Emerging Epidemic of Cardiovascular Disease in Developing Countries

K. Srinath Reddy, MD, DM; Salim Yusuf, DPhil

As the twentieth century draws to a close, it is clear that cardiovascular disease (CVD) has become a ubiquitous cause of morbidity and a leading contributor to mortality in most countries.[1,2] The rise and recent decline of the CVD epidemic in the developed countries have been well documented.[3,4] The identification of major risk factors through population-based studies and effective control strategies combining community education and targeted management of high risk individuals have contributed to the fall in CVD mortality rates (inclusive of coronary and stroke deaths) that has been observed in almost all industrialized countries. It has been estimated that during the period 1965 to 1990, CVD related mortality fell by ≈50% in Australia, Canada, France, and the United States and by 60% in Japan.[1] Other parts of Western Europe reported more modest declines (20% to 25%). The decline in stroke mortality has been more marked compared with the decline in coronary mortality. In the United States, the decline in stroke mortality commenced nearly two decades earlier than the decline in coronary mortality and maintained a sharper rate of decline. During the period 1979 to 1989, the age-adjusted mortality from stroke declined, in that country, by about one third, whereas the corresponding decline in coronary mortality was 22%.[4,5] In Japan, where stroke mortality outweighs coronary mortality, the impressive overall decline in CVD mortality is principally contributed by the former. The discordant trend of rising CVD mortality rates in Eastern Europe, however, is in sharp contrast to the decline in Western Europe.[1]

Burden of CVD in Developing Countries

The emergence of the CVD epidemic in the developing countries during the past two to three decades has attracted less comment and little public health response, even within these countries. It is not widely realized that at present, the developing countries contribute a greater share to the global burden of CVD than the developed countries.[1,4] It has been estimated that 5.3 million deaths attributable to CVD occurred in the developed countries in 1990, whereas the corresponding figure for the developing countries ranged between 8 to 9 million (ie, a relative excess of 70%).[1] Regional estimates of CVD mortality indicate that the difference would be even higher if the term "developed countries" is restricted to established market economies only and excludes the former socialist economies (Table 1).

This high, yet inadequately recognized, contribution of developing countries to the absolute burden of CVD is readily explained by the fact that 78% of the 49.9 million global deaths (from all causes) in 1990 occurred in regions other than the established market economies or former socialist economies (Table 2). Although the relative contribution of CVD deaths to total mortality was higher in the developed countries (≈49%) than that in the developing countries (≈23%), the excess total mortality in the latter is translated into excess absolute CVD mortality due to the large populations involved. Thus, in 1990 the developing countries contributed 68% of the total global deaths due to noncommunicable disease and 63% of world mortality due to CVD.[2] Although the inadequacies and imperfections of cause-specific mortality ascertainment methods currently used in many developing countries call for cautious interpretation of these estimates, the conservative assumptions made by the analysts suggest that the absolute burden of CVD mortality is indeed likely to be high in developing countries.

Early Age of CVD Deaths in Developing Countries

Although the present high burden of CVD deaths is in itself an adequate reason for attention, a greater cause for concern is the early age of CVD deaths in the developing countries compared with the developed countries. For example, in 1990, the proportion of CVD deaths occurring below the age of 70 years was 26.5% in the developed countries compared with 46.7% in the developing countries.[2] The contrast between the truly developed "established market economies" (22.8% of CVD deaths at <70 years) and a large developing country like India (52.2%) was even sharper.[2] Therefore, the contribution of the developing countries to the global burden of CVD, in terms of disability adjusted years of life lost, was 2.8 times higher than that of the developed countries (Table 1).

Epidemiological Transition

A second cause for considerable alarm is the projected rise in both proportional and absolute CVD mortality rates in the developing countries over the next 25 years.[6,7] The reasons for this anticipated acceleration of the epidemic are many. In the second half of the twentieth century, most developing countries experienced a major surge in life expectancy.[8] For example, the life expectancy in India rose from 41.2 years in

TABLE 1. Regional Differences in Burden of CVD (1990)

Region	Population, millions	CVD Mortality, thousands	Coronary Mortality, thousands	Cerebrovascular Mortality, thousands	DALYs Lost, thousands
Developed regions	1144.0	5328.0	2678.0	1447.9	39 118
Developing regions	4123.4	9016.7	2469.0	3181.2	108 802
Established market economies	797.8	3174.7	1561.6	782.0	22 058
Former socialist economies	346.2	2153.3	1116.3	665.9	17 060
India	849.5	2385.9	783.2	619.2	28 592
China	1133.7	2566.2	441.8	1271.1	28 369
Other Asian countries and islands	682.5	1351.6	589.2	350.4	17 267
Sub-Saharan Africa	510.3	933.9	109.1	389.1	12 252
Middle Eastern Crescent	503.1	992.3	276.6	327.4	12 782
Latin America	444.3	786.7	269.1	224.1	9538

DALY indicates disability-adjusted life year.
Adapted from Murray and Lopez.[2]

1951–1961 to 61.4 years in 1991–1996. This was principally due to a decline in deaths occurring in infancy, childhood, and adolescence and was related to more effective public health responses to perinatal, infectious, and nutritional deficiency disorders and to improved economic indicators such as per-capita income and social indicators such as female literacy in some areas. Although this is a cause for celebration (and much remains to be done in these areas), the demographic shifts have augmented the ranks of middle-aged and older adults. The increasing longevity provides longer periods of exposure to the risk factors of CVD, resulting in a greater probability of clinically manifest CVD events.[9] The concomitant decline of infectious and nutritional disorders (competing causes of death) further enhances the proportional burden due to CVD and other chronic lifestyle-related diseases. This shift, representing a decline in deaths from infectious diseases to an increase in those due to chronic diseases, is often referred to as the modern epidemiological transition.[6,7]

The ratio of deaths due to pretransitional diseases (related to infections and malnutrition) to those caused by post-transitional diseases (eg, CVD and cancer) varies among regions and between countries, depending on factors such as the level of economic development and literacy as well as availability and access to health care. The direction of change toward a rising relative contribution of posttransitional dis-

TABLE 2. Regional Contribution to Mortality (1990)

Region	All Causes, %	CVD, %
Established market economies	14	22
Former socialist economies	8	15
India	19	17
China	18	18
Other Asian countries and islands	11	9
Sub-Saharan Africa	10	7
Middle Eastern Crescent	9	7
Latin America	6	5
World	100	100

Values are given as percent of world total.
Adapted from Murray and Lopez.[2]

eases is, however, common to and consistent among the developing countries.[6] The experience of urban China, in which the proportion of CVD deaths rose from 12.1% in 1957 to 35.8% in 1990, is illustrative of this phenomenon.[10]

Lifestyle Changes

A third reason to arouse concern is that if population levels of CVD risk factors rise as a consequence of adverse lifestyle changes accompanying industrialization and urbanization, the rates of CVD mortality and morbidity could rise even higher than the rates predicted solely by demographic changes. Both the degree and the duration of exposure to CVD risk factors would increase due to higher risk factor levels coupled with a longer life expectancy. An increase in body weight (adjusted for height), blood pressure, and cholesterol levels in Chinese population samples aged 35 to 64 years, between the two phases of the Sino-MONICA study (1984 to 1986 and 1988 to 1989) and the substantially higher levels of CVD risk factors in urban population groups compared with rural population groups in India provide evidence of such trends.[9,10] A cross-sectional survey of urban Delhi and its rural environs revealed that a higher prevalence of coronary heart disease (CHD) in the urban sample was associated with higher levels of body mass index, blood pressure, fasting blood lipids (total cholesterol, ratio of cholesterol to HDL cholesterol, triglycerides), and diabetes.[9] The increasing use of tobacco in a number of developing countries will also translate into higher mortality rates of CVD, lung cancer, and other tobacco-related diseases.[11,12]

Nutrition Transition

As recently reviewed by Drewnowski and Popkin,[13] the global availability of cheap vegetable oils and fats has resulted in greatly increased fat consumption among low-income countries. The transition now occurs at lower levels of the gross national product than previously and is further accelerated by rapid urbanization. In China, for example, the proportion of upper-income persons who were consuming a relatively high-fat diet (>30% of daily energy intake) rose from 22.8% to 66.6% between 1989 and 1993. The lower- and middle-income classes also showed a rise (from 19% to 36.4% in the

former and from 19.1% to 51.0% in the latter).[11] The Asian countries, with a diet that is traditionally high in carbohydrates and low in fat, have shown an overall decline in the proportion of energy from complex carbohydrates along with the increase in the proportion of fat. The globalization of food production and marketing is also contributing to the increasing consumption of energy-dense foods poor in dietary fiber and several micronutrients.[14]

Potential Effect of Impaired Fetal Nutrition

A recently reported association that, if adequately validated by the tests of causation, may have special relevance to the developing countries is the inverse relation between birth size and CVD in later life.[15] The "fetal origins hypothesis" states that adverse intrauterine influences such as poor maternal nutrition lead to impaired fetal growth, resulting in low birth weight, short birth length, and small head circumference. These adverse influences are postulated to also "program" the fetus to develop adaptive metabolic and physiological responses that facilitate survival. These responses, however, may lead to disordered responses to environmental challenges as the child grows, with an increased risk of glucose intolerance, hypertension, and dyslipidemia in later life and adult CVD as a consequence. Although some supportive evidence for the hypothesis has been provided by observational studies,[16–18] it awaits further evaluation for a causal role.[19] If it does emerge as an important risk factor for CVD, the populations of developing countries will be at an especially enhanced risk because of the vast numbers of poorly nourished infants who have been born in the past several decades. The steady improvement in child survival will lead to a higher proportion of such infants surviving to adult life, when their hypothesized susceptibility to vascular disease may manifest itself.

Tobacco Trends

The rising tobacco consumption patterns in most developing countries contrast sharply with the overall decline in the industrial nations. Recent projections from the World Health Organization suggest that, by the year 2020, tobacco will become the largest single cause of death, accounting for 12.3% of global deaths.[20] India, China, and countries in the Middle Eastern Crescent will by then have tobacco contributing to >12% of all deaths. In India alone, the tobacco attributable toll will rise from 1.4% in 1990 to 13.3% in 2020.[20] A large component of this will be in the form of cardiovascular deaths. Tobacco is the leading avoidable cause of death worldwide, and its rising consumption in the developing countries warrants early and effective public health responses.

Projected Rise in CVD Mortality

The anticipated rise in CVD mortality, based solely on demographic shifts of population age profile, is staggering.[6,21] It has been projected, for example, that mortality attributable to "circulatory system diseases" in India would rise by 103% in men and by 90% in women during the period 1985 to 2015.[21] By 2015, these diseases are expected to account for 34% of all male deaths and 32% of all female deaths in India. The ratio of deaths from circulatory system diseases to deaths from infectious diseases is likely to rise from 0.60 to 2.75 in Asia and from

1.1 to 4.75 in Latin America during the period 1985 to 2015.[6,21] Although the categories of cause-specific mortality, in the surveys on which these projections are based, are vulnerable to errors of misclassification, the overall general trend is likely to be valid. The escalation will be undoubtedly large, even if the present estimates are unable to precisely identify the true magnitude of future CVD mortality. If urbanization and lifestyle change contribute to increased risk factor levels, the rise in CVD mortality may even be larger than these estimates based solely on demographic shifts.

Varied Profile Between Developing Countries

Even within the group of developing countries, the degree of development varies with a diverse profile of socioeconomic growth, demographic change, and lifestyle practices. The direction and pace of the CVD epidemics are therefore unlikely to be uniform across the wide range of development, within this group. This is illustrated by Latin America, in which countries such as Argentina, Chile, Uruguay, and Cuba demonstrated a declining trend for both CVD and CHD mortality between 1969 and 1986, whereas countries such as El Salvador, Guatemala, and Dominican Republic showed an increase in CVD as well as CHD mortality during this period.[22] Barbados and Costa Rica experienced an increase in CHD mortality but had an overall decline in CVD mortality due to a large decline in stroke mortality.[22] Despite such diversity in trends, Latin America has a high overall burden of CVD.[22,23] For example, the state of Sao Paulo, in Brazil, experienced declines of 33.6% for men and 40.6% for women in age-standardized CVD mortality rates between 1970 and 1992.[23] Despite this decrease, the mortality rates in the 45- to 64-year-old age group in Sao Paulo, Porto Alegre, and Rio de Janeiro are reported to be higher than those in the United Kingdom and as high as or nearly equal to rates in Eastern Europe.[23] The cumulative mortality rate from CHD is 42% for Brazilian men below the age of 65 years compared with 25% in the industrialized countries.[23] Death from acute myocardial infarction in Brazilian men between the ages of 35 to 44 years is stated to be three times higher than in the United States or Canada.[23] In Africa, CHD is very uncommon, whereas hypertension and stroke are frequent. However, urban dwellers are rapidly experiencing a transition in their coronary risk profile, and there are apprehensions that they may experience a rise in CHD rates in the future, akin to that of African-Americans.[24] However, the pace and direction of economic development in Africa will be the major determinants of its epidemiological transition.

Health Care and Economic Consequences

The medical and socioeconomic consequences of the projected substantial increase in the burden of CVD will be disastrous for the developing countries. Health care facilities required for providing appropriate clinical evaluation of and optimal management for the many millions of CVD patients would be far beyond the scope of most developing countries. Death or disability in the productive years of life will severely strain human as well as financial resources available to individuals, families, and the society as a whole. Expensive interven-

tions and costly drugs may not be available, accessible, or affordable, except for an elite minority. State-subsidized health care is the norm in most developing countries, but nations that must invest their scarce resources in programs of industrial growth and sustainable development may ill afford the escalated health care expenditure imposed by the technology intensive management of manifest CVD. Even at present, the high costs of CVD management utilize a disproportionately large segment of societal resources expended on health care in the developing countries, diverting them from the continued efforts to control infectious and nutritional disorders. Most developing countries will experience the double burden of pretransitional and post-transitional diseases for some time to come, despite the likely decline in the former, resulting in inadequate attention to both categories of disease.

It has been the historical experience of the developed countries that the CVD epidemic usually commences in members of the higher social classes, who are the first to change from a low-risk to a high-risk lifestyle, which is characterized by diets rich in fat and calories, sedentariness, and smoking. Later, the risk permeates across the social spectrum, affecting all classes. The higher-social classes are, again, the first to respond to the knowledge of risk factors and the message of prevention. The CVD rates begin to decline in them, with the present pattern of higher CVD rates among the lower social classes becoming increasingly established. In most developing countries, there has been an initial preponderance of CVD in the higher socioeconomic strata. However, the pattern observed in the developed countries, in which the burden of disease shifts progressively to the lower social classes, is likely to be replicated as the epidemic advances. Indeed, recent reports from India, based on community surveys and case-control studies, suggest that poor educational or economic status is associated with higher risk of CHD in some regions.[25,26] There are several countries in Latin America and the Caribbean in which the poor are more likely to be obese than the rich.[27] If the social gradient completely reverses when the CVD epidemic fully matures, progressively larger numbers of poor individuals will become its victims and will be unable to obtain the necessary health care.

CVD Control Programs: Need for National and Global Efforts

The need to contain the epidemic as well as combat its impact and minimize the CVD toll in terms of mortality and morbidity in the developing countries is, therefore, obvious and urgent. Although feasible, national strategies to meet this objective must be developed and effectively implemented by individual countries, new regional and global initiatives by international agencies concerned with health care program facilitation, policy development, and research funding are also required to strengthen and speed up these national efforts.

The essential components of any CVD control program would be the following: (1) establishment of efficient systems for estimation of CVD-related burden of disease and its secular trends; (2) estimation of the levels of established CVD risk factors (eg, smoking, elevated cholesterol, or blood pressure) in representative population samples to help identify risk factors that require immediate intervention; (3) evaluation of emerg-

ing risk factors (eg, glucose, abdominal obesity, fibrinolytic status, homocysteine) that may be of special relevance to the populations concerned; (4) identification of the determinants of health behavior that influence the levels of both traditional and emerging risk factors in the specific context of each society; and (5) development of a health policy that will integrate population-based measures for CVD risk modification and cost-effective case management strategies for individuals who have clinically manifested CVD or are detected to be at a high risk of developing it.

All of these require a strengthening of policy-relevant research that can support and evaluate CVD control programs in the developing countries. The challenge of CVD control is especially complex in settings in which epidemiological data related to the incidence of fatal and nonfatal CVD events as well as population-attributable risk of various risk factors of CVD are not readily or reliably available at present.

However, the need for tobacco control currently assumes the highest priority, both because no context-specific scientific validation is needed to establish its risk factor status as a program prerequisite and because of the wide-ranging benefit that will accrue for a whole host of chronic diseases. Although strategies for behavior modification in relation to specific dietary practices may require further research within each population, the imperatives of tobacco control are universal and should be implemented without delay.

Strengthening the Estimation of Mortality and Morbidity

A paucity of cause-specific mortality data in the developing countries is a major impediment to the estimation of the absolute and relative death toll of CVD or in evaluating the time trends in mortality. An effective program for improving the extent as well as the quality of death certification is therefore a high priority. Simultaneously, easy-to-administer verbal autopsy instruments must be developed and validated for determination of CVD-related deaths in communities in which death certification is inadequate. One such instrument, for use by trained lay interviewers, is being evaluated by the World Health Organization in a multicenter validation study in several developing countries.

Obtaining a fuller estimate of the burden of disease also requires standardized morbidity data. Although gathering such data on a national basis would be impractical, obtaining prevalence data from cross-sectional sample surveys of selected communities and incidence data from selected cohort studies would provide a reasonable basis for extrapolation. Health services of large organized sector industries may offer opportunities for convenient and cost-effective prospective studies and registries.

CVD Risk Factor Studies

With regard to CVD risk factors, the developing countries must critically appraise the vast body of knowledge that has accrued from studies in populations from the developed countries and identify the elements that are generalizable to their populations. This is of particular interest in view of the observed ethnic diversity in the profile of CVD and varied risk associations in different populations. Although conventional

CVD risk factors such as smoking, high blood pressure, and elevated blood cholesterol are likely to be relevant risk factors for most populations, other risk factors and different levels of genetic–environmental interaction may be important in different populations. The 25-year follow-up data of the Seven Country Study clearly demonstrate the variability in the cholesterol–CHD heart disease risk relation across populations.[28]

The South Asian experience also illustrates this need to evaluate risk factors in the context of ethnic diversity in CVD. Several studies around the world have consistently revealed excess, early, and extensive CHD in persons of South Asian origin.[29,30] The excess mortality has not been fully explained by the major conventional risk factors in cross-sectional comparisons with other population groups. Diabetes mellitus and impaired glucose tolerance are, however, highly prevalent in South Asian migrants.[29] Central obesity, high levels of triglycerides, and low levels of HDL cholesterol, with or without glucose intolerance, seem to characterize a phenotype frequently noted among South Asian migrants. A similar profile has been observed to be common in urban Indians in a recent population survey.[31]

However, a substantial urban excess in several of the conventional risk factors (body mass index, blood pressure, plasma cholesterol, diabetes) has been identified in cross-sectional urban-rural comparisons in India.[9] A recent case-control comparison of incident acute myocardial infarction cases and age-and sex-matched hospital controls in India revealed that the most important predictors of acute myocardial infarction were current smoking, history of hypertension, overt diabetes mellitus, and abdominal obesity as measured by waist-to-hip ratio.[26] A comparison of Indian migrants to the United Kingdom with their siblings who remained in Punjab reported that although both Indian groups had higher lipoprotein(a) levels in comparison to the Europeans in the United Kingdom, the South Asians in London had higher body mass index and plasma cholesterol and fasting blood glucose levels as well as a lower HDL cholesterol level and reduced insulin sensitivity in comparison with their siblings.[32] Thus, South Asians in urban and migrant environments may be at a higher risk of CHD due to the confluence of (1) genetic factors that predispose to higher lipoprotein(a) levels, the central obesity/glucose intolerance/dyslipidemia complex collectively labeled as the "metabolic syndrome," and a possible "thrifty gene" effect with (2) environmental influences that lead to weight gain, rise in plasma cholesterol and blood pressure levels, and, as yet inadequately studied, probable psychosocial risk factors.

Such genetic environmental interactions may need to be clarified in the varied ethnocultural populations of the developing countries so that the relevant environmental interventions could be preferentially promoted for CVD prevention.

The marked ethnic diversity in the manifestations of CVD is another potentially profitable area for study in the developing countries. The high rates of stroke coupled with low rates of CHD in Chinese (despite high smoking rates) as well as African populations must be explained.[10,33] The lack of association between the high prevalence of diabetes and CHD in groups such as the Afro-Caribbeans calls for critical enquiry.[34] Studies of CVD risk factors in the varied populations of the developing

countries may help complement the knowledge already gained from studies in Western populations by supplying the missing pieces in the multifactorial puzzle of CVD causation.

Research Priorities

Public health action for CVD control in the developing countries is therefore linked to a policy-relevant research agenda. However, the classic sequence of long-term cohort studies followed by intervention trials to initially identify and later modify risk factors will be time consuming and is likely to be impeded by financial constraints. Public health action cannot afford to wait that long to initiate interventions. The appropriate strategy would be to (1) commence control strategies, based on what we can readily extrapolate from the knowledge available from other populations (eg, tobacco control); (2) evaluate known and putative risk factors through cross-sectional studies of populations (ecological comparisons) and case-control studies, preferably using incident cases of CVD; and (3) follow-up the cross-sectional survey populations prospectively to obtain incidence data on CVD-related morbidity and mortality as well as to assess the independent and interactive risks associated with known and emerging risk factors.

Certain additional areas of CVD epidemiology need special attention in the studies to be initiated in the developing countries. Nutritional epidemiology in diverse cultural settings with widely varying dietary practices faces the challenge of identifying prudent, affordable, and culturally acceptable diets for each population. It also offers the potential opportunity of identifying protective practices (eg, vegetarianism) that may reduce the risk of CVD if adopted by other populations.

Psychosocial factors are likely to have varied components and determinants in different cultures. Apart from the challenge of cross-cultural validation and adaptation of instruments developed for a very different cultural context, these studies must explore the psychosocial factors that are conditioned by the rapid socioeconomic, cultural, and health transitions occurring in the developing countries as well as identify the elements in their tradition that are likely to offer continued protection if preserved.

Health policy research also must be strengthened. The existing health care infrastructure is equipped to handle mostly the pretransitional agenda of infectious and nutritional deficiency disorders. It must be reinforced, reoriented, and recruited to the task of meeting the challenge of posttransitional diseases. Health education (of public, providers, and patients) is a priority. Some of the knowledge and process components of Western health educational interventions are likely to be applicable but require adaptation to the needs of each community's sociocultural milieu. Integration with other chronic disease control programs also is essential. Tobacco control and diet are clearly on the agenda of several lifestyle-related disease control programs.

Dynamics of Prevention in Developing Countries

The dynamics of the prevention effort also are likely to differ from those witnessed in the developed countries. Public health activism for CVD prevention commenced in the latter when

the epidemic of CVD was close to its peak and the community had become aware and alarmed of its impact. At a high level of economic development, counseling for lifestyle modification to reduce the risk of disease is more readily accepted. Advocacy of behavior modification for health promotion, therefore, had a relatively receptive climate. In contrast, the developing countries are grappling with the "double burden" of pretransitional and posttransitional disease, and community awareness of the dangers of CVD is not high. The transition toward becoming industrial market economies is unleashing consumer aspirations that impatiently seek an affluent and indulgent lifestyle. Messages of moderation may not be welcome during such periods of change. The task of CVD control in the developing countries may therefore be more complex than that in the developed countries.

The relatively low levels of the conventional CVD risk factors in the large rural segments of the developing countries, however, do offer a window of opportunity for early and effective control of the epidemic. Strategies to prevent acquisition or augmentation of CVD risk factors in these communities (primordial prevention) must be combined with programs to reverse and reduce the risk factor elevations observed in the urban communities (primary prevention). At the present levels of these risk factors in the developing countries, the approach would be predominantly nonpharmacological, population based, and lifestyle linked. This would largely avoid the biologic and economic costs of a pharmacological approach warranted by high levels of these risk factors in the developed countries.

There also is a clear need to develop cost-effective methods for the timely diagnosis and management of manifest disease. Suitable clinical algorithms for diagnosis and low-cost life-saving interventions (eg, aspirin) must be widely available to and adopted by health professionals in primary and secondary care settings. Although tertiary care expertise is growing, the patterns of practice must include optimization of resources and avoidance of heavy investment in high-cost, low-yield technologies.

Thus, the new century dawns on a period of challenge and opportunity for the developing countries as they embark on their efforts to quell the emerging epidemic of CVD. National and international efforts must be coordinated to recognize this epidemic and respond without delay.

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