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Review

The Burden of Cardiovascular Disease in Low- and Middle-Income Countries: Epidemiology and Management

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ABSTRACT

Cardiovascular disease (CVD) is the second leading cause of mortality worldwide, accounting for 17 million deaths in 2013. More than 80% of these cases were in low- and middle-income countries (LMICs). Although the risk factors for the development of CVD are similar throughout the world, the evolving change in lifestyle and health behaviours in LMICs—including tobacco use, decreased physical activity, and obesity—are contributing to the escalating presence of CVD and mortality. Although CVD mortality is falling in high-income settings because of more effective preventive and management programs, access to evidence-based interventions for combating CVD in resource-limited settings is variable. The existing pressures on both human and financial resources impact the efforts of controlling CVD. The implementation of emerging innovative interventions to improve medication adherence, introducing m-health programs, and decentralizing the management of chronic diseases are promising methods to reduce the burden of chronic disease management on such fragile health care systems.

RÉSUMÉ

Deuxième cause de mortalité à l'échelle mondiale, la maladie cardiovasculaire (MCV) a occasionné 17 millions de décès en 2013. Plus de 80 % de ces décès se sont produits dans des pays à revenu faible ou intermédiaire. Même si les facteurs de risque de la MCV sont similaires partout dans le monde, les changements observés dans les pays à revenu faible ou intermédiaire au chapitre du mode de vie et des comportements liés à la santé, notamment l'usage du tabac, la diminution de l'activité physique et l'obésité, contribuent à la hausse de la prévalence de la MCV et de la mortalité. Bien que la mortalité par MCV soit en baisse dans les milieux à revenu élevé en raison de programmes de prévention et de prise en charge plus efficaces, l'accessibilité à des interventions fondées sur des preuves pour combattre la MCV dans les milieux où les ressources sont limitées demeure inégale. Les pressions exercées actuellement sur les ressources tant humaines que financières nuisent aux efforts visant à réduire l'incidence de la MCV. La mise en place de nouveaux programmes novateurs visant à améliorer l'observance thérapeutique, l'implantation de services de santé mobiles et la décentralisation de la prise en charge des maladies chroniques sont des avenues prometteuses qui pourraient réduire le fardeau que représentent les maladies chroniques pour les systèmes de santé fragilisés.

After cancer, cardiovascular disease (CVD) is the second most common cause of death worldwide (Fig. 1), accounting for > 17 million deaths. There was a 7% increase in global cardiovascular deaths in all age groups between 1990 and 2013. Of this number, ischemic heart disease (IHD) and stroke are the main contributors, reflected by a 40% increase in deaths from IHD during this period.

The greatest burden of CVD is in low- and middle-income countries (LMICs), with approximately 80% of cardiovascular deaths occurring in LMICs.[1] The patterns of CVD in LMICs are distinct from higher-income countries (HICs), where the majority of CVD deaths are reported in individuals aged > 60 years and mortality from IHD is decreasing. The World Health Organization (WHO) suggests that 3 times as many deaths from cardiovascular causes are occurring in LMICs, affecting males and females equally, but occurring in working-age groups (Fig. 2).[2] The number of deaths caused by non-communicable diseases is expected to increase by 15% by 2020. Further, the economic burden generated by CVD is

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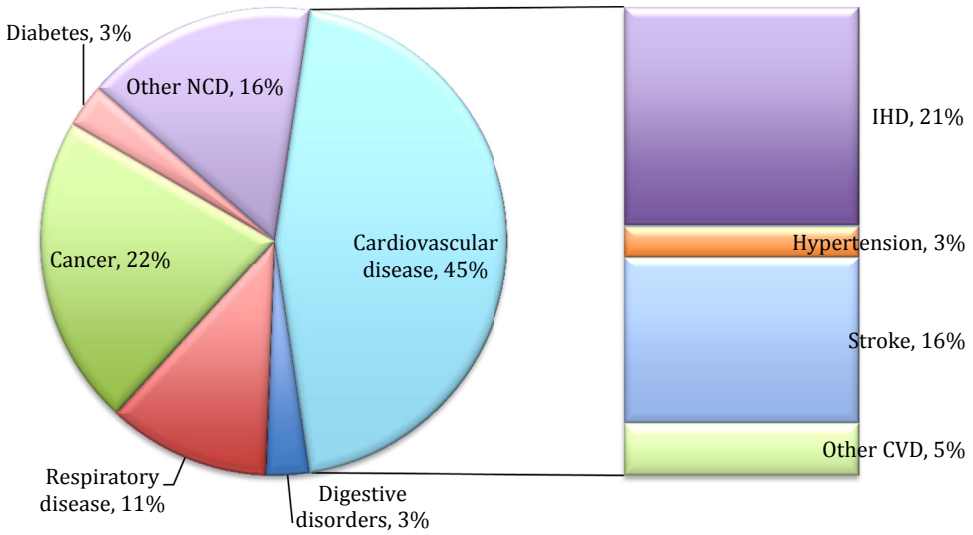

Figure 1. Global burden of noncommunicable disease in 2013.[6] CVD, cardiovascular disease; IHD, ischemic heart disease; NCD, noncommunicable disease.

estimated to reduce gross domestic product (GDP) by up to 7% in LMICs.[3] This suggests a growing social and economic burden on health care systems in LMICs, many of which do not have the adequate health infrastructure to sustain these pressures.[4]

Morbidity and mortality from CVD is largely preventable. Increasing awareness of this growing burden of CVD in LMICs, as well as focused national and international strategies to reduce risk factors and address the disparities in health care access, are of key importance to address CVD mortality in these regions.[3]

In this article, we review the burden of CVD and the distribution of cardiac risk factors in LMICs. We also discuss potential reasons for these evolving patterns and present an overview of both established and innovative interventions to decrease the burden of CVD in this setting.

Definitions

In broad terms, CVD is classified as IHD, cerebrovascular disease, hypertensive heart disease, peripheral vascular disease, and structural abnormalities. For the purposes of this review, emphasis has been placed on the first 4 diseases listed.

The World Bank identifies 6 main geographic regions that are categorized as LMICs, which is a subgroup of the middle-income countries: East Asia and the Pacific, Europe and Central Asia, Latin America and the Caribbean, the Middle East and North Africa, South Asia and Sub-Saharan Africa (Fig. 3). This distribution differs from the WHO regions and stratifies each region by income.[5] Low-income countries are defined as reporting a gross national income (GNI) per capita of $\leq$ $1045 ($USD), whereas middle-income countries report a GNI between $1045 and $12,746. Within these regions, however, there is significant variation in reported GNI.

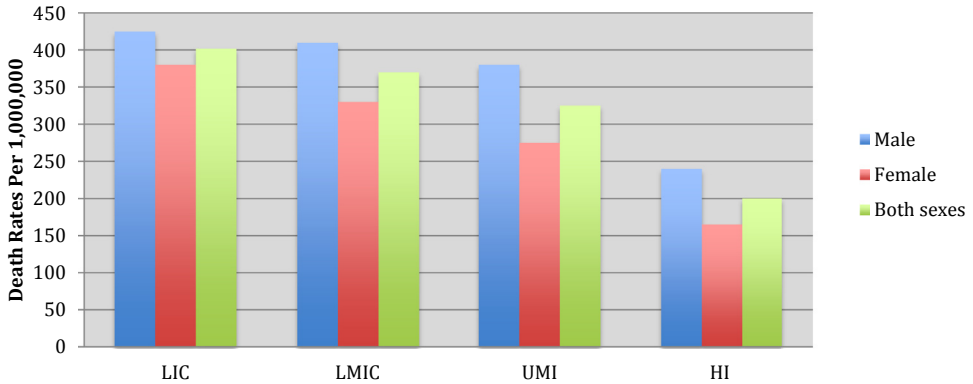

Figure 2. Cardiovascular disease mortality rates across different economic regions in 2010. HI, high income; LIC, lower-income countries; LMIC, low- to middle-income countries; UMI, upper-middle income. Modified from Mendis et al.[26] with permission from the World Health Organization. Copyright © 2011.

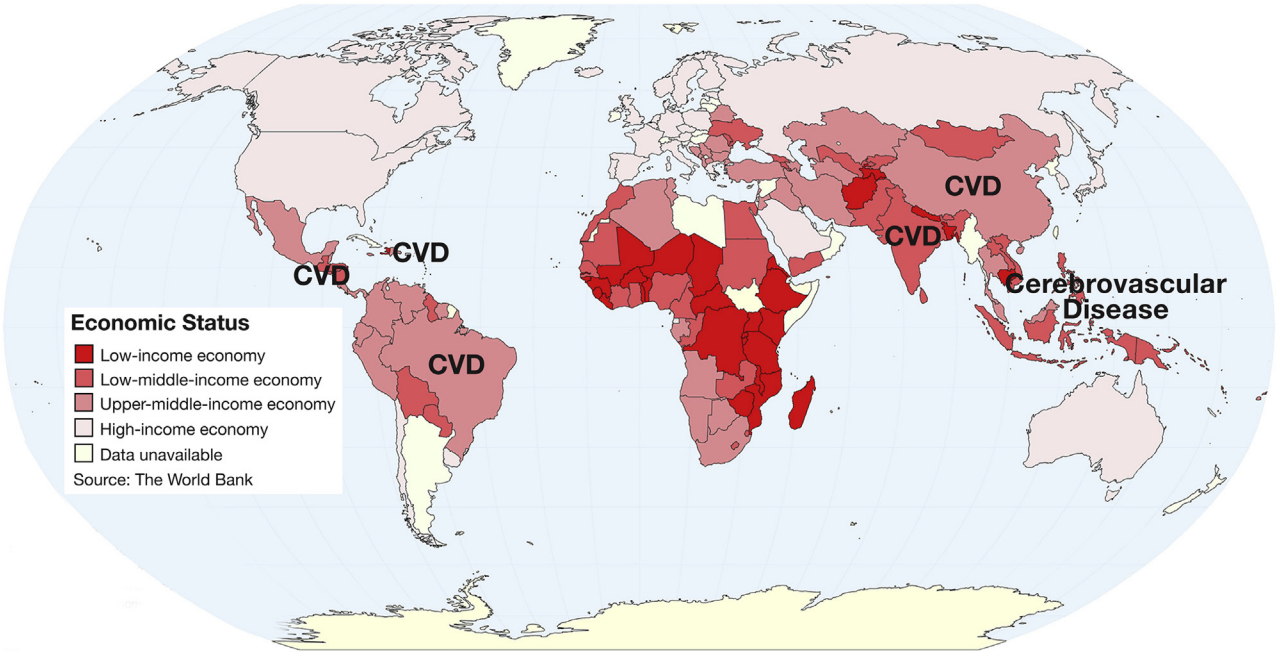

Figure 3. Distribution of cardiovascular mortality in low and low-middle income countries. CVD, cardiovascular disease. Modified from *Map of Developing and Developed Countries (as determined by GNI per capita)*, ChartsBin.com, viewed 1st January, 2015, http://chartsbin.com/view/25857.

Burden of CVD and Risk Factors in LMICs

Although CVD mortality in most HICs has decreased by 50%-80%, it remains high in LMICs (Fig. 2).[3] The average global death rate from CVD in 2010 was 320 per 1 million population.[3] The CVD mortality rate in both male and females individuals in LMICs far surpasses this average (Fig. 2). However, the distribution of CVD across LMICs has been fairly consistent. In 2013, IHD was the most common cause of cardiovascular deaths in Central and Eastern Europe, Central Asia (except Tajikistan), Latin America and the Caribbean (except Andean Latin America and Haiti), and South Asia (except Afghanistan, Nepal, and Pakistan). Stroke remains the leading cause of cardiovascular deaths in most of East and Southeast Asia (Fig. 3).[3,6]

The persistently high prevalence of CVD in LMICs largely reflects the burden of key risk factors, including hypertension, tobacco use, dietary factors, obesity, and physical inactivity.[7] Various studies have assessed regional trends of risk factors in LMICs that contribute to the growing burden of CVD.

Hypertension

Elevated blood pressure is an important risk factor for the development of CVD.[8] The impact of a disease is often described in terms of disability-adjusted life years lost (DALYs) or the number of years lost because of the condition. The prevalence of hypertension ranges from 23% in Canada to 29.6% in the United States and 30% in the United Kingdom.[8-10] Although hypertension was the fourth major risk factor contributing to DALYs lost worldwide in 1990, by 2010, it was a the major contributor to CVD mortality in East Asia, Southeast Asia, Central Asia, the Caribbean, North Africa, and the Middle East.[7] Consistent with this, in 2010, blood pressure decreased by an average of 0.8 mm Hg (for men) and 1.0 mm Hg (for women) in Australasia and Western Europe over the previous 10 years but increased by up to 2.7 mm Hg over this same period in East and West Africa and South and Southeast Asia.[11] The WHO Study on Global Aging and Adult Health demonstrated that in LMICs, the prevalence of hypertension among individuals 50 years of age or older was 53%, ranging from 32% in India to 78% in South Africa.[12] Similarly, by 2025, the global prevalence of hypertension is expected to increase by 60% to a total of 1.56 billion cases.[13] The increase in the number of individuals with uncontrolled hypertension appears largely attributable to population growth and aging.[11]

Hyperlipidemia

In the past 30 years, mean total cholesterol levels declined globally by < 0.1 mmol/L per decade. In HICs, cholesterol levels declined by approximately 0.2 mmol/L per decade, whereas mean cholesterol levels increased by 0.08-0.09 mmol/L per decade in East and Southeast Asia and the Pacific regions.[14]

Diabetes

The prevalence of diabetes has increased from 153 million to 347 million cases, affecting 9.8% of men and 9.2% of women globally.[14] Of these cases, 10% were in the United States, whereas the majority of cases were in LMICs. Approximately 40% were in China and India, and 12% were in Brazil, Pakistan, Indonesia, and Mexico. These trends are driven by population growth and increasing age-specific prevalence.[14] However, this may be an underestimate because 50% of cases are undiagnosed.[3]

Obesity

In 2008, LMICs accounted for 7% of the world's overweight individuals.[3] Although the prevalence of obesity in LMICs is generally lower than in HICs, the absolute number of overweight individuals is extremely high. For example, although the number of overweight individuals in China is 241 million, this country has more overweight individuals than the United States, in which the prevalence is 158 million individuals. Furthermore, China has seen an absolute increase of 169 million obese individuals over the past 3 decades, compared with an increase of 88 million in the United States.[15] In LMICs, studies in women show that body mass index and waist circumference have increased and may contribute to the increase in diabetes and CVD.[16,17] Unfortunately, the number of overweight children in LMICs is also increasing at a faster rate than in HICs, and this may have catastrophic consequences.[18,19] Although the increase in body mass index and obesity is concerning, several regions with LMICs have significant malnutrition and limited access to adequate nutrition, which may contribute to the development of CVD.[16,20]

Dietary factors

The intake of dietary fat is suggested to be associated with increased CVD, especially high levels of trans−fatty acid consumption.[21-24] A recent meta-analysis showed that a 2% increase in energy intake from trans−fatty acids was associated with a 23% increase in coronary heart disease.[25] Typically, the availability of total fat increases in higher-income economies, but emerging data from LMICs show that a diet high in saturated fats and trans−fatty acids is a major risk factor, particularly in North Africa and the Middle East and South East Asia.[3,7,26] Other studies show that partially hydrogenated cooking oils are used extensively in Iran and India.[15,27]

Smoking

Smoking is a major risk factor for CVD worldwide. Although 31% of tobacco users are in HICs, changes in lifestyle and increased accessibility to tobacco products in LMICs are influencing the impact of smoking on CVD.[3] Approximately 82% of the 1.1 billion smokers worldwide reside in LMICs.[28] The Global Adult Tobacco Survey showed that in 14 LMICs, 48.6% of men and 11.3% of women were tobacco users.[29] By 2030, it is estimated that approximately 10 million deaths each year will result from tobacco use. Tobacco is consumed using different vehicles, including smokeless tobacco and second-hand smoke, and is associated with an increase in coronary heart disease.[30-34]

Explaining the High Burden of CHD in LMICs

The concept of "epidemiologic transition" may help explain the growth of CVD in LMICs.[35] This represents the shift from death caused by infectious diseases to death caused by noncommunicable diseases, mainly CVD (Table 1).[35,36] This transition results from industrialization, urbanization, changes in lifestyle, medical innovation, and the improved understanding of diseases.[3] However, the stage of transition for each region differs greatly, and this has a subsequent impact on regional mortality rates and the economic burden of disease.

At a more granular level, there are numerous contributors to the observed patterns of CVD and poor risk-factor control in LMICs.

Awareness of risk factors

Underdiagnosis and suboptimal management of risk factors contribute to the burden of CVD. The PURE (**P**rospective **U**rban-**R**ural **E**pidemiology) study, which evaluated 57,840 individuals with hypertension among 142,042 participants, found that only 46.5% of participants (41% in LICs; 49% in HICs) were aware of their hypertension, compared with a 72% awareness in Russia and 80% in the United States.[12,37] Increased awareness of a diagnosis of hypertension appears to be related to increasing age, female sex, and obesity.[12]

Access to care and medications

The absence of primary prevention programs screening for risk factors has contributed to underdiagnosis in several LMICs.[38] Among those with recognized risk factors, the use of appropriate medications is low. In India, only 8% of individuals with CVD are receiving statin therapy compared with > 80% in HICs.[39] Similarly, only 32% of those in LICs (compared with 47% in HICs) were receiving treatment for hypertension.[37] Furthermore, there is significant variation in prices of medications across LMICs, which can be prohibitive to patients.[40]

The WHO-PREMISE Study (**WHO** Study on the **P**revention of **Re**currences of **M**yocardial **I**nfarction and **S**troke) examined the use of secondary prevention treatment strategies in patients with established IHD in 10 LMICs and found that although > 80% of patients reported taking aspirin, fewer than half were taking a β-blocker or angiotensin-converting enzyme inhibitor and only 30% of patients were taking a statin.[41] In the PURE study, only 3% of patients in LMICs were taking at least 3 of the 4 medications on average 5 years after a cardiovascular event.[42] Access to medications for IHD

Table 1. Stages of the epidemiologic transition in low- and middle-income countries

Stage of transition	Description	World population in this stage (%)	World region
Pestilence and famine	Predominant malnutrition and infectious disease	11	Sub-Saharan Africa
Receding pandemics	Improved nutrition and public health (increased hypertension, chronic disease)	38	South Asia, Southeast Asia, Pacific, parts of Caribbean, Latin America
Degenerative and "man-made" diseases	Lifestyle and dietary changes	35	Urban parts of low- and middle-income countries
Delayed degenerative diseases	Cardiovascular disease and cancer	15	High-income countries

Modified from Gaziano TA[35] with permission from Wolters Kluwer Health, Inc.

risk factors and secondary prevention is limited, but these medications are becoming increasingly available.

Adherence to evidence-based guidelines remains universally suboptimal, but unique challenges prevent their broader uptake and implementation in LMICs. In North America, than half of patients with IHD remain adherent to secondary prevention medications within a year of having an acute event.[43,44] Adherence to cardiovascular medications in LMICs is similarly poor because of cost, regimen complexity, and poor knowledge about medications.[45,46]

Access to hospitals capable of providing timely diagnostic and therapeutic strategies to patients with acute myocardial infarction is extremely limited for many individuals living in LMICs. In a survey of district hospitals in 7 LMICs, only 68% of hospitals had access to continuous electricity, and 85% had access to constant or frequently running water.[47]

This may hamper access to essential cardiovascular services, such as the provision of reperfusion for patients with acute myocardial infarction, especially for the most economically disadvantaged individuals. For example, the CREATE registry studied consecutive patients treated for acute coronary syndrome throughout 89 hospitals in India. Among patients with ST-elevation myocardial infarction, 59% received fibrinolysis and only 8% underwent percutaneous coronary intervention. When stratified by income, poor patients were significantly less likely to receive any reperfusion strategy and evidence-based medical therapy such as β-blockers or lipid-lowering drugs.[48]

Dietary and lifestyle choices

Dietary habits have changed significantly worldwide as described by the "epidemiologic transition" (Table 1). An analysis of sodium intake in 187 countries over 2 decades revealed that sodium intake was 3.95 g/d, twice the maximum amount recommended by the WHO.[49] A recent meta-analysis showed that mean reduction in salt intake results in a decrease in mean blood pressure, irrespective of sex.[50,51] This in turn decreases CVD risk.[52]

Reduced physical activity is thought to be responsible for 6% (3.2% in Southeast Asia; 7.8% in the Eastern Mediterranean region) of the burden of coronary artery disease so that inactivity may be responsible for 9% of premature mortality.[53] The PURE study showed an association between obesity and diabetes and ownership of a household device, mediated by changes in physical activity, time spent sitting, and dietary energy intake.[54] However, this was not seen among those with IHD or stroke.[55] Levels of physical activity have increased in some countries such as China and Cuba,[56,57] and multiple studies have shown the inverse relationship between physical activity and cardiovascular events.[58-60]

Biological heterogeneity

Genetic and biological factors may affect the prevalence of hypertension in individuals of African ancestry.[61] Notably, Asians have a higher tendency toward the development of diabetes at a lower body mass index given the propensity toward the development of visceral fat and rapid weight gain during childhood, factors that increase the risk for insulin resistance.

Strategies for Reducing CVD in LMICs

A comprehensive strategy to reduce the burden of CVD in LMICs will need to address health promotion and disease prevention, control of modifiable risk factors, and treatment of acute and chronic medical conditions. Over the past few decades, novel ways to handle this global crisis have been explored. The main limiting factor remains health system constraints in LMICs.[62] Hence, low-cost interventions with the potential to improve adherence to evidence-based medical therapies hold particular promise as a method of improving IHD burden. In this spirit, the Institute of Medicine report, "Promoting Cardiovascular Health in the Developing World," advocates an "intersectoral approach" consisting of concurrent global and national policy development, communication campaigns, health care delivery redesign, and community-based programs.[63]

Of note, health interventions in LMICs are often presented within a cost-effective framework that is far more limited than in HICs. There is no legal or ethical standard of what is cost-effective. The WHO Commission on Macroeconomics and Health suggests that cost-effective interventions are less than 3 times the GNI per capita; other programs recommend using 1-3 times the country's GDP.[64,65] If the range of cost-effective values proposed in Canada was inflated to 2008 US dollars, interventions would cost US $23,000-$117,000 per quality-adjusted life year, which is slightly less than 3 times the GNI.[65] This same standard applied to Kenya, eg, would translate into interventions that cost less than US $2500 per quality-adjusted life year.

A strategy of identifying patients most likely to benefit from intensive lifestyle modification and treatment for cardiovascular risk factors focuses limited resources on those with the highest risk for adverse events. The WHO and the International Society of Hypertension have developed risk prediction charts using regional data in LMICs to help guide the treatment of patients at high absolute risk of CVD.[40] This tool promotes a strategy of treating CVD risk factors based on absolute risk rather than single risk factor management. The application of absolute CVD risk in guiding risk factor treatment, rather than cutoff values, has been used in Europe and more recently in North America to guide treatment for hypertension or high cholesterol levels, or both.[66,67] The use of medications for primary prevention of CVD appears to be cost-effective in resource-limited settings across a range of absolute risk thresholds.[68]

Efforts to prevent the uptake of tobacco use among adolescents and young adults and smoking cessation programs have had significant impact on IHD burden in developed countries and offers promise to stem the rise of IHD in resource-limited areas. Although the majority of smokers reside in LMICs, the cessation rate is far lower than in higher income areas: 2%-5% in China and India compared with 30% in the United States.[28] Population- and individual-level interventions have been shown to be cost-effective. For example, a 33% tax increase on cigarette sales is estimated to reduce 5%-16% of all deaths in smokers living in LMICs.[69] Nonprice interventions to reduce smoking prevalence may also be cost-effective, including increasing uptake of nicotine replacement therapy, public health education, and advertising bans.

Other population strategies to reduce IHD burden include maintaining a healthy weight, participating in regular exercise,

and following a healthy diet. The North Karelia project in Finland was conducted over a 25-year period starting in the 1970s. The project demonstrated that a population-based strategy using community organization and media campaigns could reduce IHD risk factors and mortality.[70] Such a comprehensive strategy has not yet been studied in LMICs. Community-based interventions that focus on replacing palm oil with healthier fats, such soybean oil, is effective in reducing cholesterol levels and may be cost-effective.[36,71]

The polypill, a strategy of combining multiple cardioprotective medications into 1 tablet, may be highly relevant for patients at higher risk for the development of IHD or for patients with IHD who often have complex medication regimens.[72] Ongoing polypill studies are currently enrolling patients in LMICs who are at low and moderate risk for IHD as well as testing the combined approach of a polypill with simplified screening and treatment algorithms.[73] The PolyIran and HOPE-3 (**H**eart **O**utcomes **P**revention **E**valuation-3) studies are large studies evaluating the role of the polypill in primary prevention of IHD.[74,75] The **F**ixed-D**o**se **C**ombination Dr**u**g for **S**econdary Cardiovascular Prevention (FOCUS) trial randomized patients with known IHD in South America or Spain to a polypill containing aspirin, simvastatin, and ramipril vs the 3 drugs separately. At 9 months, self-reported adherence was higher among the polypill group (51% vs 41%), although no significant change in clinical factors or cardiovascular events was noted.[72] Other studies have shown that the polypill leads to improvement in adherence with either small or no changes in systolic blood pressure and low-density lipoprotein levels.[76,77]

Community health workers (CHWs) have historically played a pivotal role in reducing overburdened health care systems, with their focus on achieving the Millennium Development Goals.[78] Because of political influences and fragile health infrastructures in LMICs, CHWs have lacked sufficient training, and there is a paucity of data evaluating their effectiveness in CVD programs. Small studies in India and Sub-Saharan Africa suggest that nurse-directed antihypertension programs have been successful in primary prevention programs in India and Cameroon as well as improvements in hypertension management in Nigerian patients.[79-82] Studies from under-resourced settings in the United States report that CHW-led initiatives have improved adherence to treatment programs and better hypertension control.[83,84] Currently, efforts are under way to train 1 million CHWs in Africa.[85]

Mobile health care is rapidly evolving as a method of engaging patients in chronic disease management. There are limited published data on its effectiveness in LMICs for CVD management.[86] Its success is largely reported in improving adherence to HIV and tuberculosis treatments,[87,88] with smaller successful studies in patients with diabetes in India.[89] Large trials using mobile health interventions are currently under way in Central America and Pakistan.[90]

Conclusions

Cardiovascular disease is currently the most important noncommunicable disease in most LMICs. The growing burden of disease is attributable to multiple factors, including an increase in the prevalence of risk factors in these regions as well as limited access to health care services in both prevention and treatment of CVD. Although there is a general paucity of robust research data in this field in LMICs, current efforts appear promising, using interventions that tackle these issues at both an individual and a population level. These include risk factor reduction programs, access to acute treatments, and innovative interventions for improving medication and treatment adherence. Continued global focus on CVD in LMICs is paramount to address this growing burden of disease.

Disclosures

The authors have no conflicts of interest to disclose.

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