Chronic Diseases 4

Prevention of cardiovascular disease in high-risk individuals in low-income and middle-income countries: health effects and costs

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This is the fourth in a Series of five papers about chronic diseases

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In 2005, a global goal of reducing chronic disease death rates by an additional 2% per year was established. Scaling up coverage of evidence-based interventions to prevent cardiovascular disease in high-risk individuals in low-income and middle-income countries could play a major part in reaching this goal. We aimed to estimate the number of deaths that could be averted and the financial cost of scaling up, above current coverage levels, a multidrug regimen for prevention of cardiovascular disease (a statin, aspirin, and two blood-pressure-lowering medicines) in 23 such countries. Identification of individuals was limited to those already accessing health services, and treatment eligibility was based on the presence of existing cardiovascular disease or absolute risk of cardiovascular disease by use of easily measurable risk factors. Over a 10-year period, scaling up this multidrug regimen could avert 17·9 million deaths from cardiovascular disease (95% uncertainty interval 7·4 million–25·7 million). 56% of deaths averted would be in those younger than 70 years, with more deaths averted in women than in men owing to larger absolute numbers of women at older ages. The 10-year financial cost would be US$47 billion ($33 billion–$61 billion) or an average yearly cost per head of $1·08 ($0·75–1·40), ranging from $0·43 to $0·90 across low-income countries and from $0·54 to $2·93 across middle-income countries. This package could effectively meet three-quarters of the proposed global goal with a moderate increase in health expenditure.

There were an estimated 35 million deaths from heart disease, stroke, cancer, and other chronic diseases worldwide in 2005.[1] 80% of these deaths were in low-income and middle-income countries, and this proportion is projected to increase further in the coming decades.[2] A major driver of the rising burden is the epidemiological transition,[3] especially ageing of populations. Underlying social, environmental, and economic changes have led to increasing levels of major chronic disease determinants such as tobacco smoking, inadequate physical activity, unhealthy diets, excess bodyweight, and suboptimum levels of blood pressure, cholesterol, and plasma glucose.[4,5]

Key messages

- A global goal of reducing chronic disease death rates by an additional 2% per year was established in 2005
- Treatment of high-risk individuals with aspirin, blood pressure-lowering drugs, and cholesterol-lowering drugs to prevent cardiovascular disease is effective and cost effective. However, coverage in low-income and middle-income countries is low
- Scaling up a multidrug regimen targeted at individuals with existing cardiovascular disease or who are at high absolute risk of cardiovascular disease could avert almost 18 million deaths over the next 10 years in 23 low-income and middle-income countries
- The financial cost would be an average yearly cost of $1·10 per head, ranging from $0·43 to $0·90 across low-income countries and from $0·54 to $2·93 across middle-income countries
- This cost could effectively meet three quarters of the proposed global goal over the next 10 years

Proven cost-effective strategies are available for reducing exposure to chronic disease risk factors in low-income and middle-income settings,[6–9] including both population-wide and individual high-risk approaches. Scaling up these interventions is essential for achieving the goal of an additional 2% yearly reduction in rates of chronic disease deaths over the next 10 years.[1] Demonstrating the potential health effects and cost of scaling up is essential to build the political will for action, develop investment plans, and mobilise resources. The second paper in this Series covered the evidence base for preventing chronic disease,[10] and the third paper[11] covered population-wide strategies for preventing chronic disease. In this paper, we consider individual approaches, defined as interventions in which the primary actors are individual people and their health-care professionals.

The individual-based strategies with the greatest accumulated evidence of effectiveness are drugs to prevent cardiovascular disease: blood pressure-lowering drugs,[12,13] cholesterol-lowering drugs,[14] and aspirin.[15] Although these interventions are cost effective in low-income and middle-income countries[6,9] and are available in most markets, their current coverage in high-risk individuals in these settings remains low.[16] There is also likely to be abuse and waste in many settings. This situation represents a substantial lost opportunity for reducing the rising burden of chronic diseases.

	CMH health system strength category
Argentina	3
Bangladesh	2
Brazil	4
Burma	2
China	4
Colombia	2
Democratic Republic of the Congo	1
Egypt	4
Ethiopia	4
India	4
Indonesia	3
Iran	4
Mexico	4
Nigeria	1
Pakistan	2
Philippines	4
Poland	4
Russia	4
South Africa	1
Thailand	4
Turkey	4
Ukraine	4
Vietnam	4

CMH=Commission on Macroeconomics in Health. Categories of health system strength range from 1 to 4, where 1 is the most constrained and 4 the least constrained.

Table 1: **Countries that account for 80% of global chronic disease deaths in low-income and middle-income countries**

Unlike high-technology approaches, a simple multidrug regimen of aspirin, blood pressure-lowering drugs, and cholesterol-lowering drugs for individuals at high-risk of cardiovascular disease could more easily be brought to scale in low-income and middle-income countries, since it could be delivered mainly through primary health care or outpatient settings. Scale-up could be further facilitated by limiting screening of patients to those already accessing health services (opportunistic screening), and identifying high-risk individuals with an absolute risk approach.[17] Most people at high risk can be easily identified by their history of having had a heart attack, stroke, or other major vascular event. Others can be identified with easily measurable risk factors (eg, age, sex, blood pressure, body-mass index, tobacco use) that do not require expensive and time-consuming laboratory testing. Although ultimately these medicines could be combined into a single pill,[18–20] evidence for a combination pill is not yet definitive, nor is a cheap combination pill of aspirin and drugs for lowering blood pressure and cholesterol currently available.[21] In the meantime, the scaling up of proven individual drugs for prevention of cardiovascular disease should not be delayed.

Our aim was to establish the number of deaths between 2006 and 2015 that could be averted and the financial cost of scaling up a multidrug regimen for prevention of cardiovascular disease in a selection of low-income and middle-income countries. Countries were included in the analysis if they were classified as low-income or middle-income countries, and they accounted for at least 0·7% of the global disability-adjusted life-years (DALYs) attributable to chronic diseases for such countries.[4] 23 countries, accounting for 80% of global chronic disease deaths in all low-income and middle-income countries, were included (table 1). We adhered to the costing principles used in other studies that have estimated the worldwide costs of scaling-up health service delivery for other conditions.[22,23] A public provider perspective for costs was used, with costs reported in 2005 US$ over the period 2006 to 2015.

Definition of high-risk individuals

We defined high-risk individuals as those aged between 40 and 79 years who have had non-fatal coronary heart disease or a cerebrovascular event. Individuals within the same age range and without established disease were also deemed high-risk if they had an estimated absolute risk of dying from coronary heart disease or a cerebrovascular event of 15% or more over the next 10 years. Absolute risk was determined from country-specific risk charts, constructed as part of this analysis (see below), that relied on easily measurable risk factors only. Individuals with existing cardiovascular disease would receive aspirin, an angiotensin-converting-enzyme inhibitor, a β blocker, and a statin, whereas for those without existing cardiovascular disease but who are at high risk, a thiazide would replace the β blocker.[24] There is much debate about the choice of first-line blood pressure-lowering drugs in those without existing cardiovascular disease. The drugs listed here are simply illustrative and the general principle is that most people need two blood pressure-lowering agents. We assumed that patients who were initially without existing disease and were treated, but subsequently had an incident cerebrovascular event or non-fatal coronary heart disease, would be switched over to the regimen for those with existing disease. Individuals who were treated and adherent were assumed to be treated indefinitely.

Simulation model

A microsimulation model (webappendix) was used to create for each country a series of 10 000 individual life histories for each 5-year age-group and sex-group over the period 2006 to 2015. This simulation was done using information on the population distribution of risk factors, correlations between risk factor levels, associations between risk factors and disease, and population-level estimates of ischaemic heart disease, cerebrovascular events, and other mortality (table 2).[2,25,27–33] Age-specific and sex-specific trends in risk factor rates and mortality during this period were included by using information

See Online for webappendix

	Description	Source
Risk factor distribution		
Systolic blood pressure	Mean and SD (mm Hg) specific for country, sex, age, and calendar year	25
Total cholesterol	Mean and SD (mmol/L) specific for country, sex, age, and calendar year	25
Body-mass index	Mean and SD (kg/m^2) specific for country, sex, age, and calendar year	25
Current daily smoking	Prevalence specific for country, sex, age, and calendar year	25
Diabetes	Prevalence specific for GBD region, sex, and age	26
Coronary heart disease	Prevalence specific for GBD region, sex, and age	26
Cerebrovascular disease	Prevalence specific for GBD region, sex, and age	26
Risk factor correlations	Correlation matrix for risk factors above specific for region, sex, and age	Datasets available to the authors
Risk factor-disease associations		
Systolic blood pressure	Sex-and-age specific relative risk per mm Hg increase for ischaemic heart disease and cerebrovascular disease	27
Total cholesterol	Sex-and-age specific relative risk per mmol/L increase for ischaemic heart disease and cerebrovascular disease, adjusted for proportion of ischaemic versus haemorrhagic stroke	28
Current daily smoking	Age-specific relative risks of prevalent smoking for cerebrovascular disease	29
Diabetes	Sex-specific relative risks of prevalent diabetes for ischaemic heart disease and cerebrovascular disease	30,31
Coronary heart disease	Sex-specific relative risks of prevalent coronary heart disease for cerebrovascular disease and coronary heart disease death	32
Cerebrovascular disease	Sex-specific relative risks of prevalent cerebrovascular disease for ischaemic heart disease and death from cerebrovascular disease	33
Mortality		
Coronary heart disease	Mortality rates (ICD10 codes I20-I25) specific for country, sex, age, and calendar year	2
Cerebrovascular disease	Mortality rates (ICD10 codes I60-I69) specific for country, sex, age, and calendar year	2
Other mortality	Mortality rates from causes other than ischaemic heart disease and cerebrovascular disease specific for country, sex, age, and calendar year	2

GBD=Global Burden of Disease.

Table 2: **Main model parameters**

from the WHO Global InfoBase[25] and updated projections of the Global Burden of Disease database.[2] The model was implemented in Stata 9.2 (Stata Corporation, Texas, USA). An individual's yearly risk of coronary heart disease and cerebrovascular event was determined as a function of sex, age, continuous level of systolic blood pressure and total cholesterol, whether they currently smoke, and whether they have prevalent diabetes, coronary heart disease, or a cerebrovascular event. The 10-year combined risk of fatal coronary heart disease or cerebrovascular event for each individual in the simulation model was determined as a function of their yearly risk, assuming an exponential function.

Body-mass index is highly correlated with blood pressure, cholesterol, and diabetes. Previous studies, however, have shown no significant association between body-mass index and coronary heart disease and cerebrovascular events when adjusted for these factors.[34] On this basis, it has not been included as an independent predictor of an individual's risk of coronary heart disease and cerebrovascular events. In many low-income and middle-income countries, however, measuring blood cholesterol or plasma glucose for the diagnosis of diabetes might be too expensive or impractical. As such, although not included as an independent determinant of risk, we explicitly modelled each individual's body-mass index by incorporating known correlations of body-mass index with blood pressure, cholesterol, and diabetes (webappendix). Body-mass index is then used in the absolute risk charts as a proxy for cholesterol and diabetes because it is more easily measured.

Inevitably countries will adopt different risk prediction strategies, and the basic approach described here is only suggestive and not prescriptive. With more sophisticated algorithms that better target those at high risk, such as approaches that include measurement of cholesterol, fasting plasma glucose, or urine dipstick testing for glycosuria, both the costs and benefits can be expected to increase.

Absolute risk charts were generated by categorising the simulated population according to sex, age, smoking status (current smoker, non-smoker), systolic blood pressure (<120, 120–139, 140–159, 160–179, 180+ mm Hg), and body-mass index (<22·5, 22·5–24·9, 25·0–27·4, 27·5–29·9, 30+ kg/m^2). Risk charts were constructed by categorising the mean 10-year risk of fatal coronary heart disease or cerebrovascular events for each combination of the above risk factor strata into (i) greater than or equal to 15%; and (ii) less than 15% (figure 1).

Current coverage and estimated scale-up

Current coverage of the individual drugs was established from available sources.[16] For countries where estimates were not available, Global Burden of Disease regional averages of current coverage were used.

Scaling-up patterns used in this analysis are intended to suggest, not prescribe, how scale-up could be achieved. As with previous studies,[35] the Commission on Macroeconomics in Health (CMH) index was used to classify countries into four levels of health systems strength, where CMH1 is the most constrained and CMH4 the least constrained (table 1).[36] For countries for which there was no CMH value, we made assumptions based on total health expenditure per head.

For the most constrained countries (CMH1), we assumed a slow start due to a need for such countries to strengthen the health system in initial years before commencing scale-up of drug provision to the target coverage of 50% of those accessing health services by 2015 (figure 2). For CMH2 countries we assumed a sigmoid curve in line with the traditional shape of scale-up curves up to the target coverage of 50% of those accessing health services by 2015. Countries classified as CMH3 were assumed to need fewer initial investments; the model assumes an almost linear scale-up pattern, only slowing down near the target coverage of 80% of those accessing health services by 2015. For the least constrained (CMH4) countries,

rapid linear scale-up up to the target coverage of 80% by 2010 was assumed to be feasible.

The proportion of the population accessing health services each year, by age, sex, and country was estimated by using information from the 2002 World Health Survey.[37] For the 11 countries without World Health Survey results, the Global Burden of Disease regional population-weighted average was used.

Estimation of effectiveness and adherence

Effectiveness of the individual drugs in those with and without established disease was established in the same way as in modelling exercises[9] from previously published studies[12,14,15,38,39] (table 3). Since these studies indicated that the relative risk reduction of these drugs is roughly constant across major subgroups, the joint effect was estimated by multiplying the relative risks for each individual drug[40] and applied to an individual's estimated yearly probability of a fatal or non-fatal coronary heart disease or cerebrovascular event.

Studies of adherence under non-trial conditions to medication for cardiovascular disease prevention report long-term adherence rates of around 20–80%,[41–48] with the rate of discontinuation highest in the first 12 months after the start of treatment.[44,47] Individuals with established disease[41,42,47] and those with smaller out-of-pocket medication payments[42] are also more likely to be adherent. For the purposes of this analysis, we assumed that long-term adherence to the multidrug regimen in those with established disease would be 60% (varied between 40% and 80% in uncertainty analysis). For those without established disease we assumed a lower adherence rate of 40% (varied between 20% and 60% in uncertainty analysis). Of the individuals who discontinue treatment, we assumed that 70% of them would do so in the first year, 20% in the second year, and 10% in the third year of treatment.[44,47]

Estimation of costs

Costs were divided into patient and programme costs with inputs defined in accordance with current standards of treatment and based on general experience of health system requirements. Patient costs refer to costs at the point of delivery and include service delivery costs related to screening individuals and delivering and monitoring the intervention, drug costs, and laboratory testing (table 4). An additional 2 min was assumed to be required to assess treatment eligibility in screened individuals. For each treated individual, two additional service delivery contacts (15 min each) per year were also included. For drug costs we used median buyer prices (including buyer prices for various government health agencies) reported in the Management Sciences for Health (MSH) database for the year 2005,[49] with the low and high price used as the lower and upper ends of the uncertainty interval. A country-specific multiplier from the database WHO CHOosing Interventions that

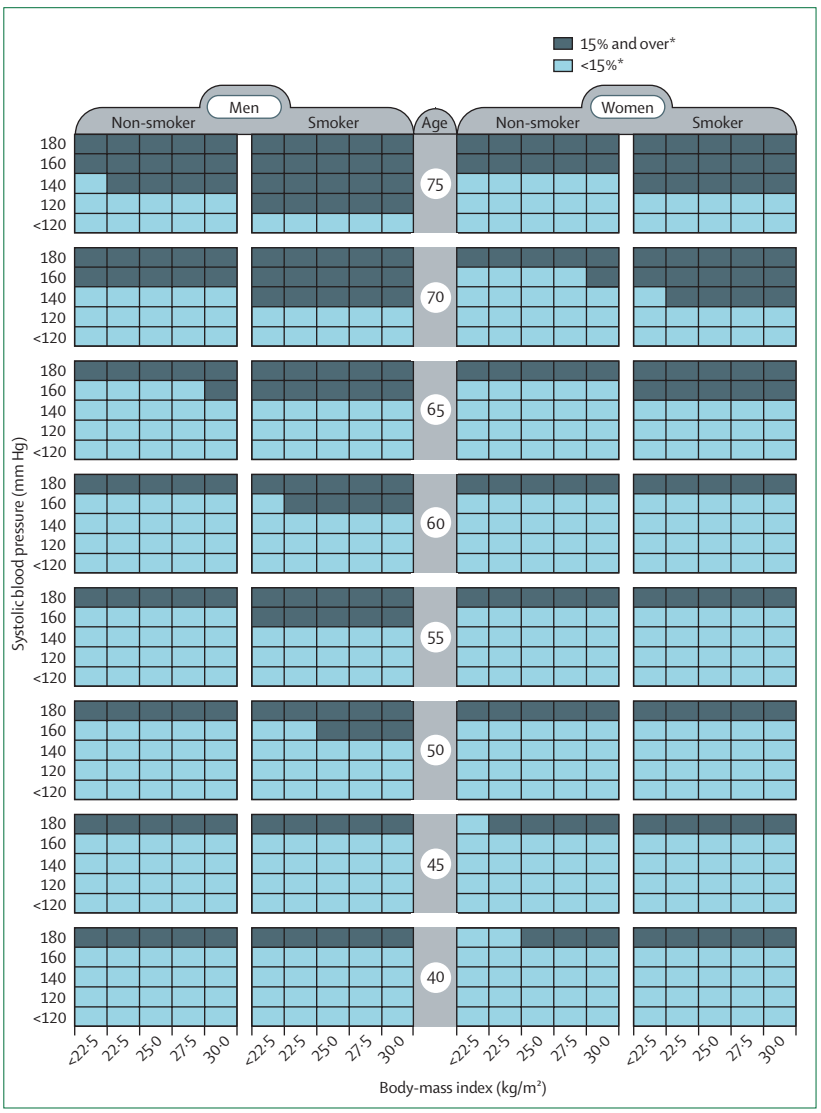

Figure 1: **Example of an absolute risk chart using age, sex, smoking status, systolic blood pressure, and body-mass index**

*Numbers are 10-year risk of fatal ischaemic heart disease or cardiovascular events in Mexico.

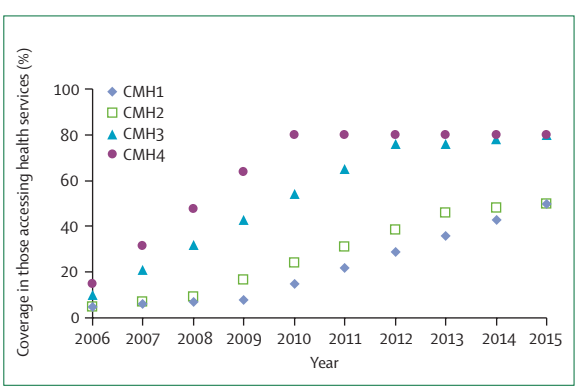

Figure 2: **Patterns of scale-up of a multidrug regimen for patients at high risk of cardiovascular disease by Commission on Macroeconomics in Health (CMH) category, expressed as a proportion of those accessing health services**

	Ischaemic heart disease (uncertainty range)	Cerebrovascular disease (uncertainty range)
Individuals without established disease		
Aspirin	0·68 (0·60–0·77)	0·84 (0·75–0·93)
Blood-pressure-lowering drug (ACE inhibitor and thiazide)	0·66 (0·60–0·71)	0·51 (0·45–0·58)
Cholesterol-lowering drug (statin)	0·64* (0·55–0·74)	0·94 (0·78–1·14)
Individuals with established disease		
Aspirin	0·66 (0·6–0·72)	0·78 (0·72–0·84)
β blocker	0·73† (0·75–0·87)	0·71 (0·68–0·74)
ACE inhibitor	0·80 (0·70–0·90)	0·68 (0·56–0·84)
Statin	0·71 (0·62–0·82)	0·81 (0·66–1·00)

*Risk is graduated by 0·89 at 1 year, 0·76 at 2 years, 0·67 at 3–5 years, and 0·64 in subsequent years. †Risk is graduated by 0·73 in first 3 years, 0·93 at 4–6 years, and 0·99 in subsequent years.

Table 3: **Effects of different individual drugs, measured as relative risk, on fatal and non-fatal ischaemic heart disease and cerebrovascular disease**

	Estimated cost in US$2005 (uncertainty range)	Source
Drug cost (per year)		
Aspirin (75 mg per day)	$1·59 ($0·22–$4·33)	49
Enalapril (10 mg per day)	$3·00 ($2·19–$8·07)	49
Hydrochlorothiazide (25 mg per day)	$1·10 ($0·66–$1·68)	49
Lovastatin (40 mg per day)	$37·99 ($8·99–$66·91)	49
Atenolol (50 mg per day)	$3·65 ($0·69–$6·14)	49
Laboratory tests (per year)		
Electrolytes	Varies by country	50
Renal function	Varies by country	50
Liver function	Varies by country	50
Service delivery (per year)		
2-min consultation (per screened individual)	Varies by country	50
Two 15-min consultations (per treated individual)*	Varies by country	50

*For people who report having contact with a medical doctor we assumed service delivery from the World Health Survey would be in the outpatient settings; for all others we assumed service delivery would be in the primary health care setting.

Table 4: **Patient cost parameters**

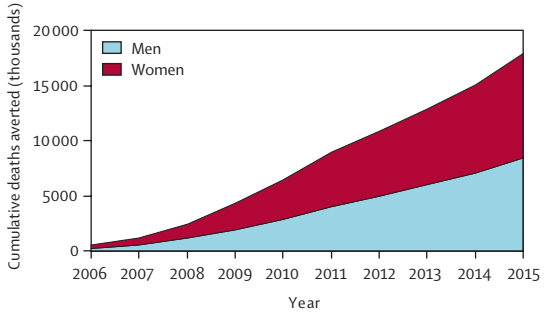

Figure 3: **Cumulative thousands of deaths averted with a multidrug regimen for the prevention of cardiovascular disease by sex, 2006–15**

are Cost Effective (WHO-CHOICE)[50] was used to account for drug transportation costs. Cost estimates do not account for storage, loss, or wastage of drugs. Laboratory tests for electrolytes, renal function, and liver function per treated individual per year were assumed to be needed.

Programme costs include those incurred at the administrative levels of districts, provinces, or countries. Programme costs include the additional yearly cost of national and provincial-level management teams responsible for administration, and for monitoring and assessment of the intervention. National and provincial-level workshops for strategic development and coordination purposes were assumed to take place every 2 years. In-service training of health-care workers to deliver the intervention was also done every year. Four 3-day training courses per health district per year with an average of 20 attendants were assumed. The cost of producing risk charts was also included. All programme costs were adjusted for the population-level coverage of the intervention. Country-specific unit prices for laboratory, service delivery, and programme-related costs were derived from the WHO-CHOICE database.[50] Since the intervention relies on opportunistic screening, and therefore existing health care infrastructure and health workers, we did not consider the additional costs of recruiting and training new health workers or building new health facilities.

Probabilistic, multivariate uncertainty analysis was used to establish the effect of uncertainty in both effect and cost parameters on the main outcome measures. Best-case and worst-case scenario analyses were also done on the cost of drugs, reduction in risk of drugs, and patient adherence.

Projected deaths averted

The programme scale-up was estimated to avert a cumulative 17·9 million deaths (95% uncertainty interval 7·4 million–25·7 million) over the period 2006 to 2015 (figure 3). This number amounts to almost a fifth of cardiovascular disease deaths that would have otherwise occurred in these countries during this time. Three-quarters of those treated would be younger than 70 years (table 5). 56% of deaths averted would be in people younger than 70 years (table 5); when measured in life-years or health-adjusted life-years gained, an even larger proportion of the health benefit can be expected to accrue at middle-ages. 54% of deaths averted would be from coronary heart disease and 46% of deaths averted would be from cerebrovascular events. With their large population sizes and high underlying risk of cardiovascular disease, the largest absolute number of deaths averted over the next 10 years would be in India (5·8 million), China (4·8 million), and Russia (1·7 million).

Projected financial cost of scaling up

The average cost per treated individual per year is $55; this translates into an estimated cumulative 10-year cost of scale-up of $47 billion (95% uncertainty interval $33 billion–$61 billion; figure 4). This cost includes resources spent on medicines ($32·1 billion, 68% of total costs), health service delivery for screening and treatment

	Person-years of treatment (thousands)		Number of deaths averted (thousands)	
	Men	Women	Men	Women
Age (years)				
40–49	73 024	41 560	515	207
50–59	111 167	133 213	1651	1365
60–69	123 900	152 660	3092	3139
70–79	94 400	127 900	3159	4780
All ages	402 490	455 333	8417	9491

Table 5: **Person-years of treatment and number of deaths averted by age and sex, 2006–15**

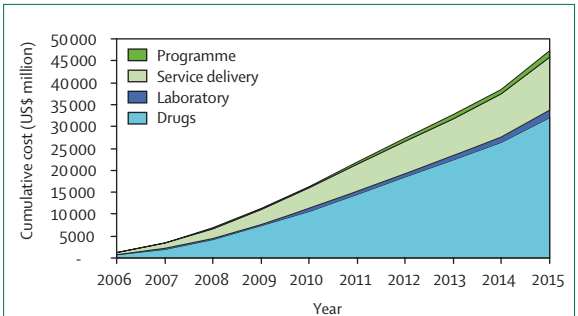

Figure 4: **Cumulative financial cost of scaling up a multidrug regimen for the prevention of cardiovascular disease, 2006–15**

($12·2 billion, 26% of total costs), laboratory testing ($1·5 billion, 3% of total costs), and programme costs ($1·4 billion, 3% of total costs) related to administration, training, monitoring, and assessment of the programme.

Total costs translate into an average yearly cost per head across the 23 countries of $1·08 (95% uncertainty interval $0·75–$1·40), ranging from $0·43 to $0·90 across low-income countries and from $0·54 to $2·93 across middle-income countries (figure 5). When expressed as a proportion of current yearly expenditure on health, however, the largest relative increases in total health expenditure are clearly required in low-income countries such as the Democratic Republic of the Congo and Burma, with smaller relative increases in expenditure required in middle-income countries such as Colombia (figure 6).

Best-case and worst-case scenario analysis

If the reduction in risk was the lower estimate for each of the individual drugs (table 3), then the cumulative number of deaths averted would decrease to 12·3 million. Conversely, if the reduction in risk was the upper estimate for each of the individual drugs (table 3) then the cumulative number of deaths averted would increase to 21·8 million.

If drug costs were the lowest buyer prices for each drug reported by MSH (table 4), the 10-year drug costs would be reduced by 74% to $8·4 billion, and total 10-year costs reduced by almost 50% to $23·5 billion or $0·54 per head. Conversely, if drug costs were the highest buyer price for each drug reported by MSH (table 4), the 10-year drug cost would increase by 83% to $58·7 billion and total 10-year costs would increase by 56% to $73·8 billion or $1·69 per head.

If long-term adherence was 40% in those with existing disease and 20% in those without existing disease then the cumulative number of deaths averted would be reduced to 12·6 million and total costs would decrease to $37·7 billion or $0·86 per head. If long-term adherence was 80% in those with existing disease and 60% in those without existing disease, then the cumulative number of deaths averted would increase to 23·1 million and total costs would increase to $57·1 billion or $1·31 per head.

Discussion

An opportunistic-screening-based multidrug regimen for the prevention of cardiovascular disease in high-risk individuals could avert almost 18 million deaths in 23 low-income and middle-income countries over the next 10 years. This intervention alone could avert almost a fifth of deaths from cardiovascular disease, which amounts to three quarters of the global goal of an additional 2% yearly reduction in chronic disease death rates in these countries. The financial resources needed to scale-up this intervention are an average investment per year of around $5 billion, or $1·08 per head. Although this amount is not insubstantial, it is less than or similar to estimated resource needs for other interventions.[22,23,35,51–55] This information provides a basis for developing country-specific agendas for action and investment plans by identifying the additional amount of resources that need to be mobilised. It suggests that in some settings monetary resources are not an insurmountable barrier to scaling up this strategy; low-income countries, however, will clearly need large amounts from external donors. In the Democratic Republic of the Congo, Burma, and Ethiopia, for example, this investment would represent around a tenth or more of current health expenditure.

There are several factors that any investment plan for this strategy should also consider. A key one will be ensuring access and supply of inexpensive cardiovascular medicines. This factor is crucial since drug costs, even at the generic-based median prices reported by MSH, account for two-thirds of the estimated resource needs. At the lowest drug price reported by MSH, the overall financial burden of this strategy could be substantially reduced to $0·56 per person per year. Availability of these multidrug regimens in the public sector, however, is low and, although availability is higher in the private sector, the price is substantially higher than prices reported by MSH and unaffordable for most individuals who need them.[56] A range of policies is required at both international and country levels, such as promoting local manufacturing of generic products, pooling procurements, and price regulation, to ensure availability of inexpensive, high-quality cardiovascular medicines.

Another crucial factor is the need for a functioning and effective primary health-care system to deliver this package

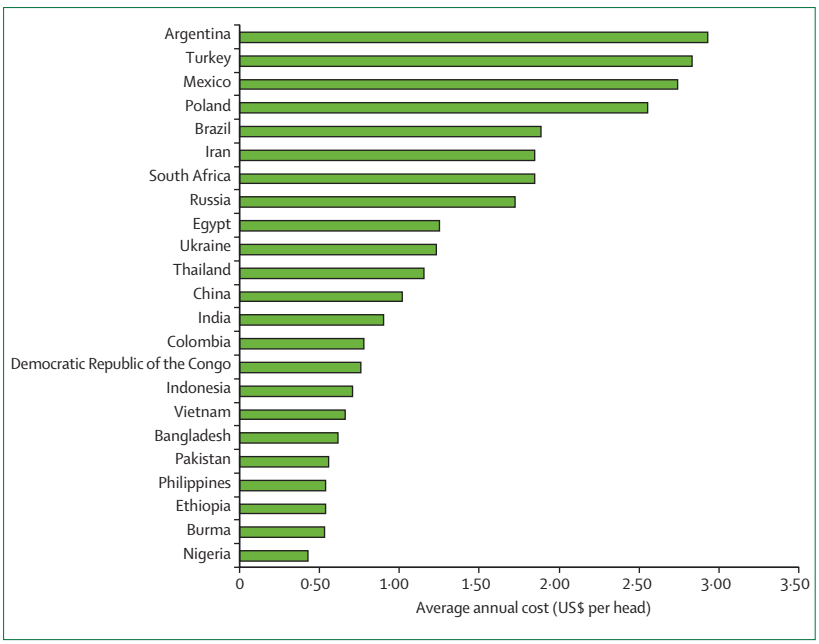

Figure 5: **Average yearly cost (US$ per head) of scaling up a multidrug regimen for the prevention of cardiovascular disease by country, 2006–15**

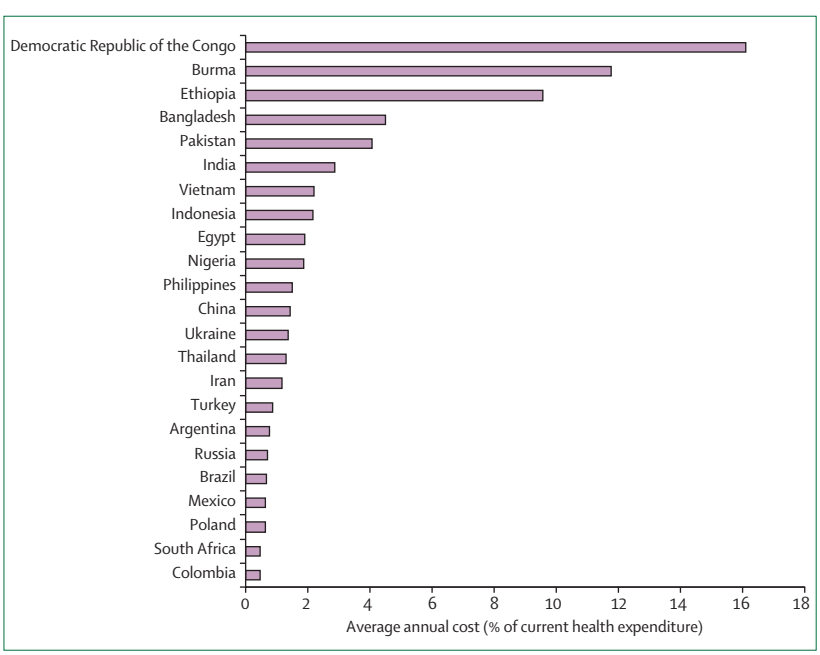

Figure 6: **Average yearly cost (proportion of current health expenditure) of scaling up a multidrug regimen for the prevention of cardiovascular disease by country, 2006–15**

of interventions. Particularly in the poorest settings, strengthening of the primary health-care system will be needed before scale-up can proceed. Related to this is the availability of human resources for health to screen and treat individuals. Non-physician health-care workers can be retrained to reliably and effectively assess and manage cardiovascular risks in primary health-care settings, even when there are no attending physicians.[57] The additional time demands of the strategy described here are also not too onerous, particularly because the risk factors (history of disease, smoking status, height, weight, and blood pressure) used to identify high-risk individuals are often part of standard clinical examinations.

A related issue is who pays for the intervention. If the financial burden is predominantly borne by the patient, this will also have a negative effect on coverage and patients' adherence,[41] particularly in low-income settings. Long-term adherence, even in high-income settings, to cardiovascular prevention medication is typically low[41–48] and its importance is highlighted by the sensitivity of the overall costs and health effects to this variable. Further research on mechanisms to improve patients' adherence[58,59] in developing countries could have a large effect on the success of the strategy proposed here.

The integration of service delivery of multidrug regimens for cardiovascular disease prevention with other ambulatory health services—ie, an opportunistic screening approach—aims to improve the cost-effectiveness and feasibility of this strategy, particularly during the early stages of scaling-up coverage. These benefits need to be balanced against a potential increase in health inequalities.[60] This problem is not unique; for example, the effect of scaling up antiretroviral therapy is receiving increasing attention.[61] Further research on the effect of different delivery methods for cardiovascular disease prevention on health inequalities are needed to inform implementation.

The acceptability of the proposed strategy for key stakeholders such as health-care professionals will probably be another key issue. Although there are legitimate concerns about large-scale medicalisation of the population, in the approach described here we focus only on those who are at highest risk in whom there is no controversy about indications for these medicines. The absolute risk stratification approach has been used for some time in settings such as New Zealand and western Europe;[17] however, this approach is counter to established clinical practice in most low-income and middle-income countries that tend to focus on risk-factor thresholds, even though risk-based care is more effective and cost effective.[6,9] Furthermore, although in this analysis we have kept the costs and demand on the health system to a minimum by limiting identification of high-risk individuals to easily measurable risk factors, some countries might choose to include cholesterol and blood sugar measurements, as is typically done in countries where the absolute risk approach is currently used. Countries might also choose to use waist circumference rather than body-mass index. Strategic development of an implementation plan that addresses these issues, in consultation with health practitioner groups, producers of national treatment guidelines, and civil society groups, will be an important component.

We have estimated the costs and health effects of scaling up a package of individual drugs. Combining these into one pill[18–20] would reduce the complexity of a

multidrug regimen and potentially improve adherence as well as reducing production, distribution, and storage costs. Evidence for the efficacy of a combination pill is not definitive,[21] nor is a four-drug combination currently available. Further information from current trials will provide eagerly awaited information on the effectiveness, safety, and adherence profile of a combination pill.

There are several limitations of the current analysis that should be considered. Although the best available data have been used, there is uncertainty, particularly in the least-developed settings where such data are scarce. For example, the estimates of patients' adherence to medication used in this analysis are derived from studies in high-income settings, and these might not be easily transferable to low-income and middle-income country settings. We have, however, done extensive uncertainty analysis to quantify a plausible range. We have also not measured potential cost savings of averting cardiovascular disease events that might offset the costs of this intervention, nor have we measured the potential costs of side-effects that might add to the costs of scaling up this intervention.

In terms of the scope and objectives of the analysis, the estimates provided here are intended to be suggestive, and not prescriptive, of how an individual high-risk approach for chronic disease could be scaled up. Country-specific approaches will, in reality, vary substantially from what is presented here. By focusing on aspirin, blood pressure-lowering drugs, and cholesterol-lowering drugs, our intention was not to discount the potential role of other individual approaches such as encouraging dietary, lifestyle, or other behavioural changes.[10] Rather, we hoped to highlight the potential of a simplified and more easily scaleable strategy for cardiovascular disease prevention in reducing the large health and economic burden attributable to chronic diseases in low-income and middle-income countries. The approach described here should also not be regarded as an alternative, but rather is complementary to population-wide approaches. For example, when the individual approach described here and the population-wide approaches described in the third paper in this Series[11] are combined, they could essentially meet the proposed global goal.

Chronic disease deaths are projected to continue to rise in low-income and middle-income countries. Urgent attention should be paid to increasing efforts to prevent this rising burden. Scaling up an individual prevention approach, based on opportunistic screening, identification of high-risk individuals by easily measurable risk factors, and treatment with a multidrug regimen, could avert almost a fifth of all deaths from cardiovascular disease, and could be realised with a moderate increase in health expenditure.

Contributors

SSL designed and did the analysis and drafted the paper. AR, TAG, and EG contributed to the framework and design of the study. TAG analysed risk factor correlations for South Africa. EG and RL analysed risk factor correlations for Mexico. KSR analysed risk factor correlations for India. FF analysed risk factor correlations for Iran. Revisions were done by SSL with input from all authors.

Conflict of interest statement

We declare that we have no conflict of interest.

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