Availability and affordability of cardiovascular disease medicines and their effect on use in high-income, middle-income, and low-income countries: an analysis of the PURE study data

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Summary

Background **WHO has targeted that medicines to prevent recurrent cardiovascular disease be available in 80% of communities and used by 50% of eligible individuals by 2025. We have previously reported that use of these medicines is very low, but now aim to assess how such low use relates to their lack of availability or poor affordability.**

Methods **We analysed information about availability and costs of cardiovascular disease medicines (aspirin, β blockers, angiotensin-converting enzyme inhibitors, and statins) in pharmacies gathered from 596 communities in 18 countries participating in the Prospective Urban Rural Epidemiology (PURE) study. Medicines were considered available if present at the pharmacy when surveyed, and affordable if their combined cost was less than 20% of household capacity-to-pay. We compared results from high-income, upper middle-income, lower middle-income, and low-income countries. Data from India were presented separately given its large, generic pharmaceutical industry.**

Findings **Communities were recruited between Jan 1, 2003, and Dec 31, 2013. All four cardiovascular disease medicines were available in 61 (95%) of 64 urban and 27 (90%) of 30 rural communities in high-income countries, 53 (80%) of 66 urban and 43 (73%) of 59 rural communities in upper middle-income countries, 69 (62%) of 111 urban and 42 (37%) of 114 rural communities in lower middle-income countries, eight (25%) of 32 urban and one (3%) of 30 rural communities in low-income countries (excluding India), and 34 (89%) of 38 urban and 42 (81%) of 52 rural communities in India. The four cardiovascular disease medicines were potentially unaffordable for 0·14% of households in high-income countries (14 of 9934 households), 25% of upper middle-income countries (6299 of 24 776), 33% of lower middle-income countries (13 253 of 40 023), 60% of low-income countries (excluding India; 1976 of 3312), and 59% households in India (9939 of 16 874). In low-income and middle-income countries, patients with previous cardiovascular disease were less likely to use all four medicines if fewer than four were available (odds ratio [OR] 0·16, 95% CI 0·04–0·57). In communities in which all four medicines were available, patients were less likely to use medicines if the household potentially could not afford them (0·16, 0·04–0·55).**

Interpretation **Secondary prevention medicines are unavailable and unaffordable for a large proportion of communities and households in upper middle-income, lower middle-income, and low-income countries, which have very low use of these medicines. Improvements to the availability and affordability of key medicines is likely to enhance their use and help towards achieving WHO's targets of 50% use of key medicines by 2025.**

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Introduction

17 million people are estimated to die of cardiovascular diseases worldwide every year.[1] About 20% occur in those with known vascular disease.[2] Many of these deaths could be avoided if the use[3] of proven medicines among patients with vascular disease (secondary prevention) were increased. Clinical guidelines recommend the use of four medicines for the secondary prevention of cardiovascular disease: aspirin, β blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs), and statins.[4] However, in a previous report from the Prospective Urban Rural Epidemiology (PURE) study, only 25% of patients with established cardiovascular disease were taking aspirin, 17% β blockers, 20% ACE inhibitors or ARBs, and 15% statins. In high-income countries, 11% of eligible patients were not taking any of these medicines, compared with 80% in low-income countries.[3]

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Research in context

Evidence before this study

We searched the PubMed database for articles about the availability and affordability of medicines for the secondary prevention of cardiovascular disease in countries at various stages of economic development published before May 1, 2014, without language restrictions. Our search terms included "availability", "affordability", "secondary prevention", "CVD medicines or drugs", "low-income countries", and "middle-income countries". We excluded studies that did not provide data for at least one of the four medicines recommended for the secondary prevention of cardiovascular disease (aspirin, β blockers, angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers, or statins), or a measure of affordability for the medicines.

We identified five reports that used different methods to measure the availability and affordability of different medicines for cardiovascular disease. Only one report considered the availability and affordability of the four medicines recommended by clinical guidelines. That report included data from five low-income and middle-income countries, and as a measure for affordability used the number of days wages it would cost the lowest paid government worker to purchase 1 month of treatment. Affordability varied by country; however, in view of the method used, the number of days wages that made treatment unaffordable (ie, a cutoff point to determine affordability) could not be determined. Additionally, information about the use of these medicines in the communities described was not collected and therefore the effects of little availability and affordability on use could not be deduced.

Added value of this study

To our knowledge, our study is the first to describe the availability and affordability of the four medicines recommended for the secondary prevention of cardiovascular disease in high-income, upper middle-income, lower middle-income, and low-income countries. It is also the first to relate these factors to medicine use. Our results suggest that the availability and affordability of these medicines is low in low-income and middle-income countries, which correlates with low rates of use. In India, these medicines are available in most communities given the large production of generic-brand medicines in the country. However, they remain unaffordable for large proportions of the community.

Implications of all the available evidence

Clinical guidelines recommend the use of four medicines for the secondary prevention of cardiovascular disease. However, the medicines remain unavailable and unaffordable for large proportions of communities in low-income and middle-income countries. Although our results show substantially lower use of key medicines when they are not available or unaffordable, it does not automatically mean that improving availability or affordability by themselves will increase their use. Additional research on how additional factors might further affect use of these medicines is needed (eg, access to health-care providers and attitudes to prevention on the part of both physicians and patients). Research on this topic is especially scarce in low-income and middle-income countries. Strategies to make proven medicines more available and affordable are crucially needed to increase their use in low-income and middle-income countries where the burden of cardiovascular disease is growing.

WHO's Global Action Plan has set a goal to achieve 50% use of medicines recommended for the prevention of cardiovascular disease worldwide by 2025.[5] To reach this goal, these medicines need to be made widely available and affordable.

In this Article, we aim to document the availability of aspirin, β blockers, ACE inhibitors, and statins in community pharmacies and assess their affordability at different country incomes. We then relate availability and affordability of medicines to their use in patients with cardiovascular disease from 18 countries.

Methods

Study design and participants

We did a post-hoc analysis of the PURE study, using data from 94 919 households with reported household incomes from 596 communities in 18 countries and 7013 people with cardiovascular disease. Individuals in households that reported or did not report income were generally similar (appendix).

Countries were selected to ensure a range of economic development, and the feasibility to collect high-quality data and complete long-term follow-up.[6] In every country chosen, communities were selected from urban and rural locations. In the PURE study, communities were defined as a group of people who have common characteristics and reside in a defined geographical area.[3] In each community, we sought to have a representative sample of adults aged 35–70 years. The characteristics and death rates of the study population were similar to their national populations.[7]

Additional details on methods, sampling and selection of countries, communities, and individuals have been published previously.[6,8,9] Ethics committees at each centre approved the protocol, which has been published elsewhere;[6,8,9] all participants provided written informed consent.[6]

Data collection and definitions

Data for availability and costs of medicines were collected from one community pharmacy in each community with the Environmental Profile of a Community's Health (EPOCH) instrument, which recorded information about environmental and societal factors that can affect cardiovascular disease.[10] Only communities with at least 30 PURE participants were

included in EPOCH (90% of PURE communities). This instrument has been shown to be a reliable and feasible indicator of measures of the health environment in diverse settings.[10]

Data collection methods included an observation walk, whereby trained field researchers walked according to a planned route covering 1 km, beginning from a prespecified central location designated as the starting point (a central area that people frequently visit, eg, busy intersections or a train station).[10] A pharmacy closest to the starting point was visited to collect information about availability and costs of medicines. If a pharmacy was not located within the 1 km observation walk, researchers were instructed to search for a pharmacy located up to 20 km from the starting point from which to gather data.

Information about the availability and cost of three ACE inhibitors (captopril, enalapril, and ramipril), two β blockers (atenolol and metoprolol), two statins (simvastatin and atorvastatin), and aspirin were gathered. Field researchers were instructed to gather information about the most common trade name for each of these medicine types as identified by the pharmacist. Although clinical guidelines recommend the use of either ACE inhibitors or ARBs, ARBs seem to be rarely used in low-income and middle-income countries.

Trained interviewers collected data at the household and individual levels with standardised questionnaires. Household income per month and expenditures on food were recorded from a knowledgeable member in each participating household. Information about previous cardiovascular disease and medicine use were obtained from consenting household members aged 35–70 years.[6] Cardiovascular disease was defined as an individual with previous stroke or coronary heart disease (eg, myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary angioplasty, or angina). Self-reported events from PURE have been previously validated against medical records, with a confirmation rate of 89%.[3]

The use of any medicine was defined as taking it at least once per week in the past month. Names of all medicines taken were recorded by direct inspection of medicines or prescriptions at face-to-face assessments.[3] Medicines were centrally coded into medicine classes by trained staff (eg, aten and betacard were coded as atenolol and lipitor as atorvastatin). Availability was defined as the presence of all four medicines (aspirin, β blockers, ACE inhibitors, and statins) at any dose in the pharmacy on the day of the survey. Costs are presented for a month's supply of all four medicines at standard doses and recommended frequencies (appendix). Affordability was expressed as the total monthly cost of the four medicines as a proportion of monthly household capacity-to-pay—the household income remaining after basic subsistence needs have been met. We defined subsistence needs as the household monthly income spent on food, which is consistent with scientific literature of catastrophic health expenditures.[11,12]

Combined costs of the four medicines were deemed affordable if they comprised less than an arbitrary threshold of 20% of a household's capacity-to-pay.[12] Sensitivity analyses for thresholds ranging from 10% to 50% of household capacity-to-pay are also presented. This approach of presenting affordability of medicines was developed by Niens and colleagues[12,13] as an extension of methods used to assess catastrophic health expenditure. Details on how affordability was calculated and validation of capacity-to-pay values are listed in the appendix.

The appendix shows that household capacity-to-pay values were correlated with household wealth index scores (r=0·71, p<0·0001). Median country household capacity-to-pay calculated from the PURE study also correlated well with capacity-to-pay values from the WHO World Health Survey[14] (r=0·85, p=0·0035), and per capita country income from the World Bank[15] (r=0·88, p<0·0001). Thus, capacity-to-pay values collected by the PURE study have reasonable external validity.

In any multinational study, variations in health systems within and across countries affect the standardised assessment of the availability and affordability of medicines. For example, the PURE study collected information on the availability of medicines in the pharmacy only; therefore, their availability in non-pharmacy sources is not known. Thus, our analyses reflect potential availability (ie, based on the assumption that patients buy their medicines from a nearby pharmacy).

Payment methods for medicines also vary by country, within regions in a country, and by individuals within each country. For example, public pharmacies might offer specific medicines free of charge to specific population groups (eg, people with low income). However, previously reported data for the availability of medicines in upper middle-income and lower middle-income countries suggest that availability is lower in the public system than the private system,[16] forcing patients to purchase medicines at full costs from non-governmental sources. Additionally, worldwide, patients who have some form of insurance pay a fraction or none of these costs; however, assessments indicate that in lower-income countries, insurance does not cover medicine costs and many patients purchase these through out-of-pocket payments.[17] The PURE study did not collect information about actual costs that participants paid for each medicine. Therefore, our analyses represent potential affordability for households (ie, based on the assumption that each household paid full cost).

Statistical analysis

We describe the potential availability of aspirin, β blockers, ACE inhibitors, and statins in 596 communities included in PURE and the potential affordability of these for

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See **Online** for appendix

	Number of communities	Number of households	Number of participants with cardiovascular disease
Total	596	94 919	7013
High-income countries	94	9934	691
Sweden	23	2427	121
United Arab Emirates	3	953	64
Canada	68	6554	506
Upper middle-income countries	125	24 776	1499
Poland	4	1499	140
Turkey	38	2553	293
Chile	5	2222	109
Malaysia	35	10 471	420
South Africa	9	2168	104
Argentina	20	2158	100
Brazil	14	3705	333
Lower middle-income countries	225	40 023	3918
Colombia	58	5069	251
Iran	20	2992	229
China	108	30 409	3336
Occupied Palestinian territory	39	1553	102
Low-income countries (excluding India)	62	3312	219
Pakistan	4	1043	117
Bangladesh	55	2001	80
Zimbabwe	3	268	22
India	90	16 874	686

Classification of countries by income groups refer to World Bank classifications at the time of data collection (2006).

Table 1: **Countries included in analyses with number of communities, households, and patients with cardiovascular disease**

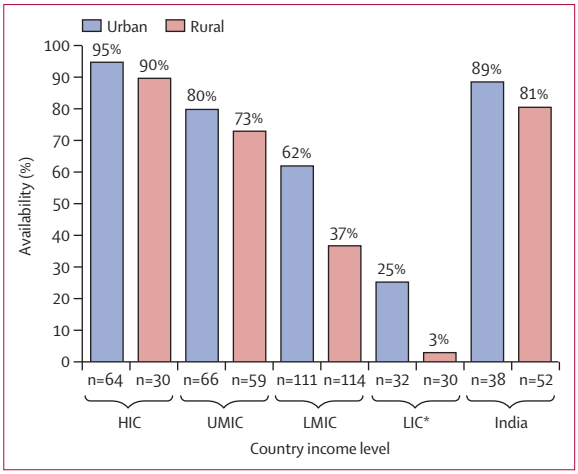

Figure 1: **Percentage availability of the four cardiovascular disease medicines in the 596 PURE communities surveyed**

n=total number of communities in each location of each country income group. Cardiovascular medicines included aspirin, β blockers, angiotensin-converting enzyme inhibitors, and statins. The value for the p_{trend} comparing high-income countries (HIC), upper middle-income countries (UMIC), lower middle-income countries (LMIC), and low-income countries (LIC; excluding India) was calculated using the trend test across a two by k table. $p_{trend}<0{\cdot}0001$ both in total and separately for urban and rural communities for all the different country income groups. *Excluding India.

1 month's supply to 94 919 households. Associations between availability and affordability and use of medicines were analysed in 7013 patients with known cardiovascular disease. Few patients were using all four medicines so we present additional post-hoc analyses for the associations between the availability and affordability of at least three of the medicines and the use of at least three.

Data were analysed using multilevel, mixed-effects logistic regression models, accounting for clustering at the community and household levels. Statistical models were adjusted for possible confounders: age, sex, education level, urban and rural setting, years since cardiovascular disease diagnosis, use of other medicines (eg, for diabetes or pain relief), cancer diagnosis, smoking status, and number of household members (either fewer than five or five or more).[18] Adjusted and unadjusted associations between availability and affordability and medicine use were reported as odds ratios (OR) and 95% confidence intervals. We used Stata (version 13.0) for all statistical analyses.

Household incomes and medicine costs were standardised to 2010 prices by inflation rates from the World Bank.[15] As secondary analyses, income and cost data were converted from local currency to US$ adjusted for purchasing power parity in 2010, as reported by the World Bank.[19] Results were presented as the median (IQR) of all participants in high-income, upper middle-income, lower middle-income, and low-income country groups. Data from India were presented separately from other low-income countries because of its large generic pharmaceutical industry.[20] In the appendix are the results at the country level in order from highest to lowest per capita gross national income.

Role of funding source

The funders of the study had no role in its design, data collection, data analysis, data interpretation, or writing of the report. The corresponding and lead (SY and RKh) authors had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Results

Recruitment of participants began in January, 2003, with most recruitment completed between 2005 and 2009.[9] Data for 94 919 eligible households' incomes were collected between Jan 1, 2003, and Dec 31, 2013, and for medicine costs were collected between Jan 1, 2009, and Dec 31, 2013. The analyses include three high-income countries (Sweden, United Arab Emirates, and Canada; 94 communities, 9934 households), seven upper middle-income countries (Poland, Turkey, Chile, Malaysia, South Africa, Argentina, and Brazil; 125 communities, 24 776 households), four lower middle-income countries (Colombia, Iran, China, and the occupied Palestinian territory; 225 communities,

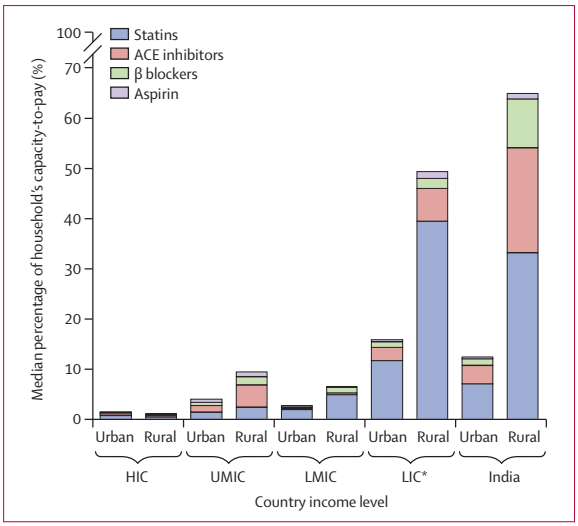

Figure 2: **Median monthly cost of each of the four cardiovascular medicines as a percentage of a household's capacity-to-pay**
Data are median (%) of 94 919 households. ACE=angiotensin-converting enzyme. HIC=high-income countries. UMIC=upper middle-income countries. LMIC=lower middle-income countries. LIC=low income-countries. *Excluding India.

40 023 households), and three low-income countries excluding India (Pakistan, Bangladesh, and Zimbabwe; 62 communities, 3312 households), in addition to India (90 communities, 16 874 households; table 1).

The availability of all four medicines was highest in high-income countries (95% [n=61] urban and 90% [n=27] rural communities) and in India (89% [n=34] urban and 81% [n=42] rural) and lowest in low-income countries excluding India (25% [n=8] urban and 3% [n=1] rural). Availability was intermediate in upper middle-income countries (80% [n=53] urban and 73% [n=43] rural) and lower middle-income countries (62% [n=69] urban and 37% [n=42] rural; figure 1). The appendix presents the availability of each of these four medicines by country's income group.

A patient with cardiovascular disease in urban and rural high-income countries would potentially need to spend a median of 1% (IQR 0·5–3 for urban and 0·5–2 for rural) of their household capacity-to-pay to buy all four cardiovascular disease medicines (figure 2). The median spend for all four medicines would be 5% (IQR 2–13) in urban and 11% (5–34) in rural upper middle-income countries, 6% (1–23) in urban and 11% (4–97) in rural lower middle-income countries, 17% (10–37) in urban and 49% (20–100) in rural low-income countries (excluding India), and 13% (5–43) in urban and 68% (23–100) in rural India. Furthermore, the costs of aspirin and β blockers were lower than the costs of ACE inhibitors and statins across the different countries' income groups (figure 2). Median cost of each medicine as a proportion of household capacity-to-pay is presented in the appendix.

Median monthly household capacity-to-pay and the median monthly cost of the four medicines (in US$ adjusted for purchasing power parity) are listed in table 2. The capacity-to-pay is highest among high-income country households and lowest in Indian and other low-income country households. Cost of medicines shows a similar trend across the different country income groups. However, the variability in the cost of the four medicines is less striking than variability in capacity-to-pay values: the median monthly capacity-to-pay is $4238 among high-income country households, and $89 among low-income country households excluding India (48 times higher in high-income countries than in low-income countries [excluding India]). By contrast, the median monthly cost of the four medicines is $61 in high-income countries compared with $17 in low-income countries, excluding India (only four times higher in high-income countries than in low-income countries excluding India). The median cost of each medicine was low in Iran and the occupied Palestinian territory compared with other countries in the same income group, which tended to decrease the overall cost in lower middle-income countries. These essential medicines are subsidised by the governments in Iran and the occupied Palestinian territory.

Using a threshold of 20% for household capacity-to-pay to define what is potentially unaffordable, our results show that 6299 (25%) and 13 253 (33%) households in upper middle-income countries and lower middle-income countries, respectively, would find

	Capacity-to-pay (US$)	Total cost of all four medicines* (US$)	Cost of aspirin (US$)	Cost of β blockers (US$)	Cost of ACE inhibitors (US$)	Cost of statins (US$)
High-income countries	4238 (2280–6180)	61 (18–91)	3 (2–7)	10 (3–16)	15 (5–23)	34 (8–46)
Upper middle-income countries	436 (176–989)	35 (18–44)	4 (2–6)	6 (2–7)	10 (7–15)	5 (5–16)
Lower middle-income countries	243 (108–463)	16 (7–50)	0·2 (0·1–3)	0·6 (0·1–13)	0·6 (0·3–2)	6 (2–17)
Low-income countries (excluding India)†	89 (34–173)	17 (17–42)	0·5 (0·5–0·7)	0·7 (0·7–4)	2 (2–9)	14 (14–21)
India	84 (27–317)	30 (26–35)	0·4 (0·3–0·6)	4 (3–4)	8 (8–9)	16 (13–21)

Costs are median (IQR) of 94 919 households, adjusted for purchasing power parity. ACE=angiotensin-converting enzyme. *The sum of the medians for each medicine (aspirin, β blockers, ACE inhibitors, and statins) is not necessarily the same as the median of the total cost for the four medicines. †Zimbabwe was not included in this analysis because purchasing power parity values were not available.

Table 2: **Monthly household capacity-to-pay, and costs of each of the four cardiovascular disease medicines in different countries**

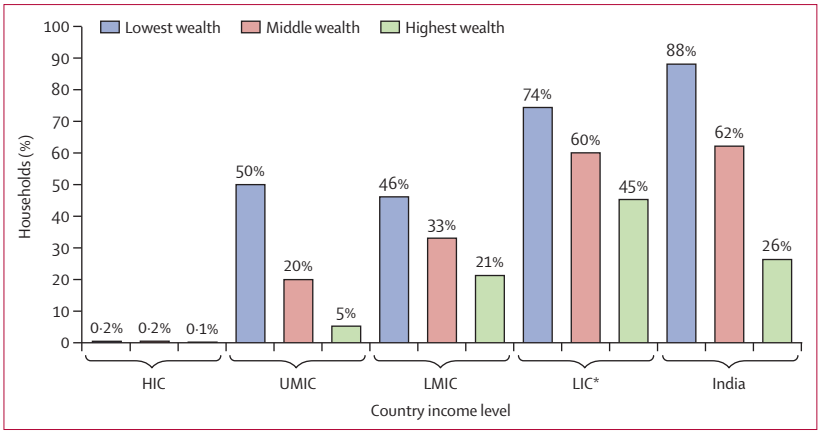

Figure 3: **Proportion of households that might not be able to afford all four cardiovascular disease medicines (using a 20% threshold) by tertiles of wealth index**
Data are of 94 919 households. HIC=high-income countries. UMIC=upper middle-income countries. LMIC=lower middle-income countries. LIC=low-income countries. *Excluding India.

	At least one medicine	At least two medicines	At least three medicines	All four medicines
Total	2589/7013 (37%)	1448/7013 (21%)	686/7013 (10%)	205/7013 (3%)
High-income countries				
Lowest wealth	251/281 (89%)	203/281 (72%)	131/281 (47%)	43/281 (15%)
Middle wealth	164/180 (91%)	143/180 (79%)	88/180 (49%)	35/180 (19%)
Highest wealth	204/230 (89%)	167/230 (73%)	108/230 (47%)	44/230 (19%)
All high-income countries	619/691 (90%)	513/691 (74%)	327/691 (47%)	122/691 (18%)
Upper middle-income countries				
Lowest wealth	213/502 (42%)	111/502 (22%)	44/502 (9%)	7/502 (1%)
Middle wealth	272/501 (54%)	163/501 (33%)	68/501 (14%)	29/501 (6%)
Highest wealth	310/496 (63%)	203/496 (41%)	110/496 (22%)	27/496 (5%)
All upper middle-income countries	795/1499 (53%)	477/1499 (32%)	222/1499 (15%)	63/1499 (4%)
Lower middle-income countries				
Lowest wealth	220/1325 (17%)	61/1325 (5%)	11/1325 (1%)	1/1325 (0·1%)
Middle wealth	343/1290 (27%)	120/1290 (9%)	31/1290 (3%)	6/1290 (0·5%)
Highest wealth	446/1303 (34%)	212/1303 (16%)	73/1303 (6%)	10/1303 (1%)
All lower middle-income countries	1009/3918 (26%)	393/3918 (10%)	115/3918 (3%)	17/3918 (0·4%)
Low-income countries*				
Lowest wealth	3/79 (4%)	1/79 (1%)	1/79 (1%)	0/79 (0%)
Middle wealth	9/71 (13%)	1/71 (2%)	0/71 (0%)	0/71 (0%)
Highest wealth	26/69 (38%)	10/69 (14%)	1/69 (2%)	0/69 (0%)
All low-income countries	38/219 (17%)	12/219 (5%)	2/219 (1%)	0/219 (0%)
India				
Lowest wealth	13/228 (6%)	3/228 (1%)	0/228 (0%)	0/228 (0%)
Middle wealth	29/236 (12%)	18/236 (8%)	10/236 (4%)	1/236 (0·4%)
Highest wealth	86/220 (39%)	32/220 (15%)	10/220 (5%)	2/220 (1%)
All India	128/686 (19%)	53/686 (8%)	20/686 (3%)	3/686 (0·4%)

Data are n/N (%) from 7013 patients. Cardiovascular disease medicines included aspirin, β blockers, angiotensin-converting enzyme inhibitors, and statins. *Excluding India.

Table 3: **Participants with a history of cardiovascular disease who reported medicine use across tertiles of income in a range of country incomes**

medicines unaffordable. 1976 (60%) households in low-income countries (excluding India) and 9939 (59%) households in India would find medicines unaffordable. In high-income countries, only 14 (0·14%) households would be unable to afford medicines—should they have to pay full costs. A sensitivity analysis, using thresholds that ranged from 10% to 50% of household capacity-to-pay, shows a similar pattern (appendix).

Among patients in the highest wealth groups, 433 (5%) patients in upper middle-income, 2776 (21%) in lower middle-income, 482 (45%) in low-income countries (excluding India), and 1476 (26%) patients in India could not afford the four medicines recommended for the secondary prevention of cardiovascular disease (figure 3). These analyses show that even medicines regarded as being low cost are potentially unaffordable by a large proportion of even the richer segments of low-income and middle-income countries.

Further analyses were restricted to the 7013 participants who reported a history of cardiovascular disease. Of patients with cardiovascular disease, use of each medicine was lower in low-income countries including India than in high-income countries. Overall, 205 (3%) patients reported using all four medicines, 686 (10%) reported using at least three, 1448 (21%) reported using at least two, and 2589 (37%) reported using at least one medicine; 2085 (30%) patients did not take any medicines. Medicine use varied substantially by wealth in upper middle-income countries, lower middle-income countries, India, and other low-income countries (table 3). However, across wealth tertiles use was similar in high-income countries (table 3).

In high-income countries medicines were available and affordable for most patients and estimates of associations with use could not be calculated. The number of patients who reported using all four medicines was small within the remaining country income groups. So our main analyses present estimates for upper middle-income countries, lower middle-income countries, low-income countries (excluding India), and India under one wealth category: low-income and middle-income countries. Results for each country income group are presented in the appendix.

Table 4 presents the adjusted and unadjusted relationships between lack of availability and affordability and use in low-income and middle-income countries. Patients living in communities with low availability of all four medicines were less likely to use them (OR 0·16, 95% CI 0·04–0·57) than communities that had all four medicines available. Patients living in communities where the medicines were available but who were unable to afford the medicines (using a threshold of 20%) were also less likely to use them (0·16, 0·04–0·55). The number of patients using the four medicines was small (n=205), so we also present the effects of availability and affordability of at least three medicines on use of at least three medicines (n=686). The results are similar but are statistically more robust compared with use of all four medicines.

	Number in group	Participants using medicines*	Odds ratio (95% CI)	
			Unadjusted	Adjusted†
Effect on use of four medicines				
Availability	6322	83 (1%)	..	..
All four available (reference)	3637	74 (2%)	1·00	1·00
Fewer than four available	2685	9 (<1%)	0·16 (0·08–0·32)	0·16 (0·04–0·57)
Affordability‡	3637	83 (1%)	..	..
Cost of four is affordable (reference)	2395	68 (3%)	1·00	1·00
Cost of four is not affordable	1242	6 (<1%)	0·17 (0·07–0·38)	0·16 (0·04–0·55)
Effect on use of at least three medicines				
Availability	6322	359 (6%)	..	..
At least three available (reference)	4855	343 (7%)	1·00	1·00
Fewer than three available	1469	16 (1%)	0·14 (0·09–0·24)	0·11 (0·04–0·28)
Affordability§	4855	343 (7%)	..	..
Cost of three is affordable (reference)	4027	319 (8%)	1·00	1·00
Cost of three is not affordable	828	24 (3%)	0·30 (0·19–0·46)	0·42 (0·22–0·80)

Four medicines are aspirin, β blockers, angiotensin-converting enzyme inhibitors, and statins. *Data are n (%) from 6322 patients. †Adjusted for age, sex, education years, years since diagnosis, cancer diagnosis, use of other medicines, smoking status, number of household members, urban versus rural location; clustered at the community and household levels. ‡Analyses restricted to 3637 patients living in communities where all four medicines were available. §Analyses restricted to 4855 patients living in communities in which at least three medicines were available.

Table 4: **Associations between availability and affordability and use of cardiovascular disease medicines in patients with a history of this disease in low-income and middle-income (including India) countries**

Comparisons of use of individual medicines in India (where availability is high, but affordability is low) and other low-income countries (where both availability and affordability are low) show little difference in the use of aspirin, but relatively higher rates of use of β blockers, ACE inhibitors, and statins in India (appendix). However, in both groups of countries the use of these medicines were low, suggesting that improvements in availability without improvements in affordability are unlikely to result in a major increase in the prevalence of these medicines being used. Our results also suggest that when the four medicines are both available and affordable, only 122 (18%) of 667 patients in high-income countries and 68 (3%) of 2395 patients in low-income and middle-income countries are using them, suggesting that factors in addition to availability and affordability affect the use of these medicines, and should be explored (appendix).

Discussion

The availability and affordability of the four medicines recommended for the secondary prevention of cardiovascular disease greatly varies across the different country income groups. These medicines were more commonly available and affordable in high-income countries, less so in upper middle-income countries and lower middle-income countries, and least available and affordable in low-income countries (excluding India). Medicines were widely available in India, however, they were not affordable, which was likely due to the low capacity-to-pay of households.

Of patients with known cardiovascular disease across 18 countries studied in PURE, only 686 (10%) used three of the recommended medicines and 205 (3%) used all four medicines. In low-income and middle-income countries, there is a strong association between scarce availability and low affordability of these medicines and their use. This finding suggests that improvements in the availability and affordability of these medicines are prerequisites to increasing their use. However, use of the recommended medicines was low in low-income and middle-income countries even when the medicines were potentially available and affordable and only reached about 18% use in high-income countries where these medicines are widely available and affordable. Thus, although the availability and affordability of medicines are prerequisites for their use, correcting these factors alone might not be sufficient to increase the proportion of patients receiving all medicines to optimum coverage. Other factors affecting medicine use could include patients' attitudes and knowledge towards taking medicines for prevention, and health-care providers' attitudes and prescribing patterns.[21] Further studies are needed to understand how these factors affect the use of medicines.

Our analyses are unique because we obtained standardised data for the availability, affordability, and rates of use of the four medicines recommended for cardiovascular disease from 18 countries and 596 urban and rural communities. Standardised information about the availability and affordability of cardiovascular disease medicines at the community level have previously been reported by the joint WHO and Health

Action International project.[20] However, unlike the PURE study, these data were not connected to rates of use among patients with cardiovascular disease. Our results support previous findings, suggesting that in low-income and middle-income countries the availability and affordability of key medicines for the prevention of secondary cardiovascular disease events are low.[20,22,23]

Our results are based on observational analyses of cross-sectional data, and not from randomised controlled trials. Although our results show substantially lower use of key medicines when they are not available or unaffordable, it does not automatically mean that improvements in availability or affordability by themselves will increase their use. Although improving availability and affordability seems logical to improve the use of key medicines for secondary prevention of cardiovascular disease, additional factors (eg, access to health-care providers and attitudes to prevention on the part of both physicians and patients) are also likely to be important.

WHO's Global Action Plan has set worldwide goals to achieve 80% availability of affordable essential medicines for non-communicable diseases and 50% use of these medicines by 2025.[5] Current rates of use of medicines for secondary prevention falls substantially short of these goals. Overcoming these large treatment gaps will initially need governments to set policies that make key medicines available and affordable, followed by other strategies to enhance their use (eg, improving access to health-care providers, setting local targets for their use, and monitoring use).

Our results represent potential rather than true or actual availability and affordability. If availability of medicines is higher in non-pharmacy vendors or in pharmacies not surveyed in our study, then our results might underestimate true availability. If patients received their medicines at a lower cost (or free of charge) in the public sector, our results might underestimate true affordability. However, data from previous studies have shown that public sector availability of medicines tends to be low in low-income and middle-income countries,[16] forcing patients to purchase their medicines from private pharmacies and at full cost. Data were collected from one pharmacy per community only, which might not be representative of true costs in the community. However, variations in costs between communities in the same country were small, suggesting that information from one pharmacy per community—in a large study like PURE—is a reasonable estimate of the estimated cost of medicines in a community.

By calculating affordability based on only costs of medicines, we have likely overestimated affordability because our approach does not take into account other medical costs, such as professional fees or travel or time taken off work to visit a doctor. Our definition of affordability does not account for patient or household priorities. Even if these medicines are affordable, patients might still judge them to be unaffordable if they have other household expenditures that they deem more important (eg, treatment of other diseases or costs of housing or education).

The PURE study did not gather data on other possible factors affecting medicine use, such as patients' attitudes and knowledge about their illness. These potential factors could explain some of the gaps in use even where medicines are available and affordable. However, given the very large effects of the availability and affordability of medicines on use that we noted, availability and affordability are likely to be essential factors influencing medicine use.

The medicines assessed in this paper have been shown to prevent recurrent cardiovascular disease events and reduce mortality rates, and are recommended for use in most clinical guidelines. However, these medicines are not available in a large proportion of communities in low-income and middle-income countries and if available they are not always affordable. Both low availability and affordability are associated with low use of these medicines. Unless both availability and affordability of these medicines are improved, their use is likely to remain low in most of the world.

Contributors

RKh wrote the analysis plan and had the primary responsibility of writing this paper. SY conceived and initiated the PURE study, supervised its conduct and data analysis, reviewed and revised all drafts of this manuscript, and oversaw the work of RKh. MM, AG, HS, and CC reviewed and commented on data analyses and drafts. SR coordinated the worldwide study and reviewed and commented on manuscript drafts. All other authors coordinated the worldwide study and reviewed and commented on drafts. All authors approved the final draft.

Declaration of interests

RKh reports grants from International Development Research Centre and the Population Health Research Institute, during the conduct of the study. MM reports travel expenses from the Population Health Research Institute, during the conduct of the study. CC reports grants from the Heart Foundation and the Australian National Health and Medical Research Council, and honorarium from AstraZeneca and Sanofi, outside the submitted work. All other authors declare no competing interests.

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