Managing Comorbidities Through Cholesterol-Lowering Agents

By Alan O. Marcus, MD, FACP

Abstract

Cardiovascular disease is not the result of a single disease but is the sum of multiple comorbid conditions that act independently and in tandem to create an increased probability for heart disease and stroke. More than 200 risk factors and/or comorbid diseases for cardiovascular disease have been identified. The correct diagnosis of comorbid diseases is integral to being able to accurately interpret individual risk profiles and to construct a rational treatment paradigm that allows multiple modalities of care. In a time when optimal delivery of healthcare is linked to the most cost-effective allocation of limited resources, determining overall risk and defining the most effective intervention strategies is not an idle intellectual exercise but a matter of vital necessity. Identifying common comorbid diseases that can exist with hyperlipidemia is essential for appropriate treatment and risk reduction. In addition to being able to identify comorbid diseases, clinicians must have an understanding of how these comorbid conditions interrelate and affect overall cardiovascular health. The primary objective of treating hypercholesterolemia is to reduce the patient's risk of developing cardiovascular disease. Modifying the additional risks that are introduced by comorbid diseases is appropriate and necessary. Therapy for comorbid conditions will add to the benefit obtained from, but can never be substituted for, the primary goal—reduction of low-density lipoprotein cholesterol.

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The events associated with atherosclerotic cardiovascular disease (CVD) exact a tremendous yearly toll—as measured by loss of life and disability—among the people of the United States. In the 25 years since the results of the Multiple Risk Factor Intervention Trial (MRFIT) were published and the medical community began recognizing the association between hyperlipidemia and the risk of coronary heart disease, we have reached a better understanding of the intracellular and physiological processes that result in pathological anatomical changes. The most recent edition of the American Heart Association's (AHA) statistical supplement predicts that in 1997 as many as 1,500,000 Americans will experience myocardial infarction (MI) and about one-third will die.[1] Based on the Framingham Heart Study, approximately 500,000 people suffer a new or recurrent stroke each year. Approximately one-third of these patients are also expected to die.[2]

New discoveries have moved us from the epidemiological linkage of lipid levels and the risk of coronary artery disease (as in the Framingham study) to a more enlightened focus on the endothelial cells—the group of cells that are central to the processes of atherosclerosis and its associated mortality and morbidity. The processes of atherosclerosis are dependent on repeated endothelial injury and enhanced lipid infiltration. Injury and infiltration are not the result of a single disease state but are the sum of multiple comorbid conditions or risk factors that act independently and in tandem to cre-

ate an increased probability for heart disease and stroke.

More than 200 risk factors and/or comorbid diseases for CVD have now been identified.[3] The three most important are abnormal lipids (there are more than 15 types of cholesterol and four kinds of triglyceride-rich particles); high blood pressure; and cigarette smoking. However, there are many other important comorbidities that put patients at serious risk for CVD. These include insulin resistance, diabetes mellitus, obesity, polycystic ovary syndrome, hypothyroidism, and menopause. Many of these overlap in etiology and effect.

The possibility of an individual disease being diagnosed together with hyperlipidemia varies in any individual or group, as does the influence of comorbid disorders on atherosclerotic disease progression and patient outcomes. The correct diagnosis of comorbid diseases is integral to being able to accurately interpret individual risk profiles and to construct a rational treatment paradigm that allows multiple modalities of care. The cost of treating heart disease for the 1.5 million people who experience MIs each year is estimated to be $151 billion.[4] In a time when optimal delivery of healthcare is linked to the most cost effective allocation of limited resources, determining overall risk and defining the most effective intervention strategies is not an idle intellectual exercise but a matter of vital necessity.

HYPERCHOLESTEROLEMIA AND COMORBID DISEASES: IDENTIFICATION

Identifying common comorbid diseases that can exist with hyperlipidemia is essential for appropriate treatment and risk reduction. Although clinicians profit from being able to identify them, an even greater benefit is derived from being able to understand the interrelatedness of comorbid conditions from a causative as well as from an effect standpoint.

Historically, the first comorbid diseases to be identified in association with hyperlipidemia were hypertension and smoking. These three became known as the "classic" three risk factors. The presence of each additional risk factor resulted in a statistical doubling of the probability for the occurrence of a coronary event. Epidemiological studies were quick to identify other diseases that similarly worsened the prospect for survival of individuals with hyperlipidemia. The first such identified was diabetes mellitus (Type 1 and Type 2) and its related abnormalities, hyperinsulinism and impaired glucose tolerance.[5] The presence of diabetes mellitus causes an increase in the risk of CVD that is equal to the presence of any two of the "classic" three risk factors.

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Identification of these disease states and their impact led to the recognition of the interrelatedness of the multiple comorbid diseases. For example, the coexistence of hyperlipidemia, hyperuricemia, hypertension, fasting insulin elevation, central and general obesity, and Type 2 diabetes mellitus would seem to indicate the presence of a metabolic syndrome that unites all these entities.[6] An evaluation of 14,000 people (males, females, Caucasians, and African-Americans between the ages of 45 and 64) found that these diseases occur together more often than mere chance would allow.[7] The only abnormality that was found to occur both independently and in association with the others was hypertension—a specific disease that is presumably related to a greater polymor-

phic cause. Patients with the most lethal dyslipidemic pattern (hypertriglyceridemia and low high-density lipoprotein cholesterol [HDL-C] matched with high levels of low-density lipoprotein cholesterol [LDL-C]), demonstrated the highest risk for coronary heart disease (CHD). In the 6-year data collected as part of the study, only 4.3 % of subjects fell into this group but they accounted for one out of every four CHD events.[8]

In seeking to comprehend the interrelationship between the heart and comorbid diseases, it is important to have a clear understanding of each of these diseases as individual entities.

Hypertension

In 1971, hypertension was associated with a progressive increased risk of stroke, congestive heart failure, coronary artery disease (CAD), renal impairment and failure, and left ventricular failure. Originally, systolic pressure was thought to have the most impact on these disease states; diastolic pressure and its risk potential were discovered later.[9]

The diagnosis of hypertension is based on three elevated blood pressure readings taken over the course of 1 to several weeks. An elevated reading is a systolic pressure of ≥140 mmHg and/or a diastolic pressure of ≥90 mmHg. If the initial blood pressure is very severely elevated (≥210 mmHg systolic and/or ≥120 mmHg diastolic) no further determinations are necessary to diagnose hypertension. Hypertension is classified according to stage, ranging from mild to very severe (Table 1). Regardless of the stage, hypertension is associated with an increased risk of both fatal and nonfatal CVD and renal disease occurrences.

Hypertension has a strong genetic predisposition. The risk of future development of hypertension in the normotensive offspring of parents with this disease can be demonstrated through abnormalities such as altered sodium lithium counter-transport.[10] The true prevalence of hypertension, which is approximately one-third of the adult US population (24% are currently hypertensive, 7% have a history of hypertension) increases with age among all ethnic groups and both genders.[11]

The addition of diabetes mellitus to hypertension imparts a greater risk for CHD upon women than men. Systolic blood pressure peaks in middle age for men but continues to increase in women until after age 80 and as a group women suffer more complications from hypertension.[12] Both diabetes mellitus and hypertension result in alterations in the structure and function of large and small arterial vessels.[13] The result of these alterations is a change in the compliance characteristics of the arterial blood vessels—an early marker for the vascular damage that ultimately predisposes to major cardiovascular events.

Insulin Resistance

Decreases in insulin sensitivity can be caused by: the depletion of insulin receptor sites on the surface of insulin-responsive cells (muscle, fat, hepatic, and endothelial tissue); alterations of the intracellular pathways or proteins that transport glucose from the extracellular to intracellular space; mutations in the genes that code for the insulin receptor site; or causes that remain to be elucidated.[14] Insulin resistance, resulting in hyperinsulinism as a compensatory mechanism to normalize glucose levels, eventually ends in the development of Type 2 diabetes.

Insulin resistance and/or resultant compensation attempts by the body to maintain glucose within normal physio-

Table 1. Stages and Prevalence of Hypertension in the US

Stage	Systolic mmHg	Diastolic mmHg	Prevalence
1 (mild)	140 - 159	90 - 99	14%
2 (moderate)	160 - 179	100 - 109	4%
3 (severe)	180 - 209	110 - 119	±1%
4 (very severe)	≥210	≥120	±1%

Source: NHANES III.[11]

logical ranges contributes to hypertension by several known mechanisms. Insulin resistance, at the endothelial tissue, causes a decrease in conversion of L-Tyrosine into nitric oxide, which acts as a dilator of vascular smooth muscle, resulting in an increase in peripheral vascular resistance. The renin-angiotensin-aldosterone system is also affected by alterations in insulin effectiveness and levels. Increases in glucose and/or insulin results in a dramatic elevation in the biological activity of renin, angiotensin II, aldosterone, and the adrenergic system (epinephrine and norepinephrine).[10] The effect of this is vascular smooth muscle constriction, increased catecholamine release from the sympathetic nervous system and adrenal medulla, increased antinatriuretic and antidiuretic effect at the renal tubule (renal tubular reabsorption of sodium and water), stimulation of the thirst center, antidiuretic hormone release, increased cardiac contractivity, increased cellular growth and differentiation, and ultimately ventricular hypertrophy.[15]

Diabetes Mellitus

The most obvious comorbid disease intertwined with insulin resistance and pancreatic beta-cell dysfunction is Type 2 diabetes mellitus. The spectrum of insulin resistance, hyperinsulinism, and Type 2 diabetes mellitus may contribute, as shown previously, to the development and/or severity of other comorbid diseases such as hypertension, obesity and PCOS. This interaction does not proceed in one direction but involves an interplay where, for instance, obesity or androgen excess worsens insulin resistance causing the pancreatic beta-cells to produce ever more insulin to elicit the desired cellular response. This increase in insulin in people at risk eventually can no longer counter the defect in insulin action. At that point serum glucose level begins to be elevated. In this scenario, the resulting disease is Type 2 diabetes mellitus.

The diagnostic criteria for diabetes mellitus has been recently modified to a system based on disease etiology rather than on pharmacologic treatment.[16] The new criteria for the diagnosis of diabetes mellitus are:

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- Symptoms of diabetes plus a casual plasma glucose concentration of ≥200 mg/dL (11.1 mmol/L). *Casual* is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes mellitus include polyuria, polydipsia, and unexplained weight loss.
- Fasting plasma glucose of ≥126 mg/dL (7.0 mmol/L). *Fasting* is defined as no caloric intake for at least 8 hours.
- 2-hour plasma glucose of ≥200 mg/dL during an oral glucose tolerance test. This test should be performed as described by the World Health Organization using a glucose load containing the equivalent of 75 grams of anhydrous glucose dissolved in water.

Between these two states—compensatory to diabetic—is a disorder called *impaired glucose tolerance.*[17] There is also an analogous intermediate stage of fasting glucose called *impaired fasting glucose.* At any age the number of people with impaired glucose tolerance is two times the number who have Type 2 diabetes. In 1991 it was estimated that approximately 15 million people in the US had Type 2 diabetes, meaning that 30 million additional people had impaired glucose tolerance or impaired fasting

glucose. As we age, our ability to compensate to external and internal changes or stresses deteriorates. With age there is, not surprisingly, an increase in glucose levels as the body's ability to continue to compensate for the induced or inherited defect in insulin action is diminished. By the age range of 64 to 74, the incidence of either diabetes or impaired glucose tolerance is approximately 35% of the US population.[18] Some studies have indicated that the progression rate from impaired glucose tolerance to outright diabetes mellitus approximates 5% per year.[19]

The vast majority of patients (>80%) in the US who have diabetes mellitus have Type 2. Because of the long interval between initial onset of Type 2 diabetes to its diagnosis, approximately 50% of patients will, at the time of diagnosis, have clinically significant atherosclerotic CVD. This risk increases, as does the underlying defect, as time passes. A few of the statistics that dramatically highlight the intertwining of CAD and diabetes are that 80% of deaths of patients with diabetes are due to CVD; almost 80% of hospital admissions for patients with diabetes mellitus are because of CVD; and the risk of congestive heart failure is up to five times greater in patients who have diabetes mellitus.[20] Gender also has an impact on outcome with diabetes mellitus. Women with diabetes mellitus have an annual rate of CAD that is five times greater than nondiabetic women. This is higher than the increase diabetes causes in men, who have an increased rate of about two and a half times.[2] At every measured level of total cholesterol, diabetic patients have two to three times more risk for CHD than do patients without diabetes.[21]

Hyperglycemia causes multiple events that increase CAD morbidity and mortality. Glucose elevation is directly toxic to endothelial cells. This toxicity results in a decrease in endothelium-mediated vascular relaxation, increased vasoconstriction, promotion of vascular smooth muscle cell hyperplasia, vascular remodeling, and over-expression of fibronectin and collagen IV.[22]

Elevated glucose, cholesterol, and blood pressure also affects the kidneys, frequently causing nephropathy, which increases the risk for CAD. The clinical finding of microalbuminuria (defined as a urinary albumin excretion rate of 20 mcg/minute to 200 mcg/minute, or 30 mg/24 hours to 300 mg/24 hours), which can be caused by either diabetes or essential hypertension, is highly predictive of the development of not only nephropathy, but also retinopathy, left ventricular hypertrophy, fatal and nonfatal CVD, and all-cause mortality. The prevalence of micro-albuminuria is approximately the same in both diabetes (20%) and hypertension (25%).[23] What links these two diseases are the common entities of endothelial dysfunction, insulin resistance, hyperinsulinemia, dyslipoproteinemia, and a procoagulant state. Effective interventions in nephropathy are not limited to glucose and blood pressure control[10] but also now include lipid lowering therapy as an effective strategy.[24] The importance of intervention to prevent nephropathy is underscored by the fact that Type 1 diabetes patients with nephropathy have a 40-fold greater relative mortality from CAD than those without nephropathy.[25]

Obesity

Although comorbid diseases linked to obesity have been extensively studied, little attention until recently has been paid to obesity itself as a chronic disease. This lack of information has unfortunately caused patients with this comorbid disease to be stigmatized while the etiology has escaped detection. The most rational explanation as to the cause of obesity is probably multifactorial with components being genetic, metabolic, and social, resulting in a disease that has increased in prevalence in the United States by 30% in the last decade.[26]

Related to insulin resistance and hyperinsulinism, obesity can also originate

the sequence of events that result in hypertension. The mechanism by which this happens is an increase in adrenergic system hormone levels and an increase in renal sodium reabsorption and retention, resulting in fluid overload. As proof of this relationship between obesity and insulin abnormalities, Reaven and colleagues demonstrated that obese individuals experience an increase in post-prandial insulin release similar to that seen in patients with insulin resistance.[27]

Obesity is associated with impaired vasodilation in response to methacholine, which (like acetylcholine and other muscarinic agents) causes endothelium-dependent vasodilation principally by stimulating release of nitric oxide. Nitric oxide acts to stimulate the production of cyclic guanosine monophosphate in vascular smooth muscle and is therefore a potent vasodilator that plays a pivotal role in maintaining vascular tone.[28]

Obesity exerts an effect on hyperlipidemia through multiple pathways. In women, central or abdominal obesity (as opposed to peripheral nonabdominal obesity) increases cardiovascular risk factors and/or exacerbating conditions by raising levels of fasting nonesterified fatty acids, lipid oxidation, and hepatic glucose output.[29] An investigative study of obesity in men was undertaken with determinations made of the ratio between total body fat and total body lean tissue.[30] This study also looked at how obesity is distributed by measuring central (android) fat versus hip and thigh (gynecoid) fat. The results conclusively showed that it was neither age nor overall adiposity that is related to CAD risk, but a high android to gynecoid ratio. Increased android fat is statistically related to low HDL-C and elevated serum triglycerides, which leads ultimately to CAD.

All diseases have a spectrum from mild to severe; for obesity the most severe form is defined as *morbid* obesity. The linkage of morbid obesity and heart disease is the ultimate magnification of the interaction of obesity and CAD. When the cause of death was determined for patients with morbid obesity the results were: sudden cardiac death 45%, severe coronary artery disease 27%, concentric left ventricular hypertrophy 18%, pulmonary embolism 5%, and hypoplastic coronary arteries 5%.[31] The sum effect of morbid obesity on the cardiac muscle is cardiomegaly, left ventricular dilation, and myocyte hypertrophy. These findings are consistent with the effects caused by hyperinsulinism and insulin resistance on cellular function and reproduction and with the production of endothelial-derived nitric oxide.

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What was in the past a source of controversy—the contribution of obesity to mortality rates—has now been clarified. In men 21% of CHD mortality was attributable to being overweight; for women the rate was 28% (body mass index $\geq$25 kg/M^2).[32] These statistics were arrived at *after* obesity was isolated as a single risk factor and after adjustments were made for the presence of smoking, hypertension, hypercholesterolemia, and diabetes mellitus.

Obesity and other chronic adult diseases do not occur suddenly in adulthood but are associated with early life experiences. Birth weight is probably the earliest marker associated with future disease risk. In adulthood, men who weighed less than 5.5 lbs or more than 10 lbs at birth had the greatest incidence of obesity along with the greatest likelihood of having hypertension and diabe-

tes mellitus.[33] After birth, body weight continues to serve as a marker of concomitant or future disease states. Childhood obesity is increased in otherwise healthy children of fathers with an established diagnosis of CAD. These children also exhibit abnormal lipid levels that have been universally acknowledged to be risk factors for CAD—elevated LDL-C, lowered HDL-C, and elevated triglyceridemia.[34] The connection between childhood obesity and progressively increasing abnormalities in lipid levels has also been demonstrated in children ages 2 to 18 who are offspring of parents with hyperlipidemia.[35]

Etiologies put forth for the development of obesity are varied but have shared threads of origin which unites obesity with the development of other comorbid diseases. One theory focuses on the functional alterations of white and brown adipose tissue. Brown adipose tissue (BAT) is thermogenic and increased activity of BAT is protective against diet-induced obesity. When mice were given "Western" diets (21% fat versus 6.5%), and exposed to hyperlipidemia, insulin resistance, or hyperglycemia, they demonstrated a decrease in BAT activity. At the same time, white adipose tissue underwent changes in function that accelerated comorbid disease development with a decrease in GLUT4 (the predominant transport protein for movement of glucose from extracellular to intracellular spaces), decreased beta 3-adrenergic receptor site numbers (metabolic activity and thermogenesis in adipose tissue is the result of beta 3-adrenergic binding), and increased expression of tumor necrosis factor alpha (a substance found to inhibit and interfere with metabolic activities in insulin sensitive tissues).[36]

Other researchers have shown that rather than insulin resistance being the *result* of obesity, it may be the *cause.* They have shown that a defect in muscle insulin receptor function gives rise to a decrease in muscle tissue ability to uptake and utilize glucose in response to insulin. This defect contributes to the development of obesity and may be, in and of itself, sufficient to cause impaired glucose tolerance, hyperinsulinemia, and dyslipidemia.[37]

Speculation as to the cause for the onset and development of obesity also revolves around abnormalities in neuropeptides, which play a role in appetite and weight setpoints by effects within the brain. Studies have shown a link between plasma leptin and obesity with higher levels of leptin being measured with men who have insulin resistance.[38] Alterations in serotonin, a neuropeptide that is intimately involved in carbohydrate craving, appetite suppression, and depression, may also play a powerful role in the etiology of obesity.[39]

Polycystic Ovary Syndrome

Closely linked to obesity is another comorbidity that puts women at higher risk for CVD. There are several disease states that result in a hormonally unbalanced condition that causes women to produce abnormally elevated amounts of androgen. An example of this is polycystic ovary syndrome (PCOS), which mainly affects obese women. The increase in androgen levels can cause a myriad of male physical characteristics and symptoms of relative estrogen insufficiency or inadequacy. These symptoms can include increased muscle mass, hirsutism, alopecia, menstrual irregularities or cessation, hot flashes, neuropathies, infertility, insomnia, neck pain, dyspareunia, psychological functions and stress reactions that are similar to those of men, and android adipose tissue distribution and function. Statistically, women with this comorbid disease have an increased risk of developing hypertension, Type 2 diabetes mellitus, and CVD. Their mortality rates are inversely proportional to the decreased level of sex hormone binding globulin, a finding seen in androgen excess. Women with polycystic ovaries generally have more extensive CVD than women with normal ovaries. The extent of CVD can be an indicator of the presence of polycystic ovaries.[40]

The importance of this disease is due not solely to the severity of abnormalities it causes, but because of its prevalence, estimated to be 5% to 10% of premenopausal women. The increase in premature CVD among patients with PCOS cannot be explained by obesity alone although developmentally the disease may be divisible into two distinct etiological groups: insulin resistant and noninsulin resistant.[41] The dyslipidemia in PCOS patients occurs irrespective of insulin resistance and is not related to body weight nor waist-to-hip ratio.[42] The significant lipid abnormalities of these patients are characterized by higher levels of total cholesterol, LDL-C, and triglycerides.

The fundamental causative processes of PCOS have only recently been identified. In both obese and slender women, PCOS is linked to beta-cell dysfunction and insulin resistance. These defects, present at the onset of PCOS, are not linked with glucose intolerance until the fourth decade of life when 20% of the obese women with PCOS will have developed impaired glucose tolerance or Type 2 diabetes mellitus.[43] With this knowledge it appears that the defect causing PCOS, which originates in the beta cell and/or its target tissues, progresses over time.

A sequencing of the events in this disease can be theorized as follows: When peripheral insulin resistance exists, the need to maintain normal glucose homeostasis—a need that is of paramount importance to survival—results in the beta-cell compensatory action of increasing insulin production and release. This systematic alteration cannot be the sole abnormality and its effects are probably moderated, both positively and negatively, by the interaction of other hormones and enzymes. It is appropriate to say that since the increased production of androgens can be reduced by re-establishment of insulin sensitivity and correction of hyperinsulinism,[44] this insulin defect must be the fundamental abnormality. This abnormality is the same one present in hypertension, obesity, Type 2 diabetes mellitus, hyperuricemia, and hyperlipidemia. Insulin responsiveness is involved with the maintenance of endothelial cell and vascular function. Therefore insulin resistance and altered beta-cell activity is to be viewed not as a byproduct but as the culprit causing the perturbations in a myriad of comorbid diseases that have a common end—coronary artery disease.

Hypothyroidism

Hypothyroidism has a somewhat unclear and questionable association with atherosclerosis. In the 1930s it was thought that hypothyroidism and its resultant hypometabolic state was a potential benefit to patients with angina as it would result in a lower cardiac metabolic rate, effectively treating intractable angina. As a result, more than 1000 patients with angina but normal thyroid function underwent thyroidectomies.[45] Follow-up analysis of these patients showed that approximately 75% experienced improvement in cardiac symptoms. The enthusiasm for this intervention waned when it was noted that the decrease in oxygen delivery associated with this therapy resulted in an increase in subendocardial ischemia. In addition, infarcts, when they did occur, were greater in size and produced more ventricular arrhythmias and more severe hemodynamic dysfunction.[46]

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The benefit that was seen in hypothyroidism may be due to the finding of a hypocoagulable state in this disease. Hy-

pothyroidism causes decreased platelet adhesiveness, low levels of platelet factor 3 activity, elevated activated partial thromboplastin times, and reduced levels of clotting Factors VII, VIII, IX and XI.[47] Infarctions, often the end result of CAD, are caused by thrombosis and occlusion—a process that is reduced by hypocoagulable conditions such as hypothyroidism.

Based upon the guilt-by-association argument, hypothyroidism and hypercholesterolemia do occur in combination.[48] Low thyroid levels result in a lowering of both lipoprotein lipase activity and cholesterol esterase. This combination causes a higher LDL-C and a significantly elevated LDL-C to HDL-C ratio. Treatment, with return to a euthyroid state, normalizes these cholesterol abnormalities that cause an increased risk of CAD for the hypothyroid patient.

A staggering amount of literature now shows that lipid lowering results in a decrease in first-time and recurrent cardiovascular events, even in the presence of comorbid diseases.

Menopause

Although regarded as a "natural" part of the female aging cycle, menopause is medically viewed as an endocrine disorder that results from the depletion of the pool of follicles that females are born with. Whether the menopause is a result of aging or surgical removal of the ovaries, the hormones produced by the ovaries—estradiol and progesterone—are no longer synthesized.

The earliest evidence of a protective role for estrogen, and therefore the classification of menopause as a comorbid disease, was presented in 1953.[49] These findings were confirmed when the Framingham study analysis demonstrated that the risk of CAD for women with premature menopause, regardless of etiology, was four times greater than their aged-matched peers and that loss of estrogen doubled the risk of CAD even when the age of menopause was considered normal (52 ± 5 years).[50]

The mechanism by which estrogen protects women from CAD until menopause, when their rates of CAD increase steadily with advancing age, is speculative. An attractive theory suggests that estrogen has an antioxidant effect on LDL-C, promoting production of endothelial derived nitric oxide in the damaged blood vessels of females.[51] No such effect is found in the damaged blood vessels of males.[52]

Smoking

Addictions are perhaps the most difficult of comorbid diseases to positively effect. Patients who smoke develop a dependence on the chemical component, nicotine, that forms the addiction.[53] Smokers face a CVD death rate that is four times that of nonsmokers, and a three-times greater chance of dying from CAD.[54]

In one study, 48% of habitual smokers were able to quit after 4 months with the use of an aggressive smoking cessation program, including nicotine supplementation and supportive group sessions.[55] In this group of successful quitters, HDL-C increased by 11% while body weight increased by 2.7 kg. The increase in HDL-C and the benefit it confers far outweighs the increased CAD risk realized from any weight gain. Cigarette smoking has a direct effect on the stimulation of thromboxane generation, a prostaglandin that causes increased platelet adhesiveness, thrombosis formation, and endothelial tissue inflammation.

HYPERCHOLESTEROLEMIA AND COMORBID DISEASES: TREATMENT

The primary objective of treating hypercholesterolemia is to reduce the patient's risk of developing CAD. Modifying the additional risks that are introduced by comorbid diseases is

appropriate and necessary. Therapy for comorbid conditions will add to the benefit obtained, but can never be substituted for, the primary goal—reduction of LDL-C to National Cholesterol Education Program (NCEP) targets.[56]

A staggering amount of literature now shows that lipid lowering results in a decrease in first-time and recurrent cardiovascular events, even in the presence of comorbid diseases. A recent subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) looked at diabetic patients.[57] As a group, these patients were more obese with higher systolic and diastolic blood pressure, heart rates, and triglycerides, and lower HDL-C levels. Reductions in risk were achieved with simvastatin, a 3-hydroxy 3-methylglutaryl coenzyme-A reductase inhibitor (HMG-CoA). When treated, these patients had 55% fewer major CHD events and 37% fewer atherosclerotic events. These results were similar to those demonstrated in the Cholesterol and Recurrent Events (CARE) trial. This study, which lasted 5 years and followed 4159 post-MI patients—with and without diabetes—randomized subjects to either 40 mg pravastatin or placebo. A 25% reduction in CHD event endpoints (death, nonfatal MI, coronary artery bypass graft, or coronary angioplasty) was reported in the diabetic cohort and a 24% reduction in the nondiabetic patients.[58]

The Role of Statins

The currently available HMG-CoA agents (statins) have demonstrated similar reductions and are well tolerated with low side effect profiles. All effectively lower LDL-C to NCEP and American Diabetes Association (ADA) target levels. These drugs can be divided into moderate reducers of LDL-C (fluvastatin, lovastatin, and pravastatin) and high reducers (simvastatin and atorvastatin). The moderate reducers can be expected to lower LDL-C by 20% to 26% and the high reducers are capable of achieving the significant level of LDL-C lowering (30% to 37%) needed by patients with severe hypercholesterolemia.

These drugs are useful for more than just lowering cholesterol numbers. The use of these agents has evolved to now include prolonging transplant survival of hearts and kidneys. Statins improve transplant survival by mechanisms that are completely unrelated to any effect on LDL-C levels.[59,60] These include increased blood flow and/or a direct immunosuppressive effect.

There are pharmaceuticals other than statins that lower cholesterol and achieve risk reduction. While effective, these agents have disadvantages in the face of comorbid diseases.[61] Resins can achieve a lowering of LDL-C in the range of 10% to 30%, but are extremely unpalatable and have a high discontinuation rate of 60% or more as measured in 1-year follow up. Niacin can lower LDL-C by similar amounts of 10% to 25% but are contraindicated in patients with diabetes mellitus, impaired glucose tolerance, and hyperinsulinism. Fibrates in combination with other agents can help lower cholesterol as much as 50%. The safety profiles of fibrates improved and their side effects were lowered when they were used in combination with statins as opposed to being used with niacin.[62,63]

A low risk for CVD requires that comorbid diseases be either not present or treated in a way that lowers the possibility of a cardiovascular event. Since many of the people who experience a cardiovascular event die, there may be only one opportunity to treat the person at risk—that opportunity is* before *the event, not after.

A Comprehensive Perspective

Lipid lowering can also be achieved by diet and exercise. These modalities form the initial step in the treatment of not only hyperlipidemia, but also diabetes mellitus, insulin resistance, hypertension, and obesity. However, their failure as a monotherapy for these co-

morbid diseases reinforces the fact that they do not achieve long-term success in the treatment of hyperlipidemia unless accompanied by pharmaceutical agent usage.[56]

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Hippocrates taught that the highest priority of any treatment regimen is to *cause no harm*. When comorbid diseases are closely linked, as they are when acting in concert with hyperlipidemia to produce CAD, the practice of the healing arts, as directed by Hippocrates, becomes more complex. This complexity translates into the need to analyze both risks and benefits, with the benefit of treating one disease being weighed heavily against the potential for exacerbating a coexisting disease.

In addition to understanding how comorbid diseases work with hypercholesterolemia to put patients at greater risk for CVD, clinicians also need to be familiar with how various therapeutic regimens for these comorbid diseases can lessen that risk.

Hypertension

Some drugs that treat hypertension effectively (such as thiazides in doses of 25 mg or higher) have also been noted to exacerbate hyperlipidemia, increase serum uric acid, worsen insulin resistance, and cause increased risk of death due to CAD. Table 2 shows prevalence rates of three of the most common comorbid diseases that can occur with hypertension.

Monotherapy for hypertension with comorbid diseases is frequently unsuccessful and antihypertensive pharmaceutical agents of different classes or actions need to be combined to achieve adequate control. In the presence of insulin resistance and/or Type 2 diabetes mellitus, for example, a review of patients seen in a hypertensive clinic revealed that 50% required three or more agents to reach target values of <140/90 mmHg.[64] An overview of various antihypertensive medicines that can positively or negatively affect comorbid diseases appears in Table 3.

In patients with diabetes, poor glycemic control can induce hypertension.[65] The opposite is also true in that subsequent control of glucose levels normalizes blood pressure. Reinforcing this is the fact that the pathological sequelae of the combination of hypertension and diabetes is more devastating to the heart than the presence of either alone.[66] The strict control of both arterial blood pressure and hypergly-

Table 2. Prevalence of Comorbid Diseases with Hypertension

Disorder	Percentage
Diabetes mellitus	13.5
Impaired glucose tolerance	25
Hyperlipidemia	30

Table 3. Various Therapeutic Agents and Their Effects

Disorder	Drugs with Particular Beneficial Effects	Drugs with Possible Harmful Effects
Diabetes mellitus	ACE inhibitors	Beta-blockers
Impaired glucose tolerance	Angiotensin II receptor blockers	High-dose thiazide diuretics
Insulin resistance	Alpha-adrenergic blockers	Short-term calcium channel blockers
	Calcium channel blockers	
Hyperlipidemia	Alpha-adrenergic blockers	Thiazide diuretics
	Calcium channel blockers	Beta-adrenergic receptor blockers
Polycystic ovary syndrome	Spironolactone	

cemia may prevent or ameliorate heart disease in patients for whom these two comorbid diseases are present.

Polycystic Ovary Syndrome

Treatments for women with PCOS vary according to the desired outcome. For the woman who has PCOS and obesity, the recommendation is weight loss. For the woman who wants to be fertile, ovarian stimulants such as clomiphene or menotropins can be given. If the woman with PCOS wishes to stop formation of male secondary sexual characteristics, such as hirsutism and alopecia, drugs that block androgens from binding to their receptor sites are useful. Restoration of normal menses can be accomplished through the use of birth control pills. None of these treatments are without risk. The repeated use of ovarian stimulants has been linked to increased risk for development of ovarian cancer, and the use of birth control pills can accelerate insulin resistance and increase the number of women who develop diabetes. Insulin resistance and diabetes, as discussed, have strong ties to the development of CAD.[67]

Instead of treating the *manifestations* of PCOS, recent studies suggest treating the *cause* of PCOS—insulin resistance—by using drugs called insulin sensitizers.[34] These drugs, such as metformin and troglitazone, have been successful in reducing androgen secretion, restoring normal pituitary-ovarian cyclic activity, restoring fertility, and normalizing insulin sensitivity. Metformin is associated with weight loss while troglitazone has demonstrated a decrease in both the level and activity of plasminogen activator inhibitor Type 1 in blood.

Obesity

Diet and exercise are clearly the mainstays of any attempt to treat obesity. Even if the patient fails to lose weight, mild exercise can increase longevity through its many beneficial effects, such as reducing levels of insulin, blood pressure, and LDL-C.[68] Experiments have demonstrated that vascular responsiveness to endothelium-dependent vasodilators are enhanced in exercise-trained animals. This reaction occurs via increased endothelial-derived nitric oxide and is also associated with a decreased sensitivity to the vasoconstrictor effects of norepinephrine.[69]

An awareness of the multifactorial nature of obesity will ideally serve as an impetus to use multiple modalities (including pharmaceutical, although aggressive pharmacological treatment of obesity may be harmful and should be pursued with caution) and to recognize the need to judge success not just by the numbers on the scale, but by the less tangible benefits that are being accrued, such as reduced risk of insulin resistance, hyperinsulinism, hypertension, androgen excess, and hyperlipidemia. Inevitably, the result of a successful multifactorial approach will be reduced risk of CAD.

Diabetes Mellitus

Macrovascular disease is the major cause of morbidity and mortality in Type 2 diabetes mellitus, the form of diabetes that accounts for 85% to 90% of all diabetic patients in the US. Hypertension, hyperlipidemia, and perhaps hyperinsulinemia—all of which can occur in these patients—play a powerful role in the risk of CAD.[70] Treatments that result in normalizing glucose levels, including exercise, diet, sulfonylureas, insulin sensitizers, and insulin, are beneficial to preventing catastrophic outcomes.

Individuals who have elevations of serum glucose have an increased risk of CVD that doubles when the elevation progresses to the level necessary to be diagnosed as Type 2 diabetes.[71] As glycohemoglobin increases, so does the risk of CAD, MI, lower-limb amputations, and death.[72-74]

The landmark study involving patients with Type 1 diabetes mellitus, the Diabetes Control and Complications Trial (DCCT)[75] ended 1 year earlier than originally planned because of the dramatic findings that a reduction of 1% in glycohemoglobin translated roughly

into a 50% reduction in microvascular complications such as retinopathy, nephropathy, and neuropathy. Not only was prevention demonstrated, but with improved blood sugar control, reversal of these complications was also seen. Macrovascular events were also reduced with improved glucose control, but did not reach statistical significance due to the small number of events.

In recognition of the need for adequate control of blood sugar due to its association with disease prevention, the ADA has published clinical practice recommendations for nonpregnant adults, along with a delineation of dangerously high glucose levels and the actions that could be taken to lower them (Table 4).[76]

It is important to put statistics in relevant terms to appreciate the magnitude of effect. A 1% point difference in hemoglobin A_1C is approximate to a 20 mg/dL difference in blood sugar levels. If this level of reduction results in a 15% protection from CAD death (an accepted estimate) that would mean that for every 1000 patients achieving this reduction for 12 years, 60 would remain disease free, and the 20 expected deaths in this group would not occur.[77]

Treatment of Type 2 diabetes mellitus is currently undergoing a type of revolution based on the explosion of knowledge regarding insulin-stimulated intracellular action. The current approach to treatment is diet and exercise followed by sulfonylurea therapy, insulin and/or metformin, and finally by troglitizone until adequate control is obtained. Advancing therapeutic intervention should be initiated every time the action points described in Table 4 are reached. There are drawbacks to this treatment hierarchy. In practice, only 15% of patients can achieve the target specified for fasting plasma glucose by diet alone. Of those who can, less than half continue to maintain normoglycemia for more than 1 year. When sulfonylureas are used, failures of 50% at onset and an additional 5% to 10% per year are reported. In the United Kingdom Prospective Diabetes Study Group trial,[77] patients treated with metformin exhibited a deterioration in blood sugar control after a 6-year period. Those on insulin therapy in this study started with insulin zinc suspension (Ultralente®) once daily in the evening, a common clinical practice used to lower elevated fasting glucoses. At the end of 6 years, 24% of these patients were on more complex insulin regimens and all noted significant weight gain.

When treating Type 2 diabetes mellitus, initial treatments should address the root cause of this disease—insulin resistance. It is ultimately more logical to use the insulin sensitizers, metformin and troglitazone, as initial therapies to prevent deterioration of diabetes control due to beta-cell decay. Metformin and troglitazone lower triglycerides and while the former lowers LDL-C levels, the latter exerts a positive effect by changing this lipid fraction from a small dense particle, which has been associated with CHD, to a fluffy floater type for which a CHD association is not seen. Troglitazone, which is currently approved by the FDA for the use of poorly controlled Type 2 diabetes, works by stimulating insulin effect and production of glucose transport proteins. This medication also lowers insulin production, which has a beneficial effect on lipids and blood pressure as well as theoretical beneficial effects on vascular smooth muscle cells.

Table 4. Glycemic Control for People with Diabetes

Biochemical Index (Laboratory Test)	Nondiabetic	Goal	Action Suggested*
Preprandial glucose (mg/dL)	<113	80 - 120	<80 >140
Bedtime glucose (mg/dL)	<120	100 - 140	<100 >160
Hemoglobin A_1C (%)†	<6	<7	>8

*Actions may include enhanced diabetes self-management education, comanagement with a diabetes team, referral to an endocrinologist, change in pharmacological agent, increased self-monitoring of blood glucose, or more frequent contact with the patient
†HgA_1C is referenced to a nondiabetic range of 4.0%-6.0% [76]

Conclusion

Attention to detail does not come easily in a stressful and cost-restrained world, but it is the detail of prevention that can best slow the progression of disease and induce regression—rather than infarction, angioplasty, bypass surgery, or death.[78]

Rational treatment programs for comorbid diseases are based on science, remembering that all interventions—educational, nutritional, and pharmaceutical—must always be tailored to the *individual.* Some therapies are universally beneficial, such as judicious diet and exercise, but because they involve lifestyle changes, these are difficult to enact.

Individual risk assessment is vital in attempting to attenuate or reverse cardiovascular disease. This task is a complex one and performance is variable among patients and between individual practitioners. The initial necessary treatment step that is common to all comorbid diseases is LDL-C reduction, a step that can be successfully accomplished with safety, efficacy, and in a cost-effective manner by using HMG-CoA inhibitors. When one or more risk factors are present, patients and physicians must be aggressive in treating them in order to achieve the endpoint both desire—prevention of disease. This common goal can only be achieved by offering, not withholding, treatment aimed at achieving established targets or goals. There is no such thing as a "borderline" or mild disease, only stages in a journey that if unaltered leads to an untimely and premature demise.

The story of comorbid diseases and their import and effective treatment is being continuously rewritten by researchers. The end of the story is a personal one and is decided upon by individual patients and their physicians. It is very much a reality that today these stories no longer need to have tragically premature endings . . . but this requires intervention. In view of the benefits that are possible, failure to intervene is no longer an acceptable option.

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CME QUESTIONS: TEST #0397S8

Long Island Jewish Medical Center and Johns Hopkins University School of Medicine are accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. Long Island Jewish Medical Center, the Long Island Campus for the Albert Einstein College of Medicine, designates this continuing medical education activity for 1.0 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association. This CME activity was planned and produced in accordance with the ACCME Essentials and Standards for Commercial Support.

Instructions

After reading this Special Report, select the best answer to each of the following questions. In order to receive 1 CME credit, at least 7 of the 10 answers must be correct. Estimated time for this activity is 1 hour. CME credits are distributed on a yearly basis.

1. Most patients (approximately 70%) would benefit from a reduction in LDL-C of:
a) at least 25%
b) 50% or less
c) 30% or less
d) 35% or less
e) at least 50%

2. The primary pharmacologic agents for the reduction of serum cholesterol are:
a) niacin or nicotinic acid
b) bile acid sequestrants
c) HMG-CoA reductase inhibitors
d) all of the above
e) b and c only

3. Recent major trials (since 1994) that confirm the benefit of lowering serum cholesterol include the:
a) Framingham Study, LRC-CPPT, and MRFIT
b) 4S, CARE, and WOSCOPS
c) Post-CABG and LCAS
d) all of the above
e) b and c only

4. It is important to be familiar with the findings of the recent lipid-lowering studies because they:
a) demonstrate that relying on diet and exercise to lower cholesterol is ultimately ineffective
b) point out that lipid-lowering therapies are not widely enough implemented
c) show that reducing LDL-C in patients with coronary heart disease (or those who are at risk for it) substantially decreases the risk of total mortality and the financial burden from cardiovascular disease
d) proved that HMG-CoA reductase inhibitors provide the only effective method of reducing serum cholesterol
e) showed that most patients with high levels of serum cholesterol should be initiated on pharmacologic therapies at the same time as diet and exercise

5. The two studies that found benefit in lowering LDL-cholesterol in patients with levels considered "normal" or statistically "average" for the US were the:
a) CARE and LCAS
b) WOSCOPS and Post-CABG
c) POSCH and 4S
d) MRFIT and LRC-CPPT
e) none of the above

6. The adult treatment guidelines of the National Cholesterol Education Program (NCEP) were established to recommend optimal cholesterol and lipid levels. NCEP guidelines, as outlined in this publication, recommend at least dietary intervention for:
a) patients who have coronary heart disease and an LDL-C level of >100 mg/dL
b) patients who don't have CHD, but have two or more CHD risk factors and an LDL-C level of >130 mg/dL
c) patients who don't have CHD and only one or no CHD risk factors, but have an LDL-C of >160 mg/dL
d) a and b only
e) a, b, and c

(CME QUESTIONS CONTINUED ON FOLLOWING PAGE)

CME TEST FORM
AJMC Test #0397S8

The Treatment of Hypercholesterolemia: A Managed Care Perspective

Application for 1 Credit Hour of AMA Category I

(Test valid through September 30, 1998. No credit will be given after this date.)

Please circle your answers:

1.	**a**	**b**	**c**	**d**	**e**
2.	**a**	**b**	**c**	**d**	**e**
3.	**a**	**b**	**c**	**d**	**e**
4.	**a**	**b**	**c**	**d**	**e**
5.	**a**	**b**	**c**	**d**	**e**
6.	**a**	**b**	**c**	**d**	**e**
7.	**a**	**b**	**c**	**d**	**e**
8.	**a**	**b**	**c**	**d**	**e**
9.	**a**	**b**	**c**	**d**	**e**
10.	**a**	**b**	**c**	**d**	**e**

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PROGRAM EVALUATION

Long Island Jewish Medical Center and Johns Hopkins University School of Medicine would like to have your opinion. Please fill out the questionnaire below, tear off along the dotted line, and mail along with your CME test form. We thank you for your evaluation, which is most helpful.

On the whole, how do you rate the information presented in the article?

____ excellent ____ good ____ fair ____ poor

Is the information presented useful in your practice?

____ yes ____ no

Comments:

_____

Do you have recommendations to improve this program?

____ yes ____ no

Comments:

_____

Were any portions of this program unsatisfactory or inappropriate?

____ yes ____ no

If so, which?

_____

Do you find the information presented in these articles to be fair, objective, and balanced?

____ yes ____ no

Is there subject matter you would like included in the future?

____ yes ____ no

Comments:

_____

In your opinion, were the authors biased in their discussion of any commercial product or service?

____ yes ____ no

Comments:

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Program Evaluation

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Physician Name

_____

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_____

Specialty

(CME QUESTIONS CONTINUED FROM PREVIOUS PAGE)

7. The NCEP guidelines recommend these target LDL-C goals:

a) ≤100 mg/dL for patients with CHD; <130 mg/dL for men over 45 and women over 55; <160 mg/dL for patients who have no CHD risk factors
b) ≤100 mg/dL for patients with CHD; <130 mg/dL for patients with no CHD but two or more risk factors; <160 mg/dL for patients with no CHD and one or no risk factors
c) <110 mg dL for patients with suspected CHD; ≤130 mg/dL for patients who have an LDL-C of >210; <160 for patients with no CHD risk factors
d) 90 - 100 mg/dL for patients who have experienced an MI; <120 for patients who have hypertension or who smoke; ≤140 mg/dL for patients who have a family history of CHD
e) <100 mg/dL for patients with CHD; <130 mg/dL for all other patients who have an LDL-C level of ≥190 mg/dL

8. In addition to high LDL-C levels, other recognized risk factors for CHD include:

a) having a high-stress lifestyle, excessive sodium intake, and being over the age of 45
b) hypertension, diabetes, and smoking
c) having a low HDL-C level, being a man over 45 or a woman over 55, and having a family history of premature CHD
d) all of the above
e) b and c only

9. Cost effectiveness, an important factor in selecting drug therapies, can be determined by evaluating:

a) acquisition cost and efficacy
b) compliance and YOLS
c) cost-identification analysis and cost-benefit analysis
d) all of the above
e) a only

10. Treating comorbid diseases can lessen the risk for CHD. Some of the most prevalent comorbid diseases that can increase the risk of CHD include:

a) hypertension, tobaccoism, diabetes, and bacterial infections
b) renal impairment, obesity, hyperthyroidism, hypoglycemia, and hypertriglyceridemia
c) low levels of serotonin, and premature menopause
d) nephropathy, peripheral vascular disease, smoking, and hyperhomocysteinemia
e) hypertension, insulin resistance, obesity, polycystic ovary syndrome, diabetes mellitus, hypothyroidism, menopause, and smoking