From Here to JUPITER
Identifying New Patients for Statin Therapy Using Data From the 1999–2004 National Health and Nutrition Examination Survey

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Background—Guidelines for statin use currently focus on patients with elevated low-density lipoprotein levels. Recent findings from the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), however, indicate that statin therapy to reduce cardiovascular risk is also effective among older persons with at-goal low-density lipoprotein but elevated high-sensitivity C-reactive protein levels. We estimate the size of and describe this new population for whom statin therapy may now be indicated based on JUPITER’s findings.

Methods and Results—Using data from the 1999 to 2004 National Health and Nutrition Examination Survey, we estimate that 57.9% of older adults (men ≥50 years and women ≥60 years), or 33 547 000 (95% CI, 32 217 000 to 34 877 000) Americans, are currently taking a statin (24.4%) or indicated for statin therapy (33.5%). In addition, we estimate that 19.2%, or 11 144 000 (95% CI, 10 053 000 to 12 235 000), may become newly eligible for statin therapy. This includes 8 071 000 (13.9%; 95% CI, 7 173 000 to 8 969 000) with high-sensitivity C-reactive protein ≥2 mg/L and low-density lipoprotein 130 mg/dL (ie, those meeting “strict” JUPITER criteria) and an additional 3 073 000 (5.3%; 95% CI, 2 404 000 to 3 743 000) with high-sensitivity C-reactive protein ≥2 mg/L and low-density lipoprotein of 130 to 160 mg/dL for whom JUPITER’s findings might reasonably be extended. Thus, ≈80% of older persons may now have an indication for statin therapy. Compared with those who would continue to have no indication for statin therapy, the JUPITER group was more likely to be female, to be older, and to have obesity, hypertension, and the metabolic syndrome.

Conclusions—JUPITER’s findings have the potential to impact treatment recommendations for ≈20% of middle-aged to elderly adults, thus increasing the proportion of this segment of the population with an indication for statin therapy to nearly 80%. (Circ Cardiovasc Qual Outcomes. 2009;2:41-48.)

Key Words: ■ prevention ■ C-reactive protein ■ lipoprotein ■ epidemiology ■ risk factors

Indications for statin therapy to prevent coronary heart disease (CHD) have significantly expanded over the past decade to include patients with ever lower serum low-density lipoprotein (LDL) cholesterol.1-9 In addition to lowering LDL, statins also decrease high-sensitivity C-reactive protein (hs-CRP) levels.10-13 Although a growing body of literature suggests that baseline and poststatin hs-CRP levels add incremental accuracy to the prediction of cardiovascular events,14-22 until now it had not been clear whether targeting individuals with elevated hs-CRP but at-goal LDL values exerts a positive effect on cardiovascular outcomes.

Clinical Perspective see p 48

The Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) sought to determine whether statin medications reduce the risk of cardiovascular events in patients who are currently not indicated for statin therapy based on LDL criteria but who have elevated hs-CRP levels.23 In this trial, men ≥50 years and women ≥60 years with no known CHD, LDL values <130 mg/dL, and hs-CRP values ≥2 mg/L were randomized to rosvastatin or placebo. The study was terminated early after patients in the rosvastatin group experienced significantly fewer cardiovascular events and deaths than those randomized to placebo.24

In light of these findings, the patient population for whom statin therapy is recommended as part of a risk-reduction strategy may be expanded beyond those with elevated LDL values. The size and characteristics of this new population have not yet been well defined. Thus, the objectives of this study are to (1) estimate the number of individuals for whom statin therapy may now be indicated based on JUPITER’s findings.
findings, and (2) describe the characteristics of this population by comparing their sociodemographic and cardiovascular risk factors to both those who meet criteria for risk-reduction therapy by the current guidelines set forth by the National Cholesterol Education Program (NCEP)/Adult Treatment Panel III (ATPIII) and those who would continue to have no indication for statin therapy.

**SUMMARY**

- Current National Cholesterol Education Program/Adult Treatment Panel III guidelines for the use of statin medications to reduce cardiovascular risk focus exclusively on individuals with low-density lipoprotein (LDL) cholesterol levels above what is recommended.
- On the basis of these guidelines, ≈58% of the middle-aged to older adult population have an indication for statin therapy, over half of whom are not treated.
- Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin’s (JUPITER) findings suggest that individuals without coronary heart disease who have at-goal LDL values but elevated high-sensitivity C-reactive protein (hs-CRP) values benefit from statin therapy.
- On the basis of JUPITER’s findings, we estimate that 19.2% of the middle-aged to older adult population, or 11 144 000 (95% CI, 10 053 000 to 12 235 000), may become newly eligible for statin therapy. This includes 8 071 000 (13.9%; 95% CI, 7 173 000 to 8 969 000) with hs-CRP levels of ≥2 mg/L and LDL levels of <130 mg/dL (ie, those meeting “strict” JUPITER criteria) and an additional 3 073 000 (5.3%; 95% CI, 2 404 000 to 3 743 000) with hs-CRP levels of ≥2 mg/L and LDL levels of 130 to 160 mg/dL for whom JUPITER’s findings might reasonably be extended.
- Thus, ≈80% of older persons may now have an indication for statin therapy.
- Sociodemographic and cardiovascular characteristics of this novel statin-eligible JUPITER group are similar to individuals with an already established indication for statin therapy.

**Methods**

**Data Source**

The data for this study come from the National Health and Nutrition Examination Survey (NHANES). Conducted by the National Center for Health Statistics, NHANES collects detailed health and nutritional data on a nationally representative, multistage probability sample of the noninstitutionalized civilian population of the US. NHANES includes both an in-home interview and a clinical examination at a mobile examination center (MEC). A subsample of respondents, selected at random with a specified sampling fraction, provides a fasting blood sample as part of their MEC examination. This subsample has its own designated weight, which accounts for the additional probability of selection into the subsample component, as well as the additional nonresponse. In 1999, NHANES transitioned from being a periodic cross-sectional survey to adopting a continuous data collection strategy, with data released every 2 years. For the purposes of this study, we combined data from 3 NHANES cohorts: 1999–2000, 2001–2002, and 2003–2004.

**Study Sample**

Consistent with the sociodemographic characteristics of the JUPITER patient population, we restricted the analysis to men aged ≥50 years and women aged ≥60 years who were included in the fasting blood draw subsample of the 1999–2004 NHANES (N=2497). We excluded 175 individuals who had missing data on statin eligibility (as described below), fasting LDL, hs-CRP, or lipid-lowering medication use, extracted from the NHANES medication file. Thus, the final sample size for this study was 2322.

We stratified the sample into 3 groups based on statin eligibility. First, we identified individuals who were currently taking a statin or indicated for statin therapy based on NCEP/ATPIII guidelines. Then, among the remainder of the sample, we used hs-CRP and LDL values to identify individuals who would now be indicated for statin therapy based on JUPITER’s findings. Finally, the third group was comprised of those without any NCEP/ATPIII or JUPITER indication for statin therapy. These groups are defined, in turn, below.

**NCEP/ATPIII-Indicated Group**

Individuals currently taking a statin were included in the NCEP/ATPIII group regardless of their risk level or LDL value, as they were assumed to have an established indication for statin therapy. Among those not on a statin, NCEP/ATPIII indications for treatment were determined by first stratifying individuals into 1 of 4 cardiovascular risk categories (high, moderately high, intermediate, or low risk) and then comparing one’s measured LDL level to their risk-group-specific LDL goal. We did not consider treatment with nonstatin, lipid-lowering medications in our eligibility stratification as such individuals may still be candidates for additional statin therapy. Subjects were deemed to be at the highest risk level if they had CHD or a CHD risk equivalent, which included diabetes, peripheral artery disease, symptomatic carotid artery disease, or abdominal aortic aneurysm. CHD was assessed through self-report of coronary artery disease, myocardial infarction, or angina pectoris. Diabetes was assessed by self-report of diabetes. Individuals without a diagnosis of diabetes but with a fasting blood glucose ≥126 mg/dL were also coded as having diabetes. Peripheral artery disease was defined as an ankle-brachial index <0.9 mm Hg; and self-report of stroke was used as a proxy for symptomatic carotid artery disease. Given the available data in NHANES, we were unable to determine the presence or absence of abdominal aortic aneurysm.

Per NCEP/ATPIII guidelines, individuals without CHD or a CHD risk equivalent were assessed for the presence of major risk factors of CHD (other than LDL), including age, smoking status, hypertension, high-density lipoprotein (HDL) level, and family history of premature CHD. Hypertension was defined as having a mean systolic blood pressure (SBP) ≥140 mm Hg or a mean diastolic blood pressure (DBP) ≥90 mm Hg, or reporting taking an antihypertensive medication. HDL cholesterol was considered low if <40 mg/dL and deemed a negative risk factor if ≥60 mg/dL. Family history of premature CHD was defined by reporting having a first-degree relative who had had a heart attack or angina before the age of 50 years.

For persons with 2 or more risk factors, we calculated their Framingham risk score (FRS). Individuals with an FRS greater than 20% were included in the high risk group, those between 10% and 20% in the moderately high risk group, and those less than 10% in the intermediate risk group. Individuals with 0 or 1 major risk factor were considered to be low risk. FRS was not calculated for individuals aged >79 years, as the FRS is not validated in this group.

To determine LDL goals for each risk category, we used the lower LDL option for initiating lipid-lowering therapy recommended by NCEP/ATPIII. We decided to use the lower treatment threshold as current clinical practice is moving toward the achievement of lower LDL values with medication therapy, more specifically with statin medications. As such, eligibility for lipid-lowering therapy was defined as follows: LDL=100 mg/dL for the high risk group,
LDL > 130 mg/dL for the moderately high risk group, and LDL > 160 mg/dL for the intermediate and low risk groups. For those aged > 79 years without known CHD or a CHD risk equivalent (and no FRS), we set the LDL goal at 160 mg/dL.

**JUPITER-Indicated Group**

Individuals with no current NCEP/ATPIII indication for lipid-lowering therapy were potentially eligible for inclusion in the JUPITER group. For these subjects, hs-CRP and LDL values were assessed. Those with hs-CRP > 2 mg/L and LDL < 130 mg/dL comprised our “strict” JUPITER group. We additionally included individuals with an hs-CRP > 2 mg/L and LDL between 130 and 160 mg/dL, the “extended” JUPITER group, as any recommendation for hs-CRP screening based on JUPITER findings would likely be extended to this cohort, assuming they had no other indication for statin therapy. Importantly, individuals with hs-CRP values > 10 mg/L were excluded from the JUPITER group and included in the “Not Indicated” group, as levels this high are thought to reflect systemic inflammatory processes other than cardiovascular disease. Patients with inflammatory diseases such as systemic lupus erythematosus were excluded from the JUPITER trial and, at present, it is unclear whether such subjects would benefit from statin therapy.²³

**Not Indicated Group**

Individuals without an NCEP/ATPIII or JUPITER indication for statin therapy were included in the Not Indicated group. These individuals had hs-CRP levels < 2 mg/L (or > 10 mg/L) and a maximum LDL of 160 mg/dL.

**Sample Characteristics**

The JUPITER group was compared to the other 2 statin-eligible groups, the NCEP/ATPIII and Not Indicated groups, based on several sociodemographic and cardiovascular risk factors. Sociodemographic characteristics included gender, age, race/ethnicity, and poverty income ratio, defined as the ratio of total family income to the family’s household size-adjusted poverty threshold.²⁴ If a family’s total income is less than their threshold income value (determined annually by the US Census Bureau), then the family, and every individual in it, is considered poor. Poverty income ratio values < 1.00 are below the official poverty threshold, whereas poverty income ratio values ≥ 1.00 indicate income at or above the federal poverty level.

Cardiovascular risk factors included smoking status, body mass index, abdominal obesity, presence of impaired glucose tolerance or diabetes, hypertension, and metabolic syndrome. Abdominal obesity was defined as a waist circumference > 88 cm for women and > 102 cm for men. Individuals without a diagnosis of diabetes (as described earlier) were considered to have impaired glucose tolerance if the fasting blood glucose was ≥ 100 mg/dL and < 126 mg/dL, and they did not report use of insulin or a hypoglycemic medication. Hypertension status was categorized into 3 levels: hypertension (SBP ≥ 140 mm Hg, DBP ≥ 90 mm Hg, or self-reported use of antihypertensive medication), prehypertension (SBP 120 to 139 mm Hg or DBP 80 to 89 mm Hg), or normal blood pressure (SBP < 120 mm Hg and DBP < 80 mm Hg).³¹,³² Metabolic syndrome was defined as the presence of three or more of the following risk factors: abdominal obesity, triglycerides > 150 mg/dL, HDL < 40 mg/dL for men and < 50 mg/dL for women, blood pressure ≥ 130/85 mm Hg or self-reported antihypertensive medication use, and impaired glucose tolerance or self-reported diabetes medication use.²⁵

Additionally assessed were global measures of cardiovascular risk, including the Framingham and Reynolds risk scores.¹⁷,³⁰ The Reynolds risk score was calculated in all individuals using the following variables: hemoglobin A1c, parental history of premature CHD, current smoking, SBP, HDL, total cholesterol, and hs-CRP.

Use of hormone replacement therapy, defined as current use of oral or transdermal estrogen in combination with progesterone or alone, is also reported, as estrogen has been shown to elevate hs-CRP levels. Finally, we assessed median values for hs-CRP, mean values for LDL and HDL, and the presence of elevated serum creatinine (> 2 mg/dL), aspartate aminotransferase (> 150 mg/dL), and alanine aminotransferase (> 180 mg/dL) in each of the 3 groups.

**Data Analysis**

All analyses were performed using SAS-callable SUDAAN to take into account the survey’s complex sample design;²⁵ this allowed for appropriate variance estimation and weighting of the data. We began by determining the proportion of the middle-aged to elderly population (men aged ≥ 50 years and women aged ≥ 60 years) in each of the 3 statin-eligible groups, specifically focusing on assessing the size of the population that is currently eligible for statin therapy according to NCEP/ATPIII guidelines and those that would be expected to be newly eligible based on JUPITER’s findings. Weighted prevalence estimates were multiplied by the 2000 US Census figure to estimate the number of individuals in each group. Prevalence estimates and their associated 95% CI are rounded to the nearest thousand. We then compared the sociodemographic and clinical characteristics of the JUPITER group with each of the other 2 statin-eligible groups using χ² tests for categorical variables and t-tests for continuous variables. Weighted percentages and means with SEs are reported for each group, along with corresponding probability values comparing JUPITER with the NCEP/ATPIII group, and JUPITER with the Not Indicated group. Statistical significance was set at the 0.05 level. For hs-CRP, median values were calculated and group distributions compared using the Mann-Whitney test in SAS version 9.1.3. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

**Results**

**Statin Eligibility**

The 1999–2004 NHANES included a total of 6544 men aged ≥ 50 years and women aged ≥ 60 years, representing approximately 57 980 000 Americans. However, the present analysis focused on the 2322 respondents in the fasting blood draw subsample with complete data to determine statin eligibility. As the results in Figure 1 show, over half (57.9%) of the population (unweighted N = 1346, or an estimated 33 547 000 persons [95% CI, 32 217 000 to 34 877 000]) had an NCEP/ATPIII indication for statin therapy. Of this group, 42% (unweighted N = 508) were currently taking a statin. The remaining 58% (unweighted N = 838) were judged to be “untreated,” of which most were in the high-risk group (unweighted N = 518).

Of the remaining 976 subjects, 330 (or 13.9% of the overall population, representing 8 071 000 persons [95% CI, 7 173 000 to 8 969 000]) met “strict” JUPITER criteria, with hs-CRP ≥ 2 mg/L and LDL < 130 mg/dL. An additional 5.3% (unweighted N = 130, or an estimated 3 073 000 persons [95% CI, 2 402 000 to 3 743 000]) had an “extended” JUPITER indication for statin therapy, with hs-CRP ≥ 2 mg/L and LDL between 130 and 160 mg/dL. Finally, 22.9% (unweighted N = 516, or 13 289 000 persons [95% CI, 11 959 000 to 14 619 000]) had no indication for statin therapy, making up the Not Indicated group.

**Comparison of JUPITER and NCEP/ATPIII Groups**

Sociodemographic and clinical characteristics of the sample, by statin eligibility, are presented in Table 1. Compared with the JUPITER group, the NCEP/ATPIII group included a significantly greater proportion of men. However, the 2 groups were similar with respect to other sociodemographic

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characteristics, including age, race/ethnicity, and poverty status. The 2 groups were also comparable in terms of their prevalence of current smoking, abdominal obesity, and hypertension. Although the prevalence of diabetes and FRS scores were significantly greater in the NCEP/ATPIII group than in the JUPITER group, reflecting the centrality of the FRS in determining need for statin therapy according to the current guidelines, the 2 groups were similar in their distribution of Reynolds risk scores. The JUPITER group had an increased prevalence of class I and II obesity, and the NCEP/ATPIII group had more metabolic syndrome; both of these differences were statistically significant. The median hs-CRP values in the NCEP/ATPIII and JUPITER groups were elevated (>5 mg/L), though the JUPITER group had significantly higher values. LDL was significantly higher and HDL was significantly lower in the NCEP/ATPIII group.

Comparison of JUPITER and Not Indicated Groups

In comparing the JUPITER group with the Not Indicated group, JUPITER subjects were significantly more likely to be female and older. Distributions of race/ethnicity, poverty status, and smoking status were similar between the 2 groups. Although the 2 groups were also similar with respect to FRS scores, individuals in the JUPITER group had significantly greater Reynolds risk scores and were more likely to be obese and to have hypertension and the metabolic syndrome, as compared with those in the Not Indicated group. The median hs-CRP value was significantly higher in the JUPITER group than in the Not Indicated group, consistent with the stratification schema for the 2 groups, though HDL and LDL levels were similar in the 2 groups.

Finally, hormone replacement therapy use was significantly higher in the JUPITER group as compared with the NCEP/ATPIII and Not Indicated groups. Liver disease and kidney disease, as defined by elevated liver enzymes and creatinine, respectively, were rare, with no significant differences between groups.

Discussion

Using nationally representative data from NHANES, we describe the magnitude of the impact JUPITER trial findings may have on the US population. We estimate an additional 19.2%, or 11,144,000 (95% CI, 10,053,000 to 12,235,000) Americans (men aged ≥50 years and women aged ≥60 years) may become newly eligible for statin therapy as a primary prevention strategy. This group is in addition to the 33.5 million older adults with an already established NCEP/ATPIII indication for statin therapy, over half of whom are undertreated. Given our failure to reach current benchmarks, and the possibility that the recommendations for statin therapy may expand to include approximately 80% of the middle-aged to elderly population, it is important to understand the characteristics of these groups to target future risk-reduction strategies more effectively.

An aim of our study was to explore potential distinguishing features of the JUPITER-indicated group. Compared with individuals with at-goal LDL cholesterol and low hs-CRP (the Not Indicated group), JUPITER subjects were more likely to be female and older. In addition, obesity (as measured by both body mass index and abdominal circumference), hypertension, and the metabolic syndrome were significantly more prevalent in the JUPITER group. Interestingly, JUPITER subjects shared many characteristics with NCEP/ATPIII subjects, including sociodemographic factors and prevalence of smoking, abdominal obesity, and hypertension.
Table 1. Distribution of Sociodemographic and Clinical Characteristics of Men Aged &ge;50 and Women Aged &ge;60 Years in the 1999–2004 NHANES by Statin Eligibility*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NCEP/ATPIII† (Unweighted N=1346), Weighted % (SE)</th>
<th>JUPITER‡ (Unweighted N=460), Weighted % (SE)</th>
<th>Not Indicated§ (Unweighted N=516), Weighted % (SE)</th>
<th>P[</th>
<th>P¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62.07 (1.58)</td>
<td>47.70 (2.93)</td>
<td>62.08 (2.29)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>37.93 (1.58)</td>
<td>52.30 (2.93)</td>
<td>37.92 (2.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 to 64</td>
<td>45.65 (1.82)</td>
<td>44.98 (3.23)</td>
<td>60.59 (2.11)</td>
<td>0.175</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>65 to 74</td>
<td>32.82 (1.79)</td>
<td>28.61 (2.80)</td>
<td>21.65 (2.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥75</td>
<td>21.53 (1.38)</td>
<td>26.41 (2.47)</td>
<td>17.76 (1.62)</td>
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<td></td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non-Hispanic white</td>
<td>81.22 (2.21)</td>
<td>80.09 (2.45)</td>
<td>81.37 (3.20)</td>
<td>0.690</td>
<td>0.588</td>
</tr>
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<td>Non-Hispanic black</td>
<td>7.16 (1.07)</td>
<td>8.92 (1.63)</td>
<td>7.43 (1.09)</td>
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<td>Mexican American</td>
<td>3.64 (0.88)</td>
<td>3.59 (0.72)</td>
<td>3.31 (0.80)</td>
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</tr>
<tr>
<td>Other</td>
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<td>7.39 (1.63)</td>
<td>7.89 (2.33)</td>
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<td></td>
</tr>
<tr>
<td>Poverty index ratio</td>
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<td></td>
<td></td>
<td>0.984</td>
<td>0.853</td>
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<td>&lt;1</td>
<td>9.91 (1.25)</td>
<td>9.88 (1.30)</td>
<td>9.44 (1.77)</td>
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<tr>
<td>≥1</td>
<td>90.09 (1.25)</td>
<td>90.12 (1.30)</td>
<td>90.56 (1.77)</td>
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<td>129</td>
<td>38</td>
<td>45</td>
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<tr>
<td>Current smoker</td>
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<td></td>
<td></td>
<td>0.880</td>
<td>0.474</td>
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<tr>
<td>No</td>
<td>84.22 (1.30)</td>
<td>83.79 (2.36)</td>
<td>86.15 (2.01)</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>15.78 (1.30)</td>
<td>16.21 (2.36)</td>
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<tr>
<td>BMI, kg/m²</td>
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<td></td>
<td>&lt;0.001</td>
<td>0.002</td>
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<td>&lt;25 (normal weight)</td>
<td>26.38 (1.59)</td>
<td>33.98 (3.03)</td>
<td>35.89 (2.43)</td>
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<td>25 to 29 (overweight)</td>
<td>42.17 (1.90)</td>
<td>28.57 (2.71)</td>
<td>39.92 (2.35)</td>
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<tr>
<td>30 to 35 (class I obesity)</td>
<td>20.34 (1.51)</td>
<td>23.32 (2.48)</td>
<td>16.58 (1.95)</td>
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<td>&gt;35 (class II obesity)</td>
<td>11.12 (0.95)</td>
<td>14.13 (2.22)</td>
<td>7.61 (1.74)</td>
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<td>16</td>
<td>16</td>
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<tr>
<td>Abdominal obesity</td>
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<td></td>
<td></td>
<td>0.794</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>42.29 (1.45)</td>
<td>51.09 (3.29)</td>
<td>65.68 (3.26)</td>
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<tr>
<td>Yes</td>
<td>57.71 (1.45)</td>
<td>48.91 (3.29)</td>
<td>34.32 (3.26)</td>
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<td>19</td>
<td>15</td>
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<tr>
<td>Diabetes</td>
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<td></td>
<td></td>
<td>&lt;0.001</td>
<td>0.090</td>
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<tr>
<td>None</td>
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<td>48.06 (2.33)</td>
<td>57.50 (3.34)</td>
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<td>IGT</td>
<td>35.53 (1.84)</td>
<td>43.78 (2.58)</td>
<td>37.99 (2.77)</td>
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<td>Diabetes</td>
<td>27.42 (1.70)</td>
<td>8.16 (1.73)</td>
<td>4.52 (1.31)</td>
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<td>0.499</td>
<td>&lt;0.001</td>
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<td>Normal</td>
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<td>13.82 (2.29)</td>
<td>20.77 (2.62)</td>
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<td>Prehypertension</td>
<td>21.60 (1.56)</td>
<td>24.61 (2.21)</td>
<td>36.38 (2.19)</td>
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<td>62.56 (1.70)</td>
<td>61.57 (2.55)</td>
<td>42.85 (2.51)</td>
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<tr>
<td>No</td>
<td>42.29 (1.45)</td>
<td>51.09 (3.29)</td>
<td>65.68 (3.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>57.71 (1.45)</td>
<td>48.91 (3.29)</td>
<td>34.32 (3.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Framingham risk score</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>0.285</td>
</tr>
<tr>
<td>Low (&lt;10%)</td>
<td>16.78 (1.48)</td>
<td>53.77 (2.77)</td>
<td>60.52 (3.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (10% to 20%)</td>
<td>23.50 (1.51)</td>
<td>29.32 (2.90)</td>
<td>26.75 (2.05)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Global cardiovascular risk scores examined in this study, namely the Framingham and Reynolds risk scores, deserve further comment. The FRS was significantly higher in the NCEP/ATPIII group than in the other 2 groups. This was as expected, because current NCEP/ATPIII guidelines identify traditional risk factors from which the FRS is derived and further use the FRS to determine statin eligibility. However, in the remainder of the population, the FRS did not help distinguish between the JUPITER and the Not Indicated groups, which, despite having different cardiovascular risk profiles, had similar FRS scores. The Reynolds risk score, which incorporates hs-CRP values, was similar for the NCEP/ATPIII and JUPITER groups but higher in the JUPITER group compared to the Not Indicated group. By definition, the JUPITER group had higher hs-CRP levels than the other 2 groups. However, the Reynolds risk score is derived from additional risk factors, beyond hs-CRP, that would have been absent (eg, diabetes) or presumably more favorable in the JUPITER group as compared to the NCEP/ATPIII group.

For this reason, the similarity in the scores between these 2 groups was not expected. There is some evidence to suggest that the Reynolds risk score reflects not only elevated hs-CRP levels, but also the increased cardiovascular risk not accounted for with traditional risk measures such as the FRS. In the Women’s Health Study, approximately 20% of subjects with FRSs between 5% to 10% and 10% to 20% were reclassified using the Reynolds risk score to predict more accurately actual event rates. Such findings challenge our current understanding of individuals deemed to be at low or intermediate risk, and may favor the use of hs-CRP and the Reynolds risk score to better guide cardiovascular risk prediction and reduction strategies.

Current NCEP/ATPIII recommendations focus exclusively on lowering LDL cholesterol and do not stipulate the class of...
lipid-lowering medication to be used to achieve the LDL goal. As statins have demonstrated unparalleled efficacy in reducing primary and secondary cardiovascular events, it seems prudent to limit the discussion on risk reduction to statin therapy. Statins have pleiotropic effects beyond LDL lowering. As a class, statins promote antiinflammatory and antioxidant effects via reducing metalloproteinase activity, increasing nitric oxide availability, and decreasing thrombus proliferation. Statins have been shown to decrease hs-CRP levels by about 15% to 35%. Of all available FDA-approved statins, rosuvastatin and atorvastatin at high doses appear to have the greatest hs-CRP-lowering effects. Still, however, LDL has remained the main target of statin therapy. JUPITER is the first prospective study to demonstrate that statin therapy lowers cardiovascular risk in patients with at-goal LDL cholesterol but elevated hs-CRP levels.

Our study has the following limitations. There was likely some degree of misclassification in our risk-group stratification, given the reliance on one-time laboratory measurements, self-reported data, and incomplete or imprecise risk factor assessments. For example, in defining our high risk group, assessments of symptomatic carotid artery disease and abdominal aortic aneurysm were suboptimal. We used history of stroke as a proxy for symptomatic carotid artery disease, acknowledging that strokes may result from other noncardiogenic etiologies; in addition, this variable would not capture those with carotid artery disease that did not result in stroke. We were not able to attain information regarding abdominal aortic aneurysms, as this was not asked or assessed in NHANES. Family history of premature CHD may have been underestimated, as NHANES asks about disease in relatives under the age of 50, whereas NCEP/ATPIII guidelines specify male relatives under age 55 and female relatives under age 65 as their cutoffs in defining premature CHD. In estimating the Framingham risk levels for the 3 groups, we may have underestimated the high risk group, as individuals over 79 were not scored. For each of these variables, however, we attempted to replicate standard evaluation techniques and commonly used definitions published in other studies. The definitions used to assign NCEP/ATPIII risk were intended to result in the most conservative estimates for the JUPITER population. It is important to note that we included women on hormone replacement therapy in the analysis of this study, acknowledging that estrogen is known to elevate hs-CRP levels. We repeated our analysis excluding women on hormone replacement therapy and found substantively similar results.

In conclusion, targeting elevated hs-CRP levels for risk-reduction therapy has the potential to impact approximately 20% of the adult population of men aged ≥50 years and women aged ≥60 years who would otherwise not be recommended for statin therapy. This translates into an estimated 11 144 000 adults, including 8 071 000 with hs-CRP ≥2 mg/L and LDL <130 mg/dL (“strict” JUPITER criteria) and an additional 3 073 000 with hs-CRP ≥2 mg/L and LDL between 130 and 160 mg/dL for whom the JUPITER findings might reasonably be extended. Thus, based on existing guidelines and JUPITER’s findings, approximately 80% of the middle-aged to elderly population in the United States may now have an indication for statin therapy. Our study suggests that JUPITER patients are largely similar to patients who already meet NCEP/ATPIII criteria for statin therapy. JUPITER’s findings question our current strategies for cardiovascular risk reduction and use of statin medications exclusively in individuals with cardiovascular risk and LDL cholesterol above what is recommended. Expanding recommendations for statin therapy to include individuals with at-goal LDL cholesterol but elevated hs-CRP values will pose increasing challenges for health care providers and systems already struggling to reach individuals with an NCEP/ATPIII indication for statin therapy, but offers a potential opportunity for advancing risk-reduction strategies.

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Disclosures
None.

References
11. Ridker PM, Rifai N, Clearefield M, Downs JR, Weis SE, Miles JS, Gotto AM, Jr. Measurement of C-reactive protein for the targeting of statin

CLINICAL PERSPECTIVE
Current strategies for the primary prevention of cardiovascular disease, based on guidelines from the National Cholesterol Education Panel/Adult Treatment Panel III, focus on lowering low-density lipoprotein (LDL) cholesterol in individuals with increased cardiovascular risk and above-goal LDL values. A new clinical trial, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), showed improved cardiovascular outcomes in patients without coronary heart disease who had at-goal LDL values but elevated high-sensitivity C-reactive protein values and were treated with a statin medication. We estimate that these findings have the potential to impact \( \approx 20\% \) of the adult population of men aged \( \geq 50 \) years and women aged \( \geq 60 \) years who would otherwise not be recommended for statin therapy. This translates into an estimated 11,144,000 (95% CI, 10,053,000 to 12,235,000) adults, including 8,071,000 (95% CI, 7,173,000 to 8,969,000) with high-sensitivity C-reactive protein \( \geq 2 \) mg/L and LDL \( < 130 \) mg/dL ("strict" JUPITER criteria) and an additional 3,073,000 (95% CI, 2,404,000 to 3,743,000) with high-sensitivity C-reactive protein \( \geq 2 \) mg/L and LDL between 130 and 160 mg/dL, for whom the JUPITER findings might reasonably be extended. Thus, based on existing guidelines and JUPITER’s findings, \approx 80\% of the middle-aged to elderly population in the United States may now have an indication for statin therapy. Expanding recommendations for statin therapy to include individuals with at-goal LDL cholesterol but elevated high-sensitivity C-reactive protein values will pose increasing challenges for health care providers and systems already struggling to reach individuals with a National Cholesterol Education Program/Adult Treatment Panel III indication for statin therapy but offers a potential opportunity for advancing risk-reduction strategies.
From Here to JUPITER: Identifying New Patients for Statin Therapy Using Data From the 1999–2004 National Health and Nutrition Examination Survey
Erica S. Spatz, Maureen E. Canavan and Mayur M. Desai

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