

ORIGINAL RESEARCH

Haptoglobin and Immunoglobulin A2 Predict Cardiovascular Risk in Asymptomatic Subjects: The BioImage Study

Ana García-Álvarez, PhD, MD; Valentín Fuster, PhD, MD; Estefanía Nuñez , PhD; Ruth Owen, PhD; Lucía Ortega-Villanueva, BsC; Virginia Mass , PhD, MD; Inés García-Lunar , PhD, MD; Antonio Quesada , PhD, MD; Jose Javier Fuster , PhD; Ana Devesa , PhD, MD; Carlos Nicolás Pérez-García , PhD, MD; Javier Sánchez-Gonzalez , PhD; Pieter Muntendam, PhD; Vicente Andrés , PhD; Luis Miguel Blanco-Colio, PhD; Jesús Vázquez , PhD; Borja Ibañez , PhD, MD; Jose Luis Martin-Ventura , PhD

BACKGROUND: Plasma levels of haptoglobin and IgA2 (immunoglobulin A2) have recently been associated with subclinical atherosclerosis in European cohorts. We sought to validate these findings in an American population and to determine whether these biomarkers predict all-cause mortality or major cardiovascular adverse events beyond traditional risk scales (Framingham Risk Score) or vascular imaging.

METHODS: We analyzed 5328 asymptomatic US adults (mean age 69 years, 56.9% women) from the BioImage study (A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population; NCT00738725). Subjects underwent carotid plaque burden assessment by ultrasound, coronary artery calcium by computed tomography, and baseline plasma haptoglobin and IgA2 levels measurement by immunoturbidimetry. The end point was a composite of major cardiovascular adverse events and all-cause death during follow-up.

RESULTS: Haptoglobin and IgA2 correlated significantly with carotid plaque burden and coronary artery calcium, independent of Framingham Risk Score. After a median follow-up of 4.6 years, 466 participants (8.8%) experienced the composite outcome. Haptoglobin and IgA2 independently predicted the outcome, and associations remained significant after further adjustment for carotid plaque burden or coronary artery calcium. Similar results were observed for predictive capacity of high-sensitivity C-reactive protein. Individuals with high levels of all biomarkers (above the median) had a 2-fold higher event rate compared with those with low levels. Combined biomarker assessment, albeit modestly, significantly improved risk prediction beyond Framingham Risk Score and imaging.

CONCLUSIONS: Haptoglobin and IgA2 predict the composite outcome of major cardiovascular adverse events and all-cause death, independently to Framingham Risk Score, in asymptomatic American adults. Their measurement, alone or in combination with imaging, may enhance cardiovascular risk stratification in primary prevention.

Key Words: atherosclerosis ■ biomarkers ■ haptoglobin ■ immunoglobulin A2 ■ prognosis

Correspondence to: Jose Luis Martin-Ventura, PhD, Vascular Research Laboratory, IIS-Fundación Jiménez Díaz, Autónoma University, Av. Reyes Católicos 2, 28040 Madrid, Spain. Email: jlmartin@fjd.es and Valentín Fuster, MD, PhD, Mount Sinai Hospital, Centro Nacional de Investigaciones Cardiovasculares Carlos III, Melchor Fernández Almagro 2, 28029 Madrid, Spain. Email: vfuster@cnic.es

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CLINICAL PERSPECTIVE

What Is New?

- Haptoglobin and IgA2 (immunoglobulin A2) are independently associated with major cardiovascular events and all-cause mortality, beyond Framingham Risk Score and imaging, indicating their potential to refine preventive strategies.

What Are the Clinical Implications?

- Haptoglobin and IgA2 can be measured using low-cost, clinically validated assays already in use in hospital laboratories, which may facilitate the early detection of atherosclerosis even in settings without access to imaging technologies.
- Haptoglobin and IgA2 could serve as accessible biomarkers of residual immune-inflammatory risk, potentially guiding personalized preventive therapies.

Nonstandard Abbreviations and Acronyms

cPB	carotid plaque burden
FRS	Framingham Risk Score
IgA2	immunoglobulin A2
MACE	major cardiovascular adverse event

Atherosclerotic cardiovascular disease and its complications represent the foremost cause of morbidity and mortality.¹ Despite decades of research on atherosclerotic cardiovascular disease pathogenesis and its associated risk factors, the incidence of clinical events remains unacceptably high. Current strategies, including lifestyle changes and pharmacological interventions to lower modifiable cardiovascular risk factors such as low-density lipoprotein and blood pressure, can slow but rarely reverse disease progression. This underscores the urgent need for novel and more effective approaches to reduce the global burden of atherosclerotic cardiovascular disease. In this regard, tools enabling earlier diagnosis and more accurate prediction of cardiovascular events would have substantial clinical and socioeconomic impact.^{1–3}

Atherosclerosis develops silently over several decades before it becomes clinically manifest. Subclinical atherosclerosis is highly prevalent in asymptomatic subjects.⁴ Imaging techniques are available as screening tools to detect the presence and severity of atherosclerotic plaques.⁵ Furthermore, direct identification of subclinical atherosclerosis by coronary artery calcium (CAC) or vascular ultrasound predicts cardiovascular events and

mortality.^{2,6–8} Beyond structural assessment, inflammation, a key driver of atherosclerosis initiation and progression,⁹ can also be detected by 18F-fluorodeoxyglucose positron emission tomography/computed tomography imaging. In this respect, arterial 8F-fluorodeoxyglucose positron emission tomography/computed tomography uptake has been demonstrated in asymptomatic subjects¹⁰ and independently predicts cardiovascular events.¹¹ Bone marrow 8F-fluorodeoxyglucose uptake has also been associated with early subclinical atherosclerosis through its relationship with metabolic syndrome.¹² However, despite their diagnostic value, these imaging techniques require specialized expertise; some of them are costly and not available worldwide. In addition, risk scales such as the Framingham Risk Score (FRS) have predictive value at the population level, but they lack precision at the individual level.

As a complement to imaging, circulating biomarkers hold promise for the early detection and prognosis of cardiovascular events in asymptomatic patients.¹³ Given the central role of inflammation in atherosclerosis initiation and progression, biomarkers related to immune-inflammatory responses are of particular interest. In this respect, the inflammatory biomarker CRP (C-reactive protein) could help to predict cardiovascular events as well as to tailor potential therapies.^{14,15} However, CRP is not directly related to atherosclerotic plaque biology, and its limited specificity underscores the need for more targeted inflammatory markers.¹⁶

We recently demonstrated in 3 independent cohorts of Spanish asymptomatic subjects that plasma levels of haptoglobin and IgA2 (immunoglobulin A2), 2 proteins linked to innate and adaptive immune responses, respectively, were able to detect subclinical atherosclerosis.¹⁷ Building on these findings, we hypothesized that these circulating immune-inflammatory biomarkers could facilitate the identification of subclinical atherosclerosis or help select individuals who might benefit most from imaging assessment. Moreover, such biomarkers may provide incremental predictive value beyond cardiovascular risk factors and imaging techniques for forecasting cardiovascular events. Accordingly, the aims of this study were first, to validate in a large US cohort^{8,18} the diagnostic performance of haptoglobin and IgA2, previously shown to be associated with subclinical atherosclerosis in European populations,¹⁷ and second, to evaluate their usefulness in predicting the composite outcome of major adverse cardiovascular events (MACEs) and all-cause mortality.

METHODS

Study Design and Participants

The Biolmage Study (A Clinical Study of Burden of Atherosclerotic Disease in an At-Risk Population;

NCT00738725) prospectively enrolled 7687 asymptomatic members of the Humana Health System (men aged 55 to 80 years and women aged 60 to 80 years) residing in the Chicago, Illinois or Fort Lauderdale, Florida metropolitan areas between January 2008 and June 2009. Eligibility criteria¹⁹ required the absence of prior cardiovascular disease (myocardial infarction, stroke, angina, heart failure, or arterial revascularization), active cancer treatment, or any medical condition precluding long-term follow-up. Of these, 6102 participants entered the imaging arm and underwent carotid vascular ultrasound and CAC scoring. Participants were followed until December 31, 2013 for MACEs and all-cause mortality. There were 1364 patients who were censored before this date; however, the reason for this loss of follow-up was not recorded in the database. Events were identified through Humana Health System administrative claims data, corroborated by source medical records, and adjudicated by an independent clinical events committee. A MACE was defined as myocardial infarction, unstable angina, stroke, or coronary revascularization, as previously defined.⁸ The composite end point comprised MACEs and all-cause death.

Ethics Approval

The BioImage Study was approved by the Western Institutional Review Board, Olympia, WA and all participants provided written informed consent and Health Insurance Portability and Accountability Act authorization.

Baseline Examinations

At baseline, all participants underwent an in-person examination and standardized interview. Diabetes was defined as self-reported physician diagnosis or current treatment with oral hypoglycemic agents or insulin. Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or current use of antihypertensive medication. Current smoking status was self-reported. A nonfasting venous blood sample was collected for routine biochemistry analyses, including plasma lipid levels. The FRS was calculated for each participant using the sex-specific risk factor categories incorporating age, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, blood pressure treatment status, smoking status, and diabetes status. The score provides an estimate of 10-year risk of coronary heart disease events.

Carotid Vascular Ultrasound

Carotid plaque burden (cPB) was assessed at baseline using a high-resolution, 2-dimensional L9-3 linear

array transducer on a Philips iU22 ultrasound system (Philips Healthcare, Bothell, WA). Both carotid arteries were scanned in longitudinal and cross-sectional orientations from the proximal common carotid artery to the distal carotid segments. All scans were analyzed at a core laboratory at the Department of Vascular Surgery, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. cPB was calculated as the sum of all plaque areas identified in cross-sectional sweeps of the right and left carotid arteries, providing a quantitative metric of total carotid plaque area (mm²), using Philips QLAB quantification software (QLAB-VPQ). Interobserver agreement for this method has been previously validated, with an intraclass correlation coefficient of 0.82.²⁰

CAC Quantification

CAC was measured by the Agatston method from non-contrast multidetector computed tomography scans of the coronary arteries acquired with a Philips Brilliance 64-slice computed tomography scanner (Philips Healthcare, Andover, MA) using prospectively electrocardiographic gating. All operators and core laboratory readers were blinded to clinical data and results from other imaging modalities.

Measurement of IgA2 and Haptoglobin

Plasma samples were collected in tubes with potassium ethylenediaminetetraacetate, subjected to centrifugation at 1000g at 4 °C for 10 minutes, and stored at –80 °C. The Binding Site Optilite analyzer was used to measure the plasma levels of IgA2 and haptoglobin by immunoturbidimetric assays (LK088.OPT and NK058.OPT, respectively) under blinded conditions. Intra- and interprecision coefficient of variance were <5% for both assays. Haptoglobin values <0.026 g/L and IgA2 values <4.9 mg/L were adjusted to those respective thresholds. Additionally, all IgA2 values >1224 mg/L were set to that value. The proportions of samples affected by the applied adjustments were 0.21% for haptoglobin (lower limit), 0.14% for IgA2 (lower limit), and 4.0% for IgA2 (upper limit).

Statistical Analysis

Baseline characteristics are expressed as mean±SD for continuous variables or median (first–third quartile) if marked skewness exists, and number (percent) for categorical variables. Participants were included in the analysis if they had available data for all biomarkers and covariates used in the analysis. Participants were classified as having no atherosclerosis or stratified by tertiles of cPB or CAC score.

In regression modeling, the continuous variables haptoglobin, IgA2, high-sensitivity CRP (hs-CRP),

cPB, and CAC were first modeled using restricted cubic splines with 4 knots to examine the shape of their associations with the respective outcome. Linearity was formally tested using the Wald test for the joint significance of the nonlinear spline terms, with $P>0.05$ taken as acceptable evidence for linearity. Where linearity or log-transformation was supported, the simpler parametric form was retained; otherwise, the restricted cubic spline term was carried forward. Association between biomarkers and cPB or CAC (as continuous or categorical variables) were examined using univariable and multivariable linear regression models. Multivariable models were adjusted for FRS.

Cumulative incidence of the composite outcome was analyzed in the overall cohort and stratified according to IgA2, haptoglobin, and hs-CRP as continuous variables or median cutoffs, with comparisons across groups performed by a log-rank test. Associations of hs-CRP, IgA2, and haptoglobin with the composite outcome (MACEs and all-cause mortality) were assessed using Cox proportional hazards regression. Multivariable models were adjusted for: FRS alone (Model 1), FRS+cPB (Model 2), and FRS+CAC score (Model 3). The incremental predictive value of haptoglobin, IgA2, hs-CRP, and their combinations (haptoglobin+IgA2 and haptoglobin+IgA2+hs-CRP) beyond each model was evaluated using the Harrell C index, continuous and categorical net reclassification improvement,²¹ integrated discrimination improvement,²¹ Akaike information criterion, likelihood ratio tests, and integrated Brier score.²² The calibration of each model was evaluated using calibration plots displaying the observed versus predicted 5-year risk across 6 risk groups (quintiles 1–4 and deciles 9–10 of the predicted risk distribution). An exploratory interaction term between each biomarker and sex was included to assess whether associations differed for men and women. All analyses were performed with Stata version 17 (StataCorp, College Station, TX).

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding authors. The corresponding authors had full access to all data in the study and take responsibility for its integrity and the data analysis.

RESULTS

Baseline Characteristics

A total of 5328 individuals with valid data on biomarkers and cPB (5179 with available CAC) were included in this analysis. Mean age was 69 years, 56.9% were women, and approximately 90% had a low or intermediate FRS. Median values were 185.1 cm² for cPB,

Table 1. Summary of Population Characteristics, Risk Factors, and Biomarkers at Baseline

	No. of patients	Summary
Age (y), mean±SD	5328	69.0±5.9
Sex	5328	
Men, n(%)		2295 (43.1)
Women, n(%)		3033 (56.9)
BMI (kg/m ²), n(%)	5328	29.0 (5.6)
Risk factors		
Current smoker, n(%)	5326	454 (8.5)
Diabetes, n(%)	5328	841 (15.8)
SBP (mmHg), n(%)	5327	139.1 (18.5)
DBP (mmHg), n(%)	5326	77.9 (8.9)
Calcium score, median (interquartile range)	5179	46 (0–245)
Total cholesterol (mg/dL), median (interquartile range)	5323	202.2 (38.8)
Glucose (mg/dL), median (interquartile range)	5323	98.0 (90.0–109.0)
HDL cholesterol (mg/dL), median (interquartile range)	5323	55.6 (15.4)
LDL cholesterol (mg/dL), median (interquartile range)	5197	113.5 (33.3)
Triglycerides (mg/dL), median (interquartile range)	5323	146.0 (106.0–208.0)
Creatinine clearance (mL/min), mean (SD)	5323	76.2 (22.2)
Lipid-lowering drug, n(%)	5328	1576 (29.6)
Framingham Risk Score	5320	
Low risk (≤10%), n(%)		3051 (57.3)
Intermediate risk (10%–20%), n(%)		1638 (30.8)
High risk (>20%), n(%)		631 (11.9)
VUS imaging		
Plaque area 2D left, median (interquartile range)	5328	73.0 (0.0–264.1)
Plaque area 2D right, median (interquartile range)	5328	73.8 (0.0–264.9)
Total plaque area 2D, median (interquartile range)	5328	185.1 (29.0–549.9)
Total plaque volume 3D, median (interquartile range)	3575	58.7 (0.0–218.0)
Biomarkers		
Haptoglobin (g/L), mean (SD)	5328	1.3 (0.5)
IgA2 (mg/L), median (interquartile range)	5328	380 (245–594)
hs-CRP (mg/L), median (interquartile range)	5321	1.9 (0.9–4.1)

Variables are summarized as n (%), mean±SD, or median (interquartile range), where appropriate. BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IgA2, immunoglobulin A2; LDL, low-density lipoprotein; SBP, systolic blood pressure; VUS, vascular ultrasound; 2D, two-dimensional; and 3D, three-dimensional.

46.0 HU for CAC, 1.3 g/L for haptoglobin, 380 mg/L for IgA2, and 1.9 mg/L for hs-CRP. Baseline characteristics and cardiovascular risk factors are shown in Table 1.

Table 2. Biomarkers Summarized According to Tertiles of cPB and CAC

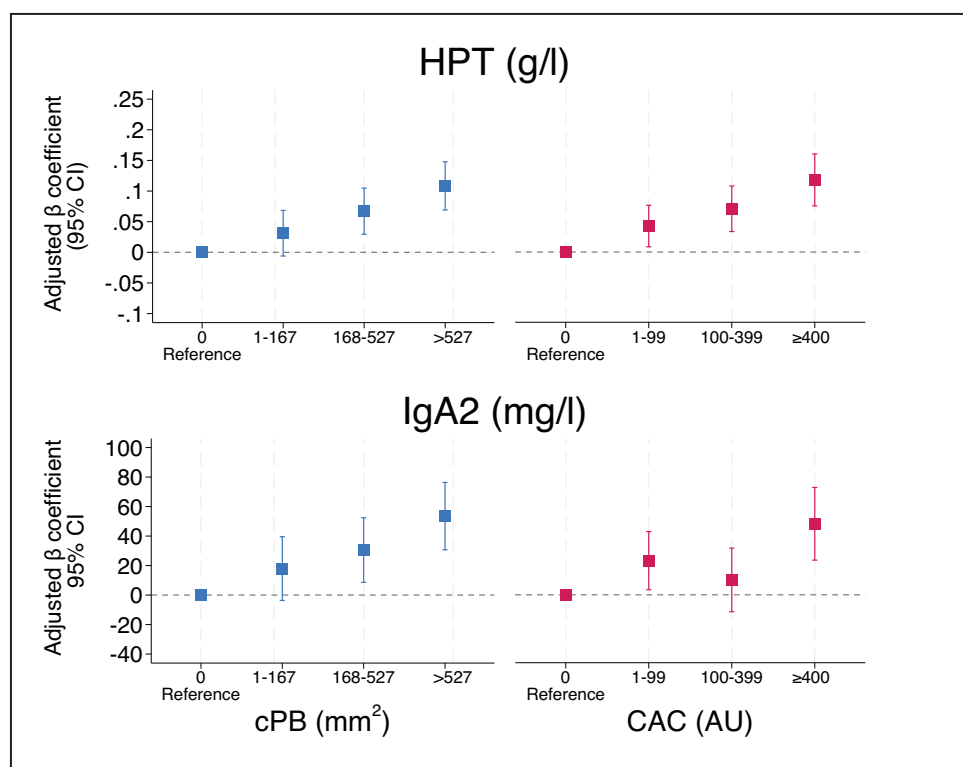
	cPB			
	0	>0–167.7	>167.7–526.6	>526.6
	(n=1168)	(n=1385)	(n=1388)	(n=1387)
Haptoglobin (g/L)	1.21 (0.93–1.54)	1.23 (0.93–1.57)	1.26 (0.97–1.62)	1.32 (1.01–1.63)
IgA2 (mg/L)	343.0 (227.2–518.0)	367.7 (235.1–558.1)	392.1 (253.2–610.9)	427.0 (270.9–684.7)
hs-CRP (mg/L)	1.9 (0.9–4.0)	1.8 (0.9–3.8)	1.9 (0.9–4.1)	1.9 (1.0–4.3)
	CAC			
	0	1–99	100–399	≥400
	(n=1661)	(n=1469)	(n=1174)	(n=875)
Haptoglobin (g/L)	1.21 (0.93–1.54)	1.26 (0.95–1.61)	1.27 (0.96–1.61)	1.32 (1.02–1.65)
IgA2 (mg/L)	342.5 (222.5–519.3)	384.0 (247.8–597.5)	387.5 (242.5–609.9)	451.5 (287.9–681.8)
hs-CRP (mg/L)	1.9 (0.9–4.2)	1.9 (0.9–4.0)	1.8 (0.9–4.0)	1.8 (0.9–3.8)

Variables are summarized as median (interquartile range). CAC indicates coronary artery calcium; cPB, carotid plaque burden; hs-CRP, high-sensitivity C-reactive protein; and IgA2, immunoglobulin A2.

Association of Haptoglobin and IgA2 With Subclinical Atherosclerosis

Both haptoglobin and IgA2 values increased progressively across categories of cPB and CAC, from absence of disease to the highest tertiles (Table 2). In contrast,

hs-CRP did not demonstrate association with atherosclerosis. In regression analyses, haptoglobin and IgA2 showed significant correlations with cPB, whether analyzed as a continuous or categorical variable (absence of plaque and tertiles of cPB). These associations were consistent in univariate and multivariate models adjusted

**Figure 1. Adjusted associations between HPT and IgA2 and cPB or CAC score.**

Models were adjusted for Framingham Risk Score. AU indicates Agatston units; CAC, coronary artery calcium; cPB, carotid plaque burden; HPT, haptoglobin; and IgA2, immunoglobulin A2.

for FRS (Figure 1 and Tables S1–S2). Similarly, haptoglobin and IgA2 were significantly correlated with CAC in all tested models (Figure 1 and Tables S1–S2).

Association of Haptoglobin and IgA2 With the Composite Outcome

During a median follow-up of 4.6 years (interquartile range, 3.6–4.9 years), 466 participants (8.8%) experienced the composite outcome, including 211 (4.0%) all-cause deaths, 79 (1.5%) myocardial infarctions, 138 (2.6%) strokes, and 144 (2.7%) coronary revascularizations.

The median values for haptoglobin and IgA2 were 1.3 g/L and 380 mg/L, respectively. Cumulative incidence analyses demonstrated that individuals with elevated levels (higher than the cutoffs) of both biomarkers had approximately a 2-fold higher event rate compared with those with low levels, with intermediate incidence in the remaining groups (Figure 2A). The corresponding median value for hs-CRP was 1.9 mg/L. Its combination with the other biomarkers' cutoff points shows a similar pattern in terms of discrimination (Figure 2B).

Both cPB and CAC were significantly associated with the composite outcome even after adjusting for FRS (Table 3), confirming the expected increase in event incidence among individuals with subclinical atherosclerosis. Importantly, haptoglobin and IgA2 also showed an independent association with the composite outcome, which remained significant after adjusting for FRS, and persisted even after further adjustment for cPB or CAC (Table 3). Similarly, hs-CRP was independently associated with the composite outcome. Figures S1–S2 show the shape of the association between each biomarker and the composite outcome. Interestingly, we found a stronger association between haptoglobin and the composite event in men, with significant interaction by sex, compared with women. This pattern was not observed for IgA2 or hs-CRP (Figure S2).

To evaluate the incremental predictive performance of haptoglobin and IgA2, we first evaluated the performance of the reference model including the FRS only (Model 1), which yielded a C statistic of 0.621 (95% CI, 0.596–0.647) for the composite outcome (Table 4). The addition of cPB (Model 2) or CAC (Model 3) improved prognostic discrimination, with C statistics of 0.669 (95% CI, 0.645–0.693) and 0.667 (95% CI, 0.642–0.692), respectively. Similar results were observed when biomarkers were analyzed using median cutoff values (Table S2).

When added individually to Model 1, haptoglobin, IgA2, and hs-CRP each reached statistical significance by likelihood ratio test ($P < 0.001$, $P = 0.005$, and $P < 0.001$, respectively) and improved continuous net reclassification improvement (0.300, 0.232, and 0.108,

respectively), with positive integrated discrimination improvement for haptoglobin and hs-CRP. However, improvements in the C statistic were small (ΔC : +0.007, +0.002, and +0.008, respectively), indicating limited incremental discriminative value individually (Table 4). Similar patterns were observed when biomarkers were added to Model 2 and Model 3, or when biomarkers were analyzed using median cutoff values (Table S2).

The combined addition of all 3 biomarkers produced the most consistent improvement across metrics. Beyond Model 1, the combination yielded a ΔC of +0.017 (95% CI, 0.001–0.033), continuous net reclassification improvement of 0.283 (95% CI, 0.155–0.411), integrated discrimination improvement of 0.011 (95% CI, 0.003–0.019), and reductions in both Akaike information criterion (7625.9 versus 7649.3) and integrated Brier score (Δ integrated Brier score of -0.0004). Comparable incremental improvements were observed beyond Model 2 (ΔC +0.013; 95% CI, 0.002–0.023) and Model 3 (ΔC +0.013; 95% CI, 0.002–0.025) (Table 4). All models demonstrated good calibration (Figure S3).

DISCUSSION

In this study, we demonstrate that the previously reported association of haptoglobin and IgA2 with subclinical atherosclerosis in European cohorts is replicated in asymptomatic American adults from the BiImage Study cohort. More importantly, we show that haptoglobin and IgA2 are also independently associated with MACEs and all-cause mortality, beyond FRS. The cumulative incidence of the composite outcome was approximately 2-fold higher in individuals with high levels of both biomarkers compared with those with low levels.

Despite substantial progress in cardiovascular care, a major challenge remains in identifying individuals with early-stage atherosclerotic disease, detectable by imaging modalities but still clinically silent.²³ This is particularly relevant given the high prevalence of subclinical atherosclerosis among apparently healthy individuals,^{4,24} and its well-established prognostic implications. We previously demonstrated in the BiImage Study cohort, that cPB and CAC, as imaging biomarkers of atherosclerosis, improve cardiovascular risk prediction beyond traditional cardiovascular risk factors.⁸ More recently, we demonstrated that these imaging markers were also independently associated with all-cause mortality.²⁵

Vascular inflammation, detectable with advanced imaging techniques,¹⁰ plays a key role in early manifestation of atherosclerosis. However, imaging is not universally available and is not routinely used in screening programs due to cost-effectiveness concerns. In contrast, circulating biomarkers may provide a more accessible and scalable approach to risk

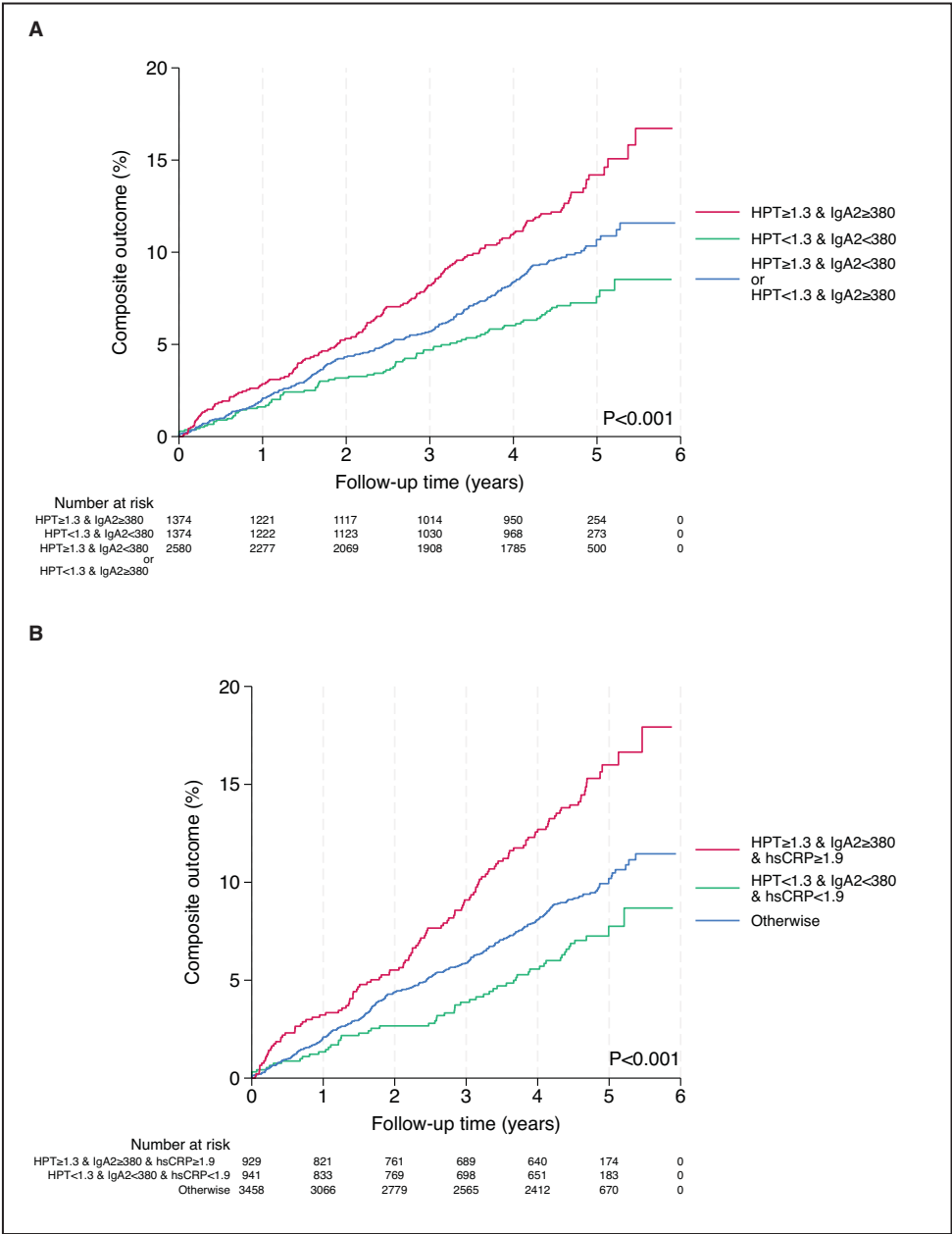


Figure 2. Cumulative incidence analyses.

A, Cumulative incidence of the composite outcome of all-cause death, myocardial infarct, stroke, and revascularization at follow-up by HPT and IgA2. **B**, Cumulative incidence of the composite outcome of all-cause death, myocardial infarct, stroke, and revascularization at follow-up by HPT, IgA2, and hs-CRP. Otherwise include all combinations out of the combinations of the 3 biomarkers either for the lowest or the highest values. HPT, haptoglobin; hs-CRP, high-sensitivity C-reactive protein; and IgA2, immunoglobulin A2.

assessment. Previously, in a proteomic analysis of the PESA (Progression of Early Subclinical Atherosclerosis) cohort, we identified haptoglobin and IgA2, along with Lp(a), as proteins independently associated with subclinical atherosclerosis. These findings were later validated in the ILERVAS (Assessing the Prevalence of Subclinical Vascular Disease and Hidden Kidney

Disease) cohort using immunoturbidimetry.¹⁷ In the present study, we focused on haptoglobin and IgA2 due to their potential role in immunomodulatory pathways relevant to early atherogenesis and their stronger performance in previous cohorts. We confirmed the association of haptoglobin and IgA2 with plaque burden and CAC, whereas hs-CRP was not associated. In this

Table 3. Unadjusted and Adjusted Associations Between the Composite Outcome and cPB, CAC, Haptoglobin, IgA2, and hs-CRP

	Unadjusted		Adjusted HR*		Adjusted HR†		Adjusted HR‡	
	P-overall value	P-nonlinearity value	P-overall value	P-nonlinearity value	P-overall value	P-nonlinearity value	P-overall value	P-nonlinearity value
cPB (RCS)	<0.001	<0.001	<0.001	<0.001	...	...	...	...
CAC (RCS)	<0.001	<0.001	<0.001	<0.001	...	...	...	...
Haptoglobin (RCS)	<0.001	0.009	<0.001	0.023	<0.001	0.020	<0.001	0.014
IgA2 (linear)	<0.001	...	0.004	...	0.034	...	0.022	...
hs-CRP (RCS)	<0.001	0.001	<0.001	0.001	<0.001	0.002	<0.001	<0.001

All exposures are modeled with RCS (4 knots at the fifth, 35th, 65th, and 95th percentiles) except IgA2, which showed no evidence of nonlinearity and was modeled as a linear term. *P*-overall: Wald test for the joint significance of all spline terms (or the linear term for IgA2). *P*-nonlinearity: Wald test for the joint significance of the nonlinear spline terms. The shape of each association is shown in Figure S3. CAC indicates coronary artery calcium; cPB, carotid plaque burden; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; IgA2, immunoglobulin A2; and RCS, restricted cubic splines.

*Adjusted for Framingham Risk Score.

†Adjusted for cPB and Framingham Risk Score.

‡Adjusted for CAC and Framingham Risk Score.

respect, the role of hs-CRP as part of the causal pathway between inflammation and cardiovascular disease is not fully established.¹⁵ Our findings in the BioImage Study cohort reinforce the idea that haptoglobin and IgA2 could be clinically useful, cost-effective tools, particularly for primary prevention in settings without access to imaging technologies.

The identification of biomarkers predictive of cardiovascular events remains a key research priority. Although low-density lipoprotein cholesterol and hs-CRP are well-established,^{26,27} they do not fully capture the multifactorial nature of atherosclerosis. Several polymorphisms in the haptoglobin gene have been associated with cardiovascular risk^{28–30} and elevated haptoglobin levels (either alone or in combination with other inflammatory markers such as hs-CRP or leukocyte count) have been linked to cardiovascular events.^{31,32} Haptoglobin is an acute-phase protein induced primarily by interleukin-6, supporting its role in systemic inflammation.³³ Nevertheless, we cannot rule out that additional noninflammatory functions of haptoglobin may contribute to the observed associations.³⁴ Interestingly, in exploratory analyses we observed a stronger association between haptoglobin and the composite outcome in men than in women; however, this finding should be interpreted with caution given the limited number of events among women.

In regard to IgA2, this is the first study to report its association with MACEs and all-cause mortality. Previous studies have linked total IgA plasma levels with severe atherosclerosis and increased cardiovascular risk.^{35,36} IgA autoantibodies, such as anti-phosphocholine, anti-streptococcus pneumoniae, and anti-phospholipid antibodies, have also been implicated in cardiovascular disease.^{37,38} Although IgA has traditionally been viewed as protective at mucosal surfaces, emerging evidence suggests a more nuanced role, with certain IgA isotypes promoting inflammation.^{39,40–42} Notably, IgA2 has been

shown to have a more proinflammatory profile compared with IgA1.⁴³ Moreover, increased plasma levels of IgA2, but not IgA1, have been observed in individuals with subclinical atherosclerosis.¹⁷ In a recent study, we also demonstrated an association between plasma IgA2, but not IgA1, and the presence of abdominal aortic aneurysm, further supporting the potential value of IgA2 measurement.⁴⁴ Given that ~90% of circulating IgA is IgA1, the specific contribution of IgA2 may have been previously underestimated. This highlights the importance of dissecting IgA subclasses when evaluating their role as biomarkers of cardiovascular disease.

Traditional risk scores are useful at the population level but have limited precision in individual risk prediction.⁴⁵ They often misestimate risk across different ethnicities, socioeconomic strata, and comorbidities such as chronic inflammation. Recent proteomic studies have shown that panels comprising tens to hundreds of proteins can modestly improve prediction of MACEs when added to existing scores.^{46,47} Similarly, we found that combination of haptoglobin, IgA2, and hs-CRP modestly but significantly enhance predictive accuracy, even beyond imaging. Importantly, haptoglobin and IgA2, as well as hs-CRP, can be measured using low-cost, clinically validated assays already in use in hospital laboratories. As such, they represent candidates for implementation in primary care settings. The latest European Society of Cardiology guidelines for cardiovascular prevention advocate for improved risk prediction strategies, including quantification of residual risk due to inflammation.⁴⁸ Our findings suggest that haptoglobin and IgA2, along with hs-CRP, could serve as accessible biomarkers of residual immune-inflammatory risk, potentially guiding personalized preventive therapies.¹³

Several limitations should be acknowledged. First, reliance on health insurance claims to identify

Table 4. Comparison of the Performance of Different Models Including Haptoglobin, IgA2, or hs-CRP, or Their Combinations (3 Biomarkers) in Continuous Form to Predict the Composite Outcome With Reference Model 1 (FRS)

Model	C statistic (95% CI)	ΔC	Cat-NRI (95% CI)	Cont-NRI (95% CI)	IDI (95% CI)	AIC	LRT χ^2 , P value	IBS	ΔIBS
Model 1									
FRS alone (reference)	0.621 (0.596 to 0.647)	...	...	...	...	7649.3	...	0.0486	...
FRS+Haptoglobin (RCS)	0.629 (0.603 to 0.655)	+0.007 (−0.006 to 0.021)	0.015 (−0.055 to 0.084)	0.300 (0.173 to 0.427)	0.008 (0.001 to 0.015)	7631.5	23.9, $P \leq 0.001$	0.0484	−0.0003
FRS+IgA2 (linear)	0.623 (0.598 to 0.649)	+0.002 (−0.005 to 0.009)	−0.011 (−0.057 to 0.035)	0.108 (0.004 to 0.212)	0.002 (−0.001 to 0.005)	7643.3	8.0, $P = 0.005$	0.0486	−0.0001
FRS+hs-CRP (RCS)	0.629 (0.603 to 0.655)	+0.008 (−0.004 to 0.020)	0.029 (−0.038 to 0.096)	0.232 (0.120 to 0.343)	0.005 (0.000 to 0.010)	7637.4	17.9, $P \leq 0.001$	0.0485	−0.0002
FRS+Haptoglobin (RCS)+IgA2 (linear)	0.633 (0.606 to 0.659)	+0.011 (−0.003 to 0.026)	0.034 (−0.040 to 0.108)	0.265 (0.135 to 0.396)	0.009 (0.002 to 0.017)	7627.1	30.2, $P \leq 0.001$	0.0483	−0.0003
FRS+all 3 biomarkers	0.638 (0.613 to 0.664)	+0.017 (0.001 to 0.033)	0.054 (−0.029 to 0.138)	0.283 (0.155 to 0.411)	0.011 (0.003 to 0.019)	7625.9	37.4, $P \leq 0.001$	0.0483	−0.0004
Model 2									
FRS+cPB (RCS) (reference)	0.669 (0.645 to 0.693)	...	...	...	...	7575.2	...	0.0478	...
FRS+cPB (RCS)+Haptoglobin (RCS)	0.676 (0.652 to 0.701)	+0.007 (−0.001 to 0.015)	0.053 (−0.004 to 0.111)	0.246 (0.108 to 0.384)	0.006 (−0.000 to 0.013)	7562.1	19.1, $P \leq 0.001$	0.0476	−0.0002
FRS+cPB (RCS)+IgA2 (linear)	0.671 (0.647 to 0.695)	+0.002 (−0.003 to 0.006)	−0.001 (−0.041 to 0.038)	0.138 (0.022 to 0.254)	0.001 (−0.002 to 0.004)	7572.8	4.4, $P = 0.036$	0.0478	−0.0000
FRS+cPB (RCS)+hs-CRP (RCS)	0.676 (0.652 to 0.701)	+0.007 (−0.001 to 0.016)	0.039 (−0.025 to 0.102)	0.230 (0.118 to 0.342)	0.006 (0.000 to 0.011)	7564.1	17.1, $P \leq 0.001$	0.0476	−0.0002
FRS+cPB (RCS)+Haptoglobin (RCS)+IgA2 (linear)	0.678 (0.653 to 0.702)	+0.009 (−0.000 to 0.017)	0.042 (−0.019 to 0.103)	0.213 (0.076 to 0.349)	0.007 (0.000 to 0.014)	7560.8	22.4, $P \leq 0.001$	0.0476	−0.0002
FRS+cPB (RCS)+all 3 biomarkers	0.682 (0.657 to 0.706)	+0.013 (0.002 to 0.023)	0.035 (−0.030 to 0.100)	0.288 (0.156 to 0.420)	0.010 (0.002 to 0.017)	7558.3	30.9, $P \leq 0.001$	0.0475	−0.0003
Model 3									
FRS+CAC (RCS) (reference)	0.667 (0.642 to 0.692)	...	...	...	...	7303.5	...	0.0474	...
FRS+CAC (RCS)+Haptoglobin (RCS)	0.673 (0.648 to 0.698)	+0.006 (−0.003 to 0.015)	0.029 (−0.026 to 0.084)	0.219 (0.077 to 0.360)	0.006 (−0.001 to 0.012)	7292.1	17.5, $P \leq 0.001$	0.0472	−0.0002
FRS+CAC (RCS)+IgA2 (linear)	0.668 (0.643 to 0.693)	+0.001 (−0.003 to 0.005)	−0.025 (−0.066 to 0.015)	0.078 (−0.030 to 0.186)	0.001 (−0.002 to 0.004)	7300.5	5.1, $P = 0.024$	0.0474	−0.0000
FRS+CAC (RCS)+hs-CRP (RCS)	0.675 (0.650 to 0.700)	+0.008 (−0.001 to 0.017)	0.021 (−0.035 to 0.077)	0.227 (0.111 to 0.343)	0.008 (0.001 to 0.014)	7287.6	22.0, $P \leq 0.001$	0.0472	−0.0002
FRS+CAC (RCS)+Haptoglobin (RCS)+IgA2 (linear)	0.675 (0.650 to 0.700)	+0.008 (−0.002 to 0.017)	0.043 (−0.013 to 0.099)	0.172 (0.032 to 0.312)	0.006 (−0.000 to 0.013)	7290.1	21.4, $P \leq 0.001$	0.0472	−0.0002
FRS+CAC (RCS)+all 3 biomarkers	0.680 (0.656 to 0.705)	+0.013 (0.002 to 0.025)	0.034 (−0.027 to 0.094)	0.280 (0.145 to 0.415)	0.011 (0.003 to 0.018)	7283.5	34.0, $P \leq 0.001$	0.0471	−0.0003

The C statistic=Harrell C. NRI measures the proportion of individuals correctly reclassified into higher or lower risk categories, ranging from −2 to +2, with positive values favoring the new model. Cat-NRI risk categories: 7.5%, 7.5% to 20%, >20% at 5.0 years. IDI quantifies the improvement in separating cases from noncases, ranging from 0 to 1, with larger values indicating better discrimination. LRT vs FRS-alone reference. IBS over 0–5.0 with inverse-probability-of-censoring weighting, a measure of calibration and discrimination combined (lower is better); computed on a 50-point grid by trapezoidal integration. ΔIBS negative values indicate improvement. $\Delta C/NRI/IDI$ 95% CIs from 500 bootstrap replications, holding model predictions fixed. ΔC indicates improvement in C statistic vs FRS-alone reference; $\Delta IBS=IBS_{\text{model}}-IBS_{\text{FRS}}$; AIC, Akaike information criterion; CAC, coronary artery calcium; Cat-NRI, NRI risk categories; Cont-NRI, continuous risk categories; cPB, carotid plaque burden; FRS, Framingham Risk Score; hs-CRP, high-sensitivity C-reactive protein; IBS, integrated Brier score; IDI, integrated discrimination improvement; IgA2, immunoglobulin A2; LRT, likelihood ratio test; NRI, net reclassification improvement; and RCS, restricted cubic splines.

adverse events may have resulted in underascertainment. Although source documents were reviewed and events were adjudicated, some might have been missed, which would have likely biased results toward the null. Second, the follow-up period (~4 years) is relatively short compared with other primary prevention studies. Despite this, the incidence

of adverse events was enough to draw significant conclusions using the composite index as outcome measure, but power was limited to assess the individual components of MACEs. Third, the BioImage Study cohort was predominantly White and older than typical primary prevention populations, potentially limiting generalizability. Last, imaging was

performed more than a decade ago, and assessment of subclinical peripheral atherosclerosis was restricted to the carotid arteries, whereas more recent evidence suggests that femoral plaques may be more prevalent and informative in early disease. Similarly, coronary assessment relied on noncontrast computed tomography, precluding evaluation of associations between haptoglobin/IgA2 with noncalcified coronary plaque.

ARTICLE INFORMATION

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Affiliations

Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain (A.G.-Á., V.F., E.N., R.O., V.M., I.G.-L., A.Q., J.J.F., A.D., C.N.P.-G., V.A., J.V., B.I.); Cardiology Department, Hospital Clínic Barcelona and August Pi i Sunyer Biomedical Research Institute, Barcelona, Spain (A.G.-Á.); Universitat de Barcelona, Barcelona, Spain (A.G.-Á.); CIBER de Enfermedades Cardiovasculares (CIBERCv), Madrid, Spain (A.G.-Á., E.N., I.G.-L., J.J.F., A.D., V.A., L.M.B.-C., J.V., B.I., J.L.M.-V.); Mount Sinai Fuster Heart Hospital, New York, New York (V.F., B.I.); Instituto de Investigación Sanitaria-Fundación Jiménez-Díaz- Autónoma University of Madrid (IIS-FJD, UAM), Madrid, Spain (L.O.-V., L.M.B.-C., J.L.M.-V.); Cardiology Department, University Hospital La Moraleja, Madrid, Spain (I.G.-L.); Hospital Universitario La Luz, Madrid, Spain (A.D.); Philips Healthcare, Madrid, Spain (J.S.-G.); and SQ Innovation, Burlington, Massachusetts (P.M.).

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Disclosures

Dr Sánchez-González is a Philips employee. Dr Muntendam is Chief Executive Officer of SQ Innovation. Philips and SQ Innovation had no role in the present study. All other authors declare no conflicts of interest.

Supplemental Material

Tables S1–S2
Figures S1–S3
Data S1

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