Received: 22 April 2016 | Revised: 5 July 2016 | Accepted: 12 July 2016

DOI 10.1002/clc.22583

PREVENTION WILEY CLINICAL CARDIOLOGY

CLINICAL INVESTIGATIONS

Residual Ischemic Risk and Its Determinants in Patients With Previous Myocardial Infarction and Without Prior Stroke or TIA: Insights From the REACH Registry

Jérémie Abtan MD | Deepak L. Bhatt MD, MPH | Yedid Elbez MSc | Emmanuel Sorbets MD | Kim Eagle MD, MACC | Yasuo Ikeda MD, PhD | David Wu PhD | Mary E. Hanson PhD | Hakima Hannachi MD | Puneet K. Singhal PhD | Philippe Gabriel Steg MD | Gregory Ducrocq MD, PhD, FESC, on Behalf of the REACH Registry Investigators

French Alliance for Cardiovascular Clinical Trials (FACT) (Abtan, Elbez, Sorbets, Steg, Ducrocq), DHU-FIRE, Hôpital Bichat (Assistance Publique–Hôpitaux de Paris), Université Paris-Diderot, Sorbonne-Paris Cité and INSERM U-1148, Paris, France, and Hôpital Avicenne (Assitance Publique–Hôpitaux de Paris) and Université Paris 13, Bobigny, France; Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School (Bhatt), Boston, Massachusetts; University of Michigan Cardiovascular Center (Eagle), Ann Arbor, Michigan; Department of Internal Medicine, Graduate School of Medicine (Ikeda) Keio University, Tokyo, Japan; Merck & Co., Inc. (Wu, Hanson, Hannachi, Singhal), Kenilworth, New Jersey; National Heart and Lung Institute, Institute of Cardiovascular Medicine and Science (Steg), Royal Brompton Hospital, Imperial College, London, United Kingdom

A list of the REACH Registry investigators has been published at Bhatt DL, Steg PG, Ohman EM, et al. *JAMA*. 2006;295:180–189.

All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Specifically, all authors made substantial contributions to the conception and design of the study and manuscript or interpretation of the data, contributed to the drafting of the article or revising it critically for important intellectual content, and all gave final approval of the version to be published. In addition, all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Background: Although the rate of in-hospital ischemic events after myocardial infarction (MI) has dramatically decreased, long-term residual risk may remain substantial. However, most of the information on current residual risk is derived from highly selected randomized trials.

Hypothesis: In patients with previous MI and no prior ischemic stroke/transient ischemic attack (TIA), residual ischemic risk increases over time.

Methods: Using the international Reduction of Atherothrombosis for Continued Health (REACH) registry, we analyzed baseline characteristics and 4-year follow-up of patients with previous MI and no history of stroke/TIA to describe annual rates of recurrent ischemic events globally and by geography. The primary outcome was the composite of cardiovascular death, MI, or stroke. Multivariate analysis identified risk factors associated with recurrent ischemic events.

Results: Data from 16 770 patients enrolled at 5587 sites in 44 countries were analyzed. The rate of the primary outcome increased annually from 4.7% during year 1 to reach a 4-year rate of 15.1%. Compared with North America, Japan experienced lower ischemic event rates ($P < 0.01$), whereas Eastern Europe ($P < 0.01$) and the Middle East ($P = 0.01$) experienced higher ischemic event rates. The presence of congestive heart failure, polyvascular disease, diabetes, atrial fibrillation or flutter, and older age were associated with increased residual risk (all $P < 0.01$). Statin use was associated with lower ischemic risk ($P < 0.01$).

Conclusions: In this study, residual ischemic risk after MI accrued progressively up to 4 years of follow-up, emphasizing the value of intensive secondary prevention strategies to minimize residual risk.

KEYWORDS

ischemic risk, Ischemic heart disease, myocardial infarction, vorapaxar

Dr. Jérémie Abtan, Mr. Yedid Elbez, Dr. Emmanuel Sorbets, and Dr. Kim Eagle have no disclosures. Dr. Deepak L. Bhatt has served on the advisory boards for Cardax, Elsevier PracticeUpdate Cardiology, Medscape Cardiology, and Regado Biosciences; has served on the boards of directors for Boston VA Research Institute and the Society of Cardiovascular Patient Care; has been chair of the American Heart Association Quality Oversight Committee; has served on data monitoring committees for Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; has received honoraria from the American College of Cardiology (senior associate editor, *Clinical Trials and News*, http://www.ACC.org), Belvoir Publications (editor in chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (editor in chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor, associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (CME steering committees); has served as deputy editor for *Clinical Cardiology*, vice chair of the NCDR-ACTION Registry Steering Committee, and chair of the VA CART Research and Publications Committee; has received research funding from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi-Aventis, and The Medicines Company; has received royalties from Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); served as site co-investigator for Biotronik, Boston Scientific, and St. Jude Medical; has served as trustee for the American College of Cardiology; and has performed unfunded research for FlowCo, PLx Pharma, and Takeda. Dr. Yasuo Ikeda has received an honorarium from Sanofi and served on the advisory board for Daiichi-Sankyo. Dr. Philippe Gabriel Steg has received research grants from Sanofi and Servier; has received speaking or consulting fees from Amarin, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, CSL-Behring, Daiichi-Sankyo, GlaxoSmithKline, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Servier, and The Medicines Company; and reports holding stock in Aterovax. Dr. David Wu, Dr. Mary E. Hanson, Dr. Hakima Hannachi, and Dr. Puneet K. Singhal are employees of Merck & Co., Inc., and own stock and/or stock options in the company. Dr. Gregory Ducrocq has received speaker and/or consulting fees from AstraZeneca, Biotronik, BMIS, Daiichi Sankyo, and Lilly; has served on the advisory board for Lilly; has served on clinical events committees for Sanofi and Phillips; has served on the data and safety monitoring board for Abbott and MicroPort; and has received travel fees from AstraZeneca.

This work was in part supported by a grant to Hopital Bichat from Merck & Co., Inc., Kenilworth, NJ, USA, for the statistical analyses which were performed by Yedid Elbez, PhD. No funding was provided for medical writing. The first draft was written by Dr. Jérémie Abtan and subsequently revised by the co-authors. Merck was allowed to review the manuscript but not change any aspect of it.

Corresponding Author: Gregory Ducrocq, MD, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris, France, gregory.ducrocq@bch.aphp.fr

1 | INTRODUCTION

During the past decade, the risk of recurrent ischemic events after acute myocardial infarction (MI) has been dramatically reduced.[1] This reduction has been driven both by the wide use of revascularization and by improvements in pharmacological treatment, especially antithrombotic[2,3] and lipid-lowering therapies.[4] As the current rate of in-hospital ischemic events (including cardiovascular mortality) is currently low,[5] registry data show that the vast majority of ischemic events occur after discharge from the index admission. In an analysis of the international Global Registry of Acute Coronary Events (GRACE) registry of acute coronary syndromes (ACS), 5-year post-MI mortality was approximately 20%, with more than two-thirds of deaths occurring within 30 days after discharge.[6] Reduction of this long-term residual risk represents one of the main challenges in current MI management. Its reduction could be achieved by more intensive antithrombotic and lipid-lowering medications. Therefore, it is important to precisely characterize long-term ischemic residual risk after MI. Because most of the existing data stem from the highly selected populations from randomized clinical trials (RCTs), it is important to use data from large contemporary international registries, which are externally validated and whose event rates may be substantially higher.[7]

We used the Reduction of Atherothrombosis for Continued Health (REACH) international registry of atherothrombosis[8,9] to characterize the residual 4-year ischemic risk in patients with previous MI and no prior ischemic stroke/transient ischemic attack (TIA) and describe the main determinants of residual risk. The choice to exclude patients with prior stroke or TIA was made a priori because the balance between risk and benefit of antithrombotic agents in this population is specific and deserves a separate analysis.[10] Specifically, the main objectives of the present study were to describe annual rates of recurrent ischemic events defined as a composite of stroke, MI, or cardiovascular (CV) death over 4 years, globally and by geographic region, and to identify the variables associated with recurrent ischemic events.

2 | METHODS

2.1 | Population

The design, methods, and main results of the REACH registry, an international, prospective, observational study, have been previously described.[8,11] Briefly, from December 2003 to June 2004, REACH enrolled consecutive outpatients age ≥45 years with established coronary artery disease (CAD), cerebrovascular disease, or peripheral artery disease (PAD), or with ≥3 atherothrombotic risk factors. Documented CAD was defined as ≥1 of the following criteria: 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.

Data were collected centrally using standardized case-report forms. The initial follow-up period was 2 years; however, centers were invited to participate in a 2-year extension. Signed informed consent was obtained from all patients, and the institutional review board in each country approved the protocol. Only patients with prior MI and no history of stroke or TIA were included in the present analysis.

2.2 | Outcomes

Following enrollment, detailed baseline characteristics, treatment, and outcomes were collected annually. Endpoints were not adjudicated but were based on physician report at the time of follow-up. Stroke was verified by either hospital records or a neurology consultation.

Cardiovascular death was defined as any MI or stroke followed by death in the next 28 days regardless of the cause, death from pulmonary embolism, heart failure (HF), death following vascular surgery, following a visceral or limb infarction, or any sudden death unless proven to be non-CV by autopsy. Polyvascular disease was defined as atherothrombosis in ≥2 arterial beds (coronary, peripheral, cerebrovascular) at baseline. Cardiovascular hospitalization was defined as any hospitalization for unstable angina, TIA, worsening of claudication related to PAD, surgery, carotid angioplasty or stenting, amputation affecting lower limbs, peripheral bypass graft, or angioplasty or stenting for PAD.

For the current study, the primary outcome was the composite of stroke, MI, or CV death. The secondary outcomes included CV death, MI, and stroke analyzed separately, as well as CV hospitalization.

2.3 | Statistical Analysis

Patients' baseline characteristics, medical history, and treatment patterns are presented with descriptive statistics, including frequencies and percentages for categorical variables and mean and SD for continuous variables, in the overall study population. Kaplan-Meier estimates were used to assess cumulative incidence rates at each year of follow-up. Patients from each region of enrollment were also investigated as subgroups. Risks of study outcomes for each region were estimated by Cox proportional hazards models adjusted for the REACH risk score predicting CV events,[12] after exclusion of the geographic items of the score.

Multivariate Cox regression models were used to assess the determinant risk factors for residual CV risk in the study population. Univariate models were first built to assess the impact of each individual variable on CV outcomes. A set of variables was then selected and introduced in multivariate models according to their statistical significance in univariate models ($P \leq 0.10$), their clinical significance, and their nonredundancy with other variables in the model.

Data were analyzed overall and by the following geographical regions: North America (Canada and United States), Latin America (Brazil, Chile, and Mexico), Western Europe (Austria, Belgium, Finland, France, Germany, Greece, the Netherlands, Portugal, Spain, Switzerland, and the United Kingdom), Eastern Europe (Hungary, Romania, Russia, and Ukraine), the Middle East (Israel and United Arab Emirates), Asia (China, Taiwan, Hong Kong, Malaysia, Philippines, and Thailand), and Japan. Japan was analyzed separately from the rest of Asia due to different timing of enrollment. Data were processed using the SAS software package version 9.3 (SAS Institute, Inc., Cary, NC).

3 | RESULTS

A total of 65 531 patients were initially enrolled at 5587 centers in 44 countries. Of these, 20 461 had a history of MI, among whom 16 770 (83.3%; 95% confidence interval [CI]: 82.9-83.9) had no history of stroke or TIA and constituted the study population. Of these, 6666 patients were from North America, 531 were from Latin America, 4703 were from Western Europe, 1795 were from Eastern Europe, 269 were from the Middle East, 1021 were from Asia, and 957 were from Japan. The proportion of patients with an available 4-year follow-up in our study cohort was 49.3%, taking into account the countries that prospectively refused to extend the follow-up over 2 years. There was no suggestion of systematic bias when comparing the characteristics of subjects with a 4-year follow up vs those without a 4-year follow up (see Supporting Information, Table 1, in the online version of this article).

3.1 | Baseline Characteristics

Mean age (SD) of the overall population was 67 ± 10 years, and 75.4% were men (Table). Proportions of patients with risks factors were as follows: diabetes mellitus (DM), 35.6%; hypercholesterolemia, 79.2%; hypertension, 76.4%; current smoker, 51.5%; and obesity, 40.1%. The time since the index MI was <1 year for 22.6% of the population. Important variations in baseline characteristics were observed according to geographic region of enrollment (Table).

3.2 | Ischemic Events

3.2.1 | Temporal Trends

The cumulative incidence of CV death, MI, or stroke was 4.7% during the first year after inclusion in the registry, with a continuous accrual of approximately 3.5% with each year of follow-up. The 4-year rate (measured starting at enrollment) of CV death, MI, or stroke in the overall population was 15.1% (Figure 1). The primary outcome was driven by each of its components: CV death increased by approximately 2.2% each year (2.2%, 4.2%, 6.1%, and 8.1% for years 1 through 4, respectively), nonfatal MI by slightly more than 1% annually (1.8%, 3.1%, 4.2%, and 5.3% for years 1 through 4, respectively), and nonfatal stroke by approximately 1% annually (1.0%, 1.8%, 2.6, and 3.6% by years 1 through 4 after enrollment, respectively). Similarly, the cumulative incidence of CV hospitalization also increased gradually over the 4 years of follow-up, from 11.8% in the first year to 17.7% in the second year, 23.1% in the third year, and up to 26.6% by the fourth year (see Supporting Information, Figure 1, in the online version of this article).

3.2.2 | Differences by Geographic Region

Compared with North America, patients enrolled in Latin America (hazard ratio [HR]: 0.75, 95% CI: 0.57-1.00, $P = 0.04$), Western Europe (HR: 0.85 95% CI: 0.76-0.95, $P < 0.01$), and Japan (HR: 0.53, 95% CI: 0.41-0.67, $P < 0.01$) had lower unadjusted rates of 4-year ischemic events (see Supporting Information, Figure 2, in the online version of this article). Ischemic event rates were lower in patients from Japan (HR: 0.52, 95% CI: 0.41-0.67, $P < 0.01$), whereas patients in Eastern Europe (HR: 1.17, 95% CI: 1.01-1.36, $P < 0.01$) and the Middle East (HR: 1.54, 95% CI: 1.11-2.15, $P = 0.01$) experienced more events compared with patients in North America when adjusted for REACH risk score (Figure 2). Results were similar when adjustments were made for sex and age (see Supporting Information, Figure 3, in the online version of this article).

TABLE 1 Baseline Patient Demographics and Clinical Characteristics According to Period Since Previous MI

	Overall, N = 16 770	North America, n = 6666	Latin America, n = 531	Western Europe, n = 4703	Eastern Europe, n = 1795	Middle East, n = 269	Asia, n = 1021	Japan, n = 957
Mean age, y (SD)	67.07 (10.28)	68.93 (10.4)	65.32 (9.86)	66.75 (9.76)	65.32 (9.86)	64.71 (10.47)	62.69 (9.94)	68.32 (9.18)
Male sex (%)	12 638 (75.4)	4621 (69.4)	413 (77.8)	3761 (80.1)	413 (77.8)	214 (80.5)	843 (82.6)	779 (81.4)
DM	5920 (35.6)	2744 (41.3)	202 (38)	1510 (32.5)	202 (38)	127 (47.6)	372 (37.1)	377 (39.6)
HTN	12 806 (76.4)	5508 (82.6)	379 (71.4)	3423 (72.8)	379 (71.4)	197 (73.5)	693 (67.9)	596 (62.3)
Dyslipidemia	13 262 (79.2)	5755 (86.5)	357 (67.2)	3862 (82.2)	357 (67.2)	234 (87)	707 (69.3)	534 (55.8)
Renal impairment[a]	331 (2.5)	172 (3.1)	6 (1.6)	54 (1.5)	6 (1.6)	9 (3.8)	40 (5)	21 (2.4)
Angina								
Stable	6711 (40.4)	2619 (39.8)	138 (26.1)	1830 (39.1)	138 (26.1)	98 (37.1)	266 (26.3)	308 (32.5)
Unstable	3159 (19.1)	1183 (17.9)	111 (21.1)	828 (17.8)	111 (21.1)	71 (26.7)	202 (20.1)	116 (12.3)
Vascular disease								
Single vascular	15 229 (90.8)	6084 (91.3)	501 (94.4)	4076 (86.7)	501 (94.4)	257 (95.5)	986 (96.6)	906 (94.7)
Polyvascular	1541 (9.2)	582 (8.7)	30 (5.6)	627 (13.3)	30 (5.6)	12 (4.5)	35 (3.4)	51 (5.3)
History of MI								
≤1 year	3792 (22.6)	1256 (18.8)	153 (28.8)	1040 (22.1)	153 (28.8)	57 (21.2)	363 (35.6)	137 (14.3)
>1 year	12 978 (77.4)	5410 (81.2)	378 (71.2)	3663 (77.9)	378 (71.2)	212 (78.8)	658 (64.4)	820 (85.7)
AF/flutter	1820 (11)	885 (13.5)	36 (6.8)	445 (9.6)	36 (6.8)	17 (6.4)	56 (5.6)	65 (6.8)
CHF	3626 (22)	1660 (25.2)	77 (14.7)	910 (19.7)	77 (14.7)	56 (21.3)	202 (20.3)	157 (16.6)
PAD	1541 (9.2)	582 (8.7)	30 (5.6)	627 (13.3)	30 (5.6)	12 (4.5)	35 (3.4)	51 (5.3)
Obesity[a]								
Overweight (BMI 25– < 30 kg/m^2)	7154 (59.8)	2559 (50.4)	271 (71.3)	2258 (64.5)	271 (71.3)	123 (62.4)	403 (84.7)	318 (91.6)
Class I (BMI 30– > 35 kg/m^2)	3322 (27.8)	1548 (30.5)	86 (22.6)	960 (27.4)	86 (22.6)	55 (27.9)	59 (12.4)	26 (7.5)
Class II (BMI 35– < 40 kg/m^2)	1018 (8.5)	606 (11.9)	19 (5)	243 (6.9)	19 (5)	14 (7.1)	8 (1.7)	3 (0.9)
Class III (BMI ≥40 kg/m^2)	460 (3.8)	367 (7.2)	4 (1.1)	39 (1.1)	4 (1.1)	5 (2.5)	6 (1.3)	0 (0)
Smoker								
Former	8396 (51.5)	3429 (52.6)	290 (55)	2472 (55.2)	290 (55)	95 (37)	422 (41.9)	519 (57.2)
Current	2299 (14.1)	875 (13.4)	45 (8.5)	631 (14.1)	45 (8.5)	35 (13.6)	137 (13.6)	126 (13.9)
Medication								
ASA	13 427 (80.2)	5412 (81.3)	467 (87.9)	3618 (77.2)	467 (87.9)	249 (92.6)	802 (78.6)	780 (81.5)
≥1 Antiplatelet	14 770 (88.1)	5726 (86)	506 (95.3)	4176 (88.9)	506 (95.3)	258 (95.9)	938 (91.9)	869 (90.8)
ACEI[a]	8756 (52.4)	3298 (49.8)	267 (50.5)	2549 (54.4)	267 (50.5)	158 (59.2)	432 (42.3)	274 (28.6)
ARB[a]	3120 (18.7)	1408 (21.3)	105 (19.9)	749 (16)	105 (19.9)	50 (18.8)	279 (27.4)	295 (30.8)
Nitrate/other antianginal	6373 (38.5)	2012 (30.8)	157 (30)	1713 (37)	157 (30)	128 (47.9)	531 (52.3)	544 (56.8)
Statin	13 356 (79.7)	5509 (82.8)	397 (74.8)	3973 (84.7)	397 (74.8)	241 (89.6)	754 (73.8)	532 (55.6)
β-Blocker	11 363 (67.9)	4591 (69)	311 (58.8)	3382 (72.2)	311 (58.8)	198 (74.2)	614 (60.1)	333 (34.8)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid (aspirin); BMI, body mass index; CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; PAD, peripheral artery disease; REACH, Reduction of Atherothrombosis for Continued Health; SD, standard deviation.

Data are presented as n (%) unless otherwise noted. The percentages are slightly off because the denominator changes dues to missing observations in some of the variables.

[a]Unless otherwise indicated, $P < 0.001$ for all comparisons.

3.2.3 | Risk Factors for Recurrent Ischemic Events

Congestive HF (HR: 1.93, 95% CI: 1.69-2.20, $P < 0.01$), polyvascular disease (HR: 1.49, 95% CI: 1.25-1.77, $P < 0.01$), history of DM (HR: 1.38, 95% CI: 1.22-1.56, $P < 0.01$), atrial fibrillation (AF) or flutter (HR: 1.35, 95% CI: 1.14-1.59, $P < 0.01$) and older age (per additional year: HR: 1.02, 95% CI: 1.01-1.03, $P < 0.01$) were associated with increased risk of ischemic events (Figure 3). Baseline statin use was significantly associated with a reduction in ischemic events (HR: 0.77, 95% CI: 0.67-0.90, $P < 0.01$).

4 | DISCUSSION

In this analysis of MI patients from the REACH registry, the residual ischemic risk increased after the first year after the index event and

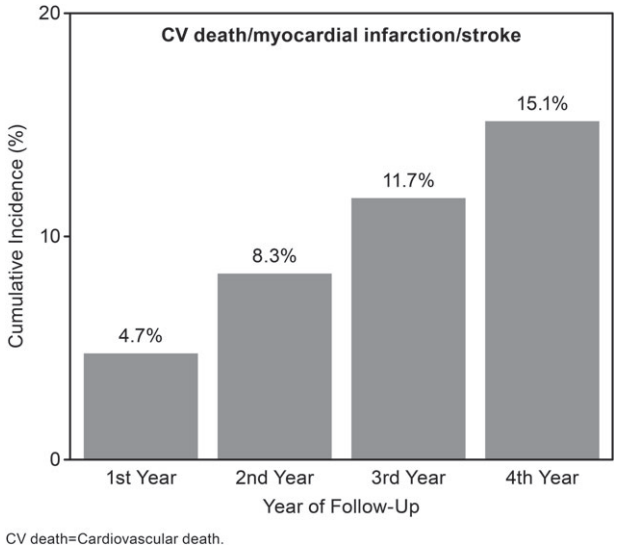

FIGURE 1 Cumulative incidence rates of the primary outcome (CV death, MI, or stroke) for post-MI patients with no history of TIA/stroke. Abbreviations: CV cardiovascular; MI, myocardial infarction; TIA, transient ischemic attack.

continuously increased at a yearly rate of approximately 3.5% per year for 4 years. There was no difference in risk between North America and Western Europe, but there was a higher risk for Eastern Europe and the Middle East and a lower risk for Japan. The independent predictors of residual risk were increasing age, presence of polyvascular disease, and history of DM, HF, or AF. The only factor that was associated with reduced risk was baseline treatment with statin.

International registries as well as large international randomized trials consistently showed an increased ischemic risk over the first year after MI and a slower but continuous accrual of ischemic events thereafter.[2,3,13] In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38), major ischemic events occurred in 10% of the population on prasugrel at 15 months and 9.8% in the ticagrelor group of Platelet Inhibition and Patient Outcomes (PLATO) at 12 months.[2,3] However, these were RCTs in which patients with ACS experienced more adverse ischemic events than did stable patients. These trials have to be separated from secondary prevention trials such as Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared With Placebo on a Background of Aspirin (PEGASUS), in which the ischemic event rate was ~ 9% at 36 months, or the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, in which the event rate was ~ 7% at 30 months.[13,14] A recent meta-analysis comparing dual to single antiplatelet therapy in >33 000 patients for 30 months showed an event rate of approximately 7%.[15] In the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction 50 (TRA 2°P-TIMI 50) trial, the rate of the composite endpoint of CV death, MI, or stroke at 3 years was slightly higher, occurring in 9.7% of patients with prior MI.[16] In comparison, the present analysis from a registry shows higher event rates than in large randomized trials.[13–15,17] These differences can be explained by the nature of our nonrandomized cohort, in which there were few selection criteria, and which, therefore, has probably greater external validity than randomized trials. Nevertheless, in all studies, event rates increased continuously over several months of follow-up, emphasizing the importance of the concept of residual ischemic risk and supporting the potential benefit of intensified therapies in post-MI patients without history of stroke or TIA.

Residual ischemic risk was uniformly distributed over the various geographic areas except for Japan, where patients experienced lower ischemic event rates, and Eastern Europe and the Middle East, where ischemic event rates were higher than in North America. The explanations for such differences have been described previously.[18] Briefly, differences in management and medication use have been reported. In addition, gaps in country-based economic organization and health care systems might explain differences in the prevalence and management of risk factors. In the end, genetic susceptibilities

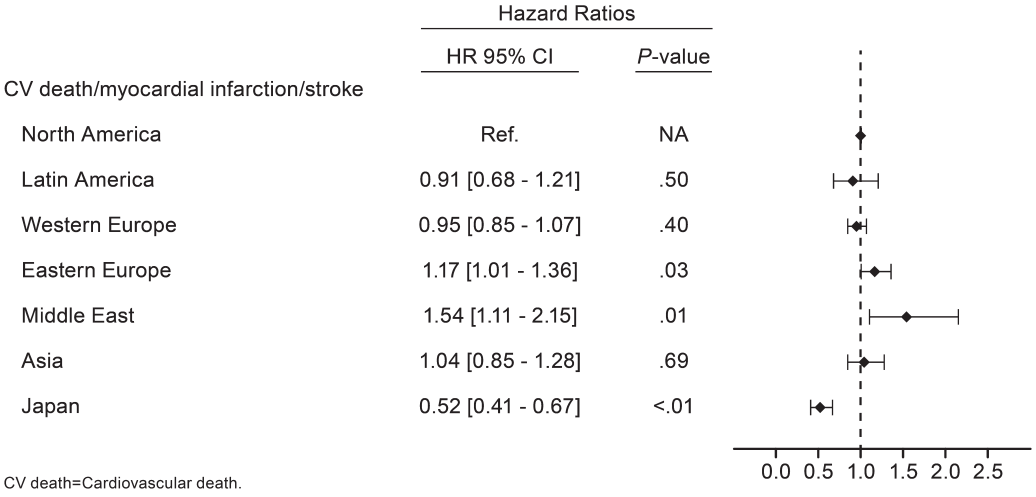

FIGURE 2 Hazard ratios for the primary outcome of CV death, MI, or stroke in post-MI patients with no history of stroke/TIA according to geographic region, adjusted for REACH risk score. Abbreviations: CI, confidence interval; CV cardiovascular; HR, hazard ratio; MI, myocardial infarction; NA, not applicable; REACH, Reduction of Atherothrombosis for Continued Health; Ref., reference; TIA, transient ischemic attack.

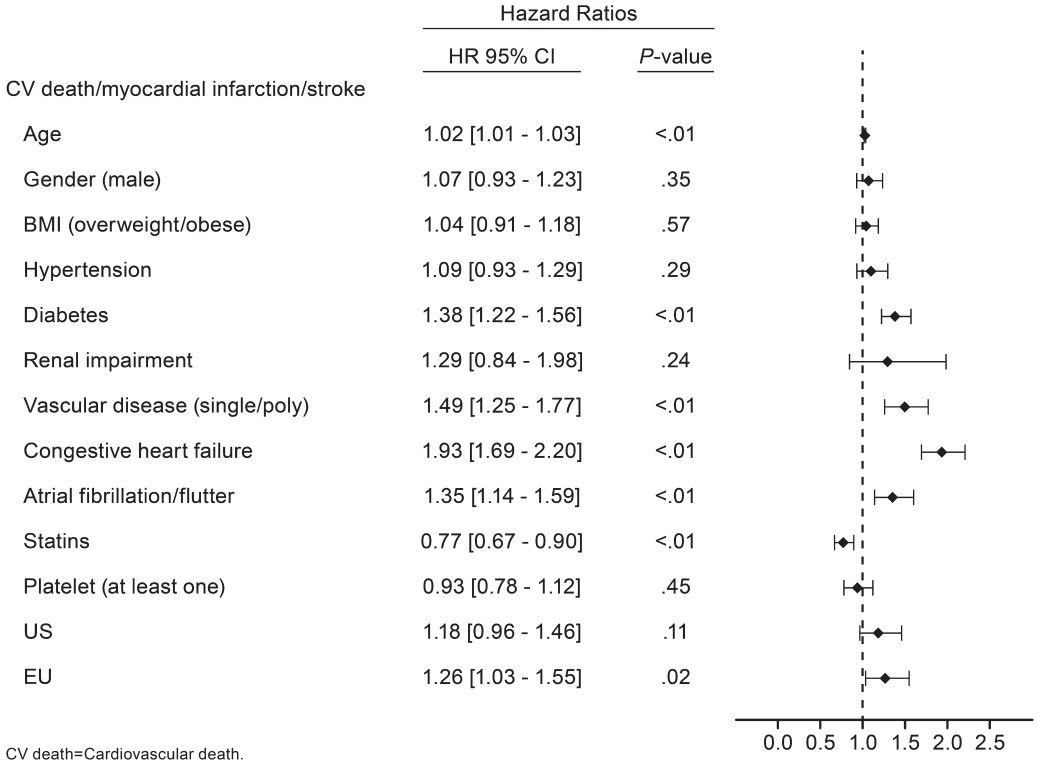

FIGURE 3 Hazard ratios of determinants for the primary outcome of CV death, nonfatal MI, or nonfatal stroke estimated by multivariate Cox models in post-MI patients with no history of TIA/stroke. BMI, body mass index; CI, confidence interval; CV, cardiovascular; EU, European Union; HR, hazard ratio; MI, myocardial infarction; TIA, transient ischemic attack; US, United States.

and lifestyle differences may play a role in risk variation.[18] Nevertheless, residual risk remains high and events accrue progressively over time across all geographic areas.

The factors associated with increased residual ischemic risk are consistent with prior observations. Increasing age is one of the strongest and most robust risk factors for CV events both in primary[19] and secondary prevention.[20] An association between AF and atherothrombotic disease has been described previously, and there is an important overlap between AF and atherosclerotic populations.[21] The presence of both conditions is associated with an increased risk of death, stroke, ACS, and bleeding.[22] This can be explained by the addition of risk from both conditions and challenges related to pharmacological treatment among these patients, such as uncertainty as to the optimal combination of anticoagulation and antiplatelet therapies in this population. That is, antiplatelet therapies do not protect from AF-related stroke; and the benefit of anticoagulation alone in protection against coronary events, particularly in MI patients who have generally undergone coronary stenting for their index MI, is at best uncertain. This leads to a greater hemorrhagic risk among these patients.[21–23] Heart failure is also an important determinant for CV events.[24,25] Left ventricular systolic dysfunction has been shown to be linked with higher mortality,[26] and chronic HF is a risk factor for ischemic events, indicating more extensive atherosclerotic disease.[27] Likewise, polyvascular disease has been well-documented to be correlated with risk in patients with established atherothrombosis.[28,29]

Several currently available agents can reduce residual ischemic risk, as we observed that statin therapy was associated with reduced risk. This observation is consistent with previously reported statin trials.[4,30,31] Further low-density lipoprotein cholesterol (LDL-C) lowering with ezetimibe has recently demonstrated additional risk reduction in total CV events when added to statin therapy.[32] Other promising LDL-C–lowering agents are currently being developed that could further decrease residual risk: PCSK9 inhibitors such as alirocumab and evolocumab,[33,34] which have demonstrated reductions in LDL-C levels when added to statins.[35] These trials have suggested a potential benefit on CV outcomes, but the results of larger, ongoing outcome trials are needed to determine whether bococizumab is effective at improving outcomes in high–CV risk patients not at LDL-C goal with maximally tolerated statin therapy (http://www.ClinicalTrials.gov: NCT01975376, NCT01975389).[36,37] In addition, other modifiable risk factors include cessation of smoking and reduction in body mass index to normal, which can lead to better control of type 2 DM and subsequently reduced CV risk.[38]

Antithrombotic agents are another option for decreasing residual risk in atherothrombotic patients. Because patients with previous stroke or TIA tend to have an unfavorable risk/benefit balance with newer antiplatelet or anticoagulant agents,[10,39] they were excluded from our study. In the present analysis, use of antiplatelet therapy was not associated with a reduced risk of ischemic events. However, because the present analysis focused on patients with CAD, the vast majority of patients (almost 90%) already received ≥1 antiplatelet agent. The timing and observational design of this study did not allow exploration of whether more intensive platelet inhibition (with P2Y12 antagonists such as clopidogrel, ticagrelor, or prasugrel, or with PAR-1 antagonists such as vorapaxar) or added anticoagulation (with low-dose factor Xa antagonists such as rivaroxaban) would further reduce ischemic events, because most of these options were not available at the time of registry enrollment. However, recent trials of long-term

antithrombotic therapy, especially after MI or, to a lesser extent, after percutaneous coronary intervention with drug-eluting stents, have demonstrated that intensive antithrombotic therapy used in secondary prevention did reduce the risk of ischemic events, although at the expense of increased risk of bleeding.[13,17,40] In the PEGASUS-TIMI 54 trial, treatment with the adenosine diphosphate receptor antagonist ticagrelor reduced the rate of ischemic events compared with placebo in patients 1 to 3 years post-MI.[13] Vorapaxar, a PAR-1 platelet receptor antagonist, has been evaluated in the TRA 2°P-TIMI 50 trial in the setting of secondary prevention in addition to aspirin and/or clopidogrel[17] in patients with stable atherosclerosis defined by prior MI, stroke, or PAD within the previous 2 weeks to 12 months prior to randomization. The results demonstrated a reduction in ischemic events at 3 years in patients with prior MI or PAD. Finally, adjunctive anticoagulation, using Xa inhibition with low-dose rivaroxaban, in addition to double antiplatelet therapy with clopidogrel and aspirin, has been shown to reduce ischemic events in patients with recent ACS.[40]

4.1 | Study Limitations

Our study has limitations worth noting. These analyses were drawn from an observational registry; therefore, the results presented are descriptive, and analyses on the determinants of residual risk and on geographic differences must be interpreted with caution. Follow-up rates were high, particularly for a registry of this scope and size. However, approximately 5.0% of the patients missed visits and, thus, we cannot actually exclude a small margin of error in the estimation of event rates; but this would be expected to result in, if anything, an underestimation of event rates. Although the registry was global, results may not be generalized to populations not represented by the registry. Moreover, clinical events were not adjudicated. However, measures were taken to select high-quality physicians, and hospitals and doctors provided diagnoses based on their expertise. Finally, the registry did not capture patient adherence to medication, which could impact patient outcomes.

5 | CONCLUSION

This analysis of the REACH registry showed residual risk of ischemic events in patients with previous MI without history of stroke or TIA continuously increasing by 15.1% over the 4 years of follow-up after enrollment. This emphasizes the importance of intensive secondary prevention efforts, including (but not limited to) enhanced antithrombotic treatment and more intense lipid lowering, to overcome this residual risk in selected patients.

ACKNOWLEDGMENTS

The REACH Registry was sponsored by Sanofi Aventis, Bristol-Myers Squibb, and the Waksman Foundation (Tokyo, Japan) and endorsed by the World Heart Federation.

REFERENCES

1. Puymirat E, Simon T, Steg PG, et al; FAST-MI Investigators. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. *JAMA*. 2012;308:998–1006.
2. Wallentin L, Becker RC, Budaj A, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.
3. Wiviott SD, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.
4. Cannon CP, Braunwald E, McCabe CH, et al; PROVE IT–TIMI 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes [published correction appears in *N Engl J Med*. 2006;354:778]. *N Engl J Med*. 2004;350:1495–1504.
5. Puymirat E, Schiele F, Steg PG, et al; FAST-MI Investigators. Determinants of improved one-year survival in non–ST-segment elevation myocardial infarction patients: insights from the French FAST-MI program over 15 years. *Int J Cardiol*. 2014;177:281–286.
6. Fox KA, Carruthers K, Steg PG, et al; GRACE Investigators. Has the frequency of bleeding changed over time for patients presenting with an acute coronary syndrome? The Global Registry of Acute Coronary Events. *Eur Heart J*. 2010;31:667–675.
7. Steg PG, López-Sendón J, Lopez DS, et al; GRACE Investigators. External validity of clinical trials in acute myocardial infarction. *Arch Intern Med*. 2007;167:68–73.
8. Bhatt DL, Steg PG, Ohman EM, et al; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006;295:180–189.
9. Bhatt DL, Eagle KA, Ohman EM, et al; REACH Registry Investigators. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA*. 2010;304:1350–1357.
10. Ducrocq G, Amarenco P, Labreuche J, et al. A history of stroke/transient ischemic attack indicates high risks of cardiovascular event and hemorrhagic stroke in patients with coronary artery disease. *Circulation*. 2013;127:730–738.
11. Ohman EM, Bhatt DL, Steg PG, et al; REACH Registry Investigators. 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.e1–786.e10.
12. Wilson PW, D'Agostino R Sr, Bhatt DL, et al; REACH Registry Investigators. An international model to predict recurrent cardiovascular disease. *Am J Med*. 2012;125:695.e1–703.e1.
13. Bonaca MP, Bhatt DL, Cohen M, et al; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372:1791–1800.
14. Bhatt DL, Fox KA, Hacke W, et al; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354:1706–1717.
15. Udell JA, Bonaca MP, Collet JP, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. *Eur Heart J*. 2016;37:390–399.
16. Scirica BM, Bonaca MP, Braunwald E, et al; TRA 2°P-TIMI 50 Steering Committee Investigators. Vorapaxar for secondary prevention of thrombotic events for patients with previous myocardial infarction: a prespecified subgroup analysis of the TRA 2°P-TIMI 50 trial. *Lancet*. 2012;380:1317–1324.
17. Morrow DA, Braunwald E, Bonaca MP, et al; TRA 2°P-TIMI 50 Steering Committee and Investigators. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med*. 2012;366:1404–1413.
18. Ducrocq G, Bhatt DL, Labreuche J, et al. Geographic differences in outcomes in outpatients with established atherothrombotic disease: results from the REACH Registry. *Eur J Prev Cardiol*. 2014;21:1509–1516.
19. D'Agostino RB Sr, Grundy S, Sullivan LM, et al. Validation of the Framingham coronary heart disease prediction scores:

results of a multiple ethnic groups investigation. *JAMA*. 2001;286:180–187.
20. Avezum A, Makdisse M, Spencer F, et al; GRACE Investigators. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J*. 2005;149:67–73.
21. Depta JP, Bhatt DL. Atherothrombosis and atrial fibrillation: important and often overlapping clinical syndromes. *Thromb Haemost*. 2010;104:657–663.
22. Ruff CT, Bhatt DL, Steg PG, et al; REACH Registry Investigators. Long-term cardiovascular outcomes in patients with atrial fibrillation and atherothrombosis in the REACH Registry. *Int J Cardiol*. 2014;170:413–418.
23. Nieuwlaat R, Prins MH, Le Heuzey JY, et al. Prognosis, disease progression, and treatment of atrial fibrillation patients during 1 year: follow-up of the Euro Heart Survey on atrial fibrillation. *Eur Heart J*. 2008;29:1181–1189.
24. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association [published correction appears in *J Am Coll Cardiol*. 2015;65:1495]. *J Am Coll Cardiol*. 2011;58:2432–2446.
25. Tang EW, Wong CK, Herbison P. Global Registry of Acute Coronary Events (GRACE) hospital discharge risk score accurately predicts long-term mortality post acute coronary syndrome [published correction appears in *Am Heart J*. 2007;154:851]. *Am Heart J*. 2007;153:29–35.
26. Jhund PS, Macintyre K, Simpson CR, et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation*. 2009;119:515–523.
27. Haeusler KG, Laufs U, Endres M. Chronic heart failure and ischemic stroke. *Stroke*. 2011;42:2977–2982.
28. Steg PG, Bhatt DL, Wilson PW, et al; REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA*. 2007;297:1197–1206.
29. Bhatt DL, Peterson ED, Harrington RA, et al; CRUSADE Investigators. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. *Eur Heart J*. 2009;30:1195–1202.
30. Kearney PM, Blackwell L, Collins R, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*. 2008;371:117–125.
31. Baigent C, Blackwell L, Emberson J, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
32. Cannon CP, Blazing MA, Giugliano RP, et al; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397.
33. Sabatine MS, Giugliano RP, Wiviott SD, et al; OSLER Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1500–1509.
34. Robinson JG, Farnier M, Krempf M, et al; ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1489–1499.
35. Desai NR, Sabatine MS. PCSK9 inhibition in patients with hypercholesterolemia. *Trends Cardiovasc Med*. 2015;25:567–574.
36. Sabatine MS, Giugliano RP, Keech A, et al. Rationale and design of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk trial. *Am Heart J*. 2016;173:94–101.
37. Schwartz GG, Bessac L, Berdan LG, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. *Am Heart J*. 2014;168:682–689.
38. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published corrections appear in *J Am Coll Cardiol*. 2014;63 (25 part B):3024–3025 and *J Am Coll Cardiol*. 2015;66:2812]. *J Am Coll Cardiol*. 2014;63(25 part B):2889–2934.
39. Ducrocq G, Wallace JS, Baron G, et al. Risk score to predict serious bleeding in stable outpatients with or at risk of atherothrombosis. *Eur Heart J*. 2010;31:1257–1265.
40. Mega JL, Braunwald E, Wiviott SD, et al; ATLAS-ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366:9–19.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Abtan J, Bhatt DL, Elbez Y, Sorbets E, Eagle K, Ikeda Y, Wu D, Hanson ME, Hannachi H, Singhal PK, Steg PG, Ducrocq G. Residual Ischemic Risk and Its Determinants in Patients With Previous Myocardial Infarction and Without Prior Stroke or TIA: Insights From the REACH Registry, *Clinical Cardiology*, 2016;39(11):670–677.