CHAPTER 1

CHOLESTEROL DRUGS ARE UNNECESSARY

IT IS virtually impossible to go a day without being reminded of the relationship of heart disease and high cholesterol levels. While walking through grocery store aisles, you are hit with a variety of no-cholesterol, low-fat foods. Simply reading a magazine or watching television will expose you to advertisements warning of the dangers of high cholesterol resulting from diet or from poor genes. Drugs to treat high cholesterol, commonly known as statins, are the most highly prescribed drugs in history. Even the spokespeople for statin drugs, such as the inventor of the artificial heart, Dr. Robert Jarvik, have become highly scrutinized.

And yet, a little over 20 years ago, the relationship between heart disease and high cholesterol levels was unproven and largely ignored.[1] In fact, in 1989 *The Atlantic Monthly* featured an article entitled "The Cholesterol Myth," which said: "Lowering your cholesterol is next to impossible with diet, and often dangerous with drugs—and it will not make you live any longer."[2] Furthermore, if you had a total cholesterol level of 300 mg/deciliter (dL), you were considered to be on the upper end of normal. And no one had a clue as to their own relative ratios of high-density lipoproteins (HDL), the so-called "good" cholesterol, and low-density lipoproteins (LDL), the "bad" cholesterol. This began to change in the 1980s with the publication of a number of studies that began to provide concrete evidence that there was truly a causative role for cholesterol and particularly LDL cholesterol in heart attacks and strokes. One such study was the Framingham Heart Study.

This landmark study has been ongoing since 1948. It has been administered by the National Heart, Lung and Blood Institute of the NIH and was begun with over 5000 adults from Framingham, Massachusetts. Studying this population for 25 years enabled the identification of a number of risk factors for identifying potential victims of heart disease. These factors included smoking, excess weight, lack of exercise, stress, hypertension, and a high total cholesterol/HDL ratio.[3] While some of these risk factors were already well-accepted, the Framingham Study provided strong evidence that abnormal lipids were also a major risk factor.

At the same time, the results of another major study appeared. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) studied the effects of lowering cholesterol levels in reducing heart disease in 3800 middle-aged

Drug Truths: Dispelling the Myths About Pharma R&D, by John L. LaMattina

asymptomatic men with high cholesterol.[4] These men were studied for seven years with half of the group on placebo and the other half on a compound called cholestyramine, a resin that acts as a bile acid sequestrant and thereby was known to lower cholesterol levels modestly. Both groups were on a moderate cholesterol-lowering diet. The results of this study proved convincing. The cholestyramine patients had their overall cholesterol lowered by 13% and their LDL cholesterol lowered by 20%, as compared to 5% and 8% for those on placebo. This lowering of cholesterol resulted in a 24% reduction in definite death due to heart disease, as well as reductions in heart attacks, angina, and coronary bypass surgeries. For the first time, proof was in hand that lowering total cholesterol and LDL cholesterol had a direct impact in reducing heart disease. These results were compelling enough that the NIH began to encourage physicians to teach patients about the importance of treating high cholesterol.[5]

While these data were encouraging, a major difficulty needed to be overcome. Cholestyramine was not a patient friendly medicine. Up to 20 grams of this drug needed to be taken in divided doses two to three times per day. These large doses tended to cause adverse gastrointestinal effects such as constipation, gas, and bloating. But the biggest hurdle for patients was taking the dose of medicine itself as it is an insoluble resin. It has been described as drinking liquid cement. Clearly, better-tolerated cholesterol-lowering medicines were needed.

At about this same time, a discovery was made that eventually revolutionized the treatment of heart disease. A Japanese microbiologist, Akira Endo at the Sankyo company in Tokyo, was searching fermentation broths of *Penicillium citrinum* for novel antimicrobial agents.[6] During this work he found a compound now known as compactin. This agent proved to be an inhibitor of an enzyme called HMG-CoA reductase. This enzyme is involved in the critical step in the body's synthesis of cholesterol. Ironically, compactin did not have useful antimicrobial activity. However, the potential for using this agent in controlling high cholesterol levels was recognized by Endo. Theoretically, if one could safely block the actions of HMG-CoA reductase, the biosynthesis of cholesterol would be reduced, thereby lowering total cholesterol.

Sankyo designed and managed a clinical trial to explore the effects of compactin in humans. This study showed that it did, in fact, effectively lower both total cholesterol and LDL cholesterol in patients who were genetically disposed to high plasma lipids.[7] Unfortunately, Sankyo had to suspend clinical trials with compactin due to unspecified adverse findings in animal studies.

Merck scientists were also actively pursuing this field of research, and their chemists discovered the HMG-CoA reductase inhibitor, lovastatin.[7] Lovastatin was shown to be safe in healthy volunteers and proved to be very effective in lowering total cholesterol and LDL cholesterol in patients with heart disease. The efficacy of lovastatin was elucidated by the Nobel Prize-winning work of Michael S. Brown and Joseph L. Goldstein, who showed that statins, by virtue of blockading cholesterol biosynthesis, improve the ability of the liver to remove LDL from the blood, thus making it less likely for LDL to deliver cholesterol to the artery wall.[8]

Lovastatin was launched by Merck under the trade name of Mevacor in 1987. They then followed this breakthrough with a superior statin, Zocor (generic name:

simvastatin) in 1991. Despite the availability of these two compounds, statins were still not universally prescribed in the early 1990s. The reason for this was twofold: First, physicians were reluctant to prescribe a drug that patients were to take for the rest of their lives without some assurances that long-term use of such drugs were indeed safe; second, while lowering cholesterol had beneficial effects in reducing the risk of heart disease, there was no evidence that long-term survival was enhanced. This all changed in 1994 with the publication of the results of the landmark Scandinavian Simvastatin Survival Study (4S).[9] In this study, 4444 patients who had a previous myocardial infarction and serum cholesterol of 215–310 mg/dL on a lipid-lowering diet were treated with either simvastatin or placebo for 5 years. Over this time period, simvastatin produced mean decreases of 25% in total cholesterol and 35% of LDL cholesterol. But more importantly, only 182 patients on simvastatin (out of 2221) had died as compared to 256 (out of 2223) on placebo—a statistically significant risk reduction of 30%. The controversy was over as was evidenced in an editorial in the *British Medical Journal* entitled "Lower Patients' Cholesterol Now."[10] Based on the 4S study and other examples, the authors concluded the following for patients with angina or with a previous myocardial infarction: "There is no longer any controversy about what to do for these patients and no justification for inertia."

Thus, by the mid-1990s the principle of lowering LDL cholesterol was established. Statins were by far the agents of choice to control high cholesterol. The safety and ease of administration of statins was such that these compounds became the biggest selling drugs of all time. But suddenly all of this was again challenged in 2008 with the announcement of the results of a clinical study known as ENHANCE.

ZETIA®: AN INHIBITOR OF DIETARY CHOLESTEROL ABSORPTION

Statins clearly are efficacious in lowering plasma cholesterol. However, one's cholesterol level is impacted not only by the body's synthesis of cholesterol but also by the amount of cholesterol and fat taken in through one's daily diet. Theoretically, a compound that could block the absorption of cholesterol in the digestive tract would lower plasma cholesterol.

Given that statins are so effective, why would one care about lowering cholesterol absorption in the gut? First of all, despite the tens of millions of people who are successfully treated with statins, not everyone can tolerate these drugs. A small minority of patients do experience side effects that prevent statin usage. This is not unusual. As will be discussed in subsequent chapters, *no* medication can be successfully used universally, not even aspirin. Thus, having an alternative to statins is important to those with high LDL cholesterol who cannot tolerate them. Second, in theory a cholesterol absorption inhibitor should be able to be used in combination with a statin because their mechanisms would be anticipated to be complementary. For those people with established heart disease and very high LDL cholesterol, the combination of a statin with a cholesterol absorption inhibitor could theoretically provide better control than a statin alone.

Scientists at Schering-Plough were successful in discovering and developing such a compound, namely, Zetia[11] (genetic name: ezetimibe). While not as potent as statins, Zetia lowers LDL cholesterol by 18% as a stand-alone agent. It was on the basis of this activity that the FDA approved Zetia.

It is important to note that, unlike the situation with cholestyramine, niacin, or statins, studies have not yet been published on the reduction of heart attacks or strokes with Zetia. The FDA approved Zetia on the basis of its ability to lower LDL cholesterol by more than 15%. Essentially, the FDA approved this drug on its effect on a surrogate marker. The FDA will give approval of new drugs on the basis of the drug's beneficial effect on well-established markers of disease. In the case of heart disease, given that the lowering of LDL cholesterol by three distinct mechanisms was shown to have great benefits for this sick population, the FDA established that novel lipid-lowering agents with unique mechanisms can also be approved provided that these agents lower LDL cholesterol by at least 15%. The FDA also requires that the manufacturer of such an agent conduct long-term studies post-approval to show the impact of this new compound on long-term outcomes such as heart attacks and strokes. However, given the strong scientific precedence in an area like this, it is felt that patients should have access to a compound that lowers LDL cholesterol in advance of the long-term outcome study results. Zetia certainly fit this paradigm.

The use of surrogate markers is not unique to the lipid-lowering field. For decades, high blood pressure has been used as a surrogate marker for heart disease and drugs have been approved solely for their ability to lower blood pressure in hypertensive patients. In the early treatment of AIDS, the FDA approved drugs on the basis of reducing the levels of human immunodeficiency virus (HIV), the virus that causes this disease. Improvements in bone mineral density scans are used as surrogates for osteoporosis. While long-term outcome studies are eventually required as ultimate proof of a drug's benefit, these can take 5–7 years to complete. Thus, surrogate markers, which are recognized and accepted by the medical community, are of value in bringing important new medicines to patients in a timely fashion.

VYTORIN® AND THE ENHANCE TRIAL

Although Zetia was an important medicine in its own right, Schering-Plough recognized that this agent would be combined with various statins. As part of their New Drug Application (NDA) filing, Schering-Plough included studies that combined Zetia with leading statins such as atorvastatin (Lipitor) and simvastatin (Zocor) to show that co-administration of Zetia was safe and that the LDL lowering of the combination was improved over the statin alone. Based on these data, it was obvious that there would be value in having a single pill that combined both types of agents. In recognition of this, Schering-Plough and Merck set up a joint venture to commercialize a new medicine that would combine this cholesterol absorption inhibitor with simvastatin. This new combination drug was called Vytorin,[12] and it was approved by the FDA in 2004.

The introduction of Vytorin was greeted with mixed reviews. Some physicians felt that the combination was a good idea. After all, evidence to date had supported the view that the lower one's LDL cholesterol was, the less likely the risk of cardiovascular disease would be. However, some cardiologists felt that there was no scientific evidence yet available to show that clinical events would be reduced using this combination as compared to using a statin alone. Until such information was in hand, these physicians felt that there was little need for Vytorin.

Schering-Plough and Merck recognized that full acceptance of Vytorin would not be realized unless such long-term cardiovascular outcome studies were successfully completed. And so, after the approval of Vytorin, a variety of studies were launched. One such study, IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial),[13] is a 5-year study involving 12,500 patients scheduled to be completed in 2011. It is designed to measure the effectiveness of Vytorin compared with simvastatin alone in reducing deaths due to any cardiovascular event.

Given that it will be years before the results of this study will be available, the joint venture has conducted other studies to attempt to show the value of the combination. One of these studies is the "Effect of Ezetimibe plus Simvastatin versus Simvastatin Alone on Atherosclerosis in the Carotid Artery" trial, commonly referred to as ENHANCE. The ENHANCE trial involved 720 patients with a relatively rare disease called heterozygous familial hypercholesterolemia (HeFH). Patients with HeFH have a reduced ability to remove LDL cholesterol from their circulation. As a result, they have LDL levels in excess of 400 mg/dL and are at high risk of atherosclerosis.

Approximately one person in 500 has HeFH. ENHANCE was an "imaging trial"—that is, a trial that didn't measure reduction of cardiovascular events but a trial that measured the thickness of the carotid arteries using vascular ultrasound. Theoretically, one would hope that the following scenario would occur:

1. The combination of a cholesterol absorption inhibitor with a statin (i.e., Vytorin) would provide greater LDL lowering than a statin alone.
2. This enhanced LDL lowering would result in less atherosclerosis in HeFH patients.
3. Less atherosclerosis would be a predictor of fewer heart attacks and strokes over an extended period of time.

That was the hope for ENHANCE. Unfortunately, science isn't always this straightforward. Analysis of the 30,000 ultrasound carotid artery images taken from these 720 patients proved more difficult than originally envisioned by the investigators, thereby delaying the final report of the ENHANCE results. This resulted in a great deal of speculation about the study and its outcome. As a result, Merck/Schering-Plough took the unusual step of issuing a press release[14] in advance of publishing the data. The press release indicated that there was no difference in the carotid arteries of patients on Vytorin versus those on simvastatin alone, despite the fact that after 2 years the Vytorin group had LDL cholesterol reductions of 58% as compared to 41% for simvastatin. The full results of the ENHANCE trial have subsequently been published.[15]

This announcement set off a firestorm in the press. In an article on January 17, 2008 the *New York Times* proclaimed "cholesterol as a danger has its skeptics" and "cholesterol as a danger is being reassessed." [16] *Business Week* ran a major story[17] asking "Do Cholesterol Drugs Do Any Good?" The thrust of this article was the following: "Research suggests that, except among high-risk heart patients, the benefits of statins such as Lipitor are overstated."

Amazingly, the results of a single study in a small subset of patients with a rare condition called into question hundreds of studies carried out using many different medicines over decades of research. A commentary[18] in the *Journal of the American Medical Association* by Greenland and Lloyd-Jones put it this way:

> It (ENHANCE) has proved an opportunity for much misinformation to circulate in the public media including articles questioning the entire validity of cholesterol lowering despite overwhelming evidence to support the concept as a cornerstone of cardiovascular disease prevention.

So why didn't the patients on Vytorin in the ENHANCE trial have a reduction in carotid artery intima wall thickness despite having a greater reduction in LDL cholesterol? No obvious answer currently exists. It could be that the extra LDL cholesterol lowering that results from adding a cholesterol absorption inhibitor to a statin has no effect on slowing or reversing artery thickness. It could be that this patient group, which had been on multiple years of statin therapy, had already experienced the maximum benefits on the artery wall. Regardless of what occurred in this study, the ultimate answer as to whether Vytorin adds benefit over statin therapy alone won't be answered until the results of the long-term cardiovascular outcome study (IMPROVE-IT) are made available in 2011.

ENHANCE was a surrogate marker trial that did little to teach the world anything new about preventing heart attacks. One could question, as Greenland and Lloyd-Jones have done, why the sponsors chose to run such a study. However, for the press to challenge a key part of current treatment paradigms for heart disease borders on irresponsibility. By calling into question the cholesterol hypothesis, one wonders how much damage has been done. Will patients not fill prescriptions given to them by their physicians because they feel that concerns about high LDL cholesterol are overblown? Will patients stop their medications because they feel that they are not getting any protection from them?

Ironically, this controversy is coming at a time when health care providers should be reveling in the progress that has been made in reducing deaths due to cardiovascular disease. Data compiled by the American Heart Association (Figure 1.1) shows that annual increases in cardiovascular deaths that were seen for the greater part of the twentieth century have been reversed in the last 25 years. This reversal can be attributed to a number of factors: improved diagnosis and treatment, better understanding of risk factors thanks to the Framingham Study, reductions in smoking, people watching their diets and exercising more, and so on. But it would be foolish to ignore the benefits that cholesterol-lowering drugs, particularly statins, have made in this great medical story.

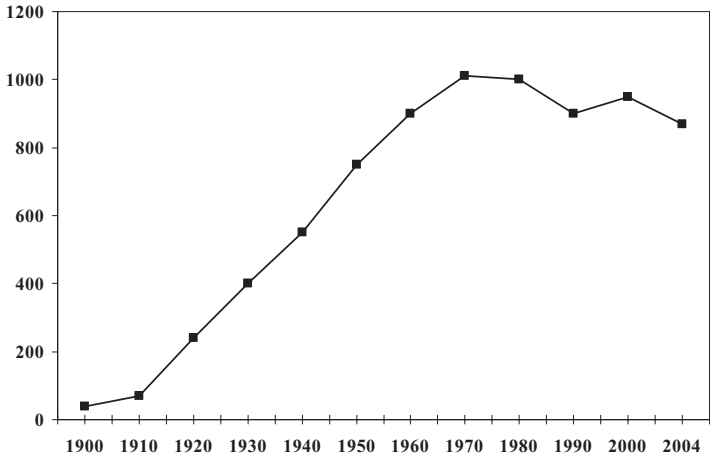
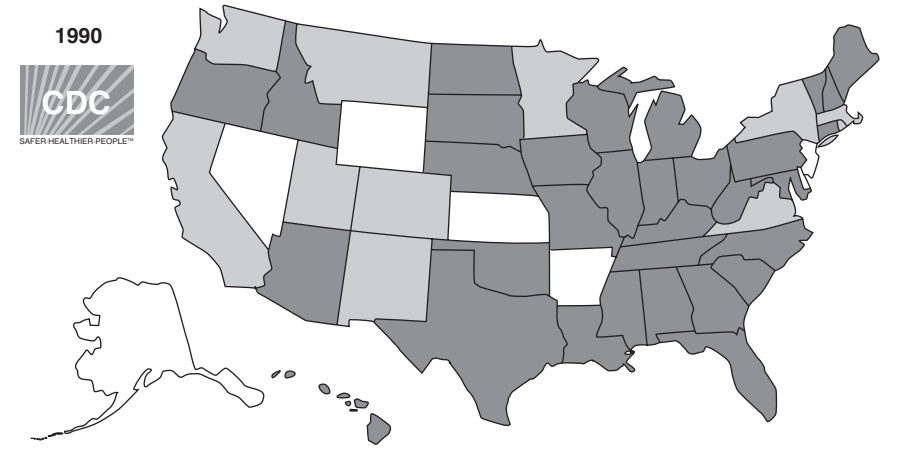


Figure 1.1 Deaths from cardiovascular disease in thousands, United States 1900–2004.

However, it is entirely possible that the progress made in lowering deaths due to cardiovascular disease will be minimized and maybe even reversed in the coming decades. The reason for this is the growing obesity epidemic that is occurring in the Western world, particularly in the United States. Epidemiology studies have shown that increased obesity in any population leads to an increase in type 2 diabetes. This, in turn, leads to an increase in deaths due to heart attacks and strokes. Unfortunately, obesity is growing at an alarming rate in the United States. The Center for Disease Control has been collecting data for obesity trends since 1985 using the Behavioral Risk Factor Surveillance System (BRFSS).[19] Obesity is defined as those people with a body mass index (BMI) of 30 or higher. To put this into perspective, a person who stands 5 feet 4 inches with a BMI of 30 would weigh 175 pounds. These data are collected from each state on an annual basis through a series of monthly telephone interviews with U.S. adults. The results from the BRFSS are jarring. In 1990, no state had an obesity prevalence of 15% or greater. The numbers were quite different in 2006, when it was found that 22 states had an obesity prevalence of greater than 25% and that two of these, Mississippi and West Virginia, had a prevalence of greater than 30% (Figure 1.2)!

As would be expected, as obesity has increased across the United States, so has diabetes. By 2005, there were 11 states that had at least 8% of their population with diabetes—a far greater prevalence than was the situation in 1994 (Figure 1.3). Cardiovascular disease increases are surely to follow.

Let's turn back to John Carey's article "Do Cholesterol Drugs Do Any Good?" Carey makes a very important point: "For anyone worried about heart disease, the first step should always be a better diet and increased physical activity. Do that, and we could cut the number of people at risk so dramatically that far fewer drugs would be needed." This is correct and everyone—physicians, health care providers, employers, and governments—should be pushing people to do this. But the fact is that



(a)

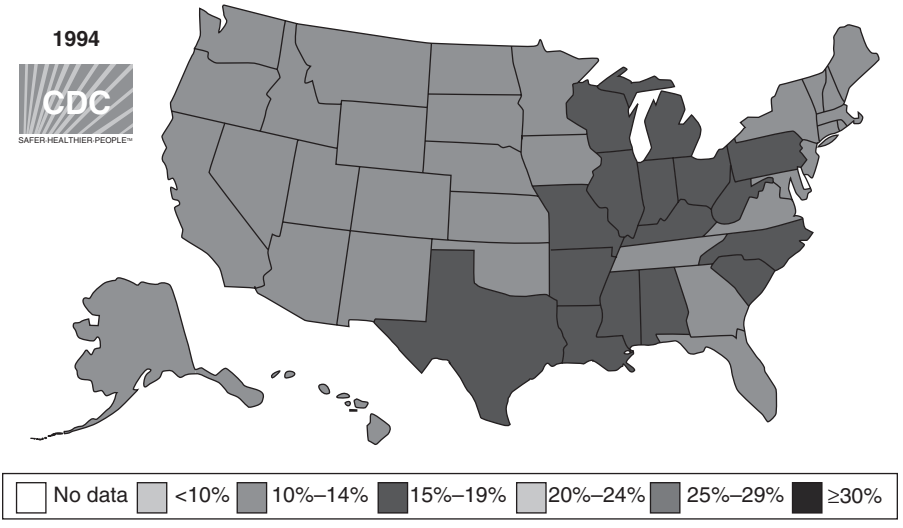


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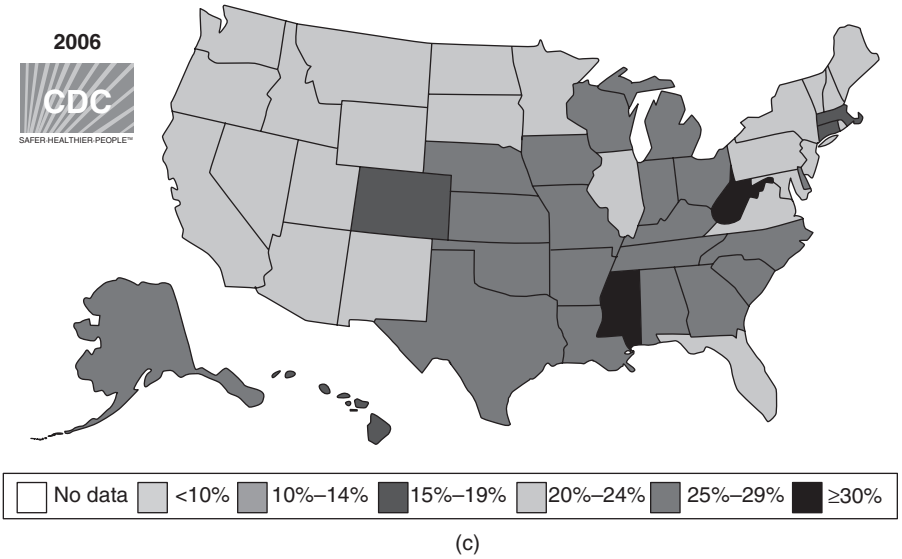
Figure 1.2 U.S. obesity prevalence: (a) 1990, (b) 1994, (c) 2006. Population with a body mass index of 30 or greater. See color insert.

effects of the obesity–diabetes–heart disease progression is going to last for decades. And this leads to a major problem in Carey's article: that only people with established heart disease should take cholesterol-lowering drugs. There is a flaw in adopting such a position. It is true that the studies which prove that reducing LDL cholesterol leads to a reduced risk of heart attacks and strokes have been done in



(c)

Figure 1.2 continued

people with documented heart disease and not in people without such documented evidence. There is a simple reason for this. Atherosclerosis is not a disease that comes on suddenly; rather, it develops over the course of decades. The long-term studies carried out with statins, despite the fact that these studies were done in people with proven disease, took as many as 5 years to complete in order to show a meaningful benefit in terms of reducing heart attacks and strokes. To show the long-term benefit of statin therapy in a young and asymptomatic population would require a decade-long trial that would be prohibitive to execute due to cost and scale. Furthermore, one might argue that the Framingham Study has already provided enough proof that reduced LDL cholesterol levels are directly related to reduced cardiovascular disease in people without documented heart disease. Finally, many people with heart disease have no symptoms until they have their first heart attack or stroke. And many times such an event is fatal. Should we be waiting for this to occur before using statins to treat people with multiple risk factors?

This brings us back to the ENHANCE trial results. Greenland and Lloyd-Jones in their *JAMA* commentary[18] make the point that "no result for the ENHANCE trial could have had any scientific or clinical importance. …" This is because ENHANCE was not designed to measure reduction of cardiovascular events but rather to measure the effect of Vytorin on a surrogate marker, a measure of carotid artery thickness. Any meaningful clinical result for Vytorin will come from a long-term trial such as IMPROVE-IT, which measures impact of this drug on heart attacks and strokes.

It is unfortunate that the media coverage of the ENHANCE trial called into question the importance of lowering LDL cholesterol. These reports confused patients and will undoubtedly lead to fewer people taking much needed medication.

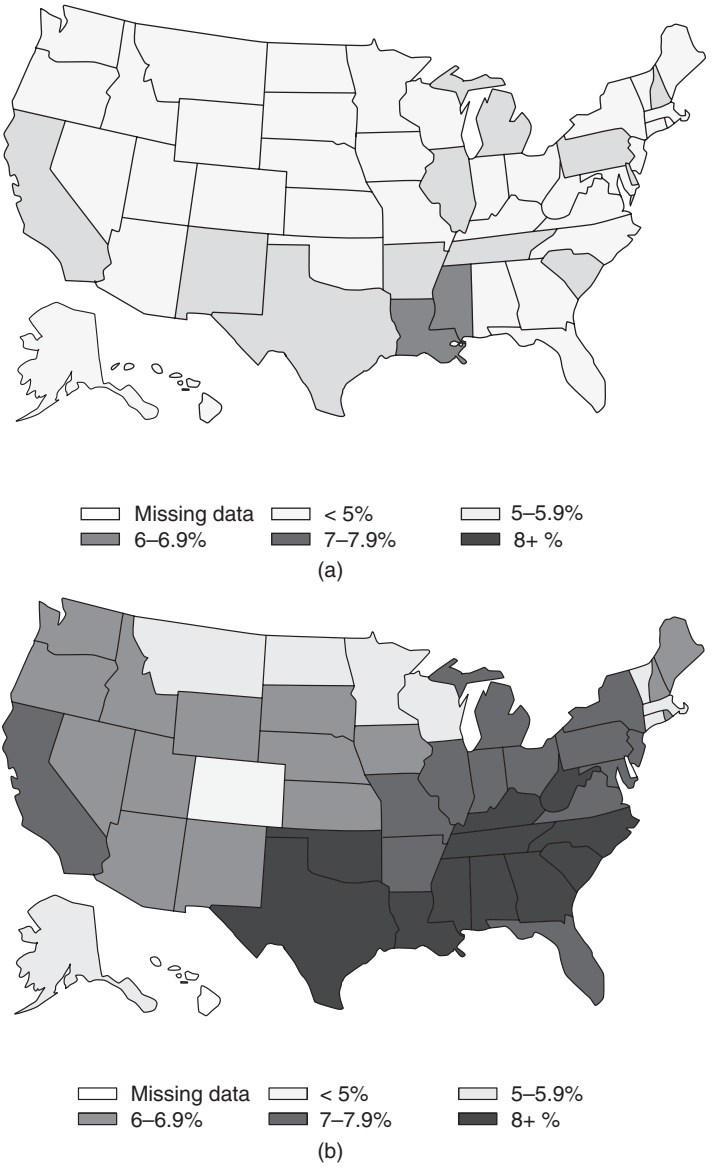


Figure 1.3 U.S. diabetes prevalence: (a) 1994 and (b) 2005. Percentage of the population with diabetes. See color insert.

Preventative medicine—be it improved diets, exercise, stopping smoking, or drugs to reduce high blood pressure and cholesterol—is critical to reducing the onslaught of cardiovascular disease that we can potentially witness in the future. Cholesterol drugs *are* necessary.