Secondary CV Prevention in South America in a Community Setting

The PURE Study

Alvaro Avezum*, Gustavo B. F. Oliveira*, Fernando Lanas†, Patricio Lopez-Jaramillo‡, Rafael Diaz§, J. Jaime Miranda‖, Pamela Seron†, Paul A. Camacho-Lopez‡, Andres Orlandini§, Antonio Bernabe-Ortiz‖, Antônio Cordeiro Mattos*, Shofiqul Islam¶, Sumathy Rangarajan¶, Koon Teo¶, Salim Yusuf¶

São Paulo, Brazil; Temuco, Chile; Bucaramanga, Colombia; Rosario, Argentina; Lima, Peru; and Hamilton, Ontario, Canada

ABSTRACT

Background: Despite the availability of evidence-based therapies, there is no information on the use of medications for the secondary prevention of cardiovascular disease in urban and rural community settings in South America.

Objectives: This study sought to assess the use, and its predictors, of effective secondary prevention therapies in individuals with a history of coronary heart disease (CHD) or stroke.

Methods: In the PURE (Prospective Urban Rural Epidemiological) study, we enrolled 24,713 individuals from South America ages 35 to 70 years from 97 rural and urban communities in Argentina, Brazil, Chile, and Colombia. We assessed the use of proven therapies with standardized questionnaires. We report estimates of drug use at national, community, and individual levels and the independent predictors of their utilization through a multivariable analysis model.

Results: Of 24,713 individuals, 910 had a self-reported CHD event (at a median of 5 years earlier) and 407 had stroke (6 years earlier). The proportions of individuals with CHD who received antiplatelet medications (30.1%), beta-blockers (34.2%), angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockers (36.0%), or statins (18.0%) were low; with even lower proportions among stroke patients (antiplatelets 24.3%, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers 37.6%, statins 9.8%). A substantial proportion of patients did not receive any proven therapy (CHD 31%, stroke 54%). A minority of patients received either all 4 (4.1%) or 3 proven therapies (3.3%). Male sex, age >60 years, better education, more wealth, urban location, diabetes, and obesity were associated with higher rates of medication use. In a multivariable model, markers of wealth had the largest impact in secondary prevention.

Conclusions: There are large gaps in the use of proven medications for secondary prevention of cardiovascular disease in South America. Strategies to improve the sustained use of these medications will likely reduce cardiovascular disease burden substantially.

During the last decades, South American (SA) countries have undergone demographic changes involving substantial population growth (about 6-fold from the beginning of the 20th century to 2010), urbanization (shifted from predominantly rural to predominantly urban [83%]), and population aging (life expectancy at birth rose from 29.2 years in 1900 to 74.2 in 2010) [1,2]. These epidemiological transitions may have contributed to the higher prevalence of cardiovascular risk factors and high cardiovascular mortality and morbidity rates [3,4]. Cardiovascular disease (CVD) is now the leading cause of death in most parts of SA and, over the last 30 years, there has been a lower rate of reduction in CVD mortality in low-income than in high-income countries [4,5].

Secondary prevention strategies after myocardial infarction (MI) and —such as antiplatelet agents, angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARB), statins, and beta-blockers—are proven therapies widely recommended by international guidelines [6–10]. Despite the availability of scientific data, a substantial gap between the implementation and uptake of proven therapies and current clinical practice remains in SA [11–13]. This leads to poorer than expected patient outcomes [14]. Therefore, in this medium-income region with emerging economies, a clear

The authors report no relationships that could be construed as a conflict of interest.
The main PURE study and its components are funded by the Population Health Research Institute, the Canadian Institutes of Health Research, and the Heart and Stroke Foundation of Ontario, and through unrestricted grants from several pharmaceutical companies (with major contributions from Boehringer Ingelheim [Germany and Canada], AstraZeneca [Canada], Sanofi-Aventis [France and Canada], Servier, and GlaxoSmithKline, with additional contributions from Novartis and King Pharma), and various national or local organizations in participating countries as follows: Fundación Estudios Clínicos Latinamérica (ECLA) (Argentina); Unilever Health Institute (Brazil); Public Health Agency of Canada and Champlain Cardiovascular Disease Prevention Network (Canada); Universidad de la Frontera (Chile); grant from Colciencias (6566-04-18062) (Colombia).
From the *Dante Pazzanese Institute of Cardiology, São Paulo, Brazil; †Universidad de la Frontera, Temuco, Chile; ‡Fundacion Oftalmologica de Santander (FOSCAL), Medical School, Universidad de Santander, Bucaramanga, Colombia; §Estudios Clínicos Latinoamérica, Rosario, Argentina; ‖Universidad Peruana Cayetano Heredia, Lima, Peru; and the ¶Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada. Correspondence: Á. Avezum (avezumjr@uol.com.br).

GLOBAL HEART

VOL. 12, NO. 4, 2017
ISSN 2211-8160/$36.00.
http://dx.doi.org/10.1016/j.gheart.2016.06.001

picture of the utilization of evidence-based therapies in coronary heart disease (CHD) and stroke patients in the community setting from both rural and urban locations may provide a foundation for strategies aimed to improve their use.

The PURE (Prospective Urban Rural Epidemiology) study examined rates and predictors of use of evidence-based secondary prevention medications in patients with CVD (CHD [MI, myocardial revascularization, and angina], and stroke) from urban and rural communities in 17 high-, medium-, and low-income countries [15]. The current report comprises the SA component of the PURE study.

METHODS

Study design and participants

We enrolled individuals from communities in Argentina, Brazil, Chile, and Colombia between January 2003 and December 2009. These countries represent nearly 75% of SA population, providing representative socioeconomic and ethnic heterogeneity. Within each country, we selected urban and rural communities using methods published elsewhere [16]. Urban communities from these middle-income countries were selected from sections of cities, and the community area was further delineated according to pre-defined geographical features. All eligible individuals provided informed consent before recruitment.

Procedures

A standardized operations manual was used to ensure high-quality data collection with pre-defined questionnaires, similar to those used in the INTERHEART (A Global Study of Risk Factors for Acute Myocardial Infarction) [17] and INTERSTROKE (Study of the Importance of Conventional and Emerging Risk Factors of Stroke in Different Regions and Ethnic Groups of the World) [18] studies. We performed a customized electronic data capture with programmed audit checks. The database was managed at the Project Office at the Population Health Research Institute in Hamilton, Ontario, Canada. We assessed medical history of CVD, other diseases, and names of all medications taken from every participant. CHD was determined on the basis of self-reported MI, coronary artery bypass graft surgery, percutaneous coronary intervention, or angina. Stroke was defined on the basis of self-reports.

Statistical analysis

We analyzed the use of 4 classes of medications: antiplatelets, beta-blockers, ACEI or ARB, and statins. Categorical variables are summarized as number (%), including disease status and medication intakes. Continuous variables are summarized as mean ± SD or, for skewed continuous measures, as median (interquartile range). We compared proportions between groups with a chi-square test and means with 2-sample Z test considering a 2-sided alternative. A multivariable analysis was performed using logistic regression model to identify independent predictors of use of evidence-based therapies. Adjusted proportions were also calculated using multivariable logistic regression with an appropriate contrast statement. All statistical analyses were performed using SAS (version 9.2; SAS Institute, Cary, North Carolina) and all figures were drawn using S-PLUS (version 6.2; TIBCO Software, Palo Alto, California).

RESULTS

Participants

We recruited 24,713 individuals (16% of the main study) ages 35 to 70 years with complete data. The number of individuals recruited and their distribution by sex, location (rural or urban), and country are shown in Table 1. The proportions of patients presenting, at baseline, with CHD varied from 1.7% in Chile to 5.4% in Brazil ($p < 0.0001$); with stroke, ranged from 1.47% in Argentina to 1.8% in Brazil (p = NS); and with CHD or stroke, from 3.2% in Chile to 6.9% in Brazil ($p < 0.0001$). The prevalence of individuals with previous cardiovascular events was higher in urban areas, male subjects, those with diabetes, higher body mass index, or hypertension, and in former smokers. Median time intervals since the diagnosis of CHD, stroke, or CHD or stroke were 5, 6, and 5 years, respectively.

Medication use

Table 2 shows the rates of antiplatelets, beta-blockers, ACEI/ARB, and statins, in CHD, stroke, and CHD or stroke participants. The overall utilization of antiplatelets in

TABLE 1. Participants in the PURE study in South America by sex and location

	Communities			Participants			Participants		
	Overall	Urban	Rural	Overall	Urban	Rural	Overall	Female	Male
Argentina	20	6 (30.0)	14 (70.0)	7,534	3,614 (47.9)	3,920 (52.1)	7,534	4,626 (61.5)	2,908 (38.5)
Brazil	14	7 (50.0)	7 (50.0)	6,081	4,664 (76.7)	1,417 (23.3)	6,081	3,350 (55.1)	2,731 (44.9)
Chile	5	2 (40.0)	3 (60.0)	3,557	2,816 (79.2)	741 (20.8)	3,557	2,342 (66.4)	1,215 (33.7)
Colombia	58	35 (60.3)	23 (39.7)	7,541	3,498 (46.4)	4,043 (53.6)	7,541	4,838 (64.2)	2,703 (35.9)
Overall	97	50 (51.6)	47 (48.5)	24,713	14,592 (59.1)	10,121 (40.9)	24,713	15,156 (61.3)	9,557 (38.7)

Values are n or n (%).

TABLE 2. Proportion of individuals on medications with CHD, stroke, and CHD or stroke in South America

Medication	CHD	Stroke	CHD or Stroke
Total number with CHD or stroke	910 (100.0)	407 (100.0)	1,257 (100.0)
Antiplatelet agents*	274 (30.1)	99 (24.3)	355 (28.2)
Beta-blockers	311 (34.2)	61 (15.0)	356 (28.3)
ACEI/ARB	328 (36.0)	153 (37.6)	452 (36.0)
Diuretics†	177 (19.5)	76 (18.7)	239 (19.0)
Calcium antagonists	104 (11.4)	47 (11.5)	144 (11.5)
Antihypertensives‡	521 (57.3)	214 (52.6)	695 (55.3)
Statins	164 (18.0)	40 (9.8)	193 (15.4)

Values are n (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CHD, coronary heart disease.
*Aspirin or other agents.
†Any type of diuretic drug.
‡n (%) of individuals with diagnosis of hypertension: 539 (59.2) with CHD, 265 (65.1%) with stroke, and 758 (60.3) with CHD or stroke.

patients with CHD was low (30.1%), ranging from 25.9% in Argentina to 48.3% in Chile ($p = 0.01$). The use of beta-blockers in CHD ranged from 22.0% in Colombia to 42.5% in Argentina ($p < 0.0001$). ACEI/ARB were used in 29.1% of CHD patients in Colombia and up to 45.6% in Brazil ($p = 0.003$). Statin use in CHD patients was 18% overall, with a wide range from 2.2% in Colombia to 30.3% in Brazil ($p < 0.0001$). Fewer stroke patients received antiplatelets (24.3%), ACEI/ARB (37.6%), and statins (9.8%) as compared with CHD patients (30.1%, 36.0%, and 18.0%, respectively). This underutilization of therapies in stroke patients varied substantially among countries, with the lowest use in Colombia (no prescription of statins). When CHD and stroke patients were combined, the proportion of utilization of antiplatelets was highest in Chile (38.1%) and lowest in Argentina (23.0%). ACEI/ARB and statins use were highest in Brazil (46.4% and 26.4%) and lowest in Colombia (26.4% and 1.4%), respectively.

Patients aged <50 years were less likely to receive evidence-based therapies than patients aged ≥50 years, except for beta-blocker use, consistently across the CVD clinical settings. For example, 39.7% of CHD patients aged ≥60 years received antiplatelets compared with 30.9% of those aged 50 to 60 years and 20.3% of those <50 years ($p < 0.0001$). A similar pattern was observed in stroke patients, with higher proportion of antiplatelet use in patients ≥60 years in comparison to younger patients (21.0% in those aged 50 to 60 years and 9.9% in those <50 years, $p = 0.0001$). Of note, inexpensive medications such as antiplatelets had similar variation in their use compared with more expensive ones (i.e., statins and ACEI/ARB). Women were less likely to receive proven therapies than men, even after adjustment for age, location, and education. Only 11.7% of women reported taking statins compared with 19.5% of men ($p = 0.0004$). Among CHD or stroke participants, there was higher utilization in those with higher education level relative to those with none, primary, or unknown education (35.6% vs. 23.6% for antiplatelets [$p = 0.002$]; 20.6% vs. 10.9% for statins [$p = 0.0007$]). Former smokers with CHD or stroke were more likely to receive proven therapies than current smokers or those who had never smoked (35.2% vs. 26.6% and 27.7%, respectively, for antiplatelets [$p = 0.039$]; 19.9% vs. 10.6% and 13.0% for statins [$p = 0.004$]).

CHD and stroke patients with body mass index <25 kg/m^2 were somewhat less likely to receive medications when compared with overweight/obese patients (25.5% vs. 36.8% and 27.6%, respectively, for antiplatelets [$p = 0.004$]; 11.1% vs. 18.7% and 15.9% for statins [$p = 0.045$]). Diabetes was also associated with higher use (antiplatelets 33.3% vs. 29.6% [$p = 0.026$]; ACEI/ARB 40.3% vs. 30.5% [$p = 0.003$]; and statins 20.1% vs. 13.8% [$p = 0.018$]).

The use of all medications either among CHD or stroke patients was higher in urban areas relative to rural ones, with absolute differences ranging from 1.3% statins in stroke patients (7.1% rural vs. 8.4% urban) to 13.8% antiplatelets in CHD patients (23.6% rural vs. 37.4% urban) (Table 3).

The use of all 4 therapies (antiplatelets, beta-blockers, ACEI/ARB, and statins) was only (4.1%), with the highest rate in Brazil (5.5%) and lowest in Colombia (0.5%) ($p = 0.02$). Use of 3 or 2 medications was remarkably low in SA (15.5% and 40.3%, respectively). Moreover, 31% of CHD patients did not receive any medication, up to 47.8% in Colombia (Fig. 1A). Additionally, use in stroke patients—such as the combination of antiplatelets, ACEI/ARB, and statins—was also low (5.8%). The values for 2 or 1 of them in stroke were also low (15.0% and 30.1%, respectively). Despite being categorized as high risk for recurrent cardiovascular events, 49.1% of stroke patients did not receive any of the 3 proven therapies (Fig. 1B). Among all CHD or stroke participants, 37.7% were not taking any of them and 12.0% were taking ≥3 therapies (Fig. 1C). CHD or stroke participants from rural areas were less likely than those from urban areas (54.5% vs. 66.4%; $p < 0.0001$) to receive

TABLE 3. Proportion of individuals on medications with CHD or stroke, by urban or rural locations in South America

	Overall South America		
	Urban	Rural	p Value
CHD	522	259	
Antiplatelet drugs	195 (37.4)	61 (23.6)	<0.001
Beta-blockers	204 (39.1)	85 (32.8)	0.10
ACEI or ARB	221 (42.3)	93 (35.9)	0.10
Statins	117 (22.4)	31 (12.0)	<0.001
Stroke	273	155	
Antiplatelet drugs	65 (23.8)	29 (18.7)	0.27
ACEI or ARB	107 (39.2)	43 (27.7)	0.02
Statins	23 (8.4)	11 (7.1)	0.76

Values are n or n (%).
Abbreviations as in Table 2.

any medication. The proportion of patients who received 3 medications was also higher in urban versus rural areas (14.7% vs. 6.9%; p = 0.01) (data not shown).

Several variables were identified through multivariable analysis as independent predictors of utilization. The following independent factors were found to be associated with increasing utilization of at ≥1 medication: age ≥60 years, urban residence, wealth, obesity, and diabetes; only age <50 years was associated with reduced utilization of ≥1 medication. For ≥2 medications, independently associated variables were similar, but they included male sex and excluded urban location. By incorporating all the variables associated with higher use of beneficial therapies, we identified that wealthy, highly educated, smoker, obese, diabetic, and older male individuals were 3-fold more likely to receive antiplatelets, 2.5-fold for beta-blockers, 3-fold for ACEI/ARB, and 9-fold for statins. Additionally, those individuals would have 4-fold greater odds to receive ≥1evidence-proven medication and 3.5-fold greater odds to receive ≥2of them (Table 4).

DISCUSSION

This study has 3 major findings. First, a very low proportion of individuals in rural and urban settings in SA self-reported taking evidence-based proven medications for secondary cardiovascular prevention; second, reported treatment with 3 (stroke) or 4 (CHD) evidence-based therapies, as a simple quality of care measure and according to current guidelines [19,20] was very low across SA countries; and finally, this is the first study to identify independent predictors associated with use of secondary cardiovascular prevention in SA indicating which variables are associated with better or worse quality of care in the region.

Reliable information regarding secondary CVD prevention from a community perspective is not available in the region and there is a clear need to better determine the situation analysis and to reliably understand reasons for improving quality of care to plan and implement CVD prevention strategies, regionally.

Even simple, inexpensive therapies, such as antiplatelets, were used only by one-third of CHD individuals and one-quarter of stroke individuals. Antiplatelets are widely available at low cost for low-income families in the region, and also even free of charge in some of the countries; therefore, the utilization rates should be higher than observed. Other medications were also not used according to current guidelines, including statins (one-fifth of CHD individuals and below 10% of stroke individuals). The gap between scientific knowledge and effective implementation into clinical practice in CVD is a global phenomenon, with striking variation concerning the use of effective therapies in CHD and stroke patients [21–24].

Clinical setting and duration of follow-up

Although nonadherence with evidence-based secondary prevention medications is common in patients with established atherothrombotic disease, long-term outcomes studies are scant [25]. The REACH (Reduction of Atherothrombosis for Continued Health) registry [26] evaluated patients either with vascular disease or at high risk for developing vascular disease, including Latin American patients, and found the following rates of use at baseline and at 3 years of follow-up, respectively: aspirin alone (56.6% and 56.9%) and statins (68.3% and 71.9%). On the longer-term follow-up, adherence was identified to be greater in high-income countries, with participants from Latin America and Asia being less likely to be completely adherent. Less than 50% of patients with atherothrombotic disease were adequately adherent to guideline-recommended medications, suggesting that secondary prevention adherence was associated with age, geographic region, and ethnicity; and CV events were inversely associated with adherence [27]. The World Health Organization PREMISE (Prevention of Recurrences of Myocardial Infarction and Stroke Study) study [28], including low-income/middle-income countries (also from SA), found the following rates of prevention therapies in CHD and cerebrovascular disease patients, respectively: aspirin (81.2% and 70.5%), beta-blockers (48.1% and 22.1%), ACEI (39.8% and 38.1%), and statins (20.8% and 12.2%). Despite these low rates of use, this was not conducted in a community setting, possibly explaining the higher prescription rates relative to our data. The lower medication use in our study is probably due to the longer time since diagnosis (medians of 5 and 6 years for CHD and stroke events, respectively). Additionally, our study was conducted in rural and urban communities, which are very different as compared with hospital and outpatient settings. In short-term analyses, medication rates seem to be reasonable, as described in a cohort of patients who underwent coronary interventional procedures with 75% of patients taking 4 or 5 classes of medication after 1 year (aspirin, clopidogrel, ACEI/ARB, beta-blockers, and

lipid-lowering agents) [29]. In Chile, 1 year after MI discharge, medication utilization from 6 public hospitals was aspirin 93%, clopidogrel 33%, beta-blockers 66%, ACEI/ARB 73%, and statins 85% [30]. However, with longer follow-up and community settings, medication rates diminish, considerably, according to the current data from SA. Conversely, for example, in New Zealand, 86,256 patients who were hospitalized for an atherosclerotic CVD event or procedure in the previous 10 years showed that 59% were maintained on triple therapy [31]. This is significantly higher—despite longer follow-up—than was found in our study. Potentially, patient characteristics, physician behavior toward CVD prevention, and the different structures of the health system could explain the different results compared with those of our study. Therapy utilization rates will often be higher in those who are actively being followed post-event than in those in the community, where there is fewer data for comparison. Importantly, our study captured data in a community setting and, consequently, rates of proven therapies would be expected to be lower than data from studies conducted in hospitals or outpatient clinics. We emphasize the fact that we did not assess adherence to medications, instead, prescription rates of specific therapies were evaluated and reported as an indicator of quality of care.

Reasons for low prescription rates

Several factors could be considered as potential explanations for the lack of effective CVD prevention worldwide, and these can be grouped into 3 major categories: physicians, patients, and health systems. From a physician's perspective, there are factors related to knowledge (lack of awareness or lack of familiarity), attitude (lack of agreement with guidelines, interpretation of evidence, applicability to patients, challenge to autonomy, lack of outcome expectancy, lack of self-efficacy, and lack of motivation), and behavior (external barriers, patient preferences, guideline recommendations, contradictory guidelines, and lack of time, resources, and reimbursement) [32]. Factors related to patients may include lack of awareness of disease consequences and of available therapeutic strategies to improve survival, morbidity, and symptoms; long distance to see a physician; or long waiting times or costs (e.g., transportation, physician fees, cost of medications). This may be related to socioeconomic status and education level, which are both relevant for a clear understanding of disease and treatment. Health system-related factors include costs, access, affordability, insurance coverage, bureaucracy, health and disease priorities, government stability, and copayments [33,34]. Even in high-income, developed countries, the use of simple, inexpensive preventive cardiovascular therapies is suboptimal [15], suggesting that implementation of proven strategies is a major challenge due to a number of factors including access and affordability to medications and health care providers.

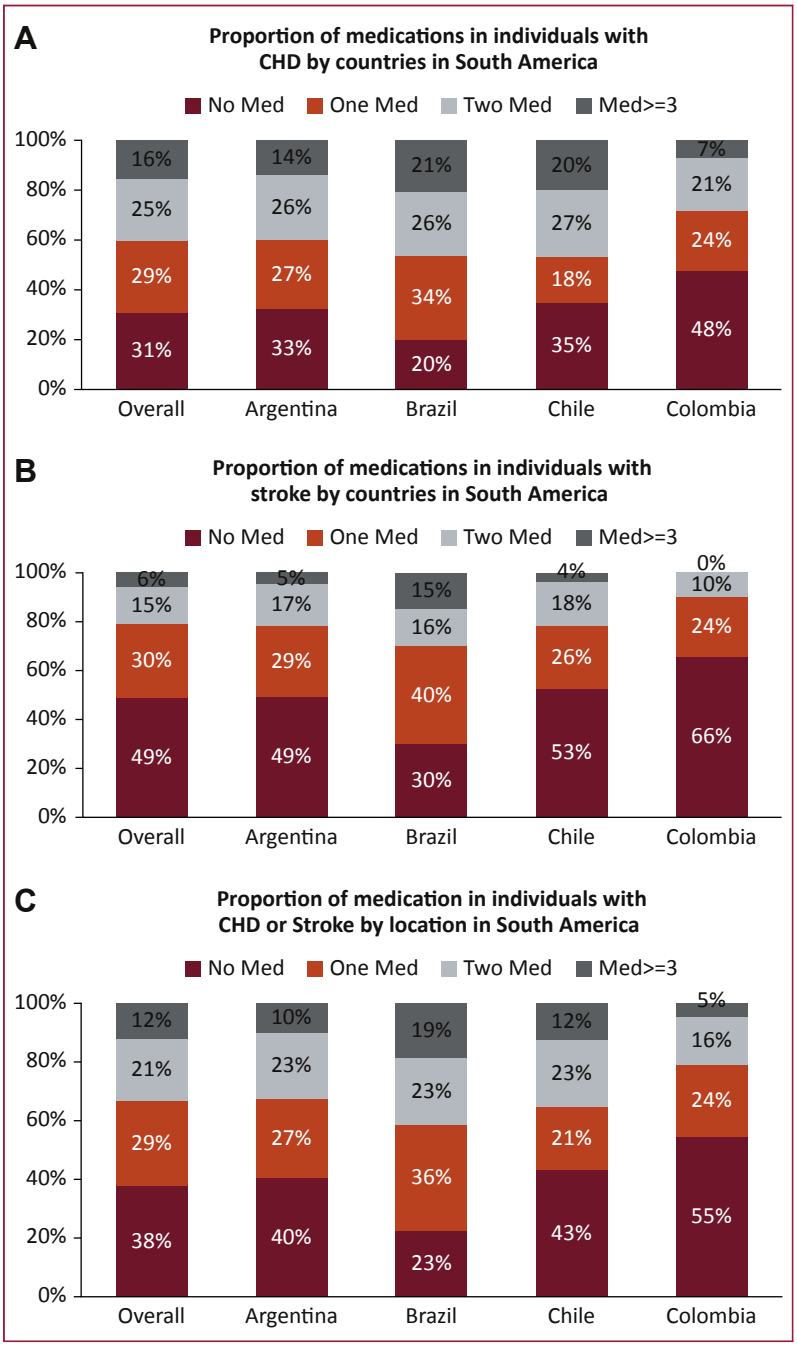

FIGURE 1. Proportion of medications in individuals with (A) coronary heart disease, (B) stroke, and (C) coronary heart disease or stroke by country in South America.

Factors associated with usage

Knowledge of the variables associated with specific lifestyle changes and preventive medication use may help in tailoring secondary prevention programs. Identification of independent predictors associated with secondary prevention use in SA would be clinically valuable in order to

TABLE 4. Independent predictors associated with medication use in individuals with either CHD or stroke in South America

Variable	Antiplatelet	Beta-Blocker	ACEI/ARB	Statin	≥1 Medication	≥2 Medications
Male sex	1.09 (0.82, 1.46)	1.16 (0.87, 1.56)	1.44 (1.09, 1.90)	1.54 (1.06, 2.24)	1.20 (0.90, 1.59)	1.63 (1.23, 2.16)
Age <50 yrs*	0.46 (0.30, 0.71)	0.63 (0.42, 0.95)	0.50 (0.34, 0.75)	0.38 (0.20, 0.71)	0.43 (0.30, 0.61)	0.52 (0.34, 0.78)
Age ≥60 yrs*	1.42 (1.05, 1.92)	1.35 (1.00, 1.84)	1.54 (1.15, 2.06)	1.32 (0.90, 1.94)	1.95 (1.43, 2.65)	1.48 (1.10, 1.99)
Urban location†	1.30 (0.93, 1.81)	1.20 (0.87, 1.66)	1.41 (1.04, 1.92)	1.01 (0.65, 1.58)	1.36 (1.00, 1.85)	1.33 (0.97, 1.84)
Secondary higher education‡	1.49 (1.03, 2.16)	1.20 (0.84, 1.73)	0.72 (0.50, 1.04)	1.18 (0.74, 1.91)	1.08 (0.74, 1.57)	1.24 (0.86, 1.78)
Trade/college/university education‡	1.74 (1.14, 2.65)	0.62 (0.39, 0.96)	0.64 (0.42, 0.98)	1.53 (0.92, 2.56)	0.84 (0.55, 1.30)	1.01 (0.66, 1.54)
Mid-wealthier§	1.47 (1.00, 2.17)	1.93 (1.30, 2.88)	1.63 (1.14, 2.32)	3.25 (1.66, 6.36)	1.92 (1.36, 2.72)	1.98 (1.35, 2.91)
Wealthiest§	1.26 (0.77, 2.08)	2.51 (1.53, 4.15)	1.20 (0.75, 1.91)	5.94 (2.80, 12.6)	1.83 (1.15, 2.92)	2.01 (1.23, 3.28)
Smoking	1.26 (0.95, 1.69)	0.89 (0.67, 1.18)	1.11 (0.84, 1.46)	1.24 (0.85, 1.81)	1.13 (0.85, 1.49)	1.07 (0.81, 1.42)
Obesity I (25 ≤ BMI < 30)‖	1.66 (1.14, 2.42)	1.22 (0.82, 1.79)	2.56 (1.74, 3.77)	1.74 (1.05, 2.90)	1.88 (1.33, 2.68)	2.09 (1.41, 3.08)
Obesity II (BMI ≥30)‖	1.05 (0.71, 1.55)	1.62 (1.10, 2.38)	2.96 (2.00, 4.38)	1.30 (0.77, 2.21)	1.93 (1.35, 2.75)	2.15 (1.45, 3.20)
Diabetes	1.14 (0.82, 1.57)	1.22 (0.88, 1.67)	1.38 (1.01, 1.88)	1.60 (1.08, 2.37)	1.63 (1.16, 2.30)	1.41 (1.03, 1.93)
Wealthy/urban/male/high education ≥60 yrs/smoker/DM/BMI ≥30 vs. others	2.96 (1.27, 7.03)	2.45 (1.09, 5.51)	3.17 (1.47, 6.84)	8.65 (1.19, 63.1)	4.27 (2.26, 8.05)	3.65 (1.54, 8.66)

Values are median (interquartile range).
BMI, body mass index; DM, diabetes mellitus; other abbreviations as in Table 2.
*Reference group: age 50 to 60 years.
†Reference group: rural location.
‡Reference group: none/primary/unknown education.
§Reference group: poor.
‖Reference group: BMI < 25.

better plan knowledge translation initiatives for improving the CVD burden in the region. In the current study, various patient-specific categories were less likely to receive preventive medications: women, younger age, rural location, lower education, lower socioeconomic status, nonobesity, and nondiabetic. However, even the categories of patients most likely to receive such proven medications were considered undertreated for effectively preventing CVD in SA. Perceived concerns about the benefits of medication play a more significant role in the prediction of adherence and perceived illness burden than the risk with their use [35]. Beliefs about the benefits of treatment predict adherence and older age predict better adherence among those at high multifactorial risk who were hospitalized for an atherosclerotic CVD event or procedure and after stroke [31,35,36], which is similar to our findings. In 1 study, the most frequent physicians' reasons cited for the nonprescription of statins (about 33%) were that patients were not high enough risk and that current guidelines did not support statin use. This suggests that secondary prevention patients continue to be undertreated as a result of physician underestimation of CV risk [21]. In an underserved American community setting of stroke and transient ischemic attack (TIA) survivors, increased concerns about medications and perceived discrimination from the health system were described as independent predictors of lower adherence [24], indicating that interventions to improve adherence should tackle health professionals, patients, and health systems in a complementary, comprehensive, and cohesive action toward CVD prevention.

CHD and stroke clinical scenarios

Even in hospital-based settings, less than two-thirds of eligible ischemic stroke patients were discharged on all 3 guideline-recommended secondary preventive drugs [37]. Among 858,835 patients with TIA or ischemic stroke, adherence to secondary prevention measures was consistently lower for the TIA cohort [38], suggesting that higher risk patients are more likely to be effectively treated, as we have suggested based on our data. In <2 years, about one-quarter of TIA patients, from a community-based setting, became nonpersistent, which was associated with younger age (<55 years), and those nonpersistent users were less adherent to other preventive medication than persistent users were [39]. In non-community-based environment rates are higher, however, they are still not appropriate to reflect guidelines recommendations as suggested by the EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events) III core survey [40] for treatment within 6 to 36 months after the stroke event. Among patients with ischemic stroke or TIA, in a population-based scenario, less than two-thirds were on antithrombotic therapy, one-third were on statins, and less than one-quarter were on an optimal regimen [41]. Sustained secondary prevention declines rapidly during the first 2 years after stroke, particularly for statins and antiplatelets (about 45% and 33% nonadherence, respectively) [42]. We observed that CHD patients are more likely than are stroke patients to use evidence-based medication, as has been shown in other populations of CHD and non-CHD patients with statins and antithrombotic therapies

[22]. Some barriers to medication adherence in survivors of strokes could be identified as potential reasons, such as increased concerns about medications (related to worry, disruption, long-term effects, and medication dependence) and perceived discrimination [24]. Possibly, underuse at stroke unit discharge may be related to uncertainties about efficacy in stroke subtypes and differences among current guidelines [43]. The most important predictor of statin use in ischemic stroke is previous history of CHD [44], and the prescription at discharge is strongly associated with statin intake prior to the event [45].

Comorbidities and drug affordability

In our study, all classes of medications were underutilized, which is supported by a comprehensive meta-analysis of 376,162 patients [23]. As adherence to preventive treatment is poor and not specifically related to the class of agent (indicating that side effects may not be the main cause), general, rather that class-specific, measures at improving adherence are needed. In a meta-analysis on statin adherence, women had 10% greater odds of nonadherence than did men [46], and, similarly, patients who were hospitalized for CVD event or procedure and elderly patients after acute MI [27,30] were more likely to use statins, as suggested in our analysis. Some studies have suggested that sicker patients are less likely to receive evidence-based therapies [21,47]. However, our data suggest that higher risk (e.g., diabetic, older, and obese) patients have higher rates of use of these therapies. Our findings indicate that patients with known risk factors may be better treated and more likely to adhere to recommended treatments in the secondary prevention setting. Corroborating our results, hospital-setting data in secondary prevention suggests that presence of comorbidities (e.g., hypertension, hypercholesterolemia, diabetes) is associated with the utilization of guideline-recommended therapies after ischemic stroke [19,48], nonfatal MI or coronary angioplasty/stenting, and acute coronary syndromes [26]. Reasons for an insufficient uptake of preventive therapies could include drug affordability or restricted availability in middle-income countries. However, even in countries such as Brazil and Chile, where these 4 medications are available free of charge, we still observed low utilization rates. Restricted access to health care could explain the lower rates of drug utilization in rural versus urban areas. Factors that could explain the underuse of effective therapies are not entirely clear. Interestingly, studies from developed countries have shown that several secondary prevention targets are often not met despite the high use of evidence-based therapy, extensive coverage for these medications, and low physician underestimation of risk [49]. In Brazil, a comprehensive and community-based program (Family Health Strategy) including health promotion, primary prevention, and management of CVD risk factors, and secondary prevention for high-risk individuals, through domiciliary visits and community interventions operated by community health workers, demonstrated the higher the coverage of the program, the lower the cerebrovascular disease mortality (odds ratio: 0.82; 95% confidence interval: 0.79 to 0.86) and heart disease mortality (odds ratio: 0.79; 95% confidence interval: 0.75 to 0.80) [50]. Potentially, the quality of care delivered by family physicians, by means of a multimodal intervention based on pay-for-performance, teamwork, continuous education, and audit and feedback, may be enhanced in SA [51]. Specific community-based strategy, conducted in underserved areas in SA, has shown efficacy and feasibility of low-cost educational initiative to improve blood glucose control and reduce CV risk in individuals with type 2 diabetes or pre-diabetes, suggesting that similar models potentially would have substantial impact [52]. Combined actions may influence health and quality of life determinants in rural and economically deprived areas where practitioners and policy makers strengthen social and human capital through capacity development of health promoters [53].

Furthermore, to the best of our knowledge, neither scores nor independent variables associated with evidence-based therapies utilization have been developed to predict the probability of use to reduce risk of recurrent cardiovascular events in SA. The current data could be seen as a "Call for Action in SA" and stimulate policy makers to narrow the large gap between guideline recommendations and secondary prevention delivery. Our findings provide the first reliable data in SA, in both rural and urban communities, and may help implement the World Heart Federation's 25×25 program, which aims to reduce cardiovascular premature mortality by 25% by the year 2025 [54,55].

Limitations and strengths

Self-reported diagnoses of CHD and stroke that had occurred prior to baseline were not validated. Nevertheless, a validity check was performed by verification of self-reports with medical or hospital records in a random sample of 455 reported events during the follow-up period of the study, which yielded nearly 90% confirmation rates when centrally adjudicated. SA records were not included; however, central adjudication and quality control audits have been continuously implemented and high levels of consistency and concordance have been observed. Furthermore, medication use was obtained through patient interviews rather than prescriptions, therefore, possibly not reflecting medications prescribed versus those actually taken by patients. The accuracy of self-reporting previous CHD and/or stroke events plus use of preventive medications might have generated association/perception biases due to family/personal high income, literacy, and quality of the information/recall related to the medication use. However, the structured questionnaire and coordinators' training to extract precise information from individuals were implemented to minimize this potential bias.

Additionally, the association between socioeconomic status and medication use are consistent with other previous reports, and the event rates ascertained during the follow-up period from these 4 SA countries were quite similar to the reported rates from national databases [56]. Lastly, there is a potential for direction and size of bias based on self-report on conditions and medication adherence in our study.

This is the largest prospective cohort study ever conducted in SA, with data broadly applicable to the entire region the 4 countries included representing about three-quarters of SA population, and most of the current lifestyle and risk factors are similar across SA. Although different in terms of country geopolitical area, languages, culture, ethnicity and population, SA countries are more similar with each other as compared with other middle-income countries such as Malaysia, Poland, South Africa, Turkey, and Iran, where greater diversity of local/regional beliefs, religiosity, and previous historical aspects including large-scale wars are evident. In addition, public health systems have a long history of limited resources and lack of adequate attention by governments, which might also be important when promoting debates to improve health quality indicators for this macrocontinental region.

CONCLUSIONS

Secondary prevention medications are clearly underused in SA and the utilization of 3 or more medications, according to current guidelines, is very low for CHD and stroke survivors. Independent predictors of medication utilization are easily identified and simply accessed, allowing knowledge translation initiatives to be launched across SA countries. Strategies to identify and overcome barriers and systems change to enhance secondary prevention in SA and worldwide are essential. Efficient platforms for comprehensive collaboration among medical societies, government, and nongovernment organizations are needed in the light of the underachievement regarding cardiovascular secondary prevention to efficiently reduce the CVD burden in SA.

REFERENCES

1. Pan American Health Organization. Regional Health Observatory: Indicadores Básicos de Salud: Mortalidad: Causas principales de defunción 2010. Available at: http://ais.paho.org/phip/viz/mort_causasprincipales_lt_oms.asp. Accessed in January 1, 2016.
2. Avezum A, Costa-Filho FF, Pieri A, Martins SO, Marin-Neto JA. Stroke in Latin America: burden of disease and opportunities for prevention. Glob Heart 2015;10:323–31.
3. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation 2001;104:2746–53.
4. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990—2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117–71.
5. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990—2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386:743–800.
6. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985;27:335–71.
7. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet 2006;368:581–8.
8. Baigent C, Blackwell L, Emberson J, et al., for the Cholesterol Treatment Trialists' 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;376:1670–81.
9. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81–106.
10. Yusuf S. Two decades of progress in preventing vascular disease. Lancet 2002;360:2–3.
11. Perel P, Avezum A, Huffman M, et al. Reducing premature cardiovascular morbidity and mortality in people with atherosclerotic vascular disease: the World Heart Federation Roadmap for secondary prevention of cardiovascular disease. Glob Heart 2015;10:99–110.
12. Cabral NL, Franco S, Longo A, et al. The Brazilian Family Health Program and secondary stroke and myocardial infarction prevention: a 6-year cohort study. Am J Public Health 2012;102:e90–5.
13. Gaziano TA, Bilton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low- and middle-income countries. Curr Probl Cardiol 2010;35:72–115.
14. Yusuf S, Rangaragan S, Teo K, et al., for the PURE Investigators. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. N Engl J Med 2014;371:818–27.
15. Yusuf S, Islam S, Chow CK, et al., for the PURE Investigators. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE study): a prospective epidemiological survey. Lancet 2011;378:1231–43.
16. Teo K, Chow CK, Vaz M, et al., for the PURE Investigators Writing Group. The Prospective Urban Rural Epidemiology (PURE) study: examining the impact of societal influences on chronic non-communicable diseases in low-, middle-, and high-income countries. Am Heart J 2009;158:1–7. e1.
17. Yusuf S, Hawken S, Ounpuu S, et al., for the INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937–52.
18. O'Donnell MJ, Xavier D, Liu L, et al., for the INTERSTROKE Investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010;376:112–23.
19. Sacco RL, Adams R, Albers F, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke 2006;37:577–617.
20. Kotseva K, Wood D, De Backer G, et al., for the EUROASPIRE Study Group. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. Lancet 2009;373:929–40.
21. Tsang JL, Mendelsohn A, Tan MK, et al., for the Vascular Protection Registry and Guidelines Oriented Approach to Lipid Lowering Registry Investigators. Discordance between physicians' estimation of patient cardiovascular risk and use of evidence-based medical therapy. Am J Cardiol 2008;102:1142–5.

22. Lopez-Carmona D, Bernal-Lopez M, Mancera-Romero J, et al. Compliance with cardiovascular drug prevention measures in a general population: the Multidisciplinary Intervention in Primary Care (IMAP) study. Eur J Prev Cardiol 2012;19:1074–81.
23. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. Am J Med 2012;125:882–7. e1.
24. Kronish IM, Diefenbach MA, Edmondson DE, Phillips LA, Fei K, Horowitz CR. Key barriers to medication adherence in survivors of strokes and transient ischemic attacks. J Gen Intern Med 2013;28: 675–82.
25. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487–97.
26. Rodriguez F, Cannon CP, Steg PG, et al., for the REACH Registry Investigators. Predictors of long-term adherence to evidence-based cardiovascular disease medications in outpatients with stable atherothrombotic disease: findings from the REACH registry. Clin Cardiol 2013;36:721–7.
27. Kumbhani DJ, Stef PG, Cannon CP, et al., for the Reduction of Atherothrombosis for Continued Health Registry Investigators. Adherence to secondary prevention medications and four-year outcomes in outpatients with atherosclerosis. Am J Med 2013;126: 693–700. e1.
28. Mendis S, Abegunder D, Yusuf S, et al. WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE). Bull World Health Organ 2005;83:820–9.
29. Cole JA, Brennan AL, Ajani AE, et al. Cardiovascular medication use following percutaneous coronary intervention: the Australian experience. Cardiovasc Ther 2014;32:47–51.
30. Nazzal C, Lanas F, Garmendia ML, et al. Universal health coverage and accomplishment of secondary prevention goals among patients with acute myocardial infarction. Rev Med Chil 2013;141:977–86.
31. Kerr A, Exeter D, Hanham G, et al. Effect of age, gender, ethnicity, socioeconomic status and region on dispensing of CVD secondary prevention medication in New Zealand: the Atlas of Health Care Variation CVD cohort (VIEW-1). N Z Med J 2014;127:39–69.
32. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282:1458–65.
33. van Mourik MS, Cameron A, Ewen M, Laing RO. Availability, price and affordability of cardiovascular medicines: a comparison across 36 countries using WHO/HAI data. BMC Cardiovasc Disord 2010;10:25.
34. Niens LM, Cameron A, Van de Poel E, Ewen M, Brouwer WB, Laing R. Quantifying the impoverishing effects of purchasing medicines: a cross-country comparison of the affordability of medicines in the developing world. PLoS Med 2010;7. pii:e1000333.
35. Rajpura J, Nayak R. Medication adherence in a sample of elderly suffering from hypertension: evaluating the influence of illness perceptions, treatment beliefs, and illness burden. J Manag Care Pharm 2014;20:58–65.
36. Murray KA, Murphy DJ, Clements SJ, Brown A, Connolly SB. Comparison of uptake and predictors of adherence in primary and secondary prevention of cardiovascular disease in a community-based cardiovascular prevention programme (MyAction Westminster). J Public Health (Oxf) 2014;36:644–50.
37. Eissa A, Krass I, Bajorek BV. Use of medications for secondary prevention in stroke patients at hospital discharge in Australia. Int J Clin Pharm 2014;36:384–93.
38. Bangalore S, Schwamm L, Smith EE, et al., for the Get With the Guidelines—Stroke Steering Committee and Investigators. Secondary prevention after ischemic stroke or transient ischemic attack. Am J Med 2014;127:728–38.
39. Ostergaard K, Madsen C, Liu ML, Bak S, Hallas J, Gaist D. Long-term use of antiplatelet drugs by patients with transient ischaemic attack. Eur J Clin Pharmacol 2014;70:241–8.
40. Heuschmann PU, Kircher J, Nowe T, et al. Control of main risk factors after ischaemic stroke across Europe: data from the stroke-specific module of the EUROASPIRE III survey. Eur J Prev Cardiol 2015;22: 1354–62.
41. Bejot Y, Zeller M, Lorgis L, et al. Secondary prevention in patients with vascular disease: a population based study on the underuse of recommended medications. J Neurol Neurosurg Psychiatry 2013;84:348–53.
42. Glader EL, Sjolander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. Stroke 2010;41:397–401.
43. Canavero I, Cavallini A, Perrone P, et al., for the Lombardi Stroke Registry Investigators. Clinical factors associated with statins prescription in acute ischemic stroke patients: findings from the Lombardia Stroke Registry. BMC Neurol 2014;14:53.
44. Li X, Gao Y, Li J, et al., for the HPS2-THRIVE China Group. Underuse of statins in patients with atherosclerotic ischemic stroke in China. Chin Med J (Engl) 2012;125:1703–7.
45. Tsai JP, Rochon PA, Raptis S, Bronskill SE, Bell CM, Saposnik G. A prescription at discharge improves long-term adherence for secondary stroke prevention. J Stroke Cerebrovasc Dis 2014;23:2308–15.
46. Lewey J, Shrank WH, Bowry AD, Kilabuk E, Brennan TA, Choudhry NK. Gender and racial disparities in adherence to statin therapy: a meta-analysis. Am Heart J 2013;165:665–78. e1.
47. Halava H, Korhonen MJ, Huupponen R, et al. Lifestyle factors as predictors of nonadherence to statin therapy among patients with and without cardiovascular comorbidities. CMAJ 2014;186:E449–56.
48. Su Q, Yuan K, Long F, et al. Evaluation on the compliance with secondary prevention and influence factors of ischemic stroke in Hainan Province, China. Vascular 2014;22:181–7.
49. Gandhi S, Dorian P, Greenlaw N, et al., for the Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease CLARIFY Registry Investigators. Characteristics and evidence-based management of stable coronary artery disease patients in Canada compared with the rest of the world: insights from the CLARIFY registry. Can J Cardiol 2014;30:132–7.
50. Rasella D, Harhay MO, Pamponet ML, Aquino R, Barreto ML. Impact of primary health care on mortality from heart and cerebrovascular diseases in Brazil: a nationwide analysis of longitudinal data. BMJ 2014;349:g4014.
51. Rubinstein A, Rubinstein F, Botargues M, Kopitowski K. A multimodal strategy based on pay-per-performance to improve quality of care of family practitioners in Argentina. J Ambul Care Manage 2009;32:103–14.
52. West-Pollak A, Then EP, Podesta C, et al. Impact of a novel community-based lifestyle intervention program on type 2 diabetes and cardiovascular risk in a resource-poor setting in the Dominican Republic. Int Health 2014;6:118–24.
53. Yuasa M, de Sa RF, Pincovsky S, Shimanouchi N. Emergence Model of social and human capital and its application to the Healthy Municipalities project in Northeast Brazil. Health Promot Int 2007;22:292–8.
54. Huffman MD, Perel P, Beller GA, et al. World Heart Federation Emerging Leaders Program: an innovative capacity building program to facilitate the 25 x 25 goal. Glob Heart 2015;10:229–33.
55. Yusuf S, Wood D, Ralston J, Reddy KS. The World Heart Federation's vision for worldwide cardiovascular disease prevention. Lancet 2015; 386:399–402.
56. Corsi DJ, Subramanian SV, Chow CK, et al. Prospective Urban Rural Epidemiology (PURE) study: baseline characteristics of the household sample and comparative analyses with national data in 17 countries. Am Heart J 2013;166:636–46. e4.