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C-reactive protein level and the incidence of eligibility for statin therapy: the Multi-Ethnic Study of Atherosclerosis (MESA)

Devin M. Mann, **Daichi Shimbo**, **Mary Cushman**, **Susan Lakoski**, **Philip Greenland**, **Roger S. Blumenthal**, **Erin D. Michos**, **Donald M. Lloyd-Jones**, and **Paul Muntner**

Department of Medicine, Division of Preventive Medicine & Epidemiology, Boston University School of Medicine, Boston, MA (DMM); Department of Medicine, Division of General Internal Medicine, Columbia University Medical Center, NY, NY (DS); Department of Medicine, University of Vermont College of Medicine, Burlington, VT (MC); Department of Medicine, University of Texas Southwestern, Dallas, TX (SL); Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL (PG, DML-J); Department of Medicine, Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD (RB, EM); Department of Epidemiology, University of Alabama at Birmingham (PM)

Abstract

Introduction—Given the results of the JUPITER trial, statin initiation may be considered for individuals with elevated high sensitivity C-reactive protein (CRP). However, if followed prospectively, many individuals with elevated CRP may become statin-eligible, limiting the impact of elevated CRP as a treatment indication. This analysis estimates the proportion of people with elevated CRP that become statin eligible over time.

Methods—We followed 2,153 Multi-Ethnic Study of Atherosclerosis (MESA) participants free of cardiovascular disease (CVD) and diabetes with LDL-cholesterol (LDL-C) <130 mg/dL at baseline to determine the proportion who become eligible for statins over 4.5 years. The proportion eligible for statin therapy, defined by the National Cholesterol Education Program (NCEP) 2004 updated guidelines, was calculated at baseline and during follow-up stratified by baseline CRP level (≥2 mg/L).

Results—At baseline, 47% of the 2,153 participants had elevated CRP. Among participants with elevated CRP, 29% met NCEP criteria for statins, compared to 28% without elevated CRP at baseline. By 1.5 years later, 26% and 22% (p=0.09) of those with and without elevated CRP at baseline reached NCEP LDL-C criteria and/or had started statins, respectively. These increased to 42% and 39% (p=0.24) at 3 years and 59% and 52% (p=0.01) at 4.5 years following baseline.

Conclusions—A substantial proportion of those with elevated CRP did not achieve NCEP based statin eligibility over 4.5 years of follow-up. These findings suggest that many patients with elevated CRP may not receive the benefits of statins if CRP is not incorporated into the NCEP screening strategy.

In 2008, The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) demonstrated a reduced risk (44% over a median 1.9 years) of pooled cardiovascular disease (CVD) events by treatment with rosuvastatin as compared to placebo among older men and women (≥50 and ≥60 years of age, respectively) with a baseline LDL-C < 130 mg/dL and high-sensitivity C-reactive protein (CRP) ≥2 mg/L but no history of coronary heart disease (CHD).(1) The National Cholesterol Education

Address correspondence and reprint requests to: Devin M. Mann, Boston University Medical Campus, 761 Harrison Ave, Boston, MA 02119, dmann@bu.edu.

Program (NCEP) published guidelines suggesting eligibility criteria for statin therapy in 2001.(2) These guidelines were last updated in 2004 but did not consider a patient's CRP level in the treatment decision algorithm.(3) Recent American Heart Association guidelines consider CRP screening to be a IIa/Level B criteria (recommendation in favor of treatment or procedure being useful / effective) and the Canadian guidelines now include CRP as part of their risk stratification algorithm.(4, 5)

The JUPITER findings have led to controversy over the use of CRP to guide the initiation of statin therapy.(6–10) Proponents of including CRP levels as part of determining whether to initiate statins among individuals with LDL-C < 130 mg/dL cite the JUPITER efficacy data and potential cost-effectiveness.(11, 12) However, critics note that this screening approach would substantially increase the target population for statins.(13) Furthermore, JUPITER did not test the use of CRP as a screening strategy; it used CRP to identify a group that benefited from statin therapy and did not estimate the benefits of statins among those without elevated CRP. Others note that at enrollment into JUPITER many patients, particularly men who had a mean Framingham CVD risk score of approximately 20%, may have already been statin eligible.(1) The LDL-C threshold for starting statin therapy was lowered during the conduct of JUPITER, at least as an optional strategy, which may negate some of the benefits from early statin initiation observed in JUPITER.(3) It is also possible that in usual care (outside of the clinical trial setting) some JUPITER participants randomized to placebo would have met NCEP-based statin eligibility criteria or have been started on statin therapy soon following enrollment into the trial. If this proportion was substantial, the impact of changing the NCEP guidelines to incorporate elevated CRP as a treatment criterion would be limited.

The goal of the current analysis was to calculate the proportion of adults with and without elevated CRP who become statin eligible or start statins according to the 2004 NCEP criteria over time. If the majority of people with elevated CRP achieve NCEP criteria within a few years, the potential impact of using elevated CRP as an indicator for statin therapy would be diminished. However if most people with elevated CRP do not achieve NCEP statin eligibility criteria in the near future then the potential CVD risk reduction benefit of using CRP as a statin initiation criterion would be preserved. To resolve this uncertainty, we analyzed longitudinal data on the incidence of statin eligibility, including statin initiation, based on NCEP 2004 criteria, among participants with and without elevated CRP in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort.

Methods

Study population

Details regarding the design and objectives of MESA have been published.(14) In brief, between 2000 and 2002, 6,814 White, African-American, Hispanic, and Chinese participants between 45 and 84 years of age, with no evidence of clinical cardiovascular disease were recruited from six geographically diverse communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota). The institutional review board at all participating institutions approved the study and all participants gave written informed consent. Individuals with atrial fibrillation, active cancer, cognitive impairment, weight greater than 300 lbs or who were pregnant were excluded. To simulate the key elements of the JUPITER study population, we limited this analysis to MESA participants not taking statins at baseline, without diabetes (fasting glucose ≥126 mg/dL or medication use, age ≥50 years for men and ≥60 years for women, and having LDL-C <130 mg/dL at baseline.(15) After applying these criteria, 2,153 of the 6,814 MESA participants were included in the current analyses.

Data Collection—Data were collected during a baseline examination (2000–2002) and three follow- up visits (exams 2, 3 and 4) occurring at eighteen month intervals. During the baseline exam, standardized questionnaires were utilized to obtain demographic data, tobacco use, medical conditions, and currently prescribed medications. Body weight, height, and waist circumference were measured by trained study staff. Height and weight were measured with participants wearing light clothing and no shoes. An Accu-Hite Stadiometer (Seca, Hamburg, Germany) was used to measure height, and a Detecto Platform Balance Scale (Titus Home Health Care, Alhambra, CA) was used to measure weight. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and overweight was defined as a BMI ≥25 kg/m^2 and obesity as a BMI ≥30 kg/m^2. Waist circumference was measured using a Gulick II anthropometric tape (Sammons Preston, Chicago, IL) applied horizontally at the level of the umbilicus and rounded to the nearest centimeter.

Resting seated blood pressure was measured three times using an automated oscillometric sphygmomanometer (Dinamap PRO 100; Critikon, Tampa Bay, FL); the mean of the last two measurements was used for analysis. Hypertension was defined by systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or antihypertensive medication use. Participants were asked to fast overnight prior to their examination. Fasting glucose and lipids were analyzed at a central laboratory. Glucose was measured by the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, NY). Among participants not on hypoglycemic drugs or insulin, impaired fasting glucose was defined as levels between 100 and 125 mg/dl.

Plasma lipids including HDL-cholesterol, and triglycerides were measured using the Roche Hitachi 911 analyzer (Roche Diagnostics). Low HDL-cholesterol was defined as levels <40 mg/dL for men or <50 mg/dl for women, and high triglycerides were defined as levels ≥150 mg/dL. CRP was measured using a particle enhanced immunonepholometric assay on the BNII nephelometer (Dade-Behring, Inc). Consistent with JUPITER, we defined elevated CRP as levels ≥2 mg/L. Metabolic syndrome was defined according to the revised National Cholesterol Education Program Adult Treatment Panel III criteria.(2)

Study Outcome—The primary outcome was becoming eligible for statin initiation, using current US guidelines as described below, or initiating statin therapy after the baseline examination. Statin eligibility was defined as an LDL-C level at or above the CHD risk category specific cut-point published in the 2004 updated NCEP criteria (Table 1). Using previously published MESA procedures, CHD events for this report were defined as definite and probable MI, definite CHD death, resuscitated cardiac arrest, and definite angina.(16) The 2004 NCEP update recommended definite and optional thresholds for statin initiation. For the main analyses, we employed the optional NCEP 2004 LDL-C statin initiation thresholds as this is increasingly recommended for those at highest risk.(17) Statin use was obtained via self-report at each study visit. In secondary analyses, the definite 2004 LDL-C initiation thresholds were used.

Statistical analysis

Characteristics of the study population were calculated for participants with and without elevated CRP (<2 or ≥2 mg/dL), separately. The proportion of participants eligible for statin therapy at baseline was determined among individuals with and without elevated CRP, overall and within each NCEP CHD risk category. Next, among participants not eligible for statins at baseline, the cumulative proportion meeting criteria for statins or initiating statin therapy was calculated at each follow-up exam, overall and for participants with and without elevated CRP.

A sensitivity analysis was performed by examining the proportion of participants eligible for statin therapy at baseline and during follow-up using the more conservative ("definite") LDL-C thresholds in the NCEP 2004 guidelines. This analysis was performed overall and within each NCEP CHD risk category. All analyses were conducted using Stata software (version 11, STATA Corp., College Station, TX).

Results

Participant characteristics

Among the 2,153 participants included in this analysis, 47% had elevated CRP. The mean age was similar among those with and without elevated CRP (Table 2). Those with elevated CRP were more often women, Black or Hispanic, smokers, hypertensive, and had higher BMI and waist circumference. They also were more likely to have impaired fasting glucose and metabolic syndrome although they had similar levels of LDL-C and HDL-C.

Baseline statin eligibility

Among the studied participants, 29% were eligible for statin therapy at baseline according to NCEP criteria (Table 3). The percentage of participants meeting NCEP criteria was similar for those with and without elevated CRP overall, and when high or moderately high risk participants were considered separately.

Incident Statin eligibility

After excluding those who met the NCEP criteria for statin therapy at baseline, 26% with elevated CRP at baseline and 22% without elevated CRP at baseline (p=0.06), met NCEP criteria or had initiated statins by Exam 2 (Table 4). By exam 3, 42% and 39% of those with and without elevated CRP, respectively, had an LDL-C at or above the NCEP criteria for initiating statins or had initiated statin therapy. At exam 4, 59% of participants with elevated CRP versus 52% of participants without elevated CRP had an LDL-C at or above the NCEP criteria for initiating statins or had initiated statin therapy, respectively (p=0.01). At each exam, a higher percentage of participants had an LDL-C above the NCEP criteria compared to the percentage who had initiated statins. About one-quarter of those achieving NCEP criteria were by incident diabetes (10%, 17%, 17%) or CHD events (15%, 6%, 6%).

Conservative NCEP criteria

Using the conservative NCEP 2004 LDL-C goals, substantially fewer participants met the NCEP criteria at baseline (Supplement Table 1). However, the proportion of participants meeting the conservative NCEP criteria or initiating statins at exams 2, 3 or 4 was nearly equivalent to the more aggressive optional LDL-C goals (Supplement Table 2).

Discussion

Over three-quarters of older MESA participants with elevated CRP and LDL <130 mg/dL (i.e., meeting the JUPITER criteria) at baseline did not meet NCEP criteria for statin initiation by the first follow-up exam at 1.5 years. Even after 4.5 years of follow-up, nearly half of this group had not achieved NCEP criteria using the optional or definite thresholds. Furthermore, 15% who did reach NCEP criteria by exam 2 had a CHD event. Since the JUPITER trial observed a small but significant CVD risk reduction in less than 2 years, the current study supports the assertion that many patients with elevated CRP may not receive the risk reduction benefit of statins if CRP is not incorporated into the NCEP screening strategy.

There has been substantial debate over whether and how to utilize CRP in screening for CVD risk and decision-making regarding intensity of prevention efforts. The data from the JUPITER trial established the benefit of high-dose statins among similar patients with elevated CRP. Although it did not evaluate the use of CRP as a screening strategy, the results have been used to support the growing movement to incorporate CRP into CVD screening among asymptomatic individuals. In 2009, the Canadian Cardiovascular Society published updated guidelines that recommend statin therapy for those at moderate risk (Framingham CHD risk score between 10 and 19%) with a CRP ≥2 mg/L in men older than 50 years and in women older than 60 years of age, irrespective of LDL-C (class IIa, level B).(5) Recently, the American College of Cardiology/American Heart Association guidelines echoed the Canadian statement with a similar class IIa, level B classification for CRP testing among men 50 years of age or older or women 60 years of age or older with LDL-C < 130 mg/dL and a recommendation that "CRP can be useful in the selection of patients for statin therapy".(4) Our data support this movement to include CRP in CHD screening strategies as we observed a large population of people with elevated CRP that would not become eligible for statin therapy even with repeated traditional NCEP screening.

Despite this observation, we also observed that about half of MESA participants without CVD or diabetes and meeting the JUPITER LDL-C and age criteria at baseline became NCEP eligible for statins over a median of 4.5 years of follow-up. While the proportion of participants becoming NCEP eligible for statins was significantly higher among those with versus without elevated CRP, this difference was less than 10% (59% vs. 52%). The substantial number of participants eligible for statins by traditional NCEP criteria but not taking them highlights the continuing problems of underutilization and likely non-adherence to statins.(18, 19)

When the optional NCEP LDL-C goals were applied, over one-quarter of the participants meeting the age and LDL-C JUPITER criteria were eligible for, but not taking, statins at baseline. Furthermore, 24% of the remaining participants became NCEP eligible or were taking statins by MESA exam 2. Sensitivity analyses using the definite NCEP 2004 LDL-C goals demonstrated results similar to those using the optional cut points in terms of meeting NCEP criteria or initiating statin therapy at each of the follow-up exams. The substantial proportion of participants meeting NCEP criteria or taking statins during follow-up is therefore unlikely to be an artifact of changing guideline targets. Thus, in the current study, many people with and without elevated CRP but not achieving NCEP criteria at baseline may have had near threshold risk factor profiles allowing them to achieve statin eligibility within a few years.

The current study should be viewed with certain strengths and limitations in mind. The strengths of this study include the large ethnically diverse population as well as the detailed clinical and metabolic characterization of the cohort over time. The limitations include that CRP was only measured at baseline so the trajectory of CRP could not be incorporated into the analysis. Also, among those starting statins we had no data on criteria used for initiation.

In the current study, almost half of individuals with elevated CRP and meeting the age and LDL-C criteria from JUPITER did not become eligible for statins over 4.5 years of follow-up and 15% of those who became NCEP eligible within the first 1.5 years of follow-up did so by having a CHD event. Furthermore, only 26% of those with elevated CRP became eligible over 1.5 years, whereas JUPITER demonstrated a clear risk reduction within two years. If elevated CRP is not included as part of the decision to initiate statins, a substantial proportion of individuals with elevated CRP but with an LDL-C < 130 mg/dL may not be recommended statin therapy. These findings highlight the imperfect nature of the current NCEP guidelines and the potential for CRP to help avoid CHD events. The observed high

rate of NCEP eligibility for statins in combination with the substantial subgroup of people with elevated CRP without traditional statin eligibility suggest that if CRP is included in the statin initiation decision process the majority of MESA participants would become eligible for statins over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

2004 Updated NCEP* statin initiation LDL-cholesterol (LDL-C) thresholds.

	Optional LDL-C Goal (mg/dL)	Definite LDL-C Goal (mg/dL)
High Risk[1]	≥ 70	≥ 100
Moderately High Risk[2]	≥ 100	≥ 130
Moderate Risk[3]	≥ 160	≥ 160
Low Risk[4]	≥ 160	≥ 190

[1] High-risk — those with CHD, diabetes or multiple (2 or more) CHD risk factors and a Framingham Risk Score (FRS) > 20%

[2] Moderately high-risk — those with multiple (2 or more) CHD risk factors and a FRS of 10–20%

[3] Moderate risk — those with multiple (2 or more) CHD risk factors together with a < 10% FRS

[4] Low risk — those with 0–1 CHD risk factors

* National Cholesterol Education Program

Table 2

Baseline characteristics of participants free of clinical cardiovascular disease and diabetes meeting JUPITER age and LDL-C threshold at the baseline exam in the Multi-Ethnic Study of Atherosclerosis (MESA) stratified by elevated CRP

Characteristic	CRP < 2 mg/L N=1151	CRP ≥2 mg/L N=1002	P value
Age, years	66 (9)	67 (8)	.10
Men, %	69	49	<.001
Race, %			<.001
White	41	40	
Black	23	32	
Hispanic	16	23	
Asian	20	5	
Smoking, %	9	14	<.001
Body mass index, kg/m^2	26 (4)	29 (5)	<.001
Body mass index, 25–29 kg/m^2 %	41	39	<.001
Body mass index ≥ 30 kg/m^2 , %	16	38	<.001
Waist Circumference, cm	94 (13)	103 (15)	<.001
Abdominal Obesity (>88cm for women, >102 for men) %	34	64	<.001
Systolic blood pressure, mmHg	128 (22)	131 (22)	<.001
Diastolic blood pressure mmHg	73 (10)	72 (11)	.004
Hypertension (≥140/90 mmHg or antihypertensive treatment), %	42	55	<.001
Family history of premature CHD, %	3	3	.57
LDL-C, mg/dL	103 (19)	102 (20)	.21
HDL-C mg/dL	52 (16)	52 (17)	.54
CRP, mg/L	1 (1)	7 (9)	<.001
Impaired fasting glucose	15	20	.002
Metabolic syndrome, %	19	34	<.001
Mean 10 year CHD Framingham Risk Score, % (SD)	11 (.07)	10 (.07)	.99

Numbers in table are mean (standard deviation) or percent

Table 3

Proportion of MESA participants free of cardiovascular disease and diabetes meeting JUPITER age and LDL-C criteria* at baseline with LDL-C above the *optional* NCEP threshold** for initiating statin therapy at baseline with and without elevated CRP

	Proportion meeting NCEP criteria for statin therapy at baseline		
	Overall (n=2,153) N (%)	**CRP< 2 mg/L (n=1,151) N (%)**	**CRP ≥2 mg/L (n=1,002) N (%)**
All	614 (29)	319 (28)	295 (29)**
High risk	295 (48)	160 (50)	135 (46)
Moderately high risk	319 (52)	159 (50)	160 (54)

Note: There are no moderate or low risk groups displayed since they are excluded by definition for having a LDL-C <130 mg/dL at baseline

* Age ≥ 50 years for men (age ≥ 60 for women), LDL-C <130 mg/dL at baseline

** Eligibility criteria (adapted from NCEP 2004 update):

- **High Risk** — CVD, diabetes or multiple (2 or more) CHD risk factors with FRS > 20% - threshold for statin initiation is LDL-C ≥ 70 mg/dL
- **Moderately high-risk** — Multiple (2 or more) CHD risk factors together with a 10–20% FRS - threshold for statin initiation is LDL-C ≥100 mg/dL

** P (comparing CRP <2 with ≥2 mg/dl) = 0.38

Table 4

Cumulative proportion of MESA participants free of cardiovascular disease and diabetes with JUPITER age and LDL criteria at baseline with and without elevated CRP stratified by whether or not they meet the *optional* NCEP threshold* for statin therapy or taking statin over 4.6 years of follow-up (excluding those NCEP eligible at baseline).

	Overall (n=1,539) N (%)	CRP< 2 mg/dL (n=832) N (%)	CRP ≥2 mg/dL (n=707) N (%)	P-value**
	Proportion meeting NCEP criteria for statins therapy or taking statins (Cumulative by MESA exam)			
By Exam 2 - Combined	367 (24)	185 (22)	182 (26)	0.11
NCEP Criteria	294 (19)	149 (18)	145 (21)	0.20
Taking statin	73 (5)	36 (4)	37 (5)	0.34
By Exam 3 – Combined	620 (40)	324 (39)	296 (42)	0.24
NCEP Criteria	470 (31)	252 (30)	218 (31)	0.82
Taking statin	150 (10)	72 (9)	78 (11)	0.12
By Exam 4 – Combined	844 (55)	431 (52)	413 (59)	0.01
NCEP Criteria	631 (41)	336 (40)	295 (42)	0.59
Taking statin	213 (14)	95 (11)	118 (17)	0.003

* Eligibility criteria (adapted from NCEP 2004 update):

- **High Risk**: CVD, diabetes or multiple (2 or more) CHD risk factors with FRS > 20% & LDL-C above statin initiation threshold ≥ 70 mg/dL
- **Moderately high-risk:** Multiple (2 or more) CHD risk factors together with a 10–20% FRS & LDL-C above statin initiation threshold ≥ 100 mg/dL
- **Moderate risk**: Multiple (2 or more) CHD risk factors together with a <10% FRS & LDL above statin initiation threshold ≥ 130 mg/dL
- **Low risk**: Multiple 0–1 CHD risk factors & LDL-C above statin initiation threshold 160 mg/dL

** P (comparing CRP <2 with ≥2 mg/L)