Ischemic heart disease (IHD) is the greatest single cause of mortality and loss of disability-adjusted life years worldwide, and a substantial portion of this burden falls on low- and middle-income countries (LMICs). Deaths from IHD and acute coronary syndrome (ACS) occur, on average, at younger ages in LMICs than in high-income countries, often at economically productive ages, and likewise frequently affect the poor within LMICs. Although data about ACS in LMICs are limited, there is a growing literature in this area and the research gaps are being steadily filled. In high-income countries, decades of investigation into the risk factors for ACS and development of behavioral programs, medications, interventional procedures, and guidelines have provided us with the tools to prevent and treat events. Although similar tools can be, and in fact have been, implemented in many LMICs, challenges remain in the development and implementation of cardiovascular health promotion activities across the entire life course, as well as in access to treatment for ACS and IHD. Intersectoral policy initiatives and global coordination are critical elements of ACS and IHD control strategies. Addressing the hurdles and scaling successful health promotion, clinical and policy efforts in LMICs are necessary to adequately address the global burden of ACS and IHD. (Circ Res. 2014;114:1959-1975.)

Key Words: acute coronary syndrome ■ coronary disease ■ epidemiology ■ world health
The epidemiological transition provides a useful framework for understanding the rise of IHD in LMICs (Figure 1).\textsuperscript{9,10} The epidemiological transition posits that populations initially start with low life expectancies with mortality primarily driven by infections, undernutrition, and illness and injury related to childbirth and early childhood (age of pestilence and famine). As sanitation and agriculture improve, these causes of death gradually recede (age of receding pandemics) until NCDs, particularly IHD and cancers, dominate the causes of death (age of degenerative and man-made diseases). A fifth stage has also been proposed, in which the burden of these diseases shift to older ages (age of delayed death (age of degenerative and man-made diseases)). Still later, as cancers and IHD become preventable or controllable, the burden of these diseases shift to older ages (age of delayed degenerative diseases).\textsuperscript{11} A fifth stage has also been proposed, in light of recent adverse trends in physical activity and diet—an age of obesity and inactivity.\textsuperscript{12}

Rapid urbanization, mechanization of transport, and increasingly sedentary jobs in LMICs have led to an acceleration and overlap between the stages of the epidemiological transition.\textsuperscript{14–17} Although infections, undernutrition, and maternal/child mortality are still important, they are no longer dominant causes of death in many LMICs: IHD is now 1 of the top 5 causes of death in all regions of the world except sub-Saharan Africa. Even in sub-Saharan Africa, cardiovascular disease is the leading cause of death among individuals >30 years.\textsuperscript{18} Overall, the numbers of deaths and DALYs attributable to IHD have risen since 1990.\textsuperscript{19,20} This acceleration in the rise of NCDs without a similar reduction of infectious diseases burden has led to a challenging double burden of disease in many countries.\textsuperscript{14,21,22} In addition, the age-standardized mortality rates from IHD are higher in many LMICs than in HICs, thus indicating more individuals are dying at a younger age from IHD in LMICs (Figure 2).\textsuperscript{20} Although much of the IHD burden in LMICs is occurring as those regions and individuals enter higher economic strata, there remains a substantial health and economic burden on the poorer segments of LMIC societies resulting from IHD and related NCDs.\textsuperscript{23–25} In addition, given population growth in LMICs, the absolute numbers of individuals with premature IHD are substantial even as global, age-standardized IHD mortality rates have declined.\textsuperscript{19,20}

There has also been a dramatic rise in several IHD risk factors. Obesity and overweight prevalence have been increasing in many LMICs,\textsuperscript{6,27–29} more than tripling between 1975 and 1997 among children in Brazil from 4.1% to 13.9%.\textsuperscript{27} The age-standardized prevalence of obesity and overweight increased from 30.8% in 1980 to 46.4% in 2008, with half of the increase occurring after 2000.\textsuperscript{29} Globally, mean body mass index has been increasing in nearly every region of the world (Figure 3). Other biological risk factors have demonstrated geographic and temporal variability. Comprehensive analyses of systolic blood pressure have revealed increases in sub-Saharan Africa and South/Southeast Asia, relatively little change in Latin America, and substantial decreases in HICs (Figure 4).\textsuperscript{5} In contrast, mean serum cholesterol levels have tended to decline in several regions of the world, although at varying rates: HICs and the former Soviet Union have experienced notable declines, South Asia has seen much more modest declines, whereas Latin America and the Middle East did not change and levels actually rose in East Asia (Figure 5).

Underpinning the rises in biological risk factors have been rises in behavioral risk factors. Although recent reports suggest that global smoking prevalence has declined since 1980, the total number of smokers has increased to nearly 1 billion people in 2012\textsuperscript{30} and remains common in many LMICs\textsuperscript{31} despite some notable successes.\textsuperscript{32–34} There is also significant geographic variability in smoking rates, with certain areas (Russia, Eastern Europe, Central Asia, China, Southeast Asia, North Africa, and parts of South America) characterized by high age-standardized prevalence of daily smoking (Figure 6). Consumption of other unhealthy products, such as sugary beverages, processed foods, and alcohol, has increased.\textsuperscript{35} Likewise, large numbers of adults around the world have low levels of physical activity; although there are significant regional variations, several LMICs have physical inactivity levels that rival those of HICs (Figure 7).\textsuperscript{36} From the most recent Global Burden of Disease estimates, the top 10 risk factors contributing to mortality and DALYs in LMICs were all behavioral or biological risks for NCDs (Figure 8).\textsuperscript{37}

In this review, we aim to describe the global perspective about ACS. However, given the limited, though growing, body of data about ACS outside of HICs, we use IHD as a surrogate for ACS when data for ACS are not available. Thus, we examine in detail the trends of IHD burden in HICs, compare and contrast the recent experience in LMICs, discuss the history of ACS treatment and prevention in HICs, and outline steps for addressing ACS in LMICs.
Rise and Fall of IHD Mortality in HICs

Current HICs struggled with growing rates of ACS and associated mortality during the mid-20th century. However, HICs have experienced significant declines in mortality rates from all cardiovascular conditions since the 1960s. Both treatment and prevention have contributed to the observed reductions in IHD mortality in HICs. Treatment includes improved care for ACS, as well as chronic medical management of IHD. Preventive efforts include both behavioral and pharmacological initiatives.

Advances in the acute management of ACS include many celebrated achievements in intensive care-related and interventional approaches to cardiovascular medicine: the creation of the coronary care unit; the introduction of streptokinase and later thrombolytic drugs; and the development of coronary artery catheterization, balloon angioplasty, and surgical revascularization. These advances made it possible, rather than to simply observe the natural history of ACS complications, to intervene and attempt to modify the natural course of illness. Use of emergency medical systems, initially established for trauma care and to transport patients with suspected ACS, has also helped reduce the time between symptom onset and intervention, despite underutilization by many individuals who have acute events.

These interventions have changed acute management from passivity and impotence to activity and intervention, with the potential to avert premature death and disability.

Additional success in IHD treatment is reflected in the multidimensional approach to medical management of IHD and secondary prevention of further events. This foundation of optimal medical therapy includes a combination of medications that is started acutely and maintained post-ACS: aspirin, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers, and statins. The evidence for their use has been established throughout several decades, including the ISIS (International Studies of Infarct Survival) series of trials for β-blockers, aspirin (alongside streptokinase), and ACE inhibitors. Long-term evidence for these medications has been built up in meta-analyses of numerous trials. Evidence for statins began to emerge with low-dose therapies in the 4S (Scandinavian Simvastatin Survival Study) and CARE (Cholesterol and Recurrent Events) trials, whereas later trials showed the increased benefits of more intensive lipid lowering.

Improvements in primordial and primary prevention were driven first by an understanding of the underlying...
risks of cardiovascular disease, particularly through the Framingham Heart Study \(^75,76\) and the Seven Countries Study.\(^77\) These and related studies\(^78\) helped define the roles of tobacco use, blood pressure, and cholesterol as risk factors for IHD, challenging beliefs about the benign nature of some risk factors and making what had seemed an inevitable consequence of aging become something that could potentially be prevented.\(^79,80\)

Building on the evidence of risk, intervention studies changed the practice of prevention. Pharmacological intervention was pioneered by the Veterans Administration Cooperative Studies,\(^81\) showing reductions in morbidity and mortality in individuals treated for hypertension. For cholesterol, the Lipid Research Clinics trial provided early evidence that cholesterol reduction using medication could reduce incidence of IHD.\(^82\)

Likewise, dietary and behavior change were first validated with the Oslo Study Group trial,\(^83\) whereas the North Karelia Project and later the Five Community Study provided evidence of the effects of public health approaches.\(^84,85\) The modern-day guidelines for cholesterol, blood pressure, and lifestyle modification are the result of decades-long efforts to accommodate the latest evidence from rigorous clinical trials into best practice recommendations.\(^86–90\) These efforts, in combination with regulatory initiatives to ban trans fats\(^91,92\) and global tobacco control,\(^93\) have made substantial impact, with corresponding decreases in blood pressure, lipid levels, and tobacco use over time.\(^94–98\)

However, there are still major gaps in the midst of these overall improvements and also concerning trends with respect to overweight, obesity, and diabetes mellitus. Body mass index has increased worldwide virtually without exception.\(^6\) Within the United States, the past decade has seen a rise in the prevalence of obesity among adult men and women belonging to racial or ethnic minorities.\(^99\) There have also been declines in physical activity and increases in caloric intake.\(^100,101\) In terms of overall cardiovascular health, \(<1\%\) of adults in the United States were found to have ideal cardiovascular health, with high prevalence noted for poor diet \((>90\%)\) and high body
mass index (>50%). Projections of these trends suggest that, without intervention, poor health behaviors will continue to be highly prevalent with increases in diabetes mellitus prevalence and subsequent cardiovascular complications.

ACS and IHD Burden in LMICs

In some respects, the ACS and IHD situation in LMICs today is more similar to that of HICs in decades past. In particular, the burden of ACS is not solely on the rich nor on the elderly but also on the poor and working age. According to the most recent Global Burden of Disease study, the median age of death from IHD among men was a decade younger in LMICs than in HICs in 2010 (Figure 9). This may be because of earlier onset of ACS and IHD, as well as shorter survival after ACS. The available results from the OASIS-1 (Organization to Assess Strategies in Acute Ischemic Syndromes) and OASIS-2 registries and epidemiological studies in India suggest that earlier age for first ACS in LMICs is a major contributing factor. Registry data from many other LMICs also support the assertion that ACS often occurs at younger ages than in HICs; strikingly, a registry from the United Arab Emirates reported a mean age of 50.8 years. Earlier age for first ACS is likely because of earlier acquisition of adverse health behaviors and IHD risk factors in the current context of economic development and globalization. One notable exception to this overall trend is the experience of an ACS registry in Thailand.

The treatment and outcomes of ACS in LMICs are variable but often suboptimal (Table 2). Observational studies do suggest that, to a large extent, the in-hospital treatment of ACS in LMICs includes the use of aspirin, ACE inhibitors, and β-blockers. The ACCESS (Acute Coronary Events – a Multinational Survey of Current Management Strategies) study, a prospective observational registry of patients hospitalized for ACS between 2007 and 2008 in 19 LMICs, found that aspirin and lipid-lowering therapies were each given to >90% of patients, whereas uptake of β-blockers and ACE inhibitors was at 78% and 68%, respectively. However, comparison of countries participating in the OASIS registries found lower use of heparin in LMICs than in HICs, whereas the ACCESS investigators found that only 39% of patients presenting with ST-elevation myocardial infarction received fibrinolysis. In addition, there also exist substantive within-country differences in the management of ACS, as is the case in India. Furthermore, continuation of these medications following discharge is poor: investigators from the Prospective Urban Rural Epidemiology study found that among individuals with previous cardiovascular events, nearly 70% of those in lower-middle-income countries and 80% of those in low-income countries were on no medication for secondary prevention. They also found lower uptake of lifestyle changes following cardiovascular events in LMICs than in HICs, with 75% of individuals in HICs quitting smoking versus 42% in lower-middle-income countries and 38% in low-income countries. Likewise, the World Health Organization (WHO) PREMISE (Prevention of Recurrences of Myocardial Infarction and Stroke) survey of patients with coronary artery disease in LMICs found that although aspirin was in widespread use and that >75% of respondents were aware of behavioral risk factors for cardiovascular disease, a majority engaged in <30 minutes of physical activity weekly and less than one third were taking statins. Administrative data among patients with IHD from Andhra Pradesh were similarly discouraging, with only 15.6% receiving aspirin and 6.0% on cholesterol-lowering medications. Evidence for the quality of clinical outcomes is conflicting. The OASIS registries found comparable mortality rates across participating countries after age adjustment. By contrast, a review of randomized trials of ST-elevation myocardial infarction treatments found that trial sites in LMICs had higher mortality rates than their counterparts in HICs, which the authors explained by increased numbers of high-risk patients. Further clarification of the quality of ACS outcomes in LMICs is needed.

Figure 5. Age-standardized mean total cholesterol (TC) by sex and region. Green indicates high-income countries; black, East Asia/Pacific; red, Eastern Europe/Central Asia; dark blue, Latin America/Caribbean; light blue, Middle East/North Africa; purple, South Asia; and yellow, sub-Saharan Africa. Data derived from Global Burden of Metabolic Risk Factors of Chronic Diseases and World Population Prospects, 2012 Revision.
productivity. Households experience a double burden both from the great expense of treating ACS and from the loss of income of the affected individual. In general, NCD expenditures increased as a proportion of out-of-pocket healthcare costs in India from 1995 to 2004 and were found to have greater odds of carrying catastrophic health expenditure than did communicable diseases among hospitalized patients. Additional work confirms that individuals with NCDs have higher health expenditures than...
individuals with communicable diseases and that households with an individual with an NCD are more likely to face catastrophic health expenditures. In a multicountry survey of individuals hospitalized for cardiovascular conditions, more than half of the hospitalized individuals reported catastrophic health expenditures or distress financing. Survival with disability, such as diminished exercise capacity that may arise from heart failure related to IHD, may further burden households’ stretched finances. Testimonies from individuals living with NCDs are notable for their desire not to be a burden on their families.

The socioeconomic gradient of ACS in LMICs is also striking. Even in low-income countries, these are diseases that inflict a large burden on the poor. For instance, in South Africa, poorer districts of Cape Town had higher rates of mortality from NCDs than did wealthier districts. In the SAGE (Study on Global Ageing and Adult Health) surveys of health in 6 middle-income countries, hypertension prevalence was high, between 30% and 36%, across all income strata. A survey of 1600 rural villages in India found higher prevalence of tobacco and alcohol use and lower intake of fruits and vegetables among poorer respondents. Likewise, >70% of individuals with suspected myocardial infarction in the Indian CREATE (Treatment and Outcomes of Acute Coronary Syndromes in India) registry were classified as poor or lower middle income. Furthermore, higher socioeconomic status was found to be protective against risk of myocardial infarction in India. Although there are likely geographic variations, the poor of sub-Saharan Africa face considerable burden from infectious and nutritional diseases, it is clear that the poor in LMICs do indeed experience a substantial burden of ACS and IHD.

Stemming the Tide: Cardiovascular Health Promotion Throughout the Life Course

Despite the challenges of addressing ACS in LMICs, the time is now to implement interventions aimed at cardiovascular health promotion throughout the life course. Health promotion activities directed at all ages, access to essential medicines, improved quality of healthcare services to manage risk factors and treat acute events, and intersectoral policy initiatives can, in combination, prevent millions of premature deaths in the coming decades. A wide array of interventions are cost-effective and scalable in LMICs, and an analysis by the WHO
of intervention packages for specific risk factors suggests that implementation can be done at low cost per person.\textsuperscript{148}

There is increasing evidence that IHD risk factors have their origins in early childhood.\textsuperscript{149–154} Health promotion interventions targeted at young children may have beneficial impacts on both short-term health behaviors and long-term risk factors.\textsuperscript{155–160} Effective school-based interventions are those that include the family and that center on realistic intermediate objectives, such as changes in attitude, knowledge, dietary patterns, or levels of physical activity, as early control measures that improve cardiovascular health.\textsuperscript{161} Critical to the success of these interventions is community engagement, cultural relevance and appropriateness, optimization of the school environment, and involvement of the family.\textsuperscript{162–164} Programs that have been implemented successfully in LMICs\textsuperscript{155,156} can be reproduced in other low-resource settings.\textsuperscript{165,166}

Addressing dietary risk factors can be cost-effective. An analysis of salt-reduction measures estimated conservatively that a 15% reduction in salt intake could save 2.4 million lives for 10 years at a cost of $0.50 per person,\textsuperscript{167} in-line with other findings suggesting that salt reduction at processing stages of food production can be cost-effective.\textsuperscript{168} Likewise, reductions in saturated and trans fats by controlling use in food processing can be cost-effective, estimated at $40 per DALY in Latin America when focusing on trans fats.\textsuperscript{147,168} By focusing on processing sources, these interventions are readily scalable, costing <$0.01 per person.\textsuperscript{148}

Physical activity remains a challenge to evaluate; however, the WHO estimates that a public awareness campaign could

### Table 1. Declines in Coronary Heart Disease Mortality in Selected High- and Middle-Income Countries, With Attributable Portions Owing to Risk Factor Changes (Prevention) and Treatment

<table>
<thead>
<tr>
<th>Region</th>
<th>Years</th>
<th>Age Range</th>
<th>Initial CHD Mortality Rate*</th>
<th>Final CHD Mortality Rate*</th>
<th>Percent Change</th>
<th>Percent Attributable to Prevention</th>
<th>Percent Attributable to Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>England and Wales\textsuperscript{47}</td>
<td>1981–2000</td>
<td>25–84</td>
<td>Males, =530</td>
<td>Males, =250</td>
<td>−53</td>
<td>58</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Females, =180</td>
<td>Females, =90</td>
<td>−50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland\textsuperscript{48}</td>
<td>1982–1997</td>
<td>35–64</td>
<td>Males, 420</td>
<td>Males, 150</td>
<td>−64.3</td>
<td>53–72</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Females, 70</td>
<td>Females, 20</td>
<td>−71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ireland\textsuperscript{49}</td>
<td>1985–2000</td>
<td>25–84</td>
<td>8681†</td>
<td>4918‡</td>
<td>−47</td>
<td>48.1</td>
<td>43.6</td>
</tr>
<tr>
<td>Italy\textsuperscript{50}</td>
<td>1980–2000</td>
<td>25–84</td>
<td>Males, 267.1</td>
<td>Males, 141.3</td>
<td>−47.1</td>
<td>55</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Females, 161.3</td>
<td>Females, 78.8</td>
<td>−51.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auckland, New Zealand\textsuperscript{51}</td>
<td>1982–1993</td>
<td>All ages</td>
<td>2366†</td>
<td>1808‡</td>
<td>−23.6</td>
<td>54</td>
<td>46</td>
</tr>
<tr>
<td>Scotland\textsuperscript{52}</td>
<td>1975–1994</td>
<td></td>
<td>21438†</td>
<td>15234‡</td>
<td>−28.9</td>
<td>51</td>
<td>40</td>
</tr>
<tr>
<td>Sweden\textsuperscript{53}</td>
<td>1986–2002</td>
<td>25–84</td>
<td>Males, 544.1</td>
<td>Males, 253.4</td>
<td>−53.4</td>
<td>55</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Females, 291.5</td>
<td>Females, 140.0</td>
<td>−52.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States\textsuperscript{54}</td>
<td>1980–2000</td>
<td>25–84</td>
<td>Males, 542.9</td>
<td>Males, 266.8</td>
<td>−50.9</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Females, 263.3</td>
<td>Females, 134.4</td>
<td>−49.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CHD indicates coronary heart disease.
\*Rates given per 100,000 population; †Expected number of deaths in final year with age-specific rates of initial year; and ‡Observed number of deaths in final year.
be implemented at $0.038 per person. One major challenge to physical activity has been urbanization, which has produced mechanized transportation environments that discourage physical activity. However, there are clear interventions for addressing lifestyle and the built environment, and WHO guidelines on physical activity provide a clear way forward. Efforts in Brazil and Colombia to improve physical activity in cities are 1 example of success in this area, although there is substantial room to improve policies promoting healthy diets and physical activity.

Effective interventions are also well known to reduce tobacco use, many of which are provisions of the Framework Convention on Tobacco Control: restrictions on advertising, packaging, marketing to minors, use in public spaces, and taxes. Extensive analysis has suggested that these interventions produce robust results, with particularly strong response to taxation in developing countries. Furthermore, these are highly cost-effective, from $3 to $42 for a 33% tax rate on tobacco to $55 to $761 per DALY in LMICs for nicotine replacement therapy. The WHO’s best buys for global health estimate that a package of interventions including taxation, packaging and advertising restrictions, counter-advertising, and use restrictions could be implemented for ≈$0.11 per person. However, there have been several challenges to ratification and implementation of the Framework Convention.
Table 2. Summary of Published Literature About ACS in Low- and Middle-Income Countries

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Study Design</th>
<th>n</th>
<th>Mean Age</th>
<th>In Hospital</th>
<th>Discharge</th>
<th>F/U</th>
<th>% Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCEPT(^1)(^4)</td>
<td>Brazil</td>
<td>Registry</td>
<td>2485</td>
<td>63</td>
<td>0.97 0.68 0.91 0.80 0.88</td>
<td>NR NR NR NR</td>
<td>30 d</td>
<td>1.6</td>
</tr>
<tr>
<td>ACCESS(^2)(^5)</td>
<td>Algeria, Argentina, Brazil, Colombia, Dominican Republic, Ecuador, Egypt, Guatemala, Iran, Jordan, Kuwait, Lebanon, Mexico, Morocco, Saudi Arabia, South Africa, Tunisia, United Arab Emirates, Venezuela</td>
<td>Registry</td>
<td>12068</td>
<td>59.2</td>
<td>0.93 0.78 0.94 0.78 0.28</td>
<td>0.90 0.75 0.89 0.76</td>
<td>12 mo</td>
<td>7.3</td>
</tr>
<tr>
<td>Aga Khan University Hospital, Nairobi(^1)(^1)</td>
<td>Nairobi, Kenya</td>
<td>Registry</td>
<td>111</td>
<td>64</td>
<td>NR NR NR NR 0.38</td>
<td>NR NR NR NR</td>
<td>In hospital</td>
<td>8.1</td>
</tr>
<tr>
<td>Brazilian Registry of Acute Coronary Syndromes(^1)(^4)</td>
<td>Brazil</td>
<td>Registry</td>
<td>2693</td>
<td>63</td>
<td>0.95 0.70 0.77 0.77 0.643(^\dagger)</td>
<td>NR NR NR NR</td>
<td>12 mo</td>
<td>5.5</td>
</tr>
<tr>
<td>BRIDGE-ACS(^2)(^7)(^8)</td>
<td>Brazil</td>
<td>Randomized trial</td>
<td>548</td>
<td>62</td>
<td>0.958 NR 0.729 NR NR 0.928 0.761 0.86 0.817</td>
<td>30 d</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>CRACE(^1)(^8)</td>
<td>China</td>
<td>Registry</td>
<td>1301</td>
<td>63</td>
<td>0.98 0.82 0.74 0.98 0.64</td>
<td>NR NR NR NR</td>
<td>In hospital</td>
<td>4</td>
</tr>
<tr>
<td>CREATE(^1)(^9)</td>
<td>India</td>
<td>Registry</td>
<td>20937</td>
<td>58</td>
<td>0.979(\dagger) 0.568 0.52 0.59 0.104(\dagger)</td>
<td>NR NR NR NR</td>
<td>30 d</td>
<td>6.7</td>
</tr>
<tr>
<td>DEMAT(^2)(^8)</td>
<td>India</td>
<td>Registry</td>
<td>1565</td>
<td>58</td>
<td>0.96 NR 0.93 0.79 0.67</td>
<td>0.94 0.66 0.88 0.79</td>
<td>30 d</td>
<td>2.1</td>
</tr>
<tr>
<td>Euro Heart Survey 2009 AMI Snapshot(^1)(^7)(^1)</td>
<td>Armenia, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Georgia, Hungary, Kazakhstan, Kosovo, Macedonia, Moldova, Poland, Romania, Russian Federation, Serbia and Montenegro, Slovakia, Slovenia, Ukraine</td>
<td>Cross-sectional survey</td>
<td>1329</td>
<td>64</td>
<td>0.96 0.86 0.92 0.84 0.62</td>
<td>0.92 0.85 0.92 0.84</td>
<td>In hospital</td>
<td>9</td>
</tr>
<tr>
<td>Gulf RACE-2(^2)(^9)</td>
<td>Bahrain, Saudi Arabia, Qatar, Oman, United Arab Emirates, Yemen</td>
<td>Registry</td>
<td>7930</td>
<td>57</td>
<td>0.98 0.76 0.95 0.74 0.18</td>
<td>0.93 0.78 0.91 0.79</td>
<td>12 mo</td>
<td>12</td>
</tr>
<tr>
<td>Kerala ACS Registry(^2)(^8)</td>
<td>Kerala, India</td>
<td>Registry</td>
<td>25748</td>
<td>60</td>
<td>0.93 0.28 0.70 0.66 0.33</td>
<td>0.76 0.26 0.70 0.63</td>
<td>In hospital</td>
<td>3.9</td>
</tr>
<tr>
<td>OASIS-2(^2)(^9)</td>
<td>Bangladesh, China, India, Lithuania, Russia, Maldives, Slovenia, Ukraine</td>
<td>Registry</td>
<td>4615</td>
<td>60.7</td>
<td>0.95 NR NR 0.67 NR NR NR NR</td>
<td>24 mo</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>PURE(^3)(^5)(^1)(^2)(^8)</td>
<td>Argentina, Bangladesh, Brazil, Canada, Chile, China, Colombia, India, Iran, Malaysia, Poland, Pakistan, South Africa, Sweden, Turkey, United Arab Emirates, Zimbabwe</td>
<td>Prospective cohort</td>
<td>153966</td>
<td>57</td>
<td>NA NA NA NA NA</td>
<td>0.21 0.16 0.09 0.17</td>
<td>NR NR</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
One major challenge has been the push for voluntary, nation-level approaches rather than a coordinated global treaty.177–181 After passage of the Framework Convention, it has been documented that the tobacco industry has attempted to undermine this treaty provisions,185 and has been noted by the WHO as actively preventing implementation of treaty provisions that aim to keep the tobacco industry out of public health policy making.187

Treatment of ACS and IHD

Approaches to treatment can be divided into 2 categories: interventions for acute events and interventions for primary and secondary prevention. According to the Disease Control Priorities Project, streptokinase was the most cost-effective reperfusion therapy at cost $634 to $734 per DALY. This strategy, however, became more expensive per DALY saved as time to treatment increased. Alteplase and coronary artery bypass surgery were both $10,000 per DALY. The use of aspirin, β-blockers, and ACE inhibitors was found to be cost-effective and in some circumstances cost-saving. To date, there remains a dearth of research on the cost-effectiveness of reperfusion therapies in LMICs.147 In-hospital use of other evidence-based management, such as anticoagulation, antiplatelet medications, and statins, can be improved with the implementation of systems-level approaches, such as reminder, checklists, case management, and educational materials.129

For primary and secondary prevention, a multidrug regimen consisting of a β-blocker or calcium channel blocker, an ACE inhibitor, aspirin, and a statin was found to be cost-effective.188

On the basis of the need for a multidrug regimen for pharmacotherapy, efforts have been made at creating a polypill that brings together these various medications and makes adherence simpler.189–192 A meta-analysis of trials found that, compared with placebo, a polypill did reduce blood pressure and serum lipids.193 The polypill strategy is generally thought to be associated with improved adherence related to fewer numbers of pills to be consumed on a daily basis. However, the data about adherence of a cardiovascular polypill are mixed. The meta-analysis concluded that the polypill strategy had lower rates of adherence, with 20% of polypill recipients discontinuing use versus 14% of those on placebo or monotherapy, although the trials included were highly heterogeneous.195 On the contrary, the more recent UMPIRE (Use of a Multi-drug Pill in Reducing Cardiovascular Events) study found much higher rates of adherence for those receiving a polypill versus usual care.194 If the challenges in developing a polypill are overcome, it is possible that this, too, will be a cost-effective and essential tool for prevention.195,196

Medication access remains a significant challenge in LMICs.197,198 Data from India indicate that poor patients are less likely to receive evidence-based in-hospital treatments, such as revascularization, thrombolytics, and lipid-lowering drugs.130 Surveys of medication use suggest low levels of uptake of therapy for primary and secondary prevention of IHD.131,133 Affordability is an important reason as to why uptake is so low: IHD medication may cost more than an individual’s daily income.25,147 As these medications must be taken daily for many years, cost is a primary concern in ensuring that the majority of those in need have the ability to access appropriate care. Innovative strategies to optimize the healthcare provision of antihypertensive medications were associated with lower levels of death from IHD in the UK.132

Table 2. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Study Design</th>
<th>n</th>
<th>Mean Age</th>
<th>In Hospital</th>
<th>Discharge</th>
<th>F/U</th>
<th>% Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENASICA</td>
<td>Mexico</td>
<td>Registry</td>
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<td>0.88</td>
<td>0.71</td>
<td>0.14</td>
<td>0.51</td>
</tr>
<tr>
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<td>Registry</td>
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<td>NR</td>
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<td>0.63</td>
<td>0.80</td>
<td>0.62</td>
</tr>
<tr>
<td>TRACS</td>
<td>Thailand</td>
<td>Registry</td>
<td>2007</td>
<td>64</td>
<td>0.99</td>
<td>0.71</td>
<td>0.94</td>
<td>0.62</td>
</tr>
<tr>
<td>UAE-ACS Registry</td>
<td>United Arab Emirates</td>
<td>Registry</td>
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<td>51</td>
<td>0.95</td>
<td>0.70</td>
<td>0.93</td>
<td>0.81</td>
</tr>
<tr>
<td>WHO-PREMISE</td>
<td>Brazil, Egypt, India, Indonesia, Iran, Pakistan, Russia, Sri Lanka, Tunisia, Turkey</td>
<td>Cross-sectional survey</td>
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<td>59</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>WHO-SAGE</td>
<td>China, Ghana, India, Mexico, Russia, South Africa</td>
<td>Prospective cohort</td>
<td>47,443</td>
<td>44</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
workforce to manage IHD and ACS,\textsuperscript{199} as well as to improve access to essential medicines,\textsuperscript{45} are required.

**Integrated Health Service Delivery, Intersectoral Policy, and Global Coordination**

Healthcare delivery systems in LMICs would benefit from a comprehensive approach that integrates services related to NCDs and communicable diseases such as human immunodeficiency virus.\textsuperscript{200} Beyond the above-described interventions for specifically ACS and IHD, overall cardiovascular care in LMICs would benefit from strengthening health systems, improving quality of care, optimizing human resources for health, establishing secure supply chains of drugs and technology, and promoting equitable access to care. Instead of vertical, disease-specific programs, a diagonal approach in which cardiovascular-related healthcare delivery is integrated into a comprehensive approach to health systems strengthening will likely yield superior results.\textsuperscript{201–205} To maximize the effectiveness of health sector-specific interventions, they should be implemented in the context of broader population-level policy changes and community-level programs.

Thus, the remaining intervention necessary, perhaps underlying all of the above interventions, is comprehensive intersectoral policy dedicated to NCDs in general.\textsuperscript{196,206,207} The roots of IHD risk are not contained solely within the health sector, and the entire spectrum of stakeholders is required to commit to policies and programs that will create the conditions that improve cardiovascular health. This would include, at a minimum, representation from the health, education, infrastructure, transportation, urban planning, trade, and finance sectors. In addition, productive partnerships among government, private sector, and civil society are possible and required.

Finally, although the large global burden of NCDs is well established, funding from donors does not match this reality. In 2010, although NCDs collectively accounted for 49.8\% of DALY burden of disease, they received only 2.3\% of development assistance for health.\textsuperscript{208} Within the WHO’s own budget, only 12\% was allocated to NCDs for the 2006 to 2007 fiscal year, out of line with disease burden.\textsuperscript{210} Analysis of spending by donors broadly, including private philanthropies such as the Gates Foundation, showed a similarly skewed allocation, with human immunodeficiency virus/acquired immune deficiency syndrome accounting for the largest portion of health spending, far in excess of its DALY-measured burden compared with NCDs and with other communicable diseases.\textsuperscript{210} Another study reported spending of $0.78 per DALY for NCDs versus $23.90 per DALY for HIV, tuberculosis, and malaria.\textsuperscript{211} Although funding for NCDs has increased during the past decade,\textsuperscript{208,211} allocation of funding that is more in-line with actual disease burden may aid the achievement of an array of global health goals. The prospects for improving this balance of funding are challenging and require greater participation among aid recipient countries and alignment of United Nations institutions around NCD goals.\textsuperscript{212} At the country level, health insurance and payment systems ideally should ensure equitable access to both in-hospital treatment of ACS and long-term outpatient access to medications and rehabilitative services.\textsuperscript{213} In addition, public–private partnerships and other innovative financing mechanisms will be required.

**Conclusions**

Similar to the situation in HICs decades ago, LMICs today are well into a transition toward increasing morbidity and mortality from ACS and IHD. However, there are features that distinguish the patterns of ACS in LMICs from HICs. First, the death toll falls more heavily on younger, productive ages in LMICs than in HICs, with mortality rates among adults aged 15 to 49 in some LMICs nearly double that in HICs. Second, the rate of the epidemiological transition to increased burden from IHD has happened more rapidly in LMICs today than in HICs in the past. In addition, ACS and IHD are not diseases confined to the privileged classes; rather, there is a significant burden that also falls hard on the low-income strata in LMICs, who often are unable to afford the costs of medical therapy for primary or secondary prevention of IHD, let alone the expensive treatments for ACS that have helped make acute events more survivable in HICs. Together, these help explain the substantial economic burden that is anticipated from ACS and IHD if no action is taken.

Despite the immense burden, the global community is aided by new knowledge and discoveries made during the past half century. We continue to evolve more efficient and efficacious treatment strategies for ACS, ranging from rapid transport of patients to hospitals via emergency medical systems, to timely reperfusion, through to long-term cardiac rehabilitation, optimal medical therapy, and risk factor control. We understand what the underlying risk factors for ACS are and how to prevent them through cardiovascular health promotion activities throughout the life course, appropriate therapeutic strategies, and intersectoral policy. The scientific challenge is primarily in translating this existing knowledge to new settings. In addition, the growing body of ACS literature from LMICs highlights the importance of local, national, and regional registries as important sources of information about current practices and inspiration for improvement and change.\textsuperscript{125,214}

The critical task is implementation: the tools that we have need to be materialized. This involves engaging in health promotion activities in early childhood, ensuring access to essential medicines to treat and prevent ACS, developing resource- and context-specific clinical guidelines, implementing laws and regulations to protect the public’s health from harmful products, planning the growth of cities to promote healthy behavior, and support from donor countries and international organizations to match the scale of the global burden of ACS, IHD, and other NCDs. We are well equipped to confront this challenge so long as our will meets it.

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References


Fle gal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and...


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Rajesh Vedanthan, Benjamin Seligman and Valentin Fuster

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Correction

In the *Circulation Research* article by Vedanthan et al (Global Perspective on Acute Coronary Syndrome: A Burden on the Young and Poor. *Circ Res.* 2014;114:1959–1975. DOI: 10.1161/CIRCRESAHA.114.302782), corrections were needed.

Figure 9 is incorrect and should have two panels.

The legends for Figures 3, 4, and 5 should include the following statement, referencing the source of the data derived to create the figures: “Data derived from Global Burden of Metabolic Risk Factors of Chronic Diseases and World Population Prospects, 2012 Revision.”

The errors have been corrected in the online version of the article, which is available at http://circres.ahajournals.org/content/114/12/1959.