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# 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

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## Summary

**Background** **Although most cardiovascular disease occurs in low-income and middle-income countries, little is known about the use of effective secondary prevention medications in these communities. We aimed to assess use of proven effective secondary preventive drugs (antiplatelet drugs, β blockers, angiotensin-converting-enzyme [ACE] inhibitors or angiotensin-receptor blockers [ARBs], and statins) in individuals with a history of coronary heart disease or stroke.**

**Methods** **In the Prospective Urban Rural Epidemiological (PURE) study, we recruited individuals aged 35–70 years from rural and urban communities in countries at various stages of economic development. We assessed rates of previous cardiovascular disease (coronary heart disease or stroke) and use of proven effective secondary preventive drugs and blood-pressure-lowering drugs with standardised questionnaires, which were completed by telephone interviews, household visits, or on patient's presentation to clinics. We report estimates of drug use at national, community, and individual levels.**

**Findings** **We enrolled 153 996 adults from 628 urban and rural communities in countries with incomes classified as high (three countries), upper-middle (seven), lower-middle (three), or low (four) between January, 2003, and December, 2009. 5650 participants had a self-reported coronary heart disease event (median 5·0 years previously [IQR 2·0–10·0]) and 2292 had stroke (4·0 years previously [2·0–8·0]). Overall, few individuals with cardiovascular disease took antiplatelet drugs (25·3%), β blockers (17·4%), ACE inhibitors or ARBs (19·5%), or statins (14·6%). Use was highest in high-income countries (antiplatelet drugs 62·0%, β blockers 40·0%, ACE inhibitors or ARBs 49·8%, and statins 66·5%), lowest in low-income countries (8·8%, 9·7%, 5·2%, and 3·3%, respectively), and decreased in line with reduction of country economic status ($p_{trend}$<0·0001 for every drug type). Fewest patients received no drugs in high-income countries (11·2%), compared with 45·1% in upper middle-income countries, 69·3% in lower middle-income countries, and 80·2% in low-income countries. Drug use was higher in urban than rural areas (antiplatelet drugs 28·7% urban *vs* 21·3% rural, β blockers 23·5% *vs* 15·6%, ACE inhibitors or ARBs 22·8% *vs* 15·5%, and statins 19·9% *vs* 11·6%; all p<0·0001), with greatest variation in poorest countries ($p_{interaction}$<0·0001 for urban *vs* rural differences by country economic status). Country-level factors (eg, economic status) affected rates of drug use more than did individual-level factors (eg, age, sex, education, smoking status, body-mass index, and hypertension and diabetes statuses).**

**Interpretation** **Because use of secondary prevention medications is low worldwide—especially in low-income countries and rural areas—systematic approaches are needed to improve the long-term use of basic, inexpensive, and effective drugs.**

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## Introduction

About 35 million people have an acute coronary or cerebrovascular event every year and about half of these events occur in individuals with pre-existing vascular disease.[1] The number of people with known prevalent cardiovascular disease worldwide probably exceeds 100 million. β blockers,[2] angiotensin-converting-enzyme (ACE) inhibitors,[3,4] statins,[5] and antiplatelet drugs[6] each reduce death, reinfarction, or stroke in patients with coronary heart disease.[7,8] Similarly, use of antiplatelet drugs, ACE inhibitors, or statins, coupled with reduction of blood pressure with diuretics, β blockers, ACE inhibitors, or angiotensin-receptor blockers (ARBs), is beneficial in patients with stroke.[9] Such drugs are widely recommended for the management of patients with cardiovascular disease or their risk factors. Some studies of hospital registries or surveys of patients recruited in out-patient or general practice clinics

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(mainly in high-income countries) report moderate to high rates of drug use.[10–12] However, treatment rates for individuals with prevalent coronary heart disease or stroke in the community are unknown, because many people might not be in medical care years after their acute event. Most available data are from high-income countries or from centres that participate in multicentre studies (generally trials) and whether their findings reflect the actual situation in communities is debateable. Because about 75% of the burden of cardiovascular disease falls on low-income and middle-income countries, relevant data for secondary prevention practices are needed in countries at various stages of economic development and in different regions.[13] Furthermore, many individuals live in rural areas where access to medical care can be restricted, and few data exist for differences in the use of secondary prevention medications between people in urban or rural settings. We designed the Prospective Urban Rural Epidemiology (PURE) study to assess rates of use of key drugs for secondary prevention in populations with prevalent cardiovascular disease from urban and rural communities in such countries.

## Methods

### Study design and participants

In our prospective epidemiological survey, we recruited individuals from communities in low-income, middle-income, and high-income countries with wide variation in economic development and sociocultural diversity. We selected the number and location of countries on the basis of a need to balance between having a large number of communities in countries with substantial heterogeneity in socioeconomic circumstances and policies, and the feasibility of centres to successfully achieve long-term follow-up. Thus, PURE includes sites at which investigators were committed to collecting high quality data with a modest budget, and which would attempt to follow up participants for 10 years or more. For reasons of practicality, we did not aim for a strict proportionate sampling of the whole world, any specific country, or region. From World Bank classifications at the time PURE study was started,[14] we included four low-income countries (Bangladesh, India, Pakistan, and Zimbabwe), seven upper middle-income countries (Argentina, Brazil, Chile, Malaysia, Poland, South Africa, and Turkey), three lower middle-income countries (China, Colombia, and Iran),

| | Communities | | | Participants | | |
|---|---|---|---|---|---|---|
| | Overall | Urban | Rural | Overall | Urban | Rural |
| All countries | 628 | 348 (55·4%) | 280 (44·6%) | 153 996 | 80 925 (52·6%) | 73 071 (47·4%) |
| High-income countries | | | | | | |
| Canada | 82 | 53 (64·6%) | 29 (35·4%) | 10 416 | 7282 (69·9%) | 3134 (30·1%) |
| Sweden | 31 | 28 (90·3%) | 3 (9·7%) | 4153 | 3251 (78·3%) | 902 (21·7%) |
| UAE | 3 | 1 (33·3%) | 2 (66·7%) | 1504 | 1000 (66·5%) | 504 (33·5%) |
| Overall | 116 | 82 (70·7%) | 34 (29·3%) | 16 073 | 11 533 (71·8%) | 4540 (28·2%) |
| Upper middle-income countries | | | | | | |
| Argentina | 20 | 6 (30·0%) | 14 (70·0%) | 7527 | 3607 (47·9%) | 3920 (52·1%) |
| Brazil | 14 | 7 (50·0%) | 7 (50·0%) | 6070 | 3949 (65·1%) | 2121 (34·9%) |
| Chile | 5 | 2 (40·0%) | 3 (60·0%) | 3451 | 2808 (81·4%) | 643 (18·6%) |
| Malaysia | 71 | 53 (74·6%) | 18 (25·4%) | 15 617 | 6841 (43·8%) | 8776 (56·2%) |
| Poland | 4 | 1 (25·0%) | 3 (75·0%) | 2036 | 1210 (59·4%) | 826 (40·6%) |
| South Africa | 8 | 4 (50·0%) | 4 (50·0%) | 4585 | 2416 (52·7%) | 2169 (47·3%) |
| Turkey | 44 | 31 (70·5%) | 13 (29·5%) | 4232 | 2765 (65·3%) | 1467 (34·7%) |
| Overall | 166 | 104 (62·7%) | 62 (37·3%) | 43 518 | 23 596 (54·2%) | 19 922 (45·8%) |
| Lower middle-income countries | | | | | | |
| China | 115 | 45 (39·1%) | 70 (60·9%) | 46 285 | 22807 (49·3%) | 23 478 (50·7%) |
| Colombia | 58 | 35 (60·3%) | 23 (39·7%) | 7444 | 3761 (50·5%) | 3683 (49·5%) |
| Iran | 20 | 11 (55·0%) | 9 (45·0%) | 6013 | 3031 (50·4%) | 2982 (49·6%) |
| Overall | 193 | 91 (47·2%) | 102 (52·8%) | 59 742 | 29 599 (49·5%) | 30 143 (50·5%) |
| Low-income countries | | | | | | |
| Bangladesh | 56 | 30 (53·6%) | 26 (46·4%) | 2934 | 1379 (47·0%) | 1555 (53·0%) |
| India | 90 | 38 (42·2%) | 52 (57·8%) | 28 747 | 13 380 (46·5%) | 15 367 (53·5%) |
| Pakistan | 4 | 2 (50·0%) | 2 (50·0%) | 1742 | 980 (56·3%) | 762 (43·7%) |
| Zimbabwe | 3 | 1 (33·3%) | 2 (66·7%) | 1240 | 458 (36·9%) | 782 (63·1%) |
| Overall | 153 | 71 (46·4%) | 82 (53·6%) | 34 663 | 16 197 (46·7%) | 18 466 (53·3%) |

UAE=United Arab Emirates.

*Table 1:* **Number of communities and participants by country income**

and three high-income countries (Canada, Sweden, and United Arab Emirates; table 1).

Within every country, we selected urban and rural communities at collaborating sites on the basis of previously published guidelines.[15] In the PURE study, we defined community as a group of people who were generally expected to have characteristics in common (sharing culture, socioeconomic status, and use of amenities, goods, and services) and reside in a defined geographical area. A city or large town was not usually regarded as one community, but communities from low-income, middle-income, and high-income areas were selected from sections of cities and the community area was further defined according to a geographical measure (eg, a set of contiguous postal code areas or a group of streets or a village). The main sampling unit for rural areas in all countries was the village or a rural area defined by a post code, and located at least 50 km away from an urban centre. The reason for inclusion of both urban and rural communities was that, for many countries, urban and rural environments were expected to have distinct characteristics in social and physical environments and variations in access to health-care facilities. Therefore, by sampling individuals from both sets of communities from low-income, middle-income and high-income countries, we ensure substantial variation in societal factors. In some countries (eg, India, China, Canada, and Colombia), we included communities from several states or provinces to capture regional diversity in policies, socioeconomic status, cultures, and physical environments within a country. In other countries (eg, Iran, Poland, Sweden, and Zimbabwe) we selected fewer communities.

Within every community, we aimed to achieve a representative sample of adults aged 35–70 years. The choice of the sampling frame within every centre was based on representativeness and feasibility of long-term follow-up, following broad study guidelines. Once a community was identified, we used common and standardised approaches for the calculation of the number of households, identification of individuals, recruitment procedures, and data collection. The method of approaching households differed between regions to avoid biases from differences in risk factors or prevalence of any disease. For example, in rural areas of India and China, announcements were made to the village or community through a community leader, followed up by door to door visits by study staff to all households. By contrast in Canada, information about the study was initially sent by post and followed up by telephone calls by study staff to every household inviting eligible representatives to a central clinic. For every approach, at least three attempts to contact an individual in the household were made. Households were eligible if at least one household member was aged 35–70 years and the household intended to live at their current address for a further 4 years. All eligible individuals within these households who provided written informed consent were enrolled. When an eligible household or eligible individual in a household refused to participate, demographics and simple data about tobacco use, education, and history of cardiovascular disease were recorded in a non-responder form.

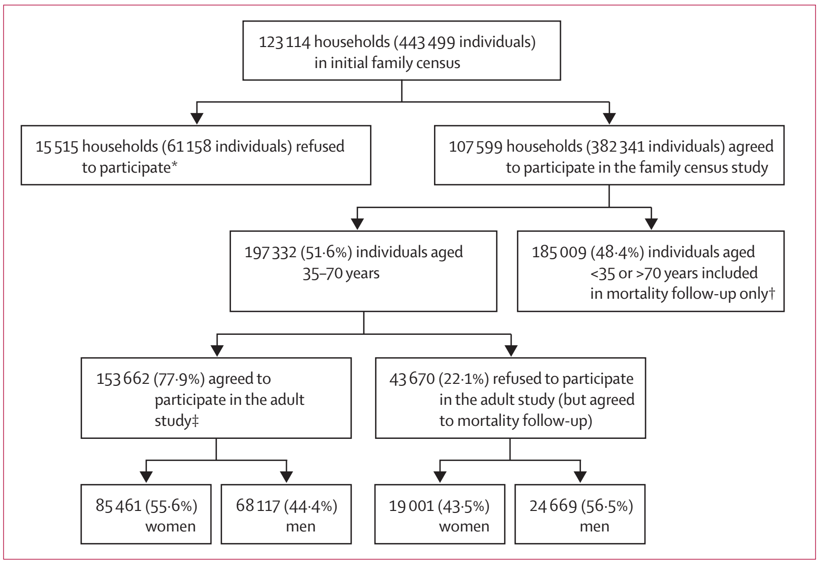


*Figure 1:* **Participant enrolment**

*No further information was available about these individuals or households. †1444 individuals younger than 35 years and 586 older than 70 years provided complete data for the adult questionnaires, anthropometric measurements, and blood and urine analysis, and were included in the main analysis. ‡151 966 (98·9%) of 153 662 individuals provided complete measurements and questionnaires (sex data were missing for 84 individuals).

## Procedures

To ensure standardisation and high quality of data, we used a comprehensive operations manual and periodical training workshops, training DVDs, and regular communication with study personnel. We entered all data in a customised database programmed with range and consistency checks and transmitted electronically to the Project Office at the Population Health Research Institute in Hamilton (ON, Canada) where further quality control measures were implemented.

We collected data at national, community, household, and individual levels with standardised questionnaires. Questions about age, sex, education, smoking status, hypertension, diabetes, and obesity were identical to those in the INTERHEART[16] and INTERSTROKE studies.[17] The names of all drugs taken by an individual (at least once per week) were recorded and classified by type. Most individuals brought their drugs to clinic visits or interviewers recorded drugs at home visits.

We assessed histories of cardiovascular and other diseases from every participant with standardised questionnaires. Coronary heart disease was ascribed on the basis of self-reported myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary angioplasty or angina (categories were not identified separately). Stroke was ascribed on the basis of self-reports.

| | Coronary heart disease | Stroke | Coronary heart disease or stroke | Neither | Overall |
|---|---|---|---|---|---|
| Participants | 5650 (3·7%) | 2292 (1·5%) | 7519 (4·9%) | 146 477 (95·1%) | 153 996 |
| High-income countries | 669 (4·2%) | 213 (1·3%) | 841 (5·2%) | 15 232 (94·8%) | 16 073 |
| Upper middle-income countries | 1396 (3·2%) | 691 (1·6%) | 1967 (4·5%) | 41 551 (95·5%) | 43 518 |
| Lower middle-income countries | 2857 (4·8%) | 1042 (1·7%) | 3669 (6·1%) | 56 073 (93·9%) | 59 742 |
| Low-income countries | 728 (2·1%) | 346 (1·0%) | 1042 (3·0%) | 33 621 (97·0%) | 34 663 |
| Urban | 3447 (4·2%) | 1367 (1·6%) | 4555 (5·5%) | 78 446 (94·5%) | 83 001 |
| Rural | 2203 (3·1%) | 925 (1·3%) | 2964 (4·2%) | 68 031 (95·8%) | 70 995 |
| Age (years) | 57·4 (8·8) | 56·8 (9·4) | 57·2 (9·0) | 50·1 (9·9) | 50·4 (9·9) |
| Sex | | | | | |
| Female | 3036 (3·4%) | 1218 (1·4%) | 4017 (4·5%) | 85 188 (95·5%) | 89 205 |
| Male | 2614 (4·0%) | 1074 (1·7%) | 3502 (5·4%) | 61 289 (94·6%) | 64 791 |
| Education | | | | | |
| None, primary school, or unknown | 2661 (4·0%) | 1185 (1·8%) | 3640 (5·5%) | 62 662 (94·5%) | 66 302 |
| Secondary or high school | 1889 (3·3%) | 731 (1·3%) | 2479 (4·3%) | 55 520 (95·7%) | 57 999 |
| Trade, college, or university | 1087 (3·7%) | 372 (1·3%) | 1383 (4·7%) | 27 887 (95·3%) | 29 270 |
| Diabetes | 1404 (8·6%) | 572 (3·5%) | 1809 (11·0%) | 14 583 (89·0%) | 16 392 |
| Body-mass index* | 27·13 (5·6) | 26·77 (5·7) | 27·01 (5·6) | 25·68 (5·4) | 25·74 (5·5) |
| <25 | 2018 (2·9%) | 851 (1·2%) | 2717 (3·9%) | 67 140 (96·1%) | 69 857 |
| 25–30 | 2110 (4·3%) | 817 (1·7%) | 2771 (5·6%) | 46 635 (94·4%) | 49 406 |
| >30 | 1284 (5·2%) | 464 (1·9%) | 1650 (6·6%) | 23 255 (93·4%) | 24 905 |
| Non-smoker | 3479 (3·4%) | 1359 (1·3%) | 4571 (4·4%) | 98 479 (95·6%) | 103 050 |
| Former smoker | 1158 (6·5%) | 447 (2·5%) | 1526 (8·5%) | 16 424 (91·5%) | 17 950 |
| Current smoker | 982 (3·1%) | 475 (1·5%) | 1382 (4·3%) | 30 576 (95·7%) | 31 958 |
| Hypertension | 4275 (6·7%) | 1749 (2·7%) | 5653 (8·8%) | 58 449 (91·2%) | 64 102 |
| Years since diagnosis | 6·84 (6·8) | 6·35 (6·9) | 6·81 (6·9) | NA | NA |

Data are n (%) or mean (SD). NA=not applicable. *Data not available for 9828 participants.

***Table 2:*** **Baseline characteristics**

We verified self-reports with medical or hospital records in a sample of 455 reported events during follow-up. The confirmation rates were 89% during central adjudication.

## Statistical analysis

We analysed use of antiplatelet drugs, β blockers, ACE inhibitors or ARBs, statin, and diuretics (because of recognised benefit after stroke). We included β blockers, ACE inhibitors or ARBs, diuretics, or calcium channel blockers in an analysis of blood-pressure-lowering drugs. We summarised categorical variables, including disease status and drug intakes, as n (%) and continuous variables as mean (SD). We compared proportions between groups with a two-sample *Z* test with a two-sided alternative.[18] We adjusted proportions for individual-level factors with a generalised linear model as appropriate, and used the Cochran-Armitage test to assess trends in subgroups. We compared the contribution of country-level factors (eg, economic status) and individual characteristics to the variations in rates of drug use with a generalised linear mixed-effect model. Country economic status, which was used to estimate between-country variances and within-country variances, was regarded as having random effects whereas individual level factors were regarded as having fixed effects. On the basis of partitioned error variance, the percentage of variance explained by country status (between-country variance), or individual factors and urban location versus rural location (within-country variance) was calculated as a percentage of the overall variance. All statistical analysis were done with SAS version 9.2 and all figures were drawn with S-PLUS version 6.2.

## Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

# Results

We recruited 382 341 individuals from 107 599 households in 628 communities (348 urban and 280 rural) in 17 countries on five continents. Recruitment started in Karnataka, India in January, 2003; however, most communities were recruited between January, 2005, and December, 2009. 197 332 (52%) individuals were eligible for the main study, and 153 996 adults participated (78%; 151 966 were aged 35–70 years, 1444 were aged <35 years,

| | Overall | High-income countries | Upper middle-income countries | Lower middle-income countries | Low-income countries | $P_{trend}$ |
|---|---|---|---|---|---|---|
| Coronary heart disease | 5650 | 669 | 1396 | 2857 | 728 | |
| Antiplatelet drugs | 1460 (25·8%) | 429 (64·1%) | 378 (27·1%) | 573 (20·1%) | 80 (11·0%) | <0·0001 |
| β blockers | 1154 (20·4%) | 311 (46·5%) | 433 (31·0%) | 329 (11·5%) | 81 (11·1%) | <0·0001 |
| ACE inhibitors or ARBs | 1128 (20·0%) | 346 (51·7%) | 432 (30·9%) | 303 (10·6%) | 47 (6·5%) | <0·0001 |
| Diuretics* | 768 (13·6%) | 102 (15·2%) | 262 (18·8%) | 375 (13·1%) | 29 (4·0%) | <0·0001 |
| Calcium-channel blockers† | 753 (13·3%) | 150 (22·4%) | 163 (11·7%) | 387 (13·5%) | 53 (7·3%) | <0·0001 |
| Blood-pressure-lowering drugs‡ | 2427 (43·0%) | 524 (78·3%) | 712 (51·0%) | 1032 (36·1%) | 159 (21·8%) | <0·0001 |
| Statins | 942 (16·7%) | 474 (70·9%) | 295 (21·1%) | 140 (4·9%) | 33 (4·5%) | <0·0001 |
| Stroke | 2292 | 213 | 691 | 1042 | 346 | <0·0001 |
| Antiplatelet drugs | 557 (24·3%) | 113 (53·1%) | 137 (19·8%) | 294 (28·2%) | 13 (3·8%) | <0·0001 |
| β blockers | 215 (9·4%) | 44 (20·7%) | 87 (12·6%) | 62 (6·0%) | 22 (6·4%) | <0·0001 |
| ACE inhibitors or ARBs | 426 (18·6%) | 89 (41·8%) | 195 (28·2%) | 135 (13·0%) | 7 (2·0%) | <0·0001 |
| Diuretics* | 348 (15·2%) | 48 (22·5%) | 109 (15·8%) | 180 (17·3%) | 11 (3·2%) | <0·0001 |
| Calcium-channel blockers† | 331 (14·4%) | 37 (17·4%) | 80 (11·6%) | 202 (19·4%) | 12 (3·5%) | 0·0307 |
| Blood-pressure-lowering drugs‡ | 916 (40·0%) | 129 (60·6%) | 293 (42·4%) | 449 (43·1%) | 45 (13·0%) | <0·0001 |
| Statins | 206 (9·0%) | 110 (51·6%) | 72 (10·4%) | 22 (2·1%) | 2 (0·6%) | <0·0001 |
| Coronary heart disease or stroke | 7519 | 841 | 1967 | 3669 | 1042 | <0·0001 |
| Antiplatelet drugs | 1900 (25·3%) | 521 (62·0%) | 484 (24·6%) | 803 (21·9%) | 92 (8·8%) | <0·0001 |
| β blockers | 1312 (17·4%) | 336 (40·0%) | 500 (25·4%) | 375 (10·2%) | 101 (9·7%) | <0·0001 |
| ACE Inhibitors or ARBs | 1469 (19·5%) | 419 (49·8%) | 590 (30·0%) | 406 (11·1%) | 54 (5·2%) | <0·0001 |
| Diuretics* | 1033 (13·7%) | 138 (16·4%) | 350 (17·8%) | 507 (13·8%) | 38 (3·6%) | <0·0001 |
| Calcium-channel blockers† | 1006 (13·4%) | 174 (20·7%) | 233 (11·8%) | 535 (14·6%) | 64 (6·1%) | <0·0001 |
| Blood-pressure-lowering drugs‡ | 3146 (41·8%) | 621 (73·8%) | 954 (48·4%) | 1371 (37·4%) | 200 (19·2%) | <0·0001 |
| Statins | 1096 (14·6%) | 559 (66·5%) | 347 (17·6%) | 156 (4·3%) | 34 (3·3%) | <0·0001 |

See webappendix p 2 for age-adjusted rates. ACE=angiotensin-converting enzyme. ARB=angiotensin II receptor blockers. *The value of diuretics for reduction of mortality or recurrent events has been shown only after a stroke, but not in non-hypertensive patients with coronary heart disease. †The value of calcium-channel blockers for secondary prevention has not been shown, but they can reduce the number of cardiovascular disease events in trials of hypertension. ‡ Blood-pressure-lowering drugs include any of β blockers, ACE inhibitors, ARBs, diuretics, or calcium-channel blockers—all of which reduce recurrent events in participants with previous strokes.

***Table 3:*** **Drug use in participants with coronary heart disease or stroke, by country economic status and overall**

See Online for webappendix

and 586 were aged >70 years; figure 1 and table 1). Of these, 36 individuals younger than 35 years and 91 individuals older than 70 years had cardiovascular disease and were retained in the analysis. Exclusion of these individuals has little effect on the results in this report. 7519 (4·9%) of 151 966 individuals who provided complete measurements and questionnaires had cardiovascular disease (table 2).

Characteristics of the 197 332 eligible adults and the 153 578 participants aged 35–70 years with complete data were much the same in both groups (mean age 50·2 years in the eligible group *vs* 50·7 years in the enrolled group; 53·0% *vs* 55·6% women; 22·1% *vs* 21·2% current smokers; 41·7% *vs* 42·3% low education; 13·3% *vs* 14·7% history of hypertension; 1·2% *vs* 1·3% stroke; 3·5% *vs* 3·9% coronary heart disease; 1·3% *vs* 1·2% cancer; and 5·2% *vs* 5·5% diabetes).

Overall, patients had had a coronary heart disease event a median of 5·0 (IQR 2·0–10·0) years before inclusion (6·0 years [3·0–10·0] in high-income countries, 4·0 years [2·0–10·0] in upper middle-income countries, 5·0 years [2·0–10·0] in lower middle-income countries, and 5·0 years [2·0–9·0] in low-income countries; $p_{trend}$=0·0241). Overall, patients had had a stroke at a median of 4·0 years (2·0–8·0) before inclusion (6·0 years [3·0–10·0] in high-income countries, 5·0 years [2·0–10·0] in upper middle-income countries, 4·0 years [2·0–8·0] in lower middle-income countries, 3·0 years [1·0–6·0] in low-income countries; $p_{trend}$<0·0001).

Table 3, figure 2, and figure 3 show rates of drug use in participants with cardiovascular disease. Similar proportions of participants were taking antiplatelet drugs (~25%) or ACE inhibitors or ARBs (~20%) after coronary heart disease or stroke, but fewer people in the stroke group than in the coronary heart disease group took β blockers (stroke 9·4% [215 of 2292] *vs* coronary heart disease 20·4% [1154 of 5650]; p<0·0001) or statins (9·0% [206 of 2292] *vs* 16·7% [942 of 5650]; p<0·0001).

Patients with coronary heart disease or stroke in high-income countries had the highest rates of drug use, which decreased with declining country economic wealth (table 3). We noted strong correlations between overall rates of drug use and per head health expenditure by country (figure 3) and gross domestic product (webappendix p 4).

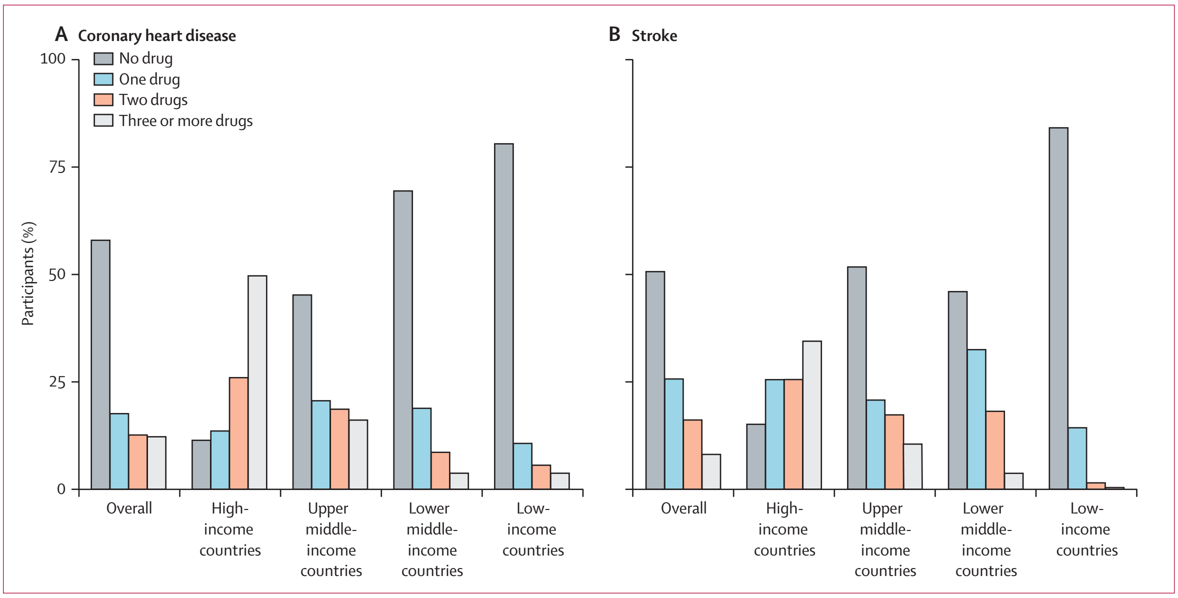


*Figure 2:* **Number of drugs taken by individuals by country economic status**
For coronary heart disease (A), drugs counted were aspirin, β blockers, ACE inhibitors or ARBs, or statins. For stroke (B), drugs counted were aspirin, statins, ACE inhibitors or ARBs, or other blood-pressure-lowering drugs (eg, β blockers, diuretics, and calcium-channel blockers). ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker.

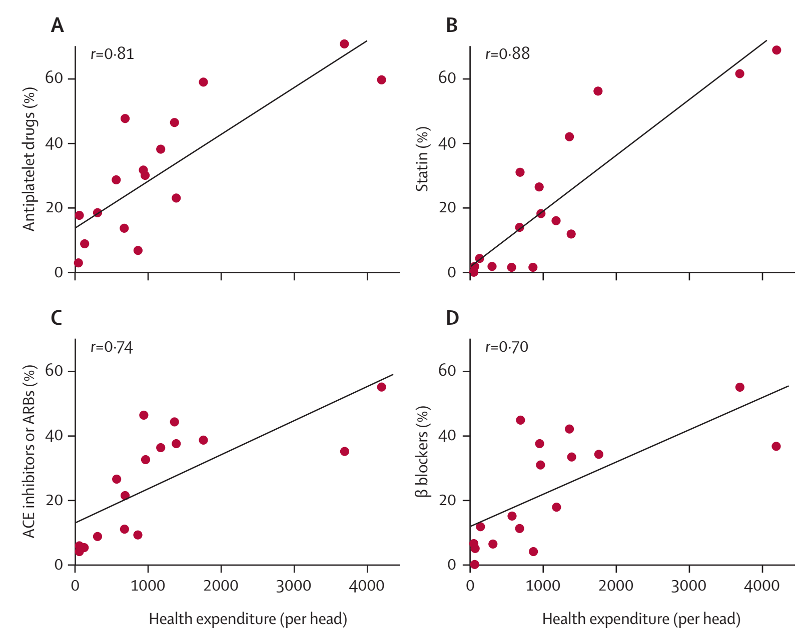


*Figure 3:* **Health expenditure per head versus drug use in every country**
Data points are countries. (A) Antiplatelet drugs. (B) Statin. (C) ACE inhibitors or ARBs. (D) β blockers. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker.

The overall rates of use of secondary prevention drugs were higher in urban areas than rural areas (table 4). We noted much the same differences in the use of diuretics and calcium-channel blockers. Proportionally, differences in drug use in urban and rural settings were least pronounced in high-income countries and most pronounced in low-income and lower middle-income countries.

Striking variations in the use of effective drugs (ie, antiplatelet drugs, β blockers, ACE inhibitors or ARBs, and statins) existed between regions with the highest rates of drug use (North America and Europe) and those with the lowest rates of use (Africa; table 5), where such drugs were used in less than 10% of patients with previous coronary heart disease or stroke. Use of statins was especially low in south Asia (3·5% [34 of 970 patients]), China (1·7% [53 of 3070]), and Africa (1·1% [3 of 283]).

Patients younger than 60 years were less likely to take the drugs than were patients aged 60 years or older (figure 4). For example, 31·9% of patients aged 60 years or older took antiplatelet drugs after coronary heart disease, compared with 24·6% of those aged 50–60 years and 13·7% of those younger than 50 years. We reported much the same prevalence of use of all four drug types by age for stroke patients, and noted these age variations irrespective of country economic status.

The subsequent data we report for prevalence of drug use in relation to sex, education, smoking status, body-mass index, diabetes, and hypertension have been mutually adjusted for individual characteristics, urban or rural location, and country economic status. Multivariate odds ratios for the rates of drug use by country economic status, urban versus rural locations, and by individual risk factors are shown in webappendix p 1.

Women were less likely to take proven effective drugs after coronary heart disease than were men (antiplatelet drugs 19·8% in women *vs* 32·8% in men; β blockers 17·4% *vs* 23·9%; ACE inhibitors or ARBs 16·0% *vs* 24·6%; statins 10·5% *vs* 23·8%; figure 4). Patients who had the highest level of education were more likely to

 

| | Overall | | High-income countries | | Upper middle-income countries | | Lower middle-income countries | | Low-income countries | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Urban | Rural | Urban | Rural | Urban | Rural | Urban | Rural | Urban | Rural |
| Coronary heart disease | 3447 | 2203 | 507 | 162 | 816 | 580 | 1673 | 1184 | 451 | 277 |
| Antiplatelet drugs | 990 (28·7%) | 470 (21·3%)† | 325 (64·1%) | 104 (64·2%) | 261 (32·0%) | 117 (20·2%) | 337 (20·1%) | 236 (19·9%) | 67 (14·9%) | 13 (4·7%) |
| β blockers | 810 (23·5%) | 344 (15·6%)† | 235 (46·4%) | 76 (46·9%) | 291 (35·7%) | 142 (24·5%) | 220 (13·2%) | 109 (9·2%) | 64 (14·2%) | 17 (6·1%) |
| ACE inhibitors or ARBs | 787 (22·8%) | 341 (15·5%)† | 277 (54·6%) | 69 (42·6%) | 291 (35·7%) | 141 (24·3%) | 183 (10·9%) | 120 (10·1%) | 36 (8·0%) | 11 (4·0%) |
| Diuretics | 478 (13·9%) | 290 (13·2%) | 74 (14·6%) | 28 (17·3%) | 163 (20·0%) | 99 (17·1%) | 226 (13·5%) | 149 (12·6%) | 15 (3·3%) | 14 (5·1%) |
| Calcium-channel blockers | 542 (15·7%) | 211 (9·6%)† | 109 (21·5%) | 41 (25·3%) | 107 (13·1%) | 56 (9·7%) | 280 (16·7%) | 107 (9·0%) | 46 (10·2%) | 7 (2·5%) |
| Blood-pressure-lowering drugs | 1666 (48·3%) | 761 (34·5%)† | 399 (78·7%) | 125 (77·2%) | 461 (56·5%) | 251 (43·3%) | 686 (41·0%) | 346 (29·2%) | 120 (26·6%) | 39 (14·1%) |
| Statins | 686 (19·9%) | 256 (11·6%)† | 369 (72·8%) | 105 (64·8%) | 202 (24·8%) | 93 (16·0%) | 87 (5·2%) | 53 (4·5%) | 28 (6·2%) | 5 (1·8%) |
| Stroke | 1367 | 925 | 160 | 53 | 425 | 266 | 625 | 417 | 157 | 189 |
| Antiplatelet drugs | 354 (25·9%) | 203 (21·9%)* | 80 (50·0%) | 33 (62·3%) | 85 (20·0%) | 52 (19·5%) | 180 (28·8%) | 114 (27·3%) | 9 (5·7%) | 4 (2·1%) |
| β blockers | 157 (11·5%) | 58 (6·3%)† | 35 (21·9%) | 9 (17·0%) | 63 (14·8%) | 24 (9·0%) | 46 (7·4%) | 16 (3·8%) | 13 (8·3%) | 9 (4·8%) |
| ACE inhibitors or ARBs | 286 (20·9%) | 140 (15·1%)* | 67 (41·9%) | 22 (41·5%) | 129 (30·4%) | 66 (24·8%) | 87 (13·9%) | 48 (11·5%) | 3 (1·9%) | 4 (2·1%) |
| Diuretics | 229 (16·8%) | 119 (12·9%)* | 38 (23·8%) | 10 (18·9%) | 67 (15·8%) | 42 (15·8%) | 119 (19·0%) | 61 (14·6%) | 5 (3·2%) | 6 (3·2%) |
| Calcium-channel blockers | 228 (16·7%) | 103 (11·1%)† | 25 (15·6%) | 12 (22·6%) | 47 (11·1%) | 33 (12·4%) | 152 (24·3%) | 50 (12·0%) | 4 (2·5%) | 8 (4·2%) |
| Blood-pressure-lowering drugs | 616 (45·1%) | 300 (32·4%)† | 97 (60·6%) | 32 (60·4%) | 188 (44·2%) | 105 (39·5%) | 309 (49·4%) | 140 (33·6%) | 22 (14·0%) | 23 (12·2%) |
| Statins | 132 (9·7%) | 74 (8·0%) | 79 (49·4%) | 31 (58·5%) | 40 (9·4%) | 32 (12·0%) | 12 (1·9%) | 10 (2·4%) | 1 (0·6%) | 1 (0·5%) |
| Coronary heart disease or stroke | 4555 | 2964 | 634 | 207 | 1172 | 795 | 2156 | 1513 | 593 | 449 |
| Antiplatelet drugs | 1264 (27·7%) | 636 (21·5%)† | 388 (61·2%) | 133 (64·3%) | 327 (27·9%) | 157 (19·7%) | 474 (22·0%) | 329 (21·7%) | 75 (12·6%) | 17 (3·8%) |
| β blockers | 925 (20·3%) | 387 (13·1%)† | 255 (40·2%) | 81 (39·1%) | 341 (29·1%) | 159 (20·0%) | 254 (11·8%) | 121 (8·0%) | 75 (12·6%) | 26 (5·8%) |
| ACE inhibitors or ARBs | 1014 (22·3%) | 455 (15·4%)† | 330 (52·1%) | 89 (43·0%) | 395 (33·7%) | 195 (24·5%) | 250 (11·6%) | 156 (10·3%) | 39 (6·6%) | 15 (3·3%) |
| Diuretics | 658 (14·4%) | 375 (12·7%)* | 103 (16·2%) | 35 (16·9%) | 218 (18·6%) | 132 (16·6%) | 317 (14·7%) | 190 (12·6%) | 20 (3·4%) | 18 (4·0%) |
| Calcium-channel blockers | 709 (15·6%) | 297 (10·0%)† | 124 (19·6%) | 50 (24·2%) | 147 (12·5%) | 86 (10·8%) | 388 (18·0%) | 147 (9·7%) | 50 (8·4%) | 14 (3·1%) |
| Blood-pressure-lowering drugs | 2147 (47·1%) | 999 (33·7%)† | 471 (74·3%) | 150 (72·5%) | 618 (52·7%) | 336 (42·3%) | 918 (42·6%) | 453 (29·9%) | 140 (23·6%) | 60 (13·4%) |
| Statins | 783 (17·2%) | 313 (10·6%)† | 429 (67·7%) | 130 (62·8%) | 230 (19·6%) | 117 (14·7%) | 96 (4·5%) | 60 (4·0%) | 28 (4·7%) | 6 (1·3%) |

ACE=angiotensin-converting enzyme. ARB=angiotensin II receptor blockers. *p<0·05. †p<0·001.

***Table 4:* Participants with coronary heart disease or stroke, by urban or rural locations stratified by country economic status**

take antiplatelet drugs or statins than were those with the lowest level of education, although this difference did not exist for patients taking β blockers or ACE inhibitors or ARBs (figure 4). Use of proven drugs was consistently lower in current smokers (antiplatelet drugs 20·6%, β blockers 11·7%, ACE inhibitors or ARBs 11·0%, and statins 6·9%) than it was in former smokers (31·3%, 19·9%, 22·2%, and 16·3%) or never smokers (24·3%, 18·4%, 17·7%, and 13·3%; figure 4). These patterns were consistent for all country economic statuses, and rates for all drug types were lowest in smokers from low-income countries (eg, only 5·4% of smokers used antiplatelets, 6·1% used β blockers, 2·2% used ACE inhibitors or ARBs, and 0·9% used statins in low-income countries). Individuals with a body-mass index of less than 25 kg/m² used the drugs less often (antiplatelet drugs 19·9%, β blockers 13·7%, ACE inhibitors or ARBs 11·7%, and statins 8·7%) than did those with body-mass indexes of 25–<30 (29·1%, 19·0%, 18·9%, and 16·2%) or 30 or more (28·2%, 23·6%, 26·1%, 17·3%; figure 4). People with diabetes used these drugs more often than did those without diabetes (antiplatelet drugs 27·7% with *vs* 25·2% without, β blockers 24·7% *vs* 19·0%, ACE inhibitors or ARBs 25·4% *vs* 18·2%, and statins 21·7% *vs* 15·0%; figure 4).

Patients with hypertension used the drugs more often than did those without hypertension (figure 5); particularly drugs that reduce blood pressure, many of which (eg, β blockers and ACE inhibitors) also reduce recurrent myocardial infarction or stroke rates, even in those without hypertension.

Among participants who had coronary heart disease or stroke, 4398 (58·5%) of 7519 individuals were not taking any of the four proven effective drugs and 233 (3·1%) of 7519 were taking all four drug types. The proportion of those receiving no drug was lowest in high-income countries (12·7%), compared with 48·4% in upper middle-income countries, 67·5% in lower middle-income countries, and 82·8% in low-income countries. The highest proportion of participants taking three or more drugs lived in high-income countries (44·2%), compared with 12·9% in upper middle-income countries, 3·1% in lower middle-income countries, and 2·6% in low-income countries.

| | North America and Europe | South America | Middle East | South Asia | China | Malaysia | Africa |
|---|---|---|---|---|---|---|---|
| Coronary heart disease | 951 | 781 | 332 | 683 | 2407 | 289 | 207 |
| Antiplatelet drugs | 527 (55·4%) | 256 (32·8%) | 175 (52·7%) | 79 (11·6%) | 373 (15·5%) | 43 (14·9%) | 7 (3·4%) |
| β blockers | 432 (45·4%) | 289 (37·0%) | 149 (44·9%) | 81 (11·9%) | 163 (6·8%) | 36 (12·5%) | 4 (1·9%) |
| ACE inhibitors or ARBs | 445 (46·8%) | 314 (40·2%) | 87 (26·2%) | 44 (6·4%) | 187 (7·8%) | 37 (12·8%) | 14 (6·8%) |
| Diuretics | 180 (18·9%) | 169 (21·6%) | 39 (11·7%) | 21 (3·1%) | 319 (13·3%) | 17 (5·9%) | 23 (11·1%) |
| Calcium-channel blockers | 194 (20·4%) | 95 (12·2%) | 65 (19·6%) | 49 (7·2%) | 316 (13·1%) | 24 (8·3%) | 10 (4·8%) |
| Blood-pressure-lowering drugs | 700 (73·6%) | 495 (63·4%) | 224 (67·5%) | 149 (21·8%) | 764 (31·7%) | 68 (23·5%) | 27 (13·0%) |
| Statins | 539 (56·7%) | 148 (19·0%) | 124 (37·3%) | 33 (4·8%) | 49 (2·0%) | 46 (15·9%) | 3 (1·4%) |
| Stroke | 323 | 428 | 69 | 316 | 872 | 193 | 91 |
| Antiplatelet drugs | 140 (43·3%) | 94 (22·0%) | 24 (34·8%) | 12 (3·8%) | 257 (29·5%) | 21 (10·9%) | 9 (9·9%) |
| β blockers | 58 (18·0%) | 58 (13·6%) | 23 (33·3%) | 22 (7·0%) | 36 (4·1%) | 14 (7·3%) | 4 (4·4%) |
| ACE inhibitors or ARBs | 135 (41·8%) | 150 (35·0%) | 13 (18·8%) | 6 (1·9%) | 101 (11·6%) | 12 (6·2%) | 9 (9·9%) |
| Diuretics | 72 (22·3%) | 72 (16·8%) | 8 (11·6%) | 1 (0·3%) | 166 (19·0%) | 11 (5·7%) | 18 (19·8%) |
| Calcium-channel blockers | 50 (15·5%) | 41 (9·6%) | 9 (13·0%) | 9 (2·8%) | 190 (21·8%) | 24 (12·4%) | 8 (8·8%) |
| Blood-pressure-lowering drugs | 187 (57·9%) | 209 (48·8%) | 36 (52·2%) | 35 (11·1%) | 389 (44·6%) | 40 (20·7%) | 20 (22·0%) |
| Statins | 125 (38·7%) | 34 (7·9%) | 19 (27·5%) | 2 (0·6%) | 7 (0·8%) | 19 (9·8%) | 0 |
| Coronary heart disease or stroke | 1216 | 1148 | 392 | 970 | 3070 | 440 | 283 |
| Antiplatelet drugs | 635 (52·2%) | 333 (29·0%) | 195 (49·7%) | 90 (9·3%) | 571 (18·6%) | 60 (13·6%) | 16 (5·7%) |
| β blockers | 465 (38·2%) | 331 (28·8%) | 168 (42·9%) | 101 (10·4%) | 190 (6·2%) | 49 (11·1%) | 8 (2·8%) |
| ACE inhibitors or ARBs | 553 (45·5%) | 435 (37·9%) | 96 (24·5%) | 50 (5·2%) | 264 (8·6%) | 48 (10·9%) | 23 (8·1%) |
| Diuretics | 233 (19·2%) | 228 (19·9%) | 44 (11·2%) | 22 (2·3%) | 440 (14·3%) | 27 (6·1%) | 39 (13·8%) |
| Calcium-channel blockers | 228 (18·8%) | 129 (11·2%) | 69 (17·6%) | 58 (6·0%) | 457 (14·9%) | 48 (10·9%) | 17 (6·0%) |
| Blood-pressure-lowering drugs | 842 (69·2%) | 664 (57·8%) | 252 (64·3%) | 182 (18·8%) | 1056 (34·4%) | 105 (23·9%) | 45 (15·9%) |
| Statins | 633 (52·1%) | 172 (15·0%) | 140 (35·7%) | 34 (3·5%) | 53 (1·7%) | 61 (13·9%) | 3 (1·1%) |

North America and Europe is Canada, Sweden, Poland, and Turkey. South America is Argentina, Brazil, Chile, and Colombia. Middle East is United Arab Emirates and Iran. South Asia is India, Pakistan, and Bangladesh. Africa is South Africa and Zimbabwe. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker.

**Table 5: Drug use in participants with coronary heart disease or stroke, by region**

Use of proven effective drugs did not differ much between the 5227 participants with coronary heart disease alone and 1869 participants with stroke alone compared with the 423 participants who had stroke and coronary heart disease. For example, rates of use of antiplatelet drugs (25·1% for one disorder *vs* 27·7% for both disorders; p=0·26) and ACE inhibitors or ARBs (19·5% *vs* 20·1%; p=0·77) did not differ in participants with both events compared with those with only one event. However, use of statins or β blockers was substantially lower when an individual had had both events compared with coronary heart disease alone (12·3% *vs* 17·0% statins [p=0·0048] and 13·5% *vs* 21·0% β blockers [p<0·0001]).

For people with coronary heart disease, there was a significant decline in use of antiplatelet drugs, ACE inhibitors or ARBs, and statins, but not β blockers, with increasing number of years between the index event and time of assessment. However, for patients who had had a stroke, although we noted a decline in the use of statins, the use of antiplatelet drugs, ACE inhibitors or ARBs, and other blood-pressure-lowering drugs (diuretics or calcium-channel blockers) was low throughout and did not change with time (figure 6).

We noted the lowest degree of variation in drug use between urban and rural communities after adjustment for country economic status and individual characteristics (table 6). However, adjustment for country economic status had the largest effect on variations in use of all drugs whereas the contribution of individual factors was generally lower. When use of any one of the drugs was considered, about 65% of the variation was at the country level.

## Discussion

Effective preventive drugs for coronary heart disease and stroke are underused globally, with striking variation between countries at different stages of economic development. Even the use of accessible and inexpensive treatments such as aspirin (the most commonly used antiplatelet drug) varied seven-fold between low-income and high-income countries but the use of statins varied 20-fold. For every group of countries, classified by economic development, rates of drug use were consistently lower in rural than urban settings. Once these factors were accounted for, individual-level factors such as age, sex, educational status (a surrogate for economic status), hypertension, diabetes, smoking, and obesity were related to the rates of drug use. After

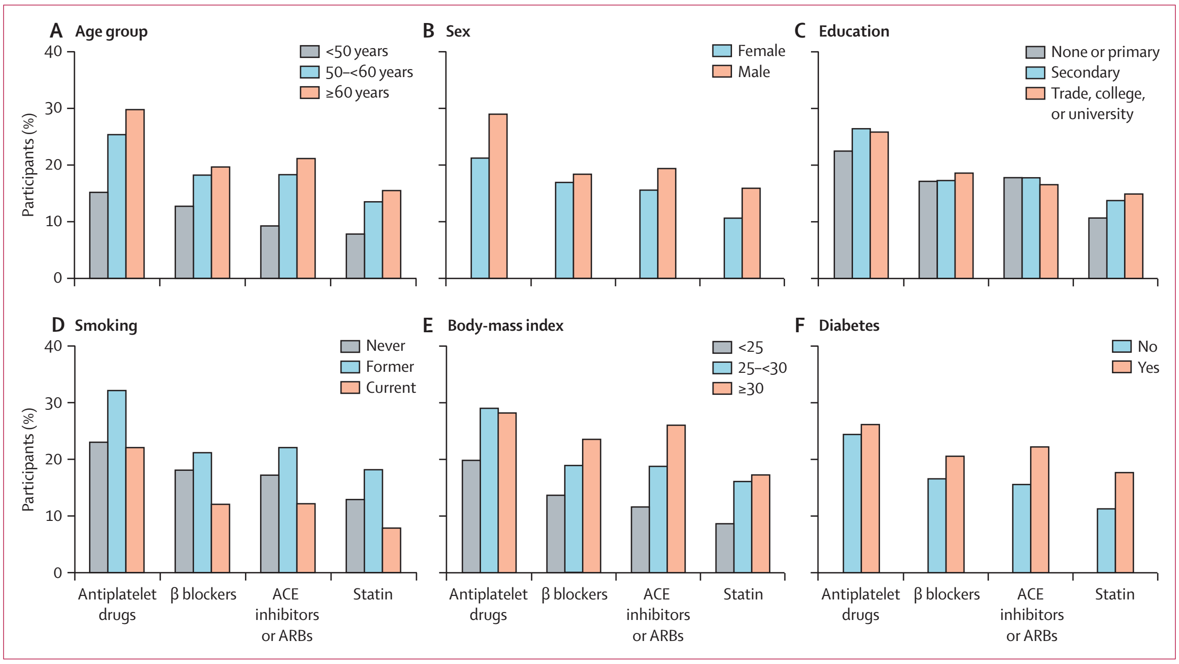


*Figure 4:* **Drug use in participants with coronary heart disease or stroke**
Classifications by age (A), sex (B), education (C), smoking history (D), body-mass index (E), and diabetes status (F) were adjusted for age, sex, education, urban versus rural location, and country economic status, if applicable. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker.

adjustment for these factors, patients who had a stroke were less likely to receive some proven drugs (eg, statins) than were those with coronary heart disease (table 3). Surprisingly, some very high risk groups (those with or both coronary heart disease and stroke) did not have a higher rate of use of drugs, but this finding is consistent with several studies in which the sickest patients received the least care (termed the inverse care law). In our analysis, 58% of individuals with coronary heart disease and 50% of individuals who had a stroke did not receive any of the four effective drug types; these rates were highest in the low-income countries.

The PURE study provided prospective data for individuals in numerous countries from the community rather than data from patients who were in the care of doctors in a hospital, clinic setting, or active follow-up by general practitioners. Such non-community studies tend to provide an overestimate of the rates of drug use in a population, because they do not include individuals who have no access to medical care, those who are not long-term drug users, or those who have discontinued active follow-up by a doctor. Consequently, data from hospital registries or general practices tend to substantially overestimate the rates of actual use of secondary prevention drugs in a population.

Substantial opportunities remain for enhancement of drug use, even in high-income countries. For example in the high-income countries in PURE, only 64·6% of patients with coronary heart disease and 52·7% of patients who had a stroke were on an antiplatelet drug and only 72·2% and 52·2%, respectively, were on statins, with lower rates for ACE inhibitors or ARBs (53·2% coronary heart disease and 41·9% stroke) and β blockers (47·6% for coronary heart disease). Only 60·6% of patients who had a stroke received a blood-pressure-lowering drug. Prevalence of drug use was substantially lower in less economically developed countries than it was in developed countries, suggesting an urgent need for systematic approaches to

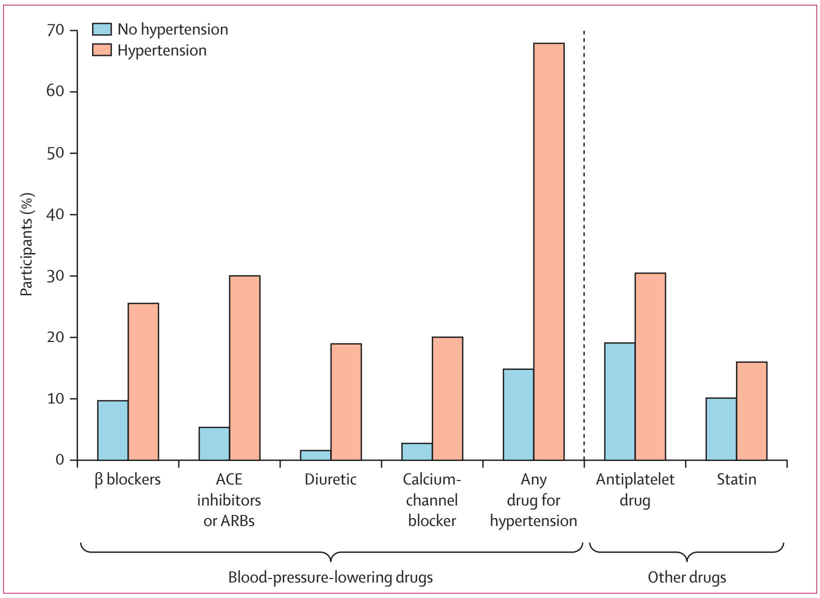


*Figure 5:* **Drug use by history of hypertension in participants with cardiovascular disease**
Adjusted for age, sex, location, education, and country economic status. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker.

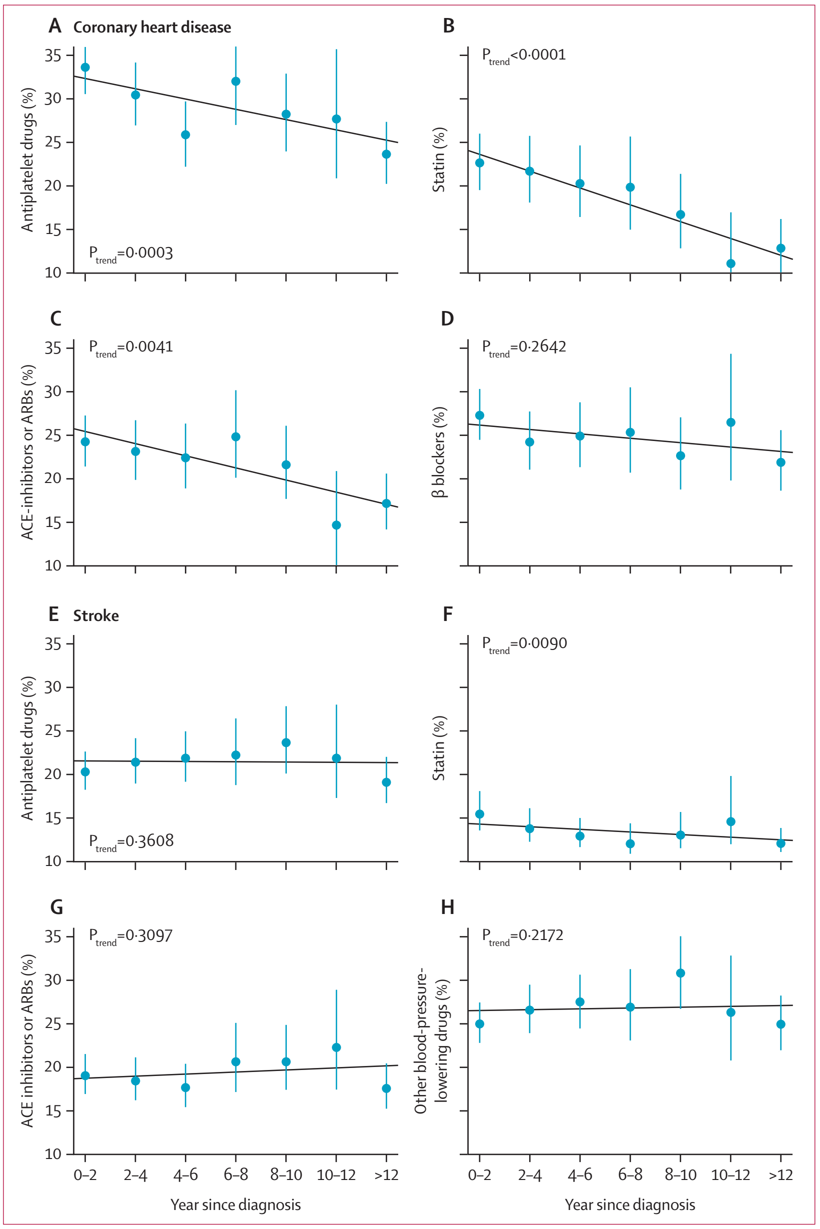


***Figure 6:*** **Proportion of individuals with coronary heart disease (A–D) or stroke (E–H) on various drugs since diagnosis**
Adjusted for age, sex, education, smoking, body-mass index, hypertension, and diabetes statuses. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker.

understand and rectify the causes of the large treatment gap in secondary prevention globally. Our data are consistent with the only other study that we are aware of done in rural communities in a low-income country (Andhra Pradesh in India),[19] in which the use of antiplatelet drugs (19·4% for coronary heart disease and 11·8% stroke), β blockers (23·5% and 41·0%), ACE inhibitors (10·3% and 4·4%), and statins (6·0% and 1·0%) was also very low. The WHO-PREMISE study,[20] which was done in 10 000 patients in ten countries, and the CREATE Registry,[21] which was done in 21 000 patients in India, have reported much higher rates of use of drugs than we reported, but these studies were mostly based on patients who were in hospital or referred to relatively large hospitals (although WHO-PREMISE had 15% of patients enrolled from primary health-care facilities). Thus, although some patients receive appropriate treatments when they access health-care providers or hospitals, most do not receive basic effective therapies long term, with many individuals receiving no preventive treatment.

Reasons for the underuse of effective drugs are not clear and need to be prospectively studied through assessment of existing multinational, national, and community databases, and qualitative research and surveys in multiple countries (including urban and rural communities) at various economic stages. Reasons might include restricted availability of these drugs in low-income and middle-income countries, especially in rural areas, unaffordability of even generic drugs,[21–23] side-effects from drugs, inconvenience, costs associated with visiting health practitioners, absence of transportation and long distances from clinics in some rural areas, restricted access to health-care providers in low-income countries, an absence of systematic programmes for long-term preventive care in most countries (including high-income ones) after an acute vascular event, and an absence of awareness of the need for lifelong therapy with such drugs by patients and their doctors.[24,25] These factors might contribute most in individuals who feel healthy several years after an acute cardiovascular disease event or feel that they are at lower risk for an event (eg, the young), contributing to a decline in their use with time.

The economic status of the country accounted for about two-thirds of the variations in drug use, whereas only a third was accounted for by individual factors. Of these, why fewer women in all settings took drugs is unclear. However, this difference has been noted in several previous studies.[26] The finding that younger individuals were treated less often than were older individuals was unexpected, as was the finding that most individuals with diabetes and a previous vascular event were not taking proven treatments. Current smokers tended to use these drugs less frequently than did former smokers or non-smokers, suggesting that there is a group of individuals who might not be willing to use any behavioural or drug prevention strategy, and these individuals are likely to be at high risk of recurrent events in the future. Moreover, this finding might be related to the crowding out effect of the cost of smoking that compromises allocation of resources for essential expenditures such as preventive drugs.[27] By contrast, obese individuals were more likely to be treated, which might be attributable to self-awareness of increased risk for cardiovascular disease events. The substantial differences in use of β blockers and ACE inhibitors or ARBs between patients with cardiovascular disease with and without hypertension (10% with *vs* 28% without for β blockers and 5% *vs* 30% for ACE inhibitors or ARBs) suggest that doctors might focus more on reduction of risk factors rather than risk for the patient. This notion suggests a need to re-educate doctors in their approach to secondary prevention. We noted a decline in rates of use of several drugs with time for inexpensive and widely available drugs such as antiplatelets, as well as for more expensive drugs such as statins (for which the reported decline was greater), suggesting that in several countries even basic generic medications for long-term chronic use might be unaffordable.

Our study had some limitations. Diagnoses of coronary heart disease and stroke were self-reported (although an interviewer used standardised questionnaires and face-to-face interviews) and therefore a small proportion of individuals might not have had vascular disease. However, previous studies showed a high degree of specificity for self-reports of coronary heart disease and stroke,[19,28–33] and in our study, confirmation by an adjudication committee occurred about 90% of the time. Therefore, individuals who reported these events probably had the disorder. Furthermore, the prevalence of cardiovascular disease in our study was much the same as that reported in age-matched individuals from other studies in high-income and low-income countries. The consistency of the pattern of our results for stroke and coronary heart disease suggests that the general trends and low rates of drug use are probably real. The degree to which our results can be generalised to entire countries or regions studied is unclear. We excluded individuals who were older than 70 years and although this group made up only 3% of household members in this study, they are likely to include a higher proportion of individuals with cardiovascular disease. For patients aged 35–70 years, smoking rates and education levels were equivalent to external findings (unpublished data), suggesting no real biases that would alter conclusions.

Our study has several strengths. We provide the only community-level estimates to date of preventive drug use in individuals with prevalent cardiovascular disease from urban and rural settings in high-income, middle-income, and low-income countries (panel). Our approach to identification of participants in the community avoided potential biases related to collection of data only for patients who visit clinics or hospitals. Therefore, our study probably provides a more realistic overview of the rates of long-term use of various proven effective cardiovascular drugs. Because of the substantial underuse of effective secondary prevention drugs in middle-income and low-income countries, the low costs of these drugs (which are generic in most parts of the world), and the high prevalence of cardiovascular disease in these countries, a large effect on reduction in global cardiovascular disease can be achieved by systematically enhancing secondary prevention. Improvements to the uptake of effective secondary prevention strategies are probably more feasible than are lifestyle modifications in primary prevention (although both are desirable).

| | Between-country variance (%) | Within-country variance (%) | Overall variance |
|---|---|---|---|
| Antiplatelet drugs | 1·488 (60·0%) | 0·990 (40·0%) | 2·478 |
| β blockers | 1·464 (59·8%) | 0·985 (41·2%) | 2·449 |
| ACE inhibitor or ARB | 1·198 (54·8%) | 0·990 (45·2%) | 2·188 |
| Statin | 3·724 (79·4%) | 0·967 (20·6%) | 4·691 |
| Any one drug type | 2·150 (68·4%) | 0·995 (31·6%) | 3·145 |

Individual factors are age, sex, education, body-mass index, hypertension, diabetes, and smoking. Variance estimates related to individual drugs are less reliable than for estimates in any one drug type because of less convergence as the cell frequencies become smaller. Nevertheless, the table shows that the dominant influence on the variations in use of statins and ACE inhibitors or ARBs is the economic status income level of the country, whereas individual factors influenced the use of antiplatelet drugs and β blockers to a greater extent. ACE=angiotensin-converting enzyme. ARB=angiotensin II receptor blocker.

***Table 6:* Country (between country) and individual (within country) variances and their contributions as a percentage to the total variance based on multilevel modelling**

### *Panel:* Research in context

**Systematic Review**

We searched the Medline database for articles about secondary prevention of cardiovascular disease at a community level in countries at various stages of economic development, without language or date restrictions, with the terms "secondary prevention", "cardiovascular disease", "community", and "developing countries". We were unable to locate any relevant publications.

**Interpretation**

Our study is the first to assesses the use of secondary prevention drugs in the community in high-income, middle-income, and low-income communities. We report substantial shortfalls in the use of proven inexpensive medications (aspirin, β blockers, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, diuretics, or statins) in patients with coronary heart disease or strokes in all countries studied, with more striking shortfalls in low-income countries. Systematic programmes to ensure increased and appropriate use of proven drugs for secondary prevention are needed in most countries to reduce this gap.

We plan therefore to systematically obtain information about the barriers to optimum care in communities participating in PURE, and in various types of individuals to inform national and community policies for improving availability, access, and affordability of essential drugs for chronic conditions. Such information will also assist in development and implementation of structured long-term programmes that could involve non-physician health workers, low cost and affordable combination therapies (eg, the polypill),[34,35] and better educate patients and health-care providers about the benefits, safety, and lifelong need for basic secondary prevention strategies.

Our study shows the large gap that exists in secondary prevention worldwide, with extremely low rates of use of effective therapies in middle-income and low-income countries. Systematic efforts are needed to understand why even inexpensive drugs are substantially underused globally. Efforts to increase the use of effective and inexpensive drugs for prevention of cardiovascular disease are urgently needed, and would substantially reduce disease burden within a few years.

**Contributors**
SY conceived and initiated the Prospective Urban Rural Epidemiology (PURE) study, supervised its conduct and data analysis, and had primary responsibility for writing of the report. SR coordinated the worldwide study and reviewed and commented on drafts. SI did all data analyses and reviewed and commented on drafts. KKT was the co-principal investigator of the study and reviewed and commented on drafts. All other authors coordinated the study in their respective countries and provided comments on drafts of the manuscript.

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**Conflicts of interest**
We declare that we have no conflicts of interest.

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**References**

1 Yusuf S, Reddy S, Ôunpuu 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.
2 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.

3 The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342:** 145–53.

4 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:** 581–88.

5 Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 2010; **376:** 1670–81.

6 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.

7 Yusuf S. Two decades of progress in preventing vascular disease. *Lancet* 2002; **360:** 2–3.

8 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003; **326:** 1419.

9 Sacco RL, Adams R, Alberts G, et al. Guidelines for the 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.

10 Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U; EUROASPIRE Study Group. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II and III surveys in eight European countries. *Lancet* 2009; **337:** 929–40.

11 Fox KA, Steg PG, Eagle KA, et al; for the GRACE investigators. Decline in rates of death and heart failure in acute coronary syndromes, 1999–2006. *JAMA* 2007; **297:** 1892–900.

12 Bhatt DL, Eagle KA, Ohman EM, et al; for the REACH Registry Investigators. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherosthrombosis. *JAMA* 2010; **304:** 1350–57.

13 World Bank. How we classify countries. http://data.worldbank.org/about/country-classifications (accessed May 19, 2011).

14 Teo K, Chow CK, Vaz M, Rangarajan S, Yusuf S; PURE Investigators-Writing Group. The Prospective Urban Rural Epidemiology (PURE) study: examining the impact of societal influences on chronic noncommunicable diseases in low, middle- and high-income countries. *Am Heart J* 2009; **158:** 1–7.

15 MacQueen KM, McLellan E, Metzger DS, et al. What is community? An evidence-based definition for participatory public health. *Am J Public Health* 2001; **91:** 1929–38.

16 Yusuf S, Hawken S, Ôunpuu S, et al; on behalf of the INTERHEART 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.

17 O'Donnell MJ, Xavier D, Lisheng L, et al, on behalf of 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.

18 Ramsey F, Schafer D. The statistical sleuth: a course in methods of data analysis, 2nd edn. New York: Duxbury, 2002.

19 Joshi R, Chow CK, Raju PK, et al. Fatal and nonfatal cardiovascular disease and the use of therapies for secondary prevention in a rural region of India. *Circulation* 2009; **119:** 1950–55.

20 Mendis S, Abegunde D, Yusuf S, et al. WHO study on prevention of recurrences of myocardial infarction and stroke (WHO-PREMISE). *Bull World Health Organ* 2005; **83:** 820–29.

21 Xavier D, Pais P, Devereaux PJ, et al, on behalf of the CREATE registry investigators. Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. *Lancet* 2008; **371:** 1435–42.

22 Cameron A, Roubos I, Ewen M, Mantel-Teeuwisse AK, Leufkens HBM, Laing RO. Differences in the availability of medicines for chronic and acute conditions in the public and private sectors of developing countries. *Bull World Health Organ* 2011; **89:** 412–21.

23 Van Mourik MSM, 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.

24 Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2008; **2:** CD000011.

25 Niëns LM, Cameron A, Van de Poel E, Ewen M, Brouwer WBF, 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:** e1000333.

26 Healy B. The Yentl syndrome. *N Engl J Med* 1991; **325:** 274–76.

27 John RM. Crowding out effect of tobacco expenditure and its implications on household resource allocation in India. *Soc Sci Med* 2008; **66:** 1356–67.

28 Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005; **353:** 487–97.

29 Bergmann MM, Byers T, Freedman DS, Mokdad A. Validity of self-reported diagnoses leading to hospitalization: a comparison of self-reports with hospital records in a prospective study of American adults. *Am J Epidemiol* 1998; **147:** 969–77.

30 Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol* 2004; **57:** 1096–1103.

31 Yamagishi K, Ikeda A, Iso H, Inoue M, Tsugane S, for the JPHC Study Group. Self-reported stroke and myocardial infarction had adequate sensitivity in a population-based prospective study JPHC (Japan Public Health Center)-based prospective study. *J Clin Epidemiol* 2009; **62:** 667–73.

32 Lampe FC, Walker M, Lennon LT, Whincup PH, Ebrahim S. Validity of a self-reported history of doctor-diagnosed angina. *J Clin Epidemiol* 1999; **52:** 73–81.

33 Heckbert SR, Kooperberg C, Safford MM, et al. Comparison of self-report, hospital discharge codes and adjudication of cardiovascular events in the Women's Health Initiative. *Am J Epidemiol* 2004; **160:** 1152–58.

34 The Indian Polycap Study (TIPS). Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. *Lancet* 2009; **373:** 1341–51.

35 Lonn E, Bosch J, Teo KK, Pais P, Xavier D, Yusuf S. The polypill in the prevention of cardiovascular diseases: key concepts, current status, challenges, and future directions. *Circulation* 2010; **122:** 2078–88.