European Heart Journal (2010) **31**, 642–648
doi:10.1093/eurheartj/ehq030

REVIEW

Novel therapeutic concepts

The epidemic of cardiovascular disease in the developing world: global implications

Bernard J. Gersh[1]*, Karen Sliwa[2], Bongani M. Mayosi[3], and Salim Yusuf[4]

[1]Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic, Rochester, MN 55905-0001, USA; [2]Hatter Institute of Cardiovascular Research, Cape Town, South Africa; [3]Department of Medicine, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa; and [4]Population Health Research Institute, McMaster Clinic, Hamilton General Hospital, Hamilton, Ontario, Canada

Received 31 July 2009; revised 6 January 2010; accepted 27 January 2010; online publish-ahead-of-print 22 February 2010

The epidemic of cardiovascular disease (CVD) is a global phenomenon, and the magnitude of its increase in incidence and prevalence in low- and middle-income countries (LIMIC) has potentially major implications for those high-income countries that characterize much of the developed world. Cardiovascular disease remains the leading cause of death in the world and approximately 80% of all cardiovascular-related deaths occur in LIMIC and at a younger age in comparison to high-income countries. The economic impact in regard to loss of productive years of life and the need to divert scarce resources to tertiary care is substantial. The 'epidemiologic transition' provides a useful framework for understanding changes in the patterns of disease as a result of societal and socioeconomic developments in different countries and regions of the world. A burning but as yet unanswered question is whether gains made over the last four decades in reducing cardiovascular mortality in high-income countries will be offset by changes in risk factor profiles, and in particular obesity and diabetes. Much of the population attributable risk of myocardial infarction is accountable on the basis of nine modifiable traditional risk factors, irrespective of geography. Developing societies are faced with a hostile cardiovascular environment, characterized by changes in diet, exercise, the effects of tobacco, socioeconomic stressors, and economic constraints at both the national and personal level in addition to exposure to potential novel risk factors and perhaps a genetic or programmed foetal vulnerability to CVD in later life. There are major challenges for primary and secondary prevention including lack of data, limited national resources, and the lack of prediction models in certain populations. There are two major approaches to prevention: public health/community-based strategies and clinic-based with a targeted approach to high-risk patients and combinations of these. There are concerns that in comparison with communicable diseases, cardiovascular and chronic diseases have a relatively low priority in the global health agenda and that this requires additional emphasis.

> The human race has had long experience and a fine tradition in surviving adversity, but we now face a task for which we have little experience, the task of surviving prosperity *Alan Gregg 1890-1957, Rockefeller Foundation*.

Keywords Cardiovascular diseases • Epidemic • Risk factors • Primary and secondary prevention • Developing world

The epidemic of cardiovascular disease: a global phenomenon

The epidemic of cardiovascular disease (CVD) is a global phenomenon, and in the current environment, the magnitude of this increase in incidence and prevalence in the developing world and newly industrialized nations has potentially major complications for those high income nations that characterize much of the developed world. The early half of the 20th century witnessed a rapidly growing epidemic of CVD as a result of industrialization, urbanization, increased prosperity, and social upheaval in the higher income countries, followed by an impressive decline in mortality from CVD during the latter half of the 20th century. Nonetheless, we are now at a stage in which much of the world's population falls

* Corresponding author. Tel: +1 507 284 4139, Fax: +1 507 266 0229, Email: gresh.bernard@mayo.edu

within the umbrella of the rapidly expanding newly industrialized nations.

This review will focus upon the changing demographics of CVD; the features of the 'epidemiologic transition' which provides a basis for understanding patterns of disease in different regions of the world and in relationship to societal changes; a discussion of the marked regional differences in disease prevalence and explanations for these, including the presence of traditional and novel risk factors, in addition to highlighting different approaches to primary and secondary prevention.

Demographics: the magnitude of the burden of disease

The facts are unequivocal and disturbing—CVD remains the leading cause of death in the world, far outstripping deaths due to malaria, HIV/AIDS, and tuberculosis.[1] Approximately 80% of the 35 million deaths annually attributable to chronic diseases and a similar proportion of the approximately 16.7 million deaths due to CVD occur in low- and middle-income countries(LI-MIC); defined as a gross national income per capita of less than $10 066 US dollars per annum in 2004.[2,3] Moreover, CVD occurs at a younger age and although this might reflect to some extent a demographic artefact due to the lower age distribution in LIMIC, the personal and macro-economic implications for the workforce and national productivity are profound. A recent study of five countries emphasizes that a much higher proportion of deaths occur in the working age population in Brazil, India, and South Africa in contrast to the USA and Portugal.[4] Despite limitations in regard to the quality of data collection, the potential consequences of the burden of CVD falling upon the 'breadwinners' of the community are sobering; LIMIC are faced with a dual burden of communicable and degenerative diseases which require tertiary care and a consequent diversion of limited resources. In conjunction with the loss of productive years of life, the consequences lead to economic constraints with an impact on both the private and the public sectors.

Moreover, the demographic tide is inexorably shifting, and it is estimated that by 2010, 70% of the world's elderly will live in LIMIC and the trend towards urbanization will accelerate.[5] Other studies project that the increase in mortality due to coronary heart disease and stroke will be approximately three-fold higher in developing countries in comparison to the developed nations. These trends are illustrated by changes in the distribution of the causes of death in China between 1973 and 2005 with a marked fall in rates due to communicable diseases and an increase in the proportion due to cerebro-CVD and cancer.[6]

India provides a striking example of a country with contrasting burdens of disease. Despite the surge in the Indian economy over the last two decades, in 1999 to 2001, the Federal Agricultural Organization reported that approximately 213.7 million people were considered undernourished.[7] This contrasts with a report on the prevalence of obesity in affluent girls' schools in Delhi, in which 22% of children to 17 years were overweight and 6% obese.[8] In addition, although India is a young country, the $\geq$60 years age group, the majority of whom are poor, is large and comprises 5% of the total population and is projected to rise to 113 million people by 2016. Similarly, South Africa is faced with a collision of four excessive health burdens; communicable diseases (HIV, Aids); non-communicable diseases among a population in whom the proportion of the elderly is predicted to triple between 1985 and 2025; maternal, neonatal, and child mortality, and the consequences of injury and violence.[9]

The epidemiological transition

The epidemiological transition provides a useful framework for understanding changes in the patterns of disease as a result of socio-economic and demographic developments.[10–12] The epidemiologic transition consists of four basic stages: pestilence and famine, receding pandemics, degenerative and man-made diseases, and the phase of delayed degenerative diseases (*Figure 1A* and *B*).[5,10–13]

Stage 1: the age of pestilence and famine

This has characterized much of human development throughout the course of history with cardiac disease (rheumatic and nutritional) accounting for less than 10% of total deaths (*Figure 1A*). In regions such as the USA and Europe, the transition into the next phase (Stage 2) occurred in the late 18th and throughout the 19th century, but in many developing countries infectious and post-infectious circulatory disorders continue to exact a major toll and are neglected in the overall global agenda for the research and control of CVD.[14–21]

Stage 2: the age of receding pandemics

In Phase 2, improved nutrition and public health results in increased longevity, less deaths due to infections and malnutrition, and the emergence of hypertension, stroke, and coronary disease, although rheumatic heart disease is still prevalent. In this phase, stroke is primarily haemorrhagic, presumably due to uncontrolled hypertension. Examples of this phase are the USA in the early part of the 20th century and parts of China and India today.[5,12]

Stage 3: the age of degenerative and man-made diseases

In stage 3, improvements in socioeconomic status and urbanization are accompanied by marked changes in risk factors including increased fat and caloric intake, tobacco use, and reduced levels of exercise leading to hypertension, obesity, and atherosclerosis (*Figure 1B*). Cardiovascular deaths account for 35–65% of all deaths, and exceed death rates due to infections and malnutrition. The commonest mode of death in stage 3 is ischaemic heart disease and stroke, and in some countries haemorrhagic stroke is still more frequent than ischaemic stroke. Examples of Phase 3 are the USA during 1930 to 1965, Western Europe approximately 10 years later, and many parts of China, India, the Middle East, Eastern Europe, and Latin America today.[5,6,12,13]

Interestingly, the emergence of cardiovascular and ischaemic heart disease during Phase 3 is primarily seen among the better educated and more affluent as shown in the INTERHEART study of a relatively small number of black Africans with myocardial infarction.[22] In contrast, among whites and coloureds, myocardial infarction was more commonly associated with lower socioeconomic status.

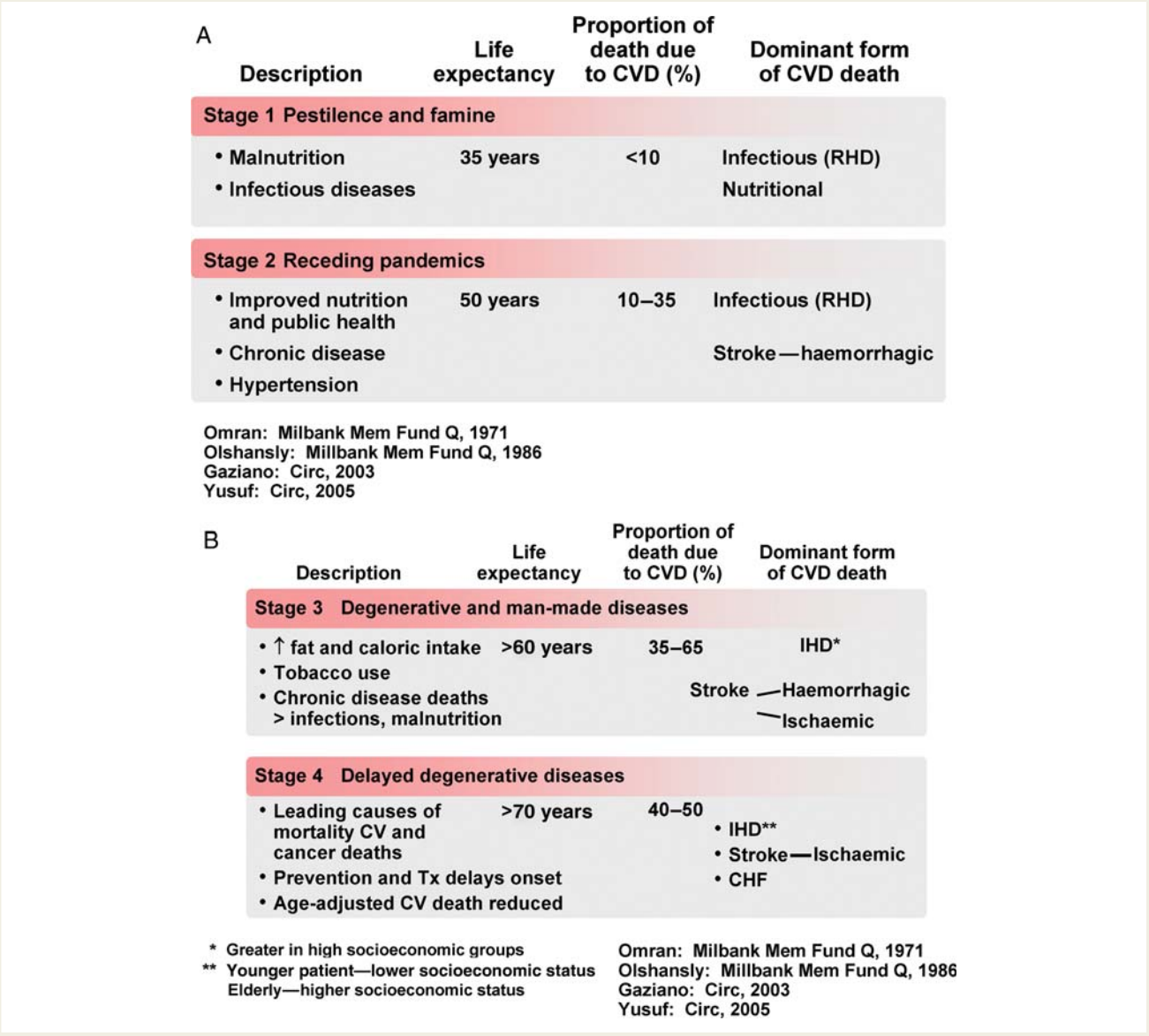

Figure 1 Stages of epidemiologic transition.

Stage 4: the age of delayed degenerative diseases

Stage 4 or the age of delayed degenerative diseases, is currently the situation in most high income and highly industrialized nations of the world (*Figure 1B*).[5,10,12] Life expectancy is greater than 70 years; leading causes of mortality are CVD and cancer, and the dominant forms of cardiovascular death are ischaemic heart disease, ischaemic stroke, and more recently congestive heart failure. In this phase of the transition, premature coronary artery disease tends to occur in patients of lower socioeconomic status since the benefits of risk factor reduction, secondary prevention, and access to evidence-based therapies and new technologies tend to be more widely implemented among the societally advantaged.[13,22–25] Among the higher socioeconomic classes, coronary artery disease is predominately a disease of the elderly. Examples of this are provided by data from the Women's Heart Study in which higher levels of education and income among apparently healthy female professionals were associated with a lower rate of cardiovascular events over a 10-year period.[23] Similarly, in a high-income country such as Canada, which also has universal healthcare, CVD mortality rates are lowest among the most affluent with evidence of an announced gradient based upon income.[25]

Is there a stage 5?

The last four decades have witnessed a gratifying fall in the USA of 2% per year in the age-adjusted coronary heart disease mortality and 3% per year in stroke mortality. This is attributable mainly to control of risk factors and to a lesser extent upon new therapeutic advances.[26] Nonetheless, in the wake of increasing prosperity and urbanization the epidemic of obesity, diabetes, and hypertension is now a world-wide phenomenon.[27] In addition, the decline in smoking rates is levelling off in some countries, and rates of detection and treatment of hypertension have not

increased.[5] A crucial question is whether therapeutic advances will offset the impact of an adverse trend in risk factors, and of concern in this respect are the data suggesting that men and women age 35–44 years in the USA, the annual decline in mortality from coronary heart disease has lessened and might be trending upward.[26] In addition to autopsy data from Olmsted County, MN, USA,[28] these mortality trends are mirrored by adverse trends in the prevalence of risk factors which demonstrate a reversal of the progress made in the 1970s and 80s.[29]

A different perspective is provided by the recent experience in Russia which perhaps illustrates the deleterious effects of social upheaval and economic instability upon mortality. Prior to the dissolution of the Soviet Union, longevity in Russian males and females steadily increased, but this was followed by a precipitous fall in the late 1980s.[30] The explanations are multifactorial, but it is estimated that heart disease and stroke accounted for approximately 65% of the decline in life expectancy with little change in death rates due to cancer. Incriminating factors include alcohol and tobacco abuse, violence, accidents, and the less tangible effects of psychosocial stress and destabilization. Of interest, it appears that during the 1980s and the 1990s that the increases in mortality in St Petersburg Russia were primarily among those with lesser levels of education with little change in individuals who had had a university education.[31]

National and regional differences in the prevalence and mortality of cardiovascular disease

The striking differences in the phases of the epidemic in different regions of the world are illustrated by the World Health Organization report on the Global Burden of Disease and Risk Factors, 2006[2,13,32] and in *Figure 2*.

The highest rates of cardiovascular death are in Eastern Europe and Central Asia and in the Middle East and North Africa. Six out of 10 countries with the highest rates of diabetes are in the Eastern Mediterranean and Middle East region.[33] Among other regions within the LIMIC, there is considerable heterogeneity in regard to the contribution of CVD to overall mortality. This may reflect in part different stages of the epidemiological transition, even within the same country, e.g. rates of coronary heart disease and stroke in rural vs. urban populations in China; the disparities in India; and in cardiovascular mortality rates between countries which were formerly part of the Eastern Bloc.[5] In this respect, declining rates have been noted in the Czech Republic, Poland, and Hungary, but rates have increased in the Ukraine, Bulgaria, and Romania. Regional standards of healthcare allocation of resources are likely major contributory factors in lifestyle and risk factor management.[34] In addition, there is considerable variability in death rates due to ischaemic heart disease vs. stroke, and in the case of the latter, whether ischaemic or haemorrhagic.

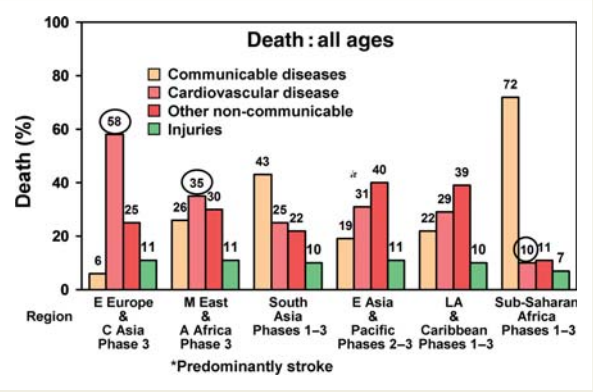

Figure 2 Major causes of mortality in low- and middle-income regions. Reproduced with kind permission from Wolters Kluwer Health.[13]

In the case of sub-Saharan Africa, despite marked regional differences, much of the continent is at an early phase of the epidemiologic transition with 70% of deaths due to communicable diseases, namely, infections and parasites. In essence, one can consider all of Africa as an epidemiological transition spanning the spectrum from Phase 1 to Phase 4 in different countries and among different ethnic groups. Recent data from South Africa are interesting and perhaps provide a window into a 'future epidemic'.[35,36] The Heart of Soweto Study in predominantly urban, black South Africans, drew attention to the rising incidence of risk factors in black Africans. In a population with a mean age of 46 years, 78% had greater than one major risk factor, primarily obesity, hypertension, and smoking, although serum cholesterol was elevated in only 14%. In 2006, however, of 1593 new cases of CVD in this study, coronary artery disease was the diagnosis in only 10% and in only blacks this was only 6%. Given the ominous trends in regard to obesity and the increase in other risk factors, it is likely that the coming years will see major increases in the incidence and prevalence of coronary heart disease in South Africa and probably in sub-Saharan Africa as a whole.

The situation in Japan is also intriguing. The Akita-Osaka study of individuals aged 40–69 years demonstrated adverse trends in the terms of myocardial infarction, sudden death, and coronary intervention in men and women, but particularly in men but with little change in the rural population.[37] Nonetheless, the incidence of coronary artery disease in Japan is still approximately three- to four-fold less than in the USA based upon the Minnesota Heart survey and the ARIC studies. Does this imply some degree of genetic protection or as is more likely that the levels of risk factors are lower?[38] This remains a plausible and a fascinating unresolved question, but the NI-HAN-SAN study of Japanese men from Japan vs. those who had immigrated many years before to Hawaii or California would suggest that changes in the environment and risk factors eventually dominate in regard to rates of death and myocardial infarction.[39] Nonetheless, the seven countries 25-year follow-up study demonstrates regional variabilities in coronary heart disease mortality rates. For a given level of serum cholesterol mortality rates in the Mediterranean countries of Southern Europe and Japan are significantly less than in Northern Europe, the USA, Serbia, and the inland countries of Southern Europe.[40,41] To what extent some of these reputed benefits could be the result of the Mediterranean diet is uncertain as are the factors contributing to the 'French paradox' which could at least in part be explained by confounding factors or perhaps genetic variabilities.[42,43]

There is evidence that in the USA and the UK in the early part of the last century, symptomatic coronary artery disease was uncommon or even rare, even allowing for under-diagnosis.[44,45] It may also have been the case in African-Americans in the 1940s and 1950s[45,46] at which time the rates were lower in blacks compared with whites in the 1950s in the USA, but rates of CVD and risk factors in African-Americans and Mexican-Americans are now reported to be higher than among whites.[29] Irrespective, it did not take long, however, for the epidemic to declare its presence in no uncertain manner. Whether the course of the epidemic in Africa will be similar remains to be seen, although the trends in risk factor prevalence are discouraging.

The role of traditional risk factors

A major contribution from the INTERHEART study was the demonstration in a case–control study in 25 countries that over 90% of the population attributable risk of acute myocardial infarction were accounted for by nine modifiable risk factors.[47–50] These were a history of smoking, diabetes, and hypertension, abdominal obesity, the ApoB/ApoA1 ratio, a psychosocial index, fruit and vegetable intake, exercise, and regular alcohol consumption. Subsequent studies identify that an unhealthy diet accounts for approximately 30% of the population attributable risk of AMI globally[51] and all forms of tobacco use constitute one of the most powerful global risk factors.[52] However, the distribution of risk factors might differ among different populations. For example, it seems that in South Africa, obesity and hypertension are a more important problem than elevated cholesterol levels. By contrast in China, elevated blood lipids are common even in 'normal weight' people.[53] This might be important for focused risk factor prevention, e.g. losing weight vs. the administration of a statin, and in particular planning of the composition of the 'polypill' per region.[54] A growing body of evidence in addition to the INTERHEART study in general suggests a strong association between psychosocial stressors in both myocardial infarction and CVD in addition to other chronic diseases.[45,47,55–57] These and other studies have clearly identified the major targets for primary prevention in the global community. The inverse relationship between socioeconomic status and CVD risk in high-income countries is primarily the result of the increased prevalence and compounding effects of behavioural and psychosocial risk factors in people of lower socioeconomic status. In LIMIC, there are often wide disparities in socioeconomic status and although data in this population science is scarce, it is likely that socioeconomically determined gradients in health are likely to be of major importance in the future.[24]

The potential role of novel risk factors

Although the rapid growth of CVD in developing countries is fuelled by the emergence of established risk factors, there are other contributors to a hostile cardiovascular environment, which have perhaps been less emphasized (*Figure 3*).

Air pollution

An explicit American Heart Association scientific statement in 2004 drew attention to the epidemiological data which demonstrated a consistent increased risk for cardiovascular events in relation to both short- and long-term exposure in present day concentrations of ambient particulate matter—a major component of air pollution.[58] Although not clarified as yet, several plausible mechanistic pathways have been described. It is sobering to note that according to a recent World Bank report of the world's 20 most polluted cities, 13 of these are in China, 5 in India, 1 in Indonesia, and the other is Cairo in Egypt—all of which are in developing or newly industrialized countries.[59,60] Nonetheless, the strength of this association between air pollution and CVD requires further evaluation as the potential for confounders is strong.

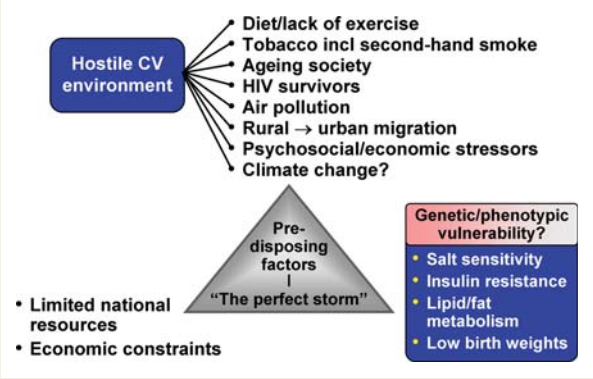

Figure 3 Factors contributing to the epidemic of cardiovascular disease in low- and middle-income countries.

Climate change

A recent report on managing the effects of climate change from *The Lancet* and the University College London Institute for Global Health concluded that climate change effects on health will exacerbate inequities between rich and poor.[61] The major impact of climate change will likely be on communicable diseases, natural disasters, and the risk of malnutrition as opposed to CVD but a secondary impact upon CVD cannot be demonstrated.[62]

HIV infection

HIV infection impacts paradoxically on cardiovascular risk factors and circulatory disease at the population and individual levels. At the population level, untreated HIV infection is associated with an overall shortening of life expectancy, a reduction of the body mass index, and a fall in the systolic blood pressure of 3 mmHg.[63,64] These effects can be expected to reduce the incidence of CVD at the population level. In contrast, at the individual level, people living with HIV have an increased incidence of inflammatory circulatory disorders, including macrovascular arteritis, pulmonary hypertension, cardiomyopathy, and tuberculous pericarditis.[65] Increasing access to retroviral therapies is however changing the landscape for patients in countries with previously limited access to these drugs and as these patients live longer, CVD now ranks as a major cause of death in people living in industrialized countries according to a recent AHA statement. Likely contributing factors are dyslipidaemia, insulin resistance, inflammation, and changes in body fat distribution in addition to drug

toxicities.[66] The potential implications for the future in regard to providing the resources to cope with the dual burden of acute and chronic HIV disease in the developing world are self evident.

The thrifty phenotype and phenotype hypothoses

The 'thrifty gene' hypothesis proposed over 50 years ago was based upon the concept that early during our evolutionary history, genes providing efficient fat deposition, salt sensitivity, and insulin resistance would provide survival during periods of famine.[67] In modern society with abundant caloric intake, the genetic substrate could be detrimental resulting in vulnerability to obesity and diabetes. In a nutshell, genes selected for times of adversity now have to function in times of plenty.[68,69]

The 'thrifty phenotype' hypothesis, which may be an adaptive maternal effect, proposes that foetal metabolic adaptations promote survival with the developing organism responding to the maternal–foetal environment which determines an appropriate rate of foetal growth.[68,69] Subsequent changes in the environment after birth may, however, determine whether previously selected growth trajectories are appropriate or not.[70,71] The combination of both models has been proposed as the 'thrifty epigenotype' hypothesis.[72]

Others have mounted a persuasive argument that these intuitively appealing concepts are flawed in many aspects and that there is little likelihood that the thrifty gene or thrifty phenotype concept plays any role in regard to the relatively recent adaptation to the current environment. Moreover, the strength of evidence supporting the hypotheses is varied among studies and considered generally to be weak.[73,74] Nonetheless, recent evidence for more rapid changes within several generations in the genotype linked to new environments, if they impact upon fertility and lifetime reproductive success, i.e. the 'fertility first' hypothesis based upon patients with the polycystic ovary syndrome has continued to stimulate interest in regard to both the thrifty gene and phenotype hypotheses.[75]

The combination of a 'hostile' cardiovascular environment characterized by a disproportionately ageing population, urbanization, tobacco use, and exposure to second-hand smoke, food and agricultural policies and unfavourable lifestyle behaviours, in addition to the psychosocial/economic stressors involved in rural to urban migration and the challenges of earning a living in struggling economies, among other factors discussed, could unleash a 'perfect storm' manifesting as an epidemic of CVD in those regions least able to deal with this (*Figure 3*).

Challenges for primary and secondary prevention

There is no global solution to the problem, and it is likely that the epidemic will traverse similar paths in different countries, but at different rates, as determined by the pace of development. A universal goal, however, is to utilize our current basis of knowledge to attempt to 'telescope or abbreviate' Phase 3 of the epidemiologic transition both in countries with established epidemics and in those at an earlier phase of the transition.[5,12,13,76]

A major challenge is the lack of data and the poor quality of information on causes of death in many but not all regions of the world.

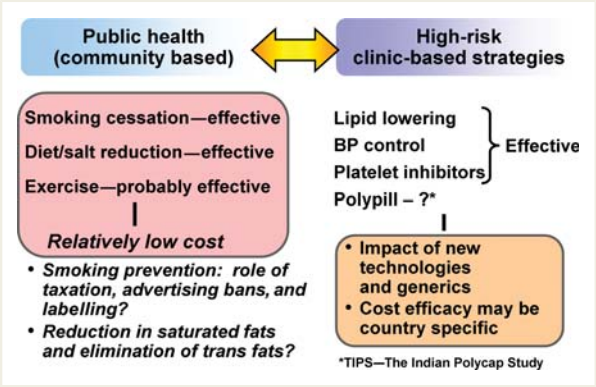

Figure 4 Strategies for the prevention of cardiovascular disease.

A second hurdle relates to the inability to predict more precisely which groups of patient are at higher risk for CVD, so as to divert scarce resources to the areas of greatest need. Although prediction models have been thoroughly evaluated in the USA and other high-income countries[77,78] and may be cost effective in the developing world,[13] the development of predictive algorithms for stroke and myocardial infarction in different population with limited facilities is a priority.[32,79] Moreover, there may be populations of patients at a much higher or lower risk of cardiovascular events than would be predicted from models such as the Framingham model, e.g. Indigenous Australians in whom event rates were two- to three-fold higher than predicted.[80]

The Framingham Study and subsequently the INTERHEART study have identified the important risk factors and as such the targets for modification. Moreover, an analysis of 10 studies across the world in which there has been a decline in CVD mortality, demonstrated that risk factor modification was associated with 44% of the decline in the Netherlands, 50–54% in the USA, and 76% in North Karelia, Finland.[81] New treatments are responsible for 23–47% of the decline in mortality.

The objectives (namely primary and secondary prevention) and the solutions are in many ways obvious, but translating these into countries with limited resources and a surfeit of health issues to be addressed is complex. Two major approaches (*Figure 4*) include public health/community-based strategies targeted at risk factors. These are relatively low cost but require extensive education programs perhaps in addition to regional and national measures, e.g. taxation on tobacco, advertising bans, and legislature in regard to second-hand smoke.

An alternative strategy is clinic-based with the emphasis on targeting high-risk subgroups with lipid-lowering, antihypertensive, and platelet-inhibitor agents. In this respect, the 'polypill' has attracted understandable interest and large scale clinical trials are in the planning phase, although a recent multicentre trial from India demonstrated the feasibility and the safety of this approach.[82] Moreover, the cost-dynamics of applying the polypill undoubtedly differ from region to region but are generally considered to be favourable across a range of LIMIC,[54] as is the composition of the pill depending upon the risk factor profile in a particular region. A combination of population-wide and high-risk strategies may be the best approach to treatment and in changing the risk

of the population at large.[83] Moreover, the critically important costs of supporting health professionals (e.g. community nurses), infrastructure (e.g. BP monitors and weight scales), and pathology tests should be emphasized.

The impact of regional cultural, logistic, and economic factors upon the development of preventive strategies is considerable. Compliance is an additional issue and a recent registry highlighted difficulties in this respect among patients from different regions and with different levels of education.[84] Community screening of voluntary adult participants via Heart Awareness Days in Soweto highlighted the lack of awareness of heart disease and the relevance of risk factors.[54] The presence of obesity was 43%, while up to 70% were overweight. The fundamental importance of this finding cannot be overstated. In a culture where low weight is either associated with a historical lack of food or, worse, the modern day epidemic of HIV/AIDS, it is difficult to educate individuals and the wider community about the dangers of excess weight.[54] These obstacles to education and to lifestyle modification may not be as difficult to surmount in parts of Latin America, a region in which obesity is also of paramount impact upon the risks of myocardial infarction.[85,86]

An ongoing challenge for healthcare delivery in many underdeveloped regions is the lack of resources, the low priority of noncommunicable disease in systems geared towards acute care and infectious diseases, and the lack of an integrated infrastructure involving communities, health services, local, and regional institutions.[9] In summary, the three major components of prevention are:

(1) Societal and policy levels to address the upstream social determinants of health, e.g. altering the tobacco, food, and activity environment.
(2) Development of comprehensive and integrated health systems that are based on the primary healthcare philosophy.
(3) Individual level prevention, primary, secondary, and tertiary prevention or acute management.

Summary

In summary, CVD is a substantial and growing problem in most of the developing regions of the world. Key questions to be posed are whether the epidemic can be postponed or abbreviated, what are the costs, how to determine when and how preventive measures should be implemented and to whom. Resources are finite and the need for additional data so as to best focus these are paramount. There is also a need to address the persisting burden of infectious and post-infectious cardiovascular disorders, such as rheumatic fever and Chaga's disease that remain a major cause of morbidity and mortality among children and young adults throughout the developing world.

Despite this broad canvas and the power of the data, there is nonetheless an impression that the global health agenda is too limited and focused upon communicable diseases. Misperceptions include the understandable fear of global infectious disease epidemics among other factors.[87] In this context, we share the concerns expressed by Fuster *et al.*[88] in regard to the low priority of cardiovascular and chronic disease in the global health agenda. We also strongly agree with their proposed modification of millennium development goal #6 which could be rephrased to state that the goals are to 'combat infectious diseases such as HIV/AIDS and malaria *along* with chronic diseases such as CVD, diabetes, mellitus, and cancer, using an integrated approach'.[1]

Conflict of interest: none declared.

References

1. Fuster V, Voute J. MDGs: chronic diseases are not on the agenda. *Lancet* 2005; **366**:1512–1514.
2. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006;**367**:1747–1757.
3. Organization WH. The Global Burden of Disease 2004 Update. http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html (March 2009).
4. Leeder S, Raymond S, Greenberg H, Liu H, Esson K. *A Race Against Time: The Challenge of Cardiovascular Disease in Developing Countries*. New York: Trustees of Columbia; 2004.
5. Gaziano T. Global burden of cardiovascular disease. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 8th ed. Saunders; 2008. pp. 1–22.
6. Critchley J, Liu J, Zhao D, Wei W, Capewell S. Explaining the increase in coronary heart disease mortality in Beijing between 1984 and 1999. *Circulation* 2004;**110**:1236–1244.
7. **http://www.unicef.org/publications/index.html (6 January 2010)**.
8. Sharma A, Sharma K, Mathur KP. Growth pattern and prevalence of obesity in affluent schoolchildren of Delhi. *Public Health Nutr* 2007;**10**:485–491.
9. Mayosi B, Flisher A, Lalloo U, Sitas F, Tollman S, Bradshaw D. The burden of noncommunicable diseases in South Africa. *Lancet* 2009;**374**:934–947.
10. Olshansky SJ, Ault AB. The fourth stage of the epidemiologic transition: the age of delayed degenerative diseases. *Milbank Q* 1986;**64**:355–391.
11. Omran AR. The epidemiologic transition. A theory of the epidemiology of population change. *Milbank Mem Fund Q* 1971;**49**:509–538.
12. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. *Circulation* 2001;**104**:2855–2864.
13. Gaziano TA. Cardiovascular disease in the developing world and its cost-effective management. *Circulation* 2005;**112**:3547–3553.
14. Carapetis JR, Mayosi BM, Kaplan EL. Controlling rheumatic heart disease in developing countries. *Cardiovasc J S Afr* 2006;**17**:164–165.
15. Commerford P, Mayosi B. An appropriate research agenda for heart disease in Africa. *Lancet* 2006;**367**:1884–1886.
16. Maguire JH. Chagas' disease—can we stop the deaths? *N Engl J Med* 2006;**355**:760–761.
17. Marijon E, Ou P, Celermajer DS, Ferreira B, Mocumbi AO, Jani D, Paquet C, Jacob S, Sidi D, Jouven X. Prevalence of rheumatic heart disease detected by echocardiographic screening. *N Engl J Med* 2007;**357**:470–476.
18. Mayosi BM. Contemporary trends in the epidemiology and management of cardiomyopathy and pericarditis in sub-Saharan Africa. *Heart* 2007;**93**:1176–1183.
19. Mayosi BM, Burgess LJ, Doubell AF. Tuberculous pericarditis. *Circulation* 2005;**112**:3608–3616.
20. Mocumbi AO, Ferreira MB, Sidi D, Yacoub MH. A population study of endomyocardial fibrosis in a rural area of Mozambique. *N Engl J Med* 2008;**359**:43–49.
21. Watkins DA, Zuhlke LJ, Engel ME, Mayosi BM. Rheumatic fever: neglected again. *Science* 2009;**324**:37.
22. Steyn K, Sliwa K, Hawken S, Commerford P, Onen C, Damasceno A, Ounpuu S, Yusuf S. Risk factors associated with myocardial infarction in Africa: the INTERHEART Africa study. *Circulation* 2005;**112**:3554–3561.
23. Albert MA, Glynn RJ, Buring J, Ridker PM. Impact of traditional and novel risk factors on the relationship between socioeconomic status and incident cardiovascular events. *Circulation* 2006;**114**:2619–2626.
24. Clark AM, DesMeules M, Luo W, Duncan AS, Wielgosz A. Socioeconomic status and cardiovascular disease: risks and implications for care. *Nat Rev Cardiol* 2009;**6**:712–722.
25. Sheth T, Nair C, Nargundkar M, Anand S, Yusuf S. Cardiovascular and cancer mortality among Canadians of European, south Asian and Chinese origin from 1979 to 1993: an analysis of 1.2 million deaths. *CMAJ* 1999;**161**:132–138.
26. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. *J Am Coll Cardiol* 2007;**50**:2128–2132.
27. Balkau B, Deanfield JE, Despres JP, Bassand JP, Fox KA, Smith SC Jr, Barter P, Tan CE, Van Gaal L, Wittchen HU, Massien C, Haffner SM. International Day

for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. *Circulation* 2007;**116**:1942–1951.
28. Nemetz PN, Roger VL, Ransom JE, Bailey KR, Edwards WD, Leibson CL. Recent trends in the prevalence of coronary disease: a population-based autopsy study of nonnatural deaths. *Arch Intern Med* 2008;**168**:264–270.
29. Ford ES, Li C, Zhao G, Pearson WS, Capewell S. Trends in the prevalence of low risk factor burden for cardiovascular disease among United States adults. *Circulation* 2009;**120**:1181–1188.
30. Notzon FC, Komarov YM, Ermakov SP, Sempos CT, Marks JS, Sempos EV. Causes of declining life expectancy in Russia. *JAMA* 1998;**279**:793–800.
31. Plavinski SL, Plavinskaya SI, Klimov AN. Social factors and increase in mortality in Russia in the 1990s: prospective cohort study. *BMJ* 2003;**326**:1240–1242.
32. Gaziano TA, Young CR, Fitzmaurice G, Atwood S, Gaziano JM. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. *Lancet* 2008;**371**:923–931.
33. Diabetes—a global threat. *Lancet* 2009;**373**:1735.
34. Group EIS. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries; principal results from EUROASPIRE II Euro Heart Survey Programme. *Eur Heart J* 2001;**22**:554–572.
35. Sliwa K, Wilkinson D, Hansen C, Ntyintyane L, Tibazarwa K, Becker A, Stewart S. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. *Lancet* 2008;**371**:915–922.
36. Tibazarwa K, Ntyintyane L, Sliwa K, Gerntholtz T, Carrington M, Wilkinson D, Stewart S. A time bomb of cardiovascular risk factors in South Africa: results from the Heart of Soweto Study 'Heart Awareness Days'. *Int J Cardiol* 2009;**132**:233–239.
37. Kitamura A, Sato S, Kiyama M, Imano H, Iso H, Okada T, Ohira T, Tanigawa T, Yamagishi K, Nakamura M, Konishi M, Shimamoto T, Iida M, Komachi Y. Trends in the incidence of coronary heart disease and stroke and their risk factors in Japan, 1964 to 2003: the Akita-Osaka study. *J Am Coll Cardiol* 2008;**52**:71–79.
38. Karthikeyan G, Teo KK, Islam S, McQueen MJ, Pais P, Wang X, Sato H, Lang CC, Sitthi-Amorn C, Pandey MR, Kazmi K, Sanderson JE, Yusuf S. Lipid profile, plasma apolipoproteins, and risk of a first myocardial infarction among Asians: an analysis from the INTERHEART Study. *J Am Coll Cardiol* 2009;**53**:244–253.
39. Robertson TL, Kato H, Gordon T, Kagan A, Rhoads GG, Land CE, Worth RM, Belsky JL, Dock DS, Miyanishi M, Kawamoto S. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Coronary heart disease risk factors in Japan and Hawaii. *Am J Cardiol* 1977;**39**:244–249.
40. Janssen F, Kunst AE. Cohort patterns in mortality trends among the elderly in seven European countries, 1950-99. *Int J Epidemiol* 2005;**34**:1149–1159.
41. Verschuren WMM, Jacobs DR, Bloemberg BPM, Kromhout D, Menotti A, Aravanis C, Blackburn H, Buzina R, Dontas AS, Fidanza F, Karvonen MJ, Nedelijkovic S, Nissinen A, Toshima H. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. *JAMA* 1995;**274**:131–136.
42. de Lorgeril M, Salen P, Paillard F, Laporte F, Boucher F, de Leiris J. Mediterranean diet and the French paradox: two distinct biogeographic concepts for one consolidated scientific theory on the role of nutrition in coronary heart disease. *Cardiovasc Res* 2002;**54**:503–515.
43. Opie LH, Lecour S. The red wine hypothesis: from concepts to protective signalling molecules. *Eur Heart J* 2007;**28**:1683–1693.
44. Morris W. Recent history of coronary disease. *Lancet* 1951;**1**:1–7.
45. White PD. Measuring the risk of coronary heart disease in adult population groups. The cardiologist enlists the epidemiologist. *Am J Public Health Nations Health* 1957;**47**:1–3.
46. Perkoff GT, Strand M. Race and presenting complaints in myocardial infarction. *Am Heart J* 1973;**85**:716–720.
47. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, Keltai M, Diaz R, Rangarajan S, Yusuf S. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J* 2008;**29**:932–940.
48. Joshi P, Islam S, Pais P, Reddy S, Dorairaj P, Kazmi K, Pandey MR, Haque S, Mendis S, Rangarajan S, Yusuf S. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. *JAMA* 2007;**297**:286–294.
49. Teo KK, Liu L, Chow CK, Wang X, Islam S, Jiang L, Sanderson JE, Rangarajan S, Yusuf S. Potentially modifiable risk factors associated with myocardial infarction in China: The INTERHEART China Study. *Heart* 2009;**95**:1857–1864.
50. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**:937–952.
51. Iqbal R, Anand S, Ounpuu S, Islam S, Zhang X, Rangarajan S, Chifamba J, Al-Hinai A, Keltai M, Yusuf S. Dietary patterns and the risk of acute myocardial infarction in 52 countries: results of the INTERHEART study. *Circulation* 2008;**118**:1929–1937.
52. Teo KK, Ounpuu S, Hawken S, Pandey MR, Valentin V, Hunt D, Diaz R, Rashed W, Freeman R, Jiang L, Zhang X, Yusuf S. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet* 2006;**368**:647–658.
53. Tibazarwa K, Ntyinyane L, Sliwa K, Gerntholz T, Wilkinson D, Stewart S. A time bomb or cardiovascular risk factors in South Africa: Results from the Heart of Soweto Study 'Heart Awareness days'. *Int J Cardiol* 2009;**132**:233–239.
54. Stewart S, Sliwa K. Preventing CVD in resource-poor areas: perspectives from the 'real world'. *Nat Rev Cardiol* 2009;**6**:489–492.
55. Figueredo VM. The time has come for physicians to take notice: the impact of psychosocial stressors on the heart. *Am J Med* 2009;**122**:704–712.
56. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Blackett KN, Sitthi-amorn C, Sato H, Yusuf S. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**:953–962.
57. Walker AR, Sareli P. Coronary heart disease: outlook for Africa. *J R Soc Med* 1997;**90**:23–27.
58. Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC Jr, Tager I. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation* 2004;**109**:2655–2671.
59. Urbanization and urban air pollution. *World Bank*. **http://www.worldbank.org/depweb/beyond/global/chapter10.html (6 January 2010)**.
60. **http://siteresources.worldbank.org/INTEAPREGTOPENVIRONMENT/resources/chinacostofsolution.pdf (6 January 2010)**.
61. Costello A, Abbas M, Allen A, Ball S, Bell S, Bellamy R, Friel S, Groce N, Johnson A, Kett M, Lee M, Levy C, Maslin M, McCoy D, McGuire B, Montgomery H, Napier D, Pagel C, Patel J, de Oliveira JA, Redclift N, Rees H, Rogger D, Scott J, Stephenson J, Twigg J, Wolff J, Patterson C. Managing the health effects of climate change: Lancet and University College London Institute for Global Health Commission. *Lancet* 2009;**373**:1693–1733.
62. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. *N Engl J Med* 1996;**334**:413–419.
63. Barnighausen T, Welz T, Hosegood V, Batzing-Feigenbaum J, Tanser F, Herbst K, Hill C, Newell ML. Hiding in the shadows of the HIV epidemic: obesity and hypertension in a rural population with very high HIV prevalence in South Africa. *J Hum Hypertens* 2008;**22**:236–239.
64. Kahn K, Garenne ML, Collinson MA, Tollman SM. Mortality trends in a new South Africa: hard to make a fresh start. *Scand J Public Health Suppl* 2007;**69**:26–34.
65. Ntsekhe M, Mayosi BM. Cardiac manifestations of HIV infection: an African perspective. *Nat Clin Pract Cardiovasc Med* 2009;**6**:120–127.
66. Grinspoon SK, Grunfeld C, Kotler DP, Currier JS, Lundgren JD, Dube MP, Lipshultz SE, Hsue PY, Squires K, Schambelan M, Wilson PW, Yarasheski KE, Hadigan CM, Stein JH, Eckel RH. State of the science conference: initiative to decrease cardiovascular risk and increase quality of care for patients living with HIV/AIDS: executive summary. *Circulation* 2008;**118**:198–210.
67. Neel JV. Diabetes mellitus: a 'thrifty' genotype rendered detrimental by 'progress'? *Am J Hum Genet* 1962;**14**:353–362.
68. Moore SE, Halsall I, Howarth D, Poskitt EM, Prentice AM. Glucose, insulin and lipid metabolism in rural Gambians exposed to early malnutrition. *Diabet Med* 2001;**18**:646–653.
69. Prentice AM, Rayco-Solon P, Moore SE. Insights from the developing world: thrifty genotypes and thrifty phenotypes. *Proc Nutr Soc* 2005;**64**:153–161.
70. Barker DJ. Fetal programming of coronary heart disease. *Trends Endocrinol Metab* 2002;**13**:364–368.
71. Gardiner HM. Early environmental influences on vascular development. *Early Hum Dev* 2007;**83**:819–823.
72. Stoger R. The thrifty epigenotype: an acquired and heritable predisposition for obesity and diabetes? *Bioessays* 2008;**30**:156–166.
73. Speakman JR. Thrifty genes for obesity and the metabolic syndrome–time to call off the search? *Diab Vasc Dis Res* 2006;**3**:7–11.
74. Speakman JR. Thrifty genes for obesity, an attractive but flawed idea and an alternative perspective: the 'drifty gene' hypothesis. *Int J Obes (Lond)* 2008;**32**:1611–1617.
75. Corbett SJ, McMichael AJ, Prentice AM. Type 2 diabetes, cardiovascular disease, and the evolutionary paradox of the polycystic ovary syndrome: a fertility first hypothesis. *Am J Hum Biol* 2009;**21**:587–598.
76. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* 2001;**104**:2746–2753.

77. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasan RS. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 2006;**355**:2631–2639.
78. Ware JH. The limitations of risk factors as prognostic tools. *N Engl J Med* 2006; **355**:2615–2617.
79. Lindholm LH, Mendis S. Prevention of cardiovascular disease in developing countries. *Lancet* 2007;**370**:720–722.
80. Wang Z, Hoy WE. Is the Framingham coronary heart disease absolute risk function applicable to Aboriginal people? *Med J Aust* 2005;**182**:66–69.
81. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *N Engl J Med* 2007;**356**:2388–2398.
82. Yusuf S, Pais P, Afzal R, Xavier D, Teo K, Eikelboom J, Sigamani A, Mohan V, Gupta R, Thomas N. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. *Lancet* 2009;**373**:1341–1351.
83. Mendis S, Fuster V. National policies and strategies for noncommunicable diseases. *Nat Rev Cardiol* 2009;**6**:723–727.
84. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, Goto S, Liau CS, Richard AJ, Rother J, Wilson PW. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006;**295**:180–189.
85. Smith SC Jr. Risk factors for myocardial infarction in Latin America: sobrepeso y obesidad. *Circulation* 2007;**115**:1061–1063.
86. Steg PG, Bhatt DL, Wilson PW, D'Agostino R Sr, Ohman EM, Rother J, Liau CS, Hirsch AT, Mas JL, Ikeda Y, Pencina MJ, Goto S. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA* 2007;**297**:1197–1206.
87. Poole-Wilson PA. Millennium development goals: an unbalanced approach to global health. *Nat Clin Pract Cardiovasc Med* 2007;**4**:289.
88. Fuster V, Voute J, Hunn M, Smith SC Jr. Low priority of cardiovascular and chronic diseases on the global health agenda: a cause for concern. *Circulation* 2007;**116**: 1966–1970.