Total cardiovascular risk approach to improve efficiency of cardiovascular prevention in resource constrain settings

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Abstract

Objectives: To determine the population distribution of cardiovascular risk in eight low- and middle-income countries and compare the cost of drug treatment based on cardiovascular risk (cardiovascular risk thresholds $\geq 30\%$ / $\geq 40\%$) with single risk factor cutoff levels.

Study Design and Setting: Using World Health Organization (WHO) and the International Society of Hypertension risk prediction charts, cardiovascular risk was categorized in a cross-sectional study of 8,625 randomly selected people aged 40–80 years (mean age, 54.6 years) from defined geographic regions of Nigeria, Iran, China, Pakistan, Georgia, Nepal, Cuba, and Sri Lanka. Cost estimates for drug therapy were calculated for three countries.

Results: A large fraction (90.0–98.9%) of the study population has a 10-year cardiovascular risk $< 20\%$. Only 0.2–4.8% are in the high-risk categories ($\geq 30\%$). Adopting a total risk approach and WHO guidelines recommendations would restrict unnecessary drug treatment and reduce the drug costs significantly.

Conclusion: Adopting a total cardiovascular risk approach instead of a single risk factor approach reduces health care expenditure by reducing drug costs. Therefore, limited resources can be more efficiently used to target high-risk people who will benefit the most. This strategy needs to be complemented with population-wide measures to shift the cardiovascular risk distribution of the whole population. © 2011 Elsevier Inc. All rights reserved.

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1. Introduction

Cardiovascular disease (CVD) is a leading cause of mortality and contributes to one-third of all global deaths [1,2].

About three-quarters of the global mortality and disease burden from CVD is borne by low- and middle-income countries (LMICs) [3–7]. Projections for global mortality and burden of disease from World Health Organization (WHO) estimates for 2002 indicate that CVD is likely to remain in the top three leading causes in 2030, regardless of the predictive scenarios used to derive these estimates [8].

The estimated 17 million CVD deaths every year are mainly because of heart attacks, strokes, and cardiac failure,

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What is new?

What was already known about this topic?

- Effective CVD prevention requires a paradigm shift from the treatment of single risk factors in isolation, to the management of total cardiovascular risk. This is supported by evidence that the cost-effectiveness of managing hypertension and hypercholesterolemia is influenced by the overall risk of CVD among patients, not simply by the level of the risk factor.
- Over the last decade, total risk assessment and management have been recommended by cardiovascular (CV) prevention guidelines in most high-income countries based on CV risk prediction equations/scores or charts derived from various sources in developed countries.
- Cost implications of changing the single risk factor approach to total risk factor approach has not been previously investigated in LMIC.

What we know after this paper.

- WHO and the International Society of hypertension (ISH) have generated 14 WHO/ISH Risk prediction charts to be used in countries of each specific WHO epidemiological sub-regions; these were generated using the best available data of countries of each specific WHO epidemiological sub-region.
- We used corresponding WHO/ISH Risk prediction charts in a representative population sample from 8 LMIC to 1) generate information on the distribution cardiovascular risk 2) estimate the cost of preventing heart attacks and strokes using the total cardiovascular risk approach and compare it with the cost of using the single risk factor approach.
- Our data show that the total risk approach would restrict unnecessary drug treatment and reduce the drug costs almost by 50%. This approach therefore provides a way to use limited resources more efficiently by targeting high risk people who will benefit the most.

which are caused by one or more cardiovascular risk factors including tobacco use, hypertension, hypercholesterolemia, and diabetes [3–5,7]. Heart attacks and stroke are preventable if cost-effective interventions that reduce cardiovascular risk can be made accessible to people [6,9]. Cardiovascular risk can be reduced through conventional management of single risk factors (hypertension, hypercholesterolemia, etc.) or by applying a total cardiovascular risk

approach. Often conventional single risk factor approach leaves patients at an unacceptably high risk of cardiovascular events because of suboptimal control and failure to address other coexistent risk factors. Effective CVD prevention requires a paradigm shift from the treatment of single risk factors in isolation to the management of total cardiovascular risk [6,9]. This is supported by evidence that the cost-effectiveness of managing hypertension and hypercholesterolemia is influenced by the overall risk of CVD among patients, not simply by the level of the risk factor [10].

The new WHO guidelines for primary prevention of CVD recommend total cardiovascular risk assessment before making decisions on drug treatment including lipid-lowering therapy [6]. According to the guidelines, the threshold for pharmacologic intervention in the public health sector needs to be decided by the Ministries of Health, based on available resources. It is recommended that pharmacologic treatment should be provided for all people at least when their calculated 10-year CVD risk is 30% or more. However, the risk threshold for drug treatment should be lowered to 20% if and when resources permit. For the development and implementation of programs for the prevention of heart attacks and strokes, it is necessary to have information on the percentage of the population in low, medium, or high cardiovascular risk categories. At present, these data are not available for LMIC, and the cost implications of shifting the cutoff for drug treatment have not been previously investigated. If available, such information would enable those involved in designing health care policy to decide on cutoff level for drug treatment based on available resources.

The World Health Organization and the International Society of Hypertension (WHO/ISH) risk prediction charts have been developed to specifically enhance implementation of an integrated and cost-effective approach by physician and nonphysician health workers to prevent heart attacks and stroke in low-resource settings. Several equations have been developed previously to predict individual absolute risk of a cardiovascular event over a specified time period [11–13]. Most of these equations have been derived from Caucasian populations in developed countries and are not necessarily valid in other populations. These charts are based on population-based observational data of risk factors and outcomes (heart attacks and stroke) analyzed longitudinally and have the same goal as existing risk equations such as those based on Framingham and SCORE [11,12]. The WHO/ISH risk prediction charts were based on standardized collection and assessment of data on risk factor prevalence and relative risk by WHO epidemiologic subregion from the Comparative Risk Assessment Project [14], conducted by the WHO. Absolute risk of cardiovascular event was determined by scaling individual relative risk to population incidence rates of major CVDs, estimated from the global burden of disease study [6,15,16]. The charts were designed to enable cardiovascular risk assessment and prediction in LMIC populations of all WHO subregions [6].

Data from the Asia Pacific Cohort Studies Collaboration [17–21] were used in the preparation of these charts.

In this study, the WHO/ISH risk predictor charts are applied to cross-sectional population samples from eight LMICs (Nigeria, Iran, China, Pakistan, Georgia, Nepal, Cuba, and Sri Lanka) that do not have locally developed algorithms to predict CVD risk. The major underlying assumption that relative cardiovascular risks and the correlations between risk factors are constant across different populations is supported by the recent case-controlled INTERHEART study [22]. The burden of coronary heart disease in the participating countries ranges from less than nine disability-adjusted life years (DALYs) lost per year in China and Sri Lanka to 20–29 in Georgia; the global burden of stroke ranges from less than nine DALYs per year in Cuba to 15–19 in Georgia. The number of deaths from coronary heart disease and stroke and the prevalence of major risk factors also vary among the participating countries [23]. These data will provide the baseline for further research to validate these charts for individual countries and confirm in these scenarios the effect and benefit of WHO recommendation on this subject [6,9,16].

The objectives of the present study were as follows

1. To determine the percentage of the population in each cardiovascular risk category based on the WHO/ISH risk prediction charts in a sample from eight LMICs selected from eight WHO epidemiologic subregions.
2. To compare the cost of giving drug treatment using cardiovascular risk thresholds ($\geq 30\%$) with single risk factor cutoff levels (blood pressure [BP] $\geq 140/90$ mm Hg and total cholesterol [TC] ≥ 6.0 mmol/L). Three participating countries with reliable data on prices of medicine have been used to address the second objective [24].

2. Methods

A cross-sectional study was conducted in defined areas in eight selected countries (Nigeria, Iran, China, Pakistan, Georgia, Nepal, Cuba, and Sri Lanka), selected from eight WHO epidemiologic subregions. The selection was based on the willingness of a team of investigators in each of these countries to conduct the study according to an agreed protocol. The estimates of the sample size were based on prevalence data on hypertension in the adult population of each selected area. A sample of individuals ($n = 8,625$) aged 40–80 years were drawn from the general population using a household survey. Samples were taken from geographically defined areas that have urban or rural and socioeconomic representation comparable with that of the general population, preferably within five miles (8.046 km) from the implementing institution. Cluster random sampling of households was used to select a sample of 1,000 households. The first 10 clusters were randomly selected from the geographically defined area using lists of municipal wards, Grama sevaka divisions, or other administrative units. Each cluster was large enough

for the random selection of 100 households based on electoral, census, or other lists of households.

Randomly selected households in each cluster were visited by a fieldworker who recorded the number of adults aged 40–80 years in each household and provided them with information about the purpose of the study. All residents of each of the selected household within the age group 40–80 years were invited to participate in the study by attending a health clinic. Participants were fasted (no food, nor drink, other than water in the 12 preceding hours). Basic information, including name, age, mailing, and contact information, of each eligible subject was entered into a household verification form. Those who were not 40–80 years old; those with confirmed coronary heart disease, cerebrovascular disease, or peripheral arterial disease; and those who did not give consent were excluded from the study. Among those excluded, there were more men than women and more young than elderly.

Invited participants were screened in 10 health clinics and seen by a physician who checked for a history of symptoms suggestive of stable angina, unstable angina, myocardial infarction, transient ischemic attacks, strokes, and peripheral vascular disease. Data on cigarette smoking and family history of premature CVD were collected using a standard data entry form. BP was measured using a standard mercury sphygmomanometer on the left arm after five minutes rest with the subject in the sitting position. The first and fifth phase of Korotkoff sounds were used for systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively. Two independent measurements were obtained with an interval of at least 10 minutes; the second measurement was taken for data analysis. In selected cases, an electrocardiogram was recorded based on the discretion of the physician to confirm coronary heart disease.

Fasting blood samples were taken from a finger puncture. Dry chemistry tests were used to measure TC and fasting blood glucose level using the Accutrend GC System (Accutrend GC; Roche Diagnostics, Germany). Measuring ranges of the device for glucose are 1.1–33.3 mmol/L and for cholesterol 3.88–7.76 mmol/L. Precision for glucose is $< 3\%$ and for cholesterol $< 5\%$.

The WHO/ISH risk prediction charts were used to grade cardiovascular risk [6,16]. These charts use age (**1**: 40–49; **2**: 50–59; **3**: 60–69; **4**: 70 years and older), sex (**0**: male; **1**: female), smoking (**0**: no; **1**: smoker or ex-smoker < 12 months), SBP (**1**: < 140 mm Hg; **2**: 140 to < 160 ; **3**: 160 to < 180 ; **4**: ≥ 180), blood cholesterol (**4**: TC, < 5 mmol/L; **5**: TC, 5 to < 6 ; **6**: TC, 6 to < 7 ; **7**: TC, 7 to < 8 ; **8**: TC, 8 and more), and presence or absence of diabetes (**0**: Yes, fasting blood glucose ≥ 7 mmol/L, 126 mg%; **1**: No, fasting blood glucose < 7 to grade cardiovascular risk) (Fig. 1). There are two sets, one for settings where blood cholesterol can be measured and the other for settings in which blood cholesterol cannot be measured [6]. In this study, we have used the charts for settings where blood cholesterol can be measured. The charts provide

Fig. 1. An example of the World Health Organization and the International Society of Hypertension (WHO/ISH) risk prediction chart for use in settings where blood cholesterol can be measured. (This chart can only be used for countries of the WHO region for Africa subregion D, in settings where blood cholesterol can be measured. There are two sets of charts. One can be used in settings where blood cholesterol can be measured, whereas the other in settings where blood cholesterol cannot be measured. Both sets are available according to the 14 WHO epidemiologic sub-regions [6].) WHO/ISH risk prediction chart WHO Region for Africa (subregion D) 10-year risk of a fatal or nonfatal cardiovascular event by gender, age, SBP, total blood cholesterol, smoking status, and presence or absence of diabetes mellitus. SBP, systolic blood pressure.

evidence-based recommendations on specific preventive actions to initiate and with what degree of intensity. The risk categories for 10-year combined acute myocardial infarction and stroke (fatal and nonfatal) are as follows: less than 10%, 10 to <20%, 20 to <30%, 30 to <40%, and ≥40% [6].

2.1. Statistical analysis

Epi Info version 3.3.2 for Windows and Excel file 2003 software (Microsoft Corp., Redmond, WA) were used for data entry, transfer, and processing. We used the per-protocol method for analysis of data. Cost estimates were

calculated for Pakistan, Nepal, and Sri Lanka, as an example. For estimating the cost of medicines per million per year (population aged 40 years or older), we used the lowest price generic preparation of each drug class available in the market (aspirin, thiazide diuretics, statins, and angiotensin-converting enzyme inhibitors). For calculation of costs based on the single risk factor approach, we included all people with BP $\geq 140/90$ and/or TC ≥ 6 mmol. For calculation of costs based on the cardiovascular risk approach, we included the following categories: (1) people with high cardiovascular risk ($\geq 30\%$), who are recommended four drugs [6]; and (2) people with cardiovascular risk $\geq 30\%$ and people with cardiovascular risk $< 30\%$ but with BP $\geq 160/100$, who are recommended antihypertensive treatment, and people with cardiovascular risk $< 30\%$ but with TC ≥ 8 mmol/L, who are recommended statin therapy.

3. Results

A total of 8,625 (3,295, 38.2% men) participants who satisfied the inclusion criteria from eight populations

participated in the study. The mean age was about 54.6 years (men, 55.6 years; women, 54.3 years) (Table 1). The participation rate was about 80.6% (range, 73.3% [Iran] to 90.0% [China]).

The prevalence of risk factors in the sample was as follows: fasting blood glucose > 7 mmol/L = 7.6%, smoking = 22.1%, total blood cholesterol ≥ 6 mmol/L = 12.1%, SBP ≥ 140 mm Hg = 33.3%, DBP ≥ 90 mm Hg = 26.9%, body mass index (BMI) 25–29.9 = 30.9, and BMI ≥ 30 = 21.3%. The prevalence of risk factors was highest in Georgia and Iran Table 2.

The distribution of cardiovascular risk in the population is shown in Table 3. Most people in all populations had a low ($< 10\%$) 10-year cardiovascular risk (range, 79.2% [Pakistan] to 96.1% [China]), and a large fraction (90.0–98.9%) of the study population had cardiovascular risk $< 20\%$. The percentage of the population with a cardiovascular risk ≥ 20 was less than 10% in all populations (Pakistan, 10.0%; Georgia, 9.6%; Nigeria, 5.0%; Cuba, 2.8%; Sri Lanka, 2.2%; Iran, 1.7%; and China, 1.1%) Table 3.

Table 1. Total cardiovascular risk thresholds for prevention of heart attacks and strokes in limited resource settings; implications for health policy (country, age and sex distribution, and mean age)

Country and WHO-subregion	Gender	Total <i>n</i> (%)	Age (years)				Mean (SD)
			40–49	50–59	60–69	≥ 70	
Nigeria/AFR D	Female	766 (70.5)	213	210	197	146	56.8 (110.1)
	Male	321 (29.5)	54	74	93	100	60.4 (19.7)
	Total	1,087	267	284	290	246	57.8 (110.1)
Cuba/AMR A	Female	835 (64.9)	302	233	229	71	54.6 (19.9)
	Male	452 (35.1)	162	107	146	37	55.4 (19.9)
	Total	1,287	464	340	375	108	54.9 (19.9)
Iran/EMR B	Female	595 (57.9)	283	217	86	9	50.6 (17.5)
	Male	432 (42.1)	159	140	116	17	53.9 (18.7)
	Total	1,027	442	357	202	26	52.0 (18.2)
Pakistan/EMR D	Female	620 (54.8)	262	164	145	49	52.7 (19.7)
	Male	512 (45.2)	131	159	160	62	56.4 (19.3)
	Total	1,132	393	323	305	111	54.4 (19.7)
Georgia/EUR B	Female	750 (66.2)	257	267	202	24	54.2 (18.9)
	Male	383 (33.8)	110	130	119	24	56.1 (18.8)
	Total	1,133	367	397	321	48	54.8 (18.9)
Sri Lanka/SEAR B	Female	800 (72.8)	273	305	203	19	54.9 (18.8)
	Male	299 (27.2)	98	98	88	15	53.6 (18.4)
	Total	1,099	371	403	291	34	54.0 (18.5)
Nepal/SEAR D	Female	316 (52.7)	129	97	78	12	52.8 (18.8)
	Male	284 (47.3)	100	90	73	21	54.3 (19.1)
	Total	600	229	187	151	33	53.5 (19.0)
China/WPR B	Female	648 (51.4)	195	248	176	29	54.3 (17.9)
	Male	612 (48.6)	182	259	147	24	54.9 (18.3)
	Total	1,260	377	507	323	53	54.6 (18.1)
Total <i>N</i> (%)	Female	5,330 (61.8)	1,914 (65.8)	1,740 (62.2)	1,316 (58.3)	359 (54.5)	54.3 (19.2)
	Male	3,295 (38.2)	996 (34.2)	1,058 (37.8)	942 (41.7)	300 (45.5)	55.6 (19.1)
	Total	8,625 (100.0)	2,910 (33.7)	2,799 (32.5)	2,258 (26.2)	659 (7.6)	54.6 (19.2)

Abbreviations: WHO, World Health Organization; SD, standard deviation; AFR D, WHO region for Africa subregion D; AMR A, WHO region for the Americas subregion A; EMR B, WHO region for Eastern Mediterranean subregion B; EUR B, WHO region for Europe subregion B; SEAR B, WHO region for South-East Asia subregion B; SEAR D, WHO region for South-East Asia subregion D; WPR B, WHO region for Western Pacific subregion B.

Table 2. Risk factors distribution by country

Country and WHO subregion	Risk factors, N (%)										
	Fasting blood glucose ^a		Smoker		Fasting blood cholesterol ^a		SBP ^b		DBP ^b		Total (%)
	<7.0	≥7.0	No	Yes	<6	≥6	<140	≥140	<90	≥90	
Nigeria/AFR D	1,063 (97.8)	24 (2.2)	764 (70.3)	323 (29.7)	1,035 (95.2)	52 (4.8)	642 (59.1)	445 (40.9)	730 (67.2)	357 (32.8)	159 (14.6)
Cuba/AMR A	1,220 (94.8)	67 (5.2)	918 (71.3)	369 (28.7)	1,211 (94.1)	76 (5.9)	846 (65.7)	441 (34.3)	991 (77.0)	296 (23.0)	258 (20.1)
Iran/EMR B	908 (88.4)	119 (11.6)	909 (88.5)	118 (11.5)	905 (88.1)	122 (11.9)	765 (74.5)	262 (25.5)	814 (79.3)	213 (20.7)	428 (41.2)
Pakistan/EMR D	977 (86.3)	155 (13.7)	880 (77.7)	252 (22.3)	942 (83.2)	190 (16.8)	766 (67.7)	366 (32.3)	905 (79.9)	227 (20.1)	175 (15.5)
Georgia/EUR B	1,006 (88.8)	127 (11.2)	1,008 (89.0)	125 (11.0)	794 (70.1)	339 (29.9)	538 (47.5)	595 (52.5)	610 (53.8)	523 (46.2)	641 (56.6)
Sri Lanka/SEAR B	990 (90.1)	109 (9.9)	1,033 (94.0)	66 (6.0)	947 (86.2)	152 (13.8)	771 (70.2)	328 (29.8)	819 (74.5)	280 (25.5)	71 (6.5)
Nepal/SEAR D	579 (96.5)	21 (3.5)	387 (64.5)	213 (35.5)	558 (93.0)	42 (7.0)	453 (75.5)	147 (24.5)	398 (66.3)	202 (33.7)	59 (9.8)
China/WPR B	1,222 (97.9)	38 (3.0)	820 (65.1)	440 (34.9)	1,193 (94.7)	67 (5.3)	973 (77.2)	287 (22.8)	1,034 (82.1)	226 (17.9)	47 (3.7)
Total	7,966 (92.4)	659 (7.6)	6,719 (77.9)	1,906 (22.1)	7,585 (87.9)	1,040 (12.1)	5,755 (66.7)	2,870 (33.3)	6,307 (73.1)	2,324 (26.9)	1,838 (21.3)

Abbreviations: WHO, World Health Organization; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

^a mmol/L.^b mm Hg.

If a $\geq 30\%$ threshold is used for drug treatment, 1.9% of the population requires drug treatment (range, 0.4% in China to 4.8% in Pakistan). Lowering the cardiovascular risk threshold (from 30% to 20%) would increase about two-fold the number of people requiring treatment (1.9% [167 of 8,625] to 4.5% [389 of 8,625]). The consequence is a substantial increase in health care expenditure Table 4. On the other hand, if a single risk factor approach is used and all those with hypertension (a persistent SBP ≥ 140 and/or DBP ≥ 90) and high fasting blood cholesterol (≥ 6 mmol/L) are treated, about 50.0% (4,414 of 8,625) of the sample would require drug treatment (39.1% antihypertensives and 12.1 lipid-lowering drugs); more than 10-fold higher than with the total cardiovascular risk approach ($\geq 30\% = 1.9\%$, $\geq 20\% = 4.5\%$) Table 4.

The risk–benefit ratio for drug treatment is higher when the cutoff used is $\geq 140/90$ and lower when the cutoff used is SBP ≥ 160 and/or DBP ≥ 100 mm Hg [6,25–29]. Younger adults with a BP $\geq 160/100$ are likely to fall into a risk category below 30% if they do not have other risk factors. Furthermore, there is also a low risk–benefit ratio with statin treatment if the cutoff used is TC ≥ 8 mmol/L [6,30,31]. Therefore, WHO guideline recommends drug treatment for those with a persistent elevated BP $\geq 160/100$ mm Hg and/or TC ≥ 8 mmol/L [6].

Including individuals with raised BP ($\geq 160/100$ mm Hg) but with a 10-year CVD risk $< 30\%$ or $< 20\%$ would increase the percentage of people requiring drug treatment to 15.5% and 16.0%, respectively. This figure is still three-fold less than with the single risk factor approach Table 4.

We compared the estimated annual cost of medicines per million population for implementing the total risk approach vs. the single risk factor approach in selected countries. The estimate shows that if the single risk factor approach is applied in Pakistan with its percentage of population at risk and the lower price of medicine in this country, the cost per million population (aged 40 years or older) of treating those with BP $\geq 140/90$ and blood cholesterol ≥ 6 mmol/L would be 27,128,625 US\$; if the absolute risk approach is used in Pakistan, the cost of treating those with 10-year risk of CVD $\geq 30\%$ per million population (aged 40 years or older) would be 5,431,200, about fivefold less. If we include those with BP $\geq 160/100$ mm Hg and blood cholesterol ≥ 8 mmol/L, but with 10-year CVD risk of less than 30% the cost would be 11,020,262, 2.3-fold less (Table 5). The estimated annual cost of medicines per million population in Nepal using the single risk factor approach would be 17,562,011 US\$. The cost decreases by about sevenfold (2,375,347 US\$) if using the 10-year risk of CVD $\geq 30\%$ and to about threefold less (5,817,625) if those with BP $\geq 160/100$ and blood cholesterol ≥ 8 mmol/L are included (Table 6). The estimated annual cost of medicines per million population in Sri Lanka using the single risk factor approach would be 3,472,610 US\$. The cost decreases by about 11-fold if a 10-year cardiovascular risk threshold 30% is used and to about 4.6-fold less if those

Table 3. Distribution of predicted 10-year cardiovascular risk (fatal or nonfatal) by gender in eight populations

Country and WHO subregion	Sex	10-year cardiovascular risk (% [n/N])				
		<10%	10% to <20%	20% to <30%	30% to <40%	≥40%
Nigeria/AFR D	Male	80.4 (258/321)	14.3 (46/321)	2.5 (8/321)	1.9 (6/321)	0.9 (3/321)
	Female	88.4 (677/766)	6.8 (52/766)	2.7 (21/766)	1.8 (14/766)	0.3 (2/766)
	Total	86.0 (935/1,087)	9.0 (98/1,087)	2.7 (29/1,087)	1.8 (20/1,087)	0.5 (5/1,087)
Cuba/AMR A	Male	83.4 (377/452)	11.9 (54/452)	3.3 (15/452)	0.9 (4/452)	0.4 (2/452)
	Female	93.1 (778/835)	4.9 (41/835)	1.0 (8/835)	0.4 (3/835)	0.6 (5/835)
	Total	89.7 (1,155/1,287)	7.4 (95/1,287)	1.8 (23/1,287)	0.5 (7/1,287)	0.5 (7/1,287)
Iran/EMR B	Male	93.5 (404/432)	5.3 (23/432)	0.5 (2/432)	0.5 (2/432)	0.2 (1/432)
	Female	94.1 (560/595)	3.9 (23/595)	1.7 (19/595)	0.2 (1/595)	0.2 (1/595)
	Total	93.9 (964/1,027)	4.5 (46/1,027)	1.2 (12/1,027)	0.3 (3/1,027)	0.2 (2/1,027)
Pakistan/EMR D	Male	71.5 (366/512)	13.7 (70/512)	7.4 (38/512)	2.7 (14/512)	4.7 (24/452)
	Female	85.6 (531/620)	8.4 (52/620)	3.4 (21/620)	1.1 (7/620)	1.5 (9/620)
	Total	79.2 (897/1,132)	10.8 (122/1,132)	5.2 (59/1,132)	1.9 (21/1,132)	2.9 (33/1,132)
Georgia/EUR B	Male	78.6 (301/383)	9.9 (38/383)	7.0 (27/383)	1.8 (7/383)	2.6 (10/383)
	Female	85.5 (641/750)	5.9 (44/750)	6.1 (46/750)	0.3 (2/750)	2.3 (17/750)
	Total	83.1 (942/1,133)	7.2 (82/1,133)	6.4 (73/1,133)	0.8 (9/1,133)	2.4 (27/1,133)
Sri Lanka/SEAR B	Male	95.3 (285/299)	3.0 (9/299)	1.0 (3/299)	— (0/299)	0.7 (2/299)
	Female	94.8 (758/800)	2.8 (22/800)	0.8 (6/800)	1.0 (8/800)	0.8 (6/800)
	Total	94.9 (1,043/1,099)	2.8 (31/1,099)	0.8 (9/1,099)	0.7 (8/1,099)	0.7 (8/1,099)
Nepal/SEAR D	Male	87.0 (247/284)	9.2 (26/284)	1.8 (5/286)	1.8 (5/286)	0.4 (1/284)
	Female	87.3 (276/316)	9.8 (31/316)	0.9 (3/316)	0.9 (3/316)	0.9 (3/316)
	Total	87.2 (523/600)	9.5 (57/600)	1.3 (8/600)	1.3 (8/600)	1.3 (4/600)
China/WPR B	Male	93.6 (573/612)	5.2 (32/612)	0.5 (3/612)	0.2 (1/612)	0.5 (3/612)
	Female	98.5 (638/648)	0.5 (3/648)	0.9 (6/648)	— (0/648)	0.2 (1/648)
	Total	96.1 (1,211/1,260)	2.8 (35/1,260)	0.7 (9/1,260)	0.1 (1/1,260)	0.3 (4/1,260)

Abbreviation: WHO, World Health Organization.

with BP 160/100 and blood cholesterol 8 mmol/L are also included in the treatment (Table 7). The cost estimation is different in the three countries because of the differences in the percentage of population at different levels of risk and the differences in the price of generic medicines. The focus of the study was on drug costs because it is the most important contributor to overall direct costs. We assume that other costs of service delivery, such as health facilities, follow-up, and wages of health workers, are +/− similar for both approaches of service delivery. Tables 5–7 also show the estimated number of people aged 40 years or older requiring drug treatment in these three countries. Information on the population distribution of cardiovascular risk and the level of resources available will enable policy makers to decide on the cutoff level (≥20% or ≥30% or ≥40%) at which drug treatment could be provided with public resources.

4. Discussion

Cardiovascular events are preventable by shifting the cardiovascular risk of populations to optimal distributions through population-wide strategies and strategies targeting high-risk groups [2,6,32,33]. There are two approaches to achieve this: one is a vertical single risk factor management addressing hypertension, hypercholesterolemia, and other

risk factors in specific programs. The other is the approach that takes into consideration age, gender, tobacco use, diabetes, BP, and blood cholesterol in computing the total cardiovascular risk. The latter approach enables treatment decisions to be made based on the predicted 10-year cardiovascular risk.

Our results demonstrate that using a single risk factor approach to manage individual cardiovascular risk factors to prevent heart attacks and strokes would cost more than when using the total risk approach. Therefore, when available resources are limited, the total risk approach enables more accurate targeting of high-risk groups when compared with a single risk factor approach [6,9,34]. In the present study, most participants (85.0% of the sample) have a low cardiovascular (<10%). More people are at low risk (<10%), than in developed countries [35,36]. The high percentage of the population at low risk (<10%) highlights the potential for reduction of cardiovascular risk through population wide cost-effective public health policies [6]. For these individuals, multiple drug treatment would not be justified based on current clinical trial evidence [6].

The percentage of people at high (≥30% to <40%) or very high (≥40%) risk (0.2–2.9% in ≥40% vs. 0.4–4.8% in ≥30%) is small. Individuals identified to have high risk (>30%) require multiple-drug therapy to prevent fatal and nonfatal cardiovascular events [6]. All drug classes used

Table 4. Total risk approach vs. single risk approaches (percentage of population requiring drug treatment)

Country and WHO subregion	Total/risk approach				Single risk approach		
	CV risk $\geq 30\%$		CV risk $\geq 20\%$		BP $\geq 140/90$ (SBP ≥ 140 + isolated raised DBP), %	TC ≥ 6.0 mmol/L, %	Total, %
	CV risk $\geq 30\%$ alone, %	CV risk $\geq 30\%$ + BP $\geq 160/100$ and/or TC > 8.0 mmol/L, %	CV risk $\geq 20\%$ alone, %	CV risk $\geq 20\%$ + BP $\geq 160/100$ and/or TC > 8.0 mmol/L, %			
Nigeria/AFR D (1,087)	2.3	23.3	5.0	23.3	48.1	4.8	52.9
Cuba/AMR A (1,287)	1.0	11.4	2.8	12.5	38.0	5.9	43.9
Iran/EMR B (1,027)	0.5	9.5	1.7	9.7	30.7	11.9	42.6
Pakistan/EMR D (1,132)	4.8	15.9	10.0	18.4	34.2	16.8	51.0
Georgia/EUR B (1,133)	3.2	32.7	9.6	32.1	58.3	29.9	88.2
Sri Lanka/SEAR B (1,099)	1.4	11.9	2.2	12.0	36.4	13.8	50.2
Nepal/SEAR D (600)	2.6	12.3	3.9	12.9	39.7	7.0	46.7
China/WPR B (1,260)	0.4	7.0	1.1	7.0	28.7	5.3	34.0
Total (8,625), % (n)	1.9% (167)	15.5 (1,337)	4.5% (389)	16.0 (1,380)	39.1 (3,374)	12.1 (1,040)	51.2% 4,414/8,625

Abbreviations: WHO, World Health Organization; CV, cardiovascular; TC, total cholesterol; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Isolated raised DBP = SBP < 140 with DBP ≥ 90 .

Table 5. Comparison of medicine costs (US\$) for implementing total risk approach vs. single risk factor approach (per million population per year) in Pakistan EMER D

Pakistan, EMER D	Percentage of population aged 40 years or older in each approach ^a	Number of people aged 40 years or older requiring drug treatment ^b	Number of people per million population (aged 40 years or older)	Estimated cost per million population per year (aged 40 years or older) ^c				
				Enalapril	Hydrochlorothiazide	Simvastatin	Aspirin	Total
Total risk approach	CV risk $\geq 30\%$ = 4.8%	3,190,641	48,000	2,190,000	219,000	2,847,000	175,200	5,431,200
	CV risk $< 30\%$ with BP $\geq 160/100$ = 10.9%	7,245,413	109,000	4,973,125	497,312	—	—	5,470,437
	or TC ≥ 8 = 0.2%	132,943	2,000	—	—	118,625	—	118,625
	Total = 15.9%	10,568,997	159,000	—	—	—	—	11,020,262
Single risk factor approach	BP $\geq 140/90$ = 34.2% ^d	22,733,314	342,000	15,603,750	1,560,375	—	—	17,165,125
	TC ≥ 6 mmol/L = 16.8% ^d	11,167,242	168,000	—	—	9,964,500	—	9,964,500
	Total	—	—	—	—	—	—	27,128,625

Abbreviations: CV, cardiovascular; TC, total cholesterol; BP, blood pressure; DBP, diastolic blood pressure; EMR D, WHO region for Eastern Mediterranean subregion D; SEAR D, WHO region for South-East Asia subregion D.

^a Source: Table 3.

^b Ministry of Population of Pakistan 2006 number of people aged 40 years or older = 66,471,681.

^c Price for 100 tablets (US\$): Enalapril 10 mg (12.5); Hydrochlorothiazide 25 mg (1.25); Simvastatin 10 mg (16.25); Aspirin 75 mg (1.00); one tablet per day.

^d Source: Table 2, isolated DBP ≥ 100 = 1.9%.

Table 6. Comparison of medicine costs (US\$) for implementing total risk approach vs. single risk factor approach (per million population per year) in Nepal, SEAR D

Nepal, SEAR D	Percentage of population aged 40 years or older in each approach ^a	Number of people aged 40 years or older requiring drug treatment ^b	Number of people per million population (aged 40 years or older)	Estimated cost per million population per year (aged 40 years or older) ^c				
				Enalapril	Hydrochlorothiazide	Simvastatin	Aspirin	Total
Total risk approach	CV risk $\geq 30\%$ = 2.6%	518,356	26,000	609,258	304,629	1,339,988	121,472	2,375,347
	CV risk $< 30\%$ with BP $\geq 160/100$ = 9.5%	1,893,994	95,000	2,226,135	1,113,067	—	—	3,339,202
	or TC ≥ 8 = 0.2%	39,874	2,000	—	—	103,076	—	103,076
	Total = 12.3%	2,452,224	123,000	—	—	—	—	5,817,625
Single risk factor approach	BP $\geq 140/90$ = 39.7% ^d	7,914,901	397,000	9,302,901	4,651,450	—	—	13,954,351
	TC ≥ 6 mmol/L = 7.0% ^d	1,395,574	70,000	—	—	3,607,660	—	3,607,660
	Total	—	—	—	—	—	—	17,562,011

Abbreviations: CV, cardiovascular; TC, total cholesterol; BP, blood pressure; DBP, diastolic blood pressure.

^a Source: Table 3.

^b The 2001 census number of people aged 40 years or older = 19,936,778.

^c Price for 100 tablets (US\$): Enalapril 10 mg (6.42); Hydrochlorothiazide 25 mg (3.21); Simvastatin 10 mg (14.12); Aspirin 75 mg (1.28); one tablet per day.

^d Source: Table 2, isolated DBP ≥ 100 = 15.2%.

Table 7. Comparison of medicine costs (US\$) for implementing total risk approach vs. single risk factor approach (per million population per year) in Sri Lanka, SEAR B

Sri Lanka, SEAR B	Percentage of population aged 40 years or older in each approach ^a	Number of people aged 40 years or older requiring drug treatment ^b	Number of people per million population (aged 40 years or older)	Estimated cost per million population per year (aged 40 years or older) ^c				
				Enalapril	Hydrochlorothiazide	Simvastatin	Aspirin	Total
Total risk approach	CV risk $\geq 30\%$ = 1.4%	88,284	14,000	47,523	9,709	201,334	62,853	321,419
	CV risk $< 30\%$ with BP $\geq 160/100$ = 10.5% ^c	662,130	105,000	356,422	72,817	—	—	429,239
	or TC ≥ 8 = 0.0%	0	0	—	—	0	—	0
	Total = 15.9%	10,568,997	123,000	—	—	—	—	750,658
Single risk factor approach	BP $\geq 140/90$ = 36.4% ^d	2,295,384	364,000	1,235,598	252,434	—	—	1,488,032
	TC ≥ 6 mmol/L = 13.8% ^d	870,228	138,000	—	—	1,984,578	—	1,984,578
	Total	—	—	—	—	—	—	3,472,610

Abbreviations: CV, cardiovascular; TC, total cholesterol; BP, blood pressure; DBP, diastolic blood pressure.

^a Source: Table 3.

^b Latest estimate available, year 2006 number of people aged 40 years or older = 6,306,000.

^c Price for 100 tablets (US\$): Enalapril 10 mg (0.93); Hydrochlorothiazide 25 mg (0.19); Simvastatin 10 mg (3.94); Aspirin 75 mg (1.23); one tablet per day.

^d Source: Table 2, isolated DBP ≥ 100 = 6.6%.

for this purpose are off patent, and this approach is cost-effective even in low-income countries if appropriate policies are in place to procure and distribute generic medicines [1,24]. Despite medicines being a major contributor to health care costs, some middle-income countries may be able to lower the threshold for drug treatment to $>20\%$ and provide medicines in the public sector for those who qualify for treatment. We did not find that reducing the cardiovascular risk threshold for drug treatment from 30% to 20% in LMIC populations substantially increased the cost of treatment. However, as the threshold for drug treatment is lowered, there is a concomitant increase in health benefits and a modest increase in expenditure to obtain each additional unit of health benefit [10].

In most LMICs, public spending on health is inadequate, and there is excessive reliance on out-of-pocket payment as a source of health financing [37]. In these settings, prevention of heart attacks, strokes, and dialysis for kidney disease is vital to prevent costly hospital health care that result in catastrophic health expenditure for people. Therefore, it is essential that at least people with $\geq 40\%$ 10-year cardiovascular risk are given drug treatment to avoid catastrophic events. Furthermore, the drug treatment threshold need to be adjusted to suit the country context to use limited public resources equitably and target people who are at highest risk, who are likely to benefit the most.

When a single risk factor approach is used, particularly in countries with inadequate investments in health, a much greater percentage of the population at risk would be prescribed drug treatment. The consequent escalation of health care costs would be prohibitive and would contribute to the widening of already existing disparities. Furthermore, the use of the single risk factor approach may result in people at low risk being treated despite a low risk–benefit ratio. As was illustrated here, when a single risk factor approach is used, nearly 40–45% of population aged 40 years or older would require drug treatment (39.1% antihypertensives and 12.1% lipid-lowering drugs). Adopting a total risk approach at a threshold $\geq 30\%$ (1.9%) or $\geq 20\%$ (4.5%) would restrict the percentage of people on drug treatment to 1.9% and 4.5%, respectively. If those with a persistently elevated BP $\geq 160/100$ mm Hg and/or TC ≥ 8 mmol/L (but with 10-year CVD risk of less than $<30\%$) are added to those with a total risk $>30\%$, as recommended in the WHO CVD prevention guideline [6], the percentage of people requiring drug treatment would increase to 15%. This percentage is still much less than for the single risk factor approach.

The estimated annual cost of medicines per million population for implementing the total risk approach vs. the single risk factor approach was calculated for three selected countries with different price structure for medicines.

Several publications have reported the limited cost-effectiveness of the simple risk factor approach. On the other hand, the implementation of the total cardiovascular risk is more cost-effective, the cost-effectiveness increases as the

threshold is raised [1,6,10,38–41]. For example, Baker et al. [41] reports setting the threshold for treatment at a 5-year risk of disease of 20% leads to about a 10% net reduction in patients for whom drug treatment would be recommended; However, the total risk approach still averted almost 200 additional disease events over 5 years compared with single risk factors approach to treatment. These data are robust across several estimates of drug efficacy and of treatment costs [42]. Developing countries should encourage the use of inexpensive drugs that are generally available as generic formulations for prevention of CVD.

The objective of WHO recommendations [6] to base drug treatment decisions on total risk is to target limited resources on people with moderate to high cardiovascular risk for reducing premature morbidity, mortality, and disability because of cardiovascular events [43–50]. Those at high CVD risk would benefit more, in terms of number of events avoided because the relative risk reduction would be applied to a higher baseline risk [51].

The cost-effectiveness of treatment is determined by the relationship between the benefits obtained and the expenditure. The prevalence of the condition and total costs of treatment in a specific setting are directly related to the affordability. In many LMICs, interventions that are cost-effective may not be implemented, as they are not affordable. As hypertension is a highly prevalent condition for many LMIC with a health expenditure of less than 100 US\$ per capita, only a total risk factor approach may be affordable. The data presented here are important because for the first time, data on total cardiovascular risk distribution in some LMIC are made available. The economic impact of the sequelae of CVD is particularly serious in LMIC where the out-of-pocket expenditures are high. When a single risk approach is used, there is also the tendency to not treat with medicines the individuals who have a high cardiovascular risk because of mild–modest elevation of multiple risk factors (i.e., a 65-year-old male smoker with a BP of 144/94 mm Hg and TC of 5.5 mmol/L has a 10-year cardiovascular risk 30% to $<40\%$ but is unlikely to be treated if a single risk approach is used) [6].

The social burden of premature death, disability from CVD, and escalating costs to provide care for those suffering from CVD are development barriers and require urgent intervention by policy makers. Clearly, cardiovascular risk distribution of the population should be lowered through national health policies targeting the whole population and those at high risk. Population-wide strategies need to address tobacco use, overweight/obesity, and poor intakes of dietary fruits, vegetables, and levels of physical activity. Simultaneously, those at high risk need to be identified and targeted through health systems using cost-effective and integrated approaches [6]. Both nonpharmacologic and pharmacologic management need to be appropriately combined. All those at risk should be offered counseling and support to adopt healthy lifestyles.

Over the last decade, total risk assessment has been adopted by a variety of national and international guidelines, supporting the above thesis that management and treatment decisions should be based on total risk rather than on single risk factor approaches [33,34,41].

5. Conclusions

The findings of this study have important policy implications particularly for settings in which resource constraints are a major barrier for prevention of CVD. First, a total risk approach compared with a single risk factor approach reduces health care expenditure by reducing drug costs. Because the funds required for the former approach is less than that for the latter, limited resources can be more efficiently used if the total risk approach is used. Furthermore, this approach enables better targeting of those who are most likely to develop heart attacks and strokes. In addition, the high percentage of people with low–moderate cardiovascular risk demands that strategies targeting high-risk individuals be complimented with public policies that reduce the cardiovascular risk of the whole population.

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