Estimating the Impact of Adding C-Reactive Protein as a Criterion for Lipid Lowering Treatment in the United States

Steven Woloshin, MD, MS[1,2,3], Lisa M. Schwartz, MD, MS[1,2,3], Kevin Kerin, MD[1,2], and H. Gilbert Welch, MD, MPH[1,2,3]

[1]VA Outcomes Group, White River Junction, VT, USA; [2]Department of Medicine, Dartmouth Hitchcock Medical Center, Lebanon, NH, USA; [3]Center for the Evaluative Clinical Sciences, Dartmouth Medical School, Hanover, NH, USA.

BACKGROUND: There is growing interest in using C-reactive protein (CRP) levels to help select patients for lipid lowering therapy—although this practice is not yet supported by evidence of benefit in a randomized trial.

OBJECTIVE: To estimate the number of Americans potentially affected if a CRP criteria were adopted as an additional indication for lipid lowering therapy. To provide context, we also determined how well current lipid lowering guidelines are being implemented.

METHODS: We analyzed nationally representative data to determine how many Americans age 35 and older meet current National Cholesterol Education Program (NCEP) treatment criteria (a combination of risk factors and their Framingham risk score). We then determined how many of the remaining individuals would meet criteria for treatment using 2 different CRP-based strategies: (1) *narrow*: treat individuals at intermediate risk (i.e., 2 or more risk factors and an estimated 10–20% risk of coronary artery disease over the next 10 years) with CRP>3 mg/L and (2) *broad*: treat all individuals with CRP>3 mg/L.

DATA SOURCE: Analyses are based on the 2,778 individuals participating in the 1999–2002 National Health and Nutrition Examination Survey with complete data on cardiac risk factors, fasting lipid levels, CRP, and use of lipid lowering agents.

MAIN MEASURES: The estimated number and proportion of American adults meeting NCEP criteria who take lipid-lowering drugs, and the *additional* number who would be eligible based on CRP testing.

RESULTS: About 53 of the 153 million Americans aged 35 and older meet current NCEP criteria (that do not involve CRP) for lipid-lowering treatment. Sixty-five percent, however, are not currently being treated, even among those at highest risk (i.e., patients with established heart disease or its risk equivalent)—62% are untreated. Adopting the narrow and broad CRP strategies would make an additional 2.1 and 25.3 million Americans eligible for treatment, respectively. The latter strategy would make over half the adults age 35 and older eligible for lipid-lowering therapy, with most of the additionally eligible (57%) coming from the lowest NCEP heart risk category (i.e., 0–1 risk factors).

CONCLUSION: There is substantial underuse of lipid lowering therapy for American adults at high risk for coronary disease. Rather than adopting CRP-based strategies, which would make millions more lower risk patients eligible for treatment (and for whom treatment benefit has not yet been demonstrated in a randomized trial), we should ensure the treatment of currently defined high-risk patients for whom the benefit of therapy is established.

INTRODUCTION

In November 2002, a study[1] suggesting that high sensitivity C-reactive protein (CRP) level might be a stronger predictor of cardiovascular events than LDL cholesterol received a great deal of attention in the media(including the cover story in US News and World Reports) and in the medical community.[2–4] Responding to growing interest in CRP testing, and recognizing that its widespread use might dramatically affect the number of people labeled "at risk" for heart disease, the Centers for Disease Control and Prevention and the American Heart Association convened a consensus panel to develop evidence-based guidelines for the role of CRP in cardiovascular risk assessment. While the panel did not support universal testing, it did acknowledge that CRP might help physicians decide whether or not to initiate lipid-lowering treatment (as primary prevention) for some individuals at moderately elevated risk based on traditional factors and their Framingham risk score.[5]

Professional and public interest in the use of CRP as a screening test for heart risk has only grown with the publica-

tion of two observational analyses, which found that a reduction of CRP levels to less than 2 mg/L was associated with improved clinical[6] and intravascular ultrasound[7] outcomes in patients with established heart disease. The incremental value of CRP testing above conventional factors (i.e., age, smoking, hypertension, and lipids) in predicting heart risk remains controversial[8–10], and there are still no randomized trials demonstrating that cholesterol-lowering treatment benefits those whose only indication for treatment is elevated CRP. Nonetheless, many clinicians use CRP to guide treatment decisions for patients without heart disease.[11] In fact, CRP testing for cardiovascular risk assessment has become so common that it now has its own billing code—CPT 86141.[12] The number of such tests performed in the Medicare population tripled (from 145,000 to 454,000) between 2002 and 2004, the only years for which data are available (personal communication, Daniel Gottlieb, Dartmouth Atlas Group, Dartmouth Medical School). Some of the popularity of CRP testing may stem from aggressive marketing by high-profile proponents of the test who also have a financial stake in its use. For example, the CRPHealth.com web site highlights that President George W. Bush, a man at low risk for cardiovascular disease, has CRP as part of his annual executive physical exam.[2,13]

In this paper, we seek to understand some of the consequences of using CRP as an indication for lipid-lowering treatment. Specifically, we estimate how many Americans who do not meet the current criteria for lipid-lowering therapy would become eligible solely because of an elevated CRP level. To put these numbers in context, we also estimated how many people are being treated under current National Cholesterol Education Program (NCEP) guidelines.

METHODS

Overview

Using a nationally representative sample from the National Health and Nutrition Examination Survey[14] (NHANES), our analysis involved the following 2 steps. First, we used the NCEP[15] algorithm to estimate how many adults are currently eligible for treatment by NCEP criteria. Second, we estimated the additional number who would become eligible if a CRP strategy were adopted.

Data Source

All data are from the 1999–2002 NHANES survey.[14] NHANES is conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention to assess the health and nutritional status of the civilian, noninstitutionalized population of the United States. NHANES surveys, conducted periodically since the 1970s, and annually since 1999, involve household interviews and standardized medical examinations including a variety of blood tests such as high-sensitivity CRP and fasting lipid profiles. Since 1999, approximately 7,000 people have participated in NHANES each year. The complex sampling design, data collection methods, response rates (approximately 80% each year), and weighting approach are described elsewhere.[16–18] As suggested in the NHANES documentation, we combined data files for years 1999–2002 (the most recent years with complete data needed for analyses) to create a single analytic file (N=21,004 persons of all ages).[16]

Approximately one third of sample adults were randomly selected to undergo the morning laboratory examination, at which fasting lipid profiles and CRP levels were drawn. We analyzed the 2,778 individuals aged 35 and older with complete data on cardiac risk factors [to assign them to a coronary heart disease (CHD) risk category and to calculate their Framingham score], fasting lipids (to determine whether they meet the NCEP LDL treatment threshold), CRP level, and current use of lipid-lowering agents. The characteristics of the NHANES participants in our analysis appear in Table 1.

Currently Eligible by NCEP Criteria

Identify treatment status. The NCEP uses a combination of fasting LDL cholesterol level and estimated CHD risk to determine recommendations for lipid-lowering therapy.[15] Because treatment alters these parameters, our first step was to distinguish treated and untreated individuals. Treatment status was determined as follows. During the NHANES in-home interview, survey participants were asked if they have taken a medication in the past month for which they needed a prescription. Those who answered "yes" were asked to show the interviewer the bottles of all the medicines and these were entered into the database. We categorized people as currently

Table 1. Characteristics of NHANES participants 35 and older with complete data

Characteristics	NHANES participants (n=2,778)	Weighted % (SE)	
Age, y			
35–49	999	47%	(2%)
50–64	847	31%	(1%)
65–79	651	17%	(0.8%)
≥80	281	5%	(0.4%)
Sex			
Female	1,433	53%	(0.8%)
Male	1,345	47%	(0.8%)
Race/ethnicity			
White	1,483	76%	(2%)
Hispanic	746	11%	(2%)
Black	475	10%	(1%)
Other	74	4%	(0.8%)
Education			
<High school	946	21%	(1%)
High school	584	25%	(1%)
More than high school	1,243	54%	(2%)
CHD or risk equivalents			
Known CHD	289	9%	(0.7%)
Diabetes mellitus	240	8%	(0.7%)
Prior stroke	99	3%	(0.4%)
CHD risk factors			
Current smoker	563	22%	(1%)
Hypertension (BP>140/90 or taking antihypertensive meds)	1,292	40%	(1%)
Low HDL (HDL<40 mg/dl)	584	21%	(0.8%)
Family history of premature CHD (before age 50)	247	11%	(0.7%)

NHANES National Health and Nutrition Examination Survey, CHD coronary heart disease.

taking lipid-lowering treatment if they were taking any of the following lipid-lowering medications available at the time: atorvastatin, cervistatin, fluvastatin, lovastatin, pravastatin, simvastatin, cholestyramine, colestipol, fenofibrate, and gemfibrozil.

Determine eligibility of the untreated. We used the NCEP's 3-step algorithm to determine whether untreated individuals were currently eligible for treatment (Fig. 1).[15] This process begins with assigning people to a risk category. Individuals who reported having CHD or diabetes mellitus were assigned to the group "CHD or CHD equivalent." While the NCEP also counts symptomatic carotid artery disease, abdominal aortic aneurysm, and peripheral arterial disease as CHD equivalents, we were not able to do so since the relevant information was not collected by NHANES. For the remaining individuals, the next step was to determine how many CHD risk factors (e.g., age≥45 for men, age≥55 for women, cigarette smoking, hypertension, low HDL, family history of premature CHD, and age) were present. For those with 2 or more CHD risk factors, we calculated the 10-year risk of myocardial infraction or CHD death according to the Framingham scoring system, a model which uses age, gender, total and HDL cholesterol, smoking, blood pressure, and diabetes status to estimate risk.[19] If the calculated risk was >20%, the individual was assigned to the group "CHD (or equivalent);" if the calculated risk was 10–20%, the individual was assigned to the group "≥2 risk factors, 10–20% risk;" if the calculated risk was lower than 10%, assignment was to "≥2 risk factors, <10% risk." The remaining individuals were assigned to the group "0–1 risk factor."

Untreated individuals were considered eligible for treatment (according to the NCEP guidelines) if their LDL level exceeded the CHD risk category-specific threshold: LDL≥100 mg/dL for individuals with CHD or CHD equivalent; ≥130 mg/dL for individuals with multiple risk factors and 10–20% 10-year risk; ≥160 mg/dL for multiple risk factors and <10% 10-year risk; and ≥190 mg/dL for 0–1 risk factors.[15]

Determine eligibility of the treated. We used the same approach for treated individuals except that we had to make assumptions about risk factors which could plausibly be affected by lipid-lowering therapy: HDL and total cholesterol levels. If we did not account for treatment effects we would tend to misclassify individuals into falsely low-risk categories. We therefore made conservative assumptions about pretreatment values: that people take their medication regularly and that they experience the lipid effects observed in studies published in the medical literature (i.e., average HDL raised by 3 mg/dL and average total cholesterol lowered by 42%[15,20]. Correcting the HDL and total cholesterol levels moved <1% of treated individuals in the study sample into higher risk categories.

Finally, we also made the assumption that all treatments were appropriate based on the NECP criteria. This assumption has 2 conservative effects. First, it biases upward our estimate of the proportion of persons eligible for lipid-lowering therapy who are being treated (i.e., we overestimate compliance with recommendations). Second, it biases our estimate of the additional number of persons eligible for treatment by CRP downward because we only consider the effect of the CRP strategies on untreated individuals.
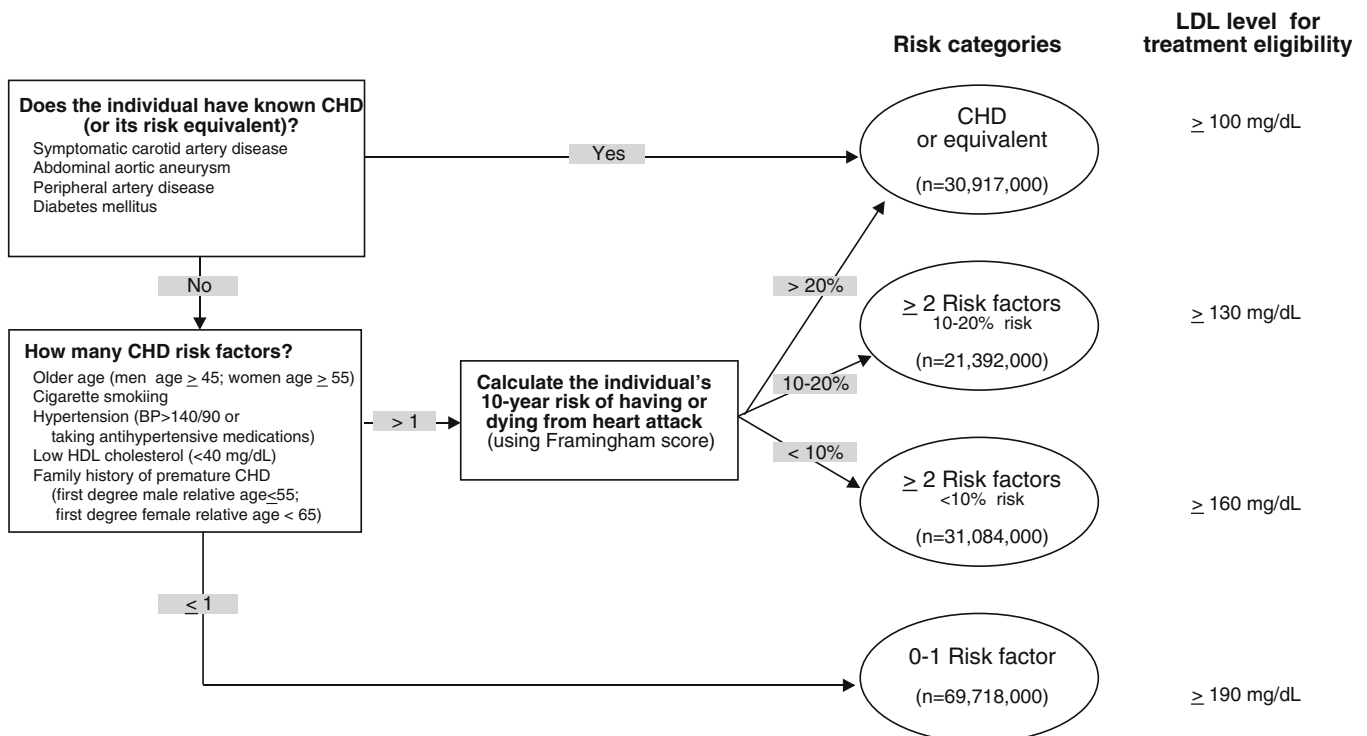

Figure 1. National Cholesterol Program's Adult Treatment Panel (ATPIII) algorithm and estimated number of American adults in each risk category.

Table 2. Number of adult Americans eligible for lipid-lowering treatment using current NCEP criteria and using 2 CRP strategies

NCEP risk category	Currently eligible by NCEP		Additional eligible by CRP	
	Treated	Untreated	CRP>3 mg/L with risk factors	CRP>3 mg/L
CHD or risk equivalent	9,952,000	16,199,000		1,211,000
≥2 risk factors with 10–20% risk CHD	3,598,000	10,182,000	2,132,000	2,132,000
≥2 risk factors with <10% risk CHD	1,990,000	5,420,000		7,480,000
0–1 risk factor	3,108,000	2,297,000		14,524,000
Total	18,648,000	34,098,000		25,347,000

CRP C-reactive protein, NCEP National Cholesterol Education Program, CHD coronary heart disease.

Additional Eligible by CRP

We then determined how many additional people (i.e., not meeting the NCEP criteria) would become eligible for lipid-lowering therapy based on an elevated CRP value. We considered 2 different CRP treatment strategies: (1) narrow CRP strategy[5]—treat individuals at moderate risk (i.e., 2 or more risk factors and an estimated 10–20% risk of coronary artery disease over the next 10 years) with CRP>3 mg/L; and (2) broad CRP strategy[21–23]—treat all individuals with CRP>3 mg/L.

Rationale for CRP Strategies

The narrow strategy is based on the American Heart Association/Centers for Disease Control statement that CRP testing "may be used at the discretion of the physician in patients judged by global risk assessment to be at intermediate risk (10% to 20% risk of CHD per 10 years) for cardiovascular disease," using a 3-mg/L threshold for treatment.[24] The broad strategy is based on published recommendations by proponents of the test[25] and one that is, anecdotally, accepted by some practicing physicians.[2,11] We restricted all analyses to persons age 35 and older because this is the age at which proponents suggest CRP first be measured.[25] Under both strategies, we excluded individuals with a CRP level >10 mg/L, as most experts believe a level this high cannot be used to predict heart disease and instead suggests the presence of a major infection, trauma, or chronic inflammatory disease.[25]

Analysis

All NHANES analyses incorporated the morning sample weights (WTSAF4YR) to account for differential probability of selection across subjects and for nonresponse (this weight was used because some blood tests required fasting) and design effects variables (SDMVPSU and SDMVSTRA) in order to account for the survey's complex, multistage sampling strategy when calculating standard errors.[18] We used the SVY series of commands in STATA 9.0 (College Station, TX) designed for analyzing complex survey designs such as NHANES. To obtain estimated counts of Americans in each category, we multiplied the nationally representative proportions from NHANES by the most recent population projection (2005) of adults aged 35 and older (153 million) from the US Census Bureau.[26]

RESULTS

Currently Eligible by NCEP Criteria

We estimate that 53 of the 153 million Americans aged 35 and older meet current NCEP criteria (that do not involve CRP) for lipid-lowering treatment (Table 2). Among the 53 million eligible, 18.6 million currently report taking a lipid-lowering medication and 34.1 million meet the NCEP criteria but are currently untreated. Overall, 65% of the people meeting current criteria are not being treated with lipid-lowering medications. Figure 2 shows how this proportion varied by risk category. For example, 42% of those meeting criteria in the lowest risk category (0–1 risk factor) were not being treated, while 62% of the highest risk patients—those with CHD or its risk equivalent—were also untreated (P<0.01).

Additional Eligible by CRP

Adopting a CRP-based strategy for lipid-lowering therapy would increase the number of Americans eligible for treatment, but the impact varies dramatically depending on which strategy is adopted. Adopting the *narrow CRP strategy*—treating individuals at intermediate risk (i.e., 2 or more risk factors and a calculated 10-year risk of coronary disease of 10–20%) if their CRP level exceeded 3 mg/L—would increase the number of adults eligible for treatment by 2.1 million (Fig. 3). Under the broad CRP strategy, treating individuals whose CRP exceeded 3 mg/L regardless of whether they meet NCEP criteria increases the number eligible for treatment by 25.3 million, making over half the adults aged 35 and older eligible for lipid-lowering therapy.

Who Would Be Affected by a CRP Treatment Strategy?

By definition, the narrow CRP strategy can only affect individuals at moderate predicted risk for CHD. In contrast, the broad strategies largely affect individuals at low risk: 57% of adults who become eligible for treatment only because of an elevated CRP level are in the lowest CHD risk category (0–1 risk factor).

DISCUSSION

Our study has two major findings. First, the majority of adults currently recommended for lipid-lowering therapy remain untreated: almost two-thirds of Americans at high risk for a myocardial infarction or CHD death are not taking lipid-lowering medications. Second, adding a CRP strategy to current cholesterol-based criteria could have a profound impact on the number of people considered for treatment. While a narrowly focused use of CRP in those at moderate risk of coronary events group would make 2.1 million people

NHANES
participants
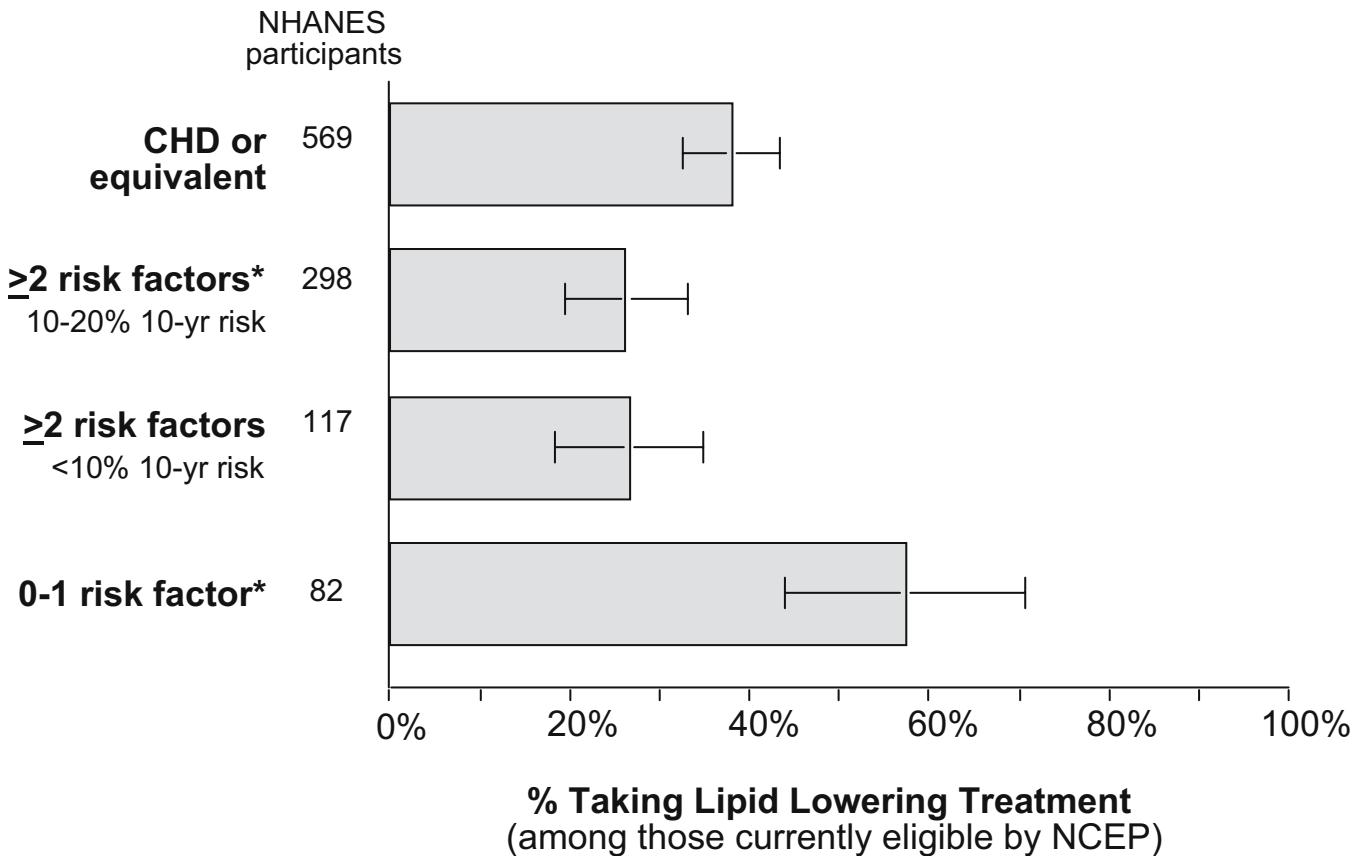
Figure 2. Proportion taking lipid-lowering treatment among those currently eligible by National Cholesterol Education Program criteria (assuming that all current treatment is appropriate). *Error bars* indicate the 95% CI for each proportion. *Asterisks* mean that the difference in the proportion taking lipid-lowering treatment was statistically significant between the "coronary heart disease (CHD) or equivalent group" and the "≥2 risk factors (10–20% 10-year risk) group (38% vs 26%, *P*=0.02)," and between the "CHD or equivalent group" and the "0–1 risk factor" group (38% vs 58%, *P*=0.009).

additionally eligible for treatment, a broad strategy would add up to over 25 million people—the majority of whom are in the lowest CHD risk category.

Our findings should be interpreted in light of several limitations. First, there is some misclassification of individuals into the National Cholesterol Education risk categories. Because the NHANES database does not have specific measures of 3 of the CHD risk equivalents (cerebrovascular disease, aortic aneurysm, or peripheral vascular disease), we may underestimate the number of individuals in the highest risk category. However, given the substantial overlap between these unknown and known factors (e.g., CHD, diabetes mellitus, a calculated risk of heart disease of greater than 20%), this misclassification is likely to be small. Another source of misclassification may result from using information that depends on respondent recall of risk factor information (e.g., history of MI) or on a single laboratory measurement. However, any consequent misclassification would be random and should largely cancel out (e.g., for every spuriously high LDL there will be a spuriously low one).

Second, we assumed that all individuals taking lipid-lowering medications were treated appropriately. Some low-risk patients, of course, receive lipid-lowering treatment even though they do not meet the NCEP indication; such inappropriate treatment has, in fact, been documented by others.[27]

Assuming that all patients were treated appropriately makes our findings conservative: it minimizes both our estimate of undertreatment and the number of people additionally eligible for treatment using a CRP criterion.

It is also important to recognize that not all people eligible for lipid-lowering treatment will require a lipid-lowering medication. The NCEP guidelines suggest that individuals whose LDL values exceed a given risk-category specific threshold value undergo a trial of diet and exercise with repeated LDL testing prior to initiating medications. Unfortunately, therapeutic lifestyle changes are not very effective at lowering LDL and few of these patients achieve the NCEP goals without medication.[28,29] Furthermore, there is mixed evidence about the effect of lifestyle changes on CRP. CRP levels did not change among female smokers randomized to exercise training (vs health education), despite a demonstrated improvement in fitness.[30] In a trial of men and women at high risk for cardiovascular disease (based on standard risk factors), CRP levels did not change appreciably (over 3 months) among participants randomized to either a low-fat diet or a Mediterranean-style diet with mixed nuts; however, CRP levels did drop by an average of 0.5 mg/L for participants randomized to a Mediterranean diet with virgin olive oil.[31] Finally, a third trial (*n*=120) found CRP levels decreased by an average of 0.8 mg/L over 2 years among obese, premenopausal women without
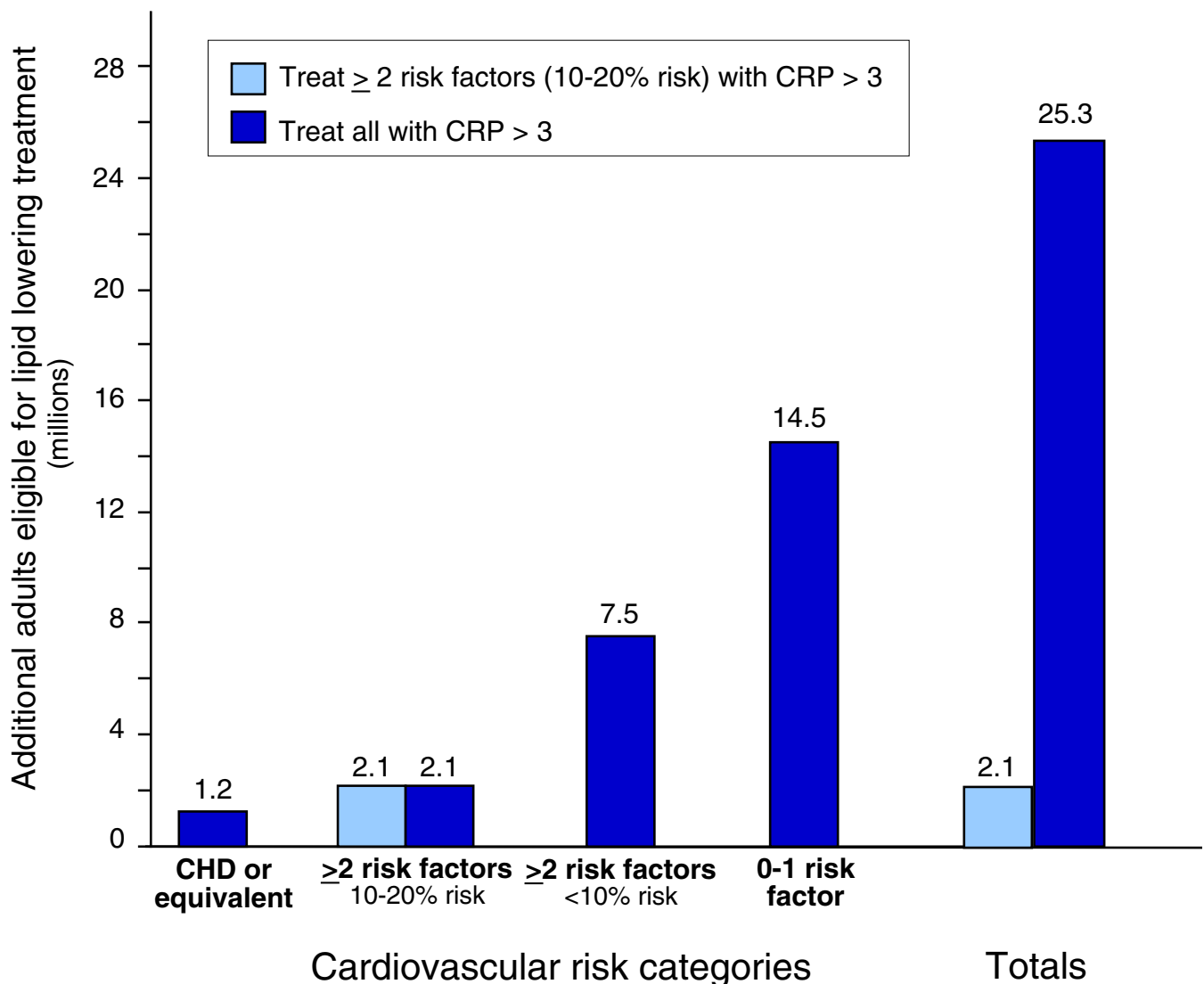
Figure 3. Additional numbers of adults estimated to be eligible for lipid-lowering treatment using two C-reactive protein strategies.

diabetes, hypertension, or hyperlipidemia randomized to an intensive multidisciplinary program that included a Mediterranean-style diet and increased physical activity (vs general information about diet and exercise).[32] To see how our results would be affected if the intensive diet/exercise intervention were successfully implemented prior to lipid-lowering medications, we performed a sensitivity analysis. Under the most optimistic assumptions—assuming long-term compliance with the intensive diet and exercise program (outside the context of a trial) and granting a full 1-mg/L decrease in CRP levels—the narrow and broad CRP strategies would still make an additional 1.5 and 18 million Americans, respectively, eligible for statins.

While it is possible that a CRP strategy will turn out to be useful, there is currently no evidence from randomized trials demonstrating that lipid-lowering treatment benefits those whose only indication for treatment is elevated CRP. Such a trial is now underway: in the Jupiter trial, patients with a CRP level of 2 mg/L or greater and an LDL<130 mg/dL are being randomized to receive rosuvastatin or placebo.[33] There is also

ongoing controversy about the value of CRP in cardiovascular risk assessment. While some suggest it is valuable because CRP predicted CHD risk independent of traditional risk factors,[1] others argue that the marginal value of CRP in risk prediction is quite limited.[9,10,34–36]

Our finding that almost two thirds of the highest risk individuals (i.e., those with CHD or CHD equivalent) are untreated is in line with other published work.[27,37,38] Unfortunately, there is no reason to think that CRP testing will do anything to ameliorate this problem: most of the patients who become eligible for treatment solely on the basis of CRP in fact face the lowest CHD risk. Instead, widespread adoption of CRP testing has the potential to turn a very real problem of undertreatment into one of overdiagnosis. For example, if the CRP threshold of the Jupiter trial[33]—2 mg/dL (the approximate median value for US adults[39]—were used, we estimate that an additional 40 million Americans would become eligible for treatment. Unless it is highly targeted, CRP testing will identify few new high-risk patients but, instead, millions of low-risk ones who consequently stand to

gain little from treatment. But treating millions of additional low-risk individuals will come at a cost. In addition to the obvious economic cost, and adverse treatment effects, there is another more subtle one: the energy going into the treatment of low-risk patients may distract physicians from more closely attending to the needs of those at high risk. Widespread CRP testing, that is, has the potential to make a bad situation worse.

In summary, depending on its precise nature, adding a CRP strategy to current cholesterol-based criterion could have a profound impact on the number of people considered for treatment. Adding a broadly applied CRP strategy to current cholesterol-based guidelines would make over half of the adults aged 35 and older in the United States eligible for lipid-lowering therapy. Before expanding treatment criteria to include more low-risk patients—for whom treatment benefit is not established—we should ensure the treatment of high-risk patients where the benefit of therapy is clear.

Corresponding Author: Steven Woloshin, MD, MS; VA Outcomes Group, White River Junction, VT, USA (e-mail: Steven.Woloshin@dartmouth.edu).

REFERENCES

1. **Ridker PM, Rifai N, Rose L, Buring JE, Cook NR**. Comparison of c-reactive protein and low density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med. 2002;347(20):1557–65.
2. **Grady D**. Study says a protein may be better than cholesterol in predicting heart disease. NY Times. 2002(November 17);A26.
3. **Brown D**. New test for risk of heart disease; study shifts focus from cholesterol. Washington Post. 2002(November 14);A1.
4. **USNWR cover**. Special report: the heart test that could save your life. US News and World Report. 2002(November 25);54.
5. **Pearson TA, Mensah GA, Alexander RW, et al**. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the centers for disease control and prevention and the American heart association. Circulation. 2003;107:499–511.
6. **Ridker P, Cannon C, Morrow D, et al**. Pravastatin or atorvastatin evaluation and infection therapy—thrombolysis in myocardial infarction. N Engl J Med. 2005;352:20–8.
7. **Nissen S, Tuzcu E, Schoenhagen P, et al**. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005;352:29–38.
8. **Cook N, Burine J, Ridker P**. The effect of including C-reactive protein in cardiovascular risk prediction models for women. Ann Intern Med. 2006;145:21–9.
9. **Folsom A, Chambless L, Ballantyne C, et al**. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers. Arch Intern Med. 2006;166:1368–73.
10. **Lloyd-Jones D, Liu K, Tian L, Greenland P**. Narrative review: assessment of C-reactive protein in risk prediction for cardiovascular disease. Ann Intern Med. 2006;145:35–42.
11. **Kolata G**. Protein's link to heart disease is a mystery. NY Times. 2005 (January 11);F5.
12. Department of Health and Human Services Centers for Medicare and Medicaid Services. Program memorandum intermediaries/carriers.

13. 2002 Clinical Laboratory Fee Schedule and Laboratory Costs Subject to Reasonable Charge Payment Methodology. Implementation date January 1, 2002, Download AB-01-162. http://www.cms.hhs.gov/Transmittals/CMSPM/itemdetail.asp?filterType=dual,%20keyword&filterValue=162&filterByDID=0&sortByDID=4&sortOrder=ascending&itemID=CMS025696&intNumPerPage=10 [accessed December 2, 2006].
14. CRPhealth.com. Your source of information on C-reactive protein. Online presentations. Presentations on CRP for patients. An introduction to high sensitivity c-reactive protein (hs-CRP) for patients: can we better predict heart attack and stroke? http://www.crphealth.com/conf/hcp/5,22/doctor.paul.m.ridker.an.introduction.to.high-sensitivity.c-reactive.protein.html [accessed July 26, 2006]
15. National Health and Nutrition Examination Survey. Public-use data files. http://www.cdc.gov/nchs/about/major/nhanes/datalink.htm [accessed December 2, 2006].
16. National Cholesterol Education Program. Third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) full report. http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm [accessed July 27 2006].
17. Centers for Disease Control and Prevention. NHANES 2000-1 analytic guidelines (June 2004 version). http://www.cdc.gov/nchs/nhanes.htm. [accessed July 26, 2006].
18. The National Health and Nutrition Examination Survey. 1999–2000 addendum to the NHANES III analytic guidelines. http://www.cdc.gov/nchs/data/nhanes/guidelines1.pdf [accessed July 26, 2006].
19. The National Health and Nutrition Examination Survey. Analytic and reporting guidelines. Last update: December, 2005. http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/nhanes_analytic_guidelines_dec_2005.pdf [accessed July 27, 2006].
20. **Wilson P, D'Agostino R, Levy D, Belanger A, Silbershatz H, Kannel W**. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;12:1837–47.
21. **Law M, Wald N, Rudnicka A**. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ. 2003;326:1423–30.
22. **Ridker PM**. C-reactive protein a simple test to help predict risk of heart attack and stroke. Circulation. 2003;108:e81–5.
23. **Ridker PM**. Clinical application of c-reactive protein for cardiovascular disease detection and prevention. Circulation. 2003;107:363–9.
24. **Ridker PM, Wilson PWF, Grundy SM**. Should c-reactive protein be added to metabolic syndrome an the assessment of global cardiovascular risk? Circulation. 2004;109:2818–25.
25. **Smith SC, Anderson JL, Cannon RO, et al**. CDC/AHA workshop on markers of inflammation and cardiovascular disease: application to clinical and public health practice report from the clinical practice discussion group. Circulation. 2004;110:e550–3.
26. Brigham and Women's Hospital. Cardiovascular Center. Understanding C-reactive protein—a simple test to help predict risk of heart attack and stroke. http://www.brighamandwomens.org/publications/publications.aspx [accessed July 27, 2006].
27. The 2006 Statistical Abstract: The National Data Book. US Census Bureau. Estimates and projections by age, sex, race/ethnicity. Table 12 - Resident Population Projections by Sex and Age: 2005 to 2050. http://www.census.gov/compendia/statab/population/ [accessed December 1, 2006].
28. **Abookire SA, Karson AS, Fiskio J, Bates DW**. Use and monitoring of "statin" lipid-lowering drugs compared with guidelines. Arch Intern Med. 2001;161:53–8.
29. **Hsia J, Rodabough R, Rosal M, et al**. Compliance with National Cholesterol Education Program dietary and lifestyle guidelines among older women with self-reported hypercholesterolemia. The women's health initiative. Am J Med. 2002;113:384–92.
30. **Henkin Y, Shai I, Zuk R, et al**. Dietary treatment of hypercholesterolemia: do dietitians do it better? A randomized, controlled trial. Am J Med. 2000;109:549–55.
31. **Hammett C, Prapavessis H, Baldi J, et al**. Effects of exercise training on 5 inflammatory markers associated with cardiovascular risk. Am Heart J. 2006;151:367e8–16.
32. **Estruch R, Martinez-Gonzalez M, Corella D, et al**. Effects of a Mediterranean-style diet on cardiovascular risk factors. Ann Intern Med. 2006;145:1–11.
33. **Esposito K, Pontillo A, Di Paolo C, et al**. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women. JAMA. 2003;289:1799–804.

33. **Mora S, Ridker P**. Justification for the use of statins in primary prevention: an intervention trial evaluating Rosuvastatin (JUPITER)—can C-reactive protein be used to target statin therapy in primary prevention? Am J Cardiol. 2006;97(suppl):33A–41A.

34. **Danesh J, Wheeler J, Hirschfield G, et al**. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med. 2004;350:1387–97.

35. **Davey Smith G, Timpson N, Lawlor D**. C-reactive protein and cardiovascular risk: still an unknown quantity? Ann Intern Med. 2006;145: 70–2.

36. **Lloyd-Jones D, Tian L**. Predicting cardiovascular risk: so what do we do now? Arch Intern Med. 2006;166:1342–4.

37. **Ko D, Mamdani M, Alter D**. Lipid-lowering therapy with statins in high risk elderly patients: the treatment risk paradox. JAMA. 2004;291: 1864–70.

38. **Majumdar S, Gurwitz J, Soumerai S**. Undertreatment of hyperlipidemia in the secondary prevention of coronary artery disease. J Gen Intern Med. 1999;14:711–7.

39. **Woloshin S, Schwartz L**. Distribution of high sensitivity C-reactive protein (CRP) values in the United States (letter). N Engl J Med. 2005;352:1611–3.