Impact of Carotid Endarterectomy on Medical Secondary Prevention After a Stroke or a Transient Ischemic Attack: Results from the Reduction of Atherothrombosis for Continued Health (REACH) Registry

Emmanuel Touzé, Jean-Louis Mas, Joachim Röther, Shinya Goto, Alan T. Hirsch, Yasuo Ikeda, Chiau-Suong Liau, E. Magnus Ohman, Alain J. Richard, Peter W. F. Wilson, P. Gabriel Steg, Deepak L. Bhatt and for the REACH Registry Investigators

Stroke 2006;37;2880-2885; originally published online Oct 26, 2006;
DOI: 10.1161/01.STR.0000249411.44097.5b
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

Impact of Carotid Endarterectomy on Medical Secondary Prevention After a Stroke or a Transient Ischemic Attack

Results from the Reduction of Atherothrombosis for Continued Health (REACH) Registry

Emmanuel Touzé, MD; Jean-Louis Mas, MD; Joachim Röther, MD; Shinya Goto, MD; Alan T. Hirsch, MD; Yasuo Ikeda, MD; Chiau-Suong Liau, MD, PhD; E. Magnus Ohman, MD; Alain J. Richard, MD, PhD; Peter W.F. Wilson, MD; P. Gabriel Steg, MD; Deepak L. Bhatt, MD; for the REACH Registry Investigators

Background and Purpose—Whether a history of carotid endarterectomy influences patient compliance with medical treatments and physician attitude toward treatments after ischemic stroke or transient ischemic attack (TIA) is not well known.

Methods—We studied the baseline data of 18 467 ischemic stroke and TIA patients from the international REduction of Atherothrombosis for Continued Health (REACH) Registry and investigated the impact of a history of endarterectomy on the secondary medical prevention measured by the use of antiplatelet agents and statins, and by the control of cholesterol level, glucose level, and blood pressure.

Results—Among the patients with a history of ischemic stroke or TIA, those with a history of endarterectomy (n=1474) were more likely to receive antiplatelet agents and statins, to have a blood pressure <140/90 mm Hg, and a fasting total cholesterol <200 mg/dL. In diabetic patients, endarterectomy was associated with lower fasting blood glucose levels. In multivariate logistic regression analyses, endarterectomy was significantly associated with the use of antiplatelet agents (odds ratio [OR], 1.6; 95% CI, 1.3 to 1.9; $P<0.0001$) and statins (OR, 1.8; 1.6 to 2.0; $P<0.0001$), and with a cholesterol level <200 mg/dL (OR, 1.3; 1.2 to 1.5; $P<0.0001$). By contrast, the associations with blood pressure and blood glucose levels were no longer significant. There was no heterogeneity across the world regions or among the specialists who enrolled the patients.

Conclusions—Carotid endarterectomy is associated with a higher use of antiplatelet agents and statins in stroke/TIA patients. The absence of such an association with blood pressure and blood glucose control suggests that the individual determinants of the quality of the secondary medical prevention vary from one risk factor to another and from one class of drugs to another. **(*Stroke*. 2006;37:2880-2885.)**

Key Words: antithrombotic agents ■ carotid endarterectomy ■ guidelines ■ prevention ■ risk factors ■ statins ■ stroke

Numerous studies have clearly shown that there is a substantial gap between recommendations in guidelines and actual care of patients with atherothrombotic diseases.[1–6] Only a minority of patients are at target goals for blood pressure, glucose, and cholesterol, and despite an overwhelming amount of data in support of statins and antiplatelet therapy, these classes of drugs are not being prescribed at optimal rates.[2] In addition to secondary medical prevention, some patients with severe atherosclerosis benefit from specific interventional approaches, such as carotid endarterectomy (CE), coronary artery bypass graft surgery, or percutaneous coronary interventions mostly with stent implantation. Whether these interventions influence patient compliance and physician medical choices remains unknown, because there is

Received May 28, 2006; final revision received July 12, 2006; accepted August 17, 2006.

From Faculté de Médecine René Descartes, Université Paris 5, EA 4055, Department of Neurology (E.T., J.-L.M.), Hôpital Sainte-Anne, Paris, France; Department of Neurology (J.R.), Klinikum Minden, Hannover Medical School, Minden, Germany; Department of Medicine (S.G.), Tokai University School of Medicine, Kanagawa, Japan (Pr Goto); Minneapolis Heart Institute Foundation and Division of Epidemiology and Community Health (A.T.H.), University of Minnesota School of Public Health, Minneapolis, Minn; Division of Hematology (Y.I.), Keio University School of Medicine, Tokyo, Japan; Department of Internal Medicine (C.-S.L.), National Taiwan University Hospital and School of Medicine, Taipei, Taiwan; Division of Cardiology (E.M.O.), Duke University, Durham, NC; Global Medical Affairs–Clinical Operations (A.J.R.), Sanofi-Aventis, Paris, France; General Clinical Research Center (P.W.F.W.), Medical University of South Carolina, Charleston; Department of Cardiology (P.G.S.), Hôpital Bichat-Claude Bernard, Paris, France; Department of Cardiovascular Medicine (D.L.B.), Cleveland Clinic Foundation, Cleveland, Ohio.

Correspondence to Jean-Louis Mas, Department of Neurology, Hôpital Sainte-Anne, 1 rue Cabanis 75674 Paris Cedex 14. E-mail jl.mas@ch-sainte-anne.fr

Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000249411.44097.5b**

no study specifically addressing this issue. CE is the most frequently performed vascular surgical procedure in the United States, and the rates continue to increase in Europe.[7] One retrospective study has suggested that medical secondary prevention of patients who had CE was not optimal.[8] However, there was no comparative group of patients without CE.

We studied the baseline data of 18 467 ischemic stroke and transient ischemic attack (TIA) patients from the international REduction of Atherothrombosis for Continued Health (REACH) Registry and investigated the impact of a history of CE on the secondary medical prevention measured by the use of antithrombotic drugs and statins, and by the control of cholesterol level, glucose level, and blood pressure.

Methods

The design and methodology of the REACH Registry, an international, prospective, observational registry have been published elsewhere.[2,9] Briefly, consecutive eligible outpatients aged 45 years or older with established coronary artery disease (CAD), cerebrovascular disease (ischemic stroke or TIA), or peripheral arterial disease (PAD), or with at least 3 atherothrombotic risk factors were enrolled over a 7-month recruitment period on a worldwide basis between December 2003 and June 2004. The protocol of the REACH registry was submitted to the institutional review board in each country according to local requirements and signed informed consent was obtained for all patients. The protocol of the present study was submitted to and approved by the REACH Steering Committee in January 2005 before all data were collected.

The diagnosis of stroke or TIA was documented by hospital or neurologist report. Documented CAD consisted of ≥1 of the following criteria: stable angina with documented coronary atheroma, history of percutaneous coronary intervention, history of coronary bypass graft surgery, or previous myocardial infarction. Documented PAD consisted of 1 or both criteria: current intermittent claudication with ankle-brachial index <0.9 or a history of intermittent claudication together with a previous and related endovascular or surgical intervention.

Among the 68 236 patients enrolled in the registry, 18 992 (27.8%) had a past history of ischemic stroke or TIA. We excluded 253 (1.3%) patients for whom the information on history of CE was missing and 272 (1.4%) patients who had a history of carotid angioplasty and no history of CE. Patients who had a history of both CE and carotid angioplasty (n=244) were not excluded. Thus, 18 467 patients formed the basis of this study. Data on risk factors, physical examination, and medications were collected centrally via use of a standardized international case report form, completed at the study enrolment visit. The risk factors consisted of those that were documented in the medical record or for which patients were receiving treatment: diabetes (any history of diabetes or current diabetes diagnosed by at least 2 fasting blood glucose measures >126 mg/dL, treated or not), hypertension previously or currently treated, atrial fibrillation (paroxysmal, persistent or permanent), and smoking status (never, former, current). Baseline seated systolic and diastolic blood pressure, and most recent available fasting glucose (n=14 285; 77%) and cholesterol levels (14 313; 78%) were obtained. Treatments taken regularly by the patients including antiplatelet agents, oral anticoagulants, lipid-lowering agents, cardiovascular agents, and antidiabetic agents at the time of enrolment were recorded.

The evaluation of secondary medical prevention was based on the current recommendations when patients were enrolled in the registry.[10] We calculated the proportion of patients receiving antithrombotic agents (antiplatelet drugs or anticoagulants) and statins.[10] Although the use of statins is not recommended in all stroke/TIA patients, we included these drugs in our analysis because growing evidence demonstrates that statins reduce the risk of coronary events, regardless of cholesterol levels in stroke/TIA patients, as mentioned in most recommendations for prevention after a stroke or a TIA.[10–12]

The quality of risk factor control was assessed by calculating the proportion of patients with blood pressure <140/90 mm Hg and fasting cholesterol level <200 mg/dL. Hemoglobin A_{1c} was not collected in the REACH Registry. Therefore, the quality of glycemic control in diabetic patients was assessed by calculating the proportion of patients having a fasting blood glucose <135 mg/dL, corresponding to 6% of hemoglobin A_{1c}.[13]

Statistical Analyses

Continuous variables are expressed as mean (SD) and categorical variables as percentages. Categorical variables were compared using the Pearson χ^2 test and continuous variables using the t test. The associations between a prior history of CE and use of antithrombotic drugs, use of statins, cholesterol level control, glucose level control, and blood pressure control were assessed by calculation of crude and adjusted odds ratios (OR) in logistic-regression analyses. Models were adjusted for region, physician's specialty, age, gender, hypertension, diabetes, hypercholesterolemia, smoking status, CAD, PAD, atrial fibrillation, time lapse from stroke/TIA, type of event (stroke, TIA), and relevant treatments. We evaluated heterogeneity in our results across world regions and specialists with Breslow-Day χ^2 tests. To assess the internal validity of the results, the same analyses were performed after exclusion of patients with atrial fibrillation (ie, those which potentially had a cardioembolic stroke) and those who had clinical manifestations of atherothrombosis in other arterial territories (CAD and PAD). Statistical analyses were performed using SAS software version 8.01 (SAS Institute Inc) and STATA software version 8.0 (StataCorp).

Results

Among the 18 467 stroke/TIA patients, 1474 (8%) had a history of CE (Table 1). In this group, patients were older and the proportion of males was higher compared with patients without previous CE. In addition, patients with a history of CE were more likely to have a history of hypertension, smoking, hypercholesterolemia, a history of clinical manifestations of atherothrombosis in other arterial territories, and they were slightly more likely to be overweight or obese. The majority (79%) of patients with a history of CE were from North America and Western Europe.

Table 2 shows that patients with a history of CE were more likely to receive antiplatelet or any antithrombotic agent and statins or any lipid-lowering agent, to have a blood pressure <140/90 mm Hg, and a fasting total cholesterol <200 mg/dL. A history of CE was also associated with lower fasting blood glucose in diabetic patients. As there was no difference in the use of anticoagulants between both groups, antiplatelet agents were used in the following analyses.

The associations between CE and use of antiplatelet agents or statins, and between CE and cholesterol level control were consistent across the different regions of the world and among the different specialists who enrolled patients (Figure). By contrast, the relation between CE and blood pressure <140/90 mm Hg was no longer significant after adjustment for world regions. These findings were similar when analyses were restricted to patients who had a diagnosis of hypertension or when blood pressures <120/80 or <160/100 mm Hg were chosen as cut-offs. Similarly, the relation between CE and blood glucose <135 mg/dL in diabetic patients was not significant after adjustment for world regions (data not shown).

In logistic regression analyses, CE remained significantly associated with the use of antiplatelet agents (OR, 1.6; 95%

TABLE 1. Main Characteristics of the Population

	History of CE		
	Yes (n=1474)	No (n=16 993)	*P*
Sociodemographic characteristics			
Age, mean (SD), years	71.5 (9.3)	69.2 (10.1)	<0.0001
Age (years), %			<0.0001
<55	6	10	
55–64	19	22	
65–74	36	36	
≥75	39	32	
Male sex, %	68	59	<0.0001
Region, %			<0.0001
North America (n=5697)	49	29	
Latin America (n=615)	2	4	
Western Europe (n=4670)	30	25	
Eastern Europe (n=2164)	5	12	
Japan (n=1992)	6	11	
Other Asia (n=2481)	2	15	
Middle East (n=217)	1	1	
Australia (n=631)	5	3	
TIA, %	38	27	<0.0001
Time since stroke/TIA ≤1 year, %	26	36	<0.0001
Risk factors			
Diabetes, %	35	37	0.21
Hypertension, %	86	83	0.002
Smoking, %			<0.0001
Never	29	49	
Former	56	37	
Current	15	14	
Hypercholesterolemia, %	75	56	<0.0001
Atrial fibrillation or flutter, %	14	13	0.30
BMI (kg/m^2), %			0.004
<25	34	38	
25–29	42	39	
30–34	18	16	
≥35	6	7	
History of atherothrombotic manifestations in other arterial territories			
CAD, %	53	34	<0.0001
PAD, %	22	9	<0.0001

Time since stroke/TIA corresponds to the time between the qualifying stroke/TIA and the inclusion in the registry.

BMI indicates body mass index (calculated as weight in kilograms divided by the square of height in meters).

Ex-smoker: at least 5 cigarettes per day as a mean >1 month before entry into registry. Current smoker: at least 5 cigarettes per day as a mean within the past month before entry into registry.

TABLE 2. Management of Risk Factors and Use of Preventive Treatments

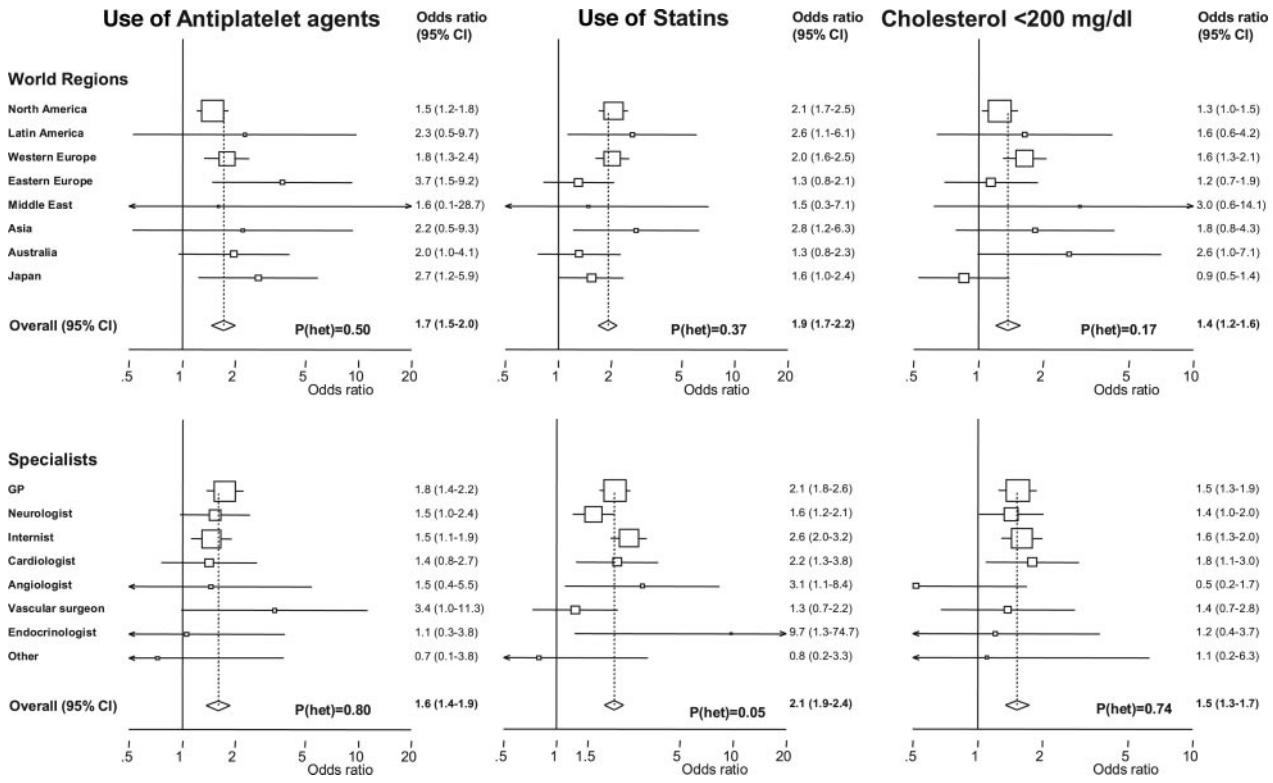
	History of CE		
	Yes (n=1474)	No (n=16 993)	*P*
Treatments			
Antiplatelet agent, %	87	81	<0.0001
Oral anticoagulants, %	17	17	0.69
At least 1 antithrombotic agent, %	96	92	<0.0001
Statins, %	74	55	<0.0001
At least 1 lipid-lowering agent, %	78	59	<0.0001
BP control			
<120/80 mm Hg, %	11	9	<0.0001
120/80 mm Hg ≤BP <140/90 mm Hg, %	39	36	
140/90≤BP <160/100 mm Hg, %	35	34	
≥160/100 mm Hg, %	15	20	
Systolic BP, mean (SD), mm Hg	138.4 (19.1)	139.8 (20.1)	0.0006
Diastolic BP, mean (SD), mm Hg	76.5 (11.0)	80.0 (11.7)	<0.0001
Biological tests			
Fasting total cholesterol <200 mg/dL, %	65	53	<0.0001
Fasting total cholesterol, mean (SD), mg/dL	189.1 (44.0)	200.2 (47.5)	<0.0001
Fasting blood glucose* <135 mg/dL, %	57	50	0.004
Fasting blood glucose,* mean (SD), mg/dL	138.9 (52.1)	146.5 (54.9)	0.006

*In patients with diagnosed diabetes mellitus.
BP indicates blood pressure.

CI, 1.3 to 1.9; $P<0.0001$), the use of statins (OR, 1.8; 1.6 to 2.0; $P<0.0001$), and a cholesterol level <200 mg/dL (OR, 1.3; 1.2 to 1.5; $P<0.0001$) in the whole population as well as in the different prespecified subgroups (Table 3). Patients with previous CE were also more likely to receive either statins or antiplatelet agents (OR, 2.0; 1.5 to 2.7) and both statins and antiplatelet agents (OR, 3.2; 2.4 to 4.3), with a significant trend ($P<0.0001$). There was a significant interaction ($P=0.0005$) between CE and statins in relation to cholesterol level. Indeed, CE was significantly associated with cholesterol <200 mg/dL in patients receiving statins (OR, 1.3; 1.1 to 1.6; $P=0.0002$) but not in those who did not receive this class of drug (OR, 1.0; 0.8 to 1.4). All these results were similar when any antithrombotic agent instead of antiplatelet agents or any lipid-lowering agent instead of statins was used for analysis (data not shown).

Discussion

We have shown that, in the large international REACH Registry, stroke/TIA patients with a history of CE were more likely to receive antiplatelet agents or statins, even more likely to receive both drugs, and to have lower cholesterol levels compared with patients with no history of CE. The association between history of CE and cholesterol level was observed in patients receiving statins. Our findings were not explained by potential confounders, such as vascular risk factors or involvement of other arterial territories, and were



Relation between history of carotid endarterectomy and the different components of the medical secondary prevention across the different world regions and enrolling physician specialty. P(het)=probability value for χ^2 heterogeneity (Breslow-Day). All pooled ORs were statistically significant with $P<0.00001$. GP indicates general practitioner.

consistent across the different regions of the world and among the different specialists who enrolled the patients.

These results contradict those of a previous smaller study showing that among 1041 patients with a history of CE, only 5% received a sustained prescription of antiplatelet agents and 38% a sustained prescription of statins.[8] However, the proportion of patients with a previous stroke or TIA was unknown and there was no comparative group. Nevertheless, our findings are consistent with those of another study suggesting that a history of percutaneous coronary intervention and bypass surgery were associated with better medical secondary prevention in CAD patients.[5]

It is unclear how CE affects the use of antithrombotic drugs or statins and the quality of cholesterol control in stroke/TIA patients. Because similar trends were observed across all world regions, factors related to health care systems are unlikely to explain our findings. They could be explained by improved patient compliance with treatments and diet regimens, as a result of the psychological impact of surgery, and/or increased physician motivation to treat patients with severe atherosclerosis more aggressively. Because patients who received lipid-lowering drugs were classified as having hypercholesterolemia, we were not able to identify whether CE patients were more likely to have been investigated (and consequently treated) for hypercholesterolemia or treated with statins independently of their cholesterol levels. However, the REACH Registry was not designed to address explanations of our findings.

By contrast, we did not find any association between a history of CE and control of diabetes and blood pressure. The

TABLE 3. Association Between History of Carotid Endarterectomy and the Different Components of the Medical Secondary Prevention in All Patients and in the Different Subgroups

	OR (95% CI)			
	All Patients	Patients Without Atrial Fibrillation	Patients Without CAD	Patients Without CAD or PAD
At least 1 antiplatelet agent	1.6 (1.3–1.9)	1.6 (1.3–1.9)	1.9 (1.5–2.5)	1.9 (1.5–2.6)
Statins	1.8 (1.5–2.0)	1.8 (1.6–2.1)	1.9 (1.6–2.3)	1.8 (1.5–2.1)
Total fasting cholesterol <200 mg/dL	1.3 (1.2–1.5)	1.3 (1.2–1.6)	1.4 (1.1–1.7)	1.4 (1.1–1.7)
Fasting blood glucose* <135 mg/dL	1.2 (0.9–1.4)	1.1 (0.9–1.4)	1.0 (0.7–1.4)	1.0 (0.7–1.5)
Blood pressure <140/90 mm Hg	1.0 (0.9–1.2)	1.1 (1.0–1.3)	1.0 (0.9–1.2)	1.1 (0.9–1.3)

*In diabetic patients.

Variables included in the models are listed in methods. In the analyses relating to control of cholesterol level, glucose level, and blood pressure, models were also adjusted for respective related treatments.

greater complexity of the management of hypertension and diabetes, requiring strict and regular monitoring to tailor treatment, could explain this finding. In both conditions, the interactions between patients and physicians are probably more complex and potentially less likely to be influenced by a surgical procedure.[14–16]

Antithrombotic therapy is the cornerstone of secondary prevention after ischemic stroke or TIA. The proportion of patients who did not receive any antithrombotic agent in the REACH Registry (8%) was similar to that reported in previous studies conducted in different countries and different settings.[3,6,17,18] Although the generally large utilization of statins observed in patients with a history of CE is somewhat reassuring, our results also emphasize the underuse of this class of drugs in the much larger group of atherothrombotic stroke/TIA patients who do not have a history of CE. In fact, the majority of patients with ischemic stroke or TIA should be considered for statins regardless of their cholesterol levels.[19]

Although we consider our findings to be valid and convincing, this study has some limitations. First, despite efforts to ensure the inclusion of representative patients from every participating country, this study was not a population-based study. Moreover, patients with CE were mostly from North America or Western Europe, which limits the generalizability of the results. The proportion of patients who underwent CE was lower in regions where the prevalence of large artery disease is known to be low (ie, mainly Japan and Asia). However, the prevalence of risk factors and the proportion of patients who had CE was very close to that observed in different stroke/TIA population-based studies,[20–22] and trends were the same across world regions. Second, as physicians participating in the registry may have been more apt to provide better care, we could have overestimated the use of preventive strategies. Conversely, we were not able to determine whether undocumented contraindications to medications or economic limitations affected the lack of medication use. However, these biases are unlikely to be related to history of CE. Moreover, because patients included in this registry were outpatients, they were unlikely to be severely disabled or to have comorbidities that could have contraindicated some treatments. Third, we used fasting blood glucose instead of hemoglobin A_{1c} to evaluate glycemic control in diabetic patients, which could have masked a relation with CE. However, using 170 mg/dL as a threshold (ie, corresponding to 7% of hemoglobin A_{1c})[13] did not change our findings (data not shown). Therefore, such an association would have probably been small and irrelevant.

In conclusion, CE is associated with an increase in the use of antiplatelet agents and statins in stroke/TIA patients. The absence of a similar relation with blood pressure and blood glucose control suggests that the individual determinants of the quality of the medical secondary prevention after a stroke or a TIA vary from one risk factor to another and from one class of drugs to another. Finally, this better medical secondary prevention in CE patients should be taken into account in the interpretation of the results of trials comparing carotid surgery to medical treatment.

Acknowledgments

Dr Mas and Dr Touzé had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design (REACH Registry): Bhatt, Steg, Ohman, Hirsch, Liau, Goto, Röther, Wilson. Acquisition of data: Bhatt, Steg, Hirsch, Ikeda, Goto, Röther. Analysis and interpretation of data: Touzé, Mas, Richard. Drafting of the manuscript: Touzé, Mas. Critical revision of the manuscript for important intellectual content: Bhatt, Steg, Ohman, Hirsch, Ikeda, Goto, Liau, Richard, Röther, Wilson. Statistical analysis: Touzé, Mas, Richard. Obtained funding: Steg. Administrative, technical, or material support: Bhatt, Steg, Röther, Wilson. Study supervision: Bhatt, Steg, Hirsch, Mas, Röther, Wilson.

Sources of Funding

The REACH Registry is sponsored by Sanofi-Aventis, Bristol-Myers-Squibb, and the Waksman Foundation (Tokyo, Japan).

Disclosures

All manuscripts in the REACH Registry are prepared by independent authors who are not governed by the funding sponsors and are reviewed by an academic publications committee before submission. The funding sponsors have the opportunity to review manuscript submissions but do not have authority to change any aspect of a manuscript.

References

1. EUROASPIRE I and II Group. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. *Lancet.* 2001;357:995–1001.
2. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, Goto S, Liau CS, Richard AJ, Rother J, Wilson PW. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006;295:180–189.
3. Hillen T, Dundas R, Lawrence E, Stewart JA, Rudd AG, Wolfe CDA. Antithrombotic and antihypertensive management 3 months after ischemic stroke: a prospective study in an inner city population. *Stroke*. 2000;31:469–475.
4. Mouradian MS, Majumdar SR, Senthilselvan A, Khan K, Shuaib A. How well are hypertension, hyperlipidemia, diabetes, and smoking managed after a stroke or transient ischemic attack? *Stroke*. 2002;33:1656–1659.
5. Newby LK, LaPointe NM, Chen AY, Kramer JM, Hammill BG, DeLong ER, Muhlbaier LH, Califf RM. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation*. 2006;113:203–212.
6. Touzé E, Cambou JP, Ferrieres J, Vahanian A, Coppe G, Leizorovicz A, Jullien G, Guerillot M, Herrmann MA, Mas JL. Antithrombotic management after an ischemic stroke in French primary care practice: results from three pooled cross-sectional studies. *Cerebrovasc Dis*. 2005;20:78–84.
7. Tu JV, Hannan EL, Anderson GM, Iron K, Wu K, Vranizan K, Popp AJ, Grumbach K. The fall and rise of carotid endarterectomy in the United States and Canada. *N Engl J Med*. 1998;339:1441–1447.
8. Betancourt M, Van Stavern RB, Share D, Gardella P, Martus M, Chaturvedi S. Are patients receiving maximal medical therapy following carotid endarterectomy? *Neurology*. 2004;63:2011–2015.
9. Ohman EM, Bhatt DL, Steg PG, Goto S, Hirsch AT, Liau CS, Mas JL, Richard AJ, Rother J, Wilson PW. The REduction of Atherothrombosis for Continued Health (REACH) Registry: an international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. *Am Heart J*. 2006;151:786–710.
10. Wolf PA, Clagett GP, Easton JD, Goldstein LB, Gorelick PB, Kelly-Hayes M, Sacco RL, Whisnant JP. Preventing ischemic stroke in patients with prior stroke and transient ischemic attack: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke*. 1999;30:1991–1994.
11. Heart Protection Study Collaborative Group. 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.
12. Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20

536 people with cerebrovascular disease or other high-risk conditions. *Lancet.* 2004;363:757–767.
13. Standards of medical care in diabetes. *Diabetes Care.* 2004;27(Suppl 1): S15–S35.
14. Borzecki AM, Oliveria SA, Berlowitz DR. Barriers to hypertension control. *Am Heart J*. 2005;149:785–794.
15. Grant RW, Cagliero E, Dubey AK, Gildesgame C, Chueh HC, Barry MJ, Singer DE, Nathan DM, Meigs JB. Clinical inertia in the management of Type 2 diabetes metabolic risk factors. *Diabet Med*. 2004;21:150–155.
16. Merz CN, Buse JB, Tuncer D, Twillman GB. Physician attitudes and practices and patient awareness of the cardiovascular complications of diabetes. *J Am Coll Cardiol*. 2002;40:1877–1881.
17. Joseph LN, Babikian VL, Allen NC, Winter MR. Risk factor modification in stroke prevention. The experience of a stroke clinic. *Stroke*. 1999;30: 16–20.
18. Hamann GF, Weimar C, Glahn J, Busse O, Diener HC. Adherence to secondary stroke prevention strategies–results from the German Stroke Data Bank. *Cerebrovasc Dis*. 2003;15:282–288.
19. 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. *Stroke*. 2006;37:577–617.
20. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, Stewart-Wynne EG. Five-year survival after first-ever stroke and related prognostic factors in the Perth Community Stroke Study. *Stroke*. 2000;31:2080–2086.
21. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of incidence and risk factors. *Stroke*. 1999;30:2513–2516.
22. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, Gutnikov SA, Edwards P, Mant D, Sackley CM, Farmer A, Sandercock PA, Dennis MS, Warlow CP, Bamford JM, Anslow P. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet*. 2004;363: 1925–1933.