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Estimation of total cardiovascular risk using the WHO/ISH CVD prediction charts and comparison of population-level costs based on alternative drug therapy guidelines in Bangladesh

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3 1 **Estimation of total cardiovascular risk using the WHO/ISH CVD prediction charts and**
4 2 **comparison of population-level costs based on alternative drug therapy guidelines in**
5 3 **Bangladesh**
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9 5 Running title: Total cardiovascular risk approach in Bangladesh

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Abstract

Objective: The objective this study is to apply estimate the population distribution of 10-year cardiovascular disease (CVD) risk among Bangladeshi adults aged 40 years and above, using the WHO recommended WHO/ISH CVD prediction charts. Additionally, we compared the cost of pharmacologic treatment based on CVD risk (cardiovascular risk threshold $\geq 30\%$ / $\geq 20\%$) to single risk factor (hypertension) cutoff levels for pharmacologic intervention in Bangladesh.

Study Design: Cross-sectional, population-based study

Setting and Participants: In 2013, we collected data from a nationally representative cross-sectional study of adults aged ≥ 40 years from urban and rural areas of Bangladesh ($n = 6189$). Using the World Health Organization / International Society of Hypertension (WHO/ISH) risk prediction charts, CVD risk was calculated and categorized as low($<10\%$), moderate($10\text{-}<20\%$), high($20\text{-}<30\%$), and very high risk($\geq 30\%$). We estimated drug therapy costs using the lowest price of each drug class available(aspirin, thiazide diuretics, statins, and angiotensin-converting enzyme inhibitors). We compared the total cost of drug therapy using the total risk vs. single risk factor approach.

Primary Outcome Measures: Our primary outcome was 10-year CVD risk categorized as low($<10\%$), moderate($10\text{-}<20\%$), high($20\text{-}<30\%$), and very high risk($\geq 30\%$).

Results: The majority of adults (85.2%, 95% CI: 84.3–86.1) have a 10-year risk of CVD of less than 10%. The proportion of adults with a 10-year CVD risk of $\geq 20\%$ and $\geq 30\%$ was 1.8% and 0.6%, respectively. Using the total risk approach would reduce drug costs per million population

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3 66 to \$635,976 (risk of $\geq 20\%$) or \$173,448 ($\geq 30\%$) for CVD treatment and prevention in
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5 67 comparison to using the single risk factor approach (\$5,665,968).
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7 68

9 69 Conclusion: To reduce health care expenditure for the prevention and treatment of CVD in
10
11 70 Bangladesh, a total risk approach using the WHO/ISH risk prediction chart may lead to cost-
12
13 71 savings and potentially improved treatment coverage.
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15 72

16 73 **Keywords:** non-communicable diseases, Bangladesh, cardiovascular disease, pharmacologic
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18 74 intervention, cost, chronic disease
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3 92 **Article Summary**
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5 93 **Strengths and Limitations of the Study**
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- 8 94 • This study utilized a multistage, geographically clustered, probability-based sampling
9
10 95 approach to produce nationally representative data for Bangladesh of adults aged 40
11
12 96 years and above.
13
- 14 97 • Currently, Bangladesh has not incorporated clinical guidelines for screening or treatment
15
16 98 of risk factors based on absolute CVD risk scores, or estimation of the population
17
18 99 distribution of CVD risk over time. This study provides evidence for incorporating the
19
20 100 WHO/ISH CVD Risk Prediction Charts and potential cost-savings of strategy
21
22 101 implementation.
23
- 24 102 • The WHO/ISH CVD Risk Prediction Charts should be applied to a population who have
25
26 103 not experienced a CVD event in the past. We were unable to confirm the medical history
27
28 104 of participants using medical charts or health records and relied on self-report, leading to
29
30 105 the potential for measurement error and recall bias.
31
32
- 33 106 • Our cost estimates were based on the prevalence of each risk approach in our study
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35 107 sample. Although we present the total number of people estimated to require drug
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37 108 treatment using 2016 census data, we were unable to identify population estimates of
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39 109 only those at risk of their first CVD event due to lack of surveillance data.
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115 **Background**

116 Globally, cardiovascular disease (CVD) is the leading cause of death and
117 disproportionately impacts low- and middle-income countries (LMICs), where over 75% of CVD-
118 related deaths occur¹. People living in LMICs are at high risk of developing CVD due to the
119 absence of integrated primary care for early detection and prevention of CVD-related risk
120 factors. Limited access to primary care and the growing burden of CVDs is a significant cause of
121 poverty in LMICs and hinders the macroeconomic development of many countries². LMICs are
122 estimated to experience cumulative economic losses exceeding 7 trillion US dollars over the
123 next 15 years due to morbidity and mortality caused by noncommunicable diseases, including
124 CVD³. As such, the significance of the CVD epidemic has gained increasing international
125 recognition over the past decade, leading to the development of several international guidelines
126 for CVD control and prevention⁴.

127 In 2007, the World Health Organization (WHO) published pocket guidelines, including
128 CVD risk prediction charts, designed for health care workers in LMICs to guide patient 10-year
129 risk stratification for heart attack or stroke. There are two possible strategies suitable for a low
130 resource setting to assess the risk of a cardiovascular event and identify those at high risk of a
131 fatal CVD outcome: 1. Utilize a single risk factor management strategy, which focuses on one
132 condition at a time, such as hypertension; 2. Utilize a more holistic approach considering
133 several risk factors such as age, tobacco use, gender, diabetes diagnosis, blood pressure, and
134 blood cholesterol when measured. Through the total risk approach, pocket guidelines help to
135 identify high-risk patients that are in imminent danger of a heart attack or stroke for timely
136 pharmacologic treatment or surgical interventions. Currently, individuals in LMIC's, including
137 Bangladesh, are often offered pharmacologic interventions based on the presence of single
138 CVD risk factors, such as high blood pressure. However, the single risk factor approach can
139 result in overtreatment or neglecting to treat those with an overall higher CVD-risk based on
140 CVD risk factors. Applying the total risk approach via the WHO/ISH prediction charts in a

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3 141 nationally representative sample may provide an opportunity to estimate population-level
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5 142 distribution of CVD risk and inform CVD treatment policy recommendations ^{5 6}.

7 143 Currently, Bangladesh has not incorporated clinical guidelines for screening or treatment
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9 144 of risk factors based on absolute CVD risk scores, or estimation of the population distribution of
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11 145 CVD risk over time. Data are needed to support the implementation of the WHO/ISH prediction
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13 146 charts among the Bangladeshi population and demonstrate the benefit of the WHO
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15 147 recommendation on CVD prevention. Prior studies conducted in Bangladesh have estimated
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17 148 CVD risk among adults residing in rural areas only and have not included a nationally
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19 149 representative population ⁷⁻⁹. Additionally, no prior studies have estimated the potential costs of
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21 150 pharmacological treatment for CVD in Bangladesh using either the single risk factor or total risk
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23 151 approach. As such, our objective was to assess the distribution of absolute CVD risk among a
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25 152 nationally representative sample of Bangladeshi adults using the WHO/ISH risk prediction chart
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27 153 recommended for the WHO South and South-East Asian Region (SEARO). We also compared
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29 154 the costs of drug treatments for CVD prevention using the total cardiovascular risk thresholds
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31 155 ($\geq 20\%$ and $\geq 30\%$) and with single risk factor cutoff levels (blood pressure $\geq 140/90$ mm Hg).
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37 157 **Methods**

38 39 158 Study design and setting

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41 159 Data for the current study were analyzed from a population-based cross-sectional study
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43 160 conducted from September to December 2013 to assess the burden of blindness and low vision
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45 161 among adults (men and women) aged 40 years and above in Bangladesh. The target population
46
47 162 of this survey included men and women residing in Bangladesh over the age of 40 years. The
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49 163 exclusion criteria included tourists and the institutionalized, such as residents of a military base,
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51 164 hospital, prisons, nursing homes, and other such institutions. We obtained ethical approval for
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53 165 this study from the Institutional Review Board of the National Institute of Ophthalmology. We
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55 166 provided participants with detailed study information using a printed handout prepared in
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2
3 167 Bengali to inform them of the objective of the study. Written consent was obtained from
4
5 168 participants through signature or, if not possible, through thumbprint.
6

7 169 Sampling Frame

9 170 We adopted a multistage, geographically clustered, probability-based sampling
10
11 171 approach to obtain a nationally representative sample of Bangladesh, as previously described
12
13 172 ¹⁰⁻¹². Population statistics were obtained using the 2011 national census conducted by the
14
15 173 Bangladesh Bureau of Statistics (BBS) to create the sample frame ¹³. The sampling frame
16
17 174 included 64,407 primary sampling units (PSUs) covering all seven divisions of the country. We
18
19 175 randomly selected seventy-two PSUs (25 urban and 47 rural) from seven divisions, with the
20
21 176 probability of selection proportional to the population size of each division. In each PSU, we
22
23 177 selected 100 consecutive households as the secondary sampling unit.
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25

26 178 For each household, a trained field data collector approached the head of the household
27
28 179 or the family member most knowledgeable of the residents to screen for eligible participants.
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30 180 The respondent for screening was asked to describe the composition of household residents
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32 181 who considered the home to be their primary place of residence as of the night before. A list
33
34 182 was composed and ordered from youngest to oldest age in years starting from 40 years. Using
35
36 183 the list of eligible residents, we used the Kish table approach to randomly select one respondent
37
38 184 from each home. The respondent was asked to come to a nearby health center the next day to
39
40 185 administer the survey by trained study interviewers and undergo the relevant medical
41
42 186 examination by the study physician. Based on the medical review, participants were followed-up
43
44 187 with by the providers at the health center for treatment, when appropriate.
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49 189 Patient and public involvement

51 190 There was no patient or public involvement in the implementation of this study or interpretation
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53 191 of analytic results.
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193 Data Collection

194 To ensure effective and uniform data collection, field interviewers underwent a 7-day
195 training on the interview process and methodology by the study ophthalmologists and
196 epidemiologists. The training included an in-depth review of the survey content and protocol for
197 completing the demographic information interview schedule questionnaire (a modified
198 WHO/PBL Version III). We provided a detailed survey protocol manual outlining the survey
199 activities, the questionnaire interview, and information about the duties and responsibilities of all
200 survey personnel to each member of the data collection team.

201 Demographic data were obtained, including age, sex, marital status, educational level,
202 and occupation, using a structured questionnaire survey. Data regarding tobacco use, health
203 history, and treatment history were also collected. Participants were asked if they smoked (e.g.
204 cigarette, hookah, pipe) or if they used smokeless tobacco (e.g. chewing tobacco, jorda, white
205 lead) to assess history of tobacco use. Medical history for a prior diagnosis of high blood
206 pressure or hypertension, diabetes, renal disease, or any cardiovascular diseases by a health
207 care provider was obtained from each participant. Medication history was obtained based on
208 self-report, including medication for high blood pressure, diabetes, malaria, steroids,
209 tuberculosis, and among women, history of oral contraception. The questionnaire was translated
210 from English to Bengali, adapted, and validated before data collection.

211 Physical measurements, including height, weight, and blood pressure were collected. BP
212 was measured by an appropriately calibrated aneroid sphygmomanometer by a trained field
213 interviewer using appropriately sized arm cuffs. BP measurements were consistently taken on
214 the right arm at the level of the heart and elbow-assisted while the participant was seated. The
215 initial measurement was performed after five minutes of rest on the right arm. After two minutes,
216 the second measurement was taken. The mean of these two BP readings was utilized as the
217 final BP for each participation. To measure blood glucose levels, we obtained random blood
218 glucose samples¹⁴. Capillary blood samples were consistently taken using the right arm and

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3 219 index finger with a glucometer, namely Accu-chek Advantage (Roche Diagnostics Division,
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5 220 Grenzacherstrasse, Switzerland).

6 7 221 Estimation of 10-year CVD risk

8
9 222 The WHO/ISH prediction charts were used to grade cardiovascular risk¹⁵. The charts
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11 223 developed by the WHO/ISH provide the 10-year risk of a fatal or non-fatal major cardiovascular
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13 224 event, such as myocardial infarction or stroke, based on age, sex, blood pressure, smoking
14
15 225 status, total blood cholesterol, and the presence or absence of diabetes mellitus for 14 WHO
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17 226 epidemiological sub-regions. Two sets of charts are available: one set is used in settings where
18
19 227 blood cholesterol can be measured, and the other set is suitable for when blood cholesterol has
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21 228 not been measured. We utilized the South-East Asian Region (SEAR) WHO/ISH prediction
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23 229 chart where total blood cholesterol cannot be measured to estimate the 10-year risk of a CVD
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25 230 event among Bangladeshi adults,

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27
28 231 The prediction chart grades cardiovascular risk using the following categories: age (1:
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30 232 40–49 years; 2: 50–59 years; 3: 60–69 years; 4: 70 years and older), sex (men and women),
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32 233 smoking (never smoker, current smoker or ex-smoker), systolic blood pressure (<140 mmHg,
33
34 234 140 to <160, 160 - <180, and ≥ 180), and the presence or absence of diabetes. The risk
35
36 235 categories for 10-year combined acute myocardial infarction and stroke (fatal and non-fatal) are
37
38 236 as follows: 10%, 10 - <20%, 20 to <30%, 30 to <40, and $\geq 40\%$. For this analysis, we combined
39
40 237 the last two categories of risk as $\geq 30\%$.

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43 238 Observations with missing values were dropped from the analysis. We did not anticipate
44
45 239 any bias from the complete-case analysis approach as the number of missing observations for
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47 240 key variables was less than 2%: smoking status, n=18 or 0.3% missing values; systolic blood
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49 241 pressure, n = 22 or 0.4% missing values; diastolic blood pressure, n = 25 or 0.4% missing
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51 242 values; and blood glucose levels, n = 7 or 0.1%;

52 53 243 Data Analysis

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3 244 We present sociodemographic variables using mean (standard deviation) or the median
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5 245 (interquartile range) for continuous variables and proportion for categorical variables. We
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7 246 conducted bivariate analyses by sex and age group. We used the chi-square test to assess for
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9 247 any significant differences in CVD risk distribution across sex. For estimating the cost of
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11 248 medicines per million per year (population aged 40 years or older), we used the lowest price of
12
13 249 each drug class available in the market (generic preparation of aspirin, thiazide diuretics,
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15 250 statins, and angiotensin-converting enzyme inhibitors). Appendix 1 includes further details
16
17 251 regarding the specific costs of common drugs used to treat cardiovascular disease in
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19 252 Bangladesh.

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21
22 253 To calculate costs using the single risk factor approach, we included all people with BP
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24 254 $\geq 140/90$. Similarly, to calculate costs based on the cardiovascular risk approach, we included
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26 255 the following categories: (1) people with high cardiovascular risk ($\geq 30\%$ and $\geq 20\%$), who are
27
28 256 recommended four drugs [6]; and (2) people with BP $\geq 140/90$, who are recommended
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30 257 antihypertensive treatment. To calculate the estimated annual total cost of CVD medication
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32 258 treatment per million population (aged 40 years or older), we multiplied the percentage of the
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34 259 population at risk and the price of medicine in Bangladesh. We included an estimate of the total
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36 260 number of people estimated to require drug treatment we multiplied the prevalence of the
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38 261 population requiring medication based on each approach based on our study estimates, by the
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40 262 number of people in the general population in 2016¹⁶ stratified by gender and age group.

263

264 **Results**

265 Demographic Characteristics

266 The mean age of included participants was 52.9 years (men: 53.5 years, women: 52.5
267 years) (Table 1). The average level of educational attainment was 3.1 years of education;
268 women were generally less educated than men (2.1 years vs. 4.3 years, respectively). The
269 majority (80%) of women were housewives, and among men, the most common occupation was

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3 270 an industrial worker or day laborer (51.2%). Overall, over one-third of participants ever used
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5 271 smoking tobacco, and over half ever used smokeless tobacco. Few participants drank alcohol in
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7 272 the past 30 days (1.2%). The mean BMI was 21.9 kg/m² and the mean waist circumference was
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9 273 82.4 cm.

11 274 Distribution of Cardiovascular Risk

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14 275 We summarized the distribution of cardiovascular risk in the population overall and
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16 276 stratified by sex in Table 2. Over 85% of participants had a low (< 10%) 10-year cardiovascular
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18 277 risk, and this proportion was significantly different across sex (p<0.001). Almost all (97.7%) of
19
20 278 the study population were categorized as having cardiovascular risk < 20%. A higher proportion
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22 279 of men (2.2%) were categorized as high risk than women (1.4%) (p = 0.029). Overall, very few
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24 280 participants (< 1%) were categorized as very high risk or with a cardiovascular risk of ≥ 30%.

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28 282 Cost of Drug Treatment

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31 283 If a ≥30% threshold of CV risk alone was applied for drug treatment, 0.56% of the total
32
33 284 population requires drug treatment (0.75% in urban areas, 0.47% in rural areas). Lowering the
34
35 285 cardiovascular risk threshold (from 30% to 20%) alone increased the number of people requiring
36
37 286 treatment by almost five times (0.56% [34 of 6090] to 2.3% [140 of 6090]) (Table 3). The
38
39 287 consequence was a substantial increase in health care expenditure, as described in Table 4.
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41 288 Conversely, if a single risk factor approach was applied, and all those with hypertension (a
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43 289 persistent SBP ≥140 and/or DBP ≥90) were treated, about 19.6% (1193 of 8,625) of the sample
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45 290 would require drug treatment, specifically antihypertensives; more than 10 times the proportion
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47 291 identified when using the total cardiovascular risk approach alone. Including individuals with
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49 292 raised BP (≥160/100 mm Hg) but with a 10-year CVD risk < 30% or < 20% would increase the
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51 293 percentage of people requiring drug treatment from 0.56 and 2.3, to 4.5% and 3.8%,
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53 294 respectively. This proportion was about three times lower than the proportion of participants
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55 295 using the single risk factor approach (Table 3).

296

297 Comparison of Cost by Approach

298 Next, we compared the estimated annual cost of medicines per million population for
299 implementing the total risk approach vs. the single risk factor approach. Table 4 shows the
300 estimated number of people aged 40 years or older requiring drug treatment stratified by age
301 group and gender. The estimate showed that if the single risk factor approach is applied in
302 Bangladesh with its percentage of population at risk and the lowest price of medicine in the
303 country, the cost per million population (aged 40 years or older) of treating those with BP
304 $\geq 140/90$ would be \$5,665,968.0 US\$; if the absolute risk approach were applied, the cost of
305 treating those with 10-year risk of CVD $\geq 30\%$ per million population (aged 40 years or older)
306 would be \$635,976.0, almost nine times less (Figure 1). The cost estimation was based on the
307 percentage of the population at different levels of risk and the differences in the price of generic
308 medicines. For this analysis, we focused on the cost of pharmacological treatment as it is the
309 most critical contributor to the overall direct costs of CVD treatment in Bangladesh. We
310 assumed that other costs of CVD treatment and prevention service delivery, such as health
311 facilities and wages of health workers, are similar for both approaches of service delivery⁶.

312

313 **Discussion**

314 Using this nationally representative survey of Bangladeshi adults aged 40 years and
315 above, we found that the majority of adults (97%) were at a low or moderate ten-year risk of
316 myocardial infarction and stroke. The proportion of adults requiring drug treatment rose from
317 0.56% to 2.3% when the threshold of CVD risk was changed from $\geq 30\%$ to $\geq 20\%$, respectively;
318 which was lower the proportion than the single risk factor approach (19.6%). Our data
319 demonstrated that using a single risk factor approach to manage individual cardiovascular risk
320 factors is costlier (\$5,665,968 per million population) than using the total risk approach (CVD
321 risk ≥ 30 , \$173,448 per million population; CVD risk ≥ 20 , \$635,976 per million population), as a

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3 322 more substantial proportion of adults will need drug treatment. Findings from this analysis
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5 323 support the implementation of clinical guidelines using CVD risk scores calculated using the
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7 324 WHO/ISH prediction charts to appropriately identify patients at highest risk of CVD development
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9 325 over ten years in Bangladesh.

11 326 In our study using nationally representative data, we found that the 10-year risk of CVD
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13 327 was low (<10%) among the vast majority of participants (85.2%). Additionally, only 2.4% of
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15 328 adults were at high risk ($\geq 20\%$) of a CVD event within the next ten years. Two prior studies
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17 329 have reported absolute CVD risk among the Bangladeshi population (using the WHO/ISH Tool
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19 330 or any other absolute risk scoring system)^{8 17}. In contrast to our study, Fatema et al. found that
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21 331 10% of Bangladeshi adults living in rural areas were at high risk ($\geq 20\%$) of a CVD event within
22
23 332 the next ten years, and half of these adults fell in the very high-risk category ($\geq 30\%$). These
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25 333 proportions were the same when total cholesterol was incorporated in the WHO/ISH CVD Risk-
26
27 334 Assessment Tool. Unfortunately, we were unable to measure total blood cholesterol and were
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29 335 unable to make similar comparisons. In another rural Bangladeshi population, the proportion of
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31 336 participants at a high-risk ($\geq 20\%$) of a CVD event in 10 years was 2.1%, which is similar in
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33 337 proportion to our finding¹⁷. Differences in CVD risk may be attributable to environmental,
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35 338 sociodemographic, and lifestyle factors. No other studies have been conducted to assess the
36
37 339 10-year risk of CVD using the WHO/ISH tool. Here, we present novel data using a nationally
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39 340 representative sample, which may be generalizable to the population of Bangladesh. Data we
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41 341 present may be used to inform policymakers decisions on clinical guidelines and resource
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43 342 allocation for treatment of CVDs in Bangladesh.

47 343 Our results demonstrate that using a single risk factor approach to manage individual
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49 344 CVD risk factors to prevent heart attacks and strokes would cost more than when using the total
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51 345 risk approach at either the 20% or 30% threshold due to higher drug costs. In Bangladesh,
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53 346 about 60% of out-of-pocket expenditure patients face goes towards drugs directly bought from
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55 347 pharmacies, diagnostics, and informal providers¹⁸. Additionally, patients in Bangladesh

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2
3 348 experience a high level of uncertainty regarding out-of-pocket costs due to unforeseen costs on
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5 349 diagnostics and medications, including under-the-table payments to providers for reliable and
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7 350 timely services¹⁹. The cost of treatment for CVD frequently leads to catastrophic health
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9 351 expenditure and impoverishment as a result of use of health services; the proportion of
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11 352 catastrophic spending for treatment is highest among those from the lowest quintiles of wealth
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13 353 (14%) compared to those with high wealth and high socioeconomic status (6.6%)²⁰. The
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15 354 economic impact of the sequelae of CVD is particularly severe in Bangladesh where the out-of-
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17 355 pocket expenditures for chronic disease management are high.

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20 356 In addition to benefits to the patient, implementing the total risk approach would also be
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22 357 beneficial to the health care system in Bangladesh by improving NCD preventive service
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24 358 delivery and the use of guidelines for adequate care. Currently, Bangladesh is categorized by
25
26 359 the World Bank as a lower-middle-income country with emerging health challenges as the
27
28 360 burden of NCDs continues to grow. In 2015, an estimated 67% of all deaths in Bangladesh were
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30 361 due to NCDs and the risk of premature death from chronic disease among adults aged 30-70
31
32 362 years was 22%²¹. Indeed, CVDs and circulatory diseases are the leading cause of mortality and
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34 363 morbidity in Bangladesh. Despite this substantial burden, preventive services for CVDs in
35
36 364 Bangladesh are limited. In 2014, an estimated 16% of health care facilities across the country
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38 365 (i.e. hospitals, community clinics) had the resources to diagnose, prescribe treatment for, and
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40 366 manage patients with CVDs²². Among facilities with the capacity to offer services for CVD
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42 367 management, about only 20% utilized established guidelines for hypertension treatment and
43
44 368 less than one-third had essential CVD medicines readily available on-site for patients²². By
45
46 369 integrating the WHO/ISH prediction charts into the national guidelines for management of
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48 370 hypertension and CVD prevention in Bangladesh, the proportion of facilities using established
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50 371 guidelines may increase as the charts are easy to implement, interpret, and access.
51
52 372 Additionally, since only one-third of facilities have essential CVD medicines readily available,
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3 373 distributing pharmacologic treatment to those at highest risk of premature mortality due to CVD
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5 374 will be crucial.

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7 375 The World Health Organization has outlined global targets in the Global Monitoring
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9 376 Framework for the control of NCDs in LMICs, which prioritizes an 80% of availability of
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11 377 affordable basic technologies and essential medicines necessary to treat significant NCDs,
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13 378 including CVDs in both rural and urban areas of the country. Additionally, the Framework
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15 379 recommends LMICs should target that at least 50% of eligible adults with a 10-year CVD risk of
16
17 380 $\geq 30\%$ receive drug therapy counseling to prevent heart attacks and strokes⁴. As such, limited
18
19 381 CVD treatment options and weak health care infrastructure to access preventive services in
20
21 382 Bangladesh is a significant public health concern. As public financing for health care is limited in
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23 383 Bangladesh (~1% of gross domestic product or GDP), cost-effective public health policies from
24
25 384 national bodies on CVD drug treatment guidelines based on cost estimates and out of pocket
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27 385 costs to the population of Bangladesh is necessary for effective CVD control. Effective policies
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29 386 should address the potential for overtreatment, which comes at a high cost to both the health
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31 387 care system and the patient. The high percentage of the Bangladeshi adult population at low 10-
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33 388 year CVD risk (<10%) highlights the potential for reduction of CVD risk through population-wide
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35 389 public health policy and availability of accessible preventive services.

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39 390 Limitations of this analytic approach should be considered when interpreting our results.
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41 391 CVD 10-year risk was developed using data compiled from each of the 14 WHO epidemiological
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43 392 sub-regions rather than individual countries. As such, the estimation used from each region's
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45 393 chart will most likely apply to the largest country within each region, or from the country where
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47 394 most of the data originated. However, over the past decade, the accuracy and predictive value
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49 395 for the current risk prediction charts have been evaluated and improved as more
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51 396 epidemiological data became available from individual countries^{6 15}. Additionally, the charts
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53 397 provide approximate estimates of CVD risk in people who do not have established coronary
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55 398 heart disease, stroke or other atherosclerotic diseases. We were unable to confirm the medical

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3 399 history of participants using medical charts or health records and relied on self-report, leading to
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5 400 the potential for measurement error and recall bias.

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7 401 Additionally, we were unable to measure total cholesterol. Future research studies
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9 402 should include the measurement of total cholesterol using blood samples. Finally, our cost
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11 403 estimates were based on the prevalence of each risk approach in our study sample. Although
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13 404 we present the total number of people estimated to require drug treatment using 2016 census
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15 405 data, we were unable to identify population estimates of only those at risk of their first CVD
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17 406 event due to lack of surveillance data. Nevertheless, our data are still valuable as we focus on
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19 407 the comparative cost difference of each approach to underscore the potential cost savings in
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21 408 implementing the total risk approach in Bangladesh.
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26 410 **Conclusion**

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28 411 Our data show that the implementation of a total risk approach compared with a single
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30 412 risk factor approach will reduce the health care expenditure by lowering drug costs, which
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32 413 accounts for 60% of out-of-pocket spending in Bangladesh. This approach would be particularly
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34 414 beneficial in Bangladesh, a low-resource country that should prioritize the development of health
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36 415 policy for effective resource allocation in the public health sector. Furthermore, using the total
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38 416 risk approach would increase service coverage and allow for the distribution of resources to
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40 417 target those at highest risk of experiencing a heart attack or stroke. As the majority of the
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42 418 Bangladeshi adult population aged ≥ 40 years have a low ten-year risk of CVD, strategies that
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44 419 target those at highest risk of CVD coupled with public health policies to reduce the population-
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46 420 level risk of CVD may be effective.
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3 425 **Figure**

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5 426 Figure 1: Comparison of estimated annual costs using three different approaches to
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7 427 pharmacologic intervention for cardiovascular disease treatment among adults in Bangladesh
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9 428 aged 40 years and above
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3 451 **Abbreviations**
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5 452 WHO: World Health Organization
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7 453 aPR: Adjusted prevalence ratio
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9 454 BBS: Bangladesh Bureau of Statistics
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11 455 BMI: Body mass index
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13 456 BP: Blood pressure
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15 457 CI: Confidence interval
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17 458 CVD: Cardiovascular disease
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19 459 ISH: International Society of Hypertension
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21 460 NCD: Non-communicable disease
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23 461 SEAR: South East-Asian Region
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25 462 SBP: Systolic blood pressure
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27 463 DBP: Diastolic blood pressure
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29 464 PSU: Primary sampling unit
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31 465 SD: Standard deviation
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3 477 **Footnotes**
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5 478 Ethics approval and consent to participate: We obtained ethical approval for this study from the
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7 479 Institutional Review Board of the National Institute of Ophthalmology (Study ID: 128). We
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9 480 provided participants with detailed study information using a printed handout prepared in
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11 481 Bengali to inform them of the objective of the study. Written consent was obtained from
12
13 482 participants through signature or, if not possible, through thumbprint.
14

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20 485 Office for Bangladesh.
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22 486 Consent to publish: All authors consent to the publication of this manuscript.
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24 487 Competing Interests: The authors declare no competing interests. The authors alone are
25
26 488 responsible for views expressed in this article and they do not necessarily represent the views,
27
28 489 decisions or policies of the institutions with which they are affiliated.
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31 490 Availability of data and materials: The de-identified participant data used and/or analyzed during
32
33 491 the current study are available from the corresponding author on reasonable request. Please
34
35 492 contact M. Mostafa Zaman at zamanm@who.int for further information and guidelines.
36

37 493 Authors contributions: JYI: conceptualized the manuscript, analyzed data, interpreted results
38
39 494 critically, and drafted the manuscript. MMZ: conceptualized the manuscript, designed the study,
40
41 495 interpreted results critically, guided manuscript writing, and critically reviewed it.: trained the field
42
43 496 team, implemented the survey, processed and analyzed data, and reviewed the manuscript.
44

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Table 1: Background Characteristics of Bangladeshi Adult Participants (n = 6189)

Characteristics	Total (n = 6189)			Men (n = 2824)			Women (n = 3365)		
	Mean (SD)	n	%	Mean (SD)	n	%	Mean (SD)	n	%
Age (years)	52.9 (9.9)			53.5 (10.1)			52.5 (9.8)		
Education (years)	3.1 (4.2)			4.3 (4.8)			2.1 (3.3)		
Area of Residence									
Urban		1873	30.2		808	28.6		1065	31.6
Rural		4316	69.8		2016	71.4		2300	68.4
Occupation									
Professional employment [‡]		1007	16.3		880	31.3		127	3.8
Industrial worker/Day Laborer		1600	25.9		1440	51.2		160	4.8
Housework		2697	43.7		-	-		2697	80.3
Unemployed/Retired		735	11.9		386	13.7		349	10.4
Other [§]		131	2.1		106	3.8		25	0.7
Smoking Tobacco Use									
Current User		1493	24.2		1432	50.7		61	1.8
Ever User		2261	36.5		2150	76.1		111	3.3
Smokeless Tobacco Use [◊]									
Current User		3078	49.7		1208	42.8		1870	55.6
Ever User		3469	56.1		1433	50.7		2046	60.5
Alcohol use in the last 30 days									
Yes		75	1.2		68	2.4		7	0.2
Body Mass Index	21.9 (4.1)				21.4 (3.7)			22.3 (4.4)	
Waist Circumference** (cm)	82.4 (13.3)				81.8 (10.5)			82.8 (15.2)	
Blood Pressure									
Systolic Blood Pressure ^{††} (mmHg)	119.7 (15.2)				119.8 (14.9)			119.7 (15.5)	
Diastolic Blood Pressure ^{††} (mmHg)	80.3 (9.5)				80.2 (9.4)			80.3 (9.7)	
Blood Glucose Levels ^{§§} (mmol/L)	6.9 (3.0)				6.9 (3.0)			6.9 (2.9)	

Abbreviations: SD: Standard Deviation; CM: centimeters; mmHg: millimeter of mercury; mmol/L: millimoles per liter

[‡]Professional occupation includes: Government employee, private company employee, businessman

[§]Other occupation includes: Shop keeper, weavers, driver, student, beggar, cook, carpenter, and tailor

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3 ¶Excluding smokeless tobacco | Missing values, n = 18; Men, n = 11; FeMen, n = 7

4 ◊Smokeless tobacco use includes jorda, white leaf (shaada pata), gul, etc.

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6 ¶Body mass index (BMI) calculated by weight in kilogram divided by height in meter squared
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Table 2: Ten-year risk of combined myocardial infarction and stroke (fatal and non-fatal) by gender, using the WHO/ISH SEAR-D charts without cholesterol (n = 6090)

	Total (n = 6090)			Men (n = 2779)			Women (n = 3311)			P*
	n	%	CI	n	%	CI	n	%	CI	
Low Risk (<10 %)	5189	85.2	84.3 - 86.1	2309	83.1	81.6 - 84.4	2880	87.0	85.8 - 88.1	<0.001
Moderate Risk (10 - <20%)	760	12.5	11.6 - 13.3	391	14.1	12.8 - 15.4	369	11.1	10.1 - 12.2	0.001
High Risk (20 - <30%)	107	1.8	1.4 - 2.1	60	2.2	1.7 - 2.8	47	1.4	1.0 - 1.9	0.029
Very High Risk (≥ 30%)	34	0.6	0.4 - 0.8	19	0.7	0.4 - 1.1	15	0.5	0.3 - 0.7	0.229

Abbreviations: CI, confidence interval; WHO, World Health Organization; ISH, International Society of Hypertension; SEAR, South East Asian Region
* P-value based on chi-square test

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Table 3: Estimation of percentage of population requiring drug treatment based on total risk approach in comparison to single risk factor approaches (n = 6090)

	<u>Total Risk Approach</u>				<u>Single Risk Factor Approach</u>
	<u>Cardiovascular Risk \geq 30%</u>		<u>Cardiovascular Risk \geq 20%</u>		BP \geq 140/90 (SBP \geq 140 + isolated raised DBP), %
	CV Risk \geq 30% alone, %	CV Risk \geq 30% + BP \geq 160/100	CV Risk \geq 20% alone, %	CV Risk \geq 20% + BP \geq 160/100	
Men	0.68	4.3	2.8	3.5	18.8
women	0.45	4.8	1.9	4.1	20.2
Total	0.56	4.5	2.3	3.8	19.6

Abbreviations: CV, cardiovascular; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 4: Population projections and comparison of medicine costs (US\$) for implementing total risk approach vs. single risk factor approach in Bangladesh SEAR-D

Estimated annual total cost of CVD medication treatment per million population†									
Total risk approach CV Risk ≥ 30% alone					Aspirin	Enalapril	Hydrochlorothiazide	Simvastatine	Total
	Total no. of people in the general population (in thousands)*	Percentage of population aged ≥40 years requiring medication (%)	Total no. of people estimated to require drug treatment (in thousands)	No. of people per million population (aged 40 years and older)					
Age Group									
Men									
40 to 49	9210	0.1	921	1000	\$1,642.5	\$8,687.0	\$3,029.5	\$15,549.0	\$28,908.0
50 to 59	6303	0.4	2521	4000	\$6,570.0	\$34,748.0	\$12,118.0	\$62,196.0	\$115,632.0
60 to 69	3730	2.5	9325	25000	\$41,062.5	\$217,175.0	\$75,737.5	\$388,725.0	\$722,700.0
≥ 70	1881	0.7	1317	7000	\$11,497.5	\$60,809.0	\$21,206.5	\$108,843.0	\$202,356.0
Total	21124	0.7	14787	7000	\$11,497.5	\$60,809.0	\$21,206.5	\$108,843.0	\$202,356.0
Women									
40 to 49	9087	0.0	0	0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
50 to 59	5662	0.3	1699	3000	\$4,927.5	\$26,061.0	\$9,088.5	\$46,647.0	\$86,724.0
60 to 69	3257	0.4	1303	4000	\$6,570.0	\$34,748.0	\$12,118.0	\$62,196.0	\$115,632.0
≥ 70	1638	3.3	5405	33000	\$54,202.5	\$286,671.0	\$99,973.5	\$513,117.0	\$953,964.0
Total	19644	0.5	9822	5000	\$8,212.5	\$43,435.0	\$15,147.5	\$77,745.0	\$144,540.0
All									
40 to 49	18296	0.0	732	400	\$657.0	\$3,474.8	\$1,211.8	\$6,219.6	\$11,563.2
50 to 59	11965	0.3	3590	3000	\$4,927.5	\$26,061.0	\$9,088.5	\$46,647.0	\$86,724.0
60 to 69	6989	1.3	9086	13000	\$21,352.5	\$112,931.0	\$39,383.5	\$202,137.0	\$375,804.0

>= 70	3518	2.0	7036	20000	\$32,850.0	\$173,740.0	\$60,590.0	\$310,980.0	\$578,160.0
Total	40768	0.6	24461	6000	\$9,855.0	\$52,122.0	\$18,177.0	\$93,294.0	\$173,448.0

Total risk approach CV Risk ≥ 20% alone

	Total no. of people in the general population (in thousands)*	Percentage of population aged ≥40 years requiring medication (%)	Total no. of people estimated to require drug treatment (in thousands)	No. of people per million population (aged 40 years and older)	Aspirin	Enalapril	Hydrochlorothiazide	Simvastatine	Total
Age Group									
Men									
40 to 49	9210	1.9	17499	19000	\$31,207.5	\$165,053.0	\$57,560.5	\$295,431.0	\$549,252.0
50 to 59	6303	1.6	10085	16000	\$26,280.0	\$138,992.0	\$48,472.0	\$248,784.0	\$462,528.0
60 to 69	3730	4.1	15293	41000	\$67,342.5	\$356,167.0	\$124,209.5	\$637,509.0	\$1,185,228.0
>= 70	1881	2.4	4514	24000	\$39,420.0	\$208,488.0	\$72,708.0	\$373,176.0	\$693,792.0
Total	21124	2.3	48585	23000	\$37,777.5	\$199,801.0	\$69,678.5	\$357,627.0	\$664,884.0
Women									
40 to 49	9087	0.8	7270	8000	\$13,140.0	\$69,496.0	\$24,236.0	\$124,392.0	\$231,264.0
50 to 59	5662	2.4	13589	24000	\$39,420.0	\$208,488.0	\$72,708.0	\$373,176.0	\$693,792.0
60 to 69	3257	2.0	6514	20000	\$32,850.0	\$173,740.0	\$60,590.0	\$310,980.0	\$578,160.0
>= 70	1638	7.4	12121	74000	\$121,545.0	\$642,838.0	\$224,183.0	\$1,150,626.0	\$2,139,192.0
Total	19644	2.1	41252	21000	\$34,492.5	\$182,427.0	\$63,619.5	\$326,529.0	\$607,068.0
All									
40 to 49	18296	1.3	23785	13000	\$21,352.5	\$112,931.0	\$39,383.5	\$202,137.0	\$375,804.0
50 to 59	11965	2.0	23930	20000	\$32,850.0	\$173,740.0	\$60,590.0	\$310,980.0	\$578,160.0
60 to 69	6989	2.9	20268	29000	\$47,632.5	\$251,923.0	\$87,855.5	\$450,921.0	\$838,332.0
>= 70	3518	4.9	17238	49000	\$80,482.5	\$425,663.0	\$148,445.5	\$761,901.0	\$1,416,492.0
Total	40768	2.2	89690	22000	\$36,135.0	\$191,114.0	\$66,649.0	\$342,078.0	\$635,976.0

Single Risk Factor Approach: BP ≥ 140/90 (SBP ≥ 140 + isolated raised DBP), %

	Total no. of people in the general population (in thousands)*	Percentage of population aged ≥40 years requiring medication (%)	Total no. of people estimated to require drug treatment (in thousands)	No. of people per million population (aged 40 years and older)	Aspirin	Enalapril	Hydrochlorothiazide	Simvastatine	Total
Age Group									
Men									
40 to 49	9210	14.5	133545	145000	\$238,162.5	\$1,259,615.0	\$439,277.5	\$2,254,605.0	\$4,191,660.0
50 to 59	6303	18.4	115975	184000	\$302,220.0	\$1,598,408.0	\$557,428.0	\$2,861,016.0	\$5,319,072.0
60 to 69	3730	24.7	92131	247000	\$405,697.5	\$2,145,689.0	\$748,286.5	\$3,840,603.0	\$7,140,276.0
≥ 70	1881	26.0	48906	260000	\$427,050.0	\$2,258,620.0	\$787,670.0	\$4,042,740.0	\$7,516,080.0
Total	21124	18.8	397131	188000	\$308,790.0	\$1,633,156.0	\$569,546.0	\$2,923,212.0	\$5,434,704.0
Women									
40 to 49	9087	16.9	153570	169000	\$277,582.5	\$1,468,103.0	\$511,985.5	\$2,627,781.0	\$4,885,452.0
50 to 59	5662	23.8	134756	238000	\$390,915.0	\$2,067,506.0	\$721,021.0	\$3,700,662.0	\$6,880,104.0
60 to 69	3257	21.3	69374	213000	\$349,852.5	\$1,850,331.0	\$645,283.5	\$3,311,937.0	\$6,157,404.0
≥ 70	1638	23.5	38493	235000	\$385,987.5	\$2,041,445.0	\$711,932.5	\$3,654,015.0	\$6,793,380.0
Total	19644	20.2	396809	202000	\$331,785.0	\$1,754,774.0	\$611,959.0	\$3,140,898.0	\$5,839,416.0
All									
40 to 49	18296	15.8	289077	158000	\$259,515.0	\$1,372,546.0	\$478,661.0	\$2,456,742.0	\$4,567,464.0
50 to 59	11965	21.2	253658	212000	\$348,210.0	\$1,841,644.0	\$642,254.0	\$3,296,388.0	\$6,128,496.0
60 to 69	6989	22.8	159349	228000	\$374,490.0	\$1,980,636.0	\$690,726.0	\$3,545,172.0	\$6,591,024.0
≥ 70	3518	24.7	86895	247000	\$405,697.5	\$2,145,689.0	\$748,286.5	\$3,840,603.0	\$7,140,276.0
Total	40768	19.6	799053	196000	\$321,930.0	\$1,702,652.0	\$593,782.0	\$3,047,604.0	\$5,665,968.0

*Source: 2016 Population Projections (using 2011 Census data) Bangladesh Bureau of Statistics, Statistics and Informatics Division, Ministry of Planning

† Price for 100 tablets in US\$: Aspirin (0.45), Enalapril (2.38), Hydrochlorothiazide (0.83), Simvastatine (4.29); one tablet is taken per day

Appendix Table 1: Cost of common drugs used to treat cardiovascular disease in Bangladesh (converted to US\$)

Drug Name	Dose	Number of Tablets	Category	Median price (in Bangladeshi Taka)	Price (in US\$)*
Aspirin	100 mg	100 tablets	Antiplatelet drugs	38BDT	0.45
Atenolol	50 mg	100 tablets	Antihypertensive, Beta-adrenoreceptor blocking drugs	77BDT	0.92
Captopril	25 mg	100 tablets	Antihypertensive, ACE inhibitors	300 BDT	3.58
Chlorthalidone	25 mg	30 tablets	Antihypertensive, thiazide diuretics	60 BDT	0.72
Enalapril	10 mg	100 tablets	Antihypertensive, ACE inhibitors	200 BDT	2.38
Frusemide	40 mg	100 tablets	Antihypertensive, loop diuretics	53 BDT	0.63
Hydrochlorothiazide	25 mg	100 tablets	Antihypertensive, thiazide diuretics	70 BDT	0.83
Isosorbide dinitrate	10 mg	100 tablets	Angina treatment, nitrates - coronary vasodilators	35 BDT	0.42
Labetalol	100 mg	60 tablets	Antihypertensive, Beta-adrenoreceptor blocking drugs	361.2 BDT	4.31
Losartan	50 mg	100 tablets	Antihypertensive, Angiotensin-II receptor blocker	600 BDT	7.15
Lovastatine	20 mg	30 tablets	Lipid regulation, statin	303.3 BDT	3.62
Methyldopa	250 mg	100 tables	Antihypertensive, Centrally acting or central sympatholytic	308 BDT	3.67
Nifedipine (slow release)	20 mg	100 tablets	Angina treatment, calcium-channel blocker	64 BDT	0.76
Propranolol hydrochloride	10 mg	100 tablets	Antihypertensive, Beta-adrenoreceptor blocking drugs	24 BDT	0.29
Simvastatine	10 mg	30 tablets	Lipid regulation, statin	360 BDT	4.29

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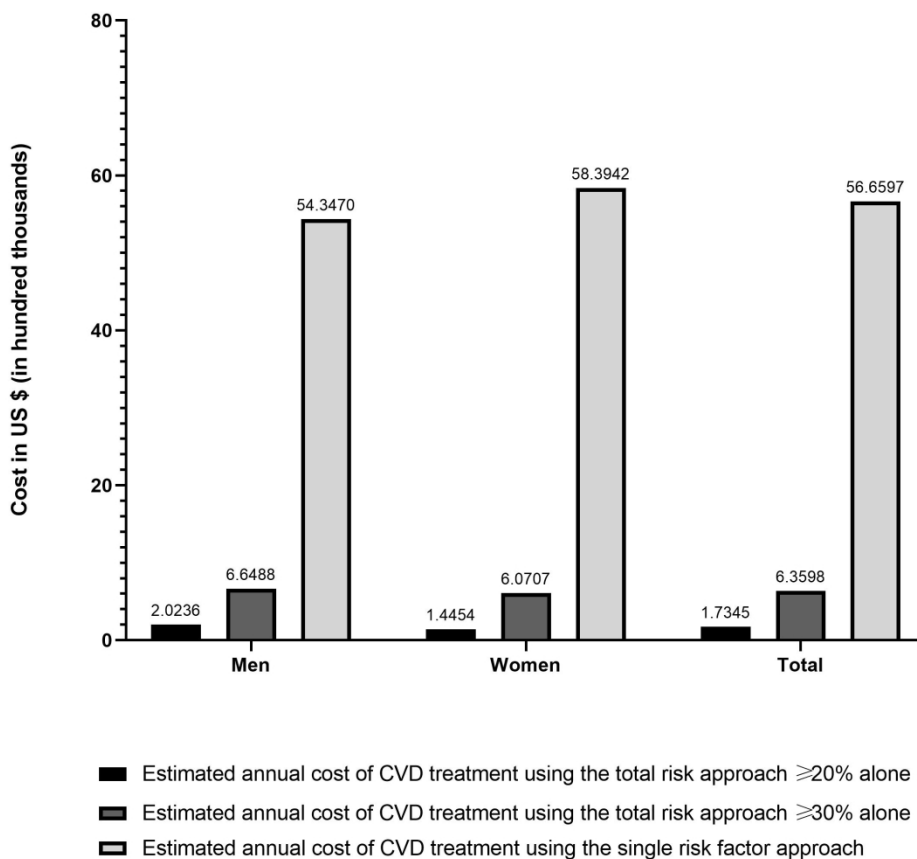
Spironolactone	25 mg	100 tablets	Antihypertensive, potassium-sparing diuretics & aldosterone antagonist	202 BDT	2.41
Streptokinase	1.5 million unit/vial	One vial	Anticoagulant	3100 BDT	36.96
Warfarin	5 mg	100 tablets	Anticoagulant	300 BDT	3.58

Abbreviations: mg, milligrams; US, United States; BDT, Bangladeshi Taka

*Price conversion based on exchange rate on 02/07/2019

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Comparison of estimated annual costs using three different approaches to pharmacologic intervention for cardiovascular disease treatment among adults in Bangladesh aged 40 years and above

196x175mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10
Bias	9	Describe any efforts to address potential sources of bias	6-7 & 15-16
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9-10
		(b) Describe any methods used to examine subgroups and interactions	8-11
		(c) Explain how missing data were addressed	9
		(d) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	9
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Estimation of total cardiovascular risk using the 2019 WHO CVD prediction charts and comparison of population-level costs based on alternative drug therapy guidelines in Bangladesh: a population-based study of adults in Bangladesh

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3 **Estimation of total cardiovascular risk using the 2019 WHO CVD prediction charts and**
4 **comparison of population-level costs based on alternative drug therapy guidelines in Bangladesh: a**
5 **population-based study of adults in Bangladesh**
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9 Running title: Total cardiovascular risk approach in Bangladesh

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Abstract

Objective: The objective of this study is to estimate the population distribution of 10-year cardiovascular disease (CVD) risk among Bangladeshi adults aged 40 years and above, using the 2019 WHO CVD prediction charts. Additionally, we compared the cost of pharmacologic treatment of CVD based on CVD risk (thresholds $\geq 30\%$ / $\geq 20\%$) to single risk factor (hypertension) cutoff levels in the Bangladeshi context.

Study Design: Cross-sectional, population-based study

Setting and Participants: From 2013-2014, we collected data from a nationally representative cross-sectional survey of adults aged ≥ 40 years from urban and rural areas of Bangladesh ($n = 6189$). Using the 2019 World Health Organization risk prediction charts, CVD risk was calculated and categorized as very low ($<5\%$), low ($5-<10\%$), moderate ($10-<20\%$), high ($20-<30\%$), and very high risk ($\geq 30\%$). We estimated drug therapy costs using the lowest price of each drug class available (aspirin, thiazide diuretics, statins, and angiotensin-converting enzyme inhibitors). We compared the total cost of drug therapy using the total risk vs. single risk factor approach.

Primary Outcome Measures: Our primary outcome was 10-year CVD risk categorized as very low ($<5\%$), low ($5-<10\%$), moderate ($10-<20\%$), high ($20-<30\%$), and very high risk ($\geq 30\%$).

Results: The majority of adults (85.2%, 95% CI: 84.3–86.1) have a 10-year risk of CVD of less than 10%. The proportion of adults with a 10-year CVD risk of $\geq 20\%$ was 0.51%. Only one adult was categorized with a 10-year CVD risk of $\geq 30\%$. Among adults with CVD risk groups of very low, low, and moderate, 17.4%, 27.9%, and 41.4% had hypertension (BP $\geq 140/90$) and 0.1%, 1.7%, and 2.9% had severe

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3 hypertension (BP \geq 160/100), respectively. Using the total risk approach would reduce drug costs per
4 million populations to \$144,540 (risk of \geq 20%).
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9 Conclusion: To reduce health care expenditure for the prevention and treatment of CVD, a total risk
10 approach using the WHO/ISH risk prediction chart may lead to cost-savings.
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15 **Keywords:** non-communicable diseases, Bangladesh, cardiovascular disease, pharmacologic
16 intervention, cost, chronic disease
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Article Summary

Strengths and Limitations of the Study

- Using the recently updated 2019 WHO CVD Risk Prediction Charts, this study provides evidence for incorporating the WHO/ISH CVD Risk Prediction Charts into CVD management and health care guidelines, and may lead to potential cost-savings from a societal perspective.
- The 2019 WHO/ISH CVD Risk Prediction Charts should be applied to a population who have not experienced a CVD event in the past, however, we were unable to confirm self-reported medical history of participants using medical charts or health records, leading to the potential for measurement error due to recall bias.
- The cost estimates we present are an underestimate of total costs for CVD-related treatment as the focus of this study is on cost of pharmacologic intervention only as the largest contributor to overall direct costs in Bangladesh.
- Although we present the total number of people estimated to require drug treatment using 2014 population data, we were unable to identify population estimates of only those at risk of their first CVD event due to lack of surveillance data.
- The CVD 10-year risk cut-offs were defined using risk prediction models derived from 85 cohorts mostly from high-income countries, as data from large-scale prospective cohort data from most low-income and middle-income countries (LMICs) are unavailable.

Background

Globally, cardiovascular disease (CVD) is the leading cause of death and disproportionately impacts low- and middle-income countries (LMICs), where over 75% of CVD-related deaths occur (1). People living in LMICs are at high risk of developing CVDs due to the absence of integrated primary care for early detection and prevention of CVD-related risk factors, such as high cholesterol, high blood pressure, and smoking. Limited access to primary care and the growing burden of CVDs is a significant cause of poverty in LMICs and hinders the macroeconomic development of many countries(2). LMICs are estimated to experience cumulative economic losses exceeding 7 trillion US dollars over the next 15 years due to morbidity and mortality caused by noncommunicable diseases, including CVD(3). As such, the significance of the CVD epidemic has gained increasing international recognition over the past decade, leading to the development of several international guidelines for CVD control and prevention(4).

In 2007, the World Health Organization (WHO) published pocket guidelines, including CVD risk prediction charts, designed for health care workers in LMICs to guide patient 10-year risk stratification for heart attack or stroke(5). There are two possible strategies suitable for a low resource setting to assess the risk of a cardiovascular event and identify those at high risk of a fatal CVD outcome: 1. Utilize a single risk factor management strategy, which focuses on one condition at a time, such as hypertension; or, 2. Utilize a more holistic approach considering several risk factors such as age, tobacco use, gender, diabetes diagnosis, body mass index, blood pressure, and blood cholesterol when measured. Through the total risk approach, pocket guidelines help to identify high-risk patients that are in imminent danger of a heart attack or stroke for timely pharmacologic treatment or surgical interventions. Additionally, applying the total risk approach via the WHO prediction charts in a nationally representative sample provides an opportunity to estimate and monitor population-level distribution of CVD risk to ultimately inform CVD treatment policy recommendations (6, 7).

Currently, Bangladesh has not incorporated clinical guidelines for screening or treatment of risk factors based on absolute CVD risk scores and estimation of the population distribution of CVD risk over time. Data are needed to support the implementation of the WHO/ISH prediction charts as clinical

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3 guidelines for Bangladesh, a resource-limited setting, to demonstrate the potential cost-savings and
4 benefit of the WHO recommendation on CVD prevention. Recently in 2019, the World Health
5 Organization updated the CVD risk charts based on newly validated risk prediction models to estimate
6 CVD risk in 21 Global Burden of Disease regions(8). The newly developed risk predictions models have
7 been calibrated using data from The Global Burden of Disease study to include estimates from low- and
8 middle-income countries. To our knowledge, here we present the first analysis to apply the updated CVD
9 risk charts among a cohort of Bangladeshi adults. Prior studies conducted in Bangladesh have estimated
10 CVD risk among adults residing in rural areas only and have not included a nationally representative
11 population (9-11). Additionally, no prior studies have estimated the potential costs of pharmacological
12 treatment for CVD in Bangladesh using either the single risk factor or total risk approach, as done
13 previously in other settings(7). As such, our objective was to assess the distribution of absolute CVD risk
14 among a nationally representative sample of Bangladeshi adults using the 2019 WHO risk prediction
15 chart recommended for the WHO South Asian Region (Bangladesh, Bhutan, India, Nepal, and Pakistan)
16 We also compared the costs of drug treatments for CVD prevention using the total cardiovascular risk
17 thresholds at $\geq 20\%$ and with single risk factor cutoff levels (blood pressure $\geq 140/90$ mm Hg).
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37 **Methods**

38 Study design and setting

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41 Data were analyzed from a population-based cross-sectional study conducted from September to
42 December 2013 to assess the burden of blindness and low vision among adults in Bangladesh. The target
43 population of this survey included men and women residing in Bangladesh over the age of 40 years. The
44 exclusion criteria included tourists and the institutionalized, such as residents of a military base, hospital,
45 prisons, nursing homes, and other such institutions. We obtained ethical approval for this study from the
46 Institutional Review Board of the National Institute of Ophthalmology. We provided participants with
47 detailed information regarding the study objectives and procedures using a printed handout prepared in
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3 Bengali. Written consent was obtained from participants through signature or, if not possible, through
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5 thumbprint.
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8 9 Sampling Frame

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11 We adopted a multistage, geographically clustered, probability-based sampling approach to
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13 obtain a nationally representative sample of Bangladesh, as previously described and outlined per the
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15 WHO STEPwise approach (12-15). Population statistics were obtained using the 2011 national census
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17 conducted by the Bangladesh Bureau of Statistics (BBS) to create the sample frame (16). The sampling
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19 frame included 64,407 primary sampling units (PSUs) covering all seven divisions of the country. We
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21 randomly selected seventy-two PSUs (25 urban and 47 rural) from seven divisions, with the probability of
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23 selection proportional to the population size of each division. In each PSU, we selected 100 consecutive
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25 households as the secondary sampling unit.
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29 For each household, a trained field data collector approached the head of the household or the
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31 family member most knowledgeable of the residents to screen for eligible participants. The screening
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33 respondent was asked to describe the composition of household residents, which was defined as those
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35 who considered the home to be their primary place of residence as of the night before. A list was
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37 composed and ordered from youngest to oldest age in years starting from 40 years. Using the list of
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39 eligible residents, we used the Kish table approach to randomly select one participant from each home.
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41 The selected participant was asked to come to a nearby health center the next day to administer the survey
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43 by trained study interviewers and undergo a medical examination by the study physician. Based on the
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45 medical review, participants were followed-up with by the providers at the health center for treatment.
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49 Patient and Public Involvement

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51 There was no patient or public involvement in the implementation of this study or interpretation
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53 of analytic results.
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Data Collection

To ensure effective and uniform data collection, field interviewers underwent a seven-day training on the interview methodology by the study ophthalmologists and epidemiologists. The training included an in-depth review of the survey content and protocol for completing the demographic questionnaire (a modified WHO/PBL Version III). Each member of the data collection team was provided a detailed survey protocol manual outlining the survey activities, the questionnaire interview, and information about the duties and responsibilities of all survey personnel.

Demographic data were collected, including age, sex, marital status, educational level, and occupation, using a structured questionnaire survey. Data regarding tobacco use, health history, and treatment history were also collected. Participants were asked if they smoked (e.g. cigarette, hookah, pipe) or if they used smokeless tobacco (e.g. chewing tobacco, jorda) to assess history of tobacco use. Each participant provided medical history for a prior diagnosis of high blood pressure or hypertension, diabetes, renal disease, or any cardiovascular diseases by a health care provider. Medication history was obtained including medication for high blood pressure, diabetes, malaria, steroids, tuberculosis, and among women, history of oral contraception. The questionnaire was translated from English to Bengali, adapted, and validated before data collection.

Physical measurements, including height, weight, and blood pressure (BP) were collected. Trained field interviewers measured BP using an appropriately calibrated aneroid sphygmomanometer with appropriately sized arm cuffs. BP measurements were consistently taken on the right arm at heart level and elbow-assisted while the participant was seated. The initial measurement was performed after five minutes of rest. After two minutes, the second measurement was taken. The mean of these two BP readings was utilized as the final BP for each participant. To measure blood glucose levels, we obtained random blood glucose samples (17). Capillary blood samples were consistently taken using the right arm and index finger with a glucometer (Accu-chek Advantage, Roche Diagnostics Division, Grenzachstrasse, Switzerland).

Estimation of 10-year CVD risk

We estimated 10-year CVD risk using the 2019 WHO CVD risk prediction charts(8, 18). The prediction charts provide the 10-year risk of a fatal or non-fatal major cardiovascular event, such as myocardial infarction or stroke, based on age, sex, blood pressure, body mass index, smoking status, total blood cholesterol, and the presence or absence of diabetes mellitus for 14 WHO epidemiological sub-regions. For each region, two sets of charts have been developed based on the availability of laboratory-based results. As total cholesterol was not measured in our cohort, we utilized the WHO cardiovascular disease risk non-laboratory-based charts developed for South Asia (including, Bangladesh, Bhutan, India, Nepal, and Pakistan). The non-laboratory-based risk charts do not account for diabetes diagnosis or total cholesterol level.

The prediction chart grades cardiovascular risk using the following categories: age (1: 40–44years; 2: 45-49 years; 3: 50-54 years; 4: 55-59 years; 5: 60-64 years; 6: 64-69 years; 7: 70-74 years), sex (men and women), smoking (smoker or non-smoker), systolic blood pressure (<120 mmHg, 120 to 139, 140 to 159, 160 - <180, and ≥ 180), and body mass index (<20, 20-24, 25-29, 30-35, and ≥ 35). The risk categories for 10-year combined acute myocardial infarction and stroke (fatal and non-fatal) are as follows: <5%, 5-<10%, 10 - <20%, 20 to <30%, and $\geq 30\%$.

Observations with missing values were dropped from the analysis. We did not anticipate any bias from the complete-case analysis approach as the number of missing observations for key variables was less than 2%: smoking status, n=18 or 0.3% missing values; systolic blood pressure, n = 22 or 0.4% missing values; diastolic blood pressure, n = 25 or 0.4% missing values; and body mass index, n=30 or 0.5%,

Data Analysis

We present sociodemographic variables using mean (standard deviation) or the median (interquartile range) for continuous variables and proportion for categorical variables. We conducted bivariate analyses by sex and age group. We used the chi-square test to assess for any significant

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3 differences in CVD risk distribution across sex. For estimating the cost of medicines per million per year
4 (population aged 40 years or older), we used the lowest price of each drug class available in the market
5 (generic preparation of aspirin, thiazide diuretics, statins, and angiotensin-converting enzyme inhibitors).
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7 Appendix 1 includes further details regarding the specific costs of common drugs used to treat
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12 cardiovascular disease in Bangladesh.

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14 To calculate costs we included the following categories: (1) people with high cardiovascular risk
15 ($\geq 20\%$ and $BP \geq 160/100$), who are recommended for pharmacological intervention using four different
16 types of drugs for treatment^(5, 7); and (2) people with $BP \geq 140/90$, who are recommended
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18 antihypertensive treatment. To calculate the estimated annual total cost of CVD medication treatment per
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20 million populations (aged 40 years or older), we multiplied the percentage of the population at risk and
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22 the price of medicine in Bangladesh. We included an estimate of the total number of people estimated to
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24 require drug treatment as follows: we multiplied the prevalence of the population requiring medication
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26 based on each approach based on our study estimates, by the number of people in the general population
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28 in 2013 (19) stratified by gender and age group.
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35 **Results**

36 Demographic Characteristics

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39 The mean age of included participants was 52.9 years (men: 53.5 years, women: 52.5 years)
40 (Table 1). The average level of educational attainment was 3.1 years of education; women were generally
41 less educated than men (2.1 years vs. 4.3 years, respectively). The majority (80%) of women were
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43 housewives, and among men, the most common occupation was an industrial worker or day laborer
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45 (51.2%). Overall, over one-third of participants ever used smoking tobacco, and over half ever used
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47 smokeless tobacco. Few participants drank alcohol in the past 30 days (1.2%). The mean BMI was 21.9
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49 kg/m^2 and the mean waist circumference was 82.4 cm.
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54 Overall, the prevalence of hypertension (defined as $BP \geq 140/90$) increased with age among men
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56 and women. Additionally, women had higher prevalence of hypertension among nearly all age-groups in
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3 both urban and rural areas. Prevalence of hyperglycemia (glucose ≥ 11.1 mmol/L) was higher among
4 urban adults compared to rural across all age groups. The highest prevalence of hyperglycemia was
5 observed among urban men aged 60-69 years at 18.2%. Finally, the prevalence of overweight and obesity
6 was higher among urban residents than rural residents. The largest prevalence of overweight and obesity
7 were observed among urban women, with prevalence as high as 51.4% among women aged 40-49 years
8 (Figure 1).
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15 16 17 18 Distribution of Cardiovascular Risk

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20 We summarized the distribution of cardiovascular risk in the population overall and stratified by
21 sex in Table 2. Eighty-five percent of participants had a low ($< 10\%$) 10-year cardiovascular risk, and
22 this proportion was significantly different across sex ($p < 0.001$). Over half (63.7%) of women had a very
23 low ($< 5\%$) cardiovascular risk. Almost all (99.5%) of the study population were categorized as having
24 cardiovascular risk $< 20\%$. A higher proportion of men (1.0%) were categorized as high risk than women
25 (0.1%) ($p = < 0.001$). Overall, only one male participant was categorized as very high risk or with a
26 cardiovascular risk of $\geq 30\%$.
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34 We summarized the prevalence of adults with hypertension by CVD risk group (Figure 2).
35 Among those with 10- $< 20\%$ CVD risk, we observed a high proportion of hypertensive (41.4%). In the
36 high risk group ($\geq 20\%$), 100% had hypertension. Additionally, among those with $\geq 20\%$ CVD risk, we
37 observed that 35% had severe hypertension (BP $\geq 160/100$).
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45 Cost of Drug Treatment

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47 We were unable to compare costs of drug treatment at two cardiovascular risk thresholds (30% to
48 20%) due to only one male adult with a CVD risk at $\geq 30\%$. We observed low proportion of adults with
49 CVD risk $\geq 20\%$ at 0.5%. When we included BP $\geq 160/100$ measurements, the number of people requiring
50 treatment more than tripled from 0.5% to 1.8% (Table 3). Conversely, if a single risk factor approach was
51 applied, and all those with hypertension (a persistent SBP ≥ 140 and/or DBP ≥ 90) were treated, 24.6% of
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3 the sample would require drug treatment, specifically antihypertensive; more than 20 times the proportion
4 identified when using the total cardiovascular risk approach alone.
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9 Comparison of Cost by Approach

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11 Next, we compared the estimated annual cost of medicines per million populations for
12 implementing the total risk approach vs. the single risk factor approach. Table 4 shows the estimated
13 number of people aged 40 years or older requiring drug treatment stratified by age group and gender. The
14 estimates showed that if the single risk factor approach is applied in Bangladesh with its percentage of
15 population at risk and the lowest price of medicine in the country, the cost per million populations (aged
16 40 years or older) of treating those with $BP \geq 140/90$ would be \$7,111,368 US\$; if the absolute risk
17 approach were applied, the cost of treating those with 10-year risk of $CVD \geq 20\%$ per million populations
18 (aged 40 years or older) would be \$144,540, almost fifty times less (Figure 3). The cost estimation was
19 based on the percentage of the population at different levels of risk and the differences in the price of
20 generic medicines. For this analysis, we focused on the cost of pharmacological treatment as it is the most
21 critical contributor to the overall direct costs of CVD treatment in Bangladesh. We assumed that other
22 costs of CVD treatment and prevention service delivery, such as health facilities and wages of health
23 workers, are similar for both approaches of service delivery(7).
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41 **Discussion**

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43 Using this nationally representative survey of Bangladeshi adults aged 40 years and above, we
44 found that the majority of adults (97%) were at a very low, low or moderate ten-year risk of myocardial
45 infarction and stroke. The proportion of adults requiring drug treatment rose from 1.0% to 2.1% when the
46 threshold for pharmacologic intervention was changed from $\geq 20\%$ only to $\geq 20\%$ and blood pressure of
47 160/100, respectively; which was lower the proportion than the single risk factor approach (24.6%). Our
48 data demonstrated that using a single risk factor approach to manage individual cardiovascular risk factors
49 is costlier (\$7,111,368 per million population) than using the total risk approach (CVD risk ≥ 20 , \$144,540
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3 per million population), as a more substantial proportion of adults will need drug treatment. Findings
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5 from this analysis support the implementation of clinical guidelines using CVD risk scores calculated
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7 using the WHO/ISH prediction charts to appropriately identify patients at highest risk of CVD
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9 development over ten years in Bangladesh.
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12 In our study using nationally representative data, we found that the 10-year risk of CVD was low
13 (<10%) among the vast majority of adults (85.1%). Additionally, only 0.5% of adults were at high risk (\geq
14 20%) of a CVD event within the next ten years. In this analysis, we applied the 2019 CVD Risk Charts
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16 for South Asia, which are newly developed and now incorporate body mass index as part of the prediction
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18 chart algorithm. Our results are comparable to data from South Asia presented in the 2019 Lancet
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20 publication by the WHO CVD Risk Chart Working Group, which showed that 0% of women from both
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22 Bhutan and Nepal had a CVD risk level above 20%. Similarly, 0% of men from Bhutan, and only <2% of
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24 men from Nepal were categorized with a risk level above 20%(8). These data demonstrate a lower
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26 prevalence of CVD risk \geq 20% than prior reports from South Asia, which utilized the original risk
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28 prediction charts published in 2007. For example, prior data from Nepal showed that 4.3% of adults were
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30 categorized with a high (\geq 20%) 10-year risk of a CVD event(20). Further, analyses from a rural area of
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32 south India revealed that seventeen percent of participants had moderate to high risk (10->20%) of
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34 cardiovascular events per the 2007 WHO prediction charts(21). Finally, data collected in 2010 from
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36 Pakistan showed that 10% of adults were categorized with \geq 20% CVD risk, with 2.9% as high as
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38 \geq 40%(7). When utilizing the 2019 WHO prediction charts on the population level to measure and monitor
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40 trends in total CVD risk in recent years, policy makers should interpret the trends with caution, and
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42 potentially compare changes in trends of CVD-risk using the criteria of both the 2007 and 2019 WHO
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44 risk prediction charts.
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50 Our data demonstrate a similar drop in proportion of adults with a CVD risk \geq 20% as observed in
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52 other South Asian countries when the 2019 risk prediction charts are applied. Utilizing the 2007
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54 prediction charts, two prior studies have reported absolute CVD risk among the Bangladeshi population
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56 (10, 22). When using the prior version of the 2007 WHO risk prediction charts Fatema et al. found that
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3 10% of Bangladeshi adults living in rural areas were at high risk ($\geq 20\%$) of a CVD event within the next
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5 ten years, and half of these adults fell in the very high-risk category ($\geq 30\%$). These proportions were the
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7 same when total cholesterol was incorporated in the WHO/ISH CVD Risk-Assessment Tool.

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9 Unfortunately, we were unable to measure total blood cholesterol and were unable to make similar
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11 comparisons. In another rural Bangladeshi population, the proportion of participants at a high-risk (\geq
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13 20%) of a CVD event in 10 years was 2.1%, which is closer in proportion to our finding(22). No other
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15 studies in Bangladesh have been conducted to assess the 10-year risk of CVD using the WHO/ISH tool.
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17 We present novel data using the 2019 WHO risk prediction charts and a nationally representative sample,
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19 which may be generalizable to the population of Bangladesh. Data we present may be used to inform
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21 policymakers decisions on clinical guidelines and resource allocation for treatment of CVDs in
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23 Bangladesh.

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26 Similar to prior analyses conducted using data from eight low- and middle-income countries(7),
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28 our results demonstrate that in the Bangladeshi context using a single risk factor approach to evaluate risk
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30 of CVD-related mortality would cost more than implementing the total risk approach due to higher drug
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32 costs. In Bangladesh, about 60% of out-of-pocket expenditure patients face goes towards drugs directly
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34 bought from pharmacies, diagnostics, and informal providers(23). Additionally, patients in Bangladesh
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36 experience a high level of uncertainty regarding out-of-pocket costs due to unforeseen costs on
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38 diagnostics and medications, including under-the-table payments to providers for reliable and timely
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40 services(24). Currently, Bangladesh does not offer universal health coverage or affordable health
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42 insurance plans. The cost of treatment for CVD frequently leads to catastrophic health expenditure and
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44 impoverishment; the proportion of catastrophic spending for treatment is highest among those from the
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46 lowest quintiles of wealth (14%) compared to those with high wealth and high socioeconomic status
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48 (6.6%) (25). As such, implementing the WHO risk prediction charts may be beneficial to patients in
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50 Bangladesh as only those at highest risk of future CVD would be recommended for life-saving treatment.

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53 In addition to benefits to the patient, implementing the total risk approach would also be
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55 beneficial to the health care system in Bangladesh by improving NCD preventive service delivery and the
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3 use of guidelines for adequate care. Currently, Bangladesh is categorized by the World Bank as a lower-
4 middle-income country with emerging health challenges as the burden of NCDs continues to grow. In
5 2015, an estimated 67% of all deaths in Bangladesh were due to NCDs and the risk of premature death
6 from chronic disease among adults aged 30-70 years was 22%(26). Indeed, CVDs and circulatory
7 diseases are the leading cause of mortality and morbidity in Bangladesh. Despite this substantial burden,
8 preventive services for CVDs in Bangladesh are limited. In 2014, an estimated 16% of health care
9 facilities across the country (i.e. hospitals, community clinics) had the resources to diagnose, prescribe
10 treatment for, and manage patients with CVDs(27). District hospitals (95%) and upazila health
11 complexes (81%), and private hospitals (77%) were more likely to provide services for cardiovascular
12 diseases than other facilities. Only 10% of community clinics and maternal and child welfare centers, and
13 17% of union level facilities, which are the most accessible providers in rural areas, provided any
14 cardiovascular services, and the services at these facilities were limited to the measurement of blood
15 pressure or referrals(27). Among facilities with the capacity to offer services for CVD management, about
16 only 20% utilized established guidelines for hypertension treatment and less than one-third had essential
17 CVD medicines readily available on-site for patients(27). By integrating the WHO risk prediction charts
18 into the national guidelines for management of hypertension and CVD prevention in Bangladesh, the
19 proportion of facilities using established guidelines may increase as the charts are easy to implement,
20 interpret, and access. Additionally, since only one-third of facilities have essential CVD medicines readily
21 available, distributing pharmacologic treatment to those at highest risk of premature mortality due to
22 CVD will be crucial.

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45 Although implementation of a total risk approach may lead to cost-savings, the WHO prediction
46 charts may underestimate CVD risk in certain categories of people such as those with persistent raised
47 blood pressure $\geq 160/100$ mmHg, blood cholesterol ≥ 8 mmol/L, or those suffering from diabetes with
48 renal disease(5). Patients who may fall in these categories should be recommended for intensive lifestyle
49 interventions, and appropriate drug therapy. In fact, the risk models used to develop the 2019 CVD risk
50 charts may have underestimated CVD risk due to limitations in the population data used to estimate
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3 incidences: As reported in the 2019 Lancet publication by the WHO CVD Risk Chart Working Group the
4 data used to develop the predictions models likely included people already on cardiovascular disease
5 prevention therapies, such as statins, which have led to an underestimate in CVD risk(8). In our study, we
6 underscore the potential for underestimation of CVD risk by comparing the proportion of adults
7 categorized as high risk ($\geq 20\%$ CVD risk) to those who would be diagnosed with hypertension (BP \geq
8 140/60) and severe hypertension (BP $\geq 160/100$). Additionally, we provided a graphical summary of
9 common risk factors of CVD, including hypertension, hyperglycemia, and overweight and obesity.
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11 Despite our very low proportion of adults who would be recommended for treatment based on the risk
12 prediction charts, we observed a high prevalence of these risk factors particularly in urban populations.
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22 Limitations of this analytic approach should be considered when interpreting our results. The
23 CVD 10-year risk cut-offs were defined using risk prediction models derived from 85 cohorts mostly
24 from high-income countries, as data from large-scale prospective cohort data from most low-income and
25 middle-income countries (LMICs) are unavailable. Data were used from the Global Burden of Disease
26 project to recalibrate the models to be representative of LMICs, however, the GBD data do not have
27 country-specific disease risk estimates. As such, the estimation used from each region's chart will most
28 likely apply to the largest country within each region, or from the country where most of the data
29 originated. The risk prediction he charts provide approximate estimates of CVD risk in people who do not
30 have established coronary heart disease, stroke or other atherosclerotic diseases. Although we included
31 simvastatin in our pharmacologic cost analysis, we were unable to measure total cholesterol or confirm
32 the medical history of participants using medical charts and relied on self-report, leading to the potential
33 for measurement error and recall bias. Further, our data were collected in 2013 and may be outdated as
34 population growth in older age groups has been observed in recent years. Our analyses should be
35 replicated using more recent data and future research studies should include the measurement of total
36 cholesterol. Finally, our cost estimates were based on the prevalence of each risk approach in our study
37 sample. Although we present the total number of people estimated to require drug treatment using 2013
38 population data, estimates of only those at risk of their first CVD event were unavailable due to lack of
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3 surveillance data. Nevertheless, our data are valuable as the first analysis to apply the 2019 WHO CVD
4 risk prediction charts to a cohort of adults in Bangladesh. Additionally, we provide data on the
5 comparative cost difference of each approach to underscore the potential cost savings in implementing the
6 total risk approach in Bangladesh. Cost data presented in this analysis may be used in future cost-
7 effectiveness analyses to compare the total risk and single risk factor approach when considering all costs
8 from a societal perspective to inform health policy in Bangladesh.
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16 The World Health Organization has outlined global targets in the Global Monitoring Framework
17 for the control of NCDs in LMICs, which prioritizes an 80% of availability of affordable basic
18 technologies and essential medicines necessary to treat significant NCDs, including CVDs in both rural
19 and urban areas of the country. Limited CVD treatment access and weak health care infrastructure in
20 Bangladesh is a significant public health concern. As public financing for health care is limited in
21 Bangladesh (~1% of gross domestic product or GDP), public health policies on CVD drug treatment
22 guidelines based on cost estimates, such as out-of-pocket costs is necessary for effective CVD control.
23 Effective policies should address the potential for overtreatment, which comes at a high cost to both the
24 health care system and the patient. The high percentage of the Bangladeshi adult population at low 10-
25 year CVD risk (<10%) highlights the potential for reduction of CVD risk through population-wide public
26 health policy and availability of accessible preventive services. However, caution should be taken to
27 ensure that risk stratification approaches are not used in inappropriate clinical circumstances, such as
28 adults with highly uncontrolled hypertension with blood pressure measurements at 160/100 mmHg.
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45 **Conclusion**

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47 Our data show that the implementation of a total risk approach compared with a single risk factor
48 approach will reduce the health care expenditure by lowering drug costs, which accounts for 60% of out-
49 of-pocket spending in Bangladesh. This approach would be particularly beneficial in Bangladesh, a low-
50 resource country that should prioritize the development of health policy for effective resource allocation
51 in the public health sector. Using the total risk approach would increase service coverage and allow for
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3 the distribution of resources to target those at highest risk of experiencing a heart attack or stroke. As the
4 majority of the Bangladeshi adult population aged ≥ 40 years have a low ten-year risk of CVD, strategies
5 that target those at highest risk of CVD coupled with public health policies to reduce the population-level
6 risk of CVD may be effective.
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Footnotes

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Availability of data and materials: The de-identified participant data used and/or analyzed during the current study are available from the corresponding author on reasonable request. Please contact M. Mostafa Zaman at zamanm@who.int for further information and guidelines.

Authors contributions: JYI: conceptualized the manuscript, analyzed data, interpreted results critically, and drafted the manuscript. MMZ: conceptualized the manuscript, designed the study, interpreted results critically, guided manuscript writing, and critically reviewed it. MM, SAS, AHMEH prepared the survey protocol, trained the field team, implemented the survey, processed the data, and reviewed the manuscript. SAS is the guarantor of data.

Figures:

Figure 1: Prevalence of hypertension, hyperglycemia, and overweight and obesity among Bangladeshi adults aged 40 years and above by area of residence and age group

Figure 2: Proportion of adults with hypertension or severe hypertension by CVD risk group

Figure 3: Annual costs of pharmacologic treatment for CVD by sex and risk stratification approach

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Table 1: Background Characteristics of Bangladeshi Adult Participants (n = 6189)

Characteristics	Total (n = 6189)			Men (n = 2824)			Women (n = 3365)		
	Mean (SD)	n	%	Mean (SD)	n	%	Mean (SD)	n	%
Age (years)	52.9 (9.9)			53.5 (10.1)			52.5 (9.8)		
Education (years)	3.1 (4.2)			4.3 (4.8)			2.1 (3.3)		
Area of Residence									
Urban		1873	30.2		808	28.6		1065	31.6
Rural		4316	69.8		2016	71.4		2300	68.4
Occupation									
Professional employment [‡]		1007	16.3		880	31.3		127	3.8
Industrial worker/Day Laborer		1600	25.9		1440	51.2		160	4.8
Housework		2697	43.7		-	-		2697	80.3
Unemployed/Retired		735	11.9		386	13.7		349	10.4
Other [§]		131	2.1		106	3.8		25	0.7
Smoking Tobacco Use									
Current User		1493	24.2		1432	50.7		61	1.8
Ever User		2261	36.5		2150	76.1		111	3.3
Smokeless Tobacco Use [◇]									
Current User		3078	49.7		1208	42.8		1870	55.6
Ever User		3469	56.1		1433	50.7		2046	60.5
Alcohol use in the last 30 days									
Yes		75	1.2		68	2.4		7	0.2
Body Mass Index [¶]	21.9 (4.1)				21.4 (3.7)			22.3 (4.4)	
Waist Circumference** (cm)	82.4 (13.3)				81.8 (10.5)			82.8 (15.2)	
Blood Pressure									
Systolic Blood Pressure ^{††} (mmHg)	119.7 (15.2)				119.8 (14.9)			119.7 (15.5)	
Diastolic Blood Pressure ^{††} (mmHg)	80.3 (9.5)				80.2 (9.4)			80.3 (9.7)	
Blood Glucose Levels ^{§§} (mmol/L)	6.9 (3.0)				6.9 (3.0)			6.9 (2.9)	

Abbreviations: SD: Standard Deviation; CM: centimeters; mmHg: millimeter of mercury; mmol/L: millimoles per liter

[‡]Professional occupation includes: Government employee, private company employee, businessman

[§]Other occupation includes: Shop keeper, weavers, driver, student, beggar, cook, carpenter, and tailor

^{||}Excluding smokeless tobacco | Missing values, n = 18; Men, n = 11; Women, n = 7

[◇]Smokeless tobacco use includes jorda, white leaf (shaada pata), gul, etc.

[¶]Body mass index (BMI) calculated by weight in kilogram divided by height in meter squared

Table 2: Ten-year risk of combined myocardial infarction and stroke (fatal and non-fatal) by gender, using the 2019 WHO CVD Risk non-laboratory based charts for South Asia (n = 5977)

	Total (n = 5977)			Men (n = 2708)			Women (n = 3269)			P*
	n	%	CI	n	%	CI	n	%	CI	
Very Low Risk (<5%)	3115	52.1	50.8-53.4	1034	38.2	36.6-40.0	2081	63.7	62.0-65.3	<0.001
Low Risk (5-10 %)	1972	33.0	31.8-34.2	1047	38.7	36.8-40.5	925	28.3	26.8-30.0	<0.001
Moderate Risk (10 - <20%)	860	14.4	13.5-15.3	600	22.2	20.6-23.8	260	7.8	7.0-8.9	<0.001
High Risk (20 - <30%)	29	0.5	0.3-0.7	26	1.0	0.6-1.4	3	0.1	0.0-0.2	<0.001
Very High Risk (≥ 30%)	1	0.0	0.0-0.01	1	0.0	0.0-0.1	0	0.0	0.0-0.0	0.272

Abbreviations: CI, confidence interval; WHO, World Health Organization; CVD, Cardiovascular disease

* P-value based on chi-square test

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Table 3: Estimation of percentage of population requiring drug treatment based on total risk approach in comparison to single risk factor approaches (n = 5977)

	Cardiovascular Risk \geq 20%		Single Risk Factor Approach
	CV Risk \geq 20% alone, %	CV Risk \geq 20% + BP \geq 160/100	BP \geq 140/90 (SBP \geq 140 + isolated raised DBP), %
Men	1.0	2.1	22.1
Women	0.1	1.6	26.7
Total	0.5	1.8	24.6

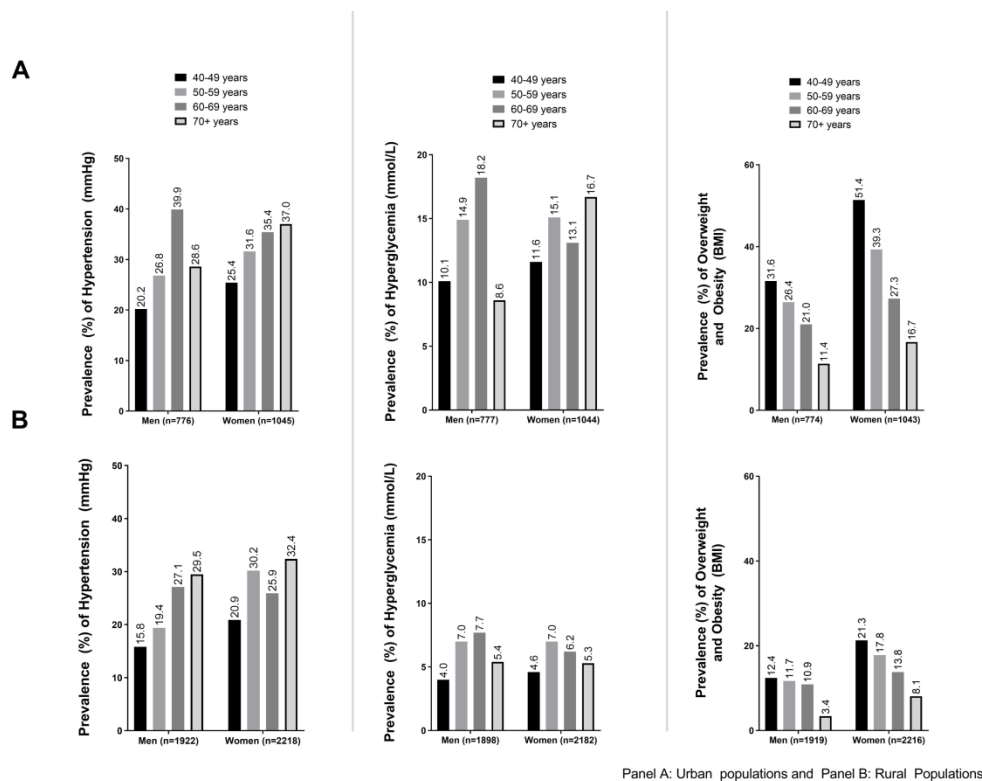
Abbreviations: CV, cardiovascular; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 4: Population projections and comparison of medicine costs (US\$) for implementing total risk approach vs. single risk factor approach in Bangladesh

Estimated annual total cost of CVD medication treatment per million population†									
Total risk approach CV Risk ≥ 20% alone									
	Total no. of people in the general population (in thousands)*	Percentage of population aged ≥40 years requiring medication (%)	Total no. of people estimated to require drug treatment (in thousands)	No. of people per million population (aged 40 years and older)	Aspirin	Enalapril	Hydrochlorothiazide	Simvastatin	Total
Age Group									
Men									
40 to 49	9210	0.4	3660	4000	\$6,570.0	\$34,748.0	\$12,118.0	\$62,196.0	\$115,632.0
50 to 59	6303	0.1	596	1000	\$1,642.5	\$8,687.0	\$3,029.5	\$15,549.0	\$28,908.0
60 to 69	3730	1.5	4733	15000	\$24,637.5	\$130,305.0	\$45,442.5	\$233,235.0	\$433,620.0
≥ 70	1881	7.0	17507	70000	\$114,975.0	\$608,090.0	\$212,065.0	\$1,088,430.0	\$2,023,560.0
Total	21124	1.0	20769	10000	\$16,425.0	\$86,870.0	\$30,295.0	\$155,490.0	\$289,080.0
Women									
40 to 49	9087	0.0	0	0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
50 to 59	5662	0.0	0	0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
60 to 69	3257	0.0	0	0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
≥ 70	1638	1.6	3965	16000	\$26,280.0	\$138,992.0	\$48,472.0	\$248,784.0	\$462,528.0
Total	19644	0.1	1958	1000	\$1,642.5	\$8,687.0	\$3,029.5	\$15,549.0	\$28,908.0
All									
40 to 49	18296	0.2	3605	2000	\$3,285.0	\$17,374.0	\$6,059.0	\$31,098.0	\$57,816.0
50 to 59	11965	0.1	1134	1000	\$1,642.5	\$8,687.0	\$3,029.5	\$15,549.0	\$28,908.0
60 to 69	6989	0.7	4206	7000	\$11,497.5	\$60,809.0	\$21,206.5	\$108,843.0	\$202,356.0
≥ 70	3518	4.3	21410	43000	\$70,627.5	\$373,541.0	\$130,268.5	\$668,607.0	\$1,243,044.0
Total	40768	0.5	20175	5000	\$8,212.5	\$43,435.0	\$15,147.5	\$77,745.0	\$144,540.0

Single Risk Factor Approach: BP \geq 140/90 (SBP \geq 140 + isolated raised DBP), %

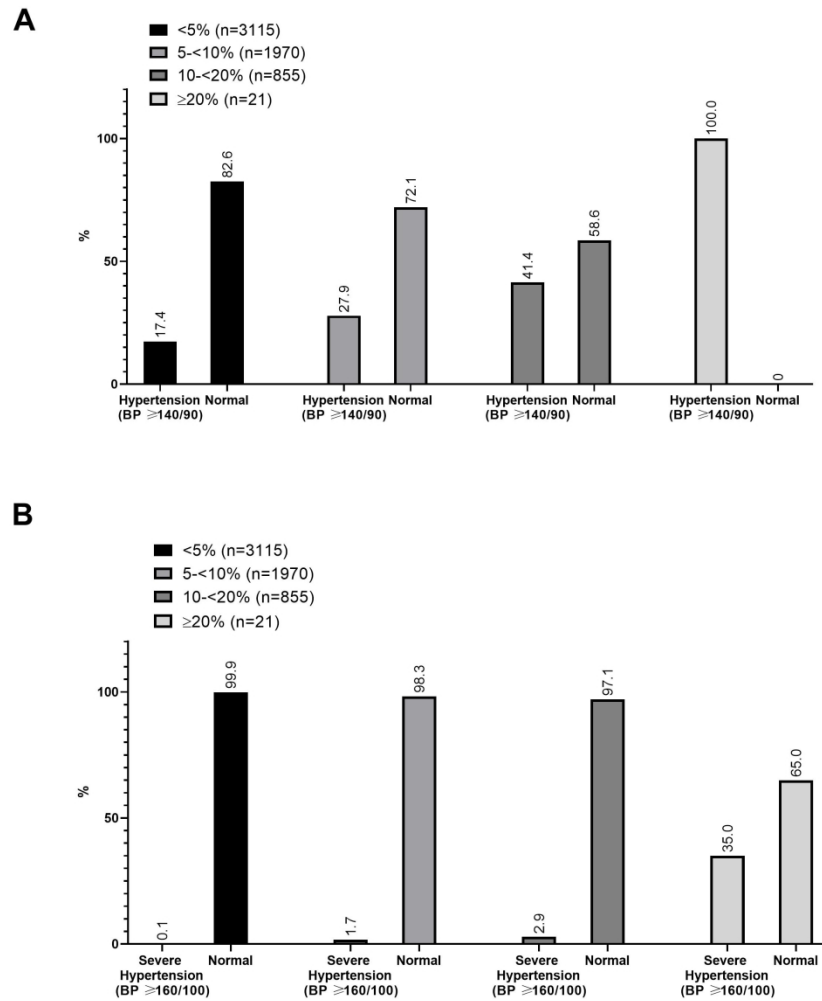
	Total no. of people in the general population (in thousands)*	Percentage of population aged \geq 40 years requiring medication (%)	Total no. of people estimated to require drug treatment (in thousands)	No. of people per million population (aged 40 years and older)	Aspirin	Enalapril	Hydrochlorothiazide	Simvastatin	Total
Age Group									
Men									
40 to 49	9210	17.1	156482	171000	\$280,867.5	\$1,485,477.0	\$518,044.5	\$2,658,879.0	\$4,943,268.0
50 to 59	6303	21.7	129375	217000	\$356,422.5	\$1,885,079.0	\$657,401.5	\$3,374,133.0	\$6,273,036.0
60 to 69	3730	30.5	96228	305000	\$500,962.5	\$2,649,535.0	\$923,997.5	\$4,742,445.0	\$8,816,940.0
\geq 70	1881	29.4	73529	294000	\$482,895.0	\$2,553,978.0	\$890,673.0	\$4,571,406.0	\$8,498,952.0
Total	21124	22.1	458995	221000	\$362,992.5	\$1,919,827.0	\$669,519.5	\$3,436,329.0	\$6,388,668.0
Women									
40 to 49	9087	22.5	199643	225000	\$369,562.5	\$1,954,575.0	\$681,637.5	\$3,498,525.0	\$6,504,300.0
50 to 59	5662	30.6	164475	306000	\$502,605.0	\$2,658,222.0	\$927,027.0	\$4,757,994.0	\$8,845,848.0
60 to 69	3257	28.7	81881	287000	\$471,397.5	\$2,493,169.0	\$869,466.5	\$4,462,563.0	\$8,296,596.0
\geq 70	1638	33.7	83509	337000	\$553,522.5	\$2,927,519.0	\$1,020,941.5	\$5,240,013.0	\$9,741,996.0
Total	19644	26.7	522759	267000	\$438,547.5	\$2,319,429.0	\$808,876.5	\$4,151,583.0	\$7,718,436.0
All									
40 to 49	18296	20.2	364085	202000	\$331,785.0	\$1,754,774.0	\$611,959.0	\$3,140,898.0	\$5,839,416.0
50 to 59	11965	26.3	298189	263000	\$431,977.5	\$2,284,681.0	\$796,758.5	\$4,089,387.0	\$7,602,804.0
60 to 69	6989	29.5	177236	295000	\$484,537.5	\$2,562,665.0	\$893,702.5	\$4,586,955.0	\$8,527,860.0
\geq 70	3518	31.6	157336	316000	\$519,030.0	\$2,745,092.0	\$957,322.0	\$4,913,484.0	\$9,134,928.0
Total	40768	24.6	992585	246000	\$404,055.0	\$2,137,002.0	\$745,257.0	\$3,825,054.0	\$7,111,368.0



Panel A: Urban populations and Panel B: Rural Populations

Figure 1: Prevalence of hypertension, hyperglycemia, and overweight and obesity among Bangladeshi adults aged 40 years and above by area of residence and age group.

281x220mm (300 x 300 DPI)



Panel A: % of adults with hypertension by CVD Risk Group
 Panel B: % of adults with severe hypertension by CVD Risk Group

Figure 2: Proportion of adults with hypertension or severe hypertension by CVD risk group

205x276mm (300 x 300 DPI)

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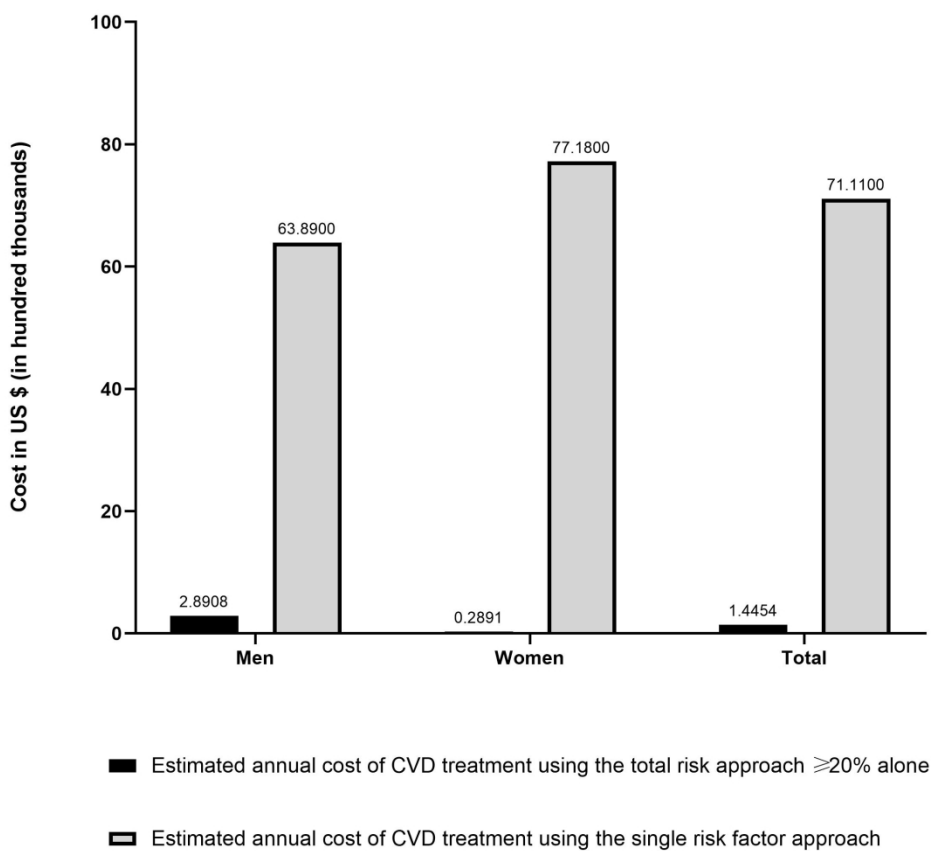


Figure 3: Annual costs of pharmacologic treatment for CVD by sex and risk stratification approach

199x175mm (300 x 300 DPI)

Appendix Table 1: Cost of common drugs used to treat cardiovascular disease in Bangladesh (converted to US\$)

Drug Name	Dose	Number of Tablets	Category	Median price (in Bangladeshi Taka)	Price (in US\$)*
Aspirin	100 mg	100 tablets	Antiplatelet drugs	38BDT	0.45
Atenolol	50 mg	100 tablets	Antihypertensive, Beta-adrenoreceptor blocking drugs	77BDT	0.92
Captopril	25 mg	100 tablets	Antihypertensive, ACE inhibitors	300 BDT	3.58
Chlorthalidone	25 mg	30 tablets	Antihypertensive, thiazide diuretics	60 BDT	0.72
Enalapril	10 mg	100 tablets	Antihypertensive, ACE inhibitors	200 BDT	2.38
Frusemide	40 mg	100 tablets	Antihypertensive, loop diuretics	53 BDT	0.63
Hydrochlorothiazide	25 mg	100 tablets	Antihypertensive, thiazide diuretics	70 BDT	0.83
Isosorbide dinitrate	10 mg	100 tablets	Angina treatment, nitrates - coronary vasodilators	35 BDT	0.42
Labetalol	100 mg	60 tablets	Antihypertensive, Beta-adrenoreceptor blocking drugs	361.2 BDT	4.31
Losartan	50 mg	100 tablets	Antihypertensive, Angiotensin-II receptor blocker	600 BDT	7.15
Lovastatine	20 mg	30 tablets	Lipid regulation, statin	303.3 BDT	3.62
Methyldopa	250 mg	100 tables	Antihypertensive, Centrally acting or central sympatholytic	308 BDT	3.67
Nifedipine (slow release)	20 mg	100 tablets	Angina treatment, calcium-channel blocker	64 BDT	0.76
Propranolol hydrochloride	10 mg	100 tablets	Antihypertensive, Beta-adrenoreceptor blocking drugs	24 BDT	0.29
Simvastatine	10 mg	30 tablets	Lipid regulation, statin	360 BDT	4.29

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3				Antihypertensive, potassium-		
4				sparing diuretics &		
5	Spironolactone	25 mg	100 tablets	aldosterone antagonist	202 BDT	2.41
6		1.5 million				
7	Streptokinase	unit/vial	One vial	Anticoagulant	3100 BDT	36.96
8	Warfarin	5 mg	100 tablets	Anticoagulant	300 BDT	3.58
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Abbreviations: mg, milligrams; US, United States; BDT, Bangladeshi Taka

*Price conversion based on exchange rate on 02/07/2019

For peer review only

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10
Bias	9	Describe any efforts to address potential sources of bias	6-7 & 15-16
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9-10
		(b) Describe any methods used to examine subgroups and interactions	8-11
		(c) Explain how missing data were addressed	9
		(d) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	9
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Estimation of total cardiovascular risk using the 2019 WHO CVD prediction charts and comparison of population-level costs based on alternative drug therapy guidelines: a population-based study of adults in Bangladesh

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3 **Estimation of total cardiovascular risk using the 2019 WHO CVD prediction charts and**
4 **comparison of population-level costs based on alternative drug therapy guidelines: a population-**
5 **based study of adults in Bangladesh**
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9 Running title: Total cardiovascular risk approach in Bangladesh

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Abstract

Objective: The objective of this study is to estimate the population distribution of 10-year cardiovascular disease (CVD) risk among Bangladeshi adults aged 40 years and above, using the 2019 World Health Organization (WHO) CVD Risk Prediction Charts. Additionally, we compared the cost of CVD pharmacologic treatment based on the total CVD risk (thresholds $\geq 30\%$ / $\geq 20\%$) and the single risk factor (hypertension) cutoff levels in the Bangladeshi context.

Study Design: Cross-sectional, population-based study

Setting and Participants: From 2013-2014, we collected data from a nationally representative cross-sectional survey of adults aged ≥ 40 years from urban and rural areas of Bangladesh ($n = 6189$). We estimated CVD risk using the 2019 WHO CVD Risk Prediction Charts and categorized as very low ($<5\%$), low ($5-<10\%$), moderate ($10-<20\%$), high ($20-<30\%$), and very high risk ($\geq 30\%$). We estimated drug therapy costs using the lowest price of each drug class available (aspirin, thiazide diuretics, statins, and angiotensin-converting enzyme inhibitors). We compared the total cost of drug therapy using the total CVD risk vs. single risk factor approach.

Primary Outcome Measures: Our primary outcome was 10-year CVD risk categorized as very low ($<5\%$), low ($5-<10\%$), moderate ($10-<20\%$), high ($20-<30\%$), and very high risk ($\geq 30\%$).

Results: The majority of adults (85.2%, 95% CI: 84.3–86.1) have a 10-year CVD risk of less than 10%. The proportion of adults with a 10-year CVD risk of $\geq 20\%$ was 0.51%. Only one adult was categorized with a 10-year CVD risk of $\geq 30\%$. Among adults with CVD risk groups of very low, low, and moderate, 17.4%, 27.9%, and 41.4% had hypertension (BP $\geq 140/90$) and 0.1%, 1.7%, and 2.9% had severe

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3 hypertension (BP \geq 160/100), respectively. Using the total CVD risk approach would reduce drug costs per
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5 million populations to \$144,540 (risk of \geq 20%).
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9 Conclusion: To reduce health care expenditure for the prevention and treatment of CVD, a total risk
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11 approach using the 2019 WHO CVD Risk Prediction Chart may lead to cost-savings.
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15 **Keywords:** non-communicable diseases, Bangladesh, cardiovascular disease, pharmacologic
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17 intervention, cost, chronic disease
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Article Summary

Strengths and Limitations of the Study

- Using the recently updated 2019 WHO CVD Risk Prediction Charts, this study provides evidence for incorporating the WHO CVD Risk Prediction Charts into CVD management and health care guidelines, and may lead to potential cost-savings from a societal perspective.
- The 2019 WHO CVD Risk Prediction Charts should be applied to a population who have not experienced a CVD event in the past, however, we were unable to confirm self-reported medical history of participants using medical charts or health records, leading to the potential for measurement error due to recall bias.
- The cost estimates we present are an underestimate of total costs for CVD-related treatment as the focus of this study is on the cost of pharmacologic intervention only as the largest contributor to overall direct costs in Bangladesh.
- Although we present the total number of people estimated to require drug treatment using 2014 population data, we were unable to identify population estimates of only those at risk of their first CVD event due to lack of surveillance data.
- The CVD 10-year risk cut-offs were defined using risk prediction models derived from 85 cohorts mostly from high-income countries, as data from large-scale prospective cohort data from most low-income and middle-income countries (LMICs) are limited.

Background

Globally, cardiovascular disease (CVD) is the leading cause of death and disproportionately impacts low- and middle-income countries (LMICs), where over 75% of CVD-related deaths occur (1). People living in LMICs are at high risk of developing CVDs due to the absence of integrated primary care for early detection and prevention of CVD-related risk factors, such as high cholesterol, high blood pressure, and smoking. Limited access to primary care and the growing burden of CVDs is a significant cause of poverty in LMICs and hinders the macroeconomic development of many countries(2). LMICs are estimated to experience cumulative economic losses exceeding 7 trillion US dollars over the next 15 years due to morbidity and mortality caused by noncommunicable diseases, including CVD(3). As such, the significance of the CVD epidemic has gained increasing international recognition over the past decade, leading to the development of several international guidelines for CVD control and prevention(4).

In 2007, the World Health Organization (WHO) published pocket guidelines, including CVD risk prediction charts, designed for health care workers in LMICs to guide patient 10-year risk stratification for heart attack or stroke(5). There are two possible strategies suitable for a low resource setting to assess the risk of a cardiovascular event and identify those at high risk of a fatal CVD outcome: 1. Utilize a single risk factor management strategy, which focuses on one condition at a time, such as hypertension; or, 2. Utilize a more holistic approach considering several risk factors such as age, tobacco use, gender, diabetes diagnosis, body mass index, blood pressure, and blood cholesterol when measured. Through the total risk approach, pocket guidelines help to identify high-risk patients that are in imminent danger of a heart attack or stroke for timely pharmacologic treatment or surgical interventions. Additionally, applying the total risk approach via the WHO prediction charts in a nationally representative sample provides an opportunity to estimate and monitor the population-level distribution of CVD risk to ultimately inform CVD treatment policy recommendations (6, 7).

Currently, Bangladesh has not incorporated clinical guidelines for screening or treatment of risk factors based on absolute CVD risk scores and estimation of the population distribution of CVD risk over time. Data are needed to support the implementation of the WHO prediction charts as clinical guidelines

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3 for Bangladesh, a resource-limited setting, to demonstrate the potential cost-savings and benefit of the
4 WHO recommendation on CVD prevention. Recently in 2019, the WHO updated the CVD risk charts
5 based on newly validated risk prediction models to estimate CVD risk in 21 Global Burden of Disease
6 regions(8). The newly developed risk prediction models have been calibrated using data from The Global
7 Burden of Disease study to include estimates from LMICs. To our knowledge, here we present the first
8 analysis to apply the updated CVD risk charts among a cohort of Bangladeshi adults. Prior studies
9 conducted in Bangladesh have estimated CVD risk among adults residing in rural areas only and have not
10 included a nationally representative population (9-11). Additionally, no prior studies have estimated the
11 potential costs of pharmacological treatment for CVD in Bangladesh using either the single risk factor or
12 total CVD risk approach, as done previously in other settings(7). Our objective was to assess the
13 distribution of absolute CVD risk among a nationally representative sample of Bangladeshi adults using
14 the 2019 WHO CVD Risk Prediction Chart recommended for the WHO South Asian Region
15 (Bangladesh, Bhutan, India, Nepal, and Pakistan). We also compared the costs of drug treatments for
16 CVD prevention using the total cardiovascular risk thresholds at $\geq 20\%$ and with single risk factor cutoff
17 levels (blood pressure $\geq 140/90$ mm Hg).
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37 **Methods**

38 Study design and setting

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41 Data were analyzed from a population-based cross-sectional study conducted from September to
42 December 2013 to assess the burden of blindness and low vision among adults in Bangladesh. The target
43 population of this survey included men and women residing in Bangladesh over the age of 40 years. The
44 exclusion criteria included tourists and the institutionalized, such as residents of a military base, hospital,
45 prisons, nursing homes, and other such institutions. We obtained ethical approval for this study from the
46 Institutional Review Board of the National Institute of Ophthalmology. We provided participants with
47 detailed information regarding the study objectives and procedures using a printed handout prepared in
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3 Bengali. Written consent was obtained from participants through signature or, if not possible through
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5 thumbprint.
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8 9 Sampling Frame

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11 We adopted a multistage, geographically clustered, probability-based sampling approach to
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13 obtain a nationally representative sample of Bangladesh, as previously described and outlined per the
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15 WHO STEPwise approach (12-15). Population statistics were obtained using the 2011 national census
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17 conducted by the Bangladesh Bureau of Statistics (BBS) to create the sample frame (16). The sampling
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19 frame included 64,407 primary sampling units (PSUs) covering all seven divisions of the country. We
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21 randomly selected seventy-two PSUs (25 urban and 47 rural) from seven divisions, with the probability of
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23 selection proportional to the population size of each division. In each PSU, we selected 100 consecutive
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25 households as the secondary sampling unit.
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29 For each household, a trained field data collector approached the head of the household or the
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31 family member most knowledgeable of the residents to screen for eligible participants. The screening
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33 respondent was asked to describe the composition of household residents, which was defined as those
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35 who considered the home to be their primary place of residence as of the night before. A list was
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37 composed and ordered from youngest to oldest age in years starting from 40 years. Using the list of
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39 eligible residents, we used the Kish table approach to randomly select one participant from each home.
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41 The selected participant was asked to come to a nearby health center the next day to administer the survey
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43 by trained study interviewers and undergo a medical examination by the study physician. Based on the
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45 medical review, participants were followed-up with by the providers at the health center for treatment.
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49 Patient and Public Involvement

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51 There was no patient or public involvement in the implementation of this study or interpretation
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53 of analytic results.
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Data Collection

To ensure effective and uniform data collection, field interviewers underwent a seven-day training on the interview methodology by the study ophthalmologists and epidemiologists. The training included an in-depth review of the survey content and protocol for completing the demographic questionnaire (a modified WHO/PBL Version III). Each member of the data collection team was provided a detailed survey protocol manual outlining the survey activities, the questionnaire interview, and information about the duties and responsibilities of all survey personnel.

Demographic data were collected, including age, sex, marital status, educational level, and occupation, using a structured questionnaire survey. Data regarding tobacco use, health history, and treatment history were also collected. Participants were asked if they smoked (e.g. cigarette, hookah, pipe) or if they used smokeless tobacco (e.g. chewing tobacco, jorda) to assess the history of tobacco use. Each participant provided medical history for a prior diagnosis of high blood pressure or hypertension, diabetes, renal disease, or any cardiovascular diseases by a health care provider. Medication history was obtained including medication for high blood pressure, diabetes, malaria, steroids, tuberculosis, and among women, history of oral contraception. The questionnaire was translated from English to Bengali, adapted, and validated before data collection.

Physical measurements, including height, weight, and blood pressure (BP) were collected. Trained field interviewers measured BP using an appropriately calibrated aneroid sphygmomanometer with appropriately sized arm cuffs. BP measurements were consistently taken on the right arm at heart level and elbow-assisted while the participant was seated. The initial measurement was performed after five minutes of rest. After two minutes, the second measurement was taken. The mean of these two BP readings was utilized as the final BP for each participant. To measure blood glucose levels, we obtained random blood glucose samples (17). Capillary blood samples were consistently taken using the right arm and index finger with a glucometer (Accu-chek Advantage, Roche Diagnostics Division, Grenzachstrasse, Switzerland).

Estimation of 10-year CVD risk

We estimated 10-year CVD risk using the 2019 WHO CVD risk prediction charts(8, 18). The prediction charts provide the 10-year risk of a fatal or non-fatal major cardiovascular event, such as myocardial infarction or stroke, based on age, sex, blood pressure, body mass index, smoking status, total blood cholesterol, and the presence or absence of diabetes mellitus for 14 WHO epidemiological sub-regions. For each region, two sets of charts have been developed based on the availability of laboratory-based results. As total cholesterol was not measured in our cohort, we utilized the WHO cardiovascular disease risk non-laboratory-based charts developed for South Asia (including, Bangladesh, Bhutan, India, Nepal, and Pakistan). The non-laboratory-based risk charts do not account for diabetes diagnosis or total cholesterol levels.

The prediction chart grades CVD risk using the following categories: age (1: 40–44years; 2: 45-49 years; 3: 50-54 years; 4: 55-59 years; 5: 60-64 years; 6: 64-69 years; 7: 70-74 years), sex (men and women), smoking (smoker or non-smoker), systolic blood pressure (<120 mmHg, 120 to 139, 140 to 159, 160 - <180, and \geq 180), and body mass index (<20, 20-24, 25-29, 30-35, and \geq 35). The risk categories for 10-year combined acute myocardial infarction and stroke (fatal and non-fatal) are as follows: <5%, 5- <10%, 10 - <20%, 20 to <30%, and \geq 30%.

Observations with missing values were dropped from the analysis. We did not anticipate any bias from the complete-case analysis approach as the number of missing observations for key variables was less than 2%: smoking status, n=18 or 0.3% missing values; systolic blood pressure, n = 22 or 0.4% missing values; diastolic blood pressure, n = 25 or 0.4% missing values; and body mass index, n=30 or 0.5%.

Data Analysis

We present sociodemographic variables using mean (standard deviation) or the median (interquartile range) for continuous variables and proportion for categorical variables. We conducted bivariate analyses by sex and age group. We used the chi-square test to assess for any significant

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3 differences in CVD risk distribution across sex. For estimating the cost of medicines per million per year
4 (population aged 40 years or older), we used the lowest price of each drug class available in the market
5 (generic preparation of aspirin, thiazide diuretics, statins, and angiotensin-converting enzyme inhibitors).
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7 Appendix Table 1 includes further details regarding the specific costs of common drugs used to treat
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12 cardiovascular disease in Bangladesh.

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14 To calculate costs we included the following categories: (1) people with high cardiovascular risk
15 ($\geq 20\%$ and $BP \geq 160/100$), who are recommended for pharmacological intervention using four different
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17 types of drugs for treatment^(5, 7); and (2) people with $BP \geq 140/90$, who are recommended
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19 antihypertensive treatment. To calculate the estimated annual total cost of CVD medication treatment per
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21 million populations (aged 40 years or older), we multiplied the percentage of the population at risk and
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23 the price of medicine in Bangladesh. We included an estimate of the total number of people estimated to
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25 require drug treatment as follows: we multiplied the prevalence of the population requiring medication
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27 based on each approach by the number of people in the general population in 2013 (19) stratified by
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31 gender and age group.

32 33 34 35 **Results**

36 37 Demographic Characteristics

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39 The mean age of included participants was 52.9 years (men: 53.5 years, women: 52.5 years)
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41 (Table 1). The average level of educational attainment was 3.1 years of education; women were generally
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43 less educated than men (2.1 years vs. 4.3 years, respectively). The majority (80%) of women were
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45 housewives, and among men, the most common occupation was an industrial worker or day laborer
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47 (51.2%). Overall, over one-third of participants ever used smoking tobacco, and over half ever used
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49 smokeless tobacco. Few participants drank alcohol in the past 30 days (1.2%). The mean BMI was 21.9
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51 kg/m^2 and the mean waist circumference was 82.4 cm.

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54 Overall, the prevalence of hypertension (defined as $BP \geq 140/90$) increased with age among men
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56 and women. Additionally, women had a higher prevalence of hypertension among nearly all age-groups
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3 in both urban and rural areas. The prevalence of hyperglycemia (glucose ≥ 11.1 mmol/L) was higher
4 among urban adults compared to rural across all age groups. The highest prevalence of hyperglycemia
5 was observed among urban men aged 60-69 years at 18.2%. Finally, the prevalence of overweight and
6 obesity was higher among urban residents than rural residents. The largest prevalence of overweight and
7 obesity was observed among urban women, with prevalence as high as 51.4% among women aged 40-49
8 years (Figure 1).
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15 16 17 18 Distribution of Cardiovascular Risk

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20 We summarized the distribution of CVD risk in the population overall and stratified by sex in
21 Table 2. Eighty-five percent of participants had a low ($< 10\%$) 10-year CVD risk, and this proportion
22 was significantly different across sex ($p < 0.001$). Over half (63.7%) of women had a very low ($< 5\%$)
23 cardiovascular risk. Almost all (99.5%) of the study population were categorized as having cardiovascular
24 risk $< 20\%$. A higher proportion of men (1.0%) were categorized as high risk than women (0.1%) ($p =$
25 < 0.001). Overall, only one male participant was categorized as very high risk or with a CVD risk of \geq
26 30%.
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35 We summarized the prevalence of adults with hypertension by CVD risk group (Figure 2).
36 Among those with 10- $< 20\%$ CVD risk, we observed a high proportion of hypertensive (41.4%). In the
37 high-risk group ($\geq 20\%$), 100% had hypertension. Additionally, among those with $\geq 20\%$ CVD risk, we
38 observed that 35% had severe hypertension (BP $\geq 160/100$).
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45 Cost of Drug Treatment

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47 We were unable to compare the costs of drug treatment at two cardiovascular risk thresholds
48 (30% to 20%) due to only one male adult with a CVD risk at $\geq 30\%$. We observed a low proportion of
49 adults with CVD risk $\geq 20\%$ at 0.5%. When we included BP $\geq 160/100$ measurements, the number of
50 people requiring treatment more than tripled from 0.5% to 1.8% (Table 3). Conversely, if a single risk
51 factor approach was applied, and all those with hypertension (a persistent SBP ≥ 140 and/or DBP ≥ 90)
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3 were treated, 24.6% of the sample would require drug treatment, specifically antihypertensive; more than
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5 20 times the proportion identified when using the total cardiovascular risk approach alone.
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8 9 Comparison of Cost by Approach

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11 Next, we compared the estimated annual cost of medicines per million populations for
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13 implementing the total risk approach vs. the single risk factor approach. Table 4 shows the estimated
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15 number of people aged 40 years or older requiring drug treatment stratified by age group and gender. The
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17 estimates showed that if the single risk factor approach is applied in Bangladesh with its percentage of the
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19 population at risk and the lowest price of medicine in the country, the cost per million populations (aged
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21 40 years or older) of treating those with $BP \geq 140/90$ would be \$7,111,368 US\$; if the absolute risk
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23 approach were applied, the cost of treating those with a 10-year risk of $CVD \geq 20\%$ per million
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25 populations (aged 40 years or older) would be \$144,540, almost fifty times less (Figure 3). The cost
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27 estimation was based on the percentage of the population at different levels of risk and the differences in
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29 the price of generic medicines. For this analysis, we focused on the cost of pharmacological treatment as
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31 it is the most critical contributor to the overall direct costs of CVD treatment in Bangladesh. We assumed
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33 that other costs of CVD treatment and prevention service delivery, such as health facilities and wages of
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35 health workers, are similar for both approaches of service delivery(7).
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41 **Discussion**

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43 Using this nationally representative survey of Bangladeshi adults aged 40 years and above, we
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45 found that the majority of adults (97%) were at a very low, low or moderate ten-year risk of myocardial
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47 infarction and stroke. The proportion of adults requiring drug treatment rose from 1.0% to 2.1% when the
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49 threshold for pharmacologic intervention was changed from $\geq 20\%$ alone to $\geq 20\%$ plus blood pressure of
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51 160/100, respectively; which was lower the proportion than the single risk factor approach (24.6%). Our
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53 data demonstrate that using a single risk factor approach to manage individual cardiovascular risk factors
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55 is costlier (\$7,111,368 per million population) than using the total risk approach (CVD risk ≥ 20 , \$144,540
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3 per million population), as a more substantial proportion of adults will need drug treatment. Findings
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5 from this analysis support the implementation of clinical guidelines using CVD risk scores calculated
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7 using the WHO CVD Risk Prediction Charts to appropriately identify patients at the highest risk of CVD
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9 development over ten years in Bangladesh.
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12 In our study using nationally representative data, we found that the 10-year risk of CVD was low
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14 (<10%) among the vast majority of adults (85.1%). Additionally, only 0.5% of adults were at high risk (\geq
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16 20%) of a CVD event within the next ten years. In this analysis, we applied the 2019 CVD Risk Charts
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18 for South Asia, which are newly developed and now incorporate body mass index as part of the prediction
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20 chart algorithm. Our results are comparable to regional data presented in the 2019 Lancet publication by
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22 the WHO CVD Risk Chart Working Group, which showed that 0% of women from Bhutan, Sri Lanka,
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24 and Nepal had a CVD risk level above 20%. Similarly, 0% of men from Bhutan, and only <2% of men
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26 from both Sri Lanka and Nepal were categorized with a risk level above 20%(8). These data demonstrate
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28 a lower prevalence of CVD risk \geq 20% than prior reports from South Asia, which utilized the original risk
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30 prediction charts published in 2007. For example, prior data from Nepal (20) and Sri Lanka(21) showed
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32 that 4.3% and 8.2% of adults respectively, were categorized with a high (\geq 20%) 10-year risk of a CVD
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34 event. Further, analyses from a rural area of South India revealed that seventeen percent of participants
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36 had moderate to high risk (10->20%) of cardiovascular events per the 2007 WHO prediction charts(22).
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38 Finally, data collected in 2010 from Pakistan showed that 10% of adults were categorized with \geq 20%
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40 CVD risk, with 2.9% as high as \geq 40%(7). When utilizing the 2019 WHO prediction charts on the
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42 population level to measure and monitor trends in total CVD risk in recent years, policy makers in LMICs
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44 should interpret the trends with caution, and assess changes in trends of CVD-risk over time using both
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46 the 2007 and 2019 WHO risk prediction charts for comparison.
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50 The WHO CVD Risk Charts were developed for use in LMICs and are now more suitable for use
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52 in these settings due to the inclusion of data from low-resource regions in the risk prediction model
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54 development. While we present the first country-specific analysis using the 2019 risk charts, several prior
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56 studies in LMICs have been conducted using the 2007 risk charts. In other countries in Asia, we observe
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3 the prevalence of "high CVD risk" ($\geq 20\%$) of 6.0%, 2.3% and 1.3% in Mongolia, Malaysia and
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5 Cambodia, respectively(23). Mendis *et al* reported the 10 year CVD risk of seven countries and the
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7 majority of these countries reported low CVD risk among its adult populations [China (96.1%) and Sri
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9 Lanka (94.9%), (Iran (93.9%), Cuba (89.7%), Nigeria (86.0%), Georgia (83.1%), and Pakistan
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11 (79.2%)](7). Studies conducted in urban areas of low- and middle-income countries show varying
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13 prevalence of high CVD risk ($\geq 20\%$): for example, one study from Malaysia shows 20.5% of adults were
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15 high-risk of CVD(24), whereas studies from urban Kenya(25) and Sri Lanka(21) reports less than 10% of
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17 their population had high CVD risk. Specifically in Bangladesh, utilizing the 2007 prediction charts,
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19 three prior studies have reported absolute CVD risk among the adult population (10, 26, 27). Fatema et al.
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21 found that 10% of rural Bangladeshi adults were at high risk ($\geq 20\%$) of a CVD event within the next ten
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23 years, and half of these adults fell in the very high-risk category ($\geq 30\%$). In another rural Bangladeshi
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25 population, the proportion of participants at a high-risk ($\geq 20\%$) of a CVD event was 2.1% (26). Finally,
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27 in an urban Bangladeshi population of 150 adults, 3.4% had high CVD risk ($\geq 20\%$), which is lower than
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29 expected as the population was urban(27). No other studies in Bangladesh have been conducted to assess
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31 the 10-year risk of CVD using the WHO CVD Risk Prediction Charts. We present novel data using the
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33 2019 charts and a nationally representative sample, which may be generalizable to the population of
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35 Bangladesh. Data we present may be used to inform policymakers decisions on clinical guidelines and
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37 resource allocation for treatment of CVDs in Bangladesh.
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41 Similar to prior analyses conducted using data from eight LMICs (7), our results demonstrate that
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43 in the Bangladeshi context using a single risk factor approach to evaluate the risk of CVD-related
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45 mortality would cost more than implementing the total risk approach due to higher drug costs. In
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47 Bangladesh, about 60% of out-of-pocket costs patients face goes towards drugs directly bought from
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49 pharmacies, diagnostics, and informal providers(28). Currently, Bangladesh does not offer universal
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51 health coverage or affordable health insurance plans. The cost of treatment for CVD frequently leads to
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53 catastrophic health expenditure and impoverishment; the proportion of catastrophic spending for
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55 treatment is highest among those from the lowest quintiles of wealth (14%) compared to those with high
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3 wealth and high socioeconomic status (6.6%) (29). As such, implementing the WHO CVD Risk
4 Prediction Charts may be beneficial to patients in Bangladesh as only those at the highest risk of future
5 CVD would be recommended for treatment.
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10 In addition to benefits to the patient, the total CVD risk approach would also be beneficial to
11 Bangladesh's health care system by improving NCD preventive service delivery and the use of guidelines
12 for adequate care. Currently, Bangladesh is categorized by the World Bank as a lower-middle-income
13 country with emerging health challenges as the burden of NCDs continues to grow. In 2015, an estimated
14 67% of all deaths in Bangladesh were due to NCDs and the risk of premature death from chronic disease
15 among adults aged 30-70 years was 22%(30). Indeed, CVDs and circulatory diseases are the leading
16 cause of mortality and morbidity in Bangladesh. Despite this substantial burden, preventive services for
17 CVDs in Bangladesh are limited. In 2014, an estimated 16% of health care facilities across the country
18 (i.e. hospitals, community clinics) had the resources to diagnose, prescribe treatment for, and manage
19 patients with CVDs(31). District hospitals (95%), Upazila health complexes (81%), and private hospitals
20 (77%) were more likely to provide services for cardiovascular diseases than other facilities. Only 10% of
21 community clinics and maternal and child welfare centers, and 17% of union level facilities, which are the
22 most accessible providers in rural areas, provided any cardiovascular services, and the services at these
23 facilities were limited to the measurement of blood pressure or referrals(31). Among facilities with the
24 capacity to offer services for CVD management, about only 20% utilized established guidelines for
25 hypertension treatment and less than one-third had essential CVD medicines readily available on-site for
26 patients(31). By integrating the WHO risk prediction charts into the national guidelines for management
27 of hypertension and CVD prevention in Bangladesh, the proportion of facilities using established
28 guidelines may increase as the charts are easy to implement, interpret, and access. Additionally, since
29 only one-third of facilities have essential CVD medicines readily available, distributing pharmacologic
30 treatment to those at highest risk of premature mortality due to CVD will be crucial.
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54 Although the implementation of a total risk approach may lead to cost-savings, there are
55 limitations to implementing the 2019 CVD Risk Prediction Charts. When compared to the single risk
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3 factor approach, the WHO charts categorizes fewer individuals as high-risk and may delay the receipt of
4 necessary life-saving treatment. For example, the prediction charts may underestimate CVD risk in certain
5 categories of people such as those with persistent raised blood pressure $\geq 160/100$ mmHg, blood
6 cholesterol ≥ 8 mmol/L, or those suffering from diabetes with renal disease(5). Patients who may fall in
7 these categories should be recommended for intensive lifestyle interventions, and appropriate drug
8 therapy, however, the CVD prediction charts will erroneously deny treatment to these potentially high-
9 risk adults.. In fact, the risk models used to develop the 2019 CVD risk charts may have underestimated
10 CVD risk due to limitations in the population data used to estimate incidences: Data used to develop the
11 predictions models likely included people already on cardiovascular disease prevention therapies, such as
12 statins, which have led to an underestimate in CVD risk(8). In our study, we underscore the potential for
13 underestimation of CVD risk by comparing the proportion of adults categorized as high risk ($\geq 20\%$ CVD
14 risk) to those who would be diagnosed with hypertension (BP $\geq 140/60$) and severe hypertension (BP \geq
15 160/100). Additionally, we provided a graphical summary of common risk factors of CVD, including
16 hypertension, hyperglycemia, and overweight and obesity. Despite our very low proportion of adults who
17 would be recommended for treatment based on the risk prediction charts, we observed a high prevalence
18 of these risk factors particularly in urban populations.

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Limitations of this analytic approach should be considered when interpreting our results. The CVD 10-year risk cut-offs were defined using risk prediction models derived from 85 cohorts mostly from high-income countries, as data from large-scale prospective cohort data from most LMICs are unavailable. Data were used from the Global Burden of Disease (GBD) project to recalibrate the models to be representative of LMICs, however, the GBD data do not have country-specific disease risk estimates. As such, the estimation used from each region's chart will most likely apply to the largest country within each region, or from the country where most of the data originated. The risk prediction charts provide approximate estimates of CVD risk in people who do not have established coronary heart disease, stroke or other atherosclerotic diseases. Although we included simvastatin in our pharmacologic cost analysis, we were unable to measure total cholesterol or confirm the medical history of participants

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3 using medical charts and relied on self-report, leading to the potential for measurement error and recall
4 bias. Additionally, we were unable to categorize participants as diabetic as we did not obtain fasting blood
5 glucose and were only able to categorize adults as hyperglycemic in our descriptive analysis as we
6 measured random blood glucose. Further, our data were collected in 2013 and may be outdated as
7 population growth in older age groups has been observed in recent years. Our analyses should be
8 replicated using more recent data and future research studies should include the measurement of total
9 cholesterol. Finally, our cost estimates were based on the prevalence of each risk approach in our study
10 sample. Although we present the total number of people estimated to require drug treatment using 2013
11 population data, estimates of only those at risk of their first CVD event were unavailable due to lack of
12 surveillance data. Nevertheless, our data are valuable as the first analysis to apply the 2019 WHO CVD
13 risk prediction charts to a cohort of adults in Bangladesh. Additionally, we provide data on the
14 comparative cost difference of each approach to underscore the potential cost savings in implementing the
15 total risk approach in Bangladesh. Cost data presented in this analysis may be used in future cost-
16 effectiveness analyses to compare the total risk and single risk factor approach when considering all costs
17 from a societal perspective to inform health policy in Bangladesh.

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35 The World Health Organization has outlined global targets in the Global Monitoring Framework
36 for the control of NCDs in LMICs, which prioritizes an 80% of availability of affordable basic
37 technologies and essential medicines necessary to treat significant NCDs, including CVDs in both rural
38 and urban areas of the country. Limited CVD treatment access and weak health care infrastructure in
39 Bangladesh is a significant public health concern. As public financing for health care is limited in
40 Bangladesh (~1% of gross domestic product or GDP), public health policies on CVD drug treatment
41 guidelines based on cost estimates, such as out-of-pocket costs is necessary for effective CVD control.
42 Effective policies should address the potential for overtreatment, which comes at a high cost to both the
43 health care system and the patient. The high percentage of the Bangladeshi adult population at low 10-
44 year CVD risk (<10%) highlights the potential for reduction of CVD risk through population-wide public
45 health policy and availability of accessible preventive services. However, caution should be taken to
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3 ensure that risk stratification approaches are not used in inappropriate clinical circumstances, such as
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5 adults with highly uncontrolled hypertension with blood pressure measurements at 160/100 mmHg.
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8 9 **Conclusion**

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11 Our data show that the implementation of a total risk approach compared with a single risk factor
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13 approach will reduce the health care expenditure by lowering drug costs, which accounts for 60% of out-
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15 of-pocket spending in Bangladesh. This approach would be particularly beneficial in Bangladesh, a low-
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17 resource country that should prioritize the development of health policy for effective resource allocation
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19 in the public health sector. Using the total risk approach would increase service coverage and allow for
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21 the distribution of resources to target those at highest risk of experiencing a heart attack or stroke. As the
22
23 majority of the Bangladeshi adult population aged ≥ 40 years have a low ten-year risk of CVD, strategies
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25 that target those at highest risk of CVD coupled with public health policies to reduce the population-level
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27 risk of CVD may be effective.
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Footnotes

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Availability of data and materials: The de-identified participant data used and/or analyzed during the current study are available from the corresponding author on reasonable request. Please contact M. Mostafa Zaman at zamanm@who.int for further information and guidelines.

Authors contributions: JYI: conceptualized the manuscript, analyzed data, interpreted results critically, and drafted the manuscript. MMZ: conceptualized the manuscript, designed the study, interpreted results critically, guided manuscript writing, and critically reviewed it. MM, SAS, AHMEH prepared the survey protocol, trained the field team, implemented the survey, processed the data, and reviewed the manuscript. SAS is the guarantor of data.

Figures:

Figure 1: Prevalence of hypertension, hyperglycemia, and overweight and obesity among Bangladeshi adults aged 40 years and above by area of residence and age group

Figure 2: Proportion of adults with hypertension or severe hypertension by CVD risk group

Figure 3: Annual costs of pharmacologic treatment for CVD by sex and risk stratification approach

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Table 1: Background Characteristics of Bangladeshi Adult Participants (n = 6189)

Characteristics	Total (n = 6189)			Men (n = 2824)			Women (n = 3365)		
	Mean (SD)	n	%	Mean (SD)	n	%	Mean (SD)	n	%
Age (years)	52.9 (9.9)			53.5 (10.1)			52.5 (9.8)		
Education (years)	3.1 (4.2)			4.3 (4.8)			2.1 (3.3)		
Area of Residence									
Urban		1873	30.2		808	28.6		1065	31.6
Rural		4316	69.8		2016	71.4		2300	68.4
Occupation									
Professional employment [‡]		1007	16.3		880	31.3		127	3.8
Industrial worker/Day Laborer		1600	25.9		1440	51.2		160	4.8
Housework		2697	43.7		-	-		2697	80.3
Unemployed/Retired		735	11.9		386	13.7		349	10.4
Other [§]		131	2.1		106	3.8		25	0.7
Smoking Tobacco Use									
Current User		1493	24.2		1432	50.7		61	1.8
Ever User		2261	36.5		2150	76.1		111	3.3
Smokeless Tobacco Use [◇]									
Current User		3078	49.7		1208	42.8		1870	55.6
Ever User		3469	56.1		1433	50.7		2046	60.5
Alcohol use in the last 30 days									
Yes		75	1.2		68	2.4		7	0.2
Body Mass Index [¶]	21.9 (4.1)				21.4 (3.7)			22.3 (4.4)	
Waist Circumference ^{**} (cm)	82.4 (13.3)				81.8 (10.5)			82.8 (15.2)	
Blood Pressure									
Systolic Blood Pressure ^{††} (mmHg)	119.7 (15.2)				119.8 (14.9)			119.7 (15.5)	
Diastolic Blood Pressure ^{††} (mmHg)	80.3 (9.5)				80.2 (9.4)			80.3 (9.7)	
Blood Glucose Levels ^{§§} (mmol/L)	6.9 (3.0)				6.9 (3.0)			6.9 (2.9)	

Abbreviations: SD: Standard Deviation; CM: centimeters; mmHg: millimeter of mercury; mmol/L: millimoles per liter

[‡]Professional occupation includes: Government employee, private company employee, businessman

[§]Other occupation includes: Shop keeper, weavers, driver, student, beggar, cook, carpenter, and tailor

^{||}Excluding smokeless tobacco | Missing values, n = 18; Men, n = 11; Women, n = 7

[◇]Smokeless tobacco use includes jorda, white leaf (shaada pata), gul, etc.

[¶]Body mass index (BMI) calculated by weight in kilogram divided by height in meter squared

Table 2: Ten-year risk of combined myocardial infarction and stroke (fatal and non-fatal) by gender, using the 2019 WHO CVD Risk non-laboratory based charts for South Asia (n = 5977)

	Total (n = 5977)			Men (n = 2708)			Women (n = 3269)			P*
	n	%	CI	n	%	CI	n	%	CI	
Very Low Risk (<5%)	3115	52.1	50.8-53.4	1034	38.2	36.6-40.0	2081	63.7	62.0-65.3	<0.001
Low Risk (5-10 %)	1972	33.0	31.8-34.2	1047	38.7	36.8-40.5	925	28.3	26.8-30.0	<0.001
Moderate Risk (10 - <20%)	860	14.4	13.5-15.3	600	22.2	20.6-23.8	260	7.8	7.0-8.9	<0.001
High Risk (20 - <30%)	29	0.5	0.3-0.7	26	1.0	0.6-1.4	3	0.1	0.0-0.2	<0.001
Very High Risk (≥ 30%)	1	0.0	0.0-0.01	1	0.0	0.0-0.1	0	0.0	0.0-0.0	0.272

Abbreviations: CI, confidence interval; WHO, World Health Organization; CVD, Cardiovascular disease

* P-value based on chi-square test

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Table 3: Estimation of percentage of population requiring drug treatment based on total risk approach in comparison to single risk factor approaches (n = 5977)

	Cardiovascular Risk \geq 20%		Single Risk Factor Approach
	CV Risk \geq 20% alone, %	CV Risk \geq 20% + BP \geq 160/100	BP \geq 140/90 (SBP \geq 140 + isolated raised DBP), %
Men	1.0	2.1	22.1
Women	0.1	1.6	26.7
Total	0.5	1.8	24.6

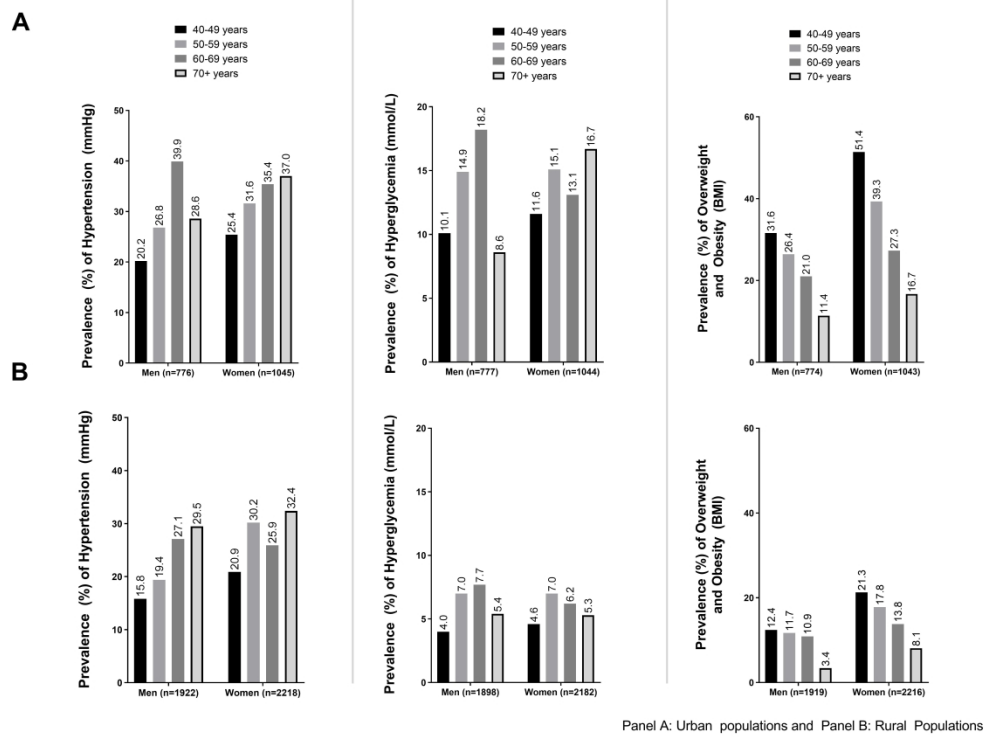
Abbreviations: CV, cardiovascular; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 4: Population projections and comparison of medicine costs (US\$) for implementing total risk approach vs. single risk factor approach in Bangladesh

Estimated annual total cost of CVD medication treatment per million population†									
Total risk approach CV Risk ≥ 20% alone									
	Total no. of people in the general population (in thousands)*	Percentage of population aged ≥40 years requiring medication (%)	Total no. of people estimated to require drug treatment (in thousands)	No. of people per million population (aged 40 years and older)	Aspirin	Enalapril	Hydrochlorothiazide	Simvastatin	Total
Age Group									
Men									
40 to 49	9210	0.4	3660	4000	\$6,570.0	\$34,748.0	\$12,118.0	\$62,196.0	\$115,632.0
50 to 59	6303	0.1	596	1000	\$1,642.5	\$8,687.0	\$3,029.5	\$15,549.0	\$28,908.0
60 to 69	3730	1.5	4733	15000	\$24,637.5	\$130,305.0	\$45,442.5	\$233,235.0	\$433,620.0
≥ 70	1881	7.0	17507	70000	\$114,975.0	\$608,090.0	\$212,065.0	\$1,088,430.0	\$2,023,560.0
Total	21124	1.0	20769	10000	\$16,425.0	\$86,870.0	\$30,295.0	\$155,490.0	\$289,080.0
Women									
40 to 49	9087	0.0	0	0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
50 to 59	5662	0.0	0	0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
60 to 69	3257	0.0	0	0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
≥ 70	1638	1.6	3965	16000	\$26,280.0	\$138,992.0	\$48,472.0	\$248,784.0	\$462,528.0
Total	19644	0.1	1958	1000	\$1,642.5	\$8,687.0	\$3,029.5	\$15,549.0	\$28,908.0
All									
40 to 49	18296	0.2	3605	2000	\$3,285.0	\$17,374.0	\$6,059.0	\$31,098.0	\$57,816.0
50 to 59	11965	0.1	1134	1000	\$1,642.5	\$8,687.0	\$3,029.5	\$15,549.0	\$28,908.0
60 to 69	6989	0.7	4206	7000	\$11,497.5	\$60,809.0	\$21,206.5	\$108,843.0	\$202,356.0
≥ 70	3518	4.3	21410	43000	\$70,627.5	\$373,541.0	\$130,268.5	\$668,607.0	\$1,243,044.0
Total	40768	0.5	20175	5000	\$8,212.5	\$43,435.0	\$15,147.5	\$77,745.0	\$144,540.0

Single Risk Factor Approach: BP \geq 140/90 (SBP \geq 140 + isolated raised DBP), %

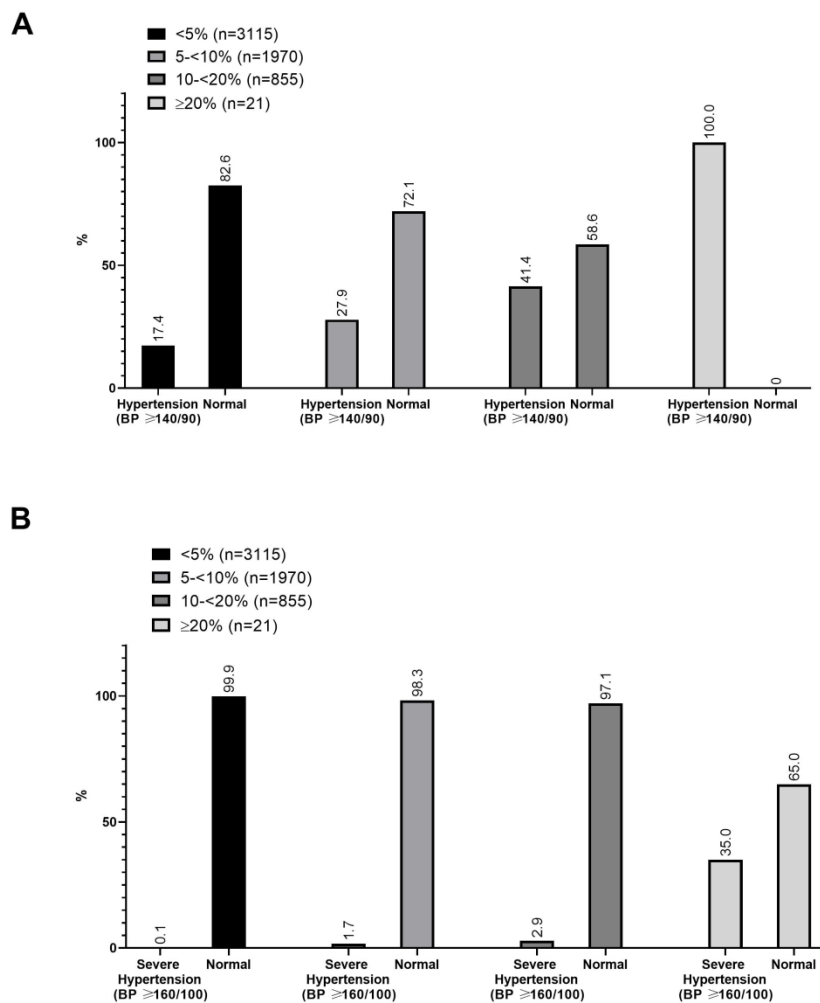
	Total no. of people in the general population (in thousands)*	Percentage of population aged \geq 40 years requiring medication (%)	Total no. of people estimated to require drug treatment (in thousands)	No. of people per million population (aged 40 years and older)	Aspirin	Enalapril	Hydrochlorothiazide	Simvastatin	Total
Age Group									
Men									
40 to 49	9210	17.1	156482	171000	\$280,867.5	\$1,485,477.0	\$518,044.5	\$2,658,879.0	\$4,943,268.0
50 to 59	6303	21.7	129375	217000	\$356,422.5	\$1,885,079.0	\$657,401.5	\$3,374,133.0	\$6,273,036.0
60 to 69	3730	30.5	96228	305000	\$500,962.5	\$2,649,535.0	\$923,997.5	\$4,742,445.0	\$8,816,940.0
\geq 70	1881	29.4	73529	294000	\$482,895.0	\$2,553,978.0	\$890,673.0	\$4,571,406.0	\$8,498,952.0
Total	21124	22.1	458995	221000	\$362,992.5	\$1,919,827.0	\$669,519.5	\$3,436,329.0	\$6,388,668.0
Women									
40 to 49	9087	22.5	199643	225000	\$369,562.5	\$1,954,575.0	\$681,637.5	\$3,498,525.0	\$6,504,300.0
50 to 59	5662	30.6	164475	306000	\$502,605.0	\$2,658,222.0	\$927,027.0	\$4,757,994.0	\$8,845,848.0
60 to 69	3257	28.7	81881	287000	\$471,397.5	\$2,493,169.0	\$869,466.5	\$4,462,563.0	\$8,296,596.0
\geq 70	1638	33.7	83509	337000	\$553,522.5	\$2,927,519.0	\$1,020,941.5	\$5,240,013.0	\$9,741,996.0
Total	19644	26.7	522759	267000	\$438,547.5	\$2,319,429.0	\$808,876.5	\$4,151,583.0	\$7,718,436.0
All									
40 to 49	18296	20.2	364085	202000	\$331,785.0	\$1,754,774.0	\$611,959.0	\$3,140,898.0	\$5,839,416.0
50 to 59	11965	26.3	298189	263000	\$431,977.5	\$2,284,681.0	\$796,758.5	\$4,089,387.0	\$7,602,804.0
60 to 69	6989	29.5	177236	295000	\$484,537.5	\$2,562,665.0	\$893,702.5	\$4,586,955.0	\$8,527,860.0
\geq 70	3518	31.6	157336	316000	\$519,030.0	\$2,745,092.0	\$957,322.0	\$4,913,484.0	\$9,134,928.0
Total	40768	24.6	992585	246000	\$404,055.0	\$2,137,002.0	\$745,257.0	\$3,825,054.0	\$7,111,368.0



Panel A: Urban populations and Panel B: Rural Populations

Figure 1: Prevalence of hypertension, hyperglycemia, and overweight and obesity among Bangladeshi adults aged 40 years and above by area of residence and age group.

281x220mm (600 x 600 DPI)



Panel A: % of adults with hypertension by CVD Risk Group
 Panel B: % of adults with severe hypertension by CVD Risk Group

Figure 2: Proportion of adults with hypertension or severe hypertension by CVD risk group

205x276mm (300 x 300 DPI)

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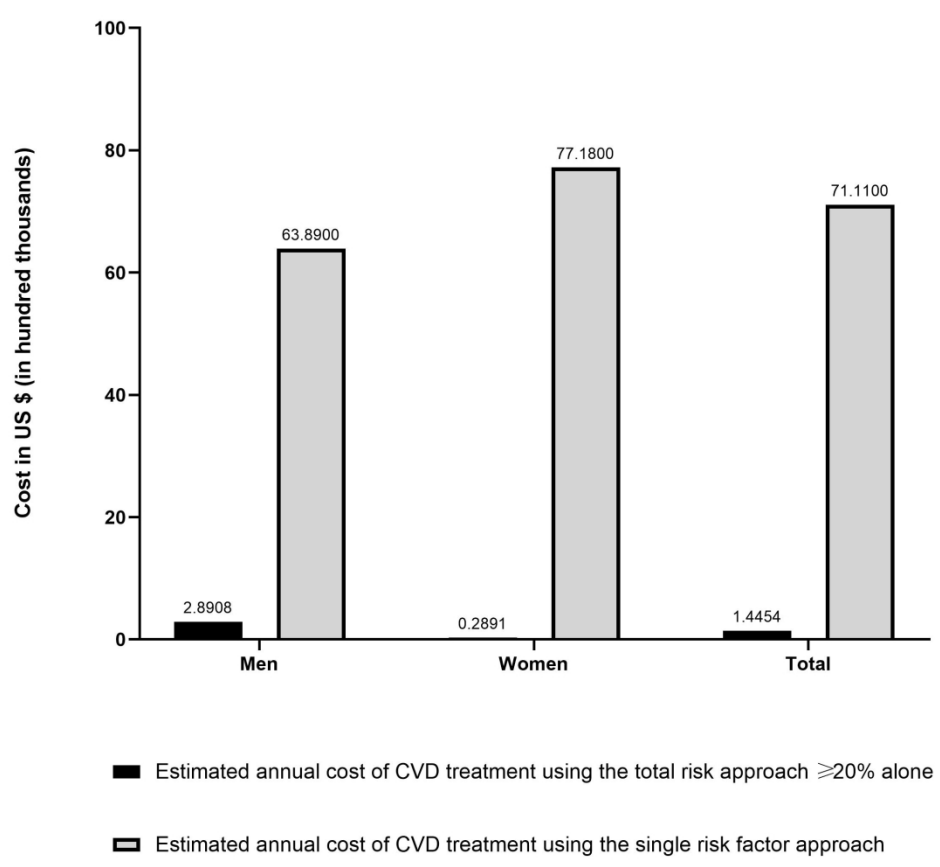


Figure 3: Annual costs of pharmacologic treatment for CVD by sex and risk stratification approach
199x175mm (300 x 300 DPI)

Appendix Table 1: Cost of common drugs used to treat cardiovascular disease in Bangladesh (converted to US\$)

Drug Name	Dose	Number of Tablets	Category	Median price (in Bangladeshi Taka)	Price (in US\$)*
Aspirin	100 mg	100 tablets	Antiplatelet drugs	38BDT	0.45
Atenolol	50 mg	100 tablets	Antihypertensive, Beta-adrenoreceptor blocking drugs	77BDT	0.92
Captopril	25 mg	100 tablets	Antihypertensive, ACE inhibitors	300 BDT	3.58
Chlorthalidone	25 mg	30 tablets	Antihypertensive, thiazide diuretics	60 BDT	0.72
Enalapril	10 mg	100 tablets	Antihypertensive, ACE inhibitors	200 BDT	2.38
Frusemide	40 mg	100 tablets	Antihypertensive, loop diuretics	53 BDT	0.63
Hydrochlorothiazide	25 mg	100 tablets	Antihypertensive, thiazide diuretics	70 BDT	0.83
Isosorbide dinitrate	10 mg	100 tablets	Angina treatment, nitrates - coronary vasodilators	35 BDT	0.42
Labetalol	100 mg	60 tablets	Antihypertensive, Beta-adrenoreceptor blocking drugs	361.2 BDT	4.31
Losartan	50 mg	100 tablets	Antihypertensive, Angiotensin-II receptor blocker	600 BDT	7.15
Lovastatine	20 mg	30 tablets	Lipid regulation, statin	303.3 BDT	3.62
Methyldopa	250 mg	100 tables	Antihypertensive, Centrally acting or central sympatholytic	308 BDT	3.67
Nifedipine (slow release)	20 mg	100 tablets	Angina treatment, calcium-channel blocker	64 BDT	0.76
Propranolol hydrochloride	10 mg	100 tablets	Antihypertensive, Beta-adrenoreceptor blocking drugs	24 BDT	0.29
Simvastatine	10 mg	30 tablets	Lipid regulation, statin	360 BDT	4.29

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Spironolactone	25 mg	100 tablets	Antihypertensive, potassium-sparing diuretics & aldosterone antagonist	202 BDT	2.41
Streptokinase	1.5 million unit/vial	One vial	Anticoagulant	3100 BDT	36.96
Warfarin	5 mg	100 tablets	Anticoagulant	300 BDT	3.58

Abbreviations: mg, milligrams; US, United States; BDT, Bangladeshi Taka

*Price conversion based on exchange rate on 02/07/2019

For peer review only

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10
Bias	9	Describe any efforts to address potential sources of bias	6-7 & 15-16
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9-10
		(b) Describe any methods used to examine subgroups and interactions	8-11
		(c) Explain how missing data were addressed	9
		(d) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	9
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.