# Assessment of Atherothrombosis and Its Treatment in Mexico: First-Year Data of the REACH Registry

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ABSTRACT

*Background:* Atherothrombosis, a generalized and progressive process, is currently a major healthcare problem in Mexico.

*Methods:* The worldwide Reduction of Atherothrombosis for Continued Health (REACH) registry aimed to evaluate risk factors for atherosclerosis, long-term cardiovascular (CV) event rates, and current management of either patients with established symptomatic atherosclerotic disease or asymptomatic subjects with multiple risk factors for atherothrombotic disease. One-year follow-up of the global REACH database was available for 64 977 outpatients. This report includes the Mexican subregistry wherein 62 internists, cardiologists, and neurologists evaluated baseline patient characteristics, risk factors, medications, and CV event rates as primary outcomes at 1-year follow-up.

*Results:* Complete 1-year follow-up data were available for 837 Mexicans. We observed a high prevalence of diabetes (47.1%), hypertension (74.7%), and hypercholesterolemia (57.8%). Antiplatelet, antihypertensive and/or glucose-lowering agents, and lipid-lowering drugs were used in 87.6%, 84.1%, and 61% of patients, respectively. The all-cause mortality rate was 3.3%. The composite outcome CV death/myocardial infarction/stroke/hospitalization for atherothrombotic events was higher in the symptomatic group (14.6%) than in asymptomatic subjects with multiple risk factors (5.1%; $P = 0.01$), similar to Latin American results of the global REACH report. The highest CV event rate occurred among symptomatic atherothrombotic patients with 3 vascular disease locations (30.2%), followed by those with 2 (21.9%) and 1 location (13.4%; $P = 0.0006$).

*Conclusions:* Prevalence of risk factors and CV event rates including hospitalization in Mexican atherothrombotic patients was high despite the current medication use, which suggests it is necessary to have more aggressive risk-factor management.

The REACH registry is sponsored by sanofi-aventis, Bristol-Myers Squibb, and the Waksman Foundation of Japan (Tokyo, Japan). The REACH registry is endorsed by the World Heart Federation. A complete list of REACH investigators is accessible online at www.reachregistry.org. The REACH registry enforces a no-ghostwriting policy. This manuscript was written and edited by the authors, who take full responsibility for its content. The first draft was written by Dr. Efraín Gaxiola.

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.

Dr. Efraín Gaxiola has received research grants from sanofi-aventis, speaker fees from Pfizer and Eli Lilly, and fees as an advisory board member from Abbott Labs and Pfizer. Dr. Luis Eng-Ceceña has received speaker fees from sanofi-aventis, Pfizer, Bayer, and AstraZeneca, and fees as advisory board member from Schering-Plough. Dr. Fernando Ortiz-Galván

Received: April 12, 2010
Accepted: May 1, 2010

Clin. Cardiol. 33, 7, 445–451 (2010)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20800 

## Introduction

Atherothrombosis affects single or multiple vascular beds such as coronary, cerebrovascular, and peripheral arteries. Its clinical manifestations, including myocardial infarction (MI), ischemic stroke, critical limb ischemia, and cardiovascular (CV) death, pose a global healthcare burden, annually accounting for more than one-fifth of deaths worldwide.[1] Mortality data showed that CV disease accounted for 1 of every 2.8 deaths, whereas stroke accounted for 1 of every 17 deaths in the United States in 2005.[2] Atherothrombotic ischemic heart disease is the second leading cause of general mortality in Mexico due to the growing prevalence of risk factors for atherosclerosis, which include diabetes, hypertension, hypercholesterolemia, overweight, smoking, male age ≥65 years, and female age ≥70 years.[3] High prevalence of CV risk factors and MI is observed among adults from low-income neighborhoods.[4]

Atherothrombosis can be a silent disease; on the other hand, symptomatic atherothrombosis in one vascular bed is usually indicative of the same process in another bed.[5] In the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial and the Reduction of Atherothrombosis for Continued Health (REACH) registry, 26% and 12% of patients, respectively, showed involvement of at least 2 arterial beds.[6,7] Because patients with atherothrombosis are at increased risk of subsequent vascular events, prevention of CV outcomes is an important goal in these patients.[5] Although the prevention of atherothrombosis requires a multidisciplinary approach including lifestyle modifications, drug therapy remains an integral part of the management of atherothrombotic patients.[7] While several randomized clinical trials have assessed evidence-based medicine for the management of atherothrombosis, very few registries/population-based studies have demonstrated a real-world estimation of current treatment strategies. The REACH registry is a large, international, observational study aimed to observe contemporary outpatients with atherothrombosis and their risk factors worldwide.[8] It demonstrated a high prevalence of risk factors and 1-year event rates such as CV death, MI, stroke, or hospitalization.[9] This report presents 1-year follow-up data on CV event rates in Mexican patients enrolled in the REACH registry and their comparison with the global results.

## Methods

### Study Design

Between December 2003 and June 2004, each of the 62 invited physicians (mainly internists, cardiologists, and neurologists) recruited a maximum of 15 eligible patients. The detailed design and methodology of the REACH registry is published elsewhere.[10] The study was designed to provide clinical 4-year follow-up. Briefly, the registry enrolled consecutively eligible outpatients age ≥45 years to form 2 research groups, a symptomatic group and an asymptomatic group.

### Symptomatic Group

The symptomatic group consisted of patients in 1 or more of the following 3 subgroups:

1. Coronary artery disease (CAD): patients who had stable angina with documented CAD, history of unstable angina with documented CAD, history of percutaneous coronary intervention, history of coronary artery bypass graft surgery, or previous MI.
2. Cerebrovascular disease (CVD): patients with diagnosis of transient ischemic attack or ischemic stroke.
3. Peripheral arterial disease (PAD): patients having current intermittent claudication with ankle brachial index (ABI) <0.9 or a history of intermittent claudication together with a previous and related intervention, such as angioplasty, stenting, atherectomy, peripheral arterial bypass graft, or other vascular intervention including amputation.

### Asymptomatic Group

The asymptomatic group consisted of patients receiving treatment for diabetes mellitus, diabetic nephropathy, ABI <0.9, asymptomatic carotid stenosis ≥70%, carotid intima media thickness ≥2× adjacent sites, systolic blood pressure (SBP) ≥150 mm Hg despite therapy for ≥3 months, hypercholesterolemia under medication, current smoking

has received institutional research grants from sanofi-aventis and Abbott Labs. Dr. Leonardo Llamas-López has received research grants from Bristol-Myers Squibb, Abbott-Biogen Idec, Bayer Schering, Serono, and Teva Pharmaceutical Industries. Dr. Ricardo Rangel-Guerra has received research grants from Bristol-Myers Squibb, UCB, Pfizer, Bial, Supernus, and Roche. Dr. Marco Alcocer-Gamba has received research grants from AstraZeneca, Bristol-Myers Squibb, sanofi-aventis, Bayer HealthCare, Pfizer, and Merck Sharp & Dohme. Dr. Deepak L. Bhatt has received institutional research grants from AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Heartscape, sanofi-aventis, and The Medicines Company. Dr. P. Gabriel Steg has received research grants from sanofi-aventis (significant); is on the speakers' bureau (all modest) for Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Nycomed, sanofi-aventis, Servier, and The Medicines Company; and is a consultant/advisory board member (all modest) for Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Endotis Pharma, GlaxoSmithKline, Medtronic, Merck Sharp & Dohme, Nycomed, sanofi-aventis, Servier, and The Medicines Company.


Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20800 

≥15 cigarettes/day, men age ≥65 years, or women age ≥70 years.

Polyvascular disease was defined as coexistent symptomatic (clinically recognized) arterial disease in 2 or 3 locations (coronary, cerebral, and/or peripheral) in each patient. Patients already in clinical trials, hospitalized patients, or those who might have difficulty returning for a follow-up visit were excluded. The protocol was submitted to the institutional review board according to local requirements and signed informed consent was obtained for all patients. The Committee of Ethics of each participating center approved the study.

### Statistical Analysis

Continuous variables were expressed as mean ± SD and categorical variables were expressed as relative frequencies. Event rates are reported after adjustment for age and gender. This adjustment was accomplished through the corrected group prognosis method in the Cox proportional hazards model.[11] The differences in 1-year incidence rates of selected endpoints (nonfatal stroke, CV death, nonfatal MI, CV death/MI/stroke, and CV death/MI/stroke/hospitalization) according to the number of disease locations were evaluated using the test for trend in the Cox proportional hazards model. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS software version 9.0 (SAS Institute, Inc., Cary, NC).

## Results

In Mexico 900 patients were recruited in the REACH registry, and 1-year follow-up data were available for 837 (93%) patients. The baseline characteristics of the 837 patients here analyzed are presented in Table 1. The mean age of these patients was 67.9 ± 10.3 years and 61.9% were male. Hypertension, hypercholesterolemia, diabetes, and overweight/obesity were the main diseases as vascular risk factors and many patients were former or current smokers. The majority of patients (85.8%) had history of symptomatic atherothrombosis, especially CAD (51.4%) and CVD (35.4%). At 1-year follow-up, the use of evidence-based medications remained high: 87.6% of patients were on antiplatelet agents, 84.1% were on antihypertensive and/or glucose-lowering agents, and 61% were on lipid-lowering agents (Table 2).

The all-cause case mortality rate at 1-year follow-up was 3.3%, but notably, without differences between symptomatic patients and asymptomatic subjects with multiple vascular risk factors (3.3% vs 3.1%, respectively) (Table 3). On the other hand, event rates for symptomatic patients were markedly higher than those for patients with multiple risk factors. The overall rate of the composite research outcome CV death/MI/stroke at 1 year was 5.3%, ranging from 2.9% in patients in multiple vascular risk factors to 9.9% of patients with PAD. The rate of the combined endpoint of CV death/MI/stroke/hospitalization for atherothrombotic events was higher in the symptomatic group (14.6%) than in

Table 1. Baseline Characteristics of Patients in the First-Year Follow-Up Analysis of the Total REACH Mexico Population (N = 837)

| Variable | % |
|---|---|
| Age, y (mean ± SD) | 67.90 ± 10.31 |
| Male gender | 61.94 |
| Hyperglycemia (≥126 mg/dL) | 47.07 |
| Hypertension (BP >140/90 mm Hg) | 74.67 |
| Hypercholesterolemia (≥200 mg/dL) | 57.83 |
| Overweight (BMI 25–30 kg/m²) | 45.88 |
| Obese (BMI ≥30 kg/m²) | 26.27 |
| Former smoker | 39.05 |
| Current smoker | 9.30 |
| History of atherosclerotic disease | |
| CAD | 51.37 |
| Stable angina with documented CAD | 18.27 |
| Unstable angina with documented CAD | 15.28 |
| MI | 29.00 |
| PCI | 27.03 |
| CABG | 13.91 |
| CVD | 35.36 |
| TIA | 15.38 |
| Stroke | 26.38 |
| PAD | 11.95 |
| Claudication and ABI <0.9 | 9.20 |
| Peripheral angioplasty/stenting/surgery | 5.02 |
| Claudication and amputation | 3.11 |
| Any symptomatic atherothrombosis | 85.78 |
| 3 risk factors only | 14.22 |

Abbreviations: ABI, ankle-brachial index; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CVD, cerebrovascular disease; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; REACH, Reduction of Atherothrombosis for Continued Health; SD, standard deviation; TIA, transient ischemic attack.


Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20800 

Table 2. Baseline Medication in First-Year Follow-Up Analysis for Total Population (N = 837)

| Medication | % |
|---|---|
| ASA | 76.79 |
| Other antiplatelet agent | 40.24 |
| ASA and other antiplatelet | 29.22 |
| ≥1 antiplatelet agent | 87.80 |
| Oral anticoagulants | 7.09 |
| NSAIDs | 9.29 |
| Statins | 59.57 |
| Other lipid-lowering agent | 11.72 |
| ≥1 lipid-lowering agent | 63.76 |
| Calcium channel blockers | 34.33 |
| β-Blockers | 27.99 |
| Nitrates | 16.51 |
| Diuretics | 31.82 |
| ACE inhibitors | 35.29 |
| ARBs | 27.37 |
| Other antihypertensives | 3.37 |
| ≥1 antihypertensive agent | 85.89 |
| PAD treatment | 7.94 |
| Insulin | 7.19 |
| Biguanides | 25.54 |
| Sulfonylureas | 29.98 |
| Thiazolidinedione | 4.44 |
| Other antidiabetics | 4.80 |
| ≥1 antidiabetic agent | 46.17 |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid; NSAIDs, nonsteroidal anti-inflammatory drugs; PAD, peripheral arterial disease.

the multiple risk factors group (5.1%; $P = 0.01$). Kaplan-Meier actuarial analysis for the combined endpoint of CV death/MI/stroke and its individual components over 1-year follow-up is shown in the Figure 1. The highest event rate in case of CV death/MI/stroke/hospitalization for atherothrombotic events was reported in patients with atherothrombotic disease at 3 vascular locations (30.1%), followed by patients with disease at 2 locations (21.9%) and 1 location (13.4%) (Table 4). The increase in the combined endpoint with any additional vascular symptomatic disease location was statistically significant ($P = 0.0006$).

## Discussion

CV disease is a leading cause of global healthcare burden and is also the most important cause of death in Mexico.[12] We present 1-year follow-up data on CV event rates and evaluate the management of atherothrombosis in the stable Mexican outpatients of the REACH registry. These results are in line with those reported for the Latin American population.[9]

Atherothrombosis is a diffuse and progressive process. The A Global Atherothrombosis Assessment (AGATHA) study on patients with or at risk of atherothrombosis showed that one-third of patients had the disease at more than 1 site.[13] In our study, 11.3% of patients had symptomatic polyvascular disease. The 1-year event rate of CV death/MI/stroke/hospitalization in Mexican patients also increased with the number of symptomatic arterial disease locations. PAD is often undiagnosed, and hence there is underestimation of the total impact of polyvascular disease.[14] Here it was observed as an additive risk in terms of event rates for the coincidence of documented vascular disease locations, so that any additional arterial bed documented increases the risk of the primary research outcome by about 50%. The endpoint CV death/MI/stroke/hospitalization for atherothrombotic events was 14.6% for patients in the symptomatic group and 5.1% for asymptomatic patients with multiple risk factors. Our results demonstrated that among symptomatic patients, those with PAD (23.3%) had higher event rates than those with CAD (14.1%) and CVD (15.6%). This suggests that, by the time the peripheral arteries are affected, central coronary or cerebral vascular beds suffer clinically significant atherosclerosis. This is an issue that awaits further confirmation in the Mexican INDAGA registry.

Our results showed high prevalence of diabetes, hypertension, and hypercholesterolemia in stable atherothrombotic outpatients. This is in line with earlier studies in the Mexican population demonstrating a high prevalence of CV risk factors such as obesity, hypertension, hypercholesterolemia, or smoking, indicating a high probability of the occurrence of atherosclerotic diseases.[3,4,15] Established international guidelines emphasize the merits of aggressive risk reduction such as lifestyle modification along with antidiabetic, antihypertensive, or antiplatelet therapy for patients with established CV disease.[16,17] Besides optimal management of risk factors for atherothrombosis, antiplatelet agents are effective in reducing the risk of further ischemic events in patients with documented arterial disease.[18] In the Mexican population, despite the fact that symptomatic patients received fairly good CV risk

Table 3. One-Year Cardiovascular Event Rates for the Total Population and Main Subsets (N = 837)

| Events | Mexico | | | | | | Global Registry | Latin America |
|---|---|---|---|---|---|---|---|---|
| | Total Symptomatic | Total CAD | Total CVD | Total PAD | Multiple Risk Factors Only | Total | Total | Total |
| No. | 718 | 430 | 296 | 100 | 119 | 837 | 64 977 | 1835 |
| All-cause mortality, % | 3.32 | 3.53 | 4.24 | 4.96 | 3.13 | 3.30 | 2.58 | 3.30 |
| Major CV event, % | | | | | | | | |
| CV death | 2.02 | 2.27 | 2.31 | 5.02 | 1.18 | 1.93 | 1.65 | 2.23 |
| Nonfatal MI | 1.10 | 1.90 | 0.59 | 0.00 | 2.55 | 1.22 | 1.14 | 0.96 |
| Nonfatal stroke | 2.76 | 1.26 | 5.12 | 4.34 | 0.00 | 2.33 | 1.66 | 2.74 |
| CV death, MI, or stroke | 5.70 | 4.93 | 7.88 | 9.90 | 2.90 | 5.32 | 4.24 | 5.76 |
| CV death, MI, stroke, or hospitalization for atherothrombotic events | 14.65 | 14.09 | 15.68 | 23.31 | 5.13 | 13.24 | 12.81 | 13.09 |

Abbreviations: CV, cardiovascular; CVD, cerebrovascular disease; MI, myocardial infarction; PAD, peripheral arterial disease.

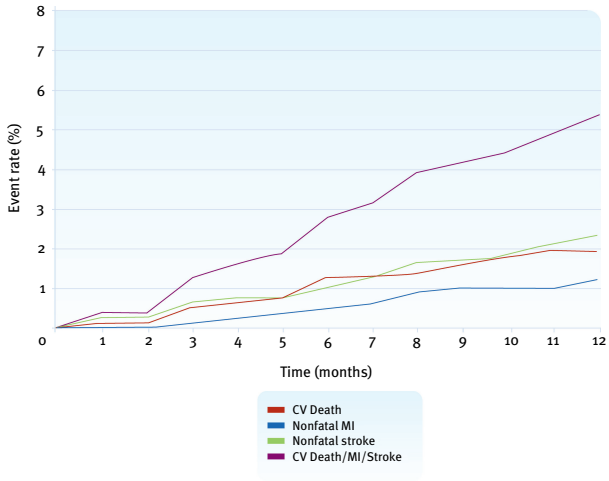


Figure 1. Event curves for CV death, nonfatal myocardial infarction, and stroke from enrollment to 1-year follow-up. Abbreviations: CV, cardiovascular; MI, myocardial infarction.

Table 4. One-Year Cardiovascular Event Rates as a Function of Number of Symptomatic Vascular Disease Locations (N = 837)

| Events | None | 1 Vascular Disease Location | 2 Vascular Disease Locations | 3 Vascular Disease Locations |
|---|---|---|---|---|
| No. | 119 | 623 | 82 | 13 |
| All-cause mortality | 3.07 | 2.74 | 5.55 | 15.96 |
| Major CV event | | | | |
| CV death | 1.13 | 1.52 | 3.78 | 13.20 |
| Nonfatal MI | 2.59 | 1.05 | 2.00 | 0.00 |
| Nonfatal stroke | 0.00 | 2.19 | 7.09 | 0.00 |
| CV death, MI, and/or stroke | 2.93 | 4.59 | 12.87 | 17.26 |
| CV death, MI, stroke, and/or hospitalization for atherothrombotic events | 5.15 | 13.41 | 21.90 | 30.16 |

Abbreviations: CV, cardiovascular; MI, myocardial infarction.

management, 1-year event rates remained high. Also, a significant minority of patients did not receive appropriate evidence-based medications for CV symptoms and risk factors.

## Clinical Implication

This report provides important evidence that in Mexico atherosclerotic disease accounts for about 2% of incident CV deaths per year and 15% of a combined endpoint of major vascular catastrophes and hospitalization. The prevalence of CV risk factors is high in the Mexican population. Mortality did not differ between the group of patients with documented or symptomatic atherothrombotic disease and the group of asymptomatic individuals with vascular risk factors. Nevertheless, there exists an


Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20800 

additive risk for the coincidence of documented vascular disease locations, so that implication of any additional arterial location increases by 50% the risk of CV death, MI, stroke, or hospitalization for atherothrombosis. PAD disease poses the major risk for this prespecified research outcome over CAD or CVD, which suggests that by the time the peripheral arteries are affected, the coronary and cerebral arteries already have significant atherosclerosis. Moreover, in patients with either symptomatic atherothrombotic disease or with its main risk factors only, the risk for the primary research outcome of this report augments steeply along 1 year of clinical observation. Our results urge the medical and lay community to implement aggressive risk-reduction intervention and profound diagnostic assessments to document the concurrence of implication of other vascular territories in a particular patient with at least 1 documented vascular disease location or risk factors.

### Study Limitations

With the original methodology of this registry, it is not possible to definitively clarify whether the high rate of CV events during follow-up could be a consequence of low patient compliance with the physician recommendations, either with respect to lifestyle changes or medications. Information on achievement of evidence-based goal parameters in clinical management (ie, target cholesterol, glucose, body weight, blood pressure) and its relationship with research outcomes is not provided.

### Conclusion

The 1-year follow-up data in the Mexican population mirror the global and Latin American REACH results in terms of high risk factor prevalence and CV event rates. Thus, our results call for a more aggressive attitude in improving awareness and recognizing other implications of atherosclerosis, a primary systemic disease, to practice active risk reduction by controlling comorbid and causal factors.

### Acknowledgments

We thank the sanofi-aventis Mexico team and the Amrit group for their assistance with coordinating revisions and providing editorial help in preparing this manuscript, including editing, checking content and language, formatting, referencing, and preparing tables and figures; and Christelle Baffie for her support with the statistical analyses. The sanofi-aventis global (Paris, France) and Mexico teams verified all statistical analyses. A special collaboration was maintained with Dr. Erwin Chiquete in review of the scientific content and final drafting.

The REACH Investigators, Mexico are Arturo Abundes Velasco, Geronimo Aguayo, Marco Antonio Alcocer Gamba, Graciela Alexanderson, Melchor Alpizar, Luis Enrique Amaya, Antonio Arauz, Armando Astorga, Jose Ramon Azpiri, Fernando Barinagarrementeria, Enrique Bernal Estrada, Hector Manuel Briseno Ramirez, Cesar Calvo, Carlos Cantu-Brito, Hector Colorado, Jorge Cortes, Jorge Cossio, Manuel Odin De Los Rios Ibarra, Rodrigo De Zatarain, Carlos Diaz, Luis Eng, Jesus Esparragoza, Luis Espinosa Sierra, Carlos Espinoza, Pedro Fernandez Bonetti, Elias Garcia Cantu, Rodrigo Garcia Martinez, Alejandro Garza Guerra, Felipe De Jesus Gonzalez Camid, Francisco Guerrero Pasqueira, Ismael Hernandez, Andrei Kostine, Jose Luis Leiva, Leonardo Llamas-Lopez, Berenice Lopez, Julio Lopez Cuellar, Mauricio Lopez Meneses, Antonio Marcos, Sergio Najar Lopez, Jacobo Nettel, Fernando Ortiz Galvan, Rogelio Peralta, Juan Carlos Perez Garcia, Alejandra Ranero, Ricardo Rangel-Guerra, Joel Rodriguez, Ildefonso Rodriguez Leyva, Jose Alberto Rojas, Aldo Romero, Gustavo Rubio, Jose Luis Ruiz, Alberto Sagastegui, Oscar Talamas, Monica Tapia, Jose Luis Antonio Toriz Melchor, Artemio Uribe, Jorge Vazquez, Jose Antonio Velasco, Erich Carlos Velasco Ortega, Raul Gerardo Velasco Sanchez, and Jorge Villarreal.

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20800 

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DOI:10.1002/clc.20800 