Supplementary Online Content

Lin JS, Evans CV, Johnson E, Redmond N, Coppola EL, Smith N. Nontraditional risk factors in cardiovascular disease risk assessment: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. doi:10.1001/jama.2018.4242

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Literature Search Strategies for Primary Literature

Key:
/ = MeSH subject heading
$ = truncation
* = truncation
? = wildcard
ab = word in abstract
adj# = adjacent within x number of words
ae = adverse effects
hw = subject heading word
id = identifier
kw = keyword
md = methodology
near/# = adjacent within x number of words
ti = word in title

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Ovid MEDLINE(R) Daily Update <May 19, 2017>

1 exp Cardiovascular Diseases/ ()
2 (heart or coronar or cardiac* or cardio* or myocardi* or vascular* or CVD or cerebrovascular or stroke or cerebral or atheroscler*).ti. ()*
3 (heart or coronar or cardiac* or cardio* or myocardi* or vascular* or CVD or cerebrovascular or stroke or cerebral or atheroscler*).ti,ab. ()*
4 limit 3 to ("in data review" or in process or "pubmed not medline") ()
5 1 or 2 or 4 ()
6 Ankle Brachial Index/ ()
7 Blood Pressure/ ()
8 Ankle/ ()
9 7 and 8 ()
10 Ankle/bs [Blood Supply] ()
11 Brachial Artery/ph, pp, us [Physiology, Physiopathology, Ultrasonography] ()
12 (brachial adj1 ankle adj4 (ratio or index* or indices or gradient* or pressur*)).ti,ab. ()*
13 (arm adj1 ankle adj4 (ratio or index* or indices or gradient* or pressur*)).ti,ab. ()*
14 ankle index.ti,ab. ()*
15 6 or 9 or 10 or 11 or 12 or 13 or 14 ()
16 C-Reactive Protein/ ()
17 (c-reactive protein or crp or hscrp).ti. ()
18 (c-reactive protein or crp or hscrp).ti,ab. ()
19 limit 18 to ("in data review" or in process or "pubmed not medline") ()
20 exp Biomarkers/ ()
21 exp Inflammation/ ()

22 18 and 20 and 21 ()
23 16 or 17 or 19 or 22 ()
24 Coronary Vessels/ ()
25 Coronary Artery Disease/ ()
26 Coronary Angiography/ ()
27 Tomography, X-Ray Computed/ ()
28 Four-Dimensional Computed Tomography/ ()
29 Tomography, Spiral Computed/ ()
30 Multidetector Computed Tomography/ ()
31 24 or 25 or 26 or 27 or 28 or 29 or 30 ()
32 Calcinosis/ ()
33 Vascular Calcification/ ()
34 Calcium/ ()
35 32 or 33 or 34 ()
36 31 and 35 ()
37 (coronary adj3 calci).ti,ab. ()*
38 cac.ti,ab. ()
39 calcium scor.ti,ab. ()*
40 coronary computed tomographic angiogra.ti,ab. ()*
41 ccta.ti,ab. ()
42 36 or 37 or 38 or 39 or 40 or 41 ()
43 5 and 15 ()
44 limit 43 to yr="2012 -Current" ()
45 5 and 23 ()
46 limit 45 to yr="2007 -Current" ()
47 5 and 42 ()
48 limit 47 to yr="2008 -Current" ()
49 44 or 46 or 48 ()
50 Animal/ not (Human/ and Animal/) ()
51 49 not 50 ()
52 limit 51 to english language ()

PubMed [Publisher Supplied]

Search	Query
#19	Search #18 AND Publisher[sb] AND English[Language]
#18	Search #13 OR #15 OR #17
#17	Search #1 AND #11 Filters: Publication date from 2008/01/01 to 2017/12/31
#16	Search #1 AND #11

#15 Search #1 AND #5 Filters: Publication date from 2007/01/01 to 2017/12/31

#14 Search #1 AND #5

#13 Search #1 AND #4 Filters: Publication date from 2012/01/01 to 2017/12/31

#12 Search #1 AND #4

#11 Search #6 OR #7 OR #8 OR #9 OR #10

#10 Search ccta[tiab]

#9 Search "coronary computed tomographic angiography"[tiab] OR "coronary computed tomographic angiograph"[tiab] OR "coronary computed tomographic angiographic"[tiab] OR "coronary computed tomographic angiogram"[tiab]

#8 Search "calcium score"[tiab] OR "calcium scores"[tiab] OR "calcium scoring"[tiab]

#7 Search cac[tiab]

#6 Search coronary[tiab] AND (calcium*[tiab] OR calcify*[tiab] OR calcifi*[tiab] OR calcinos*[tiab])

#5 Search "c-reactive protein"[tiab] OR "c-reactive proteins"[tiab] OR crp[tiab] OR hscrp[tiab]

#4 Search #2 OR #3

#3 Search ankle[tiab] AND (brachial[tiab] OR arm[tiab])

#2 Search "ankle index"[tiab] OR "ankle indexes"[tiab] OR "ankle indices"[tiab]

#1 Search heart[ti] OR coronar*[ti] OR cardiac*[ti] OR cardio[ti] OR cardiog*[ti] OR cardiol*[ti] OR cardiom*[ti] OR cardiop*[ti] OR cardiov*[ti] OR myocardi*[ti] OR vascular*[ti] OR CVD[ti] OR cerebrovascular[ti] OR stroke[ti] OR cerebral[ti] OR atheroscler*[ti]

Cochrane Central Register of Controlled Trials: Issue 4 of 12, April 2017

#1 (heart or coronar or cardiac* or cardio* or myocardi* or vascular* or CVD or cerebrovascular or stroke or cerebral or atheroscler*):ti*
#2 ankle:ti,ab,kw near/2 brachial:ti,ab,kw
#3 arm:ti,ab,kw near/2 ankle:ti,ab,kw
#4 "ankle index":ti,ab,kw or "ankle indexes":ti,ab,kw or "ankle indices":ti,ab,kw
#5 #2 or #3 or #4
#6 "c-reactive protein":ti,ab,kw or "c-reactive proteins":ti,ab,kw or crp:ti,ab,kw or hscrp:ti,ab,kw
#7 coronary:ti,ab,kw near/3 calci:ti,ab,kw*
#8 cac:ti,ab,kw

#9 "calcium score":ti,ab,kw or "calcium scores":ti,ab,kw or "calcium scoring":ti,ab,kw

#10 "coronary computed tomographic angiography":ti,ab,kw or "coronary computed tomographic angiograph":ti,ab,kw or "coronary computed tomographic angiographic":ti,ab,kw or "coronary computed tomographic angiogram":ti,ab,kw

#11 ccta:ti,ab,kw

#12 #7 or #8 or #9 or #10 or #11

#13 #1 and #5 Publication Year from 2012 to 2017, in Trials

#14 #1 and (#6) Publication Year from 2007 to 2017, in Trials

#15 #1 and #12 Publication Year from 2008 to 2017, in Trials

#16 #13 or #14 or #15

eTable 1. Inclusion Criteria

Category	Inclusion Criteria
Condition Definition	Atherosclerotic cardiovascular disease (CVD), including coronary heart disease, cerebrovascular disease, and peripheral artery disease
Populations	Adults without known cardiovascular disease • By sex, race/ethnicity, and diabetes
Risk Factors	High-sensitivity C-reactive protein, coronary artery calcium, ankle-brachial index
Treatments	KQs 4&5: interventions aimed at preventing CVD events (i.e., aspirin, HMG Co-A reductase inhibitors, antihypertension medications, and lifestyle modifications such as diet and/or exercise)
Comparisons	KQs 1–3: existing cardiovascular disease risk assessment models (focus on cardiovascular disease as opposed to coronary heart disease risk assessment) KQs 4&5: no treatment or usual care (as defined by the study)
Outcomes	KQs 1&4: CVD events (e.g., myocardial infarction, cerebrovascular accident) and/or mortality KQ 2: measures of reclassification (e.g., net reclassification index, integrated discrimination improvement), discrimination (e.g., area under the curve, c-statistic), and calibration (e.g., agreement between observed and predicted risks) KQs 3&5: serious adverse events from risk factor assessment or aggressive risk factor modification resulting in unexpected or unwanted medical attention (e.g., major bleeding, development of diabetes), exposure to radiation
Countries	Studies conducted in countries categorized as "Very High" on the 2014 Human Development Index (as defined by the United Nations Development Program)
Study Designs	KQs 1&4: systematic review of trials, RCT, CCT KQ 2: systematic review of trials, RCT, CCT, well-designed large prospective cohort studies, risk prediction studies KQs 3&5: systematic reviews, RCT, CCT, well-designed large prospective or retrospective cohort studies, well designed case-control studies (only for rare events)
Language	English language only
Study Quality	"Fair" or "Good" quality only

Abbreviations: CCT = controlled clinical trial; CVD = cardiovascular disease; HMG Co-A reductase inhibitors = 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors; KQ = key question; RCT = randomized controlled trial

eTable 2. Quality Assessment Criteria

Study Design	Criteria
Randomized and nonrandomized controlled trials, adapted from US Preventive Services Task Force methods[1]	• Valid random assignment? (NA for nonrandomized controlled trials) • Was allocation concealed? • Were eligibility criteria specified? • Were groups similar at baseline? • Were outcome assessors blinded? • Were measurements equal, valid, and reliable? • Was there adequate adherence to the intervention? • Were the statistical methods acceptable? • Was the handling of missing data appropriate? • Was there acceptable followup? • Was there evidence of selective reporting of outcomes? • Was there risk of contamination?
Cohort studies, adapted from the Newcastle-Ottawa Scale[2]	• Was the exposed cohort(s) representative of the general population? • Was the nonexposed cohort selected from the same community as the exposed cohort? • How was "exposure" ascertained? • Demonstrated that outcome of interest was not present at start of study? • Were the cohorts comparable on the basis of the design or analysis? • Were outcome assessors blind? • Was followup long enough for outcomes to occur? • Was there adequate followup of cohorts?
Risk prediction study, adapted from CHARMS[3] with selected domains pertaining to IPD meta-analyses[4] (if applicable)	• Does the IPD-MA *a priori* define the rationale, methods, and conduct of methods? If no, what don't they state?[a] • How does the IPD-MA identify relevant studies?[a] • Source of data • Does the study sample adequately represent the population of interest (participant eligibility and recruitment)? • Was there selective inclusion of participants in the model, based on data availability? • If participants are from a treatment RCT, is treatment accounted for? • Is a definition and method for measurement of the outcome reported? • Was the same outcome definition (and method for measurement) used in all patients? • Was the outcome assessed without knowledge of the candidate predictors (i.e., blinded)? • Time of outcome occurrence (average follow-up) and time horizon predicted • Is a definition and method for measurement of candidate predictors reported? • Were predictors assessed blinded for each other? • How was the predictor of interest (ABI, CAC, CRP) handled in the modelling? • Number of participants and number of outcomes/events • Number of outcomes/events in relation to the number of candidate predictors (events per variable) • Number of participants with any missing value (include predictors and outcomes) • How was missing data handled? • *Does IPD-MA use methods to investigate and account for between study heterogeneity? • Were both calibration and discrimination measures reported? Were confidence intervals reported? • Were *a priori* cut-points used for classification measures (e.g., sensitivity, specificity, predictive values, NRI)?

eTable 2. Quality Assessment Criteria Continued

Study Design	Criteria
Risk prediction study, adapted from CHARMS[3] with selected domains pertaining to IPD meta-analyses[4] (if applicable) Continued	• Was a bias-corrected NRI used? This applies only to studies presenting NRI for specific risk strata. • In what way was the population a separate external validation from the FRS or PCE? • Was the FRS or PCE recalibrated in the population before the NTRF was added to the model?

[a] Applicable for IPD meta-analyses only

Abbreviations: ABI = ankle-brachial index; CAC = coronary artery calcium; CHARMS = Checklist for Critical Appraisal and Data Extraction for Systematic Review of Prediction Modelling Studies; CRP = C-reactive protein; FRS = Framingham Risk Score; IPD MA = individual participant data meta-analyses; NA = not applicable; NRI = net reclassification improvement; PCE = Pooled Cohort Equations; RCT = randomized controlled trial

eTable 3. Examples of Types of Test Performance Measures for Comparing Risk Assessment or Prediction Models[5-9]

Purpose of outcome measure	Example measures of test performance	Description
Calibration	Calibration plot	Graphical assessment of calibration with predictions on the x-axis and outcome on the y-axis. Calibration in the large and calibration slope can be derived from calibration plots.
	O:E	The ratio of observed-to-expected events.
	Hosmer–Lemeshow test	Calculated by summing differences between observed and predicted probabilities in each group (a group being some parsing of the population, e.g., by decile, risk strata); a significant p-value signals poor fit. The test is sensitive to how groups are constructed and to sample size, often being nonsignificant for small N and significant for large N.[9] The Hosmer–Lemeshow test does not adjust for time-to-event, and several approaches have been developed to extend the test for survival data (but were not reported in included studies).[10]
Overall performance (captures both calibration and discrimination aspects)[7]	Akaike information criterion (AIC) and Bayes information criterion (BIC)	The AIC and BIC are measures used during model development to aid in inclusion or exclusion of predictors in a model. The AIC is a function of log likelihood that adds a penalty for each added predictor. The BIC is similar, although it imposes a greater penalty than the AIC for added variables. Lower values of both measures indicate better model fit. A change of >10 in the AIC has been proposed to indicate strong evidence for a difference in models.[11]
	Likelihood ratio χ^2	Likelihood ratio χ^2 is a global test of model fit and a function of the number of terms in the model. Higher values for the ratio, or difference between models, indicate better fit (as do lower absolute log-likelihood values).[12] A global χ^2 is generally the same as a likelihood χ^2 (twice the log likelihood ratio).
	Brier score	The Brier score computes the sum of squared differences between observed outcomes and fitted probability, where lower values indicate that predicted probabilities are closer to observed outcomes.[12]
	R^2	There are a number of ways to calculate an R^2 for a logistic regression.[9] Nagelkerke's generalized R^2, which is reported in included studies in this body of literature, is generally analogous to the percentage of variance explained in a linear model and is adjusted to a range of 0 to 1. Higher values indicate better fit.[12] The R^2 is more helpful than the Brier score because it can be compared across models/studies.
Discrimination	c-statistic or area under the curve (AUC); change in c-statistic or AUC	The probability that, for a randomly selected pair of individuals, one with disease and the other without, the person with disease will have the higher estimated disease probability according to the model.[12] The c-statistic can be conceptualized as the area under the ROC curve (plots sensitivity against 1−specificity); as a rank order statistic it is insensitive to systematic errors in calibration.[7] The Harrell's c-statistic is an extension of the AUC for survival analysis allowing for right-censored data and variable time to followup.[13] The change in c-statistic or AUC can be insensitive in assessing the impact of adding new predictors to a model, and the impact of a new predictor on c-statistics is lower when other strong predictors are in the model.[14]

eTable 3. Examples of Types of Test Performance Measures for Comparing Risk Assessment or Prediction Models[5-9] Continued

Purpose of outcome measure	Example measures of test performance	Description
Risk reclassification	Net reclassification index or improvement (NRI)	The sum of differences in proportions of individuals moving up a risk category minus those moving down a risk category with a cardiovascular disease outcome, plus the proportion moving down a risk category minus those moving up a risk category without an outcome. The NRI can be considered separately as the sum of the event NRI (P[up|event] – P[down|event]) and nonevent NRI (P[down|nonevent] – P[up|nonevent]). The NRI is not weighted for the prevalence of events or nonevents; some experts have advocated against combining event and nonevent NRI[15] and others have commented that NRI is naturally weighted by event and nonevent categories serving as their own denominators.[16] The NRI is of limited value in comparing models with different risk categories.
	Integrated discrimination improvement (IDI)	Integrates the NRI over all possible cutoffs; equivalent to difference in discrimination slopes of the 2 models and to the difference in R^2.[7]

eTable 4. Discrimination Outcomes in Included ABI Risk Prediction Studies (KQ2)

Model Type: Base Model	Author, Year	Study Name	Outcome	Subgroup	N	Base Model C-Statistic (95% CI)	Extended Model C-Statistic (95% CI)	Change in Discrimination (95% CI)[a]	Change P-Value
Published coefficient: PCE	Yeboah, 2016[17]	MESA[c]	Hard CVD	All Participants	5,185	0.74 (NR to NR)	0.75 (NR to NR)	0.01 (NR to NR)	0.55
Published coefficient: FRS	Geisel, 2017[18]	HNR	Hard CVD	All Participants	3,108	0.693 (0.661 to 0.726)	0.687 (0.653 to 0.721)	-0.006 (NR to NR)	0.54
	Fowkes, 2014[19]	ABI Collaboration	Hard CHD	Women[d]	6,459	0.578 (0.492 to 0.661)	0.69 (0.605 to 0.764)	0.112 (NR to NR)	NR
	Fowkes, 2014[19]	ABI Collaboration	Hard CHD	Men[d]	4,962	0.672 (0.599 to 0.737)	0.685 (0.612 to 0.749)	0.013 (NR to NR)	NR
	Yeboah, 2016[17]	MESA[c]	Hard CHD	All Participants	5,185	0.74 (NR to NR)	0.75 (NR to NR)	0.01 (NR to NR)	0.042
	Velescu, 2015[20]	REGICOR[e]	Soft CVD	All Participants	5,248	0.787 (NR to NR)	0.795 (NR to NR)	0.008[a] (0.001[a] to 0.017[a])	0.049[a]
	Velescu, 2015[20]	REGICOR[e]	Soft CHD	All Participants	5,248	0.795 (NR to NR)	0.797 (NR to NR)	0.002[a] (-0.001[a] to 0.007[a])	0.529[a]
Model development: FRS variables	Murphy, 2012[21]	ARIC	Hard CVD	All Participants	11,594	0.756 (0.739 to 0.773)	0.758 (0.741 to 0.775)	0.002 (NR to NR)	0.23
	Price, 2007[22]	EAS	Hard CVD	All Participants	1,007	0.614 (0.56 to 0.67)	0.64 (0.59 to 0.69)	0.026 (NR to NR)	0.02
	Fowkes, 2014[19]	ABI Collaboration	Hard CHD	Women[d]	6,459	0.788 (0.709 to 0.85)	0.791 (0.712 to 0.852)	0.003 (NR to NR)	NR
	Fowkes, 2014[19]	ABI Collaboration	Hard CHD	Men[d]	4,962	0.683 (0.611 to 0.748)	0.69 (0.618 to 0.754)	0.007 (NR to NR)	NR
	Murphy, 2012[21]	ARIC	Hard CHD	All Participants	11,594	NR	NR	NR	NS
	Rodondi, 2010[23]	Health ABC	Hard CHD	All Participants	1,515	0.6 (NR to NR)	0.612 (NR to NR)	0.012 (NR to NR)	NR
	Kavousi, 2012[24]	Rotterdam	Hard CHD	All Participants	5,933	0.73 (0.71 to 0.75)	NR	0.00[a] (0.00[a] to 0.00[a])	NR
	Kavousi, 2012[24]	Rotterdam	Hard CHD	Women	3,525	NR	NR	0.00[a] (0.00[a] to 0.00[a])	NR
	Kavousi, 2012[24]	Rotterdam	Hard CHD	Men	2,408	NR	NR	0.010[a] (0.00[a] to 0.01[a])	NR
	Yeboah, 2012[25]	MESA	Soft CVD	Intermediate risk (>5 to <20% 10-year risk)	1,330	0.623 (NR to NR)	0.65 (NR to NR)	0.027 (NR to NR)	0.01
	Holewijn, 2014[26]	Nijmegen Biomedical Study	Soft CVD	Women	659	0.691 (NR to NR)	0.726 (NR to NR)	0.036[a] (NR to NR)	0.26[a]
	Holewijn, 2014[26]	Nijmegen Biomedical Study	Soft CVD	Men	582	0.748 (NR to NR)	NR (NR to NR)	NR (NR to NR)[b]	NR
	Rodondi, 2010[23]	Health ABC	Soft CHD	All Participants	1,515	0.611 (NR to NR)	0.624 (NR to NR)	0.013 (NR to NR)	NR

eTable 4. Discrimination Outcomes in Included ABI Risk Prediction Studies (KQ2) Continued

Model Type: Base Model	Author, Year	Study Name	Outcome	Subgroup	N	Base Model C-Statistic (95% CI)	Extended Model C-Statistic (95% CI)	Change in Discrimination (95% CI)[a]	Change P-Value
Model development: FRS variables continued	Yeboah, 2012[25]	MESA	Soft CHD	Intermediate risk (>5 to <20% 10-year risk)	1,330	0.623 (NR to NR)	0.65 (NR to NR)	0.027 (NR to NR)	0.01

[a] Calculated as extended minus base except where noted; superscript indicates reported (not calculated) change.
[b] Extended model AUC NR because HR analysis showed that the ABI had no significant additional predictive value on top of traditional cardiovascular risk factors.
[c] Recalibrated by including the PCE in the Cox model predicting Hard CVD and used baseline survival estimated from MESA data; similar procedure used for FRS model predicting hard CHD events.
[d] External validation dataset
[e] Recalibrated by replacing Framingham means of risk factors and average event rate with those of Girona population (Marrugat, 2003)[27].
[f] Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: ABI = ankle-brachial index; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; EAS = Edinburgh Artery Study; FRS = Framingham Risk Score; Health ABC = Health, Aging, and Body Composition study; MESA = Multi-Ethnic Study of Atherosclerosis; NR = not reported; NRI = net reclassification improvement; NS = not significant; PCE = Pooled Cohort Equations; REGICOR = *Registre Gironí del Cor* (Girona Heart Registry)

eTable 5. Discrimination Outcomes in Included hsCRP Risk Prediction Studies (KQ2)

Model Type: Base Model	Author, Year	Study Name	Outcome[p]	Subgroup	N	Base Model C-Statistic (95% CI)	Extended Model C-Statistic (95% CI)	Change in Discrimination (95% CI)[a]	Change P-Value
Published coefficient: PCE[b]	Yeboah, 2016[17]	MESA	Hard CVD	All Participants	5,185	0.74 (NR to NR)	0.74 (NR to NR)	0 (NR to NR)	0.25
Published coefficient: FRS	Lyngbaek, 2013[28]	MONICA - Copenhagen	Hard CVD	Women	1,168	0.717 (0.674 to 0.759)	0.724 (0.679 to 0.769)	0.007 (NR to NR)	0.262
	Lyngbaek, 2013[28]	MONICA - Copenhagen	Hard CVD	Men	1,147	0.722 (0.686 to 0.757)	0.734 (0.699 to 0.769)	0.012 (NR to NR)	0.037
	Yeboah, 2016[17]	MESA[b]	Hard CHD	All Participants	5,185	0.74 (NR to NR)	0.74 (NR to NR)	0 (NR to NR)	0.925
	Koenig, 2004[11]	MONICA - Augsburg[c]	Hard CHD	All Participants	3,435	0.713 (NR to NR)[d]	0.740 (NR to NR)[d]	0.027 (NR to NR)	0.0077
	Zhou, 2013[29]	Framingham Offspring	Soft CVD	All Participants	1,687	0.776 (NR to NR)	0.778 (NR to NR)	0.002[a] (-0.005[a] to 0.01[a])	NR
	Hamer, 2009[30]	Scottish Health Survey	Soft CVD	All Participants	5,944	0.777 (0.754 to 0.800)	0.781 (0.758 to 0.804)	0.004 (NR to NR)	NR
	Rana, 2009[31]	EPIC-Norfolk	Soft CHD	All Participants	2,550	0.59 (0.57 to 0.61)	0.65 (0.59 to 0.64)	0.03[a] (0.01[a] to 0.05[a])	0.005
	Hamer, 2009[30]	Scottish Health Survey	Soft CHD	All Participants	5,944	0.766 (0.740 to 0.792)	0.768 (0.742 to 0.793)	0.002 (NR to NR)	NR
Model development: FRS variables	Wannamethee, 2011[32]	British Regional Heart Study	Hard CVD	All Participants	2,893	0.686 (NR to NR)	0.695 (NR to NR)	0.009 (NR to NR)	0.06
	ERFC, 2012[33]	ERFC IPD MA	Hard CVD	All Participants	166,596	0.7139 (0.7097 to 0.7182)	0.7179 (0.7136 to 0.7221)	0.0039[a] (0.0028[a] to 0.0050[a])	<0.0001
	ERFC, 2012[33]	ERFC IPD MA	Hard CVD	Women	4,535 cases[f]	NR	NR	0.0007[a] (-0.0007[a] to 0.0021[a])	Interaction p<0.001 vs Men[o]
	ERFC, 2012[33]	ERFC IPD MA	Hard CVD	Men	5,755 cases[f]	NR	NR	0.0077[a] (0.0058[a] to 0.0096[a])	Interaction p<0.001 vs Women[o]
	Wilson, 2005[34]	FHS and Framingham offspring	Hard CVD	All Participants[e]	4,446	0.78 (0.76 to 0.80)	0.78 (0.75 to 0.80)	0 (NR to NR)	NR
	Sattar, 2007[35]	PROSPER	Hard CVD	Placebo group only	1,654[g]	0.630 (NR to NR)	0.637 (NR to NR)	0.007 (NR to NR)	0.020
	Wannamethee, 2011[32]	British Regional Heart Study	Hard CHD	All Participants	2,893	0.686 (NR to NR)	0.690 (NR to NR)	0.004 (NR to NR)	0.49
	Shah, 2009[36]	Edinburgh Artery Study	Hard CHD	All Participants	962	0.68 (0.64 to 0.71)[h]	0.67 (0.63 to 0.71)[h]	-0.01 (NR to NR)[h]	NR
	ERFC, 2012[33]	ERFC IPD MA	Hard CHD	All Participants	165,586	NR	NR (NR to NR)	0.0051[a] (0.0035[a] to 0.0066[a])	NR

eTable 5. Discrimination Outcomes in Included hsCRP Risk Prediction Studies (KQ2) Continued

Model Type: Base Model	Author, Year	Study Name	Outcome[p]	Subgroup	N	Base Model C-Statistic (95% CI)	Extended Model C-Statistic (95% CI)	Change in Discrimination (95% CI)[a]	Change P-Value
Model development: FRS variables Continued	Wilson, 2005[34]	FHS and Framingham offspring	Hard CHD	All Participants	4,446	0.80 (0.77 to 0.83)	0.80 (0.77 to 0.83)	0 (NR to NR)	NR
	Wilson, 2008[37]	Framingham Offspring	Hard CHD	All Participants	3,006	0.863 (NR to NR)	0.865 (NR to NR)	0.002 (NR to NR)	NR
	Rodondi, 2010[23]	Health ABC	Hard CHD	All Participants	1,515	0.600 (NR to NR)	0.592 (NR to NR)	-0.008 (NR to NR)	NR
	Mohlenkamp, 2011[38]	Heinz Nixdorf Recall (HNR)	Hard CHD	All Participants	3,966	0.719 (0.671 to 0.767)	0.732 (0.684 to 0.780)	0.013 (NR to NR)	0.12
	Shah, 2009[36]	Northwick Park Heart Study II	Hard CHD	All Participants	2,479	0.62 (0.60 to 0.65)[h]	0.66 (0.63 to 0.68)[h]	0.04 (NR to NR)[h]	NR
	Sattar, 2007[35]	PROSPER	Hard CHD	Placebo group only	1,654[g]	0.655 (NR to NR)	0.663 (NR to NR)	0.008 (NR to NR)	0.028
	Danesh, 2004[39]	Reykjavik	Hard CHD	All Participants	6,428[i]	0.64 (0.63 to 0.65)	0.65 (0.64 to 0.67)	0.01 (NR to NR)	NR
	Elias-Smale, 2010[40]	Rotterdam	Hard CHD	All Participants	2,028	0.72 (NR to NR)	0.72 (NR to NR)	0 (NR to NR)	0.31
	Kavousi, 2012[24]	Rotterdam	Hard CHD	All Participants	3,029	0.73 (0.71 to 0.75)	NR	0.00[a] (-0.01[a] to 0.00[a])	NR
	Salim, 2016[41]	Singapore Chinese Health Study	Hard CHD	Women	528	0.778 (0.729 to 0.827)	0.780 (0.731 to 0.829)	0.002 (NR to NR)	NR
	Salim, 2016[41]	Singapore Chinese Health Study	Hard CHD	Men	965	0.679 (0.644 to 0.714)	0.689 (0.654 to 0.724)	0.01 (NR to NR)	NR
	Rana, 2012[42]	EISNER	Soft CVD	All Participants	1,286	0.73 (0.66 to 0.82)	0.73 (0.65 to 0.82)	0 (NR to NR)	0.95
	Wilson, 2005[34]	FHS and Framingham offspring	Soft CVD	All Participants	4,446	0.78 (0.76 to 0.80)	0.78 (0.76 to 0.80)	0 (NR to NR)	NR
	Wilson, 2008[37]	Framingham Offspring	Soft CVD	All Participants	3,006	0.795 (NR to NR)	0.799 (NR to NR)	0.004 (NR to NR)	NR
	Seven, 2015[43]	Inter99	Soft CVD[j]	All Participants	6,138[k]	0.697 (NR to NR)	0.701 (NR to NR)	0.004 (NR to NR)	0.26
	Yeboah, 2012[25]	MESA	Soft CVD	Intermediate Risk (>5 to <20% 10-year risk)	1,330	0.623 (NR to NR)	0.640 (NR to NR)	0.017 (NR to NR)	0.03
	Cook, 2006[12]	WHS(WHS model)[l]	Soft CVD	All Participants	15,048	0.811 (NR to NR)	0.813 (NR to NR)	0.002 (NR to NR)	NR
	Cook, 2006[12]	WHS (ATP III full recalibration)[m]	Soft CVD	All Participants	26,927	0.809 (NR to NR)	0.810 (NR to NR)	0.001 (NR to NR)	NR

eTable 5. Discrimination Outcomes in Included hsCRP Risk Prediction Studies (KQ2) Continued

Model Type: Base Model	Author, Year	Study Name	Outcome	Subgroup	N	Base Model C-Statistic (95% CI)	Extended Model C-Statistic (95% CI)	Change in Discrimination (95% CI)[a]	Change P-Value
Model development: FRS variables Continued	Welsh, 2013[44]	WOSCOPS	Soft CVD	All Participants	4,128	0.582 (0.57 to 0.60)[n]	0.588 (0.57 to 0.60)[n]	0.006 (NR to NR)[n]	<0.001
	Folsom, 2006[45]	ARIC	Soft CHD	All Participants	1,511	0.767 (NR to NR)	0.770 (NR to NR)	0.003[a] (NR to NR)	>0.05
	Rodondi, 2010[23]	Health ABC	Soft CHD	All Participants	1,515	0.611 (NR to NR)	0.622 (NR to NR)	0.011 (NR to NR)	NR
	Yeboah, 2012[25]	MESA	Soft CHD	Intermediate Risk (>5 to <20% 10-year risk)	1,330	0.623 (NR to NR)	0.640 (NR to NR)	0.017 (NR to NR)	0.03
	Schneider, 2012[46]	Study of Health in Pomerania	Fatal CVD	All participants	3,602	0.898 (0.873 to 0.923)	0.906 (0.881 to 0.93)	0.008 (NR to NR)	NR

[a] Calculated as extended minus base except where noted; superscript indicates reported (not calculated) change.
[b] Recalibrated by including the PCE in the Cox model predicting hard CVD and used baseline survival estimated from MESA data; similar procedure used for FRS model predicting hard CHD events.
[c] FRS entered categorically, not continuously. 3-category model abstracted.
[d] Authors also report AUC and p-value for FRS model stratified into 5 risk categories: base model AUC=0.735, extended model AUC=0.750; p=0.0163.
[e] In a separate analysis, when FRS calculated by published coefficient D'Agostino FRS model, tertiles of CRP were able to discriminate in low-risk individuals (<10% 10-yr risk) but not intermediate or high-risk individuals.
[f] Only studies with information on all subgroups used.
[g] Reported in Table 3 of Shepherd, 2002.
[h] Sensitivity analyses conducted using AUC instead of Harrell's c gave similar results.
[i] No change in findings when 376 (5.8%) of participants with baseline ECG abnormalities or angina were excluded from analysis (data not shown)
[j] Assumed since primary outcome
[k] Assumed from Table 5
[l] For generalizability, predicted probabilities were calibrated to observed risk from the Framingham Heart Study.
[m] ATP III beta-coefficients recalculated for all traditional risk factors before adding hsCRP to the model to be conservative and allow best possible fit.
[n] C-statistics take into account competing risk of non-CVD death.
[o] Exploratory subgroup analyses
[p] Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: ABI = ankle-brachial index; AIC = Akaike information criterion; ARIC = Atherosclerosis Risk in Communities study; BIC = Bayesian information criterion; CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; EPIC = European Prospective Investigation into Cancer and Nutrition; ERFC IPD MA= Emerging Risk Factors Collaboration individual participant data meta-analysis; FRS = Framingham Risk Score; F/U = follow up; Health ABC = Health, Aging, and Body Composition study; HNR = Heinz Nixdorf Recall study; HRT = hormone replacement therapy; hsCRP = high sensitivity C-reactive protein; HTN = hypertension; MESA = Multi-Ethnic Study of Atherosclerosis; mg/L = milligrams per Liter; MONICA = MONItoring of trends and determinants in CArdiovascular disease; NPHS = Northwick Park Heart Study; NR = not reported; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; SHIP = Study of Health in Pomerania; WHS = Women's Health Study; WOSCOPS = West of Scotland Coronary Prevention Study

eTable 6. Discrimination Outcomes in Included CAC Risk Prediction Studies (KQ2)

Model Type: Base Model	Author, Year	Study Name	Outcome[k]	Subgroup	N	Base Model C-Statistic (95% CI)	Extended Model C-Statistic (95% CI)	Change in Discrimination (95% CI)[a]	Change P-Value
Published coefficient: PCE	Yeboah, 2016[17] [b]	MESA	Hard CVD	All Participants	5,185	0.74 (NR to NR)	0.76 (NR to NR)	0.02 (NR to NR)	0.04
	Fudim, 2016[47]	MESA	Hard CVD	Women	3,556	0.766 (NR to NR)	0.784 (NR to NR)	0.018[a] (NR to NR)	0.19
	Fudim, 2016[47]	MESA	Hard CVD	Men	3,186	0.705 (NR to NR)	0.730 (NR to NR)	0.025[a] (NR to NR)	0.047
Published coefficient: FRS	Geisel, 2017[18]	HNR	Hard CVD	All participants	3,108	0.693 (0.661 to 0.726)	0.731 (0.699 to 0.763)	0.038 (NR to NR)	0.02
	Erbel, 2010[48]	HNR	Hard CHD (Wilson, 1998)	All Participants	4,129	0.681 (0.629 to 0.733)	0.749 (0.682 to 0.8)	0.068 (NR to NR)	0.003
	Erbel, 2010[48]	HNR	Hard CHD (ATPIII model)	All Participants	4,129	0.653 (0.606 to 0.7)	0.755 (0.705 to 0.805)	0.102 (NR to NR)	0.0001
	Erbel, 2010[48]	HNR	Hard CHD (Wilson, 1998)	Women	2,177	0.671 (0.582 to 0.76)	0.711 (0.621 to 0.8)	0.04 (NR to NR)	0.25
	Erbel, 2010[48]	HNR	Hard CHD (ATPIII model)	Women	2,177	0.668 (0.606 to 0.731)	0.729 (0.654 to 0.804)	0.061 (NR to NR)	0.23
	Erbel, 2010[48]	HNR	Hard CHD (Wilson, 1998)	Men	1,952	0.628 (0.558 to 0.698)	0.730 (0.667 to 0.802)	0.102 (NR to NR)	0.0003
	Erbel, 2010[48]	HNR	Hard CHD (ATPIII model)	Men	1,952	0.583 (0.523 to 0.644)	0.727 (0.665 to 0.788)	0.144 (NR to NR)	<0.0001
	Yeboah, 2016[17] [b]	MESA	Hard CHD[b]	All Participants	5,185	0.74 (NR to NR)	0.78 (NR to NR)	0.04 (NR to NR)	0.001
	Greenland, 2004[49]	South Bay Heart Watch	Hard CHD	All Participants	1,029	0.63 (0.628 to 0.632)[c]	0.68 (0.678 to 0.682)[c]	0.05 (NR to NR)	<0.001
	Wong, 2009[50]	EISNER + Cardiac Research Database	Hard CHD	All Participants	2,303	0.757 (NR to NR)[d]	0.834 (NR to NR)[d]	0.077 (NR to NR)	0.1
	Wong, 2009[50]	EISNER + Cardiac Research Database	Soft CVD	All Participants	2,303	0.763 (NR to NR)[e]	0.851 (NR to NR)[e]	0.088 (NR to NR)[e]	0.006
	Wong, 2009[50]	EISNER + Cardiac Research Database	Soft CHD	All Participants	2,303	0.748 (NR to NR)[f]	0.857 (NR to NR)[f]	0.109 (NR to NR)[f]	0.004

eTable 6. Discrimination Outcomes in Included CAC Risk Prediction Studies (KQ2) Continued

Model Type: Base Model	Author, Year	Study Name	Outcome[k]	Subgroup	N	Base Model C-Statistic (95% CI)	Extended Model C-Statistic (95% CI)	Change in Discrimination (95% CI)[a]	Change P-Value
Model development: PCE variables	Kavousi, 2016[51]	Pooled Analysis of 5 Cohortsǁǁǁǁǁ of Low-Risk Women (<7.5% 10-yr PCE risk)	Hard CVD	All Participants	6,739	0.73 (0.69 to 0.77)	0.77 (0.74 to 0.81)	0.02[a] (0.0 to 0.05)	0.08
	Bos, 2015[52]	Rotterdam	Fatal CVD	All Participants	2,408	0.78 (0.73 to 0.83)	0.81 (0.76 to 0.86)	0.03 (NR to NR)	NR
Model development: FRS variables[j]	Kavousi, 2016[51]	Pooled Analysis of 5 Cohortsǁǁǁǁǁ of Low-Risk Women (<10% 10-yr FRS risk)	Hard CHD	All Participants (DM excluded)	7,772	0.79 (0.70 to 0.88)	0.83 (0.73 to 0.93)	0.04[a] (0.01 to 0.07)	NR
	Hoffmann, 2016[53]	Framingham Heart Study Offspring and 3rd Generation	Hard CVD	All Participants	3,319[g]	0.8 (NR to NR)[h]	0.82 (NR to NR)[h]	0.02 (NR to NR)[h]	>0.05[h]
	Erbel, 2010[48]	HNR	Hard CHD	All Participants	4,129	0.712 (0.664 to 0.76)	0.763 (0.714 to 0.812)	0.051 (NR to NR)	0.004
	Elias-Smale, 2010[40]	Rotterdam	Hard CHD	All Participants	2,028	0.72 (NR to NR)	0.76 (NR to NR)	0.04 (NR to NR)	<0.001
	Kavousi, 2012[24]	Rotterdam	Hard CHD	All Participants	3,678	0.73 (0.71 to 0.75)	NR	0.05[a] (0.02[a] to 0.06[a])	NR
	Hoffmann, 2016[53]	Framingham Heart Study Offspring and 3rd Generation	Hard CHD	All Participants	3,340[g]	0.78 (NR to NR)[i]	0.82 (NR to NR)[i]	0.04 (NR to NR)[i]	<0.05
	Mohlenkamp, 2011[38]	HNR	Hard CHD	All Participants	3,966	0.719 (0.671 to 0.767)	0.763 (0.715 to 0.812)	0.044 (NR to NR)	0.0067
	Kavousi, 2012[24]	Rotterdam	Hard CHD	Women	NR	NR	NR	0.05[a] (0.03[a] to 0.07[a])	NR
	Kavousi, 2012[24]	Rotterdam	Hard CHD	Men	NR	NR	NR	0.06[a] (0.03[a] to 0.09[a])	NR
	Rana, 2012[42]	EISNER	Soft CVD	All Participants	1,286	0.73 (0.66 to 0.82)	0.84 (0.78 to 0.91)	0.11 (NR to NR)	0.003
	Yeboah, 2012[25]	MESA	Soft CVD	Intermediate risk (>5 to <20% 10-year risk)	1,330	0.623 (NR to NR)	0.784 (NR to NR)	0.161 (NR to NR)	<0.001
	Chang, 2015[54]	Houston Methodist DeBakey Heart and Vascular Center	Soft CHD	All Participants	946	0.63 (NR to NR)	0.7 (NR to NR)	0.07 (NR to NR)	0.01

Model Type: Base Model	Author, Year	Study Name	Outcome[k]	Subgroup	N	Base Model C-Statistic (95% CI)	Extended Model C-Statistic (95% CI)	Change in Discrimination (95% CI)[a]	Change P-Value
	Polonsky, 2010[55]	MESA	Soft CHD	All Participants	5,878	0.76 (0.72 to 0.79)	0.81 (0.78 to 0.84)	0.05 (NR to NR)	<0.001
Model development: FRS variables[j] continued	Yeboah, 2012[25]	MESA	Soft CHD	Intermediate risk (>5 to <20% 10-year risk)	1,330	0.623 (NR to NR)	0.784 (NR to NR)	0.161 (NR to NR)	<0.001

[a] Calculated as extended minus base except where noted; superscript indicates reported (not calculated) change.
[b] Recalibrated by including the PCE in the Cox model predicting Hard CVD and used baseline survival estimated from MESA data; similar procedure used for FRS model predicting hard CHD events.
[c] CIs calculated from standard deviations
[d] For categorical CAC analyses; p=0.08 for LogCAC analyses (AUCs NR); p=0.07 for LogCAC volume analyses (AUCs NR).
[e] For categorical CAC analyses; p=0.004 for LogCAC analyses (AUCs NR); p<0.01 for LogCAC volume analyses (AUCs NR).
[f] For categorical CAC analyses; p=0.002 for LogCAC analyses (AUCs NR); p=0.02 for LogCAC volume analyses (AUCs NR).
[g] N assumed based on NRI analyses
[h] Same results obtained for entry of CAC continuously in the model (log transformed) and when entered categorically in the model (0, 1-100, 101-300, >300)
[i] CAC entered continuously in the model (log-transformed). Results were similar when CAC entered categorically in the model (0, 1-100, 101-300, >300): base model 0.78 (NR to NR); extended model 0.83 (NR to NR); change in discrimination: 0.05 (NR to NR).
[j] Two model development[56,57] studies focusing exclusively on subpopulation analyses in participants with diabetes are available in the full report.
[k] Hard CVD defined as fatal or nonfatal MI or CVA or CVD mortality; hard CHD defined as fatal or nonfatal MI or CHD mortality; soft CVD could additionally include angina, revascularization, TIA or claudication in composites defined by the study. Similarly, hard CHD could additionally include angina or coronary revascularization in composites defined by the study.

Abbreviations: ABI = ankle-brachial index; ATP III = Adult Treatment Panel III; AUC = area under the concentrated curve; CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; DHS = Dallas Heart Study; DM = diabetes mellitus; EISNER = Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research; FHS = Framingham Heart Study; FRS = Framingham Risk Score; F/U = follow up; HNR = Heinz Nixdorf Recall study; MESA = Multi-Ethnic Study of Atherosclerosis; MetS = metabolic syndrome; NR = not reported; NRI = net reclassification improvement; PCE = Pooled Cohort Equations

eTable 7. Evidence Overview for ABI, hsCRP, and CAC in Cardiovascular Risk Assessment

		ABI	hsCRP	CAC	Considerations
Benefits	KQ1: Direct evidence for nontraditional risk factor assessment	No evidence	No evidence	k=1; n=2,137 No statistically significant difference in MI and/or mortality at 4 years	Ongoing screening trials in progress but these trials may not directly address incremental benefit over traditional risk factor assessment[58-60]
	KQ2: Calibration	k=5; n=26,286 Improved calibration	k=9; n=50,343 Improved calibration	k=8; n=29,775 Improved calibration	Preferred measures rarely reported; clinical meaning of changes in calibration unclear
	KQ2: Discrimination[a]	k=10; n=79,583 Generally no to small improvement, but large improvement in women in IPD MA	k=25; n=265,704 Inconsistent; at most very small to small improvement	k=18; n=60,486 At least small, sometimes large improvement	Improvement likely influenced by discrimination of base model; generally not applicable to PCE
	KQ2: Reclassification	k=9; n=46,979 NRIs are at best <0.1 and are usually much smaller and often nonsignificant; women without events inappropriately reclassified	k=15; n=115,686 Best evidence shows NRIs <0.02, otherwise inconsistent improvement when added to FRS; no improvement when added to PCE	k=15; n=58,289 NRIs of 0.084 to 0.35; people without events inappropriately reclassified	NRI may overstate benefit; applicability of risk thresholds
	KQ4: Treatment guided by NTRF in addition to FRS/PCE	No evidence	No evidence	No evidence	Unlikely such a trial will occur due to required sample
	KQ4: Treatment guided by NTRF alone vs usual care	Aspirin: k=2; n=4,626 No benefit in CVD outcomes at 7-8 years	Statin: k=1; n=17,802 Benefit for high-intensity statin at 1.9 years of followup	Statin: k=1; n=1,005 No benefit for moderate-intensity statin at 4 years of followup	Results and conclusions not comparable across nontraditional risk factors. Absolute benefit is small in statin trial showing benefit; unclear whether benefit is exclusive to those with elevated hsCRP as the evidence is mixed for whether the effect of statins is modified by hsCRP level.[61-63]
Harms	KQ3: Screening	No evidence	No evidence	Radiation: k=4; n=11,473 Low effective dose, ≤2.1 mSv Psychological outcomes: k=2; n=1,619	Incidental findings not reported in included studies but in broader literature are not uncommon; unclear whether identification of incidental findings and/or increased health care utilization is a net benefit or net harm

eTable 7. Evidence Overview for ABI, hsCRP, and CAC in Cardiovascular Risk Assessment Continued

		ABI	hsCRP	CAC	Considerations
Harms Continued	KQ3: Screening Continued			No association with depression, anxiety, or decline in mental health at 6 to 12 mo CVD outcomes: k=2; n=11,364 No paradoxical increase in CVD events approximately up to 2 to 3 y Health care utilization: k=3; n=13,204 Mixed results for downstream cardiac testing/procedures	
	KQ5: Treatment guided by NTRF	Aspirin: k=2; n=4,626 Mixed results for increase in bleeding events	Statin: k=1; n=17,802 Increase in incident diabetes but not in other serious adverse events	No evidence	Larger body of evidence not included in this review informs harms of aspirin and statins; inappropriate reclassification addressed in KQ2.

[a]"For changes in the c-statistic, the term "large" is used to denote changes of 0.1 or greater, "moderate" for changes of 0.05-0.1, "small" for 0.025-0.05, and "very small" for changes less than 0.025.

Abbreviations: ABI = ankle-brachial index; CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease; FRS = Framingham Risk Score; hsCRP = high sensitivity C-reactive protein; KQ = key question; mo = month; IPD MA = individual participant data meta-analysis; NRI = net reclassification improvement; NTRF = non-traditional risk factor; PCE = Pooled Cohort Equation

eReferences

1. U.S. Preventive Services Task Force. *U.S. Preventive Services Task Force Procedure Manual.* Rockville, MD: U.S. Preventive Services Task Force; Dec 2015.

2. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014; http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed April 8, 2015.

3. Moons KG, de Groot JA, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. *PLoS Med.* 2014;11(10):e1001744.

4. Tierney JF, Vale C, Riley R, et al. Individual Participant Data (IPD) Meta-analyses of Randomised Controlled Trials: Guidance on Their Use. *PLoS Med.* 2015;12(7):e1001855.

5. Ioannidis JP, Tzoulaki I. What makes a good predictor?: the evidence applied to coronary artery calcium score. *JAMA.* 2010;303(16):1646-1647.

6. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med.* 2008;27(2):157-172; discussion 207-112.

7. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology.* 2010;21(1):128-138.

8. Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. *Clin Chem.* 2008;54(1):17-23.

9. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med.* 2015;162(1):W1-73.

10. Demler OV, Paynter NP, Cook NR. Tests of calibration and goodness-of-fit in the survival setting. *Stat Med.* 2015;34(10):1659-1680.

11. Koenig W, Lowel H, Baumert J, Meisinger C. C-reactive protein modulates risk prediction based on the Framingham Score: implications for future risk assessment: results from a large cohort study in southern Germany. *Circulation.* 2004;109(11):1349-1353.

12. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. *Ann Intern Med.* 2006;145(1):21-29.

13. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med.* 2004;23(13):2109-2123.

14. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation.* 2007;115(7):928-935.

15. Kerr KF, Wang Z, Janes H, McClelland RL, Psaty BM, Pepe MS. Net reclassification indices for evaluating risk prediction instruments: a critical review. *Epidemiology.* 2014;25(1):114-121.

16. Pencina MJ, D'Agostino Sr RB, Vasan RS. Response to 'Net reclassification improvement and decision theory' by Vickers et al. *Stat Med.* 2009;28(3):526-527.

17. Yeboah J, Young R, McClelland RL, et al. Utility of Nontraditional Risk Markers in Atherosclerotic Cardiovascular Disease Risk Assessment. *J Am Coll Cardiol.* 2016;67(2):139-147.

18. Geisel MH, Bauer M, Hennig F, et al. Comparison of coronary artery calcification, carotid intima-media thickness and ankle-brachial index for predicting 10-year incident cardiovascular events in the general population. *Eur Heart J.* 2017.

19. Fowkes FG, Murray GD, Butcher I, et al. Development and validation of an ankle brachial index risk model for the prediction of cardiovascular events. *Eur J Prev Cardiol.* 2014;21(3):310-320.

20. Velescu A, Clara A, Penafiel J, et al. Adding low ankle brachial index to classical risk factors improves the prediction of major cardiovascular events. The REGICOR study. *Atherosclerosis.* 2015;241(2):357-363.

21. Murphy TP, Dhangana R, Pencina MJ, D'Agostino RB, Sr. Ankle-brachial index and cardiovascular risk prediction: an analysis of 11,594 individuals with 10-year follow-up. *Atherosclerosis.* 2012;220(1):160-167.

22. Price JF, Tzoulaki I, Lee AJ, Fowkes FG. Ankle brachial index and intima media thickness predict cardiovascular events similarly and increased prediction when combined. *J Clin Epidemiol.* 2007;60(10):1067-1075.

23. Rodondi N, Marques-Vidal P, Butler J, et al. Markers of atherosclerosis and inflammation for prediction of coronary heart disease in older adults. *Am J Epidemiol.* 2010;171(5):540-549.

24. Kavousi M, Elias-Smale S, Rutten JH, et al. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. *Ann Intern Med.* 2012;156(6):438-444.

25. Yeboah J, McClelland RL, Polonsky TS, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA.* 2012;308(8):788-795.

26. Holewijn S, den Heijer M, Kiemeney LA, Stalenhoef AF, de Graaf J. Combining risk markers improves cardiovascular risk prediction in women. *Clinical Science.* 2014;126(2):139-146.

27. Marrugat J, D'Agostino R, Sullivan L, et al. An adaptation of the Framingham coronary heart disease risk function to European Mediterranean areas. *J Epidemiol Community Health.* 2003;57(8):634-638.

28. Lyngbaek S, Marott JL, Sehestedt T, et al. Cardiovascular risk prediction in the general population with use of suPAR, CRP, and Framingham Risk Score. *Int J Cardiol.* 2013;167(6):2904-2911.

29. Zhou QM, Zheng Y, Cai T. Subgroup specific incremental value of new markers for risk prediction. *Lifetime Data Anal.* 2013;19(2):142-169.

30. Hamer M, Chida Y, Stamatakis E. Utility of C-reactive protein for cardiovascular risk stratification across three age groups in subjects without existing cardiovascular diseases. *Am J Cardiol.* 2009;104(4):538-542.

31. Rana JS, Cote M, Despres JP, et al. Inflammatory biomarkers and the prediction of coronary events among people at intermediate risk: the EPIC-Norfolk prospective population study. *Heart.* 2009;95(20):1682-1687.

32. Wannamethee SG, Welsh P, Lowe GD, et al. N-terminal pro-brain natriuretic Peptide is a more useful predictor of cardiovascular disease risk than C-reactive protein in older men with and without pre-existing cardiovascular disease. *J Am Coll Cardiol.* 2011;58(1):56-64.

33. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, et al. C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med.* 2012;367(14):1310-1320.

34. Wilson PW, Nam BH, Pencina M, D'Agostino RB, Sr., Benjamin EJ, O'Donnell CJ. C-reactive protein and risk of cardiovascular disease in men and women from the Framingham Heart Study. *Arch Intern Med.* 2005;165(21):2473-2478.

35. Sattar N, Murray HM, McConnachie A, et al. C-reactive protein and prediction of coronary heart disease and global vascular events in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). *Circulation.* 2007;115(8):981-989.

36. Shah T, Casas JP, Cooper JA, et al. Critical appraisal of CRP measurement for the prediction of coronary heart disease events: new data and systematic review of 31 prospective cohorts. *Int J Epidemiol.* 2009;38(1):217-231.

37. Wilson PW, Pencina M, Jacques P, Selhub J, D'Agostino R, Sr., O'Donnell CJ. C-reactive protein and reclassification of cardiovascular risk in the Framingham Heart Study. *Circ Cardiovasc Qual Outcomes.* 2008;1(2):92-97.

38. Mohlenkamp S, Lehmann N, Moebus S, et al. Quantification of coronary atherosclerosis and inflammation to predict coronary events and all-cause mortality. *J Am Coll Cardiol.* 2011;57(13):1455-1464.

39. Danesh J, Wheeler JG, Hirschfield GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med.* 2004;350(14):1387-1397.

40. Elias-Smale SE, Proenca RV, Koller MT, et al. Coronary calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. *J Am Coll Cardiol.* 2010;56(17):1407-1414.

41. Salim A, Tai ES, Tan VY, et al. C-reactive protein and serum creatinine, but not haemoglobin A1c, are independent predictors of coronary heart disease risk in non-diabetic Chinese. *Eur J Prev Cardiol.* 2016;12:1339-1349.

42. Rana JS, Gransar H, Wong ND, et al. Comparative value of coronary artery calcium and multiple blood biomarkers for prognostication of cardiovascular events. *Am J Cardiol.* 2012;109(10):1449-1453.

43. Seven E, Husemoen LL, Sehested TS, et al. Adipocytokines, C-reactive protein, and cardiovascular disease: a population-based prospective study. *PLoS ONE.* 2015;10(6):e0128987.

44. Welsh P, Doolin O, Willeit P, et al. N-terminal pro-B-type natriuretic peptide and the prediction of primary cardiovascular events: results from 15-year follow-up of WOSCOPS. *Eur Heart J.* 2013;34(6):443-450.

45. Folsom AR, Chambless LE, Ballantyne CM, et al. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study. *Arch Intern Med.* 2006;166(13):1368-1373.

46. Schneider HJ, Wallaschofski H, Volzke H, et al. Incremental effects of endocrine and metabolic biomarkers and abdominal obesity on cardiovascular mortality prediction. *PLoS ONE.* 2012;7(3):e33084.

47. Fudim M, Zalawadiya S, Patel DK, Egolum UO, Afonso L. Data on coronary artery calcium score performance and cardiovascular risk reclassification across gender and ethnicities. *Data Brief.* 2016;6:578-581.

48. Erbel R, Mohlenkamp S, Moebus S, et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. *J Am Coll Cardiol.* 2010;56(17):1397-1406.

49. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA.* 2004;291(2):210-215.

50. Wong ND, Gransar H, Shaw L, et al. Thoracic aortic calcium versus coronary artery calcium for the prediction of coronary heart disease and cardiovascular disease events. *JACC Cardiovasc Imaging.* 2009;2(3):319-326.

51. Kavousi M, Desai CS, Ayers C, et al. Prevalence and Prognostic Implications of Coronary Artery Calcification in Low-Risk Women: A Meta-analysis. *JAMA.* 2016;316(20):2126-2134.

52. Bos D, Leening MJ, Kavousi M, et al. Comparison of Atherosclerotic Calcification in Major Vessel Beds on the Risk of All-Cause and Cause-Specific Mortality: The Rotterdam Study. *Circ Cardiovasc Imaging.* 2015;8(12).

53. Hoffmann U, Massaro JM, D'Agostino RB, Sr., Kathiresan S, Fox CS, O'Donnell CJ. Cardiovascular Event Prediction and Risk Reclassification by Coronary, Aortic, and Valvular Calcification in the Framingham Heart Study. *J Am Heart Assoc.* 2016;5(2).

54. Chang SM, Nabi F, Xu J, et al. Value of CACS compared with ETT and myocardial perfusion imaging for predicting long-term cardiac outcome in asymptomatic and symptomatic patients at low risk for coronary disease: clinical implications in a multimodality imaging world. *JACC Cardiovasc Imaging.* 2015;8(2):134-144.

55. Polonsky TS, McClelland RL, Jorgensen NW, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. *JAMA.* 2010;303(16):1610-1616.

56. Malik S, Budoff MJ, Katz R, et al. Impact of subclinical atherosclerosis on cardiovascular disease events in individuals with metabolic syndrome and diabetes: the multi-ethnic study of atherosclerosis. *Diabetes Care.* 2011;34(10):2285-2290.

57. Yeboah J, Erbel R, Delaney JC, et al. Development of a new diabetes risk prediction tool for incident coronary heart disease events: the Multi-Ethnic Study of Atherosclerosis and the Heinz Nixdorf Recall Study. *Atherosclerosis.* 2014;236(2):411-417.

58. Diederichsen AC, Rasmussen LM, Sogaard R, et al. The Danish Cardiovascular Screening Trial (DANCAVAS): study protocol for a randomized controlled trial. *Trials.* 2015;16:554.

59. Ijkema R, Aerde MA, Aalst CM, Ballegooijen M, Oudkerk M, Koning HJ. A randomized controlled trial measuring the effectiveness of screening for cardiovascular disease using classic risk assessment and coronary artery calcium: The ROBINSCA study. *Eur J Prev Cardiol.* 2014;21(1 suppl. 1):S21.

60. Lindholt JS, Søgaard R. Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial. *Lancet.* 2017.

61. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med.* 2001;344(26):1959-1965.

62. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. *N Eng J Med.* 2016;374(21):2021-2031.

63. Heart Protection Study Collaborative G, Jonathan E, Derrick B, et al. C-reactive protein concentration and the vascular benefits of statin therapy: an analysis of 20,536 patients in the Heart Protection Study. *Lancet.* 2011;377(9764):469-476.