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ORIGINAL RESEARCH

Secondary Prevention Medications in 17 Countries Grouped by Income Level (PURE)

A Prospective Cohort Study

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ABSTRACT

BACKGROUND It is unclear whether global use of medications for secondary cardiovascular (CVD) prevention is improving over time.

OBJECTIVES This study across 17 high-, middle- and low-income countries described variations in secondary CVD prevention medication use over a median follow-up of 12 years.

METHODS In the multinational PURE (Prospective Urban Rural Epidemiology) cohort study, we conducted a repeated cross-sectional analysis to examine temporal variations in the use of secondary prevention medications in participants with CVD. In participants with coronary artery disease, we focused on antiplatelet agents, statins, renin-angiotensin system (RAS) inhibitors, and β-blockers. In participants with stroke, we focused on antiplatelet agents, statins, RAS inhibitors, and other blood pressure–lowering drugs. Medications were collected at baseline and on 4 subsequent follow-up visits.

RESULTS The analysis included 7,409 participants with a diagnosis of CVD at the baseline visit, 8,792 at the second visit, 9,236 at the third visit, 11,082 at the fourth visit, and 11,677 at the last visit. The median age at baseline was 58.0 years, and 52.9% of the participants were female. The median follow-up was 12 years, with the median year of the baseline visit in 2007 and the fifth visit in 2019. Over this period, use of 1 or more classes of medications for secondary CVD prevention was 41.3% (95% CI: 40.2%-42.4%) at baseline, peaked at 43.1% (95% CI: 42.0%-44.1%), and then decreased to 31.3% (95% CI: 30.4%-32.1%) by the last study visit. In high-income countries, this use decreased from 88.8% (95% CI: 86.6%-91.0%) to 77.3% (95% CI: 74.9%-79.6%). In upper-middle-income countries, this use increased from 55.0% (95% CI: 52.8%-57.3%) to 61.1% (95% CI: 59.1%-63.1%). In lower-middle-income countries, use of at least 1 class of medications was 29.5% (95% CI: 28.1%-30.9%) at baseline, peaked at 31.7% (95% CI: 30.4%-33.1%), and then decreased to 13.4% (95% CI: 12.5%-14.2%) by the last visit. In low-income countries, use of at least 1 class of medications was 20.8% (95% CI: 18.1%-23.5%) at baseline, peaked at 47.3% (95% CI: 44.8%-49.9%), and then decreased to 27.5% (95% CI: 25.2%-29.9%) by the last study visit.

CONCLUSIONS Globally and in most country income-level groups, the use of medications for secondary CVD prevention has been low, with little improvement over time. (JACC. 2025;85:436-447) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Over the last decade, leading international organizations have issued aggressive targets to reduce premature mortality from cardiovascular disease (CVD). In 2013, the World Health Organization (WHO) Global Action Plan called for a target reduction in premature noncommunicable disease-related mortality of 25% by 2020, with at least 50% of eligible individuals receiving evidence-based medications to prevent myocardial infarction or stroke.[1,2] Similarly, in 2015, the United Nations (UN) sustainable development goal (SDG) 3.4 targeted a one-third reduction in premature mortality from noncommunicable diseases, including CVD, by 2030 through improvements in treatment and prevention.[3]

In populations with CVD, previous studies have reported underuse of medications that prevent further CVD events (ie, secondary CVD prevention), with the lowest use occurring in middle-income countries (MICs) and low-income countries (LICs). However, these studies were mostly cross-sectional analyses, and so it has been unclear whether the use of these medications is improving over time.[4-6] To understand better whether global progress is being made in the management of CVD, a study using a contemporary multinational cohort conducted a descriptive analysis to quantify variations in the use of evidence-based medications for the treatment of CVD over a median period of 12 years.

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METHODS

STUDY PARTICIPANTS. The design of the PURE (Prospective Urban Rural Epidemiology) study has been previously reported.[4,7] In summary, PURE is a multinational, community-based, prospective cohort study that enrolled participants between 35 and 70 years of age, with ongoing longitudinal follow-up. Communities from each participating country were selected on the basis of prespecified criteria to represent urban and rural areas, and then a broadly representative sampling of adults within each community was performed. This analysis of PURE focuses on the original 17-country cohort where enrollment occurred between 2003 and 2009 and where periodic 3-year visits were ongoing. Of the 17 original countries in PURE, 3 were high-income countries (HICs) (Canada, Sweden, United Arab Emirates), 7 were upper-middle-income countries (UMICs) (Argentina, Brazil, Chile, Malaysia, Poland, South Africa, Turkiye), 3 were lower-middle-income countries (LMICs) (China, Colombia, Iran), and 4 were LICs (Bangladesh, India, Pakistan, Zimbabwe) on the basis of their World Bank classification at the time of their initiation into the study. The study was centrally approved by the Hamilton Integrated Research Ethics Board, Hamilton, Ontario, Canada, as well as by local research ethics boards within each participating country.

At the baseline study visit, participants with a history of CVD and at least 1 follow-up assessment were included in this analysis. Participants were defined as having CVD at the baseline visit if they had a history of coronary artery disease (CAD) (on the basis of a self-reported history of myocardial infarction, coronary revascularization, or angina) or stroke. At subsequent follow-up visits, participants were added to the sample group if they developed a nonfatal CVD event (defined as myocardial infarction, angina, or stroke) and had at least 1 subsequent follow-up visit documenting medication use.

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
CVD = cardiovascular disease
HIC = high-income country
LIC = low-income country
LMIC = lower-middle-income country
MIC = middle-income country
RAS = renin-angiotensin system
SDG = sustainable development goal
UMIC = upper middle-income country
UN = United Nations
WHO = World Health Organization

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Myocardial infarctions and strokes were routinely collected as clinical outcome events in the PURE study at each follow-up visit. Participants were routinely asked whether each of these events occurred since the last study visit. If an event occurred, additional clinical data were collected using standardized questionnaires to allow for central adjudication of the event, and participants who had an unrefuted myocardial infarction or stroke were subsequently included in our analyses at each follow-up visit. New angina was also routinely collected during follow-up, and participants who reported this event were subsequently included in the analysis. Participants were removed from the sample group if they died before their next study visit or if all data were missing for the visit. Written informed consent was obtained from all participants, and the study was approved by local research ethics boards.

MEDICATION USE. Data on medication use were collected at the baseline and at each subsequent follow-up visit by using standardized questionnaires. At each study visit, participants were asked to provide their medications (or a list of their medications) to interviewers. Drugs that were taken by a participant at least once per week were recorded and then were centrally categorized to standard therapeutic classes. During the COVID-19 pandemic, data on medication use were collected by telephone if an in-person visit could not be performed. The following classes of medications used for secondary CVD prevention were included in this analysis: antiplatelet agents (defined as either aspirin or clopidogrel), renin-angiotensin system (RAS) inhibitors (defined as either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers), β-blockers, statins, calcium-channel blockers, and diuretic agents. In participants with CAD, we focused on the use of antiplatelet agents, statins, RAS inhibitors, and β-blockers as distinct classes for the evaluation of combinations of treatments. In participants with stroke, we focused on antiplatelet agents, statins, RAS inhibitors, and other blood pressure–lowering drugs (ie, β-blockers, calcium-channel blockers, or diuretic agents) as distinct classes. This categorization allows for distinguishing the specific benefits of RAS inhibitors in vascular disease, β-blockers following myocardial infarction, and blood pressure lowering in stroke.[8-11]

STATISTICAL ANALYSIS. We conducted a repeat cross-sectional analysis across 5 study visits in participants with CVD at baseline or those who developed a new CVD event at any of the 4 subsequent follow-up cycle visits. Demographic data for the cohort at each study visit were summarized using median values with quartile 1 to quartile 3 ranges (Q1-Q3) for continuous variables and proportions for categorial variables. For each visit, we calculated the proportion of participants taking each class of secondary CVD prevention medications, as well as their combinations. In cases of missing medication data at a visit, imputation was performed using the last observation carried forward, by using the medications from the most recent previous visit where these data were available, because we believed that this approach would be the most informative of medication use if data were missing. Results were reported in participants with a history of CVD at the time of enrollment, in participants who developed a nonfatal CVD event during the study, and in all participants with CVD (either at baseline or occurring during follow-up). Results are also reported after stratification by country income level, age, sex, urban-rural area, and designated CVD type (ie, CAD or stroke). For stratification by CVD type, participants were classified as being treated for CAD if there was a history of CAD at baseline or if their first CVD event during follow-up was either a myocardial infarction or angina. Participants were classified as being treated for stroke if there was a history of stroke at baseline (without a history of CAD) or if the first CVD event during follow-up was a stroke. Additional analyses were conducted among LICs by comparing rates of medication use in India with rates in the other LICs. Given the varying sample sizes among study visits, data on medication use are primarily presented as percentages with 95% CIs. Analyses were conducted using SAS software (SAS Institute).

ROLE OF THE FUNDING SOURCE. The external sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

A total of 153,996 participants were enrolled from the original 17 countries participating in the PURE study, and 149,947 of these participants had at least 1 follow-up documented. Of the participants with at least 1 follow-up, 7,409 participants with a previous history of CVD were included in the baseline analysis. During follow-up, 1,503 participants with a new CVD event were added at the second visit, 1,085 at the third visit, 2,640 at the fourth visit, and 2,131 at the fifth visit.

TABLE 1 Demographics of the Study Cohort at Baseline and at Each Follow-Up Visit

	Baseline	Visit 2	Visit 3	Visit 4	Visit 5
Median visit year	2007 (2006-2008)	2011 (2010-2012)	2015 (2014-2016)	2016 (2016-2017)	2019 (2018-2020)
Number of patients with CVD	7,409	8,792	9,236	11,082	11,677
Median age, y	58.0 (51.0-64.0)	61.2 (54.1-67.5)	64.1 (56.8-70.3)	66.0 (58.9-72.5)	68.2 (61.2-74.6)
Female	3,917 (52.9)	4,547 (51.7)	4,799 (52.0)	5,782 (52.2)	6,151 (52.7)
Rural	3,052 (41.2)	3,695 (42.0)	3,932 (42.6)	4,837 (43.7)	5,320 (45.6)
HIC	813 (11.0)	967 (11.0)	1,095 (11.9)	1,165 (10.5)	1,227 (10.5)
UMIC	1,837 (24.8)	2,129 (24.2)	2,356 (25.5)	2,453 (22.1)	2,322 (19.9)
LMIC	3,902 (52.7)	4,371 (49.7)	4,498 (48.7)	5,987 (54.0)	6,726 (57.6)
LIC	8,57 (11.6)	1,325 (15.1)	1,287 (13.9)	1,477 (13.3)	1,402 (12.0)

Values are median (Q1-Q3) or n (%).
CVD = cardiovascular disease; HIC = high-income country; LIC = low-income country; LMIC = lower-middle-income country; UMIC = upper-middle-income country.

After removing participants who died or who had no clinical data at a given visit, the total numbers of participants with CVD available for analysis were 7,409 at the first visit, 8,792 at the second visit, 9,236 at the third visit, 11,082 at fourth visit, and 11,677 at the last visit (**Table 1**, Supplemental Table 1). Data on vital status were available for 100% of participants at baseline, 100% of participants at visit 2, 98.1% of participants at visit 3, 96.2% of participants at visit 4, and 91.0% of participants at visit 5 (Supplemental Table 1). On average, participants were missing medication data for 1 of the 5 study visits, for which imputation occurred.

The median age of study participants at the baseline visit was 58.0 years (Q1-Q3: 51.0-64.0 years), and 52.9% of the patients were female (**Table 1**). The median follow-up period for the cohort between the baseline and last visits was 12 years. The median visit year of the baseline visit was in 2007 (Q1-Q3: 2006-2008), the second visit was in 2011 (Q1-Q3: 2010-2012), the third visit was in 2015 (Q1-Q3: 2014-2016), the fourth visit was in 2016 (Q1-Q3: 2016-2017), and the fifth (ie, last) visit was in 2019 (Q1-Q3: 2018-2020). The last follow-up visit partly coincided with the COVID-19 pandemic. At the fifth study visit, the median age of the cohort was 68.2 years (Q1-Q3: 61.2-74.6 years), and 52.7% of the participants were female.

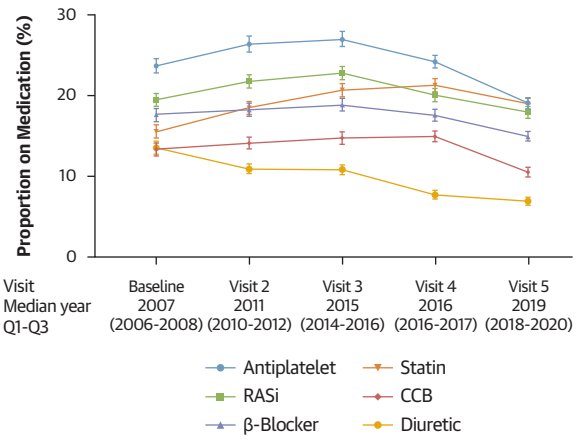
TRENDS IN SECONDARY CARDIOVASCULAR DISEASE PREVENTION MEDICATION USE. At the baseline visit, 23.6% (95% CI: 4.8%-5.1%) of participants with a baseline history of CVD were taking an antiplatelet agent, 15.5% (95% CI: 14.7%-16.4%) were taking a statin, and 19.4% (95% CI: 18.5%-20.3%) were taking an RAS inhibitor. In participants with a history of CVD at baseline, 41.3% (95% CI: 40.2%-42.4%) were taking 1 or more classes of medications for secondary CVD

TABLE 2 Use of Secondary Prevention Medications in All Participants With Cardiovascular Disease

	Baseline	Visit 2	Visit 3	Visit 4	Visit 5
Number of participants with CVD	7,409	8,792	9,236	11,082	11,677
Medications					
Antiplatelet agent	1,751 (23.6) (22.7-24.6)	2,308 (26.3) (25.3-27.2)	2,484 (26.9) (26.0-27.8)	2,673 (24.1) (23.3-24.9)	2,214 (19.0) (18.2-19.7)
Statin	1,151 (15.5) (14.7-16.4)	1,617 (18.4) (17.6-19.2)	1,903 (20.6) (19.8-21.4)	2,353 (21.2) (20.5-22.0)	2,210 (18.9) (18.2-19.6)
ACEI/ARB	1,440 (19.4) (18.5-20.3)	1,909 (21.7) (20.9-22.6)	2,099 (22.7) (21.9-23.6)	2,211 (20.0) (19.2-20.7)	2,084 (17.9) (17.2-18.5)
β-blocker	1,302 (17.6) (16.7-18.4)	1,599 (18.2) (17.4-19.0)	1,740 (18.8) (18.0-19.6)	1,940 (17.5) (16.8-18.2)	1,743 (14.9) (14.3-15.6)
Calcium-channel blocker	987 (13.3) (12.5-14.1)	1,239 (14.1) (13.4-14.8)	1,355 (14.7) (13.9-15.4)	1,650 (14.9) (14.2-15.6)	1,223 (10.5) (9.9-11.0)
Diuretic	1,000 (13.5) (12.7-14.3)	962 (10.9) (10.3-11.6)	997 (10.8) (10.2-11.4)	848 (7.7) (7.2-8.1)	802 (6.9) (6.4-7.3)
Number of medication classes used[a]					
None	4,347 (58.7) (57.6-59.8)	5,007 (56.9) (55.9-58.0)	5,296 (57.3) (56.3-58.3)	6,737 (60.8) (59.9-61.7)	8,027 (68.7) (67.9-69.6)
1 or more	3,062 (41.3) (40.2-42.4)	3,785 (43.1) (42.0-44.1)	3,940 (42.7) (41.7-43.7)	4,345 (39.2) (38.3-40.1)	3,650 (31.3) (30.4-32.1)
2 or more	1,794 (24.2) (23.2-25.2)	2,355 (26.8) (25.9-27.7)	2,567 (27.8) (26.9-28.7)	2,946 (26.6) (25.8-27.4)	2,593 (22.2) (21.5-23.0)
3 or more	900 (12.2) (11.4-12.9)	1,324 (15.1) (14.3-15.8)	1,497 (16.2) (15.5-17.0)	1,741 (15.7) (15.0-16.4)	1,577 (13.5) (12.9-14.1)

Values are N or n (%) (95% CI). [a]In participants with coronary artery disease, medications were categorized into the following classes: antiplatelet drugs, statins, renin-angiotensin system inhibitors, and β-blockers. In participants with stroke, medications were categorized into the following classes: antiplatelet drugs, statins, renin-angiotensin system inhibitors, and other blood pressure–lowering medications (defined as β-blockers, calcium-channel blockers, or diuretic agents).
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CVD = cardiovascular disease.

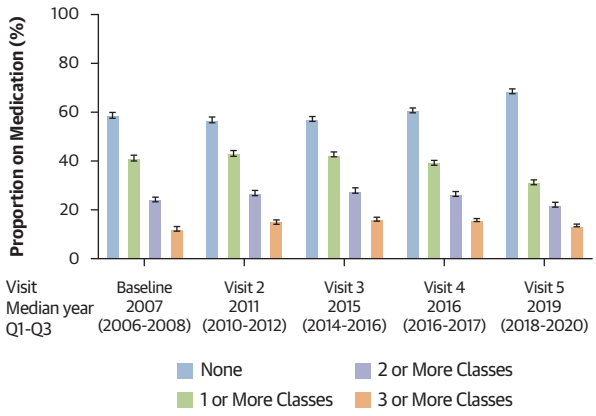
FIGURE 1 Use of Individual Classes of Secondary Prevention Medications in All Participants With Cardiovascular Disease



CCB = calcium-channel blocker; RASi = renin-angiotensin system inhibitor.

prevention, and 12.2% (95% CI: 11.4%-12.9%) were taking 3 or more medication classes. Over the median study period of 12 years, the proportion of these participants taking 1 or more medications classes decreased from 41.3% (95% CI: 40.2%-42.4%) to 30.7% (95% CI: 28.8%-31.3%) (Supplemental Table 2). In participants without a baseline history of CVD, but who developed a nonfatal CVD event during follow-up, the proportion taking 1 or more medication classes at their subsequent study visit varied from 22.4% (95% CI: 20.6%-24.1%) to 53.6% (95% CI: 50.6%-56.5%) (Supplemental Table 3), and the proportion taking 3 or more medication classes varied from 10.4% (95% CI: 9.1%-11.7%) to 26.6% (95% CI: 24.0%-29.3%).

FIGURE 2 Number of Secondary Prevention Medication Classes Used in All Participants With Cardiovascular Disease



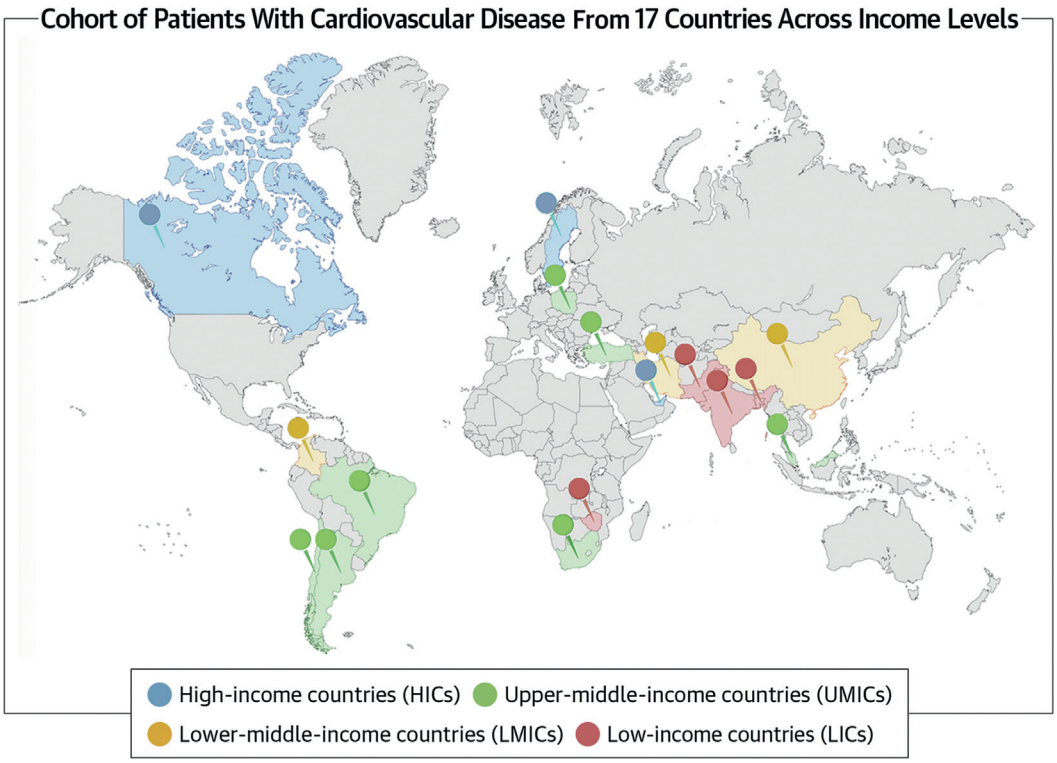
Data are presented in all participants either with a baseline history of cardiovascular disease or with cardiovascular disease that developed during follow-up. In participants with coronary artery disease, medications were categorized into the following classes: antiplatelet drugs, statins, renin-angiotensin system inhibitors, and β-blockers. In participants with stroke, medications were categorized into the following classes: antiplatelet drugs, statins, renin-angiotensin system inhibitors, and other blood pressure–lowering medications (defined as β-blockers, calcium-channel blockers, or diuretic agents).

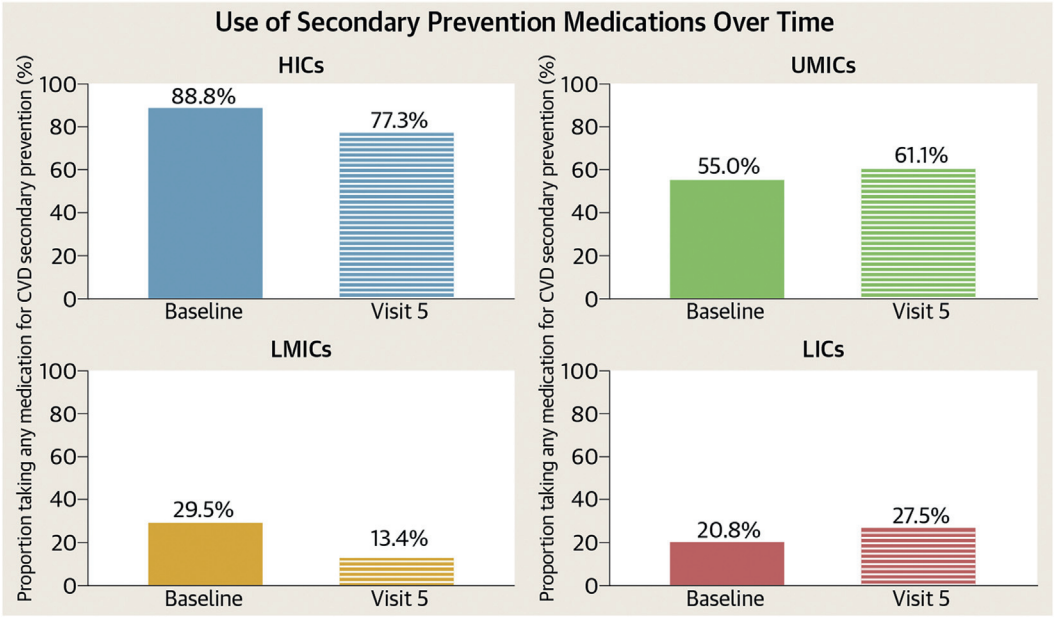
Use of medications for the overall study cohort that included both baseline and new CVD cases are summarized in **Table 2** and in **Figures 1 and 2**. In all participants with CVD, statin use was 15.5% (95% CI: 14.7%-16.4%) at baseline, peaked at 21.2% (95% CI: 20.5%-22.0%), and then decreased to 18.9% (95% CI: 18.2%-19.6%) at the last study visit. For each of the other medication classes, use did not increase by >5% at any follow-up visit when compared with the baseline visit (**Table 2**, **Figure 1**). The proportion of participants taking 1 or more classes of secondary CVD prevention medications at baseline was 41.3% (95% CI: 40.2%-42.4%), peaked at 43.1% (95% CI: 42.0%-44.1%) at the second visit, and then decreased to 31.3% (95% CI: 30.4%-32.1%) at the last visit. The proportion of patients taking 3 or more classes was 12.2% (95% CI: 11.4%-12.9%) at baseline, peaked at 16.2% (95% CI: 15.5%-17.0%) at the third visit, and then decreased to 13.5% (95% CI: 12.9%-14.1%) by the last visit (**Table 1**, **Figure 2**).

TRENDS IN MEDICATION USE BY COUNTRY INCOME LEVEL. The number of classes of medications used for secondary CVD prevention among countries grouped by income level is summarized in the **Central Illustration**, **Table 3**, and **Figure 3**. The use of each medication class is further summarized in Supplemental Table 4. In HICs, the proportion of participants with CVD who were taking 1 or more classes of secondary prevention medications was highest at the baseline visit at 88.8% (95% CI: 86.6%-91.0%) and decreased to 77.3% (95% CI: 74.9%-79.6%) by the last study visit. The proportion taking 3 or more classes was 51.8% (95% CI: 48.3%-55.2%) at baseline, peaked at 52.5% (95% CI: 49.4%-55.7%) at the second visit, and decreased to 47.6% (95% CI: 44.8%-50.4%) by the last visit.

In UMICs, the proportion of participants with CVD taking 1 or more medication classes increased from 55.0% (95% CI: 52.8%-57.3%) at baseline to 61.1% (95% CI: 59.1%-63.1%) at the last visit. The proportion taking at least 3 medication classes increased from

CENTRAL ILLUSTRATION **Secondary Prevention Medication Trends in Patients With Cardiovascular Disease in 17 Countries Across Income Levels**





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CVD = cardiovascular disease; HICs = high-income countries; LICs = low-income countries; LMICs = lower-middle-income countries; UMICs = upper-middle-income countries.

TABLE 3 Use of Secondary Prevention Medications in All Participants With Cardiovascular Disease Stratified by Country Income Level

	Baseline	Visit 2	Visit 3	Visit 4	Visit 5
High-income countries					
Number of participants with CVD	813	967	1,095	1,165	1,227
Number of medication classes used[a]					
None	91 (11.2) (9.0-13.4)	166 (17.2) (14.8-19.5)	213 (19.5) (17.1-21.8)	239 (20.5) (18.2-22.8)	279 (22.7) (20.4-25.1)
1 or more	722 (88.8) (86.6-91.0)	801 (82.8) (80.5-85.2)	882 (80.5) (78.2-82.9)	926 (79.5) (77.2-81.8)	948 (77.3) (74.9-79.6)
2 or more	617 (75.9) (73.0-78.8)	681 (70.4) (67.5-73.3)	768 (70.1) (67.4-72.8)	811 (69.6) (67.0-72.3)	827 (67.4) (64.8-70.0)
3 or more	421 (51.8) (48.3-55.2)	508 (52.5) (49.4-55.7)	554 (50.6) (47.6-53.6)	584 (50.1) (47.3-53.0)	584 (47.6) (44.8-50.4)
Upper-middle-income countries					
Number of participants with CVD	1,837	2,129	2,356	2,453	2,322
Number of medication classes used[a]					
None	826 (45.0) (42.7-47.2)	1,013 (47.6) (45.5-49.7)	1,120 (47.5) (45.5-49.6)	992 (40.4) (38.5-42.4)	904 (38.9) (36.9-40.9)
1 or more	1,011 (55.0) (52.8-57.3)	1,116 (52.4) (50.3-54.5)	1,236 (52.5) (50.4-54.5)	1,461 (59.6) (57.6-61.5)	1,418 (61.1) (59.1-63.1)
2 or more	644 (35.1) (32.9-37.2)	783 (36.8) (34.7-38.8)	886 (37.6) (35.7-39.6)	1,092 (44.5) (42.6-46.5)	1,023 (44.1) (42.0-46.1)
3 or more	298 (16.2) (14.5-17.9)	408 (19.2) (17.5-20.8)	514 (21.8) (20.1-23.5)	628 (25.6) (23.9-27.3)	577 (24.9) (23.1-26.6)
Lower-middle-income countries					
Number of participants with CVD	3,902	4,371	4,498	5,987	6,726
Number of medication classes used[a]					
None	2,751 (70.5) (69.1-71.9)	2,984 (68.3) (66.9-69.6)	3,144 (69.9) (68.6-71.2)	4,728 (79.0) (77.9-80.0)	5,828 (86.6) (85.8-87.5)
1 or more	1,151 (29.5) (28.1-30.9)	1,387 (31.7) (30.4-33.1)	1,354 (30.1) (28.8-31.4)	1,259 (21.0) (20.0-22.1)	898 (13.4) (12.5-14.2)
2 or more	463 (11.9) (10.9-12.9)	617 (14.1) (13.1-15.1)	639 (14.2) (13.2-15.2)	628 (10.5) (9.7-11.3)	543 (8.1) (7.4-8.7)
3 or more	151 (3.9) (3.3-4.5)	264 (6.0) (5.3-6.7)	290 (6.5) (5.7-7.2)	329 (5.5) (4.9-6.1)	324 (4.8) (4.3-5.3)
Low-income countries					
Number of participants with CVD	857	1,325	1,287	1,477	1,402
Number of medication classes used[a]					
None	679 (79.2) (76.5-81.9)	844 (63.7) (61.1-66.3)	819 (63.6) (61.0-66.3)	778 (52.7) (50.1-55.2)	1,016 (72.5) (70.1-74.8)
1 or more	178 (20.8) (18.1-23.5)	481 (36.3) (33.7-38.9)	468 (36.4) (33.7-39.0)	699 (47.3) (44.8-49.9)	386 (27.5) (25.2-29.9)
2 or more	70 (8.2) (6.3-10.0)	274 (20.7) (18.5-22.9)	274 (21.3) (19.1-23.5)	415 (28.1) (25.8-30.4)	200 (14.3) (12.4-16.1)
3 or more	30 (3.5) (2.3-4.7)	144 (10.9) (9.2-12.5)	139 (10.8) (9.1-12.5)	200 (13.5) (11.8-15.3)	92 (6.6) (5.3-7.9)

Values are N or n (%) (95% CI). [a]In participants with coronary artery disease, medications were categorized into the following classes: antiplatelet drugs, statins, renin-angiotensin system inhibitors, and β-blockers. In participants with stroke, medications were categorized into the following classes: antiplatelet drugs, statins, renin-angiotensin system inhibitors, and other blood pressure–lowering medications (defined as β-blockers, calcium-channel blockers, or diuretic agents).

CVD = cardiovascular disease.

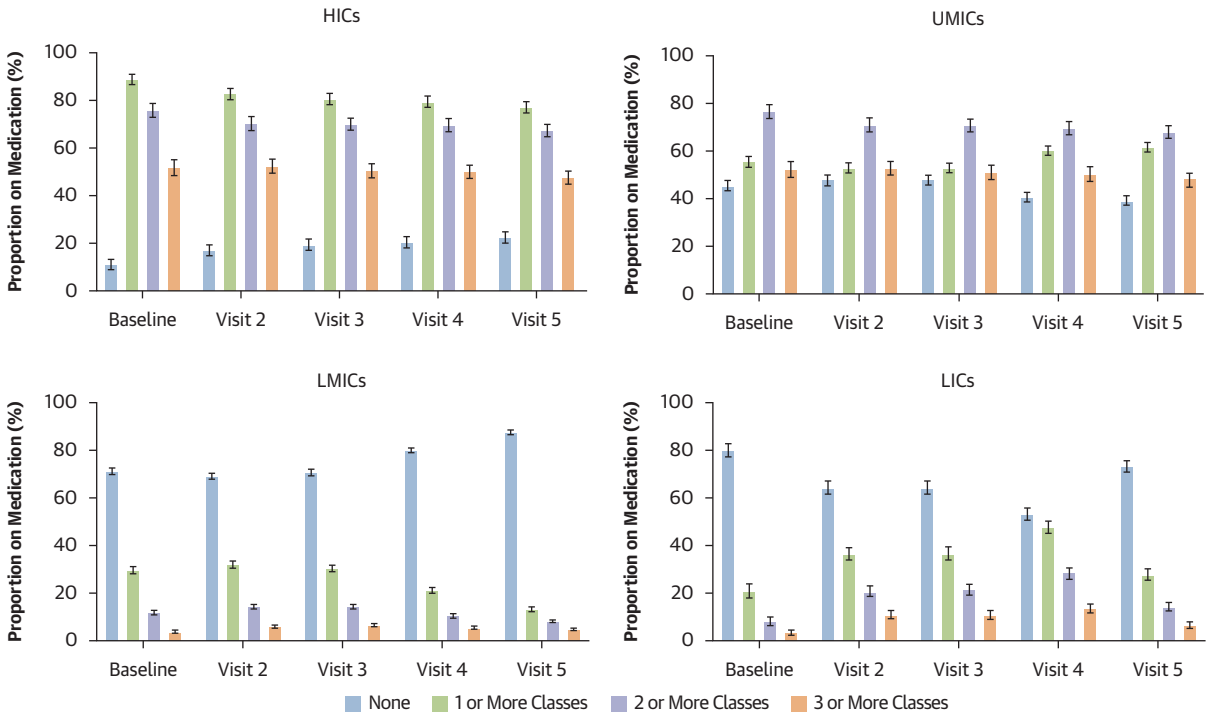
16.2% (95% CI: 14.5%-17.9%) at baseline to 24.9% (95% CI: 23.1%-26.6%) by the last visit.

In LMICs, the proportion of participants taking 1 or more medication classes for secondary CVD prevention was 29.5% (95% CI: 28.1%-30.9%) at baseline, peaked at 31.7% (95% CI: 30.4%-33.1%) at the second visit, and then decreased to 13.4% (95% CI: 12.5%-14.2%) by the last visit. Use of 3 or more medication classes was 3.9% (95% CI: 3.3%-4.5%) at baseline, peaked at 6.5% (95% CI: 5.7%-7.2%) at the third visit, and decreased to 4.8% (95% CI: 4.3%-5.3%) by the last visit.

In LICs, 20.8% (95% CI: 18.1%-23.5%) of participants were taking 1 or more classes of medications for secondary CVD prevention at baseline; this rate which peaked at 47.3% (95% CI: 44.8%-49.9%) at the fourth visit and then decreased to 27.5% (95% CI: 25.2%-29.9%) by the final visit. At the baseline visit, 3.5% (95% CI: 2.3%-4.7%) of participants were taking 3 or more medication classes, a rate that peaked at 13.5% (95% CI: 11.8%-15.3%) at the fourth visit and then decreased to 6.6% (95% CI: 5.3%-7.9%) by the last visit.

Among LICs, medication use was higher in India compared with other countries for most of the study period (Figure 4). In India, 21.4% (95% CI: 18.2%-24.7%) of participants were taking 1 or more medication classes at baseline; this rate peaked at 43.0% (95% CI: 38.5%-47.6%) at the fourth visit and then decreased to 21.6% (95% CI: 17.5%-25.8%) by the last visit. The highest use of 3 or more medication classes was 10.7% (95% CI: 8.1%-13.2%) during the study period. In other LICs, use of 1 or more classes of medications was 19.1% (95% CI: 14.1%-24.0%) at baseline, peaked at 35.2% (95% CI: 30.9%-39.5%) at the fourth visit, and was 33.3% (95% CI: 28.7%-37.8%)

FIGURE 3 Number of Secondary Prevention Medication Classes Used in All Participants With Cardiovascular Disease Stratified by Country Income Level



Data are presented in all participants either with a baseline history of cardiovascular disease or with cardiovascular disease that developed during follow-up by countries grouped by income level. In participants with coronary artery disease, medications were categorized into the following classes: antiplatelet drugs, statins, renin-angiotensin system inhibitors, and β-blockers. In participants with stroke, medications were categorized into the following classes: antiplatelet drugs, statins, renin-angiotensin system inhibitors, and other blood pressure-lowering medications (defined as β-blockers, calcium-channel blockers, or diuretic agents). HICs = high-income countries; LICs = low-income countries; LMICs = lower-middle-income countries; UMICs = upper-middle-income countries.

at the final visit. In these countries, the highest use of 3 or more medication classes was 7.6% (95% CI: 5.2%-10.0%) during the study period.

TRENDS IN MEDICATION USE IN OTHER SUBGROUPS

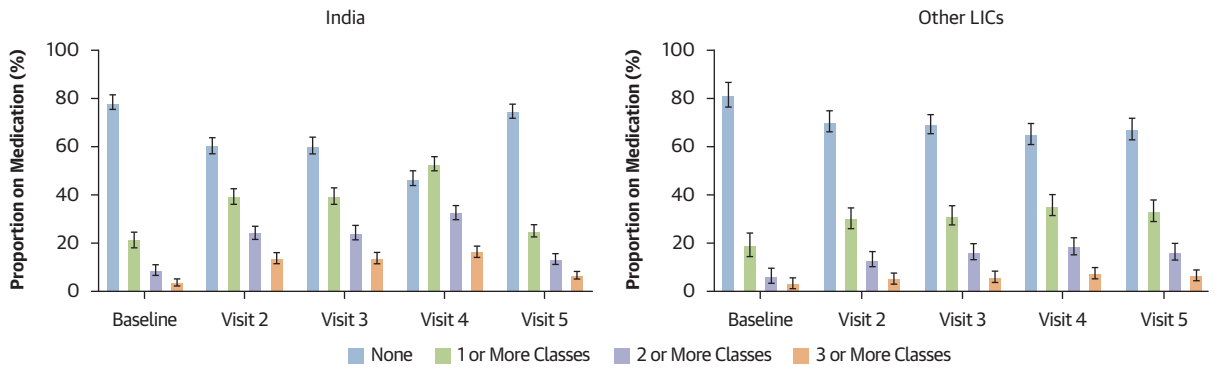
Stratified analyses by age, sex, urban-rural area, and CVD type are summarized in Supplemental Tables 5 to 8. During the study period, use of 1 or more classes of these medications was consistently higher in participants ≥60 years of age compared with participants <60 years of age and in male participants compared with female participants. Among HICs, medication use was similar in urban and in rural areas at most study visits. In UMICs, LMICs, and LICs, medication use was consistently higher in urban areas compared with rural areas. Medication use at baseline was initially higher in participants with stroke compared with CAD, but by the last study visit medication use was higher in participants with CAD compared with stroke.

DISCUSSION

In this contemporary, multinational cohort study with representation from 17 HICs, MICs, and LICs, we have observed little to no progress in the use of medications for secondary CVD prevention over median visit cycles occurring between 2007 and 2019. Medication use varied substantially by country income level; with the exception of UMICs, medication use was lower at the last study visit compared with the first visit. Our findings suggest that current implementation strategies continue to leave the majority of persons with CVD either untreated or undertreated.

Trends in the use medications for secondary CVD prevention differed among groups of countries at different income levels. In HICs, most participants were taking at least 1 medication class throughout the

FIGURE 4 Number of Secondary Prevention Medication Classes Used in Participants With Cardiovascular Disease in India vs Other LICs



Data are presented in all participants either with a baseline history of cardiovascular disease or with cardiovascular disease that developed during follow-up. In participants with coronary artery disease, medications were categorized into the following classes: antiplatelet drugs, statins, renin-angiotensin system inhibitors, and β-blockers. In participants with stroke, medications were categorized into the following classes: antiplatelet drugs, statins, renin-angiotensin system inhibitors, and other blood pressure-lowering medications (defined as β-blockers, calcium-channel blockers, or diuretic agents). Abbreviation as in Figure 3.

study period. However, only one-half of participants were taking 3 or more medication classes, and the overall use of these medications generally decreased over time. In UMICs, medication use increased by 6% during the study period, with most participants taking at least 1 medication class by the last study visit. Trends in UMICs suggest modest progress made in the adoption of secondary CVD prevention medications over time in this group of countries, but optimal use of these medications remains low, with only one-fourth of participants taking at least 3 medication classes over the study period. In LMICs, medication use remained low across the study period, and it decreased over the last 2 visits, with <20% of participants taking any CVD prevention medications in these latter periods. In LICs, medication use increased during most of the study period and then markedly decreased at the last study visit. These trends were largely driven by data from India, which has been successful in its capacity to produce generic medications and increasing their availability to the population.

Previous data from PURE suggest that the availability of medications for secondary CVD prevention within India is comparable to that in UMICs.[12] Garg et al[13] reported that the majority of states in India mandate the availability of essential medications for CVD outlined by the WHO. Some of these factors may explain the progress we observed in secondary CVD prevention medication use in LICs over the first 4 study visits.[13] Finally, we observed that medication use sharply decreased in LMICs and in India at the last visit, a decrease that partly coincided with the COVID-19 pandemic. This finding may reflect broader barriers to accessing health care resources disproportionately affecting these countries during the pandemic.

Few community-based studies have reported on contemporary trends in the use of medications for secondary CVD prevention, and these have been conducted in HICs. Studies in the United States conducted over time periods similar to those of our study suggest modest to no improvement in the use of statins and antiplatelet drugs for secondary CVD prevention.[14-16] Studies in European HICs have reported an increase in the use of medications for secondary CVD prevention over time, but these studies were conducted in selected clinics and may not reflect treatment patterns in the general community setting.[17,18] Our findings suggest that secondary CVD medication use is generally declining in HICs, and this decline may be more specific to the group of HICs included in PURE or trends occurring in the broader community setting. In addition, most earlier studies used medication prescription data to infer use, and this approach may overestimate actual use. Two recent cross-sectional analyses using health survey data from multiple MICs and LICs have also reported low use of statins and aspirin in persons with CVD, findings that are largely consistent with our observations.[5,6] We are not aware of previous community-based studies from MICs or LICs that have reported on

how the use of medications for secondary CVD prevention has changed over time, and so our data from PURE provide key metrics for these groups of countries on the extent of progress that has been made.

Although our analysis is largely descriptive, its findings are important in that they highlight the general lack of progress being made to increase the use of secondary CVD prevention medications in many parts of the world, even after introducing the WHO Global Action Plan and the UN SDGs. Outside of setting targets and issuing guidelines, there have been few systematic implementation efforts to increase the uptake of secondary CVD prevention medications in most countries, and new strategies are needed. Barriers to effective CVD prevention have been identified at the patient, provider, and system levels, but strategies to overcome these barriers have been implemented with varying levels of success. There is a need for more implementation research to understand better the contextual barriers to CVD medication use in different populations and health resource settings and for the co-creation of effective implementation-science measures along with the population through design-thinking strategies.[19,20] Two such strategies that can be rapidly implemented in many health resource settings are the use of medications in a combination pill or "polypill," and shifting components of medication management from physicians to trained nonphysician health workers (ie, task shifting or sharing). Recently, a polypill strategy was shown to reduce CVD events in secondary CVD prevention compared with usual care through better adherence to the combinations of these drugs.[21] Studies in both primary and secondary CVD prevention have shown that nonphysician health workers can safely and effectively manage CVD medications after a short period of training and with support (eg, treatment algorithms, physician oversight).[22-25] Such a strategy could substantially increase adoption of these medications in communities where barriers exist to accessing physician care.

STUDY LIMITATIONS. First, we limited this analysis to the original 17 countries included in the PURE study because of the extended follow-up period available in this group. Although this group does not represent all countries, the countries included were from a broad range of geographic regions in the world, as well as at different levels of economic development. Participants in our study were not sampled representatively from each country's population. However, criteria were applied within each country to provide a broad sample population of urban and rural communities and to minimize biases in their inclusion, and as such participant demographics and mortality rates across countries correlate well with national data.[26,27] Our approach to collecting medication data directly from participants could underestimate medication use if participants did not provide investigators with all of their medications or a complete medication list. Despite this potential limitation of our approach, it was likely the only feasible method to collect such data in a standardized manner across widely variable health resource settings. Our analysis did not examine the extent to which changes in population demographics, CVD duration, or CVD severity within the cohort affected variations in medication use over time. Factors such as aging, duration of CVD, or deaths of participants with more severe CVD can partly affect changes in medication use in the cohort over time. Baseline participants with CVD will also differ from participants with new CVD cases by their duration of CVD, as well as by the definitions of CVD used in our study. However, most of the medication classes that were studied are considered to be lifelong therapies for the majority of persons who are identified as having CVD, irrespective of disease severity, and so our findings of underuse remain valid. Finally, the time period in which our last follow-up visit cycle occurred partially coincided with the COVID-19 pandemic, which restricted the ability to conduct research in many countries. This situation contributed to a lower proportion of visit completions among participants with CVD at the last study visit compared with previous study visits. During this period, we also allowed follow-up data to be collected by telephone to overcome restrictions to in-person visits, including the collection of data on medication use. At the same time, barriers to accessing care during the pandemic may have also affected access to medications in these countries. Because communities across PURE differed considerably in the timing, duration, and severity of pandemic-related restrictions, we were not able to delineate clearly the extent of the impact of the COVID-19 pandemic on changes in medication use in the cohort from the fourth visit to the last study visit. However, for most country income-level groups (with the exception of LICs), trends in the use of these medications were already being observed before this last visit.

CONCLUSIONS

Variations in the use of secondary CVD prevention medications over time in our contemporary cohort study suggest little to no improvement globally and at most economic levels. There continues to be substantial underuse of these medications such that global targets for their use are unlikely to be reached. Additional strategies to increase their use are needed to make meaningful improvements in CVD management.

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KEY WORDS cardiovascular disease, coronary artery disease, medication use, stroke

APPENDIX For supplemental tables and an interactive Central Illustration, please see the online version of this paper.