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ORIGINAL INVESTIGATIONS

Negative Risk Markers for Cardiovascular Events in the Elderly

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ABSTRACT

BACKGROUND Cardiovascular risk increases dramatically with age, leading to nearly universal risk-based statin eligibility in the elderly population. To limit overtreatment, elderly individuals at truly low risk need to be identified.

OBJECTIVES Discovering "negative" risk markers able to identify elderly individuals at low short-term risk for coronary heart disease and cardiovascular disease.

METHODS In 5,805 BioImage participants (mean age 69 years; median follow-up 2.7 years), the authors evaluated 13 candidate markers: coronary artery calcium (CAC) = 0, CAC ≤10, no carotid plaque, no family history, normal ankle-brachial index, test result <25th percentile (carotid intima-media thickness, apolipoprotein B, galectin-3, high-sensitivity C-reactive protein, lipoprotein(a), N-terminal pro-B-type natriuretic peptide, and transferrin), and apolipoprotein A1 >75th percentile. Negative risk marker performance was compared using patient-specific diagnostic likelihood ratio (DLR) and binary net reclassification index (NRI).

RESULTS CAC = 0 and CAC ≤10 were the strongest negative risk markers with mean DLRs of 0.20 and 0.20 for coronary heart disease (i.e., ≈80% lower risk than expected from traditional risk factor assessment) and 0.41 and 0.48 for cardiovascular disease, respectively, followed by galectin-3 <25th percentile (DLR 0.44 and 0.43, respectively) and absence of carotid plaque (DLR 0.39 and 0.65, respectively). Results obtained by other candidate markers were less impressive. Accurate downward risk reclassification across the Class I statin-eligibility threshold defined by the American College of Cardiology/American Heart Association was largest for CAC = 0 (NRI 0.23) and CAC ≤10 (NRI 0.28), followed by galectin-3 <25th percentile (NRI 0.14) and absence of carotid plaque (NRI 0.08).

CONCLUSIONS Elderly individuals with CAC = 0, CAC ≤10, low galectin-3, or no carotid plaque had remarkable low cardiovascular risk, calling into question the appropriateness of a treat-all approach in the elderly population. (J Am Coll Cardiol 2019;74:1-11) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

ACC/AHA = American College of Cardiology/American Heart Association

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcium

CHD = coronary heart disease

cIMT = carotid intima media thickness

cPB = carotid plaque burden

CVD = cardiovascular disease

DLR = diagnostic likelihood ratio

Lp(a) = lipoprotein(a)

NRI = net reclassification index

PCE = pooled cohort equation

Current guidelines for the use of statin therapy for primary prevention of atherosclerotic cardiovascular disease (ASCVD) share the concept of allocating statins to those assumed to be at highest risk for future ASCVD (1,2). Given the broadened indication for statin therapy in recent guidelines combined with the dominant impact of age on estimated ASCVD risk using traditional risk calculators, most elderly individuals will eventually be considered to be at so high risk for ASCVD that everyone will qualify for lifelong preventive statin therapy (3,4). The appropriateness of treating all elderly, however, is controversial for at least 2 reasons. First, many elderly individuals do not have the underlying disease, that is, subclinical atherosclerosis, that statin therapy is meant to prevent or stabilize (5). Second, polypharmacy, drug-drug interactions, and potential side effects are increasing concerns among elderly individuals that may potentially offset the benefit of statin therapy (6–8). Thus, to avoid overtreatment with statins in the elderly that inevitably follows a near-universal statin indication, there is a strong need for more individualized risk prediction with accurate identification of elderly individuals at low ASCVD risk despite advancing age.

The purpose of the present study was to compare the ability of circulating biomarkers and noninvasive imaging tests to downgrade coronary heart disease (CHD) and cardiovascular disease (CVD) risk in elderly individuals. To do so, we took advantage of the contemporary multiethnic BioImage (BioImage Study: A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population) cohort of elderly individuals with extensive biomarker and imaging evaluation at baseline examination.

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METHODS

STUDY POPULATION. The design and objectives of the BioImage study (NCT00738725) have been published previously (5,9–11). In brief, the BioImage study is a prospective cohort of elderly men (55 to 80 years of age) and women (60 to 80 years of age) without known ASCVD at baseline examination. Participants were included between January 2008 and June 2009 in Chicago, Illinois, and Fort Lauderdale, Florida. The cohort is sex balanced and includes racial/ethnic minorities corresponding to the overall U.S. population. The primary objective of the study was to identify clinically useful biomarkers for near-term CHD and CVD events. The study was approved by the Institutional Review Board, and all study participants provided written informed consent and Health Insurance Portability and Accountability Act authorization before enrollment.

BASELINE EXAMINATION. Baseline examination included assessment of traditional cardiovascular risk factors, measurement of novel biomarkers, and screening for subclinical (asymptomatic) atherosclerosis as previously described and specified in the Online Appendix. A nonfasting venous blood sample was drawn and processed for routine chemistry test, including lipid levels. Selection and analysis of circulating biomarkers that might be clinically useful as negative risk markers for cardiovascular disease are described later in the text. Smoking status and family history were self-reported. Diabetes mellitus was defined as current use of oral hypoglycemic agents or insulin, or self-reported. All study participants underwent electrocardiogram-gated, noncontrast computed tomography scanning to determine the Agatston coronary artery calcium (CAC) score and carotid ultrasound imaging (Philips iU22 ultrasound system, Philips Healthcare, Bothell, Washington) to detect and quantify carotid intima-media thickness (cIMT) and carotid plaque burden (cPB). Measurement of cIMT was performed offline from a video clip of the distal common carotid artery in long-axis view. cPB was assessed using a novel sweep method described previously (12,13). In brief, the carotid artery was scanned cross-sectionally, slowly moving the transducer manually in the cranial direction from the proximal common carotid artery into the distal internal carotid artery. From the obtained video clip, all cross-sectional plaque areas were summed as cPB. Ankle-brachial index (ABI) was measured as previously described (12).

SELECTION OF NEGATIVE RISK MARKER CANDIDATES. The intention with the BioImage study under the High-Risk Plaque (HRP) initiative was to identify novel imaging and circulating biomarkers for high cardiovascular risk. Thus, all biomarkers available in the BioImage database were originally selected and measured with this purpose in mind. Given that the great majority of BioImage participants, just because of their age would be considered statin eligible under the 2018 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines (14), we decided to explore the BioImage database for "negative" biomarkers that could identify elderly people at low cardiovascular risk and help avoid overtreatment with statins.

The HRP biomarker discovery panel measured in all study participants include the following 6 circulating biomarkers: apolipoprotein A1, apolipoprotein B, high-sensitivity C-reactive protein (hsCRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), galectin-3, transferrin, and lipoprotein(a) (Lp[a]).

DEFINITION OF NEGATIVE RISK MARKERS. Because the distribution of CAC and carotid plaque is highly right skewed with many individuals having values of zero, we defined CAC = 0 and absence of carotid plaque as negative risk markers. Because it may be argued that not only CAC = 0 but also just low CAC scores (i.e., ≤10) may confer low risk, we also defined CAC ≤10 as a negative risk marker. For the other continuous biomarkers, a value <25th percentile was used to define the presence of a negative risk marker (cIMT, apoB, galectin-3, hsCRP, Lp(a), NT-proBNP, and transferrin) or apoA1 >75th percentile. In addition, normal ABI (index >0.9) and no family history of CVD were defined as negative risk markers.

CLINICAL OUTCOMES. Results are presented separately for the following 2 outcomes: 1) CHD (spontaneous myocardial infarction, unstable angina, and coronary revascularization); and 2) CVD (CHD + ischemic stroke and cardiovascular death). In sensitivity analyses, we excluded coronary revascularization that occurred within 30 days of baseline examination. An independent clinical events committee used source medical records to adjudicate CHD and CVD events as described in the Online Appendix.

STATISTICAL ANALYSES. Baseline characteristics of BioImage study participants are presented as mean ± SD or median (interquartile range).

First, we calculated the CHD and CVD event rate per 1,000 person-years among individuals in whom each of the negative risk markers was present. To assess the independent association (hazard ratios [HRs]) of negative risk markers (i.e., CAC = 0) with development of CHD and CVD, we used Cox regression models analyzing time to event. Analyses were performed adjusting for age and sex (Model 1) as well as multivariable adjusting for baseline characteristics (Model 2). We further calculated the diagnostic likelihood ratio (DLR). The DLR assesses the value of performing a diagnostic test (15). Thus, we used DLR to compute the change in pre-test (based on traditional cardiovascular risk factors alone) to post-test risk caused by the results of a subsequent test showing that a negative risk marker is present (i.e., CAC = 0). A DLR value >1 specifies that the post-test risk is higher than the pre-test risk (i.e., tested risk marker is not useful for downgrading risk), whereas a DLR value <1 specifies that the post-test risk is lower than the pre-test risk (i.e., tested risk marker may be useful for downgrading risk). We calculated DLRs as previously done (16), comparing coefficients from multivariable adjusted logistic regression models:

$$\text{Pre-test risk} = \text{logit P}\,(\text{CHD} = 1 \mid \text{X}) = \beta_{\text{O}}* + \beta\text{X}*\text{X}$$

$$\begin{aligned}\text{Post-test risk} &= \text{logit P}\,(\text{CHD} = 1 \mid \text{X},\ \text{Y}) \\ &= \beta_{\text{O}} + \beta_{\text{X}}\text{X} + \beta_{\text{y}}\text{Y} + \beta_{\text{XY}}\text{XY}\end{aligned}$$

The multivariable adjusted DLR is then calculated by subtracting pre-test risk from post-test risk:

$$\text{Log DLR}_{\text{C}}(\text{Y}) = (\beta_{\text{O}} - \beta_{\text{O}}*) + (\beta_{\text{X}} - \beta_{\text{X}}*) + \beta_{\text{Y}}\text{Y} + \beta_{\text{XY}}\text{XY}$$

Importantly, the DLR for a given negative risk marker varies from patient to patient, that is, the value and ability of a negative risk marker to reduce post-test risk depends on the combination of risk factors present in the particular patient. Thus, the DLR may be small for some patients even though the odds ratio for the negative risk marker obtained from the logistic regression analyses is large in the overall cohort.

To assess whether the negative risk markers could lead to clinically meaningful changes in clinical decision making, we assessed the ability of the negative risk markers to improve overall risk classification (to treat or not to treat) in the context of the 2018 ACC/AHA statin guidelines (14,17). First, we evaluated a simple negative risk marker-guided reclassification approach. Thus, among the BioImage individuals who qualified for statins with the 2018 ACC/AHA guideline using the guideline-recommended pooled cohort equations (PCEs) (10-year ASCVD risk ≥7.5%), we assessed the consequences of simply down-classifying (from statin eligible to ineligible) those in whom the negative risk marker was present. Thus, we calculated the binary net reclassification index (NRI) for each of the negative risk markers. Because the negative risk markers are only able to downgrade risk, the positive NRIs will be driven solely by improvements in specificity (indicating less overtreatment). This is especially relevant for elderly individuals in the current setting of a low-risk-based treatment threshold recommended by most international guidelines. The binary NRI across the 7.5% 10-year ASCVD risk threshold (to treat or not to treat) is calculated as the sum of Δsensitivity and Δspecificity.

In a secondary analysis, we also assessed NRI across a 7.5% 10-year CVD risk threshold using a BioImage-derived, well-calibrated logistic risk model (developed in the BioImage cohort). Because all participants in the BioImage study had <10 years of follow-up, we used an exponential survival function to scale participants' risk to their length of follow-up, as previously performed (18–20).

TABLE 1 Baseline Characteristics

	All (N = 5,805)	10-Year ASCVD Risk Calculated by PCE			
		<5% (n = 318)	5% to <7.5% (n = 521)	7.5% to 20% (n = 2,719)	≥20% (n = 2,247)
Age, yrs	68.9 ± 6.0	61.8 ± 2.8	63.6 ± 4.0	67.2 ± 4.9	73.1 ± 4.8
Male	44	10	23	40	57
Diabetes	15	0	2	8	28
Current smoker	9	1	3	9	11
Hypertension	62	16	30	56	83
Systolic blood pressure, mm Hg	139.5 ± 18.5	120.9 ± 12.6	127.4 ± 13.5	136.4 ± 16.2	148.5 ± 18.2
Total cholesterol, mg/dl	202.5 ± 38.6	204.6 ± 36.0	205.6 ± 35.7	205.9 ± 38.4	197.4 ± 39.3
HDL cholesterol, mg/dl	55.7 ± 15.3	65.0 ± 15.4	60.7 ± 15.4	56.4 ± 14.9	52.3 ± 14.7
LDL cholesterol, mg/dl	114.2 ± 33.2	112.5 ± 30.2	114.6 ± 31.1	117.2 ± 32.1	110.6 ± 33.9
Lipid-lowering medication	34	28	29	32	40
10-year ASCVD risk, %*	16.4 (9.9–25.9)	3.9 (3.4–4.5)	6.3 (5.8–7.0)	13.1 (10.3–16.3)	28.8 (24.0–36.5)

Values are mean ± SD, %, or median (interquartile range). *Estimated using the Pooled Cohort Equations.
ASCVD = atherosclerotic cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PCE = pooled cohort equations.

All analyses were performed using Stata version 14 (StataCorp, College Station, Texas).

RESULTS

The study population consisted of 5,805 adults (56% women) with a mean age of 69 years. A total of 4,198 individuals (72%) were >65 years of age. Baseline characteristics of the study population are shown in Table 1. The great majority (86%) of the BioImage cohort of elderly individuals recruited in 2008 to 2009 turned out to be statin eligible under the 2018 ACC/AHA cholesterol guidelines because of a 10-year ASCVD risk ≥7.5% estimated by the PCEs.

Over a median follow-up of 2.7 years (interquartile range: 2.5 to 3.1 years), 91 individuals had a first CHD event, and 138 individuals had a first CVD event.

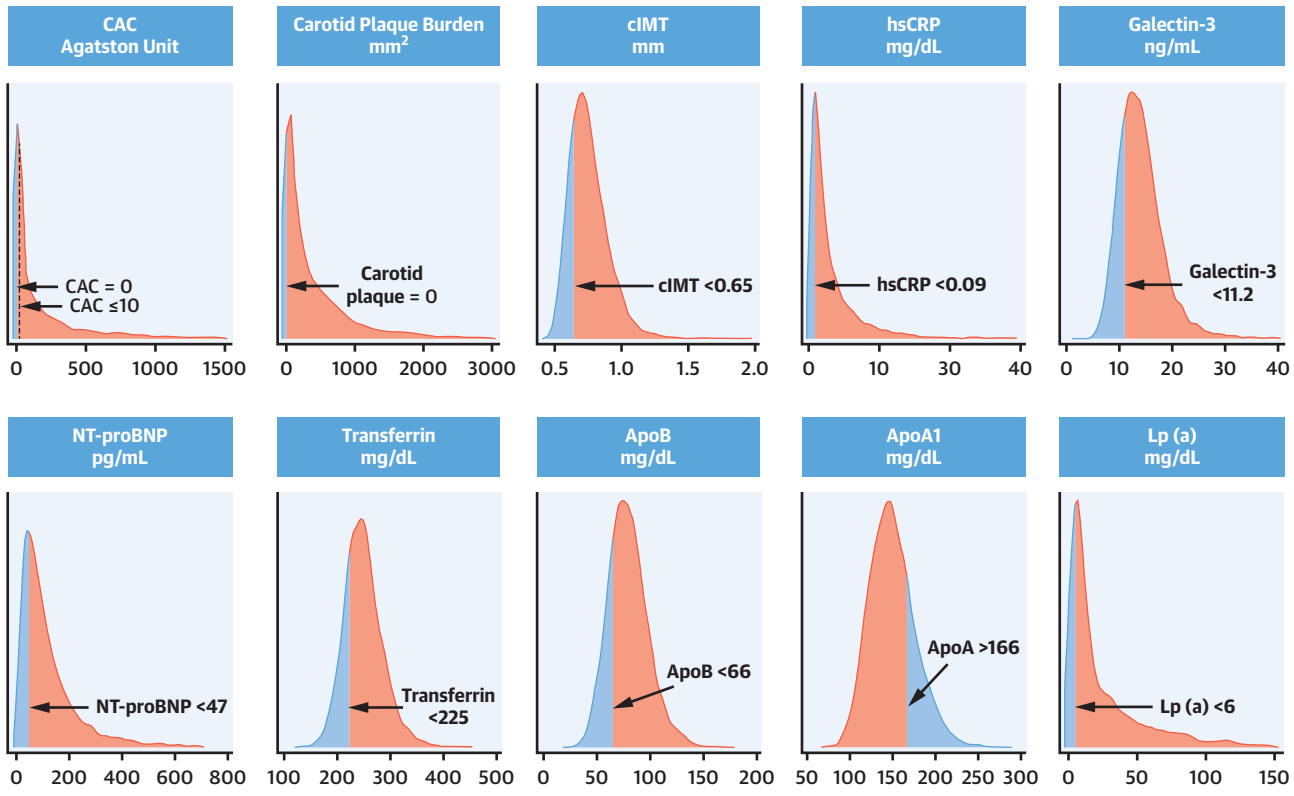
PREVALENCE AND EVENT RATES ACCORDING TO NEGATIVE RISK MARKERS. The prevalence of each negative risk marker is shown in Table 2, and distribution plots of the continuous biomarkers and cut-points when used as negative risk markers are shown in Figure 1. Normal ABI was most prevalent (64%),

TABLE 2 Number of Events and Event Rates According to Negative Risk Markers

Negative Risk Markers	Prevalence	Number of Events		Event Rates per 1,000 Person-Years	
		CHD	CVD	CHD (95% CI)	CVD (95% CI)
Overall cohort	5,805 (100)	91 (1.6)	138 (2.4)	6.07 (4.95–7.46)	9.23 (7.81–10.91)
Subclinical atherosclerosis					
CAC = 0	1,852 (32)	4 (0.2)	15 (0.8)	0.85 (0.32–2.26)	3.19 (1.92–5.29)
CAC ≤10	2,224 (38)	5 (0.3)	16 (0.9)	0.87 (0.36–2.10)	2.80 (1.71–4.57)
No carotid plaque	1,325 (23)	6 (0.5)	15 (1.1)	1.74 (0.78–3.88)	4.37 (2.63–7.25)
cIMT <25th percentile	1,459 (25)	14 (1.0)	20 (1.4)	3.78 (2.24–6.38)	5.41 (3.49–8.39)
Normal ABI	3,696 (64)	53 (1.4)	82 (2.2)	5.52 (4.22–7.22)	8.56 (6.89–10.63)
Clinical history					
No family history	2,708 (47)	37 (1.4)	57 (2.1)	5.25 (3.80–7.24)	8.10 (6.25–10.50)
Circulating biomarkers					
Galectin-3 <25th percentile	1,490 (26)	10 (0.7)	15 (1.0)	2.63 (1.42–4.89)	3.95 (2.38–6.55)
hsCRP <25th percentile	1,529 (26)	13 (0.9)	27 (1.8)	3.34 (1.94–5.75)	6.96 (4.78–10.16)
NT-proBNP <25th percentile	1,460 (25)	17 (1.2)	25 (1.7)	4.63 (2.88–7.44)	6.82 (4.61–10.10)
Transferrin <25th percentile	1,488 (25)	20 (1.3)	32 (2.2)	5.23 (3.38–8.11)	8.39 (5.94–11.87)
ApoB <25th percentile	1,452 (25)	16 (1.1)	31 (2.1)	4.22 (2.58–6.89)	8.21 (5.77–11.67)
ApoA1 >75th percentile	1,494 (26)	13 (0.9)	27 (1.8)	3.38 (1.96–5.81)	7.03 (4.82–10.25)
Lp(a) <25th percentile	1,475 (25)	26 (1.8)	38 (2.6)	6.85 (4.66–10.05)	10.02 (7.29–13.77)

Values are n (%) unless otherwise indicated.
ABI = ankle-brachial index; ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; cIMT = intima media thickness; CVD = cardiovascular disease; hsCRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein(a); NT-proBNP = N-terminal pro-B-type natriuretic peptide.

FIGURE 1 **Distribution Plots of Continuous Biomarkers and Cutpoints Defining Negative Risk Markers**



The numeric values used to define negative risk markers are shown in each plot: CAC = 0, CAC ≤10, no carotid plaque, cIMT <0.65 mm, hsCRP <0.09 mg/dl, galectin-3 <11.2 ng/ml, NT-proBNP <47 pg/ml, transferrin <225 mg/dl, apoB <66 mg/dl, apoA1 >166 mg/dl, and Lp(a) <6 mg/dl. For all but CAC and carotid plaque burden, these values correspond to the 25th (or 75th for apoA1) percentile. apoA1 = apolipoprotein A1; apoB = apolipoprotein B; CAC = coronary artery calcification; cIMT = carotid intima-media thickness; hsCRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein(a); NT-proBNP = N-terminal pro-B-type natriuretic peptide.

followed by no family history (47%), CAC ≤10 (38%), and CAC = 0 (32%). By definition, the prevalence of negative risk factors of continuous biomarkers was ≈25%. Accordingly, the number needed to screen to identify 1 individual with a negative risk marker varied from 1.6 for normal ABI to 4.0 for the continuous biomarkers (Online Table 1).

The overall CHD and CVD event rates among BioImage individuals were 6.1 and 9.2 per 1,000 person-years, respectively (**Table 2**). Among those who had a negative risk marker, event rates were lowest for CAC = 0 (0.9 and 3.2 per 1,000 person-years, respectively) and CAC ≤10 (0.9 and 2.8 per 1,000 person-years, respectively) followed by absence of carotid plaque (1.7 and 4.4 per 1,000 person-years, respectively) and galectin-3 <25th percentile (2.6 and 4.0 per 1,000 person-years, respectively).

HR AND DLR. As shown in **Table 3**, the multivariable-adjusted HRs for CHD and CVD in the presence of each negative risk marker varied greatly from 0.12 to 1.30 for CHD and 0.27 to 1.48 for CVD. CAC = 0 and CAC ≤10 had the lowest HRs (CHD 0.13 vs. 0.12; CVD 0.35 vs. 0.27), followed by galectin-3 <25th percentile and no carotid plaque (HRs: 0.31 to 0.55).

CAC = 0 and CAC ≤10 also provided the greatest downward change in pre-test-to-post-test risk, with mean multivariable-adjusted DLR of 0.20 and 0.20 for CHD and 0.48 and 0.41 for CVD, respectively (**Table 4, Central Illustration**). This equates to a relative risk reduction of ≈80% and ≈59% for CHD and CVD, respectively, compared with that expected from traditional risk factor assessment. Galectin-3 <25th percentile and absence of carotid plaque also provided significant downward changes in pre-test-to-post-test risk.

NET RECLASSIFICATION INDEX. First, we evaluated the simple negative risk marker-guided reclassification approach in context of the current 2018 ACC/AHA guidelines. Thus, among the 4,966 BioImage

TABLE 3 HRs for Negative Risk Markers in BioImage for CHD and CVD

Negative Risk Markers	CHD		CVD	
	Model 1	Model 2	Model 1	Model 2
Subclinical atherosclerosis				
CAC = 0	0.11 (0.04–0.33)	0.13 (0.05–0.36)	0.33 (0.18–0.57)	0.35 (0.20–0.61)
CAC ≤10	0.11 (0.04–0.27)	0.12 (0.47–0.29)	0.25 (0.15–0.43)	0.27 (0.16–0.45)
No carotid plaque	0.27 (0.12–0.64)	0.31 (0.14–0.72)	0.48 (0.28–0.83)	0.55 (0.32–0.94)
cIMT <25th percentile	0.64 (0.35–1.14)	0.73 (0.40–1.30)	0.60 (0.37–0.98)	0.69 (0.42–1.11)
Normal ABI	1.01 (0.65–1.57	1.00 (0.65–1.55)	1.01 (0.71–1.43)	0.97 (0.68–1.38)
Clinical history				
No family history	0.71 (0.46–1.08)	0.71 (0.46–1.08)	0.73 (0.52–1.03)	0.72 (0.51–1.02)
Circulating biomarkers				
Galectin-3 <25th percentile	0.31 (0.16–0.60)	0.34 (0.18–0.67)	0.32 (0.18–0.55)	0.34 (0.20–0.59)
hsCRP <25th percentile	0.43 (0.24–0.78)	0.52 (0.29–0.94)	0.64 (0.42–0.98)	0.76 (0.49–1.16)
NT pro-BNP <25th percentile	0.57 (0.33–0.99)	0.58 (0.33–1.01)	0.59 (0.37–0.92)	0.53 (0.40–0.99)
Transferrin <25th percentile	0.74 (0.45–1.21)	0.72 (0.44–1.19)	0.79 (0.53–1.17)	0.79 (0.52–1.16)
ApoB <25th percentile	0.57 (0.33–0.98)	0.58 (0.30–1.12)	0.78 (0.52–1.16)	0.87 (0.52–1.44)
ApoA1 >75th percentile	0.66 (0.36–1.22)	1.30 (0.61–2.76)	0.95 (0.61–1.48)	1.48 (0.83–2.60)
Lp(a) <25th percentile	1.05 (0.67–1.66)	1.06 (0.67–1.68)	1.01 (0.69–1.47)	1.03 (0.71–1.51)

Values are HR (95% CI). Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, smoking status, diabetes, total cholesterol, HDL cholesterol, systolic blood pressure, and lipid-lowering drugs.

HR = hazard ratio; other abbreviations as in Tables 1 and 2.

participants (86%) who qualified for risk-based statin therapy under the 2018 ACC/AHA guideline (PCE ≥7.5%), we assessed the consequences of simply down-classifying those in whom the negative risk marker was present. Using this approach, absence of CAC and CAC ≤10 resulted in substantial positive NRIs of 0.23 and 0.28, respectively, for CHD and 0.18 and 0.23, respectively, for CVD followed by galectin-3 <25th (NRI of 0.14 for both CHD and CVD) and absence of carotid plaque (NRI of 0.14 for CHD and 0.10 for CVD) (Table 5).

Finally, in a secondary analysis, we then assessed the usefulness of the negative biomarkers to correctly down-classify CVD risk across a 7.5% 10-year CVD risk threshold derived from the BioImage cohort. Thus, we calculated the binary NRI among individuals with an estimated 10-year pre-test risk for CVD ≥7.5%. Correct down-classification was a post-test risk <7.5% among individuals without CVD event. As shown in Online Table 2, absence of CAC and CAC ≤10 resulted in the largest NRIs (0.16 and 0.22, respectively) followed by galectin-3 (0.14) and absence of carotid plaque (0.08).

TABLE 4 Multivariable Adjusted DLR

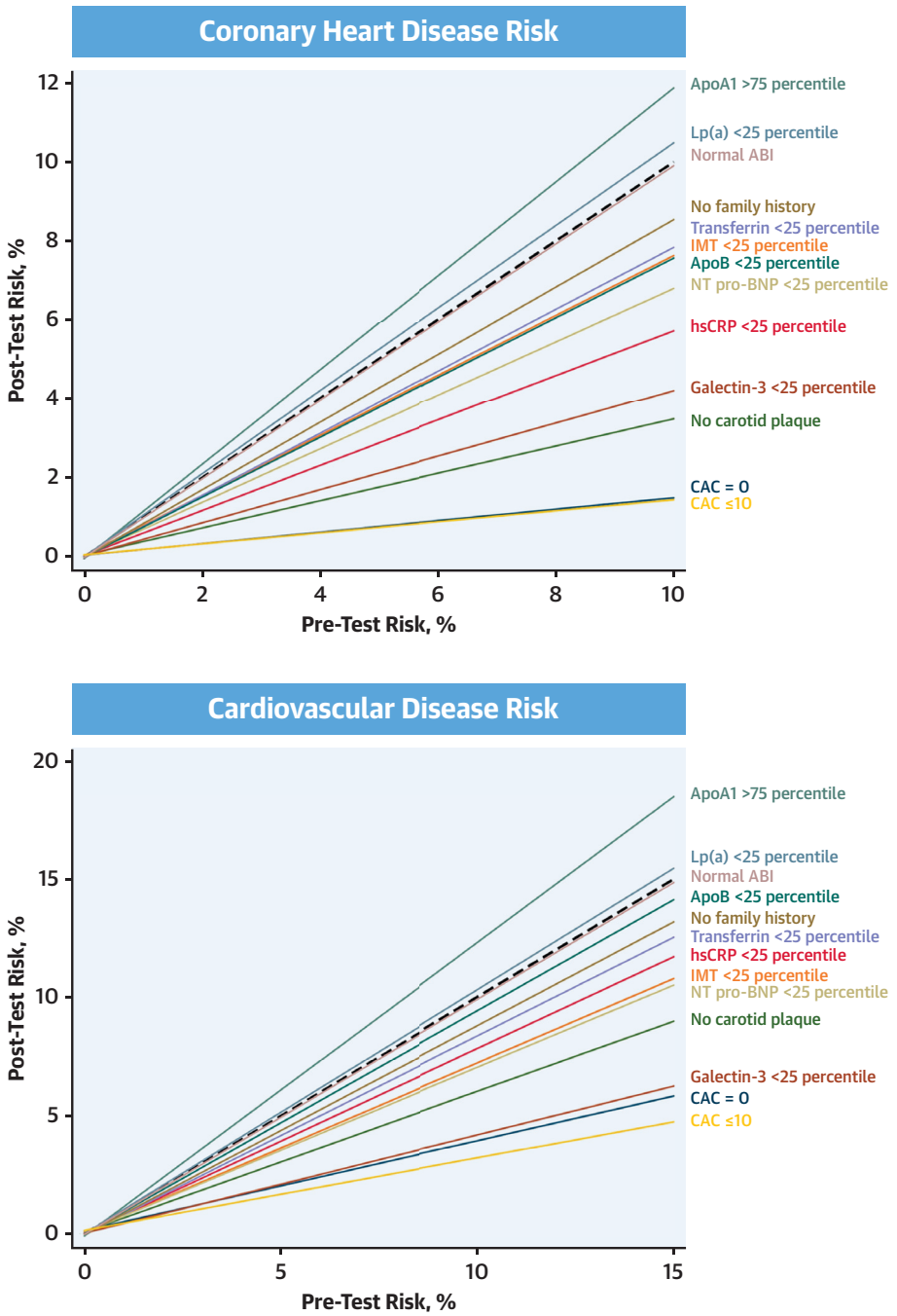
Negative Risk Markers	CHD	CVD
Subclinical atherosclerosis		
CAC = 0	0.20 ± 0.03	0.48 ± 0.04
CAC ≤10	0.20 ± 0.03	0.41 ± 0.05
No carotid plague	0.39 ± 0.02	0.65 ± 0.02
cIMT <25th percentile	0.80 ± 0.02	0.76 ± 0.02
Normal ABI	0.98 ± 0.03	0.98 ± 0.02
Clinical history		
No family history	0.84 ± 0.02	0.86 ± 0.02
Circulating biomarkers		
Galectin-3 <25th percentile	0.44 ± 0.04	0.43 ± 0.04
hsCRP <25th percentile	0.60 ± 0.03	0.80 ± 0.02
NT-proBNP <25th percentile	0.69 ± 0.06	0.73 ± 0.05
Transferrin <25th percentile	0.77 ± 0.02	0.82 ± 0.01
ApoB <25th percentile	0.75 ± 0.05	0.94 ± 0.02
ApoA1 >75th percentile	1.11 ± 0.05	1.16 ± 0.05
Lp(a) <25th percentile	1.05 ± 0.004	1.03 ± 0.002

Values are mean ± SD.

DLR = diagnostic likelihood ratios; other abbreviations as in Table 2.

SENSITIVITY ANALYSIS. In sensitivity analyses, we excluded revascularizations occurring within 30 days of the baseline examination. As shown in Online Figure 1 and Online Tables 3 and 4, this yielded similar results. In another sensitivity analysis, we restricted the analyses to those not taking statins at baseline examination. As shown in Online Tables 5 to 7, this did not change the results. Finally, we limited the study population to elderly individuals ≥75 years (n = 1,146). Due to the limited number of CHD events in this subgroup, we only assessed the ability of the negative risk markers to downgrade CVD risk. As shown in Online Tables 8 to 10, CAC = 0, CAC ≤10, and galectin-3 <25th percentile continued to improve risk classification in this very elderly subgroup.

CENTRAL ILLUSTRATION **Shift in Pre- to Post-Test Risk for Coronary Heart Disease and Cardiovascular Disease in the Presence of Each Negative Risk Marker**



Mortensen, M.B. et al. J Am Coll Cardiol. 2019;74(1):1–11.

CAC = 0, CAC ≤10, no carotid plaque, and galectin-3 <25th percentile yielded substantial changes in the pre-test (based on Framingham risk factors alone) to post-test risk for both CHD and CVD. ApoA1 >75th percentile, Lp(a) <25th percentile, normal ankle-brachial index (ABI), or no family history did not reduce post-test risk. ApoA1 = apolipoprotein A1; apoB = apolipoprotein B; CAC = coronary artery calcification; hsCRP = high-sensitivity C-reactive protein; IMT = intima-media thickness; Lp(a) = lipoprotein(a); NT-proBNP = N-terminal pro-B-type natriuretic peptide.

TABLE 5 Simple Negative Risk Marker–Guided Reclassification Approaches for Individuals Who Qualify for Statin Therapy Under the ACC/AHA Guidelines (N = 4,966)

Predicted Outcome and Negative Risk Markers	Down-Classification of Events	Down-Classification of Nonevents	NRI
Coronary heart disease			
Subclinical atherosclerosis			
CAC = 0	4 (5)	1,369 (28)	0.23
CAC ≤10	5 (6)	1,680 (34)	0.28
No carotid plaque	6 (7)	1,001 (21)	0.14
cIMT <25th percentile	11 (13)	1,069 (22)	0.09
Normal ABI	51 (59)	3,069 (63)	0.04
Clinical history			
No family history	35 (41)	2,301 (47)	0.06
Circulating biomarkers			
Galectin-3 <25th percentile	10 (11)	1,226 (25)	0.14
hsCRP <25th percentile	20 (23)	1,253 (26)	0.03
NT pro-BNP <25th percentile	17 (20)	1,223 (25)	0.05
Transferrin <25th percentile	20 (23)	1,262 (26)	0.03
ApoB <25th percentile	14 (16)	1,196 (25)	0.09
ApoA1 >75th percentile	12 (14)	1,168 (24)	0.10
Lp(a) <25th percentile	24 (28)	1,230 (25)	−0.03
Cardiovascular disease			
Subclinical atherosclerosis			
CAC = 0	13 (10)	1,360 (28)	0.18
CAC ≤10	14 (11)	1,671 (34)	0.23
No carotid plaque	14 (11)	993 (21)	0.10
cIMT <25th percentile	15 (11)	1,065 (22)	0.11
Normal ABI	79 (60)	3,041 (63)	0.03
Clinical history			
No family history	54 (41)	2,282 (47)	0.06
Circulating biomarkers			
Galectin-3 <25th percentile	15 (11)	1,221 (25)	0.14
hsCRP <25th percentile	26 (20)	1,239 (26)	0.06
NT pro-BNP <25th percentile	25 (19)	1,215 (25)	0.06
Transferrin <25th percentile	32 (24)	1,255 (26)	0.02
ApoB <25th percentile	27 (20)	1,183 (24)	0.04
ApoA1 >75th percentile	26 (20)	1,154 (24)	0.04
Lp(a) <25th percentile	35 (27)	1,219 (25)	−0.02

Values are n (%) unless otherwise indicated.

ACC/AHA = American College of Cardiology and American Heart Association; NRI = net reclassification index; other abbreviations as in Table 2.

DISCUSSION

Little is known about how to downgrade ASCVD risk in elderly people. In the contemporary BioImage cohort of elderly at-risk individuals, we found that among the 13 potentially negative risk markers studied, absence of detectable subclinical atherosclerosis by imaging and low galectin-3 concentrations resulted in the greatest changes in pre- to post-test risk of both CHD and CVD and, thus, in the greatest improvements in overall risk classification. These results may have important implications for personalizing preventive treatment in elderly individuals and should be considered in future iterations of guidelines as a potential tool to reduce unnecessary overtreatment in the growing elderly population.

DERISKING IN ELDERLY INDIVIDUALS. Age is the most important determinant of predicted risk using traditional risk models (3,4,21). As expected, the vast majority (86%) of the elderly BioImage participants was therefore statin-eligible according to the 2018 ACC/AHA guidelines because of a high estimated ASCVD risk. This nearly universal treatment principle will inherently be accompanied by a high sensitivity (detection rate), that is, assignment of statin therapy to most of the individuals who later develop CHD or CVD events (22). However, the specificity of this approach is exceedingly poor with allocation of statins to a substantial proportion of individuals who were never destined to develop ASCVD (5,23). Because frailty, comorbidity, and polypharmacy are increasing concerns in elderly individuals and have been proposed to increase the risk for adverse effects, the appropriateness of treating almost all elderly individuals is questionable (4,7,24). Accurate identification of elderly individuals at truly low risk for ASCVD despite advancing age is therefore gaining increasing interest. An emerging way to personalize treatment in the elderly segment of the population is by so-called derisking, that is, improving risk prediction using novel negative risk markers applied to identify elderly individuals at so low ASCVD risk that statins and other preventive treatment may be safely avoided (16). This approach is fundamentally different from the conventional high-risk approach where novel biomarkers are used to "up-risk" those who do not qualify for treatment after traditional risk assessment despite being at truly high risk for a near-term ASCVD event.

NEGATIVE RISK MARKERS IN THE ELDERLY. In the present study, we evaluated the ability of 13 different risk markers to downgrade ASCVD risk in elderly individuals. Among these risk markers, CAC = 0 and CAC ≤10 resulted in the greatest changes in pre- to post-test risk for CHD and CVD. For example, the estimated risk for CHD based on traditional risk factors went down by a remarkable ≈80% if CAC was absent or the CAC score was ≤10. Because CAC = 0, and especially CAC ≤10, were also prevalent findings in the elderly BioImage cohort (≈1 of 3), the great changes in pre- to post-test risk with CAC = 0 and CAC ≤10 yielded substantial improvements in overall risk classification driven solely by major gains in specificity (= less overtreatment). These results confirm previous studies showing that CAC = 0 is associated with low event rates and mortality (25-28). Our data further extend them to also include elderly

individuals where CAC = 0, if anything, is at least as strong a marker of low ASCVD risk as in the previously studied younger populations. These data provide strong support for the new 2018 ACC/AHA guidelines that recommend to consider withholding statin therapy in individuals at "intermediate risk" (PCE risk ≥7.5% to <20%) if CAC = 0 (14). Another novel finding from our study is the strong negative predictive value of CAC ≤10 among elderly individuals. Because the prevalence of CAC ≤10 was 38% compared with 32% for CAC = 0, CAC ≤10 resulted in further improvements of overall risk classification with NRI 0.28 for CHD compared with 0.23 for CAC = 0. Absence of carotid plaque on serial cross-sectional 2-dimensional images using carotid ultrasound also showed considerably reductions in post-test risk (i.e., 61% for CHD). It is worth noting that absence of carotid plaque performed much better than cIMT <25th percentile, particularly for downgrading CHD risk. This is not surprising because assessment of cPB has been shown to better capture ASCVD risk than assessment of cIMT (13,29–32). This likely reflects that cIMT is a nonspecific marker of vascular damage, including hypertension-mediated changes, rather than being a marker of atherosclerosis per se.

Our results confirm data from the slightly (≈8 years lower median age) younger MESA (Multi-Ethnic Study of Atherosclerosis) cohort where CAC = 0 was the strongest negative risk marker among 13 studied predictors (16). However, CAC = 0 and absence of carotid plaque seem to be even stronger markers of low risk in the BioImage study than in the MESA study (i.e., DLR 0.20 vs. 0.41 for CHD with CAC = 0, and 0.39 vs. 0.84 for no carotid plaque), which may at least partly be explained by an 8-year-older study population in the BioImage study. Consistent with this suggestion, the DLRs became progressively lower with advancing age in our analyses (data not shown), which is supported by previous observations in the MESA study (16,33). It is likely that the younger study population in the MESA study, probably together with using a novel, more sensitive sweep method to detect carotid plaque in the BioImage study, also explain why cIMT <25th percentile (similar prevalence in the MESA and BioImage studies) was a stronger negative risk marker than absence of carotid plaque in the MESA study (prevalence 58% in MESA vs. 23% in the BioImage study). Additionally, the shorter follow-up time in the BioImage study compared with the MESA study may also partly explain why the observed negative predictive value of the different risk markers was stronger in our study.

Of the circulating biomarkers, only galectin-3 provided substantial changes in pre- to post-test risk of both CHD and CVD. Galectin-3 is a β-galactoside-binding lectin expressed in many cells relevant to ASCVD, including monocytes, activated macrophages, and endothelial cells, and experimental research has suggested that galectin-3 plays important regulatory roles in several biological processes such as fibrosis, inflammation, and cell migration (34). High galectin-3 levels (at baseline as well as longitudinal changes over time) have emerged as a prognostic biomarker for heart failure, CVD, and all-cause mortality in both the general population and patients with known heart failure (34–37). Regarding ASCVD, high galectin-3 has been shown to predict cardiovascular mortality in patients with established CHD (35,36), but little is known about the value of galectin-3 in predicting ASCVD events in apparently healthy people. We found, for the first time, that a low galectin-3 level was a strong marker of low CHD and CVD risk among elderly individuals, associated with ≈55% lower risk than expected based on traditional risk factors. Notably, galectin-3 <25th percentile performed as well or better than assessment of subclinical atherosclerosis by carotid ultrasound (i.e., absence of carotid plaque), yielding substantial improvements in overall risk classification (NRI of 0.14 for both CHD and CVD events). Pharmacological inhibition of galectin-3 in various preclinical cardiovascular models has been associated with prevention of fibrosis, preservation and restoration of function, and reduced mortality (37–40). This raises the question of whether inhibition of galectin-3 in individuals with higher levels of galectin-3 can one day be part of a strategy to reduce ASCVD risk.

Interestingly, some risk markers currently recommended by U.S. and European guidelines to "up-risk" patients who do not qualify for statin treatment on the basis of traditional risk assessment (i.e., family history, abnormal ABI, or high concentrations of Lp[a]) (14,41,42), were not able to provide significant changes in pre- to post-test risk. Thus, normal ABI or low levels of Lp(a) cannot be used to reassure patients about a good prognosis. These results highlight important aspects of risk prediction. Thus, although some risk markers may be useful for upgrading risk if the test is abnormal or high, this does not necessarily mean that the same tests can be used to downgrade risk if test results are normal or low (i.e., normal ABI or low levels of Lp[a]). This understanding is important for clinically meaningful decision making, and is the reason that the 2018 ACC/AHA guideline specifically used the term "risk enhancers" for several of these risk markers.

Although the focus of the present study has been on the value of negative risk markers to guide statin treatment, the potential value of such markers increases when considering preventive treatment beyond statins including blood pressure control and aspirin. Further, with the continued introduction of novel preventive therapies, correct identification of those individuals who are less likely to benefit from intensified prevention is becoming increasingly important.

A major strength of the present study is the use of a contemporary elderly cohort with extensive baseline examination and of whom the vast majority qualifies for preventive treatment under the current guidelines.

STUDY LIMITATIONS. A limitation that the BioImage study shares with other contemporary cohorts is the lower-than-expected event rates, which, at least partly, may be explained by the "healthy volunteer effect" and common use of preventive therapies in modern people free of ASCVD. We included coronary revascularization in the composite endpoints as it comprises an increasing proportion of ASCVD burden in the population. However, excluding revascularization within 30 days from baseline examination did not change the conclusions of the study. The follow-up in our study was 2.7 years. The durability of our short-term results may therefore be questioned, but growing evidence indicates that the warranty period for CAC = 0 may be as long as 15 years (43), likely indicating life-long low risk in elderly people.

CONCLUSIONS

In a contemporary cohort of elderly individuals, absence of subclinical atherosclerosis, especially CAC = 0 and CAC ≤10, as well as galectin-3 <25th percentile, provide substantial changes in the pre- to post-test risk as well as improvements in the overall risk classification. Interestingly, galectin-3 <25th percentile performed as well or better than assessment of subclinical atherosclerosis by carotid ultrasound. These novel data indicate that galectin-3 may be a clinically useful negative risk marker for ASCVD derisking. Our results hold the potential to markedly improve statin allocation in elderly individuals by de-escalating or even withholding preventive therapy in elderly individuals at truly low ASCVD risk despite advancing age.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In elderly people, low levels of coronary artery calcification, galectin-3, and absence of carotid plaque are common and associated with a lower risk of ASCVD than expected based on traditional risk assessment.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine the threshold of risk at which it is safe to withhold therapy for prevention of ASCVD in elderly people.

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APPENDIX For an expanded Methods section and a supplemental figure and tables, please see the online version of this paper.