women. Quality improvement strategies should target these patient subgroups. (*Stroke*. 2009;40:1417-1424.)

Key Words: cardiovascular disease ■ stroke ■ diabetes ■ dyslipidemia ■ prevention ■ treatment ■ guidelines

Received July 28, 2008; final revision received August 27, 2008; accepted September 8, 2008.

From the Canadian Heart Research Centre and Terrence Donnelly Heart Centre, Division of Cardiology, University of Toronto, Canada (R.T.Y., S.G.G., D.H.F., A.L., A.T.Y.); and Division of Endocrinology and Metabolism, St. Michael's Hospital, University of Toronto (L.A.L.); Canadian Heart Research Centre (A.C.), University of Toronto, Canada; Stroke Research Unit, Mobility Program, Division of Neurology, Department of Medicine, St. Michael's Hospital, University of Toronto, Canada (G.S., N.H.B.); and Health Policy Management and Evaluation (HPME), University of Toronto and Institute of Evaluative Clinical Sciences (ICES), Canada (G.S.).

*A list of participating VP and GOALL Investigators may be found in the Supplemental Appendix, available online at <http://stroke.ahajournals.org>. Correspondence to Dr Gustavo Saposnik, Stroke Research Unit, St. Michael's Hospital, Division of Neurology, 55 Queen St E, Room 93, Toronto, Ontario, Canada M5C 1R6. E-mail saposnikg@smh.toronto.on.ca

© 2009 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.108.533018

Cardiovascular diseases are a major cause of morbidity and mortality, and their prevalence will continue to increase as the population ages.¹ For example, according to Statistics Canada, a 75% increase in the prevalence of cardiovascular disease is expected among those 80 years and older in the next 2 decades,² with important implications for public health and resource utilization. Professional cardiovascular associations worldwide, including the American Heart Association, American College of Cardiology, and the Canadian Cardiovascular Society, have established guidelines to stress the importance of risk factor assessment and management.^{3,4} These guidelines are based on convincing evidence from clinical trials conducted during the past decade, which have demonstrated an important reduction in cardiovascular morbidity and mortality with antihypertensive and LDL cholesterol (LDL-C)-lowering therapies.⁵⁻⁷ Furthermore, the benefits of treatment appear more pronounced among patients with established cardiovascular disease or in those at high risk of developing cardiovascular disease. Therefore, the Canadian Guidelines for the Management of Dyslipidemia and Hypertension and the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines, revised in 2001, continue to focus on LDL-C as the primary therapeutic target and recommend individualized treatment goals tailored to the estimated cardiovascular risk.⁸⁻¹⁰ However, despite the well-established efficacy of lipid-modifying and antihypertensive therapy, limited data are available on guideline attainment in ambulatory patients with known cardiovascular disease who are at the highest risk of a recurrent vascular event.

We herein aimed to compare (1) whether attainment of the recommended blood pressure (BP; <140/90 mm Hg, or 130/80 mm Hg in patients with coexisting diabetes) and LDL-C (<2.5 mmol/L [97 mg/dL], which was the LDL-C target at the time these registries were undertaken) targets are similar in ambulatory high-risk patients with cerebrovascular disease (CVD), coronary artery disease (CAD), or both; (2) sex differences in attainment of guideline-recommended targets for patients with CVD; and (3) treatment patterns and their relation to the targets achieved.

Patients and Methods

Study Design

The Vascular Protection (VP) and Guidelines-Oriented Approach to Lipid-Lowering (GOALL) registries are 2 Canadian national registries whose aim was to examine clinical management practices and to identify gaps between patient care recommended in the guidelines and that delivered in the "real world" from December 2001 to December 2004. We recruited physicians across Canada through direct mail or fax campaigns, scientific meetings, continuing medical education events, and investigator meetings in previous or other ongoing registries organized by the Canadian Heart Research Centre. Primary care physicians were invited to participate regardless of their prescribing patterns. Overall, 278 physicians participated in the VP Registry and 254 participated in the GOALL Registry. Participation in the registries was completely voluntary, and all enrolled patients gave written, informed consent. Further details have been published elsewhere.^{11,12} The present study is a cross-sectional analysis of the prospective, observational VP and GOALL Registries including participants with CAD (n=3817), CVD (n=647), or both (n=469).

Patient Population

Both registries aimed to enroll patients at high risk for or those with established cardiovascular disease and used similar inclusion criteria, including CAD, peripheral arterial disease, and/or CVD, according to standard definitions.^{11,12} CAD was defined as prior coronary artery bypass surgery or percutaneous coronary intervention, previous documentation of myocardial infarction or unstable angina, or stable angina with positive stress test or >50% stenosis of at least 1 major coronary artery on angiography. Peripheral arterial disease included a history of intermittent claudication, decreased pulses or bruit with ankle-brachial index <0.90, or abnormal duplex ultrasound findings (>50% stenosis in ≥ 1 major artery). CVD was defined as previous stroke or transient ischemic attack. In the VP Registry, diabetic patients with at least 1 other cardiovascular risk factor (systolic BP >160 mm Hg, diastolic BP >90 mm Hg, or use of antihypertensive medication; total cholesterol [TC] >5.2 mmol/L or HDL-C <0.9 mmol/L; current cigarette smoking; microalbuminuria) were eligible. The GOALL Registry also included any diabetic patients, and elderly patients (age >65 years) with 2 or more risk factors (as stated earlier). The presence of diabetes was determined on the basis of current standard laboratory diagnostic criteria, previous diagnosis of diabetes by a physician, or the use of antihyperglycemic medications or insulin. There were no specific exclusion criteria, and participating physicians were instructed to enroll consecutive eligible patients. The present study focused on the 5791 patients with established cardiovascular disease (CAD, CVD, or both).

Data Collection

On standardized case report forms, the participating physicians collected data on patient demographics, vascular risk factors, past history of atherosclerotic diseases (as detailed earlier), medication use, height, weight, heart rate, BP, and routine blood work. Lipid-modifying medications included statins, cholesterol absorption inhibitors, fibrates, niacin, and bile acid sequestrants. Antihypertensive medications included diuretics, β -blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.

Plasma lipid profile was measured in commercial laboratories as in routine clinical practice. Patients with familial hypercholesterolemia (TC >9.4 mmol/L, LDL-C >6.8 mmol/L), as well as those with a triglyceride level [TG] >4.5 mmol/L [400 mg/dL], which precluded accurate calculation of LDL-C level by the Friedewald formula¹³ and those without a complete lipid profile of fasting TC, LDL-C, HDL-C, and TG measured on the same day were excluded in the present analysis (n=858, 14.8%). Thus, the final study population consisted of 4933 patients.

Completed case report forms were scanned into an electronic database (Teleform, version 7.0, Cardiff, San Diego, Calif) at the Canadian Heart Research Centre. Queries for incomplete or unclear data on case report forms were sent to the study investigators. Two independent ethics review boards approved the study protocols.

Outcome Measures

Both NCEP ATP III and Canadian guidelines in place at the time of the registries recommended a very similar target for LDL-C (<2.6 mmol/L [100 mg/dL] and <2.5 mmol/L [97 mg/dL], respectively) for these high-risk patients (all 3 groups).⁹ A TC to HDL-C ratio <4.0 is a secondary lipid target as stated in the Canadian guidelines.⁹ According to the Canadian Hypertension Society and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the optimal BP was <140/90 mm Hg for nondiabetic patients and <130/80 mm Hg for diabetic patients.

In this study, the primary outcome measure was attainment of the recommended LDL-C goal <2.5 mmol/L (97 mg/dL) and BP <140/90 mm Hg (<130/80 mm Hg for diabetic patients) or a composite treatment success of both LDL-C and BP. Secondary outcome measures include use of antithrombotic, antihypertensive, and lipid-lowering agents, and "optimal therapy" was defined as the combi-

Table 1. Demographic and Clinical Characteristics

	All Patients (n=4933)	Patients With CAD Only (n=3817)	Patients With Concomitant CAD and CVD (n=469)	Patients With CVD Only (n=647)
Age, y, mean±SD	67±11	66±11	72±9	69±10
Female, %	28.8	26.2	32.5	42.2
Hypertension, %	54.7	51.5	63.5	67.2
Diabetes, %	37.2	35.8	45.2	40.0
Stable angina, %	37.3	42.8	44.8	0†
Previous myocardial infarction, %	48.6	56.2	53.9	0†
Current smoker, %	12.9	12.2	12.2	17.6
Prior PCI, %	20.9	25.0	16.0	0†
Prior CABG, %	26.8	30.4	34.1	0†
Heart failure, %	11.4	11.7	17.7	5.0
Peripheral arterial disease, %	12.2	9.9	29.2	13.8
Family history of premature cardiovascular disease	38.9	40.6	40.4	27.5
Transient ischemic attack, %	12.8	0†	62.7	51.8
Stroke, %	12.0	0†	46.3	58.3
Hospitalization in the past 6 months before enrollment	12.7	13.6	13.3	7.2
Chronic kidney disease	28.7	25.9	44.7	33.5
Heart rate, bpm*	70 (64,76)	70 (64, 75)	70 (64, 76)	72 (68, 80)
Systolic BP, mm Hg*	130 (120,140)	130 (120, 140)	130 (120, 140)	130 (122, 140)
Diastolic BP, mm Hg*	76 (70, 80)	76 (70, 80)	75 (70, 80)	78 (70, 80)
BMI*	28.5 (25.6, 32)	28.6 (25.7, 32.0)	28.4 (25.5, 31.9)	28.1 (25.3, 31.9)

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; and BMI, body mass index. Chronic kidney disease was defined as creatinine clearance <60 mL/min.

*Median and 25th and 75th percentiles.

†According to the stratification of patients into 3 mutually exclusive groups.

nation of prescribed antithrombotic therapy and achievement of both lipid and BP targets.

Data Analysis

The study population was stratified into 3 mutually exclusive groups: (1) patients with CAD only; (2) patients with CVD only; and (3) patients with both CAD and CVD (group CAD+CVD). The dose of statin was classified as low, standard, or high, according to previously published LDL-C reduction comparison charts.^{11,12} To determine sex-related differences in the care of CVD patients, both the CVD group and the CAD+CVD group were combined.

Continuous variables were summarized as medians with 25th and 75th percentiles or mean±SD for normally distributed data, and group comparisons were made with the *t* test or ANOVA. Tukey’s honestly significant test was used for post hoc pairwise comparisons. Categorical variables are presented as percentage and were compared by χ^2 test. We performed multivariable logistic-regression analysis to determine the factors associated with achievement of BP and lipid targets. Based on the results of prior studies^{14,16,17} and bivariate analyses, the predictor variables considered in the models were age, sex, diabetes, prior coronary revascularization, history of heart failure, obesity, and use of antihypertensive, statin, and other lipid-modifying drugs.¹⁸ We report adjusted odds ratios with 95% CIs. Model discrimination was assessed by the c-statistic (area under the receiver-operating characteristic curve) and calibration by the Hosmer-Lemeshow goodness-of-fit test. We performed statistical analyses with SPSS version 12.0 (SPSS Inc, Chicago, Ill). A 2-sided probability value of <0.05 was considered statistically significant.

Results

Of the 4933 patients in the present analysis, 3817 (77.3%) had CAD only,, 647 (13.1%) had established CVD only, and

469 (9.5%) had coexisting CAD and CVD. Their demographic and clinical characteristics are summarized in Table 1. Overall, there was a high prevalence of cardiovascular risk factors such as diabetes, hypertension, and obesity. More than 12% of patients were still smoking. Patients with CVD were older and had a higher prevalence of hypertension and smoking compared with those without CVD. Women with CVD had higher systolic BP than their male counterparts (135.2 vs 132.3 mm Hg, *P*=0.006). However, there were no differences in diastolic BP or body mass index between men and women.

Medication Profile

Lipid-Lowering Therapy

Overall, 4167 patients (84.5%) were prescribed at least 1 lipid-modifying drug, with 4096 (98.2%) and 837 (1.8%) receiving statin and nonstatin therapy, respectively (Table 2). The majority of patients (60.3%) were taking a standard dose of statin, 9.4% were taking a low dose, and 13.2% were taking a high dose (see supplemental Table I and footnote for details, available online at <http://stroke.ahajournals.org>). Patients with CVD alone were less frequently given statin or nonstatin therapy (*P*<0.001). Among patients taking a statin, a lower proportion in the CVD group were prescribed a high dose (*P*=0.01). Atorvastatin (n=2124) was the most commonly used lipid-lowering agent. Women were less likely to

Table 2. Outcome Measures by Patient Groups

Outcome Measures	All Patients (n=4933)	CAD Only (n=3817)	CAD+CVD (n=469)	CVD Only (n=647)	P Value (3-Group Comparisons)
Primary					
Achieved LDL-C <2.5 mmol/L, %	50.6	52.0*	53.9*	40.5	<0.001
Achieved BP <140/90 mm Hg (or <130/80 for diabetics), %	54.7	57.3*	45.3	46.0	<0.001
Achieved BP <140/90 mm Hg (or <130/80 mm Hg for diabetic patients) and LDL-C <2.5 mmol/L, %	28.6	30.5*	25.6*	19.4	<0.001
Secondary					
Statin use, %	83.0	84.4*	81.0*	76.5	<0.001
Use of any lipid-modifying agent, %	84.5	85.7*	82.3	78.7	<0.001
Antithrombotic therapy, %	93.0	93.3	92.5	91.3	0.18
Antihypertensive therapy, %	92.0	93.1	93.8	83.6	<0.001
Optimal care†	27.2	20.3*	23.5*	17.7	<0.001

Recommended target in the Canadian Dyslipidemia guidelines is LDL-C <2.5 mmol/L (equivalent to LDL-C 97 mg/dL, similar to NCEP ATP III Expert Panel LDL-C of <100 mg/dL).

* $P<0.01$ for post hoc pairwise comparisons with the CVD-only group.

†Optimal care defined as BP <140/90 mm Hg (or <130/80 mm Hg for persons with diabetes), LDL-C <2.5 mmol/L, and treated with antithrombotic therapy.

be treated with statins than men (80.4% vs 84%, respectively; $P=0.002$).

Antihypertensive Therapy

Overall, 4471 patients (90.6%) were prescribed at least 1 antihypertensive agent, with 1281 (28.6%) receiving 1 agent, 1280 (41.2%) receiving 2 agents, and 1350 (30.2%) receiving 3 or more agents. Patients with CVD alone were less frequently given an antihypertensive agent (83.6% vs 93.2%, $P<0.001$).

Angiotensin-converting enzyme inhibitors were the most commonly (n=2826, 57%) prescribed agent among all 3 groups. Angiotensin receptor blockers were prescribed for 840 (17%) patients. Angiotensin-converting enzyme inhibitors were less likely to be prescribed for patients with CVD alone (49.9% vs 59.1%, $P<0.001$), whereas angiotensin receptor blockers were most commonly prescribed in this group (15% vs 22%; $P<0.001$).

Antithrombotic Therapy

Overall, 4587 patients (93.0%) were prescribed an antithrombotic agent (antiplatelet or anticoagulant therapy), with 4293 (87.0%) receiving an antiplatelet agent and 443 (9.0%)

receiving anticoagulation therapy (Table 2). The most common antiplatelet agent was aspirin. Patients with CVD alone were more commonly taking clopidogrel (or ticlopidine) than were patients with CAD (21.9% vs 9.2%, $P<0.0001$). There was no significant sex difference in the use of antithrombotic therapy (91.3% for men vs 92.8% for women, $P=0.37$).

Lipid Profile

Table 3 summarizes the lipid profile for the 3 patient groups. The average TC and LDL-C levels were highest in the CVD-only group ($P<0.001$ for pairwise comparisons with CAD-only and CAD+CVD groups). There were no significant differences in TG and the TC to HDL-C ratio among groups. Among patients with CVD (CVD only and CAD+CVD), women had significantly higher TC (5.10 ± 1.10 vs 4.58 ± 1.02 mmol/L), TG (1.84 ± 0.79 vs 1.73 ± 0.76 mmol/L), HDL-C (1.39 ± 0.39 vs 1.16 ± 0.33 mmol/L), and LDL-C (2.87 ± 1.05 vs 2.64 ± 0.88 mmol/L) levels than did men ($P<0.001$ for all differences).

Achieving Treatment Goals

Overall, 50.6% of patients achieved the target LDL-C value of <2.5 mmol/L (97 mg/dL), and 54.7% attained the BP

Table 3. Lipid Profile by Patient Groups

Lipid Values	All Patients	CAD Only	CAD+CVD	CVD Only	P Value
N or n	4933	3817	469	647	
TC, mmol/L	4.61 ± 1.03	$4.57\pm 1.00^*$	$4.58\pm 1.00^*$	4.92 ± 1.12	<0.0001
LDL-C, mmol/L	2.61 ± 0.88	$2.59\pm 0.86^*$	$2.55\pm 0.91^*$	2.85 ± 0.97	<0.0001
HDL-C, mmol/L	1.19 ± 0.34	$1.18\pm 0.32^*$	$1.19\pm 0.35^*$	1.29 ± 0.38	<0.0001
TG, mmol/L	1.75 ± 0.80	1.75 ± 0.80	1.82 ± 0.78	1.74 ± 0.77	0.15
TC:HDL-C	4.06 ± 1.21	4.28 ± 1.24	4.15 ± 1.22	4.03 ± 1.20	0.78

To convert cholesterol and TG units from mmol/L to mg/dL, multiply by 38.67 and 88.57, respectively.

* $P<0.001$ for post hoc pairwise comparisons with the CVD-only group.

Table 4. Sex Differences in the Attainment of Guideline-Recommended Targets in Patients With CVD

Outcome Measures	CVD Patients		P Value
	Male, n=679	Female, n=415	
Medication use			
Statin, %	77.8	79.2	0.57
Any lipid-modifying agent, %	79.8	80.6	0.75
Antihypertensive therapy, %	87.2	89.0	0.37
Antithrombotic therapy, %	91.3	92.8	0.38
Outcome measures			
Achieved LDL-C <2.5 mmol/L, %	48.7	41.9	0.02
Achieved BP <140/90 mm Hg (<130/80 for diabetic patients), %	47.9	42.2	0.048
Achieved BP <140/90 mm Hg (<130/80 for diabetic patients) and LDL-C <2.5 mmol/L, %	23.8	18.7	0.047
Optimal care, %*	21.3	17.9	0.18

*Optimal care defined as BP <140/90 mm Hg (or <130/80 mm Hg for diabetic patients), LDL-C <2.5 mmol/L, and treated with antithrombotic therapy.

target of <140/90 mm Hg (or 130/80 mm Hg for persons with diabetes). Table 2 shows the percentages of patients achieving these goals in the 3 groups. The proportion of patients reaching the LDL-C target was highest in the group with concomitant CAD and CVD. Patients with CVD alone were less likely to meet the recommended BP target or the combined BP and LDL-C targets. Of note, patients with CVD alone were also more likely to continue smoking (Table 1). Compared with patients not prescribed statins, those on statin therapy more frequently attained the target LDL-C level (33.9% vs 54.1%, $P<0.0001$) and the TC:HDL-C target (41.0% vs 55.7%, $P<0.0001$). Among patients with CVD (CVD only and CAD+CVD), women were less likely to meet the BP and lipid targets despite a similar history of hypertension and use of antithrombotic, antihypertensive, and lipid-modifying agents (Table 4).

Multivariable Analysis

In multivariable logistic-regression analysis, patients with CVD alone were less likely to meet the recommended lipid target. Patients with CVD (either alone or with CAD) were less likely to meet the recommended BP targets after adjusting for independent predictors (Tables 5 and 6). Hosmer-Lemeshow goodness-of-fit probability values were 0.55 and 0.67 for the BP and lipid target models, respectively, indicating that the models provided adequate fit with the data. Similar findings were observed when adjusting for use of concomitant medications, use of statins, or antihypertensive drugs (data not shown).

Discussion

In this large, prospective, observational study of 4933 high-risk ambulatory patients with known cardiovascular disease, we demonstrated that only about half achieved the target BP

Table 5. Multivariable Analysis: Factors Associated With Attainment of BP Target

Variable	BP <140/90 mm Hg (<130/80 for diabetic patients), Adjusted OR (95% CI)	P Value
Age		
<65 years	Referent group	
65–74 years	0.74 (0.64–0.83)	<0.001
≥75 years	0.63 (0.53–0.76)	<0.001
Female	0.83 (0.72–0.96)	0.012
Diabetes	0.16 (0.14–0.19)	<0.001
BMI >30	0.71 (0.62–0.82)	<0.001
History of heart failure	1.70 (1.38–2.11)	<0.001
CAD alone		
CAD alone	Referent group	
CVD alone	0.71 (0.58–0.86)	<0.001
CAD+CVD	0.72 (0.57–0.90)	0.004

OR indicates odds ratio; BMI, body mass index. Note that patients with CVD alone or with concomitant CAD were less likely to achieve the BP target. c-statistics (95% CI)=0.74 (0.73–0.76).

and LDL-C levels recommended by guidelines, and 12.9% were still smoking. Patients with CVD were less likely to achieve these targets when compared with patients with CAD alone and those with coexisting CAD and CVD. This held true even after adjusting for covariates in the multivariable analysis. Interestingly, the multivariable analysis showed that patients with CVD (either alone or with concomitant CAD) were less likely to attain the recommended BP targets, suggesting a differential gap in the prevention of hypertension and dyslipidemia between patients with CVD alone and those with concomitant CAD. Furthermore, a considerable proportion of patients who failed to reach target were either prescribed submaximal doses of statins or not treated with statins at all. In particular, women with CVD were less likely to meet the recommended BP and lipid targets compared with men with CVD.

Table 6. Multivariable Analysis: Factors Associated With Attainment of Lipid Target

Variable	LDL-C <2.5 mmol/L [97 mg/dL] Adjusted OR (95% CI)	P Value
Age		
<65 years	Referent group	
65–74 years	1.16 (1.02–1.33)	0.03
≥75 years	1.42 (1.22–1.66)	<0.001
Female	0.76 (0.67–0.87)	<0.001
Diabetes	1.45 (1.28–1.63)	<0.001
Prior PCI or CABG	1.42 (1.25–1.60)	<0.001
Statin use	2.25 (1.92–2.65)	<0.001
CAD alone		
CAD alone	Referent group	
CVD alone	0.79 (0.66–0.95)	0.01
CAD/CVD	1.00 (0.83–1.25)	0.86

OR indicates odds ratio. Multivariable analysis was adjusted for age, sex, diabetes, coronary artery bypass graft surgery (CABG), or percutaneous coronary intervention (PCI). Note that patients with CVD alone were less likely to achieve the lipid target. c-statistics (95% CI)=0.62 (0.61–0.64).

Our study provides new insights into the contemporary management of hypertension and dyslipidemia in these high-risk patients. Several randomized, clinical trials have shown the important benefit of antihypertensive, lipid-lowering, and antithrombotic therapy in stroke prevention.^{5,19–22} For example, in the PROGRESS study (Perindopril Protection against Recurrent Stroke Study), a decrease of 12/5 mm Hg reduced the relative risk of a recurrent cerebrovascular event by 36% (95% CI, 19% to 49%) for ischemic stroke and 76% (95% CI, 55% to 87%) for hemorrhagic stroke.²³ Similarly, in the HOPE (Heart Outcomes Prevention Evaluation) study, patients with vascular disease treated with ramipril experienced a relative risk reduction of 32% ($P<0.001$) in stroke with a small reduction in BP of 3/1 mm Hg.²⁴ In the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study, 4731 patients with noncardioembolic stroke or transient ischemic attack in the preceding 6 months were randomized to atorvastatin 80 mg daily or placebo. The risk for stroke (primary outcome) decreased by 16% (95% CI, 1% to 29%; $P=0.03$) while the risk of acute coronary events (secondary outcome) decreased by 35% (95% CI, 16% to 50%; $P<0.001$).²⁰ A similar risk reduction was observed in a large meta-analysis that included 90 056 randomized individuals in 14 clinical trials of statins.²⁵ In addition, the calculated cumulative risk reduction for implementing lifestyle modifications, aspirin, statins, and antihypertensive therapy (crucial applicable strategies in secondary stroke prevention) was 80% as revealed from a recent meta-analysis.²⁶ In the Life Long After Cerebral Ischemia (LiLAC) study, the 10-year major vascular event rate was 44.1%, with the corresponding absolute risk reduction of 35%, equivalent to a number needed to treat of only 3.²⁷

Despite the significant advances made during the last decade regarding cardiovascular prevention, there are only limited data on the contemporary treatment of hypertension and dyslipidemia, especially among high-risk patients.^{3,8,9} Previous studies in the 1990s documented significant gaps between evidence-based medicine and “real world” clinical practice.^{14,28,29} For example, among 4888 outpatients enrolled in the Lipid Treatment Assessment Project, overall only 38% attained the LDL-C goal recommended by NCEP ATP II. In the highest-risk group with known CAD, the proportion of patients achieving target levels was even lower, at 18%.¹⁴ In the analysis of treatment adherence including 2894 participants in the Vitamin Intervention for Stroke Prevention (VISP) trial, half of stroke patients were not taking a statin, and of those receiving statin treatment, less than half achieved the recommended lipid goals.²⁹ Our results also concur with those of a recent US national survey, which documented an LDL-C goal-attainment rate of 57% among 2708 high-risk patients.¹²

The results of this study highlight the substantial gap between current guidelines and target achievement in an outpatient setting. A few studies showed the importance of optimizing discharge planning for future adherence to the guidelines,^{30,31} but most of the studies were conducted in inpatient settings. The Reduction of Atherothrombosis for Continued Health (REACH) Registry was an international, prospective, cohort study in ambulatory patients with either

established atherosclerotic disease (CAD, peripheral artery disease, CVD) or at least 3 risk factors for atherothrombosis. Guideline attainment results from this key study have not been yet published. Our study provides a comprehensive assessment of the lipid profiles and almost doubles the number of high-risk Canadian patients recruited in the REACH multicenter study, in which LDL-C measures were not collected prospectively.

More concerning is that less than one third of high-risk patients were receiving optimal care, defined as the achievement of LDL-C <2.5 mmol/L, BP $<140/90$ mm Hg (or $<130/80$ for persons with diabetes), and being on antithrombotic therapy. This gap was greater in patients with CVD alone. Several reasons may account for the poor adherence to treatment guidelines. Differences in the emphasis of recommended targets between cardiovascular and stroke prevention guidelines may explain our findings. It is possible that a medical procedure such as coronary revascularization, chronic anginal symptoms, or ongoing specialty care could improve patients' awareness and consequent treatment success. Barriers to the implementation of treatment guidelines are perhaps another contributing factor to the suboptimal management of these patients. These may include inappropriate drug or dose selection, lack of aggressive management of hypertension/dyslipidemia, patient nonadherence, or limited drug efficacy. For example, among 83% of patients receiving a lipid-lowering agent in our study, 11.4% were receiving low doses, and only 50% achieved the recommended targets. It is also possible that the lack of definitive value for LDL-C lowering for the reduction of recurrent stroke (since the results of SPARCL were published after the time period of data collection) may have influenced our results. To the best of our knowledge, this is the first study comparing differences in guideline attainment between high-risk patients with CAD and CVD. The study had a large sample size and included relatively unselected ambulatory patients in primary care.

Practical Implications

In 2006, the Canadian guidelines for the management of dyslipidemia and the NCEP in 2004 recommended an LDL-C <2.0 mmol/L (77 mg/dL) for high-risk patients with cardiovascular disease.^{32,33} Our results confirm that only a minority of such patients (24.7% of 4933 high-risk patients) would have achieved this target in 2001 to 2004, and more effective therapeutic strategies are warranted. As recent clinical trials continue to support more aggressive LDL-C lowering,^{20,34,35} our data should also serve as a useful benchmark to reevaluate the attainment of new LDL-C goals in the future.

This study is unique in providing evidence that patients with CVD received suboptimal therapy and were less likely to achieve the targets when compared with patients with CAD. Moreover, our study reveals a differential gap in the treatment of hypertension and dyslipidemia between patients with both CVD and CAD and those with CVD alone, who were also more likely to be current smokers. In addition, women with CVD are less likely to achieve the BP and lipid targets. Our results are consistent with a recent study of high-risk women managed in a care setting, in which only

12% achieved the American Heart Association optimal combined lipid levels.¹⁷

More important, antithrombotic, antihypertensive, and lipid-lowering therapies are established quality indicators of in-hospital stroke care.³⁶ The implementation of standardized preprinted orders may optimize adherence to therapy after discharge. However, lack of titration of medications (or add-on therapy) is another important barrier to achieve optimal targets. We believe that outpatient titration of evidence-based therapies should also be carefully and regularly assessed, particularly in patients with CVD, with close follow-up by the family physician, general practitioner, or specialist.

Several limitations deserve comment. First, we have no information on the duration of statin therapy and lifestyle modifications, although dietary and other lifestyle interventions had likely been implemented concurrently according to current guidelines. Second, although we attempted to minimize bias by enrolling consecutive eligible patients in diverse practice settings, the nonrandom selection of participating physicians and consenting patients with a complete lipid profile might limit the generalizability of our findings. It is also possible that patients with severe stroke were underrepresented in our study. However, we believe our results were probably conservative and underestimated the prevalence of treatment failure in the general population. Third, lipid measurements were not performed in a central core laboratory. However, this reflects “real world” practice where physicians initiate or titrate therapy based on available test results. Fourth, we were unable to distinguish stroke subtypes among participants included in the present study. Finally, we did not evaluate adherence to prescribed medications by pill count or pharmacy records.

Despite these limitations, this large study constitutes the first step in understanding the differential gaps in ambulatory management of high risk-patients with known cardiovascular disease. Current management of dyslipidemia and hypertension remains suboptimal, with a persistent underutilization of proven antihypertensive and lipid-modifying therapies. Our study reaffirms the ongoing need to narrow this treatment gap—in particular, quality improvement strategies should be directed to patients with CVD alone and women, who were less likely to achieve the recommended targets in comparison with patients with CAD, to ensure that they will also derive the important treatment benefits demonstrated in clinical trials.

Acknowledgments

We are indebted to all of the study investigators and patients who participated in the GOALL and VP Registries.

Disclosures

This research was sponsored by the Canadian Heart Research Centre (a federally incorporated not-for-profit academic research organization), Stroke Outcome Research Canada (SORCan) Working Group, Astra-Zeneca (GOALL), Sanofi Aventis (VP), and Pfizer (VP). Dr Gustavo Saposnik is supported by the Clinician-Scientist Award from Heart Stroke Foundation Ontario, Connaught Foundation (University of Toronto), and the Research Department at St. Michael's Hospital. Dr Andrew Yan is supported by the Canadian Institutes of Health Research and the Heart and Stroke Foundation of

Canada. Dr David Fitchett received CME and consultation honoraria from Sanofi-Aventis, Astra Zeneca, and Pfizer and research funding from Sanofi-Aventis. Dr Lawrence Leiter received CME on behalf of, and has acted as a consultant to, Astra-Zeneca, Sanofi-Aventis, and Pfizer. Dr Shaun Goodman has received research grant support and speaker/consulting honoraria from Sanofi-Aventis, Pfizer, and Astra Zeneca. Dr Anatoly Langer has received research grant support and speaker/consulting honoraria from Sanofi-Aventis, Pfizer, and Astra Zeneca. The industry sponsors had no involvement in the study conception or design; collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

References

- Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, Culebras A, DeGraba TJ, Gorelick PB, Guyton JR, Hart RG, Howard G, Kelly-Hayes M, Nixon JV, Sacco RL. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: co-sponsored by the Atherosclerotic Peripheral Vascular Disease interdisciplinary working group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research interdisciplinary working group. *Circulation*. 2006; 113:e873–e923.
- Saposnik G, Cote R, Phillips S, Gubitz G, Bayer N, Minuk J, Black S; Stroke Outcome Research Canada (SORCan) Working Group. Stroke outcome in those over 80: a multicenter cohort study across Canada. *Stroke*. 2008;39:2310–2317.
- Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Schwamm LH, Tomsick T. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Circulation*. 2006;113:e409–e449.
- Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol*. 2004;44:671–719.
- Amarenco P, Lavalley P, Touboul PJ. Stroke prevention, blood cholesterol, and statins. *Lancet Neurol*. 2004;3:271–278.
- Gorelick PB, Sacco RL, Smith DB, Alberts M, Mustone-Alexander L, Rader D, Ross JL, Raps E, Ozer MN, Brass LM, Malone ME, Goldberg S, Booss J, Hanley DF, Toole JF, Greengold NL, Rhew DC. Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *JAMA*. 1999;281: 1112–1120.
- McAlister FA, Zarnke KB, Campbell NR, Feldman RD, Levine M, Mahon J, Grover SA, Lewanczuk R, Leenen F, Tobe S, Lebel M, Stone J, Schiffrin EL, Rabkin SW, Ogilvie RI, Larochelle P, Jones C, Honos G, Fodor G, Burgess E, Hamet P, Herman R, Irvine J, Culleton B, Wright JM. The 2001 Canadian recommendations for the management of hypertension: part two—therapy. *Can J Cardiol*. 2002;18:625–641.
- Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143–3421.
- Fodor JG, Frohlich JJ, Genest JJ Jr, McPherson PR. Recommendations for the management and treatment of dyslipidemia: report of the working group on hypercholesterolemia and other dyslipidemias. *Can Med Assoc J*. 2000;162:1441–1447.
- De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Manger Cats V, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D. European guidelines on cardiovascular disease prevention in clinical practice: third joint task force of European and other societies on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2003;24:1601–1610.

11. Yan AT, Yan RT, Tan M, Hackam DG, Leblanc KL, Kertland H, Tsang JL, Jaffer S, Kates ML, Leiter LA, Fitchett DH, Langer A, Goodman SG. Contemporary management of dyslipidemia in high-risk patients: targets still not met. *Am J Med.* 2006;119:676–683.
12. Hackam DG, Tan MK, Honos GN, Leiter LA, Langer A, Goodman SG. How does the prognosis of diabetes compare with that of established vascular disease? insights from the Canadian vascular protection (VP) registry. *Am Heart J.* 2004;148:1028–1033.
13. Williams RR, Hunt SC, Schumacher MC, Hegele RA, Leppert MF, Ludwig EH, Hopkins PN. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am J Cardiol.* 1993;72:171–176.
14. Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med.* 2000;160:459–467.
15. Deleted in proof.
16. Davidson MH, Maki KC, Pearson TA, Pasternak RC, Deedwania PC, McKenney JM, Fonarow GC, Maron DJ, Ansell BJ, Clark LT, Ballantyne CM. Results of the National Cholesterol Education (NCEP) program evaluation project utilizing novel e-technology (Neptune) II survey and implications for treatment under the recent NCEP writing group recommendations. *Am J Cardiol.* 2005;96:556–563.
17. Mosca L, Merz NB, Blumenthal RS, Cziraky MJ, Fabunmi RP, Sarawate C, Watson KE, Willey VJ, Stanek EJ. Opportunity for intervention to achieve American Heart Association guidelines for optimal lipid levels in high-risk women in a managed care setting. *Circulation.* 2005;111:488–493.
18. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, Lovelock CE, Binney LE, Bull LM, Cuthbertson FC, Welch SJ, Bosch S, Alexander FC, Silver LE, Gutnikov SA, Mehta Z. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet.* 2007;370:1432–1442.
19. Bhatt DL, Topol EJ. Clopidogrel added to aspirin versus aspirin alone in secondary prevention and high-risk primary prevention: rationale and design of the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance (CHARISMA) trial. *Am Heart J.* 2004;148:263–268.
20. Amarencu P, Bogousslavsky J, Callahan A III, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med.* 2006;355:549–559.
21. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci.* 1996;143:1–13.
22. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet.* 2004;364:331–337.
23. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet.* 2001;358:1033–1041.
24. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients: the Heart Outcomes Prevention Evaluation study investigators. *N Engl J Med.* 2000;342:145–153.
25. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet.* 2005;366:1267–1278.
26. Hackam DG, Spence JD. Combining multiple approaches for the secondary prevention of vascular events after stroke: a quantitative modeling study. *Stroke.* 2007;38:1881–1885.
27. van Wijk I, Kappelle LJ, van Gijn J, Koudstaal PJ, Franke CL, Vermeulen M, Gorter JW, Algra A. Long-term survival and vascular event risk after transient ischaemic attack or minor ischaemic stroke: a cohort study. *Lancet.* 2005;365:2098–2104.
28. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. Euroaspire I and II group. European action on secondary prevention by intervention to reduce events. *Lancet.* 2001;357:995–1001.
29. Ovbiagele B, Saver JL, Bang H, Chambless LE, Nassief A, Minuk J, Toole JF, Crouse JR. Statin treatment and adherence to national cholesterol guidelines after ischemic stroke. *Neurology.* 2006;66:1164–1170.
30. Hayes SM, Dupuis M, Murray S. Issues and challenges in the assessment, diagnosis and treatment of cardiovascular risk factors: assessing the needs of cardiologists. *BMC Med Educ.* 2008;8:30.
31. Ovbiagele B, Saver JL, Fredieu A, Suzuki S, Selco S, Rajajee V, McNair N, Razinia T, Kidwell CS. In-hospital initiation of secondary stroke prevention therapies yields high rates of adherence at follow-up. *Stroke.* 2004;35:2879–2883.
32. Brown DJ. New guidelines for low-density lipoprotein levels from the National Cholesterol Education Program (NCEP): a 2004 update. *Prog Cardiovasc Nurs.* 2004;19:165.
33. McPherson R, Frohlich J, Fodor G, Genest J, Canadian Cardiovascular Society. Canadian Cardiovascular Society position statement—recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. *Can J Cardiol.* 2006;22:913–927.
34. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360:7–22.
35. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005;352:1425–1435.
36. Lindsay MP, Kapral MK, Gladstone D, Holloway R, Tu JV, Laupacis A, Grimshaw JM. The Canadian stroke quality of care study: establishing indicators for optimal acute stroke care. *Can Med Assoc J.* 2005;172:363–365.