Rationale for Targeted Rather Than Population Based Screening With C-Reactive Protein Using the National Health and Nutrition Examination Survey (1999 to 2002)

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C-reactive protein (CRP) is the most well-studied inflammatory marker for the prediction of coronary artery disease. It was hypothesized that population-wide screening would have minimal impact but that a target population might be identified for whom CRP testing could be appropriate. The National Health and Nutrition Examination Survey (NHANES; 1999 to 2002) included 7,399 subjects who represented 171 million United States residents aged 20 to 79 years. Subjects were risk stratified according to National Cholesterol Education Program Adult Treatment Panel III guidelines. Subjects with CRP levels >3 mg/L then had their risk profiles adjusted by adding 1 risk factor and multiplying their Framingham risk scores by 1.5. Subjects had their low-density lipoprotein (LDL) cholesterol goals adjusted as necessary and were then recategorized as above or below their CRP-adjusted LDL cholesterol goal. LDL cholesterol goals were met initially by 67.8% (116 ± 8 million) of United States residents, and 64.8% (111 ± 8 million) achieved their LDL cholesterol goals after CRP adjustment. Thus, 5.3 ± 1.1 million of the population (3.1 ± 0.1%) had their risk modified in a clinically meaningful way by CRP adjustment. Targeting the screening to 2 groups, those with 1 risk factor and LDL cholesterol levels 130 to 159 mg/dl and those with moderately high risk and LDL cholesterol levels 100 to 129 mg/dl, we were able to identify all 5.3 million by screening only 14.8 million, achieving a screening yield of 35%. In conclusion, population-based screening with CRP provided a clinical impact for only 3.1% of United States residents. Patients with 1 risk factor and LDL cholesterol levels of 130 to 159 mg/dl and those with moderately high risk and LDL cholesterol levels of 100 to 129 mg/dl represent high-yield subgroups for routine CRP screening. **(Am J Cardiol 2007;100:1130–1133)**

The relation between inflammation and atherosclerosis has stimulated the study of inflammatory markers that might improve cardiovascular risk prediction. C-reactive protein (CRP) is the most intensely studied of these markers. In this study, we quantified the clinical impact of CRP screening in the entire United States population for the presence of elevated CRP. We hypothesized that a population-based approach would be inefficient and that a more targeted group for screening might be identified. To accomplish this, we developed an algorithm on the basis of current data and applied it to those subjects in the National Health and Nutrition Examination Survey (NHANES) data sets for 1999 to 2002, representing the population of the United States.

Methods

The National Center for Health Statistics conducted NHANES in 2-year phases. NHANES is a collection of demographic, historical, physical examinations, and laboratory data on those subjects enrolled. The survey uses demographic and geographic data and complex sampling algorithms to assign weights to all of its samples, such that the sum of the samples' weights represents the entire civilian noninstitutionalized United States population. This study used data from all subjects aged 20 to 79 years from 2 phases: the 1999 to 2000 and 2001 to 2002 surveys. A detailed description of the methods and protocols of NHANES has been previously published.[1] Currently, pregnant women and subjects who were receiving cancer chemotherapy within 4 weeks of the exam were excluded. Subjects who lacked sufficient cholesterol or blood pressure data to allow risk assessment and low-density lipoprotein (LDL) cholesterol goal stratification were also excluded. Subsequent numbers provide the population estimates in millions of subjects, with SEs. Population totals and percentages were calculated using sampling weights to produce unbiased population estimates. SEs were determined, taking into account the complex survey design. Analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

CRP measurement in the NHANES data sets was per-

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Table 1
Study population and exclusions from the National Health and Nutrition Examination Survey 1999 to 2002 data set

Variable	Subjects	Population-based Numbers (millions) (group weight)
Mobile examination center group, ages 20 to 79 yrs	8,747	190.4 (100%)
Pregnant	582	4.3 (2.2%)
Recent or pending chemotherapy	28	0.6 (0.3%)
Missing cholesterol data	524	10.3 (5.4%)
Missing blood pressure data	214	4.3 (2.3%)
Total exclusions	1,348	19.4 (10.2%)
Study population	7,399	171 (89.8%)

formed using latex-enhanced nephelometry with a Behring Nephelometer (Behringwerke, Marburg, Germany) for quantitative protein determination.[2] This method has been well validated and is currently approved by the United States Food and Drug Administration for clinical use in the United States.[3]

The National Cholesterol Education Program Adult Treatment Panel (ATP) III guidelines describe risk assessment and treatment goals for patients on the basis of LDL cholesterol levels.[4] These goals are assigned on the basis of a 3-step risk assessment: (1) identifying the presence of coronary heart disease or its equivalents (e.g., diabetes mellitus, peripheral arterial disease), (2) the enumeration of traditional risk factors, and (3) calculation of the Framingham risk score (FRS). Subjects with <2 risk factors are at lower risk, and those with ≥2 risk factors have their FRSs calculated. Those with FRSs of 0% to <10% are at moderate risk, and those with FRSs of 10% to <20% are at moderately high risk. Subjects with FRSs ≥20% or coronary risk equivalents are at high risk. Subjects were stratified into 1 of these 4 risk levels: lower, moderate, moderate high, and high. Their respective LDL cholesterol goals were <160, <130, <130 and <100 mg/dl. Subjects were then categorized as above or below their LDL cholesterol goals. Subjects with CRP levels >3 mg/L then had their risk scores modified according to the following algorithm. High-risk subjects did not have their risk altered. Moderate and moderately high-risk subjects had their FRSs multiplied by 1.5. Lower risk subjects had 1 risk factor added. If the result was ≥2 risk factors, their FRSs were calculated per ATP III guidelines and multiplied by 1.5. LDL cholesterol goals were then reassigned if needed, and subjects were then recategorized as above or below their CRP-modified LDL cholesterol goals.

Subjects who were initially below their LDL cholesterol goals, had their LDL cholesterol goals reduced by CRP adjustment, and were then found to be above their CRP-adjusted LDL cholesterol goal were considered clinically affected by CRP screening. These subjects represented the group of interest for this study.

Results

All 8,747 subjects (representing 190.4 million United States residents) were included in the data set. The final analysis included 7,399 subjects representing 171.0 million United States adults (Table 1). The distribution of CRP among the NHANES population was relatively uniform among the 3 categories used (Figure 1). This is consistent with cutpoints established by the American Heart Association and Centers for Disease Control and Prevention, which were based on distributions from >15 studies involving >40,000 patients.[5] CRP levels ≥3 mg/L were present in 51.2 million subjects (SE 48.0 to 54.4 million), or 38% of the population.

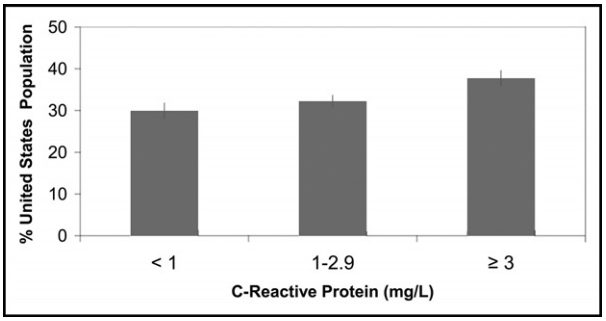

Figure 1. The distribution of CRP according to levels.

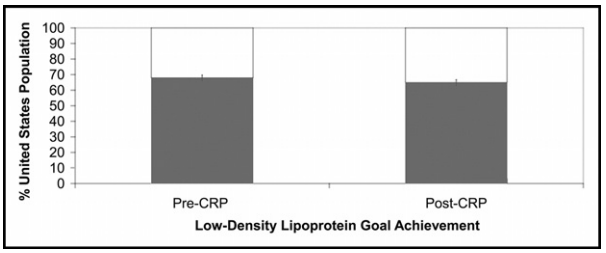

Figure 2. Achievement of LDL cholesterol goals before and after adjustment for CRP levels.

Initially, 68% of the United States population (116 ± 8 million) met their LDL cholesterol goals. After CRP evaluation and LDL cholesterol goal adjustment, 65% of the population (110.8 ± 7.6 million) met their LDL cholesterol goals. The difference of 3.1% (5.3 ± 1.1 million) represents the yield of clinically important results using a population-wide screening approach. Figure 2 demonstrates the results with LDL cholesterol goal achievement before and after CRP enhancement. The distribution of these 5.3 million subjects was equal across the genders.

All 5.3 million subjects were categorized in 2 subgroups (Figure 3). The first group was the 12.8 ± 1.1 million individuals at lower risk, with single risk factors and LDL cholesterol levels of 130 to 159 mg/dl. The second group was the 2.0 ± 0.5 million subjects at moderately high risk, with LDL cholesterol levels of 100 to 129 mg/dl. Together, these 2 groups represented 14.8 million United States residents, including all 5.3 million subjects whose clinical assessments would be affected by high CRP levels. Limiting screening to this group of 14.8 million resulted in a 35% yield of clinically affected subjects.

Discussion

CRP is associated with future cardiovascular events, but the optimal patient population for CRP screening is unclear. Our data support 2 conclusions. First, global screening with

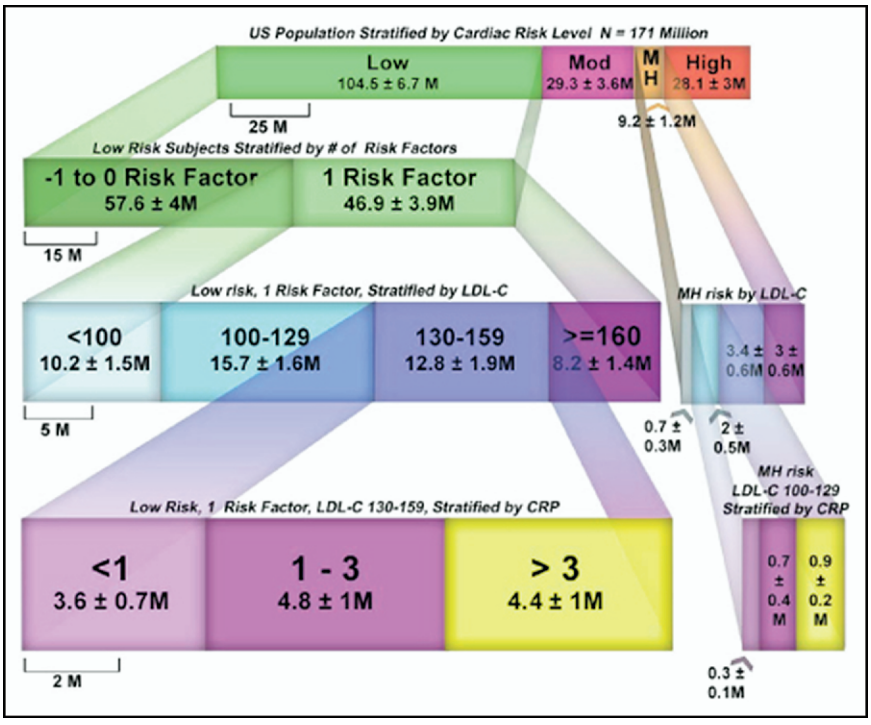

Figure 3. Risk groups subdivided by number of risk factors and LDL cholesterol (LDL-C) levels, with identification of a screening group in whom screening for CRP is of high yield *(yellow box)*. M = million; MH = moderately high risk; Mod = moderate risk.

CRP is inefficient and does not affect risk management in 97% of the population. Second, targeted screening could more efficiently identify the small subsets of the population who may benefit by the identification of elevated CRP levels. These subgroups include those with 1 risk factor and LDL cholesterol levels of 130 to 159 mg/dl and those with moderately high risk and LDL cholesterol levels of 100 to 129 mg/dl. This approach identified all subjects in whom elevated CRP levels modified their risk in a clinically relevant way and limited the total screening population to a relatively small number of subjects with a 35% yield of clinically significant information.

After separating out subjects with high-risk diagnoses, the ATP III risk assessment uses the enumeration of risk factors and the calculation of FRSs to characterize subjects' risk levels. Traditional risk factors are enumerated with a binary result. Those with <2 risk factors are considered at lower risk, whereas those with ≥ 2 risk factors use FRS evaluation to separate among moderate, moderately high, and high-risk groups. Because this method is well established, we conducted a thought experiment to evaluate the impact of additional information provided by CRP levels. To this end, risk factor enumeration and FRS were addressed. Evidence indicates that CRP has similar and independent association to cardiovascular risk as many of the traditional risk factors used by ATP III.[6] In this regard, adding 1 risk factor appears logical and necessary to have any impact on the lower risk group. Functionally, the only subgroup affected by this step is that with 1 traditional risk factor already and elevated CRP levels. This step alone changes the risk assessment for 4.4 million United States residents, such that they no longer meet their LDL cholesterol goals (Figure 3).

The selection of a FRS multiplier for the elevated CRP group represents an estimate of CRP's impact, and our value of 1.5 is grounded in numerous studies associating a CRP level ≥ 3 mg/L with cardiovascular risk, including a large meta-analysis.[7–11] This modification affects 0.7 million moderately high-risk subjects whose FRSs eclipse 20% after CRP adjustment (Figure 3). Functionally, our multiplier upgrades the risk for subjects with CRP levels ≥ 3 mg/L compared with those who do not have CRP measured (a group assumed to have average CRP levels). Thus, we are potentially overestimating the risk of an elevated CRP level, because most studies have compared high and low tertiles of CRP.

A previous evaluation of the integration of CRP measures into the FRS showed no difference in the overall receiver-operating characteristic curves with and without CRP.[12] This is consistent with our findings that population screening has a low yield. However, we do not believe that this recent evaluation rules out the potential benefit of screening a smaller subset. A recent study in women found that 3% of their population was placed in a higher risk category using the cohort-derived Reynolds risk score, compared with categorization by ATP III risk.[13] Their discussion directed attention to those at intermediate ATP III risk, yet 50% of the subjects who moved categories were initially at lower risk. In addition, our end point of a need to intensify LDL cholesterol therapy may be more clinically relevant than the recharacterization of risk categories. Our results support those of both the ATP III guideline and a recent review that a targeted approach is the best use of CRP.[4,14] As with the Reynolds risk score, their target is the intermediate-risk group, yet screening only the 9.2 million moderately high or "intermediate"-risk group in NHANES

would identify only 0.9 million subjects for whom screening yields clinical impact. The remaining 4.4 million low-risk subjects would be unrecognized. Our screening group was only slightly larger (14.8 million) and found all 5.3 million who would derive clinical impact. This thought experiment will require confirmation in a prospective series; however, it ultimately may represent an appropriate addition to the guidelines emphasizing a more targeted approach with CRP screening.[4]

We acknowledge several limitations to our study. Use of the NHANES data set brings with it the limitations of that survey. NHANES data collected by examination and laboratory testing are subject to sampling and nonsampling errors. In particular, this is a 1-time measure of CRP, and recent evidence has suggested significant variation in repeat measures of CRP. Interview data based on self-report are subject to recall bias and misunderstanding of questions. Additionally, NHANES does not include the incarcerated or institutionalized populations of the United States. Cardiovascular risk is a continuous variable, but the ATP III defines arbitrary cutpoints in its risk algorithm and uses the FRS with a 10-year risk model. These features may result in limited applicability to any 1 patient. Although the LDL cholesterol goals may be adjusted in future guidelines, the impact of CRP is focused on those groups with LDL cholesterol levels <30 mg/dl higher than the goal. Future changes to the LDL cholesterol goals or risk group definitions or routine aggressive therapy of LDL cholesterol in the highlighted groups may shift the group of interest to a lower LDL cholesterol level and is unlikely to affect the total numbers or percentage yield. Finally, this study included two 2-year snapshots of the United States population, which may become less applicable to the current population over time.

Our risk-adjustment algorithm for elevated CRP assumes clinical impact only for those who cross to new risk levels and thus require changes in LDL cholesterol management. It is easy to define examples of patients who are very close to their goals and for whom elevated CRP levels might push them far enough from their goals to stimulate changes in therapy. We do not intend to limit the use of CRP testing to exclude these populations, but we suggest that testing groups outside the ones defined start with a clear plan for the future management based on the results of the test.

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