Increasing Global Burden of Cardiovascular Disease in General Populations and Patients With Schizophrenia

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Cardiovascular disease (CVD), which includes coronary heart, cerebrovascular, and peripheral vascular disease, is the leading cause of death in the United States and most developed countries, accounting for about 50% of all deaths. The major risk factors include obesity and its consequences, dyslipidemia, hypertension, insulin resistance leading to diabetes, and cigarette smoking. In developing countries, CVD will become the leading cause of death due to alarming increases in obesity, sedentary lifestyles, cigarette smoking, and improvements in prevention and treatment of malnutrition and infection. Compared with nonschizophrenics, patients with schizophrenia have a 20% shorter life expectancy (i.e., from 76 to 61 years). In general populations, about 1% die from suicide compared with about 10% among patients with schizophrenia (relative risk = 10). For CVD, the corresponding figures are 50% and about 75% (relative risk = 1.5). In patients with schizophrenia, however, CVD occurs more frequently and accounts for more premature deaths than suicide. Patients with schizophrenia have alarmingly higher rates of obesity, dyslipidemia, hypertension, diabetes, and cigarette smoking than nonschizophrenic individuals in the general population. Compounding these data, patients with schizophrenia have less access to medical care, consume less medical care, and are less compliant. Primary prevention strategies should include the choice of antipsychotic drug regimens that do not adversely affect the major risk factors for CVD.
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Cardiovascular disease (CVD), which comprises coronary heart disease (CHD), stroke, and peripheral vascular disease, is and will remain the leading cause of death in the United States and most developed countries. Furthermore, during the next decade, CVD will become the leading cause of death in developing countries and, eventually, in the entire world.[1] Patients with schizophrenia have a markedly reduced life expectancy compared with the general population, mainly due to CHD, but also due to suicide.[2] In this report, the reasons for these alarming trends, as well as their implications for patients with schizophrenia, are reviewed.

CVD IN DEVELOPED COUNTRIES

Cardiovascular disease is far and away the leading cause of death in the United States, accounting for 51.2% of deaths.[3] Initial improvements in primary prevention and later improvements in diagnosis and treatment have resulted in a steady decline in the age-adjusted death rates due to CVD (i.e., a 60% decrease from 1950 to 1996).[4] Despite the overall decline, the decrease in the CVD mortality rate has been leveling off, and recent trends of some health indicators are alarming. One example is the growing epidemic of overweight and obesity. Among adults, the prevalence of overweight and obesity rose from 48% during 1971 to 1974 to 65% during 1999 to 2002. Even more alarming is the 3-fold increase from 5% to 16% in overweight and obesity among adolescents during the same period.[5] Physical inactivity is a major factor contributing to this increasing epidemic. Not surprisingly, the rise in obesity and physical inactivity among children and adolescents is accompanied by an increase in type 2 diabetes.[6] In addition, 23% of high school students were cigarette smokers in 2005.[7] When this cohort reaches middle age, there will be corresponding increases in CVD morbidity and mortality in the United States.

CVD IN DEVELOPING COUNTRIES

Cardiovascular disease accounts for 16.7 million total worldwide deaths, or 29.2%.[8] In addition, 80% of worldwide CVD deaths take place in developing countries.[8] Global trade and food market globalization have led a transition toward a diet that is energy dense and nutrient poor. The resultant increases in obesity are accompanied by physical inactivity. In addition, tobacco consumption is increasing at alarming rates in developing countries. For these reasons, the World Health Organization estimates that by 2010, CVD will become the leading cause of death in developing countries. Worldwide, this will raise CVD from the fifth to the first leading cause of death.[8]

CVD IN PATIENTS WITH SCHIZOPHRENIA

Among patients with schizophrenia, the life expectancy is 20% shorter than that in the general population (i.e., from 76 to 61 years).[2] The leading causes of premature death in patients with schizophrenia are suicide (10-fold increase)[9] and CHD (2-fold increase).[10] Thus, compared with CHD, suicide is a far more significant cause of premature death in patients with schizophrenia. In contrast, in the general population, suicide occurs in about 1%[9] and CHD in about 33% of individuals.[3]

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However, because CVD is so much more common, there are larger numbers of premature deaths due to CVD than suicide among patients with schizophrenia.

MAJOR RISK FACTORS FOR CVD

Numerous landmark prospective cohort studies[11,12] have identified several major risk factors for CVD (Table 1). The Framingham Heart Study, comprising greater than 40 years of follow-up among greater than 5000 residents of a white middle-class community in Massachusetts, identified numerous independent risk factors, including cigarette smoking, total cholesterol (and its components, particularly low-density lipoprotein cholesterol [LDL-C], but also high-density lipoprotein cholesterol [HDL-C] and triglycerides), blood pressure, obesity, and physical inactivity. These major risk factors for CVD are additive. Based on available data, a simple prediction tool (available online at http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof) has been developed to determine 10-year CHD risk and guide primary preventive therapy.[13,14] The simple electronic calculator also assesses the estimated 10-year risk of developing "hard" CHD events (e.g., myocardial infarction and coronary death). Eliminating or improving these risk factors provides unequivocal benefits in improved clinical outcomes.[1] For example, a 10% decrease in blood cholesterol translates to a 30% risk reduction in CHD. Further, a 3– to 5–mm Hg decrease in blood pressure among those with mild-to-moderate hypertension results in a 16% decrease in CHD and a 42% decrease in stroke. Finally, cessation of smoking leads to a 50% decrease in risk of CHD.[1] The time course of these improvements begins within months, and maximum impact is achieved within several years.

With respect to reducing total cholesterol, and particularly LDL-C, with the use of statins, recent randomized trials using higher than usual doses in patients who survived an acute coronary syndrome (in the Pravastatin or Atorvastatin Evaluation and Infection Therapy trial[15]) and those with chronic stable CHD (in the Treating New Targets trial[16]) have shown that statistically significant and clinically important incremental benefits in CHD, stroke, and CVD mortality appear to begin within months and reach their maximum within 1 year. The totality of evidence clearly continues to indicate that LDL-C should be the primary therapeutic target in primary and secondary prevention, and that intensive treatment to reach a lower LDL-C target with statin therapy provides greater clinical benefits.[15–17] Table 2 lists the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) recommended cholesterol reduction goals.[17]

DIABETES: FROM RISK FACTOR TO RISK EQUIVALENT

The NCEP ATP III guidelines[17] have elevated diabetes from a risk factor to a risk equivalent. In other words, patients with diabetes are considered to have risks of a first CHD event that are similar to risks in nondiabetic patients with prior CHD. In a Finnish cohort study,[18] the 7-year incidence rate of myocardial infarction (MI) in nondiabetic patients with a prior history of MI (18.8%) was found to be similar to that of diabetic patients with no prior MI (20.2%).

The results of a primary prevention trial of statins among diabetic patients support this U.S. national guideline. In the Collaborative Atorvastatin Diabetes Study (CARDS),[19] 2838 diabetic patients with no prior history of CVD and without hypercholesterolemia were randomized to atorvastatin 10 mg daily or placebo. The trial was terminated early due to the clear benefit observed in the group receiving atorvastatin. At baseline, patient characteristics were similar. Mean baseline LDL-C was 117 mg/dL for the placebo group and 118 mg/dL for the atorvastatin group. After a median follow-up of 3.9 years, the atorvastatin-treated group demonstrated a significant decrease in LDL-C to a mean of 81.5 mg/dL, whereas the placebo group remained at a similar mean level of 121 mg/dL. The trial had been scheduled to terminate after 5 years. but the Independent Data and Safety Monitoring Board voted unanimously to terminate CARDS early due to the emergence of a statistically extreme ($p = .001$) and clinically important 37% risk reduction in major cardiovascular events in the atorvastatin-treated group compared with the placebo group. With regard to individual cardiovascular events, atorvastatin reduced acute CHD events by 36%, coronary revascularization by 31%, and risk of stroke by 48%.[19]

Table 1. Risk Factors for Heart Disease[a]

Modifiable	Nonmodifiable
Smoking[b]	Male sex[b]
Obesity	Older age[b]
Physical inactivity	Family history of heart disease
Diabetes	
High cholesterol[b]	
Hypertension[b]	

[a]Based on National Cholesterol Education Program[11] and Torpy et al.[12]
[b]These risk factors are used to determine the patient's 10-year risk for "hard" coronary heart disease outcomes (myocardial infarction and coronary death), so as to determine appropriate low-density lipoprotein cholesterol goals and interventions. This simple-to-use risk calculator is available online at: http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof.

METABOLIC SYNDROME

In recent years, increased attention has focused on the metabolic syndrome. The U.S. national guidelines define metabolic syndrome as the presence of greater than or equal to 3 metabolic risk factors (Table 3).[17,20] Causes of the metabolic syndrome include overweight/obesity, physical inactivity, and genetic predisposition. Most patients with metabolic syndrome have insulin resistance. Excess body fat and physical inactivity promote the development of insulin resistance and predispose to the development of type 2 diabetes.[17]

Metabolic syndrome affects 22% (47 million) of the U.S. general population.[17] The incidence is even higher among patients with schizophrenia (41%).[21] Further, the 10-year risk of a first CHD event in patients with metabolic syndrome is 16% to 18%. Management of the metabolic syndrome should include lipid modification with statins and blood pressure reduction with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, as well as therapeutic lifestyle changes of weight reduction and increased physical activity.[17] In patients with borderline elevated triglycerides (150–199 mg/dL), the primary aim is to achieve a target LDL-C goal, along with improvements in total cholesterol and physical activity. Among patients with high (200–400 mg/dL) or very high (> 500 mg/dL) levels of triglycerides, the addition of fibrates or nicotinic acid should be considered. Patients with metabolic syndrome should be treated

Table 2. Adult Treatment Panel III (ATP III) Cholesterol Goals and Thresholds for Lifestyle Changes and Drug Therapy[a]

Risk Category	LDL-C Goal	Initiate Therapeutic Lifestyle Changes	Consider Drug Therapy
CHD or CHD risk equivalents[b] (10-y risk > 20%)	< 100 mg/dL (optional goal: < 70 mg/dL)	≥ 100 mg/dL[c]	≥ 100 mg/dL (< 100 mg/dL: consider drug therapy)[d]
2+ risk factors[e] (10-y risk 10%–20%)	< 130 mg/dL (optional goal: < 100 mg/dL)	≥ 130 mg/dL	≥ 130 mg/dL (100–129 mg/dL: consider drug therapy)[d]
2+ risk factors[e] (10-y risk < 10%)	< 130 mg/dL	≥ 130 mg/dL	≥ 160 mg/dL
0 or 1 risk factor	< 160 mg/dL	≥ 160 mg/dL	> 190 mg/dL (160–189 mg/dL: LDL-C–lowering drug optional)

[a]Based on National Heart, Lung, and Blood Institute.[17]
[b]Coronary heart disease (CHD) risk equivalent includes the presence of peripheral arterial disease, carotid artery disease, abdominal aortic aneurysm, diabetes, and ≥ 2 risk factors, with a 10-year risk for hard CHD of > 20%.
[c]Patients who have lifestyle-related risk factors are candidates for therapeutic lifestyle changes for modification of these risk factors, regardless of LDL-C level.
[d]Initiation of drugs to lower LDL-C is a therapeutic option on the basis of available clinical trial results.
[e]Major risk factors exclusive of LDL-C that modify LDL-C goals include cigarette smoking, hypertension or being on antihypertensive medication, low HDL-C, family history of premature CHD, and age (men ≥ 45 years; women ≥ 55 years).
Abbreviations: HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

Table 3. Clinical Identification of the Metabolic Syndrome[a]

Risk Factor	Defining Level
Waist circumference	
Men	> 40 in
Women	> 35 in
Triglycerides	≥ 150 mg/dL
HDL-C	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	≥ 130/≥ 85 mm Hg
Fasting glucose	≥ 110 mg/dL (≥ 100 mg/dL)[b]

[a]Based on National Heart, Lung, and Blood Institute[17] and Grundy et al.[20]
[b]The Joint Statement from the American Heart Association and National Heart, Lung, and Blood Institute recommends using the lower threshold for fasting glucose to correspond with recently modified American Diabetes Association criteria for impaired fasting glucose.
Abbreviation: HDL-C = high-density lipoprotein cholesterol.

according to the blood pressure goals suggested by the Seventh Joint National Committee (JNC 7) report (Table 4).[22]

MAJOR RISK FACTORS FOR CVD IN PATIENTS WITH SCHIZOPHRENIA

Among patients with schizophrenia, the prevalence rates of major CVD risk factors are higher than those in the general population.[2,23] An estimated 42% of patients with schizophrenia have a body mass index (BMI) of greater than or equal to 27 compared with 27% among the general U.S. population.[2] Cigarette smoking among patients with schizophrenia is about 75%, compared with 25% in the general population.[2] In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial,[24] patients with schizophrenia had rates of diabetes and hypertension of 13% and 27%, respectively, which were significantly higher than the respective 3% and 17%, observed in a random sample from the general population in the Third National Health and Nutrition Examination Survey (NHANES III). Both male and female patients with schizophrenia in the CATIE trial were more likely to have metabolic syndrome than their NHANES III–matched counterparts (138% and 251%, respectively).[21] The CATIE trial[25] further showed that patients with schizophrenia have limited access to and/or receive suboptimal medical care. Of patients with schizophrenia diagnosed with dyslipidemia, only 12% received treatment, compared with about 33% in the general population.[25] For schizophrenia patients diagnosed with hypertension, the rate of treatment was 37.6% versus greater than 50% in the general population.[25]

QT Interval

The QT interval is an electrocardiographic parameter that measures the time of ventricular depolarization and repolarization, corrected for heart rate. The mean (± SD) QT interval in the general population is 400 to 440 ms (20–40 ms).

There are several conditions for which prolonged QT intervals have been associated with an increased risk of Torsades de pointes, a polymorphic ventricular tachycardia associated with syncope and sudden death.[26] These include the rare familial prolonged QT interval of greater than 500 ms or increases of greater than 60 ms due to pharmacokinetic or pharmacodynamic drug interactions. In the general population, the risk of cardiovascular mortality and sudden cardiac death associated with QT interval prolongation is small and difficult to detect reliably.[27] Some second-generation antipsychotic drugs (SGAs) cause mild prolongations of 5 to 10 ms, with no pharmacodynamic interactions with other drugs. Not surprisingly, there have been no reports of Torsades de pointes resulting from QT interval prolongation associated with currently available SGAs, and current evidence suggests that prolongation of the QT interval by these agents does not appear to be associated with Torsades de pointes or sudden death.[27]

CONCLUSION

Cardiovascular disease is the leading cause of death in most developed countries, including the United States. In the next decade, CVD will become the leading cause of death in developing countries and ultimately in the entire world. Among patients with schizophrenia, suicide is a more important cause of premature death than CVD. Nonetheless, since CVD is so much more common, there are larger numbers of premature deaths due to CVD than suicide among patients with schizophrenia.

Favorable modification of risk factors is important, but efforts aimed at the primary prevention of risk factors assume even greater importance in patients with schizophrenia. Treatment and prevention strategies should encourage healthy lifestyles, smoking cessation, appropriate diets and levels of activity, and the integration of behavioral and medical services, as well as routine

Table 4. Seventh Report of the Joint National Committee (JNC 7) Recommendations for Management of Blood Pressure[a]

Blood Pressure Classification	Systolic Blood Pressure[b] (mm Hg)		Diastolic Blood Pressure[b] (mm Hg)	Lifestyle Modification	Initial Drug Therapy	
					Without Compelling Indication	With Compelling Indication[c]
Normal	< 120	and	< 80	Encourage	No antihypertensive drug indicated	Drugs for compelling indications[d]
Prehypertension	120–139	or	80–89	Yes		
Stage 1 hypertension	140–159	or	90–99	Yes	Thiazide-type diuretics for most; may consider ACEI, ARB, BB, CCB, or combination	Drug(s) for the compelling indications[d]; other antihypertensive drugs (diuretics, ACEIs, ARBs, BBs, CCBs) as needed
Stage 2 hypertension	≥ 160	or	≥ 100	Yes	2-drug combination for most[e] (usually thiazide-type diuretic and ACEI or ARB or BB or CCB)	

[a]Based on National Heart, Lung, and Blood Institute.[22]
[b]Treatment determined by highest blood pressure category.
[c]Compelling indications for drug therapy include heart failure, post–myocardial infarction, high risk for coronary heart disease, diabetes, chronic kidney disease, and recurrent stroke prevention. Refer to guidelines for recommended drugs from compelling indications.
[d]Treat patients with chronic kidney disease or diabetes to blood pressure goal of < 130/80 mmHg.
[e]Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.
Abbreviations: ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BB = β-blocker, CCB = calcium channel blocker.

screening and treatment. Finally, the choice of antipsychotic drug therapies of comparable efficacy and a lower likelihood of adversely affecting the major risk factors of CVD is an important consideration for patients with schizophrenia.

Drug names: atorvastatin (Lipitor), pravastatin (Pravachol and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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