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Predictors of Long-term Adherence to Evidence-based Cardiovascular Disease Medications in Outpatients With Stable Atherothrombotic Disease: Findings From the REACH Registry

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ABSTRACT

Background: Despite overall improvements in cardiovascular-disease therapies and outcomes, medication nonadherence remains an important barrier to effective secondary prevention of atherothrombotic disease.

Hypothesis: Long-term medication adherence in outpatients with stable atherothrombotic disease is impacted by demographic and clinical factors.

Methods: We examined data from the prospective international Reduction of Atherothrombosis for Continued Health (REACH) Registry. Analyses were derived from 25 737 patients with established atherothrombotic disease with complete adherence data at enrollment and at year 4. Adherence was defined as patients' self-report of taking medications based on class I American College of Cardiology/American Heart Association guidelines for secondary prevention as defined, including antiplatelet agents, statins, and antihypertensive medications.

Results: Among patients with atherothrombotic disease, 12 500 (48.6%) were deemed adherent to guideline-recommended medications. Adherent patients were younger, white, and had less polyvascular disease. Hispanic and East Asian patients were less likely to be adherent as compared with white patients (odds ratio [OR]: 0.72, 95% confidence interval [CI]: 0.59-0.88; and OR: 0.67, 95% CI: 0.53-0.83, respectively). Patients who had a nonfatal MI or underwent coronary angioplasty/stenting during follow-up were more likely to be adherent compared with patients without these events (OR: 1.73, 95% CI: 1.25-2.38; and OR: 2.15, 95% CI: 1.72-2.67, respectively). On the other hand, nonfatal stroke during follow-up was inversely associated with adherence (OR: 0.77, 95% CI: 0.61-0.97).

Conclusions: Using a large international registry of outpatients with atherothrombotic disease, we found that age, region, race/ethnicity, and incident cardiovascular events were predictive of long-term guideline adherence for secondary prevention, suggesting that certain patient groups may benefit from targeted interventions to improve adherence.

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A complete list of investigators can be found in Bhatt DL et al.[16]

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Introduction

Despite compelling evidence that medical therapy for atherothrombotic disease improves clinical outcomes,[1–3] medication nonadherence remains an important barrier to secondary prevention.[2,4–7] Medication nonadherence is associated with both higher costs and adverse clinical outcomes.[1,5,8] Ensuring adherence to evidence-based drug regimens remains a central public-health priority.

Several medications have been demonstrated in large clinical trials to be efficacious in reducing cardiovascular (CV) endpoints of death and recurrent events.[3,9–11] Among these, secondary prevention through the long-term use of antiplatelet agents, statins, and antihypertensives has been shown to improve outcomes, reduce readmissions, and decrease overall health care costs.[2,12,13]

Medication nonadherence has been linked to patient, disease, and system factors.[1,14,15] However, studies have largely focused on in-hospital and postdischarge adherence to CV medications. Few studies have specifically explored long-term medication-adherence patterns for patients with stable atherothrombotic disease at an international level, and, specifically, which factors predict adherence.

Methods

The global Reduction of Atherothrombosis for Continued Health (REACH) registry recruited 69 055 consecutive patients from 44 countries in outpatient clinical settings. The methods of the REACH Registry have been well described in prior publications.[16–18] Briefly, patients age >45 years with ≥3 risk factors for atherosclerosis, and patients with established cerebrovascular disease (documented ischemic stroke or transient ischemic attack), coronary artery disease (stable angina, unstable angina, history of percutaneous coronary intervention, history of coronary artery bypass grafting [CABG] or previous myocardial infarction [MI]), and peripheral arterial disease (intermittent claudication, ankle-brachial index <0.9 or prior intervention), were eligible for enrollment. All participants provided informed consent, and the ethics committees in each country approved the study.

Patient follow-up was conducted at years 1, 2, 3, and 4 after enrollment. Patients were enrolled between 2003 and 2004 and followed up to 2008. Participating physicians were asked to provide data on subjects' clinical outcomes and medication use.

Study Variables

Primary Outcome: Adherence was defined as meeting class I American College of Cardiology/American Heart Association guidelines for secondary prevention in patients with stable atherothrombotic disease.[19,20] Data relating to medication use were patient self-reported at the time of study visit and collected centrally via use of a standardized international case-report form. In patients with a previous history of a cerebrovascular disease or peripheral arterial disease, complete adherence included the use of ≥1 antiplatelet agent (defined as aspirin or other antiplatelet agent), a statin and/or other lipid-lowering agent, and ≥1 antihypertensive medication if blood pressure was documented as >140/90 mm Hg at the initial visit or >130/80 mm Hg in a patient with diabetes mellitus or chronic kidney disease. For eligible patients, antihypertensive-agent adherence was defined as use of either angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, β-blockers, calcium channel blockers, diuretics, nitrates, or other antihypertensive agents. For patients with coronary artery disease, adherence was defined as above in addition to the concomitant use of a β-blocker. Medication use was assessed at time of enrollment and at each year of follow-up. Nonadherence was defined as failure to adhere to any of the recommended medications.

Covariates: We explored the association between patient-level factors and adherence at baseline and at 4 years of follow-up. Predictors included patient age as a continuous variable and sex. Attained educational level was defined at baseline based on the number of years of formal education completed, defined by 4 categories: 0 to 8 years, 9 to 12 years (or high school), trade or technical school, or university or college. Race/ethnicity was defined by self-report. Participants were categorized as white, Hispanic, East Asian, South Asian, black, or other. Employment status was characterized as full-time, part-time, unemployed, retired, incapacitated, or other according to self-report at time of enrollment.

Additional covariates included region (North America, Latin America, Western Europe, Eastern Europe, Middle East, and Asia, including Japan). Clinical variables were smoking status (former, current, or never smoker), diabetes mellitus, body mass index, and polyvascular disease vs single vascular disease.

We also explored the association between incident CV events, including myocardial infarction (MI), coronary artery bypass grafting, coronary angioplasty or stenting, and stroke with adherence to evidence-based medical therapies for secondary prevention.

Statistical Analysis

Analyses were restricted to patients who were eligible for the 4-year follow-up study, defined as patients who completed ≥1 postbaseline follow-up visit and who were enrolled at centers that agreed to participate in the 4-year study. Patients with missing data for the 4-year follow-up study (defined as patient attending visit or death recorded by investigator) and patients without established atherothrombotic disease were excluded from the final analyses. Continuous variables are expressed as means ± SD; categorical variables are expressed as frequencies and percentages.

In a secondary analysis, the study sample was restricted to the US population eligible for follow-up at 4 years (n = 7210).

To compare categorical variables, χ^2 tests of independence were used; 2-sided t tests were used for continuous variables. Multivariate logistic regression models were conducted to explore the relationship between covariates and adherence at 4 years.

We used SAS version 9.2 (SAS Institute Inc., Cary, NC) for all analyses. All reported P values are 2-tailed, and values <0.05 were considered statistically significant.

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Results

Analyses were derived from 25 737 patients with established atherothrombotic disease who had adherence data at enrollment and at year 4 (Figure 1). At baseline, 12 500 (48.6%) received all classes of medications and were thus deemed complete guideline-adherent. The baseline characteristics of the study sample are shown in Table 1. Fully adherent patients were likely to be younger, have less polyvascular disease, be of white race, and report full-time employment as compared with nonadherent patients. Greater adherence was observed in North America, Europe, and the Middle East, whereas participants from Latin America and Asia were less likely to be complete guideline-adherent.

Table 2 describes adherence by medication category at each year of follow-up. Patients reported the highest adherence rates for antihypertensive agents followed by antiplatelet drugs, with similar rates of adherence during each year of follow-up.

In unadjusted analyses, predictors of complete adherence at 4 years of follow-up included younger age, male sex, higher educational attainment, full-time employment, geographic region, body mass index, polyvascular disease, smoking, and Hispanic, East Asian, and other Asian ethnicity (Table 3). As compared with patients in North America, patients from Latin America and Asia were less likely to be complete guideline-adherent at 4 years. Similarly, nonfatal incident MI, coronary artery bypass grafting, and coronary angioplasty were strongly associated with full medication adherence, whereas incident stroke was inversely associated with adherence. On multivariate analyses, younger age, region, polyvascular disease, Hispanic and East Asian ethnicity, and current smoking status remained predictive of nonadherence. As compared

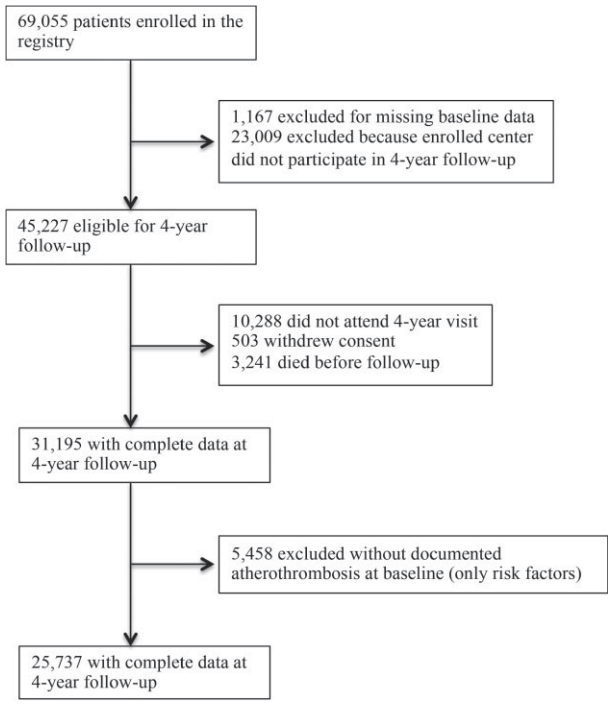

Figure 1. Flow of diagram of study participants.

Table 1. Study Sample Baseline Characteristics (N = 25 737)

	Fully Adherent, n = 12 500	Nonadherent, n = 13 237	*P* Value[a]
Age, y, mean (SD)	66.3 (9.7)	68.7 (9.8)	<0.0001
Male sex, n (%)	8612 (48.90)	8999 (51.10)	0.1146
DM, n (%)	4407 (48.93)	4600 (51.07)	0.4312
PVD, n (%)	1975 (41.30)	2807 (58.70)	<0.0001
BMI, kg/m², mean (SD)	28.1 (5.0)	27.1 (5.1)	<0.0001
Region, n (%)			<0.0001
North America	3861 (53.55)	3349 (46.45)	<0.0001
Latin America	371 (45.47)	445 (54.53)	0.0096
Western Europe	4456 (52.56)	4022 (47.44)	<0.0001
Eastern Europe	1923 (51.51)	1810 (48.49)	0.0644
Middle East	206 (64.98)	111 (35.02)	<0.0001
Asia	1683 (32.47)	3500 (67.53)	<0.0001
Smoking status, n (%)			0.0009
Former	5549 (50.11)	5524 (49.89)	0.8122
Current	1730 (47.45)	1916 (52.55)	0.0021
Never	4925 (47.86)	5365 (52.14)	<0.0001
Race/ethnicity, n (%)			<0.0001
White	8077 (52.86)	7204 (47.14)	<0.0001
Hispanic	402 (44.08)	510 (55.92)	0.0003
East Asian	1236 (29.58)	2942 (70.42)	<0.0001
South Asian	119 (53.13)	105 (46.88)	0.3496
Other Asian	629 (47.98)	682 (52.02)	0.1433
Black	278 (52.06)	256 (47.94)	0.3411
Other	512 (55.96)	403 (44.04)	0.0003
Educational attainment, n (%)			<0.0001
0–8 years	3902 (48.18)	4196 (51.82)	0.0011
9–12 years	3576 (47.44)	3962 (52.56)	<0.0001
Trade/technical	2147 (51.30)	2038 (48.70)	0.0920
University	2319 (50.78)	2248 (49.22)	0.2934
Employment status, n (%)			<0.0001
Full time	2450 (53.96)	2090 (46.04)	<0.0001
Part time	799 (50.54)	782 (49.46)	0.6690
Unemployed	660 (38.35)	1061 (61.65)	<0.0001
Retired	7474 (48.23)	8024 (51.77)	<0.0001
Incapacitated	680 (48.99)	708 (51.01)	0.4523
Other	342 (44.71)	423 (55.29)	0.0034

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Table 1. *Continued*

	Fully Adherent, n = 12 500	Nonadherent, n = 13 237	*P* Value[a]
Antiplatelet agents, n (%)			
ASA	10 725 (57.60)	7894 (42.40)	<0.0001
Other	4231 (58.22)	3036 (41.78)	<0.0001
Lipid-lowering agents, n (%)			
Statins	11 774 (66.30)	5984 (33.70)	<0.0001
Other	1653 (62.40)	996 (37.60)	<0.0001
CV agents, n (%)			
CCBs	3682 (41.89)	5107 (58.11)	<0.0001
β-Blockers	10 046 (74.29)	3477 (25.71)	<0.0001
Nitrates/other antianginal agents	3593 (48.50)	3815 (51.50)	0.8794
Diuretics	4809 (50.11)	4788 (49.89)	0.0001
ACEIs	6386 (53.84)	5476 (46.16)	<0.0001
ARBs	2511 (47.92)	2729 (52.08)	0.3239
Other antihypertensives	907 (44.75)	1120 (55.25)	0.0004

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid (aspirin); BMI, body mass index; CABG, coronary artery bypass surgery; CCB, calcium channel blocker; CV, cardiovascular; DM, diabetes mellitus; PVD, polyvascular disease; SD, standard deviation.
[a]*P* values were derived using the independent sample *t* test for continuous variables and the χ^2 test for categorical values.

Table 2. Overall Adherence Rates by Medication Class and Year of Follow-up

	Overall Adherence, %	Antiplatelet Agents, %[a]	Lipid-Lowering Agents, %[a]	Antihypertensives, %[a]	β-Blockers, %[b]
Baseline	48.57	85.80	73.83	99.11	64.13
Year 1	49.31	85.86	74.28	97.92	65.25
Year 2	48.73	85.35	74.92	97.64	65.23
Year 3	46.70	84.32	75.63	97.16	65.02
Year 4	47.45	84.20	76.69	96.97	65.32

[a]Defined as being on ≥1 agent in each class at enrollment and each year of follow-up. [b]β-Blocker adherence rates are based on patients with coronary artery disease.

with patients who did not experience CV events during follow-up, incident coronary angioplasty and nonfatal MI were predictive of complete guideline adherence (odds ratio [OR]: 2.15, 95% confidence interval [CI]: 1.72-2.67; and OR: 1.73, 95% CI: 1.25-2.38, respectively), whereas incident nonfatal stroke was associated with a lower odds of adherence (OR: 0.77, 95% CI: 0.61-0.97).

In a secondary analysis restricted to participants in the United States eligible for 4-year follow-up with stable atherothrombotic disease (n = 7210), there was a total of 213 Hispanic and 115 East Asian participants. Hispanic race/ethnicity as compared with white race was associated with a lower likelihood of complete medication adherence (OR: 0.71, 95% CI: 0.52-0.98). However, East Asian race/ethnicity was no longer associated with adherence (OR: 1.10, 95% CI: 0.73-1.66).

Discussion

Using an international prospective registry of patients with a broad spectrum of established atherothrombotic disease, we found that <50% of eligible patients were fully adherent with cardioprotective drug regimens over a 4-year study observation period. We identified several important independent predictors of long-term adherence to secondary prevention therapies. Complete adherence was associated with younger age and geographic region. Hispanic and East Asian patients were less likely to be adherent at 4 years of follow-up. We found that patients with polyvascular disease were less adherent as compared with those with single vascular disease, and that current smokers were less likely to be adherent as compared with nonsmokers. On the other hand, incident MI and coronary angioplasty were strongly associated with increased adherence. Notably, patients with incident stroke were less likely to be adherent.

Our findings are consistent with and complementary to prior studies, which have documented the importance of both clinical and demographic variables on patient adherence.[1,4,8,14,15,21,22] Similar to other studies,[23–25] age influenced complete guideline adherence, with younger patients reporting greater complete guideline adherence. Older adults are more likely to have more total medications prescribed and are less likely to live independently, both of which are important predictors of medication nonadherence.[6] We also found that Hispanic and East Asian participants were less likely to be adherent at 4 years of follow-up as compared with non-Hispanic whites. Given the growing problem of health care disparities in cardiovascular disease,[26] our finding that certain racial and ethnic groups have lower levels of adherence warrants attention. Medication nonadherence may in fact be an important contributor to the persistent gap in CV outcomes for certain racial/ethnic populations.

Similarly, it is likely that geographic region is driving some of the disparity in adherence for Hispanic and East Asian ethnic groups. The Prospective Urban Rural Epidemiological (PURE) study showed similar geographic variation in rates of self-reported adherence to recommended therapies for secondary prevention, with the lowest adherence rates in low-income countries.[27] Statins and other medications are particularly costly in developing countries, such as in Latin America, which may limit adherence. There may also be geographic differences in prescribing patterns by providers based on differences in physician perceptions of the risks and benefits of certain drug classes, such as antiplatelet therapy and statins, particularly in East Asian countries.

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Table 3. Crude and Adjusted Logistic Regression Models of Medication Adherence

	Unadjusted Models		Adjusted Models	
Predictors	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Male sex	1.11 (1.05-1.17)	<0.0001	1.04 (0.98-1.12)	0.2312
Age, y[a]	0.97 (0.97-0.98)	<0.0001	0.97 (0.97-0.98)	<0.0001
Region (ref = North America)		<0.0001		<0.0001
Latin America	0.67 (0.57-0.77)	<0.0001	0.78 (0.63-0.96)	0.0216
Western Europe	1.05 (0.99-1.12)	0.1271	0.92 (0.85-1.00)	0.0403
Eastern Europe	1.06 (0.98-1.12)	0.1449	0.95 (0.86-1.05)	0.2920
Middle East	1.50 (1.19-1.89)	0.0005	1.39 (1.05-1.83)	0.0197
Asia	0.45 (0.41-0.48)	<0.0001	0.49 (0.40-0.61)	<0.0001
Race/ethnicity (ref = white)		<0.0001		<0.0001
Hispanic	0.59 (0.51-0.67)	<0.0001	0.72 (0.59-0.88)	0.0015
East Asian	0.39 (0.37-0.42)	<0.0001	0.67 (0.53-0.83)	0.0004
South Asian	0.99 (0.76-1.29)	0.9649	1.30 (0.95-1.78)	0.0988
Other Asian	0.71 (0.63-0.79)	<0.0001	0.99 (0.80-1.23)	0.9089
Black	0.85 (0.72-1.01)	0.0697	0.93 (0.76-1.15)	0.5125
Other	1.09 (0.95-1.25)	0.2031	1.01 (0.87-1.18)	0.8825
Attained educational level (ref = 0–8 years)		0.0001		0.9872
9–12 years	0.95 (0.89-1.01)	0.1012	1.01 (0.94-1.09)	0.7764
Trade/technical	1.11 (1.03-1.20)	0.0060	1.00 (0.92-1.10)	0.9401
University	1.07 (1.00-1.15)	0.0651	1.00 (0.91-1.09)	0.9324
Employment status (ref = full time)		<0.0001		0.1032
Part time	0.83 (0.74-0.94)	0.0019	1.04 (0.91-1.19)	0.5879
Unemployed	0.59 (0.53-0.66)	<0.0001	1.10 (0.96-1.27)	0.1679
Retired	0.77 (0.72-0.82)	<0.0001	1.07 (0.97-1.17)	0.1605
Incapacitated	0.87 (0.77-0.98)	0.0210	0.90 (0.78-1.04)	0.1496
Other	0.71 (0.61-0.83)	<0.0001	1.17 (0.97-1.41)	0.0973
BMI, kg/m^2[a]	1.03 (1.03-1.04)	<0.0001	1.00 (1.00-1.01)	0.2228
Smoking status (ref = never)		0.0163		0.0870
Former	1.07 (1.02-1.13)	0.0090	1.00 (0.94-1.07)	0.9346
Current	1.08 (1.01-1.17)	0.0386	0.91 (0.83-1.00)	0.0486
DM (ref = no)	1.00 (0.95-1.05)	0.9577	1.06 (1.00-1.13)	0.0591
PVD (ref = SVD)	0.70 (0.65-0.74)	<0.0001	0.69 (0.64-0.74)	<0.0001
Incident CV events				
CABG	1.68 (1.21-2.34)	0.0019	1.20 (0.82-1.77)	0.3465
Coronary angioplasty/stenting	2.30 (1.91-2.76)	<0.0001	2.15 (1.72-2.67)	<0.0001
Nonfatal MI	2.05 (1.58-2.65)	<0.0001	1.73 (1.25-2.38)	0.0009
Nonfatal stroke	0.74 (0.61-0.91)	0.0041	0.77 (0.61-0.97)	0.0258

Abbreviations: BMI, body mass index; CABG, coronary artery bypass surgery; CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; MI, myocardial infarction; OR, odds ratio; ref, reference; PVD, polyvascular disease; SVD, single vascular disease.
[a]Per 1-unit increase.

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In a secondary analysis, we attempted to further control for the effect of geographic region on our findings by restricting the study sample to the United States; Hispanic ethnicity remained significantly predictive of lower medication adherence, suggesting an independent association between Hispanic ethnicity and medication adherence. Another possible explanation is that certain racial/ethnic status may be linked with lower understanding of the benefits of continued medication adherence. A study by Roth and colleagues found that black and Hispanic patients had significantly higher rates of medication-related problems and overall higher rates of nonadherence.[28] Adverse cultural beliefs about the perceived benefits of medications and poor provider-patient relationships have also been cited as reasons for reduced medication adherence among certain patient groups.[5,29,30]

Interestingly, we found a strong association between incident CV events and long-term adherence. Evidence is mixed about adherence to therapies after a hospitalization for acute coronary syndromes.[22,25,31] It is likely that patients with an incident event, such as an MI or angioplasty/stenting, will have additional opportunities for medication-adherence reinforcement. Alternatively, patients who have undergone these procedures may have fewer ischemic symptoms and may therefore perceive less need of adherence to prescribed medications. After adjusting for comorbidities, we found that patients who experienced a nonfatal MI or required coronary angioplasty with or without stent placement were more likely to be fully adherent during follow-up, whereas patients who suffered from an incident stroke were less likely to be adherent. One could speculate that stroke patients are more likely to suffer from cognitive and physical deficits that may impede complete adherence. Recent studies have suggested that posttraumatic stress disorder (PTSD) may partially explain the high rates of medication nonadherence among stroke survivors.[32,33] Stroke survivors who suffer from PTSD may be more likely to avoid medications because the drugs may serve as reminders of their triggering event. Also, PTSD has been independently linked with cognitive dysfunction, which may in turn lead to medication nonadherence.[34] Alternatively, it is possible that stroke patients may have contraindications for certain therapies that we could not account for in our analyses. Because patients with a history of a stroke are at especially high risk for recurrent stroke and other CV events, these patients may benefit from additional resources, such as rehabilitation and case managers, to ensure adequate medication adherence.

To improve complete guideline adherence for secondary prevention of CVD, some have advocated the use of a polypill.[35] The Use of a Multidrug Pill in Reducing Cardiovascular Events (UMPIRE) trial used a fixed-dose combination of aspirin, a statin, and 2 blood pressure–lowering agents to improve guideline-recommended adherence for secondary prevention of CVD.[36] Preliminary results from this trial demonstrated that a polypill was associated with a 33% increase in adherence over a 15-month period.[37] Perhaps such approaches may be particularly useful in reducing the observed geographic guideline-adherence differences between low-income and high-income countries, as a polypill would be associated with reduced dispensing costs of multiple medications. Government subsidies of such fixed-dose combination pills may also improve adherence. Additionally, patients deemed at high risk for nonadherence, such as the elderly and stroke patients, may benefit from a simplified medical regimen of a single daily pill.

Several limitations warrant mention. Only a subset of the total population was eligible for the 4-year follow-up. We defined adherence based on physician and patient self-report. We did not have access to direct methods, such as observed therapy or measurement of biological markers of the drugs in the blood. However, direct methods are usually not practical in the clinical setting. Self-report methods may be biased, although we expect this finding to be nondifferential between comparison groups. Gehi and colleagues found that patient self-report of medication nonadherence was strongly correlated with adverse CV events.[38] We were not able to account for medication side-effects or other important contributors to nonadherence. Similarly, selection bias for both patients and physicians is inherent in registry data, although this is likely to overestimate adherence rates.

This study has several important strengths. First, the study's large size and international representation increase its external validity. Our findings are applicable to a broad spectrum of outpatients with stable atherothrombotic disease followed longitudinally. Most studies on medication adherence have focused on in-hospital and post–hospital discharge adherence and have not explored long-term follow-up in the outpatient setting.

Our study highlights the importance of ascertaining medication adherence at each clinic visit. Recognizing patient-level characteristics of poor adherence is useful to help physicians and medical providers identify patients who may benefit the most from targeted interventions to improve adherence.

Conclusion

Using a large, international prospective registry of stable outpatients with atherothrombotic disease, we found that age, race/ethnicity, region, and incident CV events were strong, independent predictors of long-term adherence with medications. These findings suggest that certain patient groups may benefit from targeted interventions to improve adherence.

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