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AS PRESENTED IN THE ROUNDS OF THE CARDIOVASCULAR DIVISION
OF BRIGHAM AND WOMEN'S HOSPITAL, BOSTON, MASSACHUSETTS

Cardiovascular Disease in the Developing World and its Cost-Effective Management

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At the beginning of the 20th century, cardiovascular disease (CVD) was responsible for < 10% of all deaths worldwide. Today, that figure is about 30% and CVD is the leading cause of death worldwide with about 80% of the burden now occurring in developing countries (Figure 1).¹⁻³ This issue of *Cardiology Rounds* explains the epidemiological transition that has made CVD the leading cause of death in the world, assesses the status of the transition by region, and shows the regional differences in the burden of CVD. Further, this issue reviews the cost-effectiveness of various interventions addressing the most relevant causes of CVD morbidity and mortality.

The epidemiologic transition

Over the last two centuries, the industrial and technological revolutions and the economic and social transformations associated with them have resulted in a dramatic shift in the causes of illness and death. Prior to 1900, infectious diseases and malnutrition were the most common causes of death. With improved nutrition and public health measures, they have gradually been supplanted by CVD and cancer deaths in most high-income countries. Omran developed an excellent model of the epidemiological transition dividing the transition into three basic stages: pestilence and famine, receding pandemics, and degenerative and man-made diseases (Table 1).⁴ Olshansky and Ault added a fourth stage, delayed degenerative diseases.⁵

- **The stage of pestilence and famine** is characterized by the predominance of malnutrition and infectious disease and by the relative infrequency of CVD. In this situation, CVD is responsible for only ~ 10% of deaths, mostly attributed to rheumatic heart disease and cardiomyopathies due to infection and malnutrition.
- **The stage of receding pandemics** is marked by increases in wealth that lead to better availability of food, improved sanitation, and access to vaccines and antibiotics. The results are lower rates of communicable, maternal, perinatal, and nutritional diseases, and an increase in cardiovascular risk factors, particularly hypertension. These changes, along with increased lifespan, eventually lead to a greater incidence of CVD, particularly hemorrhagic stroke.
- **The stage of degenerative and man-made diseases** is characterized by dramatic lifestyle changes in diet, activity levels, and smoking that set the stage for the emergence of atherosclerosis. The average lifespan increases to beyond 50 years and mortality from CVD, in particular, and other non-communicable diseases now exceeds mortality from malnutrition and infectious diseases. The predominant form of CVD is coronary heart disease (CHD), but ischemic stroke also emerges as a significant cause of mortality and morbidity.
- **In the stage of delayed degenerative diseases**, CVD and cancer continue to be the major causes of morbidity and mortality. Due to widespread primary and secondary prevention efforts, however, the age-adjusted CVD mortality tends to decline. Congestive heart failure (CHF) prevalence increases due to improved survival of those with ischemic heart disease and life expectancy increases to >70 years.

New trends suggest that the United States (USA) could be entering a fifth as-yet-unnamed phase of the epidemiologic transition, characterized by an epidemic of obesity. Although rates of CVD fell 2% to 3% per year through the 1970s and 1980s in most developed countries, the rate of decline has slowed. In the USA, physical activity continues to decline as total caloric intake increases. Overweight



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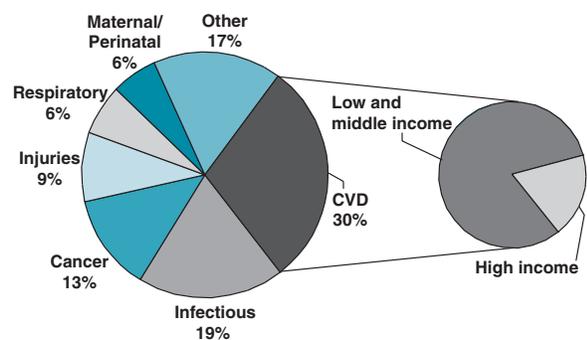
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The editorial content of *Cardiology Rounds* is determined solely by the Cardiovascular Division of Brigham and Women's Hospital. This publication is made possible by an educational grant.

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Figure 1: CVD compared to other causes of death



and obesity are escalating at an alarming pace, while rates of type 2 diabetes, hypertension, and lipid abnormalities associated with obesity are on the rise. This trend is not unique to developed countries only. According to the World Health Organization (WHO), > 1 billion adults worldwide are overweight and 300 million are clinically obese. Even more disturbing are increases in childhood obesity, leading to large increases in diabetes and hypertension. If these trends continue, age-adjusted CVD mortality rates could increase in the USA and other countries in the coming years.

While countries tend to enter these stages at different times, the progression from one stage to the next tends to proceed in a predictable manner, with both the rate and the nature of CVDs changing over the course of the transition. The USA and most other developed economies, for example, spent most of their early history in the first stage and then progressed through the next 3 stages over the course of the last century and a half.

Japan is unique among high-income countries because the transition started later, but proceeded much more rapidly. In the early part of the 20th century, stroke rates increased dramatically, eventually becoming the highest in the world by the middle of the century. CHD rates in Japan, however, have

not risen as sharply as in other industrialized countries and have remained lower. Since the 1970s, stroke rates have declined dramatically, but there are indications of a possible recent increase in CHD. The historically lower heart disease rates may be at least partly attributable to genetic factors, but it is more likely that the average plant-based, low-fat diet and resultant low cholesterol levels have played a more important role. If CHD is increasing, it could be related to changes in dietary habits that Japan is currently experiencing with increased dairy and fat consumption.⁶

Status of the epidemiologic transition in 2004

The World Bank groups countries based on economic and geographic variation. The high-income countries are those with a gross national income (GNI) per capita of ≥\$9,200. The rest of the low- and middle-income countries are divided according to geographic region. The 6 developing regions are:

- East Asia and the Pacific (EAP) with China representing the bulk of its population
- Europe and Central Asia (ECA)
- Latin America and the Caribbean (LAC)
- Middle East and North Africa (MNA)
- South Asia (SAR) with India as its largest member
- Sub-Saharan Africa (SSA).

The stage of the transition for each region varies widely (Table 1). With roughly 840 million people, the USA and the other established market economy countries currently comprise a little more than 15 % of the world’s population. Rapid declines in CHD and stroke rates since the early 1970s indicate that these countries are in the fourth phase of the epidemiologic transition, the stage of delayed degenerative diseases. In these countries, CHD rates tend to be higher than stroke rates and overall CVD deaths are about 30% of the total with a rate of 320 deaths per 100,000 population.

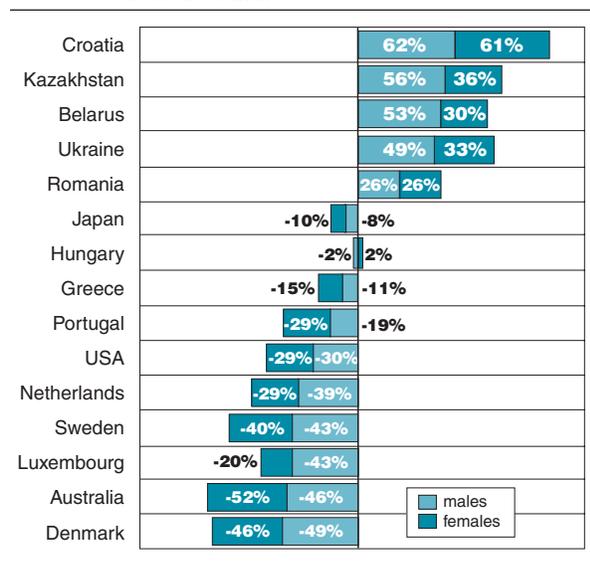
As a result of the epidemiological transition outlined above, CVD is the leading cause of death in all World Bank developing regions, with the exception of SSA.¹ Most develop-

Table 1: Stages of the epidemiological transition and its global status, by region

Stage	Description	Life expectancy (years)	Dominant form of CVD	% of deaths due to CVD	% of the world's population in this stage	Region affected
Pestilence and famine	Predominance of malnutrition and infectious diseases	35	RHD, cardiomyopathy due to infection and malnutrition	5-10	11	SSA, parts of all regions excluding high-income regions
Receding pandemics	Improved nutrition and public health leads to increase in chronic diseases, hypertension	50	Rheumatic valvular disease, IHD, hemorrhagic stroke	15-35	38	SAR, southern EAP, parts of LAC
Degenerative and man-made diseases	Increased fat and caloric intake, widespread tobacco use, chronic disease deaths exceed mortality from infections and malnutrition	60	IHD, stroke (ischemic and hemorrhagic)	>50	35	ECA, northern EAP, LAC, MNA, and urban parts of most low-income regions (especially India)
Delayed degenerative diseases	CVD and cancer are leading causes of morbidity and mortality, prevention and treatment avoids death and delays onset; age-adjusted CVD declines	>70	IHD, stroke (ischemic and hemorrhagic), CHF	<50	15	High-income countries, parts of LAC

RHD = rheumatic heart disease; IHD = ischemic heart disease; CHF = congestive heart failure

Figure 2: Percentage change in ischemic heart disease death rates in people age 35-74, 1988-98, selected countries



ing regions appear to be following a similar pattern as developed countries with an initial rise in stroke (EAP and SSA) and then a predominance of CHD; however, the transition has occurred at a more compressed rate than in the high-income countries. Between 1990 and 2020, CHD alone is anticipated to increase by 120% for women and 137% for men in developing countries, compared to age-related increases of between 30% and 60% in developed countries.⁷ The INTERHEART study suggests that the same risk factors found in the developed countries also appear to account for the rapid increase in the developing countries.⁸ This case-control study, conducted in 52 countries with over 15,000 cases of myocardial infarction (MI), demonstrated that smoking, diabetes mellitus, hypertension, abdominal obesity, dyslipidemia, physical inactivity, and poor fruit and vegetable intake had a population attributable risk (PAR) of 90%. The PAR for current and past smokers was 36%.

The EAP region appears to be straddling the second and third stages with apparent regional differences in CVD rates. A north/south gradient has emerged, with higher CVD rates in northern China than in southern China. The ECA region is firmly at the peak of the third transition stage with CVD representing 60% of all deaths. Croatia, Belarus, and the Ukraine saw an increase of 40% to 60% in CHD death rates between 1988-98 (Figure 2). The ECA region has a rate of 690 CVD deaths per 100,000, more than double that of the high-income countries. Within the region of the MNA, the majority of the Middle Eastern crescent appears to be entering the third stage of the epidemiologic transition; increasing economic wealth has been accompanied by a rapid increase in CVD. As a whole, the LAC region also seems to be in the third stage, but this region, as defined by the World Bank, includes all of South America. Residents of some of these countries are still at risk of contracting malaria and dengue fever; as a result, those portions of the region are still in the first transitional phase. Despite large regional variations, HIV/AIDS-plagued

SSA remains largely in the first phase of the epidemiologic transition. Heterogeneity is also apparent throughout the rest of the developing world – even within countries (eg, some regions of India appear to be in the first phase of the transition, whereas others are in the second or even the third phase).

Social and economic impact

While no detailed data exist on the direct economic burden of the individual risk factors, the costs of CVD treatment in developing countries is significant and appears similar to that in developed countries. In South Africa, for example, 2% to 3% of the gross domestic product (GDP) was devoted to the direct treatment of CVD or roughly 25% of the South African healthcare expenditures.⁹ An indication of possible future expenditures in developing countries is also provided by current expenditures in developed countries. For example, the USA spent an estimated \$368 billion relating to direct and indirect costs of CVD in 2004.¹⁰ In 1998, US\$109 billion was spent on hypertension, or about 13% of the healthcare budget.¹¹ In 2004, an estimated \$26 billion was spent for the care of CHF patients. Studies are limited, but suggest that obesity-related diseases are responsible for 2% to 8% of all healthcare expenditures in developed countries.¹²

While the disease burden and the social costs of CVD are high, the resources devoted towards healthcare are extremely scarce. The GNI per capita of developed countries (\$27,000) is nearly 25-fold that of developing countries (\$1,100). Further, developed countries devote twice as much of its GNI (10%) to healthcare compared to low- and middle-income countries (6%). This results in about a 40-fold difference between developed and developing countries in funds devoted to healthcare.¹³ This is further compounded by the fact that a high proportion of the CVD burden occurs earlier among adults of working age in developing countries. In 5 of the countries surveyed (Brazil, India, China, South Africa and Mexico), conservative estimates indicated that at least 21-million-years of future productive life are lost because of CVD each year.⁷

Cost-effectiveness analysis (CEA) of interventions

There are many interventions with strong evidence for significant reductions in morbidity and mortality associated with CVD, but few intervention trials have been carried out solely in developing countries. As a result, estimates of cost-effectiveness ratios have been extrapolated to the developing world based on changes in key input prices.¹⁴ This process is limited, however, by the fact that both the underlying epidemiology and the costs can be quite different across countries and regions. The following section reviews results of interventions based on models using prices and epidemiological data from the World Bank developing regions. The analyses comply with the Disease Control Priorities Project (DCPP) Guidelines for Authors of July 2003.¹⁵ Only the costs related to the intervention itself and CVD events are included in the model. Costs include personnel salaries, healthcare visits, diagnostic tests, and hospital stays, according to DCPP September 2004 draft of unit costs.¹⁶ Indirect costs, such as work loss or family assistance, are not included in the analysis. Drug

Table 2: Incremental cost-effectiveness ratios (ICERs) for multiple CVD interventions, by region

	A. Medical therapy for AMI compared with baseline of no treatment (\$/QALY)				B. Medical therapy and CABG for IHD compared with baseline of no treatment, hospital access (\$/QALY)				C. Medical therapy and CABG for IHD compared with baseline of no treatment, limited hospital access (\$/QALY)			D. ACEIs and beta-blockers for CHF compared with baseline of diuretics, hospital access (\$/QALY)		E. ACEIs and beta-blockers for CHF compared with baseline of diuretics, limited hospital access (\$/QALY)		
Region	ASA, BB		ASA, BB, SK, t-PA		C/S	ASA, BB, ACEI, Statin		CABG	ASA, BB, ACEI, Statin		C/S	ACEI, MET		C/S	ACEI, MET	
	ASA	BB	SK	t-PA		BB	ACEI		Statin	BB		ACEI	Statin		ACEI	MET
EAP	13	15	672	15,867	C/S	781	1,914	33,846	461	942	2,220	C/S	189	27	274	
ECA	19	21	722	15,878	C/S	866	2,026	47,942	530	1,097	2,470	C/S	144	30	275	
LAC	20	22	734	15,887	C/S	821	1,942	62,426	545	1,111	2,497	C/S	124	31	275	
MNA	17	20	715	15,893	C/S	672	1,686	72,345	527	996	2,305	C/S	128	29	275	
SAR	9	11	638	15,860	C/S	715	1,819	24,040	386	828	2,034	C/S	219	25	273	
SSA	9	11	634	15,862	C/S	660	1,720	26,813	389	783	1,955	C/S	218	25	273	

ASA = aspirin, BB = atenolol, SK = streptokinase, t-PA = tissue plasminogen activator, ACEI = enalapril, Statin = lovastatin, MET = metoprolol, C/S = cost-saving
IHD = ischemic heart disease; CHF = congestive heart failure **Source:** Authors' calculations.

Note: The intervention in the first column of each set of strategies is compared to baseline; each successive intervention for each set of strategies is compared with the intervention immediately to its left.

costs are from the International Drug Price Indicator Guide.¹⁷ All costs unless otherwise specified are in \$US. For a detailed explanation of the methods for the following analyses, please refer to the DCPD Working Papers Series on Cardiovascular Disease.¹⁸ Results are reported in costs per quality-adjusted life-year (QALY) gained. This section reviews only drug-related interventions; however, smoking cessation interventions through taxation policies, physician education, and advertising regulations are also extremely cost-effective.

Coronary heart disease

Acute MI

Four incremental strategies were evaluated for the treatment of acute MI (AMI) and compared to a strategy of no treatment as a base case. The 4 strategies were: aspirin (ASA); ASA and beta-blocker (BB [atenolol]); ASA, BB, and streptokinase (SK); and ASA, BB, and tissue plasminogen activator (t-PA). Doses for the ASA and SK were those used in ISIS-2. The BB regimen was that of ISIS-1 and the t-PA dosing was that used in GUSTO-I. All patients receiving the medications had relative risk reductions in the risk of dying from AMI. Patients receiving the thrombolytics also faced the complication of increased risks of major bleeds and hemorrhagic strokes. Two further sensitivity analyses were completed comparing SK in those aged >75-years and those aged <75-years, and whether or not patients received the intervention >6 hours or <6 hours from onset of symptoms, since treatment effectiveness diminishes over time.

Incremental cost-effectiveness ratios (ICERs) for each therapy by region are listed in Table 2, section A. The incremental cost per QALY gained for both ASA and BB interventions was <\$25 for all 6 regions. Costs per QALY gained for SK were between \$630-\$730 across the regions. ICERs for t-PA were around \$16,000/QALY gained compared to SK. Minor variations occurred between regions due to small differences in follow-up care based on regional costs.

Table 3 displays the results of the sensitivity analysis for streptokinase. Giving SK in <6 hours reduces the incremental cost per QALY gained to around \$500 compared to over \$1200 per QALY gained if given after >6 hours. Equivalent effects are seen when SK is given to those aged <75 (\$600/QALY) compared to those aged >75 (\$1300/QALY). Other criteria that would improve the cost-effectiveness of thrombolytics, but were not analyzed include location of the infarct (anterior) or the presence of a new left bundle branch block.

Secondary prevention

Four medical therapies, ASA, BBs, statins, and angiotensin-converting enzyme inhibitors (ACEIs) have been the mainstay of treatment for those with CHD in the developed world. To evaluate the best medical intervention, the 15 different possible combinations of the 4 standard medical therapies were examined in an incremental cost-effectiveness analysis. The 4 therapies were ASA (75-100 mg/day), BB (atenolol, 100 mg/day), ACEI (enalapril, 10 mg/day) and statin (lovastatin, 40 mg/day), all are available as generics. In addition, coronary artery bypass graft (CABG) plus all 4 medications for those with left main disease or with 3-vessel coronary artery

Table 3: Sensitivity analyses: Effect of time to treatment and age on use of thrombolytics in acute myocardial infarction (all regions combined)

	SK* (\$/QALY)	t-PA* (\$/QALY)
Time to thrombolysis		
<6 hours	374-437	15,800
6-12 hours	1,300-1,440	15,700
Age at treatment		
<75	559-650	14,800
75 or older	1,260-1,350	21,000

SK = streptokinase; t-PA = tissue plasminogen activator
Source: Authors' calculations.

*In addition to aspirin and atenolol

disease and reduced left ventricular function, was evaluated. Since the above therapies have significant effects on the incidence of stroke, the impact on QALYs gained and the costs for these events are included in the analysis.

In addition to the mortality benefits in the trials of individual medications or the surgery listed above, significant reductions in hospitalizations also occurred in developed countries. The cost-savings from these reduced admissions to hospitals make the cost-effectiveness of such interventions quite favorable in developed countries. However, given that hospital facilities may not be available to a majority of patients in many developing regions, separate analyses were conducted — one including hospital costs and one without. In the first analysis, it was assumed that hospitals would be available (eg, in urban areas of many middle-income countries) and savings would be realized in these settings. In the second analysis, hospitals were assumed not to be available and the intervention focused primarily on mortality reduction with little savings in morbidity costs. There is likely some benefit to mortality for hospitalization; however, the analysis does not reflect that benefit. Further investigations should be done to quantify the benefit of hospitalization itself.

In the setting of all regions where hospitals are available, a combination of ASA and BB was cost-saving when compared to no therapy (Table 2 section B). The ICERs for the combination of ASA, BB, and ACEI ranged from \$660 in the SSA region to \$866 per QALY gained in the ECA region. The combination of all 4 medications ranged from \$1700-2000/QALY gained across the regions. CABG compared to the 4-drug combination had ICERs ranging from \$24,000/QALY (SAR) to \$62,000/QALY (LAC) gained. Despite having similar benefits on mortality, the ACEI and statin had fewer beneficial effects on the ICER because of the added cost of monitoring renal and liver function, respectively, as required for these 2 medications in comparison with ASA and the BB.

When it was assumed that hospitals were not available (Table 2 section C), no therapy combination was cost-saving compared to no therapy. The combination of ASA and BBs was the next best strategy, with ICERs ranging from \$386/QALY gained in the SAR region to \$545/QALY gained in the LAC region. The addition of ACEI resulted in ICERs ranging from \$783/QALY gained to \$1111/QALY gained in SSA and LAC, respectively. The addition of a statin increased the ICERs to between \$2000-\$2500/QALY gained over the 6 regions. CABG was not evaluated because of the underlying assumption that hospitals were not available.

Congestive heart failure

The interventions examined for CHF were the addition of an ACEI, enalapril, and/or metoprolol, to a baseline of diuretic treatment. As in CHD interventions, separate analyses were based on assumptions of whether hospital facilities would be available or not. Table 2 section D lists the results of the treatment model for CHF assuming hospitalization. In this intervention, ACEI is cost-saving and the ICER for metoprolol is in the range

Table 4: Gross national income (GNI) per capita in 2000

	GNI per capita 2000, US\$	GNI per capita x 3
East Asia & Pacific	1,060	3,180
Europe & Central Asia	2,010	6,030
Latin America & Caribbean	3,670	11,010
Middle East & North Africa	2,090	6,270
South Asia	440	1,320
Sub-Saharan Africa	470	1,410
Low-income countries	1,230	3,690
High-income countries	27,680	83,040

of \$120 to \$220 per QALY gained, depending on the region. When the availability of hospitals is limited (Table 2 section E), the ACEI strategy is no longer cost-saving, but only costs approximately \$30/QALY gained and the beta-blocker ICER only increases to about \$275/QALY gained. These are likely underestimates of the cost/QALY gained, since the model does not capture mortality benefits for hospitalization.

Rheumatic heart disease

For rheumatic heart disease (RHD), secondary prevention after acute rheumatic fever is more effective than primary prevention (except in epidemics). Secondary prevention (using monthly benzathine penicillin injections) is cost-saving according to a WHO multicenter study¹⁹ and should be considered for all developing countries with the infrastructure to do the required follow-up. Primary prevention (through antibiotic treatment of *Streptococcus* infections of the pharynx) is not highly cost-effective in endemic situations, given that only 10% to 20% of such infections are from *Streptococcus*, <3% of these will evolve into rheumatic fever, and only a proportion of these continue on to rheumatic heart disease.¹⁹ The use of a rapid antigen test for diagnosing group A streptococcal pharyngitis may make primary prevention more cost-effective.²⁰ Similarly, in an epidemic where the proportion of infections from *Streptococcus* is higher (or the rate of progression to rheumatic fever higher), primary prevention may become cost-effective.

Cost-effectiveness ratios in context

Cost-effectiveness ratios differ from region to region based on input prices. What determines cost-effectiveness in an individual country? Certainly, the lower the cost-effectiveness ratio the better, but what should determine an upper limit? There is no legal standard or regulation for what is cost-effective in the USA, but values between \$50,000 to \$100,000 per QALY have become an accepted benchmark for policy makers and insurance agencies. That level is unrealistic in developing countries. The WHO's Commission on Macroeconomics and Health chaired by former Harvard economist Jeffrey Sachs recommended choosing interventions that were <3-times the GNI per capita.²¹ With a GNI per capita of \$26,000 in the United States, \$78,000 as the upper end is within this benchmark. Table 4 lists the GNI multiplied by 3 in the 6 regions. Most of the strategies reviewed above would

be acceptable in all regions with the exceptions of t-PA and CABG. Countries within the SSA and SAR regions could evaluate whether statins for secondary prevention are amenable with their willingness and ability to pay.

Conclusions: pitfalls and promises

A global CVD epidemic is rapidly evolving, and the burden of disease is shifting. Twice as many deaths from CVD now occur in developing as compared to developed countries.²² The vast majority of CVD can be attributed to conventional risk factors. Even in Sub-Saharan Africa – a developing country with high mortality – high blood pressure, high cholesterol, tobacco and alcohol use, as well as low vegetable and fruit consumption, are already among the top risk factors for disease.²³ Because of the lag time associated with CVD risk factors – especially in children – the full effect of exposure to these factors will only be seen in the future. Information from >100 countries reveals that more 13- to 15-year-olds smoke than ever before and studies demonstrate that obesity levels in children are increasing markedly in countries as diverse as Brazil, China, India, and almost all island states.⁷ Population-wide efforts to reduce risk factors through multiple economic and educational policies and programs that are implemented now will reap savings later, both in medical and other direct costs, as well as indirectly in improved quality of life and economic productivity.

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Dr. Gaziano has no disclosures to announce.

Intensive Review of Internal Medicine Course (IRIM)

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This publication is made possible by an educational grant from

Novartis Pharmaceuticals Corporation

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