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ORIGINAL RESEARCH

Biomarkers of Vascular Inflammation for Cardiovascular Risk Prognostication

A Meta-Analysis

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ABSTRACT

OBJECTIVES The purpose of this study was to systematically explore the added value of biomarkers of vascular inflammation for cardiovascular prognostication on top of clinical risk factors.

BACKGROUND Measurement of biomarkers of vascular inflammation is advocated for the risk stratification for coronary heart disease (CHD).

METHODS We systematically explored published reports in MEDLINE for cohort studies on the prognostic value of common biomarkers of vascular inflammation in stable patients without known CHD. These included common circulating inflammatory biomarkers (ie, C-reactive protein, interleukin-6 and tumor necrosis factor-a, arterial positron emission tomography/computed tomography and coronary computed tomography angiography–derived biomarkers of vascular inflammation, including anatomical high-risk plaque features and perivascular fat imaging. The main endpoint was the difference in c-index (Δ[c-index]) with the use of inflammatory biomarkers for major adverse cardiovascular events (MACEs) and mortality. We calculated I^2 to test heterogeneity. This study is registered with PROSPERO (CRD42020181158).

RESULTS A total of 104,826 relevant studies were screened and a final of 39 independent studies (175,778 individuals) were included in the quantitative synthesis. Biomarkers of vascular inflammation provided added prognostic value for the composite endpoint and for MACEs only (pooled estimate for Δ[c-index]% 2.9, 95% CI: 1.7-4.1 and 3.1, 95% CI: 1.8-4.5, respectively). Coronary computed tomography angiography–related biomarkers were associated with the highest added prognostic value for MACEs: high-risk plaques 5.8%, 95% CI: 0.6 to 11.0, and perivascular adipose tissue (on top of coronary atherosclerosis extent and high-risk plaques): 8.2%, 95% CI: 4.0 to 12.5). In meta-regression analysis, the prognostic value of inflammatory biomarkers was independent of other confounders including study size, length of follow-up, population event incidence, the performance of the baseline model, and the level of statistical adjustment. Limitations in the published literature include the lack of reporting of other metrics of improvement of risk stratification, the net clinical benefit, or the cost-effectiveness of such biomarkers in clinical practice.

CONCLUSIONS The use of biomarkers of vascular inflammation enhances risk discrimination for cardiovascular events. (J Am Coll Cardiol Img 2022;15:460–471) © 2022 by the American College of Cardiology Foundation.

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Cardiovascular disease remains a major cause of mortality worldwide (1). Cardiovascular risk stratification is the cornerstone for the deployment of effective prevention measures, which currently focus on lifestyle interventions and the optimal control of traditional risk factors (2). Recently, the routine assessment of inflammatory burden is also advocated for better cardiovascular risk stratification (3). The notion of "residual inflammatory risk" has been coined to indicate those patients who despite optimal control of their risk factors, remain at high risk for future cardiovascular events because of vascular and/or systemic inflammation (3,4).

The targeting of vascular inflammation for the prevention of coronary heart disease (CHD) has a sound pathophysiological basis and is also supported by the findings of recent large clinical trials (5,6). However, a major problem with the notion of "residual inflammatory risk" is that there is uncertainty around its reliable quantification. The most widely accepted strategies to detect vascular inflammation currently include the measurement of circulating levels of inflammatory biomarkers, eg, C-reactive protein (CRP). Noninvasive imaging, particularly coronary computed tomography angiography (CCTA) also can be used to detect anatomic high-risk plaque (HRP) features (7,8) that can capture plaque inflammation (9). Direct detection of coronary inflammation is also feasible by positron emission tomography (PET) imaging and the arterial uptake of radiotracers, such as 18F-fluorodeoxyglucose (^{18F}FDG) or 18F-sodium fluoride (^{18F}NaF) (10) or even coronary perivascular adipose tissue (PVAT) imaging by CCTA, eg, Fat Attenuation Index (11,12).

The independent association of circulating biomarkers of inflammation with the risk of future cardiovascular events has been previously demonstrated in clinical studies (13,14). However, a systematic review of the quality of published literature, and the added prognostic information that circulating or imaging biomarkers may offer on top of clinical risk factors for cardiovascular risk stratification is lacking. Moreover, there is little evidence on the comparative performance of such approaches. We performed a meta-analysis of published literature to address these questions.

METHODS

STUDY DESIGN AND OBJECTIVES. Published literature in MEDLINE before April 22, 2021, was systematically searched via PubMed for studies assessing the prognostic value of biomarkers of vascular inflammation. The concordance index or c-index of the best model was selected as the metric of choice to assess the prognostic performance of each biomarker, because this is the most common metric used for risk discrimination in published medical literature (15). In particular, we focused on the added prognostic value of each biomarker and extracted where possible the difference in the c-index of the best clinical model with and without the biomarker (ie, Δ[c-index]).

LITERATURE SEARCH AND STUDY ELIGIBILITY.

Rationale for biomarker selection. We limited our search to studies reporting: 1) common circulating biomarkers of vascular inflammation, ie, CRP, interleukin-6, and tumor necrosis factor-α (TNF-α), which have been all independently associated with CHD; 2) arterial PET/computed tomography (CT) imaging by use of any radiotracer; 3) CCTA imaging biomarkers of plaque phenotype (anatomical HRP features, such as spotty calcification, low attenuation/non-calcified plaque, positive remodeling, napkin-ring sign) that are anatomical biomarkers of plaque inflammation associated with the risk of plaque rupture; and 4) CCTA-imaging of PVAT, which has recently been used for the noninvasive detection of coronary inflammation (12).

Eligibility criteria. Eligibility criteria for included studies were as follows:

Types of studies: prospective clinical cohorts or registries (in English language).

Types of participants: populations without established CHD.

Types of prognostic factor: as described previously (section on Rationale for biomarker selection).

Time definition: no time constraints on the duration of follow-up period. Prespecified subgroup analysis performed for short (<5 years), medium (5-10 years), and long follow-up duration (>10 years).

Types of outcome measures: the primary outcome was the composite of major adverse cardiovascular events (MACEs) and mortality; secondary analyses were performed for outcome type (ie, MACEs only or for all-cause mortality). Cardiovascular mortality was not included as a separate outcome, as an initial review of the literature suggested that specific c-index for cardiovascular mortality was only rarely reported in the literature (cardiovascular mortality was reported as part of MACEs). Prespecified subgroup analysis per biomarker type was carried out.

Search methods for identification of studies. Published literature was assessed by at least 2 independent

ABBREVIATIONS AND ACRONYMS

^{18F}**FDG** = 18F-fluorodeoxyglucose

CCTA = coronary computed tomography angiography

CHD = coronary heart disease

CRP = C-reactive protein

CT = computed tomography

EPV = event per variable

HRP = high-risk plaques

MACE = major adverse cardiovascular event(s)

PET = positron emission tomography

PVAT = perivascular adipose tissue

TNF-α = tumor necrosis factor-α

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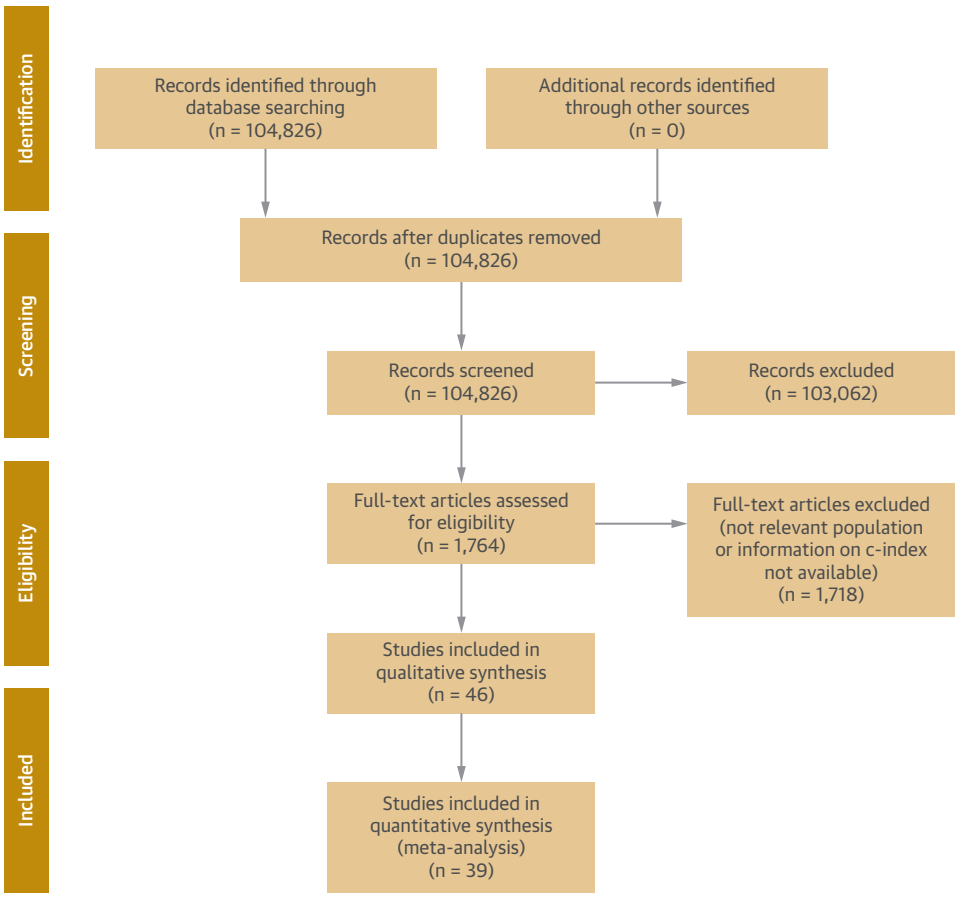
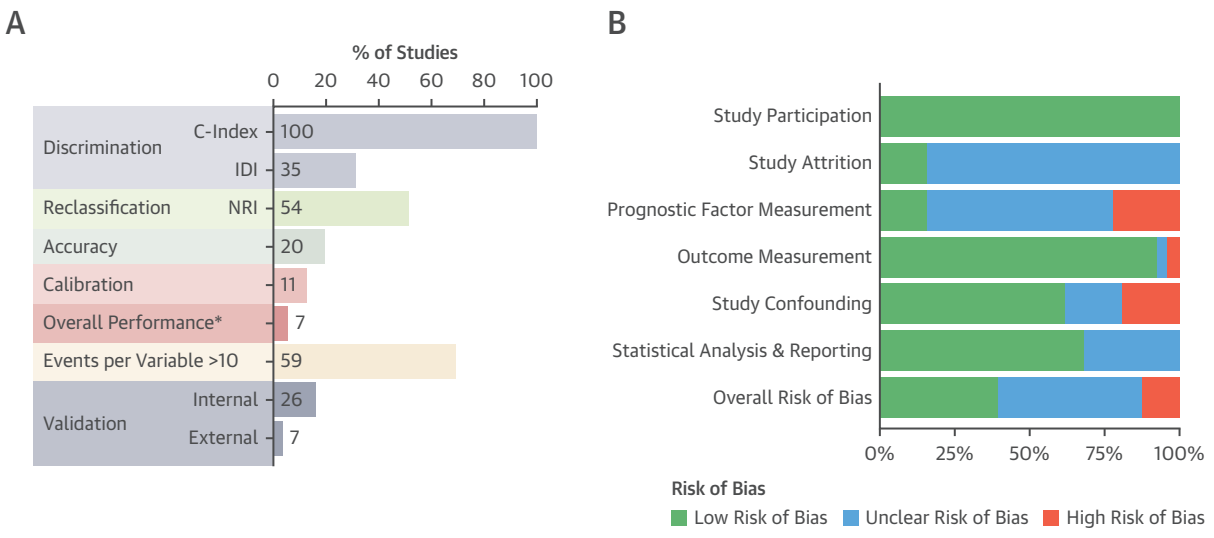
FIGURE 1 PRISMA Flow Chart of the Study



reviewers. Eligible studies were drawn from a systematic review of the English literature in Medline database published before April 22, 2021. When a full-text article was eligible for inclusion in the quantitative synthesis, but there were missing data, the corresponding author was also contacted. The exact search strategy, MeSH terms used, and the search algorithm are presented in the Supplemental Appendix. This study is registered with PROSPERO (CRD42020181158).

Data extraction. From each study, data were extracted on the year of publication, sample size, population enrolled, the length of follow-up period, the definition of MACEs, the c-index of the multivariable models for MACEs, and all-cause mortality with and without the biomarker, ie, the Δ[c-index]; the number of covariates included in the model; the number of events (MACEs/deaths); the degree of multivariable adjustment categorized as none; + adjusted for a single factor or age and sex, ++ adjusted for age, sex, and cardiovascular risk factors, or +++ adjusted for age, sex, and cardiovascular risk factors plus additional biomarkers, such as biochemical (eg, renal function, plasma B-natriuretic peptide levels or others) or functional ones (eg, left ventricle ejection fraction). The event per variable (EPV) was calculated as the ratio of total events per number of covariates in the model to assess the methodological soundness of variable selection for the study sample size and the risk of overfitting. The event incidence was calculated as the ratio of events to study sample, as an index of the level of risk of the study population. In addition, for each study we recorded the reporting of risk discrimination by the Integrated Discrimination Index (IDI), reclassification capacity by the Net Reclassification Index (NRI), model calibration, classification, accuracy metrics (sensitivity, specificity, positive/negative predictive value), overall model performance metrics (such as Akaike's Information Criterion, R^2, or Brier score), and the internal/external validation of the model. The quality of the prognostic studies and the potential risk of bias were

FIGURE 2 **Summary Statistics Provided on Model Performance in the Identified Studies**



(A) The bar graphs indicate the reporting of information on model performance (as % of studies). **(B)** Quality assessment and risk of bias of eligible prognostic studies included in the meta-analysis. *Information on Akaike's Information Criterion (AIC), Brier Score, or R^2 of the model. IDI = integrated discrimination index; NRI = net reclassification index; n/a = not available.

evaluated using the Quality in Prognostic Studies tool (16).

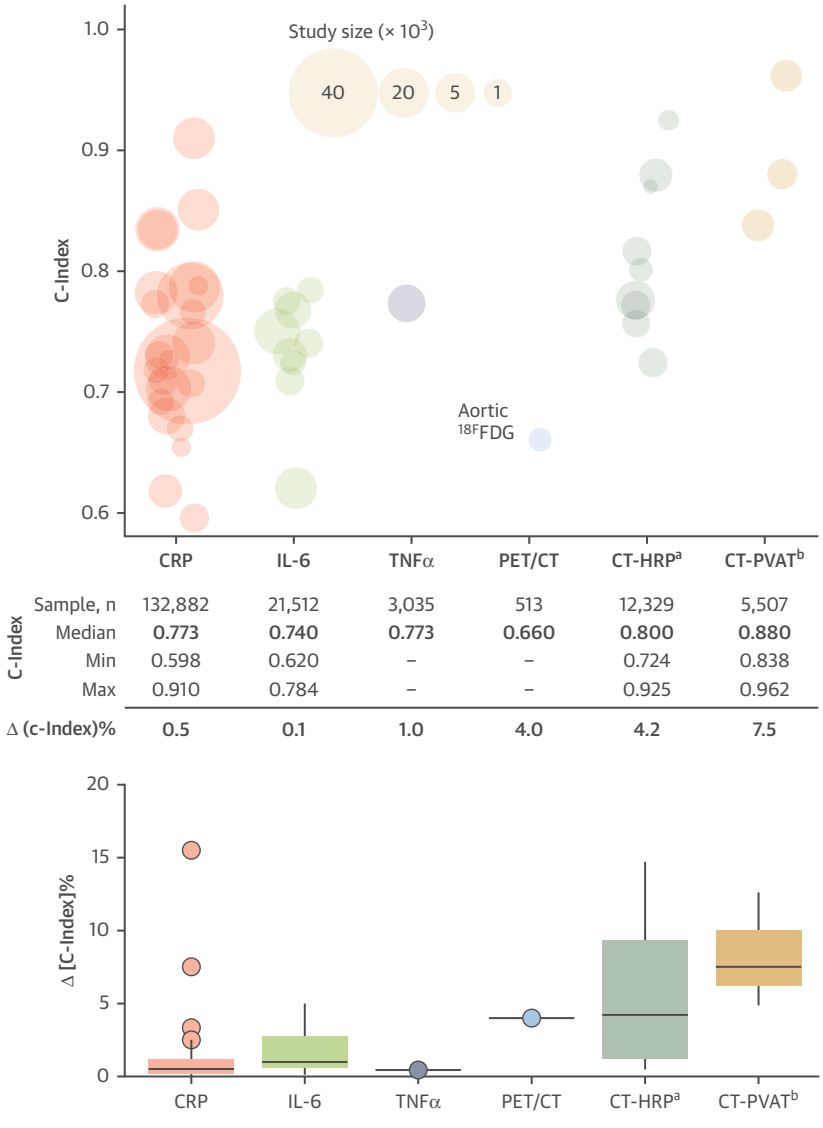
STATISTICAL ANALYSIS. We selected the Δ[c-index] as the most reliable marker of the added prognostic value offered by each biomarker to be included in the meta-analysis. The reason for this is that the value of the c-index of a clinical model is largely affected by the covariates included in the model, the sample size, the ratio of total events to the number of covariates in the model, and the degree of model overfitting to the study population, all factors that make the statistical comparison between c-indices of nonnested models irrelevant and not methodologically sound. In eligible studies that were included in the meta-analysis, the area under the curve of a receiver-operating characteristics curve analysis was typically used as the metric of the c-index.

The meta-analysis of the extracted values of Δ[c-index] in the eligible studies was carried out using a random effects model (given the differences in the study population, clinical setting, length of follow-up, and biomarkers investigated between studies) and by the method of DerSimonian and Laird (17). For those studies reporting a c-index for both MACEs and mortality, we included the Δ[c-index] for MACEs in the meta-analysis for the composite outcome (MACEs and/or mortality), as the prediction of cardiovascular events was the main focus of our study. The estimate of heterogeneity was taken from the inverse-variance random-effect model. Subgroup and meta-regression analyses were carried out to explore causes of statistical heterogeneity between studies and identify predictors of the effect size on Δ[c-index]. The pooled estimate random effects model was used to obtain the overall (and for each biomarker) pooled estimate of Δ[c-index] (and 95% CIs) which were illustrated in relevant forest plots. The presence of statistical heterogeneity was assessed using the I^2. Subgroup analyses were also performed for the length of the follow-up, the clinical setting (primary/secondary prevention of CHD), outcome type (MACEs/all-cause mortality), biomarker type, study sample size, and EPV (categorized as >10 or ≤10 as previously suggested) (18), event incidence, and the level of statistical adjustment. Multivariable meta-regression analysis was also used to explore predictors of the effect size on Δ[c-index]. All statistical analyses were completed with R (www.r-project.org; version 3.6.0) (19) and package *meta* (20).

RESULTS

STUDIES IN PUBLISHED LITERATURE WITH AVAILABLE INFORMATION ON THE PROGNOSTIC VALUE OF BIOMARKERS OF VASCULAR INFLAMMATION. From a total of 104,826 relevant studies, a total of 39 studies (n = 175,778 individuals) were finally included

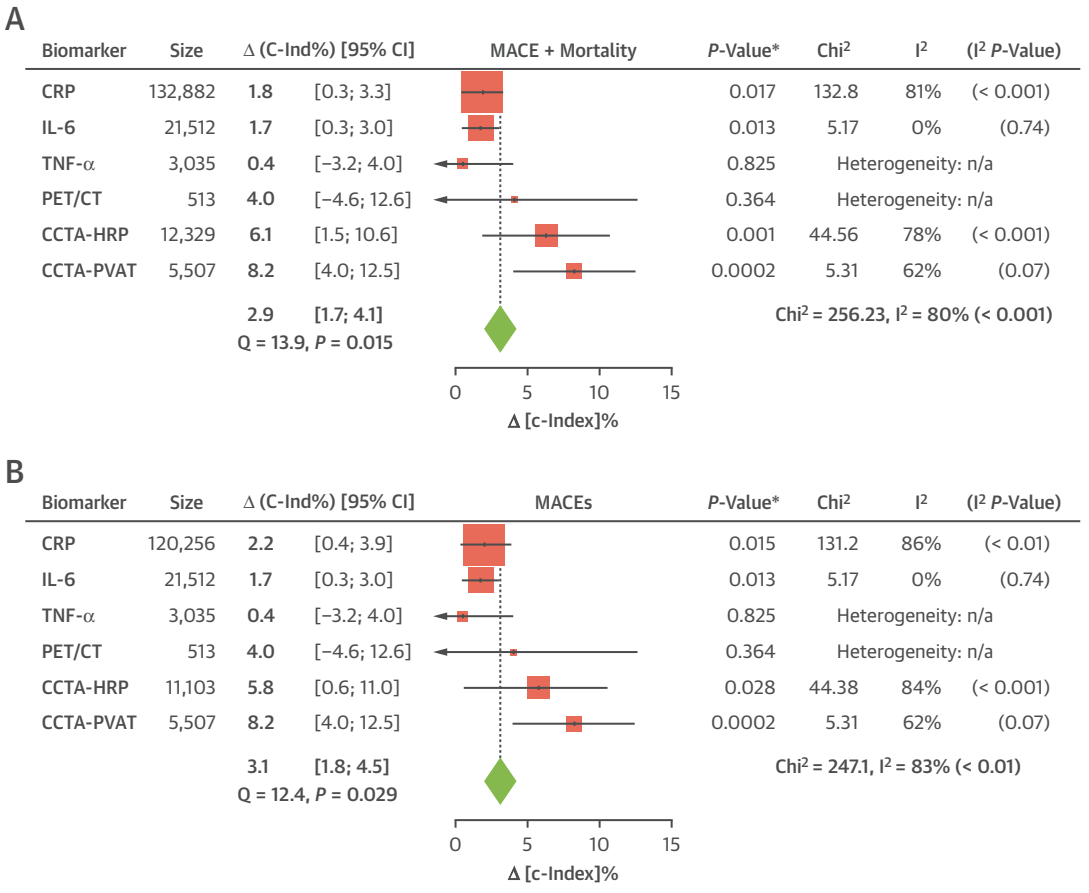
FIGURE 3 Bubble Plot of the Prognostic Performance (c-index) of Each Biomarker for the Composite Endpoint of Major Adverse Clinical Outcomes and All-Cause Mortality



Each **bubble** on the graph represents a study with its size being proportional to the sample size. Boxplots of the added prognostic value (Δ[c-index]) provided by each biomarker (calculated as the difference in c-index of the best clinical model in each study with the addition of the biomarker of interest, lower part of the panel). [a]The added prognostic value of CCTA-HRP is reported on top of coronary atherosclerosis extent, whereas [b]that of CCTA-PVAT on top of coronary atherosclerosis extent and HRP. ^{18F}FDG = 18F-fluorodeoxyglucose; CCTA = coronary computed tomography angiography; CT = computed tomography; CRP = C-reactive protein; HRP = high risk plaque features; IL-6 = interleukin-6; PET/CT = arterial positron emission tomography/computed tomography; PVAT = perivascular adipose tissue; TNF-α = tumor necrosis factor-α.

in the quantitative synthesis. The PRISMA flowchart for the study is presented in **Figure 1**. The PRISMA checklist (21) is also provided in the Supplemental Appendix. The list of identified studies and the extracted information as included in the quantitative synthesis is provided in Supplemental Table 1. The Δ[c-index] of the biomarker reported by each study was negatively correlated with the performance (c-index) of the baseline model ($r = -0.342$; $P = 0.014$), the length of follow-up ($r = -0.363$; $P = 0.011$), relationships that were accounted for in meta-regression analysis.

FIGURE 4 **Forest Plot for the Added Prognostic Value of Common Biomarkers of Vascular Inflammation in Stable Patients in the Overall Population**



For **(A)**, the composite of major adverse clinical outcome events (MACEs) and all-cause mortality or **(B)** MACEs only. The size of the **squares** corresponds to the weight of each biomarker subgroup in the quantitative synthesis. The **diamond** and its width represent the pooled estimate for the Δ[c-index] and the 95% CIs, respectively. *P value for statistically significant difference in Δ[c-index] from the overall pooled estimate. CRP = C-reactive protein; CT = computed tomography; HRP = high-risk plaque; IL = interleukin; n/a = not available; PET/CT = arterial positron emission tomography/computed tomography; PVAT = perivascular adipose tissue; TNF = tumor necrosis factor.

QUALITY OF INCLUDED STUDIES AND ASSESSMENT FOR RISK OF BIAS. The identified studies consistently reported the c-index of the clinical model, but less frequently other metrics such as IDI, NRI, classification, calibration of the model, or overall model performance metrics, whereas only a minority of the studies used internal validation (eg, bootstrap or cross-validation) or external validation of their findings (summarized in **Figure 2A** and provided separately for each study in Supplemental Figure 1). The quality of the prognostic studies for potential risk of bias is shown in **Figure 2B** (and for individual studies in Supplemental Figure 2). The overall risk of bias was low in 37% of studies, unclear in 48% of studies, and high in 15% of studies.

META-ANALYSIS ON THE ADDED PROGNOSTIC VALUE OF BIOMARKERS OF VASCULAR INFLAMMATION. An overview of the identified studies and the prognostic information of each biomarker for the composite of MACEs and total mortality is provided in **Figure 3**. There was a significant difference between biomarkers in the c-index of the predictive models (by Kruskal-Wallis test; $P = 0.038$) and the Δ[c-index] (by Kruskal-Wallis test; $P = 0.001$). There were no significant differences in the performance of baseline clinical models between biomarkers (by Kruskal-Wallis test; $P = 0.358$).

To better understand these data of **Figure 3**, we included studies with available information on Δ[c-index] in a meta-analysis. The forest plots for

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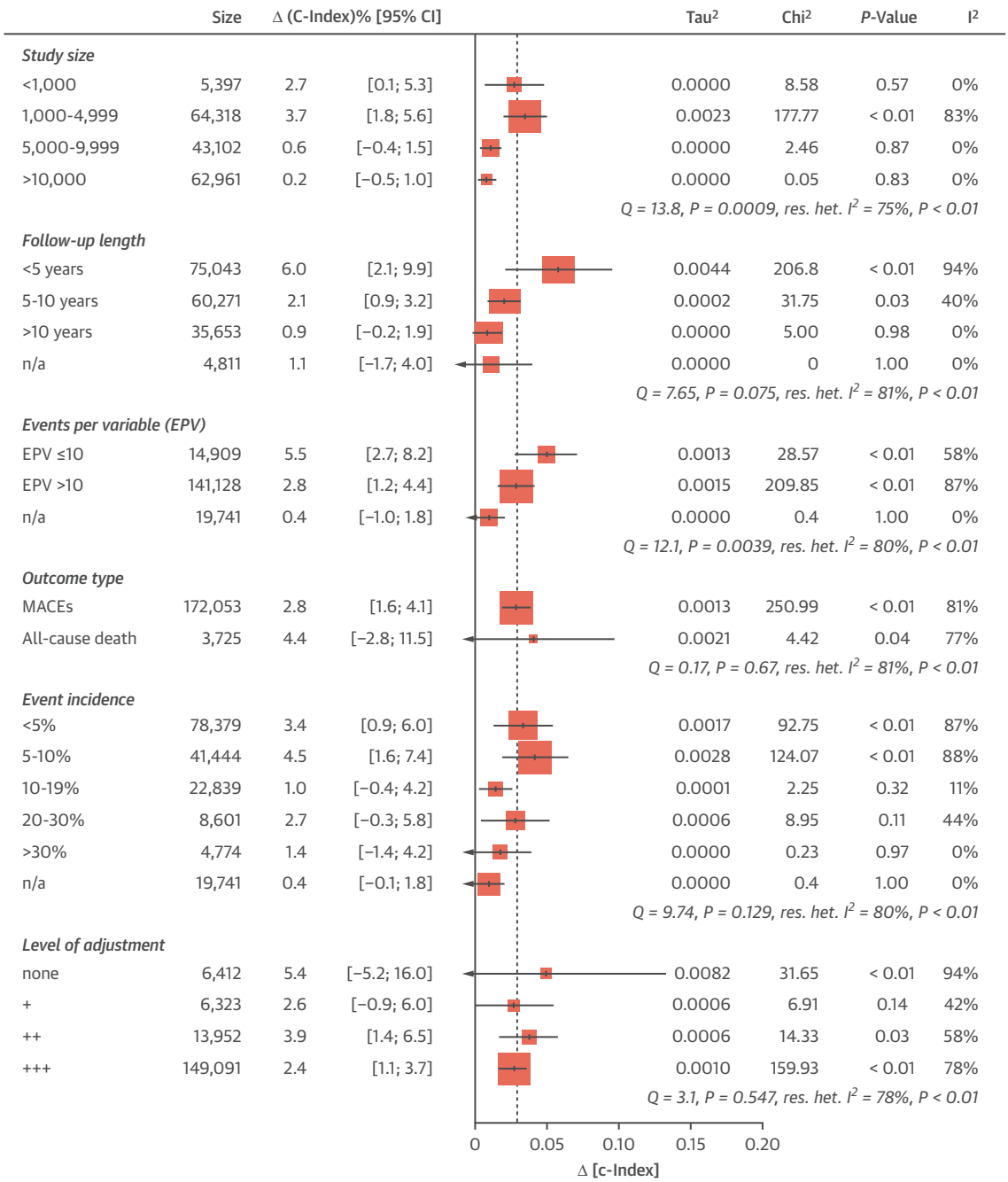
FIGURE 5 **Subgroup Analyses on the Incremental Prognostic Value of Biomarkers of Vascular Inflammation for the Pooled Estimate of Δ[c-index] of the Composite Endpoint of MACEs and All-Cause Mortality**



The **size of the squares** corresponds to the weight of each subgroup in the quantitative synthesis. MACE = major adverse cardiovascular event; n/a = not available.

individual studies included in the meta-analysis are shown in Supplemental Figures 3 to 5. The results of the quantitative synthesis for the overall pooled estimate on Δ[c-index] and by biomarker subgroups are shown in **Figure 4**. The overall pooled estimated of Δ[c-index] for the composite endpoint (MACEs and all-cause mortality) was 2.9%, 95% CI: 1.7 to 4.1, and for MACEs only 3.1%, 95% CI: 1.8 to 4.5. There was

substantial heterogeneity between studies for both the composite endpoint (I^2 = 80%; P < 0.01) and MACEs (I^2 = 83%; P < 0.01). Within each biomarker subgroup, heterogeneity was high for CRP and CCTA-HRP (Supplemental Figures 3 to 5). Importantly, the added prognostic value of CCTA biomarkers significantly outperformed that of circulating biomarkers both for the composite endpoint (**Figure 4A**) and for MACEs only (**Figure 4B**).

In subgroup analyses (**Figure 5**), studies with smaller sample sizes and EPV ≤10, reported significantly higher Δ[c-index] values. There was also a trend toward higher Δ[c-index] with shorter follow-up duration. Nonetheless, none of these factors accounted for the statistical heterogeneity between studies. There was no significant interaction between the pooled estimate for Δ[c-index] and the event incidence, the clinical outcome type (MACEs or all-cause mortality), or the level of statistical adjustment.

MULTIVARIABLE META-REGRESSION ANALYSIS TO EXPLORE INDEPENDENT PREDICTORS FOR THE REPORTED PROGNOSTIC VALUE OF BIOMARKERS OF VASCULAR INFLAMMATION. To explore whether the relationship between the Δ[c-index] of studies and the prognostic value of each biomarker was independent of other confounding risk factors such as the study sample size, the length of follow-up, population observed event incidence, or even the performance of the baseline prediction model, all these covariates were included together with the type of biomarker in multivariable meta-regression analysis. In this analysis, the c-index of the baseline model and the biomarker type (ie, CCTA biomarkers) were identified as independent predictors of the effect size on Δ[c-index], accounting for 39% of the heterogeneity between studies (**Table 1**). These findings suggest that despite differences between clinical studies in population type/study design, the performance of the baseline model used, sample size, and length of follow-up, the type of biomarker determined the added prognostic value (Δ[c-index]) of each study.

TABLE 1 Meta Regression Analysis for Independent Predictors of the Effect Size on Δ[c-index]

	Estimate	SE	*Z* Value	*P* Value	95% CI	
Log (study sample size)	0.001	0.014	0.10	0.922	−0.026	0.029
Biomarker type (CCTA)	**0.042**	**0.017**	**2.49**	**0.012**	**0.009**	**0.076**
Event incidence, %	−0.002	0.001	−1.34	0.180	−0.005	0.001
Log (length follow-up), y	**−0.015**	**0.007**	**−2.11**	**0.035**	**−0.029**	**−0.001**
Level of statistical adjustment	0.001	0.008	0.12	0.903	−0.014	0.016
Baseline c-index	**−0.240**	**0.073**	**−3.28**	**0.001**	**−0.383**	**−0.096**
Intercept	0.212	0.007	2.92	0.003	0.070	0.354

R^2 (amount of heterogeneity accounted for): 39.2%. Text in **bold** are presented the significant predictors of the effect size on Δ[c-index].

CCTA = coronary computed tomography angiography.

DISCUSSION

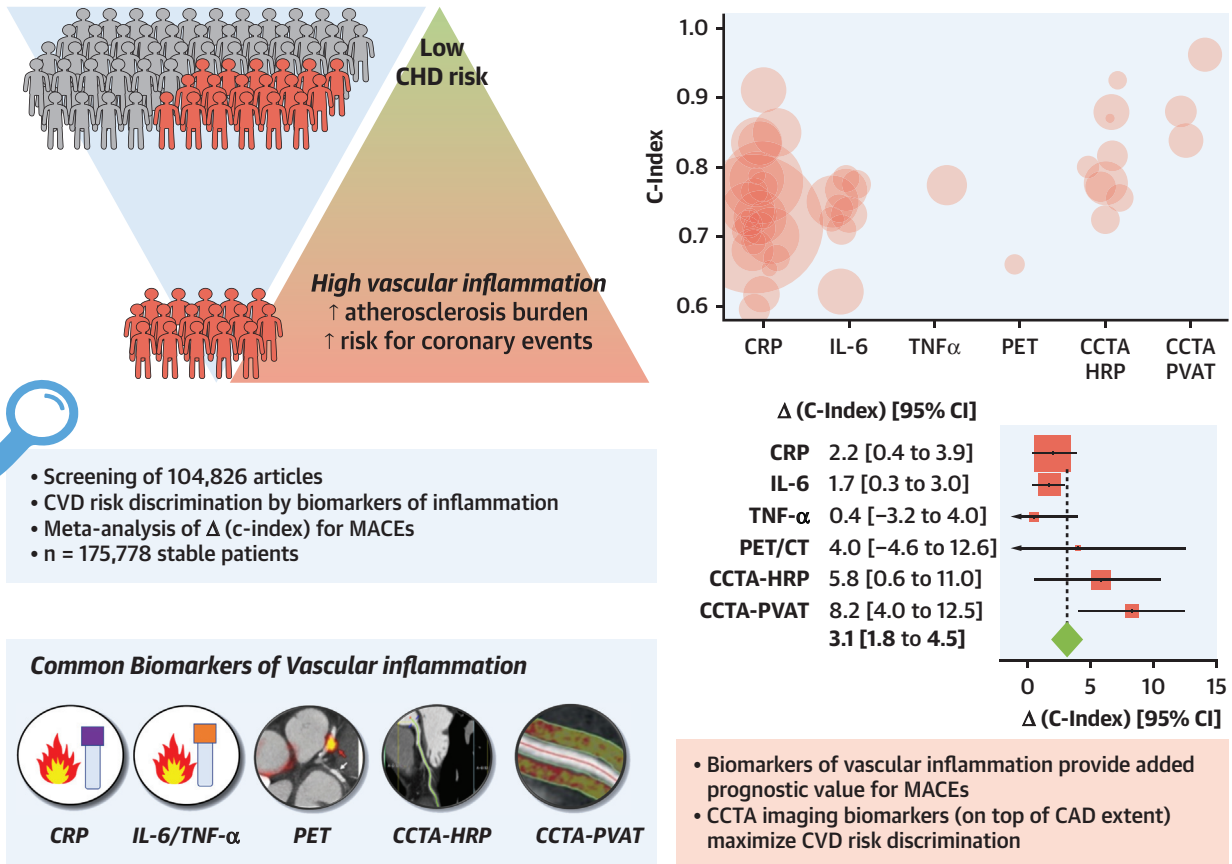
In the present study, we systematically explored published literature to assess the value of a cardiovascular prognostication strategy based on inflammatory burden assessment. Our findings suggest that biomarkers of vascular inflammation provide added prognostic information for future cardiovascular events over clinical risk factors. Meta-analyzed data of published studies also suggest that the prognostic value of biomarkers of vascular inflammation is maximized with the use of CCTA imaging biomarkers. These findings provide the first robust evidence for the value of inflammatory risk assessment for cardiovascular prognostication and risk stratification purposes (**Central Illustration**).

Coronary artery calcium is a good surrogate marker of coronary atherosclerosis extent and possibly the most useful biomarker for the risk stratification of asymptomatic individuals (22). Other biomarkers, such as carotid intima media thickness or pulse wave velocity, may also offer independent prognostic information for cardiovascular events. However, the previously listed biomarkers are not useful metrics of systemic and/or vascular inflammation, which has a well-recognized role in coronary plaque formation and rupture (23).

Recently, the CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) provided the first clinical evidence that reducing systemic inflammation by the interleukin-1b inhibitor canakinumab significantly lowers the risk of MACEs (5), whereas in the LoDoCo-2 (Low-Dose Colchicine 2) trial (24), anti-inflammatory treatment with colchicine in high-risk patients post-myocardial infarction also improved clinical outcomes. The use of inflammatory biomarkers is currently advocated for improved risk stratification and the detection of the vulnerable patient at risk for events (3,25). Nonetheless, it is still unclear how well biomarkers of vascular inflammation perform on top of clinical models for CHD prognosis. In addition, many important questions, such as the effectiveness of this approach, or the added prognostic value of inflammatory biomarkers over clinical risk factors, as well as their comparative assessment, remain unanswered.

Our findings suggest that the measurement of circulating levels of common inflammatory biomarkers such as CRP, interleukin-6, or TNF-α provides incremental prognostic information on top of clinical risk models, although the estimated effect

CENTRAL ILLUSTRATION **A Roadmap for Cardiovascular Risk Prognostication by Biomarkers of Vascular Inflammation**



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CCTA = coronary computed tomography angiography; CVD = cardiovascular disease; HRP = high-risk plaque; CRP = C-reactive protein; IL = interleukin; n/a = not available; PET = positron emission tomography; PVAT = perivascular adipose tissue; TNF = tumor necrosis factor.

size on cardiovascular risk discrimination (Δ[c-index]) is rather marginal. These findings are not totally unexpected, as these systemic inflammatory biomarkers are nonspecific for vascular inflammation and their circulating levels can be influenced by various systemic factors. For example, it is estimated that approximately 60% of subjects in the secondary prevention setting of CHD could be classified as having "high inflammatory risk" by CRP levels (3).

More recently, the use of noninvasive imaging offers alternative ways to quantify vascular inflammation. ^{18F}FDG-PET/CT imaging is considered the gold standard modality for the detection of arterial inflammation in vivo, but there are sparse data on its prognostic value (10,26), and its clinical availability remains limited. Newer radiotracers, such as ^{18F}NaF, have high diagnostic accuracy for the detection of coronary inflammation (10), but evidence on the added prognostic value of arterial ^{18F}NaF-PET/CT imaging is needed.

Next to PET/CT, noninvasive imaging by CCTA has emerged as a promising alternative to the use of circulating biomarkers for detecting the vulnerable patient (25). CCTA can be used for plaque characterization and the detection of anatomical HRP features (such as spotty calcification, low attenuation plaque, positive remodeling, napkin-ring sign) or even PVAT imaging to detect coronary inflammation, which are both independent prognostic factors for future cardiovascular events (7,8,11,27). In the present analysis, we found that both these approaches are associated with substantial improvements in the c-statistic of clinical models; pooled estimate in Δ[c-index]% for CCTA-HRP of 6.1% over and above coronary

atherosclerosis extent, and for CCTA-PVAT 8.2% over and above coronary atherosclerosis extent and HRP. New technologies that have received regulatory clearance for clinical use in Europe combine pericoronary Fat Attenuation Index with plaque analysis and the patient's clinical risk profile (ie, CaRi-Heart) (28) and provide integrated risk prediction and standardized quantification of coronary inflammation from routine CCTAs.

STUDY LIMITATIONS. Several methodological aspects of our analysis should be noted. The comparison of the added prognostic value of biomarkers is a demanding task, typically constrained by the significant heterogeneity between studies (29). In the present study, we focused on the c-index, which is a metric of risk discrimination and estimates the probability that a patient with the outcome is given a higher risk than a patient without the outcome. Despite the limitations the c-index carries, it is still the most widely used metric to assess the diagnostic/prognostic accuracy of a model. Importantly, the magnitude of Δ[c-index] depends on both the value of the additional biomarker, but also on the predictive performance of the baseline clinical model (15,30). However, in our analysis, we show that: 1) there were no significant differences in the c-index of the baseline clinical models between biomarkers; 2) in subgroup meta-analysis, there were significant differences in the Δ[c-index] between biomarkers; and 3) in multivariable meta-regression analysis, the type of biomarker was an independent predictor of the effect size on Δ[c-index]. One may argue that the prognostic value of CCTA biomarkers may relate to information captured on plaque burden; however, in our analysis, the added prognostic value of HRP features and PVAT biomarkers was assessed over and above metrics of coronary atherosclerosis extent. Therefore, the observation on the overall better added performance of CCTA imaging biomarkers should be viewed as a safe conclusion of our analysis.

Notably, we have not used other model performance metrics to explore the clinical value of introducing biomarkers in risk prediction models, such as the net benefit (31) or decision curve analysis (32), therefore the estimated clinical benefit or the cost-effectiveness of a risk stratification strategy based on inflammatory biomarkers need to be determined. Moreover, any possible improvements in risk stratification by PET/CT or CCTA use need to be weighed against their costs and radiation exposure to decide whether they are rational screening strategies at the population level. Whether measurement of vascular inflammation across different vascular beds (ie, coronary arteries, carotids, or aorta) has equally good prognostic value is another issue that needs to be investigated. Finally, the findings of a meta-analysis are constrained by heterogeneity between studies, publication bias (studies with nonsignificant results are more likely to not be reported), as well as the quality of published studies. Notably, the quality of prognostic studies in the field is moderate, and only a minority of studies have internally or externally validated their findings. Certainly, there is space for improvement in this area, and this should be considered by any future studies in the field (21,33).

CONCLUSIONS

In conclusion, we have systematically reviewed published studies on the prognostic value of inflammatory biomarkers, and demonstrate that the measurement of vascular inflammation on top of clinical risk factors enhances risk discrimination for cardiovascular events. We show that CCTA biomarkers such as high-risk plaque features or pericoronary fat imaging (alone or in combination) enhance risk discrimination on top of coronary atherosclerosis extent and are significantly better to circulating biomarkers of inflammation. These findings could serve as a roadmap for biomarker selection and their further use in daily clinical practice or by randomized clinical trials with anti-inflammatory agents for CHD prevention.

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Dr Antoniades is a founder and shareholder of Caristo Diagnostics Ltd, a company that specialized in computed tomography imaging diagnostics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: The use of biomarkers of vascular inflammation provides incremental prognostic value over the clinical risk profile for cardiovascular outcomes.

COMPETENCY IN MEDICAL KNOWLEDGE 2: The use of biomarkers of vascular inflammation is a rational strategy for risk stratification in clinical practice and could lead to improved coronary heart disease prevention.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Detection of vascular inflammation by imaging or plasma biomarkers may be useful to select patients eligible for novel high-cost anti-inflammatory treatments.

TRANSLATIONAL OUTLOOK: The exact clinical settings on which the use of biomarkers of vascular inflammation may provide the maximum clinical benefit requires further investigation.

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KEY WORDS biomarkers, cardiovascular disease, coronary computed tomography, inflammation, prevention, prognosis

APPENDIX For the exact search strategy, MeSH terms used, the search algorithm, and the PRISMA checklist, as well as a supplemental table and figures, please see the online version of this paper.