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Utility of Non-Traditional Risk Markers in Individuals Ineligible for Statin Therapy According to the 2013 ACC/AHA Cholesterol Guidelines

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Abstract

Background—In the general population, the majority of cardiovascular events occur in people at the low to moderate end of population risk distribution. The 2013 American College of Cardiology/ American Heart Association guideline on the treatment of blood cholesterol recommends consideration of statin therapy for adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk ≥7.5% based on traditional risk factors. Whether use of non-

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traditional risk markers can improve risk assessment in those below this threshold for statin therapy is unclear.

Methods and Results—Using data from the Multi-Ethnic Study of Atherosclerosis (MESA), a population sample free of clinical CVD at baseline, we calibrated the Pooled Cohort Equations (cPCE). ASCVD was defined as myocardial infarction, coronary heart disease death, fatal or non-fatal stroke. Adults with initial cPCE <7.5% and elevated levels of additional risk markers (abnormal test) whose new calculated risk ≥ 7.5% were considered statin eligible: low-density lipoprotein cholesterol (LDL) ≥160 mg/dL, family history of ASCVD (FH), high-sensitivity C-reactive protein≥2 mg/dL, coronary artery calcium (CAC) score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity, and ankle-brachial index<0.9. We compared the absolute (AR) and relative (RR) ASCVD risks among those with vs without elevated post-test estimated risk. We calculated the number needed to screen to identify one person with abnormal test (NNSI) for each risk marker, defined as the number of participants with baseline cPCE risk <7.5% ÷ number with abnormal test reclassified as statin eligible. Of 5,185 participants not taking statins with complete data (age 45-84), 4185 had a cPCE risk <7.5%. During 10 years of follow up, 57% of the ASCVD events occurred among adults with a cPCE risk <7.5% (183/320). Excluding people with diabetes, the CAC criterion reclassified 6.8% upward, with an event rate of 13.3%, AR of 10%, RR (95%CI) of 4.0(2.8-5.7) and NNSI of 14.7. The corresponding numbers for FH were 4.6%, 15.1%, 12%, 4.3(3.0-6.4) and 21.8 respectively; hs-CRP criterion were 2.6%, 10%, 6%, 2.6(1.4-4.8) and 39.2 respectively; ABI criterion were 0.6%, 9%, 5%, 2.3(0.6-8.6) and 176.5 respectively and LDLc criterion were 0.5%, 5%, 1%, 1.2(0.2-8.4) and 193.3 respectively. 431/3882(11.1%) of those with < 7.5% cPCE were reclassified to ≥ 7.5 %(statin eligible) by at least one of the additional risk marker criterion.

Conclusions—In this generally low-risk population sample, a large proportion of ASCVD events occurred among adults with a 10-yr. cPCE risk <7.5%. We found that the CAC, hsCRP, FH and ABI recommendations by the ACC/AHA cholesterol guidelines (Class IIB) identify small subgroups of asymptomatic population with <7.5% 10 yr. cPCE but with observed ASCVD event rates higher than 7.5% who may warrant statin therapy considerations.

Keywords

Cholesterol guidelines; Additional risk markers; Coronary artery calcium score; Risk Assessment; Atherosclerotic cardiovascular disease

Introduction

In the recently published guidelines on assessment of cardiovascular risk and treatment of blood cholesterol to reduce atherosclerotic risk in adults[1,2], the American College of Cardiology (ACC) and American Heart Association (AHA) introduced a new approach to decision making regarding statin therapy. Specifically, the guidelines recommended that “In selected individuals who are not in 1 of the 4 statin benefit groups, and for whom a decision to initiate statin therapy is otherwise unclear, additional markers may be considered to inform treatment decision making (Class II)[1]”. The markers mentioned included LDLc ≥160 mg/dL, other genetic hyperlipidemias, family history of premature atherosclerotic cardiovascular disease (ASCVD), high sensitivity C-reactive protein, coronary artery

calcium (CAC), lifetime ASCVD risk and ankle-brachial index (ABI). If these additional markers could be used to identify subsets of lower risk people (<7.5% 10-yr ASCVD risk) who are actually higher risk based on additional risk marker testing, this could be extremely important since on a population level the greatest number of cardiovascular events occur, somewhat paradoxically, in those traditionally assessed as low to moderate risk[3-5].

The Guidelines did not cite data or provide evidence concerning what the yield would be when using these additional risk markers as additional tests in an otherwise low risk (not 1 of the 4 statin benefit) group and whether their use in this group adds useful information beyond the newly proposed Pooled Cohort Equation[2] risk estimates. To address this gap, in this report we describe the yields and increases in risk assessment and risk category assignment afforded by the addition of elevated/abnormal levels of CAC, CRP, ABI, LDLc, and family history of ASCVD to the Pooled Cohort Equation (PCE) risk estimates in asymptomatic adult participants in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods

Study Population and Data Collection

The design for the MESA study has been published elsewhere [6]. In brief, MESA is a prospective population-based cohort study to investigate the prevalence, correlates, and progression of subclinical CVD in persons without known CVD at baseline. The full cohort includes 6,814 women and men ages 45 to 84 years recruited from 6 U.S. communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, New York; and St. Paul, Minnesota). MESA included 38% white, 28% African American, 22% Hispanic, and 12% Chinese adults. Demographics, medical history, anthropometric and laboratory data for the present study were taken from the first examination (July 2000 to August 2002). The MESA study was approved by the institutional review boards of each study site, and written informed consent was obtained from all participants.

For the current analysis, we excluded participants who had missing data related to traditional or additional risk factors, follow-up, or those who were using statins at baseline.

Conventional Risk Factors

As part of the baseline examination, clinical teams collected information on traditional and additional putative cardiovascular risk factors. Current smoking was defined as having smoked a cigarette in the last 30 days. Use of medications was based on medication inventory. Diabetes mellitus was defined as self-reported history of diabetes mellitus, diabetes medication use or fasting glucose ≥126mg/dl. Resting blood pressure was measured three times in the seated position, and the average of the second and third readings was recorded.

Hypertension was defined as a systolic blood pressure (SBP) of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or use of antihypertensive medication. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Total and high density lipoprotein (HDL) cholesterol were measured from blood samples obtained after a

12-h fast. Low-density lipoprotein (LDL) cholesterol was estimated by the Friedewald equation [7].

Additional Risk Markers Recommended in the Guidelines

The presence of genetic hyperlipidemias as recommended in the guidelines[1] was not assessed in the current analysis because it was not collected in MESA. Lifetime ASCVD risk was also not assessed in the present study because it can only be calculated in adults ages 20-59 and many MESA participants are older than 59. In addition, to create the lifetime risk calculator only cohorts with more than 15 years of follow-up were included, which is beyond the duration of follow-up in MESA.

1. Primary LDL–C ≥160 mg/dL—Measurement of baseline LDLc is as reported above. Individuals without type 2 diabetes mellitus, LDLc <190mg/dL but with a 10 year ASCVD risk of <7.5% and LDL-c ≥ 160 mg/dL were classified as having primary LDLc ≥ 160mg/dL.

2. Family history of ASCVD—In MESA we did not specifically define family history of ASCVD as premature (i.e. before the age of 55 for men and 65 for women). Family history of ASCVD was obtained by asking participants whether any member in their immediate family (first-degree relatives: parents, siblings and children) experienced fatal or nonfatal myocardial infarction (MI) or stroke. Age of onset of the event was not specified, and so it is not known whether the events were premature.

3. high-sensitivity C-reactive protein≥ 2 mg/dL—hsCRP was measured using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, Illinois) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, Vermont). Analytical intra-assay coefficient of variations ranged from 2.3% to 4.4%, and inter-assay coefficient of variation ranged from 2.1% to 5.7% with a detection level of 0.18 mg/L.

4. CAC score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity—Details of the MESA CT scanning and interpretation methods have been reported by Carr et al[8]. Scanning centers assessed CAC by chest computed tomography (CT) with either a cardiac-gated electron-beam CT scanner (Chicago, Illinois; Los Angeles, California; and New York, New York field centers) or a multidetector CT system (Baltimore, Maryland; Forsyth County, North Carolina; and St Paul, Minnesota field centers). Certified technologists scanned all participants twice over phantoms of known physical calcium concentration. A radiologist or cardiologist read all CT scans at a central reading center (Los Angeles Biomedical Research Institute at Harbor–UCLA, Torrance, California). We used the mean Agatston score for the 2 scans in all analyses[9]. Intraobserver and interobserver agreements were excellent ($\kappa = 0.93$ and $\kappa = 0.90$, respectively).

5. Ankle-brachial index <0.9—Details of the MESA ankle-brachial index measurement protocol have been published by Criqui et al[10]. Briefly, SBP measurements in the bilateral brachial, dorsalis pedis, and posterior tibial arteries were obtained in the supine position

using a hand-held Doppler instrument with a 5-mHz probe. To avoid potential bias from subclavian stenosis, the higher of the brachial artery pressures was used as the denominator. For each lower extremity, the ABI numerator used was the highest pressure (dorsalis pedis or posterior tibial) from that leg. Reproducibility of the ABI was evaluated using measurements of 43 participants by two technicians. The inter- and intra- reader correlation coefficients were 0.845 and 0.937 respectively with an intra- and inter- reader coefficient of variation of 5.14% and 3.27% respectively. Participants with an ABI ≥ 1.4 were excluded.

Event Ascertainment

A detailed description of the event ascertainment procedures and the adjudication process in MESA has been published[11]. Briefly, every 9-12 months since the baseline examination, MESA participants or when necessary their proxies are contacted to inquire about hospital admissions, cardiovascular disease diagnosis and death which may have occurred. Hospital and other documentation of possible cardiovascular events and deaths are subsequently obtained. These documentations are sent to at least two MESA morbidity and mortality committee members for adjudication using a standard protocol. The MESA morbidity and mortality committee include cardiologists, physician epidemiologists, and neurologists. All possible events with disagreements after adjudication by at least two MESA morbidity and mortality members are discussed and voted on by the committee during their monthly meetings. For the purposes of this study, we define incident ASCVD as adjudicated myocardial infarction (MI), coronary heart disease (CHD) death, and fatal and non-fatal stroke as described by the MESA protocol (www.mesa.nhlbi.org).

Statistical Analysis

Baseline characteristics are presented as mean (± S.D.) for continuous variables and percentages for categorical variables. To avoid overestimating the contribution of the additional risk factors to the Pooled Cohort Equation (PCE) risk estimates and to account for estimated baseline survival and censoring. Calibration was accomplished by including the PCE in a Cox model predicting ASCVD events[12]. These calibrated PCE (cPCE) were used in all subsequent analyses. Analyses were performed to address two specific questions.

1. What proportion of ASCVD events occurred in participants with 10 yr. c PCE risk <7.5%?

This was obtained by dividing the number of adjudicated ASCVD events which occurred in participants with initial cPCE <7.5% by the total number of ASCVD events that occurred in the whole cohort (N=5185)

2. Among MESA participants with initial risk estimation <7.5% 10 yr. ASCVD risk using the new cPCE, what proportion will become statin eligible based on each abnormal test?

Participants with levels of each additional marker that were above the predefined thresholds outlined in the ACC/AHA guidelines (CAC≥300 or 75th percentile for age, sex, race; hsCRP≥2 g/dl; ABI<0.9; LDL>160 mg/dl, positive family history in any first-degree relative) whose new calculated 10yr. risk for ASCVD event were ≥7.5% in a Cox proportional hazard model of cPCE + additional test in question as a binary variable (using the recommended thresholds) were considered potentially statin eligible. Thus, while all

participants with levels of the additional test below the recommended ACC/AHA thresholds remained statin ineligible, only those with abnormal test with new calculated risk in the Cox model ≥7.5% were reclassified as statin eligible. The number of <7.5% cPCE individuals needed to screen to identify one potential statin eligible participant for each additional marker was calculated as follows:

Number Needed to Screen to identify one statin eligible person (NNSI) = (Total number of participants with <7.5% cPCE screened) ÷ (Number of participants with abnormal test reclassified as statin eligible).

In addition, the actual 10 yr. event rate in those with abnormal test and also reclassified as having ≥7.5% risk (statin eligible) was compared to the event rate in those not meeting the criteria(10yr. risk remained <7.5% in the cPCE + additional risk model) using absolute and relative risk. The statistical analysis was performed using STATA 12.0.

Results

Of the 6,814 MESA participants, 1,629(23.9%) were either on statins, had an ABI>=1.4, or had incomplete data and were therefore eliminated from this analysis. Baseline characteristics are described in Table 1 for the remaining 5,185 participants. The mean age of the participants included in this analysis was 61.2 years, 53.1% female, 38%% whites, 12.1% Chinese, 27% Blacks and 22.9% Hispanics. After a median of 10.2 years (25^{th} percentile =9.6yrs.; 75^{th} percentile 10.7yrs) of follow up, 320(6.2%) ASCVD events occurred; 139 (43.4%) were MIs, 132 (41.3%) were fatal or non-fatal strokes, and 49 (15.3%) were CHD death.

Prior to recalibration of the PCE, 1791/2456(72.9%) of participants with initial 10 yr. risk <7.5% had at least one abnormal test. 53/320 (16%) adjudicated ASCVD events occurred in those classified by PCE (not calibrated) as <7.5% 10 yr. risk at baseline. However 3157/4185(75.4%) of participants with initial <7.5% cPCE had at least one abnormal test after recalibration of the PCE. Table 1 shows the demographic characteristic, risk factor and proportion of sub cohort (<7.5% and ≥7.5% cPCE) with abnormal test for each additional marker.

1. What proportion of ASCVD events occurred in participants with cPCE 10 yr. risk <7.5%?

More than half of the events (183/320, 57%) were among participants with a 10-year estimated ASCVD risk <7.5% based on the cPCE. However, the ASCVD event rate of the subgroup with 10yr.cPCE ≥ 7.5% was higher than that of the <7.5% subgroup (13.8% vs. 4.7%).

2. Among MESA participants with initial risk estimation <7.5% 10 yr. ASCVD risk using the new cPCE, what proportion would have an abnormal result for one of the additional risk markers and what proportion will become statin eligible based on each abnormal test?

Among the 3,882 participants with a cPCE 10-yr. risk <7.5% and no diabetes, 264 (6.8%) had CAC score that exceeded the threshold recommended in the new guidelines and also became statin eligible (Table 2). Accordingly, the number needed to screen to identify one

statin eligible participant (NNSI) for CAC was 14.7. The mean 10-yr. ASCVD event rate in these participants otherwise not recommended for statin therapy was 13.3% - well above 7.5% risk threshold adopted in the new guidelines. When compared with the event rate among those who remained statin ineligible (3.3%), the absolute risk (AR) associated with statin eligibility due to an abnormal CAC score was = 10% and the relative risk (RR) (95%CI) was 4.0 (2.8-5.7), p<0.0001). In a similar manner, 178 of the 3882 participants (4.6%) became statin eligible based on a positive family history of ASCVD (NNSI=21.8), and the event rate in the statin eligible group was 15.1% (AR = 12.0%; RR (95%CI): 4.3(3.0-6.4), p<0.0001). For hsCRP, 99 out of the 3882 participants (2.6%) became statin eligible (NNSI=39.2) and the event rate in the statin eligible group based on an abnormal hsCRP was 10.1% (AR = 6.0%; RR (95%CI): 2.6(1.4-4.8), p=0.002). Although the prevalence of abnormal ABI was very low among participants not recommended for statin therapy based on cPCE risk estimates alone (0.5%, NNSI = 176), the event rate among those who became statin eligible still exceeded the 7.5% threshold (9.1%, AR = 5.0%; RR(95%CI): 2.3(0.6-8.6),p=0.22). The NNSI and event rate in those with LDLc>/= 160 mg/dl who became statin eligible were 193.3 and 5.0 %, respectively (Table 2). 431/3882(11.1%) of participants with initial cPCE were reclassified to ≥7.5%c PCE (statin eligible) by at least one of the additional risk marker criterion.

Discussion

The current study shows that among the additional risk markers enumerated in the new cholesterol guidelines[1] CAC, FH and hsCRP each identified a small subgroup among those with baseline cPCE <7.5% who in fact had a 10-yr ASCVD event rate significantly higher than 7.5%. Based on the risk threshold for statin therapy advocated in the guidelines (7.5% 10-yr ASCVD risk), these people would be potentially eligible for statin therapy. Among the risk markers studied, the number needed to screen to identify one additional person potentially eligible for statins was lowest for CAC (14.7). Family history and hsCRP also have promising yields for identification of higher risk people. Ultimately a decision to use these additional risk markers as screening tests for statin therapy will depend on many additional factors including the risks and costs of the specific tests (nominal for FH, more so for CAC), and the efficacy of statin therapy in the subgroups they identify. Nevertheless, these data emphasize the potential (albeit small) for further refinement of risk assessment through targeted application of additional risk markers such as the ones considered in this study.

The current study sits at the nexus between the Geoffrey Rose Prevention Paradox[3,4] and more recently advocated goals of precision medicine[13]. More than 20 years ago Dr. Rose described the fundamental epidemiologic observation that although conventional risk factors identify patients with high relative risk for cardiovascular events, they still miss the much larger number of apparently low risk people who go on to experience cardiovascular disease. This observation continues to justify a two-tiered strategy for cardiovascular disease prevention including targeted interventions (+ therapeutic lifestyle changes) for those at highest risk and population-based (untargeted) therapeutic lifestyle changes for the rest of the population.

However, for the last 30 years the proper boundary between targeted therapy and therapeutic lifestyle changes has been vigorously debated and frequently revised, as evidenced most recently by the newest iteration of the AHA/ACC primary prevention guidelines[1]. It is not surprising that the proper definition of this boundary has been so vigorously debated[14-17]. Achieving the proper balance between cardiovascular disease reduction and the risks and costs of achieving those reductions has enormous implications for both public health and public healthcare expenditures. The two essential elements required to define the boundary between targeted and untargeted interventions are 1.) the risk threshold for targeted therapy, and 2.) the tests used to estimate the risk for each individual under consideration. The first issue has received tremendous attention since the publication of the new guidelines[14-17] and is not the subject of the current analysis. This report is focused on the second question of whether additional tests are useful to more precisely identify individuals classified as low risk by current risk tools who should still be considered for targeted intervention.

The additional risk markers recommended in the new guidelines and evaluated here have been extensively studied previously [18-20]. However, these studies have generally focused on the incremental information of these markers in “intermediate risk” people defined by the Framingham Risk Score (FRS). Now that the risk threshold and the method of estimating that risk have changed, it is important to re-consider the utility of these markers to identify additional higher risk individuals - especially since the utility of any screening test is in part determined by the prior probability of events in the population to be screened. Understanding which, if any, additional screening tests should be used among the roughly 70 million Americans adults[2] who would otherwise be considered ineligible for statins (but will produce majority of cardiovascular events) has major implications for the optimization of screening and treatment for primary prevention of ASCVD.

The present study has limitations. Even though we excluded participants who were taking statins during the baseline MESA exam from this analysis, some of the participants included in this analysis were prescribed statins (28%) during the follow up. This may have affected the observed event rates and therefore the results described here. However participants with abnormal test (based on the additional risk markers) were about 3 times as likely to be prescribed statins compared with those with normal test in this MESA cohort. Hence the absolute risk associated with an abnormal test (based on the additional risk markers) in the present study is most likely underestimated, further strengthening our findings and conclusions. Finally, MESA included participants from four race/ethnic groups without baseline clinical CVD aged 45 to 84 years at baseline. Our result was also not stratified by gender or race given the relative few ASCVD events which occurred in this low risk cohort. The findings of this study may not apply to dissimilar populations.

Conclusion

In this study of well-characterized multi-ethnic cohort followed for 10 years, we found that the majority of ASCVD events occurred in individuals with < 7.5% 10yr. cPCE. We also found that the CAC, hsCRP, FH and ABI recommendations by the ACC/AHA cholesterol guidelines(Class IIB) identify small subgroups of asymptomatic population with <7.5% 10 yr. cPCE but with observed ASCVD event rates higher than 7.5% who may warrant statin

therapy considerations. Replication of our findings in other race/ethnic groups and other cohorts is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of Multi-Ethnic Study of Atherosclerosis participants.

Variable	< 7.5% cPCE (N=4185)	≥ 7.5 cPCE (N=1,000)	Total Cohort (n=5185)
Age, yrs (Mean ± SD)	58.2 ± 8.6	73.6 ± 6.6	61.2 ±10.3
Females, n (%)	2380(56.9)	371(37.1)	2751(53.1)
Race/Ethnicity (%)			
Whites	1606(38.4)	363(36.3)	1969(38)
Chinese	518(12.4)	107(10.7)	625(12.1)
Black	1117(26.7)	285(28.5)	1402(27.0)
Hispanic	944(22.6)	245(24.5)	1189(22.9)
Diabetes mellitus, n (%)	236 (5.6)	270 (27.0)	506(9.8)
Cholesterol, mg/dl (Mean ± SD)			
Total	196.2 ± 35.1	197.2 ± 37.9	196.4 ±35.7
LDL*	119.3 ± 31.2	121.2 ± 32.0	119.7± 31.4
HDL	51.6 ± 15.0	48.4 ± 14.4	51.0 ±15.0
Triglycerides	126.6 ± 75.5	142.7 ± 125.8	129.7 ±87.7
BMI, Kg/m2 (Mean ± SD)	28.2 ± 5.6	28.0 ± 4.9	28.2 ±5.4
Blood Pressure, mmHg (Mean ± SD)			
Systolic	121.0 ± 18.5	145.0 ± 21.9	125.6± 21.4
Diastolic	71.3 ± 10.1	75.1 ± 11.0	72.1 ±10.4
Cigarette smoking, n (%)			
Never	2177(52.0)	447(44.7)	2624(50.6)
Former	1457(34.8)	397(44.7)	1854(35.8)
Current	551(13.2)	156(15.6)	707(13.6)
Antihypertensive medication use, n (%)	1092(26.1)	591(59.1)	1683(32.5)
CAC >/= 300 or >/= 75	903 (21.6)	346 (34.6)	1249(24.1)
hsCRP >/= 2 mg/dl	2004(47.9)	506 (50.6)	2510(48.4)
ABI < 0.9	63(1.5)	94(9.4)	157(3.0)
LDLc >/= 160 mg/dl	401(9.7)	108(11.0)	509(9.9)
Family history	1688(40.3)	433(43.3)	2121(40.9)

Footnote: cPCE, calibrated Pooled Cohort Equation; ASCVD, atherosclerotic cardiovascular disease; MI, myocardial infarction; CAC, coronary artery calcium score; Hs-CRP, high sensitivity C-reactive protein; ABI, ankle brachial index; LDL, low density lipoprotein, HDL, high density lipoprotein; IQR, inter quartile range.

* LDL sample size = 5123 (due to missing values)

Table 2

Improvement gained by the addition of coronary artery calcium (CAC) score, high sensitivity C - reactive protein (hsCRP) and index (ABI) and LDLc dichotomized using the recommendation by the ACC/AHA cholesterol guidelines and Family history of Atherosclerotic cardiovascular disease (ASCVD) to MESA participants with 10 year calibrated Pooled Cohort Equation (cPCE) risk of <7.5% and their corresponding Number needed to screen (**Excluding Type 2 Diabetics**).

cPCE + CAC >/= 300 or >/= 75 percentile for age, race, and sex						
	10-yr ASCVD Event					
	Negative	**Positive**	**Total**	**Event Rate**	**Relative Risk(95%CI)**	**NNSI****
Risk < 7.5%** Abnormal + Risk ≥ 7.5%* Total	3497	121	3618	0.03		
	229	35	264	0.13	4.0(2.8-5.7),p<0.0001	14.7
	3726	156	3882			

cPCE + hsCRP ≥ 2mg/dl						
	10-yr ASCVD Event					
	Negative	**Positive**	**Total**	**Event Rate**	**Relative Risk(95%CI)**	**NNSI****
Risk < 7.5%** Abnormal + Risk ≥ 7.5%* Total	3637	146	3783	0.04		
	89	10	99	0.10	2.6(1.4-4.8),p=0.002	39.2
	3726	156	3882			

cPCE + ABI <0.9						
	10-yr ASCVD Event					
	Negative	**Positive**	**Total**	**Event Rate**	**Relative Risk(95%CI)**	**NNSI****
Risk < 7.5%** Abnormal + Risk ≥ 7.5%* Total	3706	154	3860	0.04		
	20	2	22	0.09	2.3(0.6-8.6),p=0.22	176.5
	3726	156	3882			

cPCE + LDLc ≥ 160mg/dl*						
	10-yr ASCVD Event					
	Negative	**Positive**	**Total**	**Event Rate**	**Relative Risk(95%CI)**	**NNSI****
Risk < 7.5%** Abnormal + Risk ≥ 7.5%* Total	3671	155	3846	0.04		
	19	1	20	0.05	1.2(0.2-8.4),p=0.83	193.3
	3690	156	3866			

cPCE + FH						
	10-yr ASCVD Event					
	Negative	**Positive**	**Total**	**Event Rate**	**Relative Risk**	**NNSI****
Risk < 7.5%** Abnormal + Risk ≥ 7.5%* Total	3575	129	3704	0.03		
	151	27	178	0.15	4.3(3.0-6.4),p=<0.0001	21.8
	3726	156	3882			

Footnote:

Risk < 7.5%**: Participants with normal or abnormal test whose 10yr. ASCVD risk was still <7.5% after adding the additional marker

Abnormal + Risk ≥ 7.5%*: Participants with abnormal test whose ASCVD risk increased to ≥7.5% after adding the additional marker (statin eligible).

Positive: Participants who had an adjudicated ASCVD event during the follow up period.

Negative: Participants who did not have an adjudicated ASCVD event during the follow up period.

NNSI** indicates the number of individuals with 10yr. cPCE <7.5% needed to be screen to identify one abnormal test who is statin eligible for each additional marker.

*Sample size is 3866.