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Rationale and Public Health Implications of Changing CHD Risk Factor Definitions

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Key Words

risk factors, heart disease, prehypertension, impaired fasting glucose, JNC VII, ATP III

Abstract

The definition of disease is central to the practice of medicine and to public health policy. Practice guidelines set standards for disease identification and treatment. Quality care is often defined as adherence to these guidelines. Over the past few years, the diagnostic thresholds for several common medical conditions have been lowered, resulting in a substantial expansion in the market for health care. The most recent guidelines for high blood pressure, high cholesterol, and impaired fasting glucose each define a high percentage of the adult population as in need of regular medical attention. Under the latest proposed thresholds, virtually the entire adult population qualifies for a chronic condition diagnosis. We evaluate the health and financial outcomes associated with changes in diagnostic thresholds for the prevention of three risk factors for cardiovascular disease and stroke: blood pressure, serum cholesterol, and fasting plasma glucose. Estimates of the numbers of people affected, the cost implications, and the overall public health consequences are offered.

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INTRODUCTION

In 1992 Rose published *The Strategy of Preventive Medicine* (71). Many consider the book to be one of the most important statements about epidemiology and public health produced in the twentieth century. Rose noted that there is a systematic relationship between risk factors for coronary heart disease (CHD) and poor health outcomes. For example, the relationship between systolic blood pressure and both CHD and stroke moves systematically upward with systolic blood pressures above 115 mm Hg (30, 38). Similarly, the Medical Research Foundation/British Heart Foundation (MRC/BHF) heart protection study demonstrated that lowering LDL cholesterol using simvastatin (Zocor®) reduced the development of vascular disease independent of the initial levels of serum cholesterol (10).

Rose argued that only small portions of cardiovascular events occur in those with risk factor scores above typical therapeutic thresholds. For example, in comparison to those with a systolic blood pressure less than 120 mm Hg, only ~24% of the excess deaths from stroke occur in patients with systolic blood pressures higher than 160 mm/Hg (59). The great majority of cases of CHD and stroke occur in patients with risk factor scores below the therapeutic threshold. According to Rose (70), too much attention has been devoted to case identification and treatment, and not enough attention has been paid to shifting the entire distribution of blood pressure and cholesterol downward. A population-based intervention that shifts the distribution of blood pressure toward the left will have greater impact on population health than will targeted screening (59). This argument forms the basis for population-based preventive medicine.

Rose argued that population-based preventive measures must meet several criteria. First, they must be low cost. Second, they must be minimally invasive. Any intervention applied to an entire population must produce as little pain and discomfort as possible. Rose urged the use of public health approaches to the management of CHD risk factors. He did not argue for changing the diagnostic threshold for treating disease, nor did he advocate for the use of high-cost pharmaceutical products (71). Nevertheless, Rose's arguments have been used to justify more aggressive treatment of CHD risk factors using expensive pharmaceutical interventions (5, 49). In the following section, we consider the rationale for changing thresholds for the initiation of treatment.

CHANGING DISEASE DEFINITIONS

Over the past few years, the diagnostic thresholds for several common medical conditions have been lowered, resulting in a substantial expansion in the market for health care (36, 53). For example, the most recent guidelines for high cholesterol (32) and high blood pressure (21) each define most of the older adult population as in need of regular medical attention. One analysis published in 1999 suggested that three quarters of the adult population now qualify for a chronic disease diagnosis (73). In the past few years, proposals have emerged to lower disease thresholds even further. Under the latest proposed thresholds, virtually the entire adult population qualifies for a chronic condition diagnosis (42).

The purpose of this chapter is to evaluate what is known about the health and financial outcomes associated with changes in diagnostic thresholds for the prevention of cardiovascular disease and stroke. Benefits include increased life expectancy and improved quality of life associated with early detection. They also include dollar savings leading to other spending opportunities and improved health outcome. Harms include consequences of treatment resulting from side effects and the potentially damaging effects of labeling. Financial harms could include dollars spent, reducing opportunities to invest in other programs that might have a greater

potential to enhance public health. To evaluate these issues, we consider three case studies: blood pressure, serum cholesterol, and fasting plasma glucose.

EXAMPLE 1: PRE-HYPERTENSION

Hypertension is a major public health problem. According to a variety of data sets, ~24% of the adult population have prevalent hypertension under the current definition as systolic blood pressure (SBP) > 140 or diastolic blood pressure (DBP) > 90 mm Hg (16). Using population surveys, the proportion of the population with hypertension has remained stable over the past 40 years. Between 1970 and 2000, the proportion of the population aware that they had hypertension, treated for high blood pressure, and with blood pressure controlled systematically increased (89). Changing the diagnostic threshold for hypertension from 160/95 to 140/90 approximately doubled the number of cases (82).

The National Heart Lung and Blood Institute (NHLBI) has administered the National High Blood Pressure Education Program (NHBPEP) for more than three decades. In May 2003, the commission released its seventh national report, known as Joint National Committee (JNC) VII (21). Successive JNC reports have pushed for lower diagnostic thresholds for high blood pressure. JNC VI defined high-normal blood pressure as SBP = 130–139 mm Hg and DBP = 85–89 mm Hg. JNC VII goes a step further by defining a new condition known as prehypertension. Individuals in this category have a SBP of 120–139 mm Hg or a DBP of 80–89 mm Hg (21).

On the surface, the rationale for creating the new category of prehypertension is compelling. Epidemiologic studies of adults between the ages of 40 and 70 years suggest that each increase in SBP of 20 mm Hg and each increase in DBP of 10 mm Hg results in a doubling of cardiovasular disease (CVD) risk, except for those with blood pressures lower than 115/75 mm Hg (51). The report argued that management of blood pressure using medication results in 40% reduction in the incidence of stroke, a 25% reduction in the incidence of myocardial infarction (MI), and a 50% reduction in the incidence of heart failure (64). However, large clinical trials have not shown benefits for lowering high-normal to optimal blood pressure.

SBP: systolic blood pressure

DBP: diastolic blood pressure

The rationale for the JNC VII definition of prehypertension was that people with moderately high blood pressure are at increased risk for heart attack and stroke just as those with very high blood pressure are. The most important piece of evidence supporting the rationale came from the Prospective Studies Collaborative. This group performed a meta-analysis of 61 studies involving more than one million adults. The results of the meta-analysis are summarized in **Figure 1**. The graph shows the relationship between SBP and stroke and the relationship between DBP and stroke. The four lines on the left and right of the figure are for different age groups. There appears to be a linear relationship between blood pressure and stroke. Concerning DBP, for example, the benefit one gains from reducing blood pressure by 5 mm Hg is the same for people whose initial values are very high, for example, higher than 100 mm Hg, and for those who are initially low, for instance, 75 mm Hg.

Although the Prospective Studies Collaborative suggests a linear relationship between blood pressure and stoke, it is important to examine **Figure 1** in more detail. Two features are important. First, values closer to normal (i.e., DBP 70 mm Hg) are actually above the diagonal. The Prospective Collaborative investigators simply decided to ignore these points in their curve-fitting exercise. The most important feature of **Figure 1** is that the y-axis is a logarithmic rather than a linear scale. The relationship between blood pressure and stroke is approximately log-linear rather than linear. Each point on the y-axis is twice as large as the preceding point.

To gain a better understanding of the relationships, we redrew the SBP portion of

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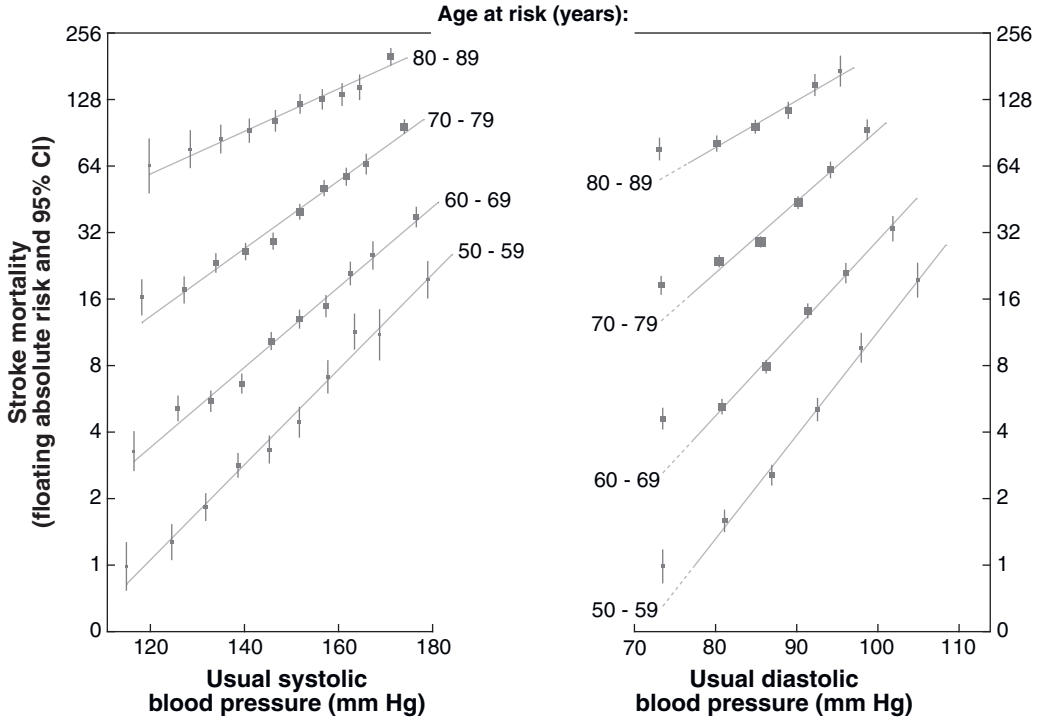

Figure 1

Blood pressure and the risk of stroke. From Reference 51. Reproduced by permission of the *Lancet*.

Figure 1. The revised graph is shown as **Figure 2**. The difference between the two graphs is that our figure uses ordinary units on the y-axis. The most striking feature in the redrawn graph is that the inflection point is at about 90 mm Hg, at which the probability of stroke rises more steeply. The relationships are quite similar for SBP (not shown). For the lower age groups, the relationship between SBP and stroke is quite flat up to ~140 mm Hg. These results are consistent with most articles previously published in the literature. For example, Neaton & Wentworth (65) also found log-linear relationships between SBP/DBP and death from CHD using data from 316,099 white male participants in the Multiple Risk Factor Intervention Trial. The MRC trial in mild hypertension showed threshold values for both coronary event and stroke at ~150 mm Hg (61). This log-linear relationship has been confirmed in a variety of populations, including studies in Asia (50). In other words, the probability of stroke is not linearly related to blood pressure. In fact, the previous thresholds for initiation of treatment at 140 mm Hg for SBP or 90 mm Hg for DBP appear to have a clear rationale.

We fit third-degree polynomials to the curves and estimated the differences in absolute risk of stroke mortality in 5–10-year intervals on the basis of these data. The fits for the polynomials were excellent (all above $R^2 = 0.99$). These fit polynomials are shown in **Figure 2**. A 50- to 59-year-old who lowers DBP from 84 to 79 reduces his risk of stroke from 0.0026 to 0.0021 (about 5 chances per 10,000). However, a person the same age who reduces DBP from 110 to 105 experiences a risk change from 0.0084 to 0.0066 (about 2 chances per 1000). The benefit for those who

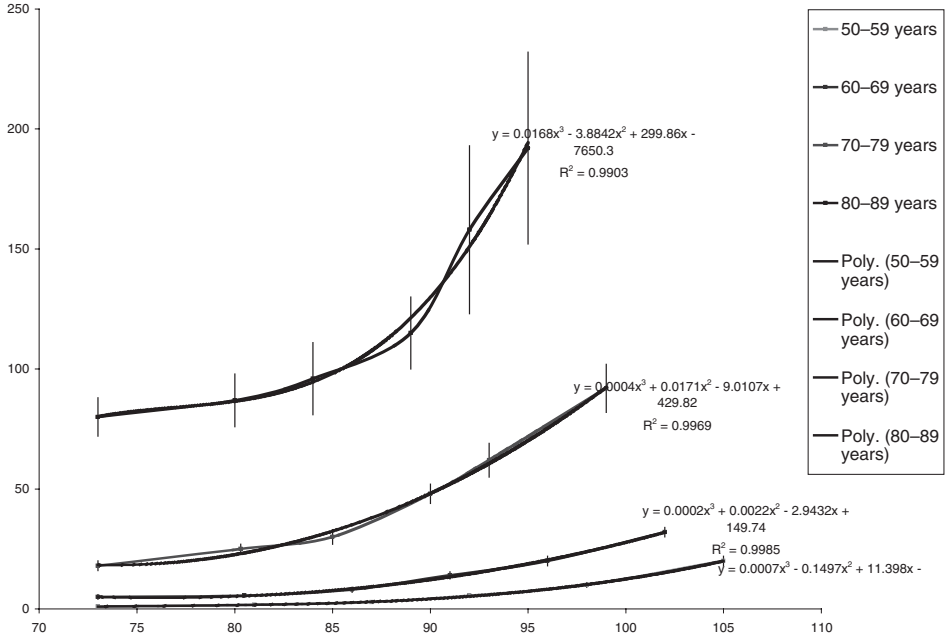

Figure 2

Redraw of the relationship between diastolic blood pressure and probability of stroke mortality using natural units on the Y axis. For each age group the second curve was fit using a third-degree polynomial.

start at high risk is much larger. The goal of therapy is to normalize blood pressure. An 80- to 89-year-old who reduces DBP from 85 to 79 experiences a risk reduction for stroke from 0.0091 to 0.0081. However, the 80- to 89-year-old who normalizes DBP to 79 mm Hg from a starting point of 110 experiences a risk reduction from 0.0696 to 0.0081 (more than eightfold). Benefits of therapy are much stronger for those who begin at higher risk.

Another concern about the treatment of people with mild-spectrum hypertension is that few clinical trials have evaluated people who have prehypertension but do not have other risk factors. **Table 1** summarizes a sampling of studies that have often been cited as supporting aggressive management of blood pressure. The few studies that included participants with relatively normal blood pressure focused on patients with other CHD risk factors, including established coronary disease, diabetes mellitus, and renal disease. There are few studies of people in the prehypertensive range who do not exhibit other risk factors. The one exception is the Trial of Preventing Hypertension (TROPHY) (40). In this trial, 409 adults with SBP between 130 and 139 mm Hg and DBP < 89 or DBP between 85 and 89 mm Hg and SBP < 139 mm Hg were randomly assigned to an angiotensin-receptor blocker (ARB) or to a placebo. The placebo group was significantly more likely to progress to hypertension and to experience serious adverse events over the next four years.

HOW MANY PEOPLE WILL BE AFFECTED BY THE NEW GUIDELINES?

Using simulation techniques, we estimated the impact of lowering diagnostic thresholds upon population health status. A variety of assumptions were used to create these models. First, the population distribution of blood pressure was estimated using data from the Third National Health and Nutrition Examination Survey (NHANES III). NHANES III was conducted between 1999 and 2002 by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC). The purpose of the survey was to evaluate the health and nutritional status of

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Table 1 Characteristics of participants in selected studies of hypertension treatment

Study	Sample size	Predominate risk factor	Blood pressure at baseline
Hypertension Detection and Follow-up Program (3)	10,940	Hypertensive, but not on medication	All DBPs >90 and <104 mm Hg
Prospective Randomized Evaluation of the Prospective Ransomized Evaluation of the Vascular Effects of Norvasc Trial (PRE-VENT)(17)	825	History of CV complications	129/79 mm Hg (34% measured while on medication)
African American Study of Kidney Disease and Hypertension (AASK)(90)	1094 (all African American ages 18–70	1094 hypertensive renal disease	150/95 mm Hg
Irbesartan Diabetic Nephropathy Trial LIFE(52)	9193	Hypertensive patients with nephropathy due to type 2 diabetes	174/98 mm Hg
Appropriate Blood Pressure Control in Diabetes Trial (ABCD)(26)	480	All subjects had diabetes mellitus	136/84 mm Hg
Diabetes, hypertension, microalbuminuria or proteinuria, cardiovascular events, and ramipril (DIABHYCAR)(55, 60)	4912	All subjects had diabetes mellitus	146/83 mm Hg
Hypertension in the Very Elderly Trial (HYVET)(15)	1283 (all elderly)	Previous hypertension	181/100
The Irbesartan Type II Diabetic Nephropathy Trial (IDNT2)(68, 69)	1715	All subjects had diabetes mellitus and renal disease	159/87
NIsoldipine in COronary artery disease in LEuven (NICOLE)(24)	819	All subjects had established coronary disease and underwent PTCA	129/78
Treatment of Mild Hypertension Study (TOMHS) (54)	844	All subjects had mild hypertension, defined as DBP 90–99 mm Hg without medication or 85–99 mm Hg if using medications	140/91
Trial of Preventing Hypertension (TROPHY)(40)	772	56% had total cholesterol values >200 mg/dl, 38% had triglycerides 150 mg/dl	134/84

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the civilian noninstitutionalized population of the United States. The study uses a national sample of ~34,000 people 2 months of age or older. In addition to household interviews, 73% of the sample had blood drawn and underwent physical examination. Our analysis focused on ~20,000 men and women aged 17 years or older for whom physical examination data were available.

Figure 3 shows the distribution of SBP in the U.S. population. This distribution is relatively normal. We estimated that ~4% of the population is in the highest risk category with SBP greater than 160 mm Hg. About 14% of participants had SBPgreater than 140 mm Hg. However, using the new definition of prehypertension, nearly 60% qualify for a diagnosis. Furthermore, this number goes up systematically with age. Using either current medication user, SBP > 120 mm Hg, or DBP > 80 mm Hg, more than 90% of those older than 65 have hypertension or prehypertension. These analyses are consistent with Wang & Wang (87) who independently reported that 58.2% of the total adult population is eligible for a diagnosis of prehypertension or hypertension and 88.3% of those older than 60 may fall into this category.

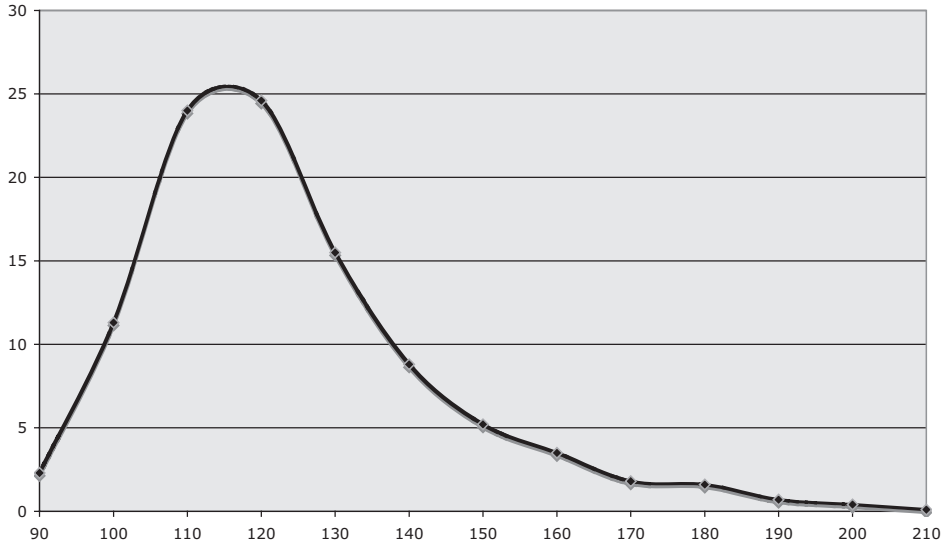

Figure 3

Distribution of systolic blood pressure from NHANES III.

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HOW MANY WILL PROGRESS TO CARDIOVASCULAR DISEASE?

Progression from prehypertension to actual hypertension has been investigated in the Framingham cohort for different age groups (35–64 and 65–94) (83). After adjusting for sex, age, body-mass index, baseline examinations, and baseline SBP and DBP, individuals with SBP between 130 to 139 or DBP between 85 to 89 progressed to hypertension after 4 years in 37.3% of those aged 35 to 64 and 49.5% of those aged 65 to 94. Individuals with SBP between 120 to 129 or SBP between 80 to 84 progressed to hypertension after 4 years in 17.6% of those aged 35 to 64 and 25.5% of those aged 65 to 94. Of note, 20% to 30% of individuals with blood pressure in the prehypertension range spontaneously reduced their blood pressure to normal.

It is interesting to consider the results of the TROPHY clinical trial in light of these observational data. In the TROPHY trial, the rate of progression from prehypertension to hypertension was significantly higher in the placebo group (63%) than would be expected on the basis of observational data. The rate of progression in the treated group (53%) is closer to what observational studies would suggest (40).

Hypertension leads to increased risk of stroke and CHD. MacMahon and colleagues pooled the results from seven observational studies with stroke outcomes and nine observational studies on CHD outcomes in hypertensive patients. The relative risk of stroke began to increase systematically with DBP exceeding 91 mm Hg. Those at 105 mm Hg were nearly 3.5 times more likely to experience stroke than were those at 90 mm Hg or lower. Similarly, the risks for CHD increased to more than 2.0 for those with DBP of 105 mm Hg or higher (58).

Whereas the Joint National Commission on high blood pressure noted that aggressive treatment of high blood pressure coincided with significant declines in stroke between 1960 and 1990 (4), the evidence about the effectiveness of aggressive management of high blood pressure is not so clear. For example, the decrease in strokes exceeds what would be expected given studies on the effects of blood

pressure control. One analysis pooled results from nine clinical trials and noted that a 5.6-mm-Hg decrease in DBP was associated with a 38% decrease in stroke. Between 1970 and 1980 there was a ~1 mm Hg/year decline in DBP, which should have resulted in an ~18% decrease in stroke. However, the actual observed decline was 43% (48). The Minnesota Heart Study showed significant annual declines in stroke over the course of time, but the decline in stroke was uncorrelated with hypertension in their population (57). Ivanovic and colleagues (39) used insurance records to compare policy holders who had equivalent blood pressure but were either treated or not treated for hypertension. Those treated for hypertension were significantly more likely to die during the following 5.2 years (39). It remains unclear whether the decline in stroke is associated with better control of blood pressure. Other public health measures may be responsible for the decline. For example, the decline in stroke coincides with the precipitous decline in tobacco use in most U.S. states. Several studies have shown a decline in stroke risk as a function of smoking cessation (45, 88).

In summary, changes in the diagnostic threshold for high blood pressure have led to the identification of at least 13 million new cases. The new category of prehypertension in addition to hypertension will include up to 60% of the population and 90% of adults 60 years of age or older. The consequences of high blood pressure, including stroke and CHD, have been systematically declining, and the changes in diagnostic thresholds have resulted in better population health. However, the observed decline in stroke and CHD has been much more rapid than would be expected from changes in blood pressure.

EXAMPLE 2: HIGH SERUM CHOLESTEROL

Following the Coronary Primary Prevention Trial (2) the national cholesterol education program argued for the aggressive management of elevated serum cholesterol. The arguments in favor of population-based cholesterol lowering are multiple. Perhaps the two most persuasive arguments come from the Multiple Risk Factor Intervention Trial (MRFIT) (79) and the British Medical Research Council/British Heart Foundation Heart Protection Study (10). The MRFIT study demonstrated that the relationship between total cholesterol and death from CHD was systematic and independent of the original level. Reducing total cholesterol from 300 to 280 mg/dl, for example, provided the same percentage reduction in death from coronary disease as would be afforded someone reducing total cholesterol from 220 to 200 mg/dl (79). Ironically, the MRFIT study was an intervention trial that failed to demonstrate a benefit for intervening on risk factors (1).

The Coronary Primary Prevention Trial (CPPT) used cholestyramine to reduce elevated serum cholesterol for men at risk for coronary disease. Over the next decade, a significant controversy about the benefits of cholesterol lowering ensued. Meta-analysis consistently showed benefits for reduction in deaths from heart disease but no benefit for total mortality (62, 63). Furthermore, some investigators were concerned that reductions in deaths from heart disease were compensated for by increases in deaths from other causes (31).

The introduction of the HMG-CoA reductase inhibitors or statin medications helped silence this controversy. Studies involving statins tended to show reductions in both deaths from heart disease and total mortality (19, 25). Nevertheless, some controversy remained. The MRC/BSF Heart Protection study was particularly important because it was large ($n = 20{,}536$) and randomized (10). Perhaps the most interesting finding was that simvastatin was given to a wide range of individuals at risk for coronary disease. There was a benefit in terms of CHD mortality irrespective of the initial cholesterol concentrations. Consumption of 40 mg of simvastatin daily was associated with

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the reductions in MI, stroke, and the number of the revascularization procedures. The study has been interpreted as suggesting the need for greater use of statin drugs in the population (10). However, whereas the relative risk reduction afforded by the statins appears fairly constant over all risk groups, the absolute risk reduction is much smaller in those at lower risk. Furthermore, some have questioned the value of statins for low-risk women (86). Walsh & Pignone performed a meta-analysis of six trials of lipid lowering. The trials included 11,435 women without CVD. In these trials, lipid lowering did not reduce either CHD or total mortality. Among nearly 2400 women randomly assigned to take statins or placebos in secondary prevention trials, there were 102 deaths among women taking the active drug and 103 deaths among women taking the placebo (86). Thus, little evidence indicates that statins reduce total mortality in women. The rationale for statin therapy in older adults has also been challenged. For example, Packard and colleagues noted that low-density lipoprotein (LDL) cholesterol is a good predictor of neither outcome nor response to therapy in adults older than age 70. HDL cholesterol or the ratio of total to HDL may offer more information (23, 66).

ATP III

The third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high cholesterol in adults (ATP III) (7) is the current standard for cholesterol screening and treatment. ATP III is the third step in an evolutional process and follows two previous sets of guidelines. The first report (ATP I) outlined the strategy for the prevention of heart disease for adults with LDL >160mg/dl and for those with high cholesterol (LDL 130–159 mg/dl). The second report (ATP II) expanded ATP I by discussing the intensive management of LDL cholesterol for people who had established heart disease. ATP III, published in 2001, called for more intensive intervention. Departing from previous recommendations, ATP III identified LDL cholesterol levels between 130–159 mg/dl as borderline high and total cholesterol levels between 200 and 239 mg/dl as borderline high for otherwise low-risk individuals.

The ATP III argues that a linear relationship exists between the LDL cholesterol and the chances of MI or death (see **Figure 4**). The argument is that those who lower their LDL cholesterol from 170 to 160 gain about the same amount as those who lower their LDL cholesterol from 110 to 100. However, the y-axis on the graph is in logarithmic rather than regular units. As with blood pressure, the relationship between risk factor and outcome is not linear. It is log-linear. In addition, **Figure 4** disguises some of the relationship by excluding the small groups of the population with very low or very high LDL levels. **Figure 5** redraws the relationship using natural units on the y-axis and the full range of LDL values reported in the NHANES survey along the X-axis. Those who start with lower levels of LDL cholesterol gain significantly less than those who start with high levels of LDL cholesterol.

ATP III recommends lifestyle intervention for those with borderline high LDL or total cholesterol but also acknowledges that drug treatment may be appropriate for

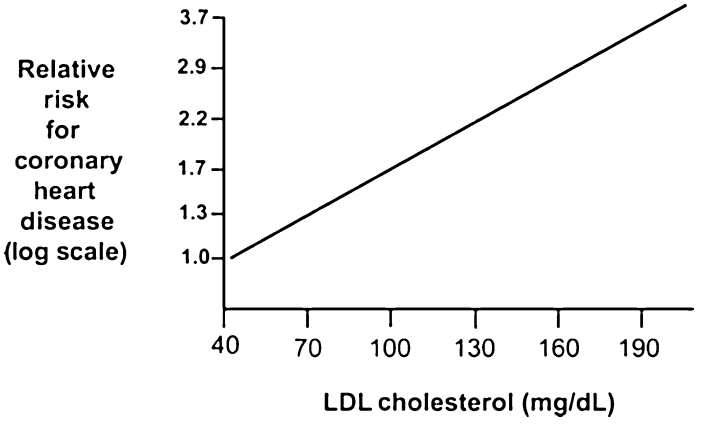

Figure 4

Figure 2 NCEP Revision July 2004.

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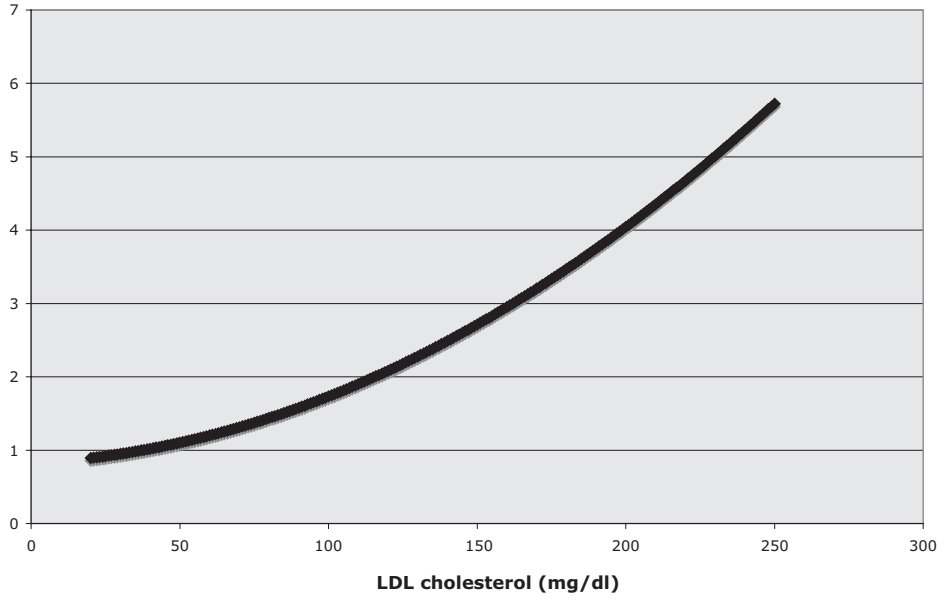

Figure 5

Relationship between LDL and CHD risk using natural unit.

those who fail lifestyle interventions. Direct-to-consumer advertising sponsored by the pharmaceutical industry suggests that most patients fail dietary interventions and that patients should speak to their doctors about drug therapy (see **http://www.Lipitor.com**).

The ATP III report discusses the cost-effectiveness of treatment, recognizing that drug therapy is expensive. However, it also dismisses some cost concerns by suggesting that drug prices are likely to decline in the future. ATP III suggests that the threshold for considering treatment is an LDL level of 130 mg/dl. Following the publication of the Heart Protection study (22), the guidelines were revised to lower the threshold to 100 mg/dl (32, 34).

HOW MANY PEOPLE WILL BE AFFECTED BY THE NEW GUIDELINES?

Using data from the National Health and Nutrition Examination survey we reevaluated the proportion of the adult population affected by the change in guidelines. The distribution of LDL cholesterol in the U.S. population, and for the U.S. population age 60 or older, is shown in **Figure 6**. The updated ATP III guidelines suggest that optimal levels of LDL cholesterol are below 70 mg/dl (32). Considering the entire adult population in the United States, only ~7% are at this level; 93% have levels that are higher. For adults older than age 60, 97% have LDL values higher than 70 mg/dl. The first threshold for clinical concern is 100 mg/dl. According to the analysis of the NHANES data, ~73% of the adult population of the United States falls into this category. According to our analysis of the NHANES data, 84% of adults older than age 60 have LDL levels higher than 100, so 84 in each 100 might need attention for cholesterol management.

HOW MANY WILL PROGRESS TO CVD?

Pharmaceutical advertising suggests statin therapy for patients with mildly elevated LDL

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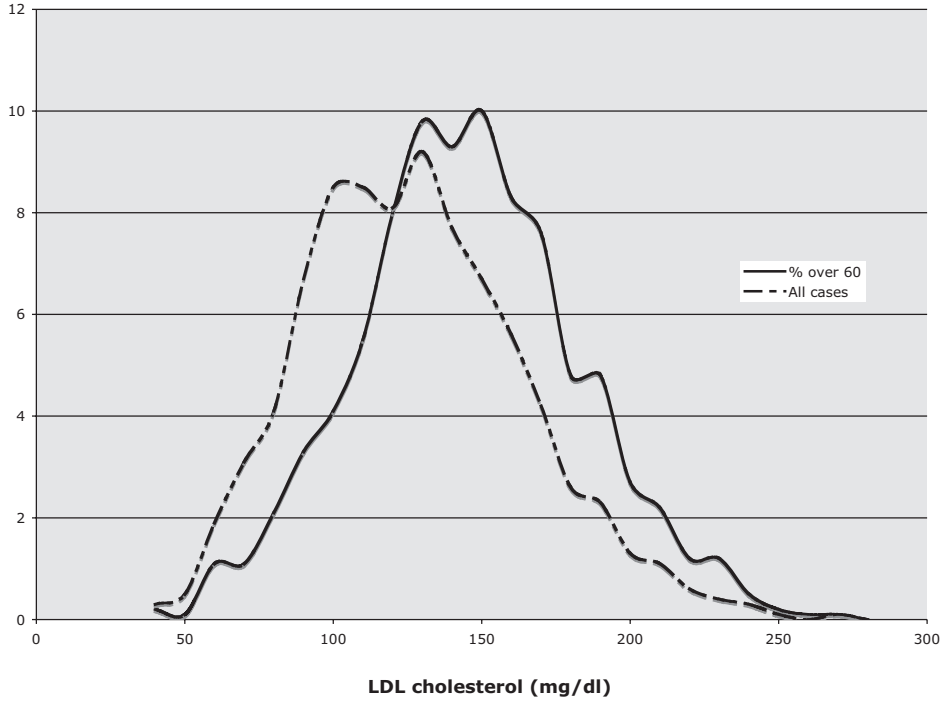

Figure 6

Distribution of LDL cholesterol for all participants and for those >60 years in NHANES.

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cholesterol and without other risk factors. However, statins have not been studied in populations without risk factors. **Table 2** summarizes the entry criteria in several of the major recent clinical trials. These are the exact trials used as the rationale for the recent revision of ATP III. The third column of the table shows that none of these trials used adults who did not have heart disease or did not have established risk factors. We remain uncertain about the benefits for lowering cholesterol in adults with relatively normal levels of LDL cholesterol. These populations have not been studied in lipid-lowering trials.

EXAMPLE 3: IMPAIRED FASTING GLUCOSE

Among the many adjustments in disease thresholds are recent changes in the definition of diabetes mellitus (DM) and impaired fasting glucose (IFG). The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus recommended that the threshold for diabetes be changed from a fasting plasma glucose level of 140 mg/dl to 126 mg/dl (6). With a simple change in disease definition, the prevalence of diabetes increased 14%. More recently, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus recommended that the lower limit for IFG be reduced from 110 mg/dl to 100 mg/dl (or down to 5.6 mmol/l) (28).

DM: diabetes mellitus

IFG: impaired fasting glucose

The rationale for the recommendation was the panel's belief that metabolic and clinical complications of hyperglycemia rise sharply for those above the 100 mg/dl level. However, the committee noted that very little evidence indicated that cardiovascular risk factors and all-cause mortality increase with IFG. They also noted that some studies did not support lowering the threshold (8, 35). As part of their discussion, the group noted that lowering the threshold to 100 mg/dl would significantly

Table 2 Entry criteria in trials used as the basis for the ATP-III revised guidelines

Study	Population	Entry criteria
Heart Protection Study(10)	20,536 adults, ages 40–80 in United Kingdom	Coronary disease, other occlusive artery disease, or diabetes
Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)(76)	5804 adults, ages, 70–82	History of heart disease or CVD risk factors
Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT)(9)	10,355 adults 55 years or older	LDL levels between 120 and 189 mg/dl and triglycerides <350 mg/dl
Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowing Arm (ASCOT-LLA)(74)	19,342 patients ages 40–79 years	All had hypertension and at least 3 other CHD risk factors
Pravastatin or Atorvastatin Evaluation and Infection-Thrombolysis in Myocardial Infarction 22 (PROVE IT)(18)	4162 patients from Australia, Canada, France, Germany, Italy, Spain, the United Kingdom, or the United States	All participants had been hospitalized for acute coronary syndrome within 10 days prior to randomization

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increase the number of patients with a diagnostic label. The committee felt this was desirable because it would bring medical attention to more individuals. The committee argued that population studies from Mauritius (75) and from the Pima Indians (27) supported the lower threshold. The only American population considered was the San Antonio Heart Study population, which had a high ad-mix of Native Americans (56). In making their recommendation, the committee acknowledged that risks associated with IFG were not consistently documented and that the few studies identifying the risks tended to use populations that were not representative of the general U.S. population.

HOW MANY PEOPLE WILL BE AFFECTED BY THE NEW GUIDELINES?

Our preliminary analysis suggests that 37% of the U.S. population 50 years of age or older would have IFG or DM under the new definition. Using data from the National Health and Nutrition and Examination Survey, it appears that ~9 million adults in America would qualify for a diagnosis of IFG or diabetes if the definition was fasting plasma glucose (FPG) >110 <126. Lowering the threshold to 100 mg/dl would increase the number of individuals deemed eligible for treatment by 24 million people to about 33 million cases of IFG. This represents a 166% increase in the number of people eligible for a diagnosis.

DOES IFG INCREASE THE RISK OF DIABETES OR DIABETIC COMPLICATIONS?

The American Diabetes Association (ADA) suggests that impaired fasting glucose or "prediabetes" is the pathway to full diabetes. Furthermore, they urge the general population to be tested because elevated blood glucose may result in diabetic complications. The recommendation was based on the assumption that those with IFG are at risk for transition to DM and the complications of impaired glucose metabolism. But what do we know about the long-term consequences of minor elevations in blood glucose? With colleagues at the University of California, San Diego, we evaluated the benefit of the new definition of IFG. In 1972–1974, 82% of an upper-middle-class white community (Rancho Bernardo, California) were screened for heart disease risk factors as part of the Lipid Research Clinic Prevalence Program. The average age at baseline was 49.9 years. A follow-up visit of this cohort was conducted 20 years later and included ~75% of the

surviving Rancho Bernardo cohort (n = 1781). Among these, 1494 subjects had valid plasma glucose values for both visits (n = 1494).

FPG levels were measured at both visits and four categories of fasting plasma glucose were created: nonimpaired (lower than 100 mg/dl), low IFG (100–110 mg/dl), IFG (111–126 mg/dl), and diabetes mellitus (greater than 126 mg/dl and/or diagnosed or taking diabetic medications). Each participant was placed in one of the four categories at the baseline (1972–1974) and the follow-up (1992–1996) visits. Diabetic complications were also measured at the second visit. These included kidney function and eye problems. A self-report questionnaire was used to ask questions relating to neuropathy including three categories: (*a*) numbness or tingling, (*b*) loss of sensation in both hands or feet, and (*c*) decreased ability to feel temperature by touching. For this analysis, a participant was scored as having neuropathy if he or she reported any one of the three symptoms. The questionnaire was also used to determine self-reported use of prescription medications for diabetes and whether a health professional had told the respondent that he or she had diabetes.

About 83% of those FPG values lower than 100 mg/dl at baseline maintained FPG values lower than 100 mg/dl over the next 20 years and less than 3% progressed to diabetes. For those with baseline FPG values between 100 and 110, transition to diabetes was similar (4%). Chances of conversion to diabetes significantly increased for those in the 111–126 range (7%) in comparison with the nonimpaired (<100 mg/dl) (3%) but not the low IFG (100–110 mg/dl) groups (4%). Twenty years later, little evidence indicated that those with FPG levels between 100 and 110 were at elevated risk for diabetic complications, including elevated urinary albumin/creatinine ratios, retinopathy, and neuropathy (RM Kaplan, D Morton, DL Wingard, E Barrett-Connor, submitted manuscript). Several other studies are consistent with our analysis. A 6.8-year follow-up of 2763 women with established heart disease did not find a relationship between the new definition of IFG (100–110 mg/dl) and incident events of CHD, stroke, TIA, or CHF (41).

From a public health perspective, cost must also be considered. The committee suggested, "We do not yet know the total benefit or the total cost to an individual who is designated at risk for diabetes by either test, by any criterion. The higher the ratio of benefit to cost, the lower the optimum cut point that should be selected." The committee felt that there was a cost advantage to lowering the threshold because complications of diabetes could be prevented. They cited the Diabetes Prevention Program (DPP) as evidence (46). However, lowering the threshold will mean that many people will be subjected to treatment even though they have a very low probability of complications. Furthermore, the DPP did not study isolated IFG; participants had to have IFG and impaired glucose tolerance.

Multiple studies have shown that lifestyle modifications or pharmacotherapy can delay or prevent the progression from impaired glucose control (as measured either by impaired glucose tolerance or IFG) (14, 20, 46, 67, 81). Only one study, the Diabetes Prevention Program (DPP) (46), has compared lifestyle modifications and pharmacotherapy together.

The DPP study enrolled individuals with a FPG of 95 to 125 mg/dl and an oral glucose tolerance test of 140 to 199 mg/dl, which was considered elevated but did not meet the threshold for diabetes by the 1997 ADA guidelines. The DPP study had three arms that enrolled ~1000 patients each: placebo, lifestyle intervention, and pharmacotherapy intervention (metformin), in which the lifestyle intervention combined a healthy low-calorie, low-fat diet with a physical activity regimen of moderate intensity, such as brisk walking, for at least 150 min per week. The placebo rate of progression to diabetes in the DPP study was 11 per 100 person-years,

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and both the lifestyle and pharmacotherapy intervention (metformin) reduced progression to diabetes compared with placebo by 58% and 31%, respectively.

The DPP also included a cost/utility analysis. Quality of life was measured using the Quality of Well-Being Scale (QWB) (44). The measure was chosen because it can be used to estimate quality-adjusted life years (QALYs) (43). Over the course of three years, those randomly assigned to the lifestyle intervention accrued 0.050 more QALYs than did those assigned a regular dose of metformin. Among the three interventions, the lifestyle approach was the most expensive (total cost $27,065 in 2000 U.S. dollars). Metformin was less expensive ($25,937), whereas the placebo was the least expensive option ($23,525). Although both interventions offer significant benefits over placebo or doing nothing, the cost/QALY for the lifestyle invention was significantly lower than for metformin. In other words, even though the lifestyle intervention was more expensive, it offers significantly better value for money.

In conclusion, we find little evidence that FPG levels between 100 and 110 mg/dl are strong predictors of transition to diabetes or the development of diabetic complications. These data contrast the recommendation of the expert committee on the diagnosis and classification of DM. The expert committee recognized that the selection of disease thresholds is arbitrary. We believe that the selection of disease thresholds requires continuing thought and evaluation. Furthermore, given the benefits of diet and exercise for those with prediabetes, we see little justification for use of medication by those in the 100–110 mg/dl range.

HOW MANY PEOPLE HAVE AT LEAST ONE OF THE THREE LOW THRESHOLD CONDITIONS?

Using data from the NHANES III we estimated the percentage of the adult population meeting the criteria for IFG, prehypertension, or modestly elevated LDL cholesterol (greater than 100 mg/dl). This preliminary analysis concentrated on the 62 million Americans 50 years of age or older. The results are summarized in **Figure 7**. Our preliminary estimates suggest that 37% of the population ages 50 or older have fasting glucose levels greater than 100 mg/dl. Furthermore, nearly 60% of the population has SBP greater than 120 mm Hg. For LDL cholesterol, nearly three quarters of the population (73%) have levels greater than 100 mg/dl.

Figure 7 also shows the percent of the population with any one of these three conditions. According to this preliminary analysis, 97% of American adults ages 50 or older have one of the three conditions. The expanded markets for health care will include virtually the entire population of adults older than age 50. These changes in diagnostic thresholds are likely to have profound impacts on the costs of health care, and their effects on population health have not been comprehensively evaluated.

Because the effect of risk factors is multiplicative, some in the field may be concerned that people with multiple borderline risk factors may be at greater risk than those with only one concern. An analysis conducted by Vasan and colleagues (84) suggests that even when accounting for multiple preconditions, treating them will have only modest effects on morbidity and mortality. The analysis considered three preconditions (prehypertension, borderline high LDL cholesterol, and IFG) plus borderline low HDL cholesterol and previous smoking. Using this information, the investigators calculated the proportion of 10-year CHD event rates, defined as either myocardial infarction or coronary death from these five risk factors using weights from the Framingham Heart Study. The event rates were then applied to the NHANES III non-Hispanic white cohort between the ages of 35 and 74 without a previous vascular event and extrapolated to the U.S. population

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on the basis of the 2000 census. The analysis suggested that of these, only 8% of CHD events will occur in individuals with any combination of these borderline conditions but without any of the five actual conditions. This number would be even lower if restricted to prehypertension, borderline high LDL cholesterol, and IFG; the two other risk factors have high prevalence rates, with borderline low HDL cholesterol seen in 50% of men and 53% of women in NHANES-III, and former smoking seen in 42% of men and 30% of women in NHANES-III.

CONSEQUENCES

The greatly expanded market for health care associated with these definition changes may have important public health consequences. In this section, we consider some of these issues.

Labeling

Labeling adults with a "disease" is not without consequence. In a classic study Haynes and colleagues (37) screened for hypertension in an industrial setting. Hypertension is usually considered to be a silent disease. Those who were labeled as hypertensive had an increase in absenteeism from work of more than 5 days per year. This amounted to nearly an 80% increase in days missed from work. The authors suggested that simply becoming aware that a person had a diagnosis was a major factor in absenteeism. Days missed from work was attributed to the labeling because the increases in absenteeism were observed for those who were previously unaware of their condition and happened independently of whether the person started hypertensive therapy (72). However, a variety of concerns about the Haynes study have been noted. For example, absenteeism may have increased because people were diagnosed at work and may have attributed their high blood pressure to work-related stress. More recent reviews have downplayed the effect of labeling. Evidence on the psychological consequences of labeling is less of a concern. A review of 10 cohort studies examined the adverse effects of screening for hypertension and subsequently labeling a person as hypertensive, and it found fair-quality evidence suggesting that screening and labeling adults with hypertension produce no adverse effects on psychological well-being (77).

Increased Health Care Utilization

Current recommendations suggest that these new definition changes will lead to increased health care utilization. The U.S. Preventive Services Task Force (USPSTF) makes recommendations regarding screening visit frequencies. The USPSTF has yet to update its recommendations for people with high blood pressure, high cholesterol, and IFG since the change in these definitions. In the past, the USPSTF recommendations for high blood pressure and high cholesterol screening have mirrored prior iterations of the JNC and ATP. The USPSTF has previously stated there was insufficient evidence to screen for diabetes (USPSTF 2003).

JNC VII recommends that individuals with prehypertension have their blood pressure screened yearly for progression to hypertension and recommends individuals with "normal" blood pressures be screened every two years. ATP III recommends reevaluating individuals with borderline high cholesterol levels (LDL 130–159) after one year and recommends individuals with "normal" cholesterol levels be screened every five years. The ADA recommends screening individuals over the age of 45 with a FPG every three years and more frequently for those with IFG (or impaired glucose tolerance). Adherence to these recommendations for visit frequency will add significant burdens to scheduling resources if carried through given the huge numbers of people who would meet these definition changes. Assuming a cost of $50 for a physician visit, these recommendations would add more than a billion dollars to current health care expenditures.

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Medication Prescriptions

The recommended treatment for prehypertension, borderline high cholesterol, and IFG is lifestyle and dietary changes. However, prescription medication therapy will undoubtedly also occur. Compliance rates with recommendations for lifestyle and dietary changes are likely to be lower than those seen in clinical trials (70%) (13). Individuals who are nonadherent may be placed on medication therapy despite lack of current recommendations for such a strategy. In addition, individuals prescribed medication may be less motivated to change their lifestyles. We also estimated the costs of these prescriptions. The costs are based on actual wholesale prices (AWP). AWP are often high estimates of costs because many patients get prescriptions through the bulk purchasing discounts of their insurers. We examined the AWP available from the 2004 Red Book for all medications and selected the lowest price for medications purchased in quantities of 100.

The TROPHY study has demonstrated that antihypertensives can be used as pharmacotherapy in prehypertensive individuals (40), which may lead to prescriptions of the study medication, candesartan, in prehypertensive individuals. Most prehypertensive individuals who are started on medication therapy will use monotherapy (i.e., one medication) and will likely have utilization patterns similar to hypertensive patients using monotherapy. Data from the 1999–2002 NHANES show that among hypertensive patients using monotherapy, more than 50% of patients use a calcium-channel blocker (CCB) or an angiotensin-converting enzyme (ACE) inhibitor, and only one of ten uses diuretics, which are the recommended vehicle by JNC VII guidelines for uncomplicated hypertension monotherapy (33). Angiotensin receptor blockers, like candesartan, are used as monotherapy by less than 4% of hypertensive patients and are the furthest away from patent expiration. For prehypertension, the least expensive medication is hydrochlorothiazide. The one-year cost of this medication is $9 (hydrochlorothiazide 25 mg tablets, assuming doses of 12.5 mg per day). However, the one-year cost of candesartan, one of the most expensive antihypertensives, is $541. Systematic clinical trials have failed to show that newer high-cost antihypertensives are more effective than older, cheaper products (78). Recently, a review suggested that the more expensive ARBs are not as effective as cheaper ACE inhibitors in preventing cardiovascular and all-cause deaths (80).

Prescriptions of lipid-lowering medications to low-risk individuals are highly prevalent. A medical record review of all outpatients affiliated with the Brigham and Women's Hospital who were using statins for primary prevention of coronary artery disease on January 1, 1996, showed that 32.6% were individuals with fewer than two risk factors that did not meet National Cholesterol Education Program (NCEP) criteria for statin use (i.e., LDL cholesterol > 190 mg/dl) (12). This group consisted of 47.5% of all individuals using statins for primary prevention of coronary artery disease. Even after excluding those who did not receive any LDL testing, 25.9% of statin users had fewer than two risk factors and documented LDLs below 190 mg/dl. As this data predates the declaration of LDL cholesterol levels of 130–159 mg/dl as borderline-high, we expect that such prescribing has increased since ATP III. The most common cholesterol medications prescribed are HMG-CoA reductase inhibitors, commonly known as statins. Currently, some statins but not all have lost patent protection. The most inexpensive one-year cost of a generic statin prescription is $491 (lovastatin 10 mg tablets), whereas the most expensive one-year cost of a statin still under patent protection is $793 (atorvastatin 10 mg tablets).

Public health approaches such as lifestyle modification are typically preferred over pharmaceutical interventions. Despite the superiority of the lifestyle intervention, there has been concern that physicians will prefer metformin over lifestyle intervention for preventing progression to diabetes. This concern

is grounded in part by the difficulty of getting patients to adhere to lifestyle interventions and the ease of prescribing compared with teaching the lifestyle intervention. At the closure of the DPP study, the adherence rate to the lifestyle intervention (58%) was lower than to the metformin or placebo intervention (72% and 77%, respectively). Metformin makes up only about one third of all antidiabetic prescriptions (91), but it is commonly used as oral monotherapy for people with diabetes. This recommendation, combined with the findings from the DPP study, suggests that those with prediabetes using pharmacotherapy would likely use metformin. The medication regimen from the Diabetes Prevention Program trial was metformin 850 mg tablets twice a day. The one-year cost of this regimen is $460.

Wald & Law (85) argued that CVD could be lowered by 88% if the entire population took a "polypill" composed of atorvastatin (10 mg), three blood pressure medications, folic acid (.8 mg), and aspirin (75 mg). The recommendations were based on a meta-analysis of 15 trials of low-dose aspirin and other published meta-analyses of trials and cohort studies. Although the polypill is an interesting idea, it has also encountered significant criticism. A multidisciplinary public health research working group considered the strengths and concerns of combination pharmacotherapy proposals (11). Most important, they noted that no clinical trial has shown the benefit of the pill. Furthermore, the group raised questions about possible side effects and problems with patient adherence. Another concern is that a footnote to the polypill paper notes that the authors have filed for a patent on the combined pill. At this point, it seems a bold step to advocate a policy for the entire public without direct evidence for effectiveness of this combined agent.

Although most of the current medications that would be used in these preconditions are or will be generic in a few years, the costs of medication treatment may be on the low end of these estimates. However, pharmaceutical companies will likely develop new treatments targeting those with preconditions, given the huge potential markets. As a result, medication costs will likely be higher than these estimates. The reader should note that we have reported only the one-year costs. In most cases, patients will be asked to comply with these or similar medications continually for the remaining years of their lives. The yearly cost of a statin medication for a person with a 25-year current life expectancy should be multiplied by 20.

Likelihood of Benefit/Chances of Side Effects

No treatment is without side effects. Because side effects occur, patients must decide if they are willing to expose themselves to these risks. Glasziou & Irwig (29) have analyzed this problem and concluded that the benefits of treatment go disproportionately to patients at the greatest risk. Similarly, the lower the risk of the disease is, the lower the benefit of treatment is. **Figure 8** provides a pictorial explanation of their ideas. In this case, imagine the risk is blood pressure and the outcome is stroke. As blood pressure increases, the chances of stroke also increase. Everyone exposed to the treatment experiences these consequences, and they are independent of the level of risk. However, not all people respond to treatment the same way. Some are very responsive to treatment (high responders) and others are less responsive (low responders). Similarly, some people are more sensitive to the medication and are highly vulnerable to side effects. Others may have low vulnerability. The treatment threshold should be higher for those who are more vulnerable to side effects.

WHAT IS UNKNOWN

Geoffrey Rose convincingly argued the rationale for public health approaches to common medical problems. Given the normal distribution of most CHD risk factors, the traditional medical approach has been to seek

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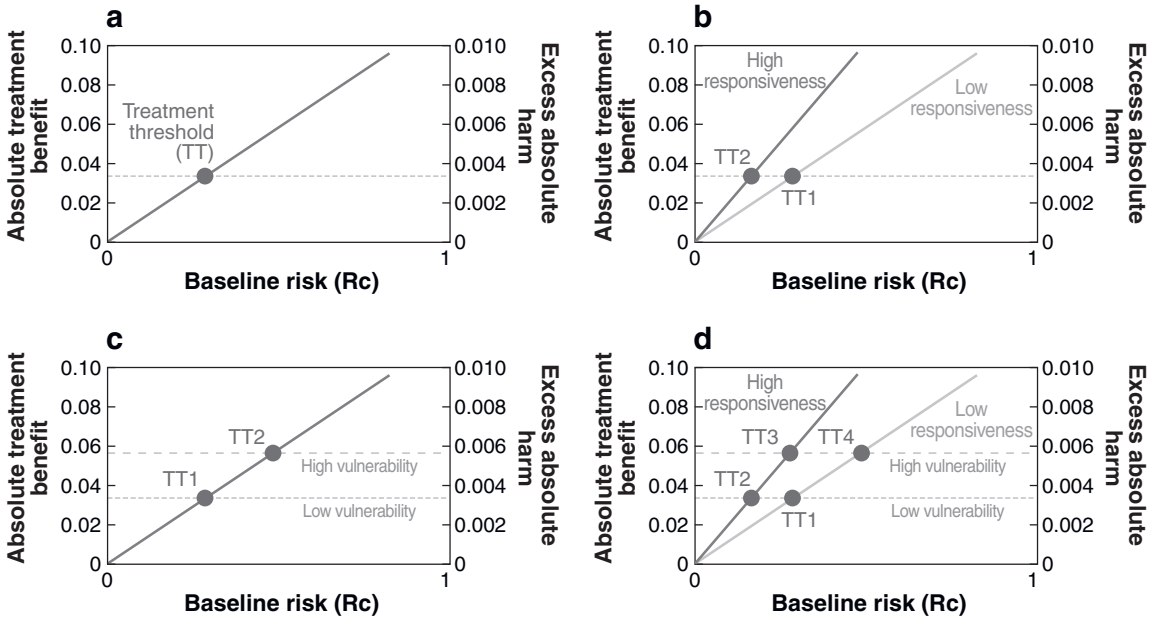

Figure 8

The solid line in panel *A* shows the relationship between the benefits of treatment and the risks of the illness. The dashed line shows the chances of harm due to side effects of treatment. The point where the lines intersect is the treatment threshold, or the point at which treatment should be considered. Panels *B*, *C*, and *D* outline other situations. Panel *B* shows that the treatment threshold should be lower for high responders than for low responders. The different horizontal dashed lines in Panel *C* indicate patients who are sensitive to medication and highly vulnerable to side effects. Panel *D* shows treatment thresholds for different combinations or response to treatment and vulnerability to side effects (from Reference 47, reproduced with permission of Blackwell Publishing).

out and treat those in the upper tail of the curve. Rose suggested that more public health benefit could result from focus on the entire distribution and greater attention to those toward the center. Attacking the entire distribution might produce more public health benefit than would concentration on clinical cases at the extremes. Recent changes in treatment guidelines place a much greater portion of the population in categories for concern. However, the new guidelines emphasize medical approaches to these problems. Rose proposed public health rather than clinical solutions to this problem. New guidelines appear to medicalize ordinary variation in CHD risk factors. We clearly need efforts to apply and evaluate public health approaches before exposing a large portion of the population to clinical measures.

Perhaps the major discrepency in the current literature is that we do not know the benefits of treatment for people not previously believed to be at risk. **Tables 1** and **2** suggest that we have very little evidence on the health benefits and consequences of pharmacological treatment for people not at risk. Furthermore, we have not formally evaluated public approaches or compared the relative value of population versus clinical approaches. Furthermore, we need more evidence on the costs, risks, and benefits of the expanded definitions of disease.

SUMMARY

This chapter has explored the implications of changing the definitions of CHD risk factors. JNC VII created a new category known as

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prehypertension. Individuals previously categorized as normal now qualify for this diagnosis. ATP III lowered the threshold for concern about serum cholesterol. An ADA committee lowered the threshold for IFG from 110 mg/dl to 100 mg/dl. Analysis of the National Health and Nutrition Examination survey shows that these definition changes produce profound effects on the number of people who could be labeled as having these risk factors. Considering blood pressure, for example, the number of people affected would go from ~14% to ~40% of the adult population, a 185% increase. Considering the three risk factors, more than 97% of the adult population would need to be under medical surveillance.

We do not know how many people would seek or gain treatment for these new diagnoses or whether the treatment would be effective. Clinical trials have not evaluated pharmaceutical interventions for people who were previously thought to have normal blood pressure, cholesterol, or glucose. Using observational data, it appears that the benefit of treatment will be quite small. However, the costs of the treatment are likely to be substantial. New pharmacological approaches to the treatment of high blood pressure are very expensive and can cost several dollars per day. For a 50-year-old diagnosed with prehypertension, a drug cost could be $500 or more per year, and this cost would be repeated each year for the remainder of the lifespan. In addition, monitoring costs would be substantial because people taking medications need to visit their physicians more often. The cost would be high and the benefits would be uncertain. The value of treatment for low-threshold illness must be assessed in systematic empirical studies and clinical trials. Considerably more research is needed to estimate the costs and public health implications of these changes in diagnostic thresholds.

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LITERATURE CITED

1. 1982. Multiple risk factor intervention trial. Risk factor changes and mortality results. Multiple Risk Factor Intervention Trial Research Group. *JAMA* 248:1465–77
2. 1984. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA* 251:365–74
3. 1988. Persistence of reduction in blood pressure and mortality of participants in the Hypertension Detection and Follow-up Program. Hypertension Detection and Follow-up Program Cooperative Group. *JAMA* 259:2113–22
4. 1993. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch. Intern. Med.* 153:154–83
5. 1993. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 269:3015–23
6. 1997. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabet. Care* 20:1183–97
7. 2001. Executive summary of the third report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–97
8. 2001. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch. Intern. Med.* 161:397–405
9. 2002. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs. usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 288:2998–3007

10. 2002. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 360:7–22
11. 2005. Combination pharmacotherapy for cardiovascular disease. *Ann. Intern. Med.* 143:593–99
12. Abookire SA, Karson AS, Fiskio J, Bates DW. 2001. Use and monitoring of "statin" lipid-lowering drugs compared with guidelines. *Arch. Intern. Med.* 161:53–58
13. Appel LJ, Champagne CM, Harsha DW, Cooper LS, Obarzanek E, et al. 2003. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. *JAMA* 289:2083–93
14. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, et al. 2002. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes* 51:2796–803
15. Bulpitt C, Fletcher A, Beckett N, Coope J, Gil-Extremera B, et al. 2001. Hypertension in the Very Elderly Trial (HYVET): protocol for the main trial. *Drugs Aging* 18:151–64
16. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, et al. 1995. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension* 25:305–13
17. Byington RP, Miller ME, Herrington D, Riley W, Pitt B, et al. 1997. Rationale, design, and baseline characteristics of the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT). *Am. J. Cardiol.* 80:1087–90
18. Cannon CP, McCabe CH, Belder R, Breen J, Braunwald E. 2002. Design of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-TIMI 22 trial. *Am. J. Cardiol.* 89:860–61
19. Caro J, Klittich W, McGuire A, Ford I, Norrie J, et al. 1997. The West of Scotland coronary prevention study: economic benefit analysis of primary prevention with pravastatin. *BMJ (Clin. Res. Ed.)* 315:1577–82
20. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. 2002. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 359:2072–77
21. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, et al. 2003. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 42:1206–52
22. Collins R, Armitage J, Parish S, Sleigh P, Peto R. 2003. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 361:2005–16
23. Criqui MH, Golomb BA. 2004. Low and lowered cholesterol and total mortality. *J. Am. Coll. Cardiol.* 44:1009–10
24. Dens JA, Desmet WJ, Coussement P, De Scheerder IK, Kostopoulos K, et al. 2001. Usefulness of Nisoldipine for prevention of restenosis after percutaneous transluminal coronary angioplasty (results of the NICOLE study). NIsoldipine in COronary artery disease in LEuven. *Am. J. Cardiol.* 87:28–33
25. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, et al. 1998. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 279:1615–22
26. Estacio RO, Savage S, Nagel NJ, Schrier RW. 1996. Baseline characteristics of participants in the Appropriate Blood Pressure Control in Diabetes trial. *Control Clin. Trials* 17:242–57

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27. Gabir MM, Hanson RL, Dabelea D, Imperatore G, Roumain J, et al. 2000. The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. *Diabet. Care* 23:1108–12
28. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, et al. 2003. Follow-up report on the diagnosis of diabetes mellitus. *Diabet. Care* 26:3160–67
29. Glasziou PP, Irwig LM. 1995. An evidence based approach to individualising treatment. *BMJ* 311:1356–59
30. Goldstein LB, Adams R, Becker K, Furberg CD, Gorelick PB, et al. 2001. Primary prevention of ischemic stroke: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke* 32:280–99
31. Golomb BA. 1998. Cholesterol and violence: Is there a connection? *Ann. Intern. Med.* 128:478–87
32. Grundy SM, Cleeman JI, Merz CN, Brewer HBJ, Clark LT, et al. 2004. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 110:227–39
33. Gu Q, Paulose-Ram R, Dillon C, Burt V. 2006. Antihypertensive medication use among US adults with hypertension. *Circulation* 113:213–21
34. Gurm HS, Hoogwerf B. 2003. The Heart Protection Study: high-risk patients benefit from statins, regardless of LDL-C level. *Cleve Clin. J. Med.* 70:991–97
35. Hanefeld M, Temelkova-Kurktschiev T, Schaper F, Henkel E, Siegert G, Koehler C. 1999. Impaired fasting glucose is not a risk factor for atherosclerosis. *Diabet. Med.* 16:212–18
36. Haugh R, Thrall TH, Scalise D. 2002. Prescription for concern. *Hosp. Health Netw.* 76:44–49
37. Haynes RB, Sackett DL, Taylor DW, Gibson ES, Johnson AL. 1978. Increased absenteeism from work after detection and labeling of hypertensive patients. *N. Engl. J. Med.* 299:741–44
38. Howard G, Howard VJ. 2001. Ethnic disparities in stroke: the scope of the problem. *Ethn. Dis.* 11:761–68
39. Ivanovic B, Cumming ME, Pinkham CA. 2004. Relationships between treated hypertension and subsequent mortality in an insured population. *J. Insur. Med.* 36:16–26
40. Julius S, Nesbitt SD, Egan BM, Weber MA, Michelson EL, et al. 2006. Feasibility of treating prehypertension with an angiotensin-receptor blocker. *N. Engl. J. Med.* 354:1685–97
41. Kanaya AM, Herrington D, Vittinghoff E, Lin F, Bittner V, et al. 2005. Impaired fasting glucose and cardiovascular outcomes in postmenopausal women with coronary artery disease. *Ann. Intern. Med.* 142:813–20
42. Kaplan RM. 2006. Effects of changes in diagnostic thresholds on healthcare for older adults. In *Handbook of the Health Psychology and Aging*. ed. CM Aldwin, AI Spiro, C Park, pp. 390–411. New York: Guilford
43. Kaplan RM, Ganiats TG. 1990. QALYs—their ethical implications. *JAMA* 264:2502–3
44. Kaplan RM, Ganiats TG, Sieber WJ, Anderson JP. 1998. The Quality of Well-Being Scale: critical similarities and differences with SF-36. *Int. J. Quality Health Care* 10:509–20
45. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, et al. 1993. Smoking cessation and decreased risk of stroke in women. *JAMA* 269:232–36
46. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, et al. 2002. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* 346:393–403
47. Kravitz RL, Duan N, Braslow J. 2004. Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. *Milbank Q.* 82:661–87

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48. Langer RD. 1995. The epidemiology of hypertension control in populations. *Clin. Exp. Hypertens.* 17:1127–44
49. Law MR, Wald NJ. 2002. Risk factor thresholds: their existence under scrutiny. *BMJ* 324:1570–76
50. Lawes CM, Rodgers A, Bennett DA, Parag V, Suh I, et al. 2003. Blood pressure and cardiovascular disease in the Asia Pacific region. *J. Hypertens.* 21:707–16
51. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. 2002. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 360:1903–13
52. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, et al. 2001. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N. Engl. J. Med.* 345:851–60
53. Liberman A, Rubinstein J. 2002. Health care reform and the pharmaceutical industry: crucial decisions are expected. *Health Care Manag. (Frederick)* 20:22–32
54. Liebson PR, Grandits GA, Dianzumba S, Prineas RJ, Grimm RHJ, et al. 1995. Comparison of five antihypertensive monotherapies and placebo for change in left ventricular mass in patients receiving nutritional-hygienic therapy in the Treatment of Mild Hypertension Study (TOMHS). *Circulation* 91:698–706
55. Lievre M, Marre M, Chatellier G, Plouin P, Reglier J, et al. 2000. The noninsulin-dependent diabetes, hypertension, microalbuminuria or proteinuria, cardiovascular events, and ramipril (DIABHYCAR) study: design, organization, and patient recruitment. DIABHYCAR Study Group. *Control Clin. Trials* 21:383–96
56. Lorenzo C, Serrano-Rios M, Martinez-Larrad MT, Gabriel R, Williams K, et al. 2002. Prevalence of hypertension in Hispanic and non-Hispanic white populations. *Hypertension* 39:203–8
57. Luepker RV, Jacobs DRJ, Folsom AR, Gillum RF, Frantz IDJ, et al. 1988. Cardiovascular risk factor change—1973–74 to 1980–82: the Minnesota Heart Survey. *J. Clin. Epidemiol.* 41:825–33
58. MacMahon S. 1990. Antihypertensive drug treatment: the potential, expected and observed effects on vascular disease. *J. Hypertens. Suppl.* 8:S239–44
59. Marmot MG, Poulter NR. 1992. Primary prevention of stroke. *Lancet* 339:344–47
60. Marre M, Lievre M, Chatellier G, Mann JF, Passa P, Menard J. 2004. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ* 328:495–501
61. Millar JA, Lever AF, Burke V. 1999. Pulse pressure as a risk factor for cardiovascular events in the MRC Mild Hypertension Trial. *J. Hypertens.* 17:1065–72
62. Muldoon MF, Manuck SB, Matthews KA. 1991. Does cholesterol lowering increase nonillness-related mortality? *Arch. Intern. Med.* 151:1453–54
63. Muldoon MF, Manuck SB, Mendelsohn AB, Kaplan JR, Belle SH. 2001. Cholesterol reduction and nonillness mortality: meta-analysis of randomised clinical trials. *BMJ* 322:11–15
64. Neal B, MacMahon S, Chapman N. 2000. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 356:1955–64
65. Neaton JD, Wentworth D. 1992. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. *Arch. Intern. Med.* 152:56–64

Annu. Rev. Public. Health. 2007.28:321-44. Downloaded from arjournals.annualreviews.org
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66. Packard CJ, Ford I, Robertson M, Shepherd J, Blauw GJ, et al. 2005. Plasma lipoproteins and apolipoproteins as predictors of cardiovascular risk and treatment benefit in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). *Circulation* 112:3058–65
67. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, et al. 1997. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabet. Care* 20:537–44
68. Pohl MA, Blumenthal S, Cordonnier DJ, De Alvaro F, Deferrari G, et al. 2005. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. *J. Am. Soc. Nephrol.* 16:3027–37
69. Rodby RA, Rohde RD, Clarke WR, Hunsicker LG, Anzalone DA, et al. 2000. The Irbesartan type II diabetic nephropathy trial: study design and baseline patient characteristics. For the Collaborative Study Group. *Nephrol. Dial. Transplant.* 15:487–97
70. Rose G, Day S. 1990. The population mean predicts the number of deviant individuals. *BMJ* 301:1031–34
71. Rose GA. 1992. *The Strategy of Preventive Medicine*. Oxford, UK/New York: Oxford Univ. Press. xii: 138 pp.
72. Sackett DL, Macdonald L, Haynes RB, Taylor DW. 1983. Labeling of hypertensive patients. *N. Engl. J. Med.* 309:1253
73. Schwartz LM, Woloshin S. 1999. Changing disease definitions: implications for disease prevalence. Analysis of the Third National Health and Nutrition Examination Survey, 1988–1994. *Eff. Clin. Pract.* 2:76–85
74. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, et al. 2003. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 361:1149–58
75. Shaw JE, Zimmet PZ, Hodge AM, de Courten M, Dowse GK, et al. 2000. Impaired fasting glucose: How low should it go? *Diabet. Care* 23:34–39
76. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, et al. 2002. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 360:1623–30
77. Sheridan S, Pignone M, Donahue K. 2003. Screening for high blood pressure: a review of the evidence for the U.S. Preventive Services Task Force. *Am. J. Prev. Med.* 25:151–58
78. Staessen JA, Wang JG, Thijs L. 2003. Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until 1 March 2003. *J. Hypertens.* 21:1055–76
79. Stamler J, Daviglus ML, Garside DB, Dyer AR, Greenland P, Neaton JD. 2000. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. *JAMA* 284:311–18
80. Strauss MH, Hall AS. 2006. Angiotensin receptor blockers may increase risk of myocardial infarction: unraveling the ARB-MI paradox. *Circulation* 114:838–54
81. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, et al. 2001. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.* 344:1343–50
82. Vallbona C, Pavlik V. 1992. Advances in the community control of hypertension: from epidemiology to primary care practice. *J. Hypertens. Suppl.* 10:S51–57

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83. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. 2001. Assessment of frequency of progression to hypertension in nonhypertensive participants in the Framingham Heart Study: a cohort study. *Lancet* 358:1682–86
84. Vasan RS, Sullivan LM, Wilson PW, Sempos CT, Sundstrom J, et al. 2005. Relative importance of borderline and elevated levels of coronary heart disease risk factors. *Ann. Intern. Med.* 142:393–402
85. Wald NJ, Law MR. 2003. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 326:1419–25
86. Walsh JM, Pignone M. 2004. Drug treatment of hyperlipidemia in women. *JAMA* 291:2243–52
87. Wang Y, Wang QJ. 2004. The prevalence of prehypertension and hypertension among US adults according to the new joint national committee guidelines: new challenges of the old problem. *Arch. Intern. Med.* 164:2126–34
88. Wannamethee SG, Shaper AG, Whincup PH, Walker M. 1995. Smoking cessation and the risk of stroke in middle-aged men. *JAMA* 274:155–60
89. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, et al. 2002. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA* 288:1882–88
90. Wright JTJ, Bakris G, Greene T, Agodoa LY, Appel LJ, et al. 2002. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 288:2421–31
91. Wysowski DK, Armstrong G, Governale L. 2003. Rapid increase in the use of oral antidiabetic drugs in the United States, 1990–2001. *Diabet. Care* 26:1852–55

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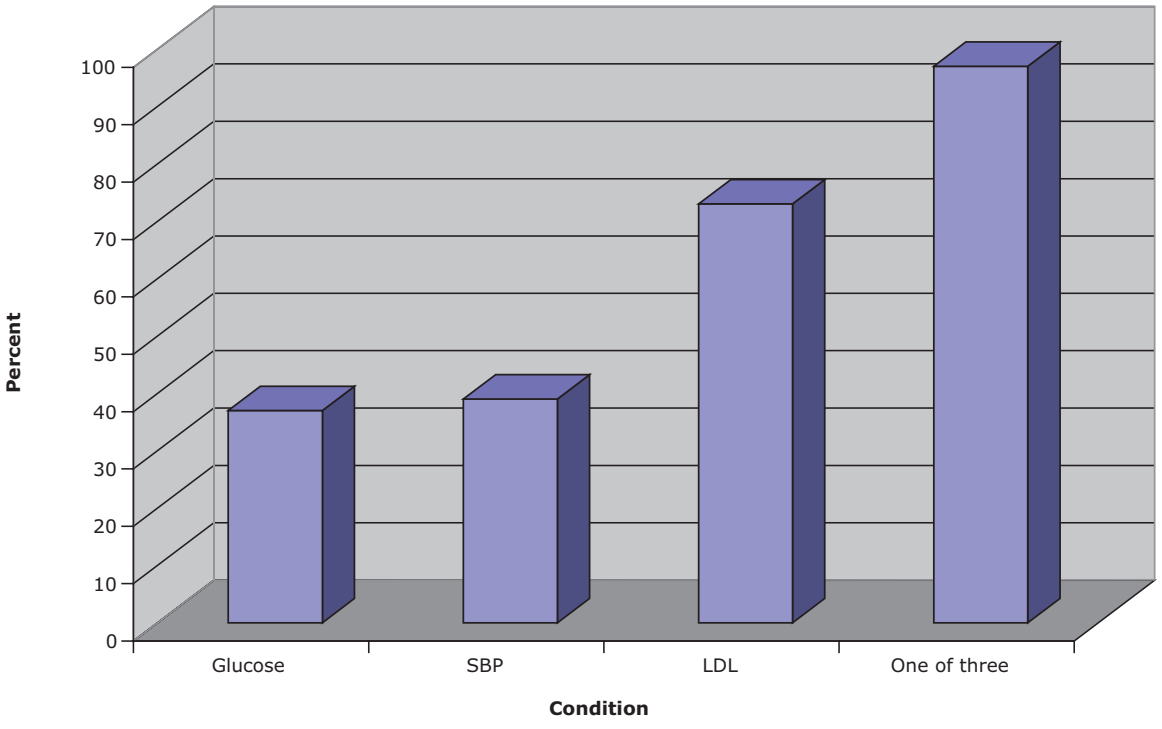

Figure 7

Percent of adult U.S. population with early disease.

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