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RESEARCH ARTICLE

Highly-Sensitive Cardiac Troponin-I and Beta-2-Glycoprotein-I IgA Antibodies May Guide Atherosclerosis Screening and Surveillance in Rheumatoid Arthritis

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ABSTRACT

Objectives. Subclinical coronary atherosclerosis screening independently predicts cardiovascular risk in rheumatoid arthritis. Yet, it is unclear if or when to recommend it and whether it should be repeated. We explored whether cardiovascular risk biomarkers like highly-sensitive cardiac troponin-I (hs-cTnI), anti-Beta-2-Glycoprotein-I (anti-β2GPI) IgA antibodies, or their combination may inform the recommendation of a screening and surveillance assessment.

Methods. The sample included 144 patients with complete biomarker data who underwent plaque evaluation with coronary computed tomography angiography; 95 were re-imaged within 6.9±0.3 years. Presence of >5 segments with plaque or coronary artery calcium >100 constituted extensive disease; lesions rendering >50% stenosis were considered obstructive. The Framingham 2008 cardiovascular risk score was included in all models.

Results. Hs-cTnI added to the cardiovascular risk score increased area-under-the curve (AUC) from 0.710 to 0.729 and improved prediction accuracy for baseline plaque presence [Net Reclassification Improvement =0.538 (95% confidence interval 0.143-0.895)] and Integrated Discrimination Improvement (IDI) =0.035 (0.001-0.128). In contrast, a-b2GPI-IgA did not, and the combination offered no added benefit over hs-cTnI alone. While hs-cTnI alone did not predict plaque progression, a-b2GPI-IgA presence did (p=0.005), especially in patients with >median hs-cTnI (p=0.015). In patients with >median hs-cTnI, adding a-b2GPI-IgA to a cardiovascular risk score model predicting progression from non-extensive/non-obstructive to extensive/obstructive plaque increased AUC from 0.796 to 0.878 and improved model precision [IDI=0.277 (0.011-0.946)].

Conclusion. High hs-cTnI significantly improved prediction of baseline plaque presence and may trigger an initial non-invasive coronary atherosclerosis evaluation. A-b2GPI-IgA presence may justify a follow-up interrogation in patients with non-extensive, non-obstructive plaque at baseline.

Keywords: Rheumatoid arthritis, cardiovascular disease, coronary plaque, atherosclerosis progression, computed tomography, highly-sensitive cardiac troponin-I, anti-beta-2-Glycoprotein-I IgA antibodies

Introduction

Patients with rheumatoid arthritis (RA) experience higher cardiovascular risk compared to the general population.[1] Standard risk calculators used in clinical practice underperform in RA.[2,3] Attempts at their adaptation or generation of RA-specific risk estimators have similarly failed to improve risk prediction.[2,3] Greater atherosclerosis burden and plaque vulnerability was shown on non-invasive coronary computed tomography angiography (CCTA) in patients with RA compared to ones without autoimmune disease[4] and predicted both mid and long-term cardiovascular events beyond traditional risk factors, inflammation and immunomodulatory treatments.[5–7] In the absence of coronary atherosclerosis, no patients suffered ischemic events at five years; in contrast, 45% of patients with extensive or obstructive plaque and 3-4% of those with non-extensive and non-obstructive disease suffered events over the same period.[5] CCTA imaging has been reliably used to monitor atherosclerosis progression in general patients,[8] and CCTA-based initiation of preventive therapies improved cardiovascular outcomes in large prospective trials.[9–11] On the other hand, various serum candidate biomarkers are rigorously tested for their ability to optimize risk prediction. Highly-sensitive cardiac troponin-I (hs-cTnI) is a structural cardiac biomarker associated with coronary atherosclerosis burden, plaque vulnerability and midterm cardiovascular events in RA.[6] Likewise, IgA antibodies against beta-2 glycoprotein-1 (anti-b2GPI IgA)—an apolipoprotein avidly expressed in atherosclerotic lesions—predicted coronary plaque progression and vulnerability over time and influenced the effect of inflammation on cardiovascular risk in RA.[12]

It is currently unknown if and/or when to recommend a screening coronary atherosclerosis evaluation with CCTA in RA patients without symptoms or history of cardiovascular disease. It is also unknown whether, when and under what circumstances should a follow-up assessment be repeated in the future. The utility and implementation of sensitive biomarkers to guide the decision on screening and serial coronary imaging may streamline and operationalize successful and cost-effective cardiovascular risk stratification and prevention strategies. The present study had two specific aims; first, to explore whether hs-cTnI or anti-b2GPI IgA alone or in combination can improve the prediction of any coronary plaque presence on a screening CCTA. Second, to evaluate whether either biomarker or their combination can predict progression from non-extensive and non-obstructive atherosclerosis to extensive or obstructive disease on a follow-up evaluation.

MATERIALS AND METHODS

Patient recruitment

One hundred-fifty patients enrolled in the the *PR*O*spec*T*ive* *E*valuation of Latent Coronary A*t*herosclerosis in *R*heumatoid *A*rthritis [PROTECT RA] observational cohort underwent baseline atherosclerosis evaluation with CCTA between March 2010 and March 2011. One hundred one received follow-up imaging for plaque progression 6.9±0.3 years later. Participants were between the ages of 18 and 75, satisfied 2010 classification criteria for RA and reported no history of diagnosed cardiovascular disease such as angina, myocardial infarction, stroke, transient ischemic attack, claudication, revascularization, or heart failure. Patients reporting concurrent systemic autoimmune disease (other than Sjogren's syndrome), malignancy within 5 years, active or chronic infections, weight exceeding 147.7 kg, glomerular filtration rate <60 mL/min, or allergy to iodine were excluded. Likewise, patients with a prior diagnosis of antiphospholipid syndrome based on history of arterial or venous thrombotic event, pregnancy loss or preeclampsia and positive antiphospholipid antibodies confirmed 12 weeks apart were also excluded.[13] The study was approved by the local Institutional Review Board and all patients signed informed consent according to the Declaration of Helsinki.

Multi-Detector Coronary Computed Tomography Angiography (CCTA)

Baseline assessments were performed with a 64-multidetector row scanner between March 2010 and March 2011; follow-up evaluations were completed in a 256-multidetector row scanner between March 2017 and March 2018. Detailed protocols for image acquisition and processing and scoring reproducibility have been previously reported.[14,15] Coronary calcium score (CAC) was measured according to Agatston.[16] Coronary atherosclerosis was evaluated on contrast-enhanced scans employing a standardized 17-segment model from the American Heart Association.[15] Images from both baseline and follow-up studies were read at the same time and in random order by a single, experienced and blinded interpreter (MJB).[14] For longitudinal comparisons, coronary segments in both sets of studies were coaligned using fiducial points and evaluated side-by side. Segment involvement score described the total number of segments with plaque per patient (0-17). Plaque composition was

reported as noncalcified, partially and fully calcified as previously described.[17] Lesions conferring >50% luminal stenosis were considered obstructive. Extensive atherosclerotic disease was the composite of >5 segments with plaque or CAC>100. Both obstructive and extensive disease associated with significantly higher cardiovascular risk.[6,18]

Laboratory evaluations

Comprehensive metabolic panel, complete blood counts, c-reactive protein (CRP), erythrocyte sedimentation rate (ESR) were completed on the day of both CCTA assessments, and every scheduled clinic visit in between. Lipids were measured on the days of both scans and according to EULAR recommendations for cardiovascular risk stratification in the interim.[11] Serum for biomarker studies was also collected on the day of both CCTA assessments and aliquots frozen to -80^{0}C until processing.

Hs-cTnI was measured with a micro-particle immunoassay and single-molecule counting at Singulex Inc. (Alameda, CA) by technicians blinded to patient information.[4]

Antiphospholipid antibody testing

Lupus anticoagulant was assessed with a lupus-sensitive activated partial thromboplastin time (aPTT-LA) and a diluted Russell's viper venom time (dRVVT) as screening tests. Any positive aPTT-LA screen (>40sec) was subsequently confirmed with a hexagonal phase phospholipid test and any positive dRVVT (>45 sec) with a dRVVT confirmatory test. All tests were performed at Quest Diagnostics, Nichols Institute, San Juan Capistrano, CA by technicians blinded to clinical data and reported per manufacturer's specifications for positivity. Likewise, anticardiolipin and anti-β2GPI antibody isotypes (IgG, IgM, IgA) were measured with commercially available Elisa kits (Varelisa, Pharmacia Diagnostics, Freiburg, Germany) at Quest Diagnostics, Nichols Institute. Anticardiolipin IgG, IgM and IgA were considered positive if >40U/ml, >40U/ml and >20U/ml respectively. Anti- β 2GPI IgG, IgM and IgA were considered positive if >20U/ml, >15U/ml and >15U/ml respectively. Positive tests at baseline screen were rerun 12 weeks later and if confirmed, they were considered true positive.[13]

Definitions of covariates and outcomes

Ten-year cardiovascular risk was estimated at baseline by the Framingham 2008 modified general cardiovascular risk score (FRS-CVD).[19] Waist-to-height ratio was computed as an index of abdominal obesity.[20] Disease activity based on a 28-joint exam for tenderness, swelling and CRP (DAS28-CRP) was calculated on both study dates and all scheduled clinic visits (every three to four months) in between. Medication use and doses for conventional synthetic disease modifying anti-rheumatic drugs (DMARDs), biologic DMARDs, prednisone, and statins were recorded and reconciled with pharmacy prescriptions on each clinic visit.

Presence of any coronary plaque at screening (segment involvement score >0) was the first outcome of interest. Transition from non-extensive and non-obstructive atherosclerosis at baseline to extensive or obstructive disease at follow-up was the second outcome of interest.

Statistical analysis

Categorical variables were expressed as frequencies and percentages and continuous variables as means and standard deviations. Robust binary logistic regression was used to assess dichotomous outcomes including plaque presence, non-extensive non-obstructive and extensive or obstructive plaque at baseline and incident extensive or obstructive plaque at follow-up. All models adjusted for FRS-CVD. The incremental predictive value of Hs-cTnI, anti- β2GPI IgA or both beyond FRS-CVD was assessed with area under the receiver operating curve (AUC), net reclassification improvement (NRI) and integrated discrimination improvement (IDI) analyses. Incremental AUCs were calculated from consecutive logistic regression models predicting any plaque presence at baseline and progression from non-extensive non-obstructive to extensive or obstructive disease at follow-up, to compare the AUC based on the models without and with Hs-cTnI and/or anti- β2GPI IgA. The continuous NRI and continuous IDI were calculated from adjusted models for the binarized outcomes of plaque presence at baseline and new extensive or obstructive plaque at follow-up. Incremental predictive analyses were performed using the Stata incrisk module with 10-fold cross-validation and standard errors and 95% confidence intervals (CIs) using 1000 bootstrap samples. Analyses were performed using SPSS 26.0 and Stata 15.0. P values < 0.05 were considered significant.

RESULTS

The sample included 144 participants with complete biomarker data. They were largely middle-aged females with long-term, seropositive, erosive, and well-controlled disease (Table 1). All received an average of two conventional synthetic DMARDs and 87 of 144 (60.4%) were also on biologic DMARDs (all tumor necrosis factor inhibitors) at baseline.

Median Hs-cTnI was higher in patients with atherosclerosis [1.8 (IQR 1.1-2.6) pg/ml] compared to those without [1.3 (IQR 0.9-1.8) pg/ml, p=0.009]. Patients with high Hs-cTnI (>median of 1.5 pg/ml) were older, had a higher waist-to-height ratio, longer disease duration, more erosions and higher FRS-CVD compared to those with low Hs-cTnI. Likewise, they had greater plaque presence, burden, and CAC score versus those with low Hs-cTnI (Table 1). Forty-six patients (31.9%) had positive anti-β2GPI IgA antibodies at baseline confirmed 12 weeks later. All other subclasses of antiphospholipid antibodies were uncommon (<4%, Supplementary Table S1). One hundred two (70.8%) patients had coronary atherosclerosis and 28 (19.4%) had extensive or obstructive disease at baseline. In contrast, cardiac risk score was high (FRS-CVD>20) in 11 (7.6%).

Table 1 Patient Demographics

	cTnI ≤ 1.5 pg/ml (n=70)	**cTnI > 1.5 pg/ml (n=74)**	**P-value**
Demographics			
Age (years)	49.03 ± 10.24	57.02 ± 9.45	<0.001
Female	61 (87.1%)	64 (86.5%)	
b2GPI-IgA positive	15 (21.4%)	31 (41.9%)	0.008
RA-associated parameters			
RA duration	9.11 ± 7.10	11.80 ± 8.08	0.036
RF positive	60 (85.7%)	64 (86.5%)	
ACPA positive	58 (82.9%)	64 (86.5%)	
Erosions	39 (55.7%)	55 (74.3%)	0.019
CRP (mg/dL), median (IQR)	4.0 (1.8, 9.3)	4.4 (2.0, 12.8)	0.042
Tender joint counts	1.16 ± 1.89	2.07 ± 4.45	
Swollen joint counts	1.74 ± 2.47	1.64 ± 2.71	
DAS28 CRP	2.50 ± 0.89	2.66 ± 1.17	
Cardiac risk factors			
Hypertension	28 (40.0%)	43 (58.1%)	0.030
Cholesterol (mg/dL)	170.49 ± 34.62	170.62 ± 34.50	
LDL-c (mg/dL)	96.66 ± 25.75	95.80 ± 29.06	
HDL-c (mg/dL)	51.00 ± 14.47	51.84 ± 14.04	
Diabetes	10 (14.3%)	15 (20.3%)	
Current smoking	4 (5.7%)	8 (10.8%)	
Waist-to-height ratio	0.58 ± 0.08	0.62 ± 0.07	0.004
FRS-CVD	7.08 ± 7.44	10.23 ± 7.64	0.013
Medications			
Prednisone	25 (35.7%)	27 (36.5%)	
N-conc csDMARDs	1.80 ± 0.73	2.19 ± 0.85	0.004
bDMARD	45 (64.3%)	42 (56.8%)	
Statins	25 (35.7%)	32 (43.2%)	
Atherosclerosis burden			
Any plaque (SIS>0)	41 (58.6%)	61 (82.4%)	0.002
SIS total	1.54 ± 2.24	2.49 ± 2.28	0.013
CAC>0	16 (22.9%)	38 (51.4%)	<0.001
CAC score, median (IQR)	0 (0, 0)	2.50 (0, 75)	<0.001

Values are n (%) or mean ± standard deviation unless indicated otherwise.
Hs-cTnI: Highly-sensitive cardiac troponin-I, anti-b2GPI-IgA: Anti-Beta-2-Glycoprotein-I IgA antibodies, RA: Rheumatoid arthritis, RF: Rheumatoid factor, ACPA: Anti-cyclic citrullinated peptide antibodies, CRP: C-reactive protein, DAS28-CRP: Disease Activity Score in 28 joints CRP, HDL-c: High density lipoprotein, LDL-c: Low-density lipoprotein, FRS-CVD: Framingham 2008 modified cardiovascular risk score, csDMARDs: Conventional synthetic DMARDs, bDMARD: Biologic disease modifying anti-rheumatic drug, SIS: Segment involvement score, CAC: Coronary artery calcium.

Hs-cTnI improves prediction of coronary atherosclerosis presence at baseline

Sixty-one (82.4%) patients with high hs-cTnI had atherosclerosis compared to 41 (58.6%) with low hs-cTnI (Figure 1A, Pearson X^2=9.91, p=0.002). Patients with high hs-cTnI had a 2.3 times higher likelihood of having coronary plaque at screening after adjusting for FRS-CVD [odds ratio OR (95% confidence interval CI) 2.30 (1.15-6.07), p=0.022]. Additionally, 23 (31%) patients with high hs-cTnI had extensive or obstructive disease compared to five (7.1%) of those with low hs-cTnI (Figure 1B, Pearson X^2=13.16, p<0.001). High hs-cTnI associated with 5.6 times higher likelihood of extensive or obstructive disease at baseline after adjusting for FRS-CVD [OR 5.63 (95% CI 1.77-17.8), p=0.003]. In contrast, no difference in atherosclerosis presence at baseline was seen between anti-β2GPI IgA positive and negative patients (67.4% vs. 72.5% respectively, Figure 1A).

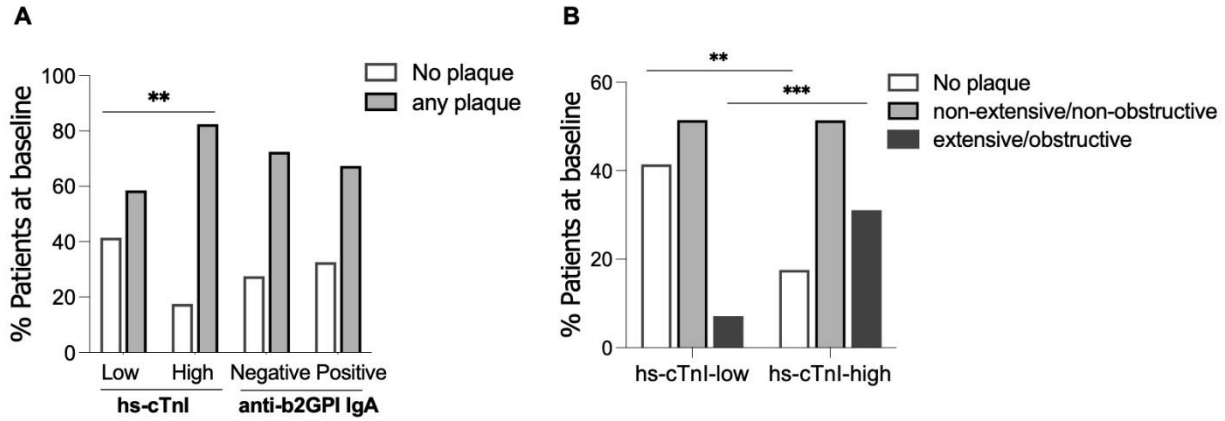

Figure 1. Association of Hs-cTnI and anti-β2GPI IgA status with atherosclerosis presence at baseline. A. Greater plaque presence in patients with high vs. low hs-cTnI. No difference in baseline atherosclerosis presence is observed between patients with and without anti-β2GPI IgA antibodies. B. Greater prevalence of extensive or obstructive plaque at screening in patients with high vs. low hs-cTnI. Comparisons made with Pearson's X^2 test. Hs-cTnI: highly sensitive cardiac troponin I, anti-b2GPI IgA: IgA antibodies against beta 2 glycoprotein 1
**p<0.01, ***p<0.001

In incremental AUC analysis the addition of high hs-cTnI to a base model of FRS-CVD increased prognostic accuracy (from 0.710 to 0.729, p=0.465, Figure 2). In contrast, the addition of anti-b2GPI IgA status to a base model of FRS-CVD did not increase prognostic accuracy (from 0.710 to 0.714, p=0.617). Likewise, the addition of anti-b2GPI IgA status to a base model of FRS-CVD and Hs-cTnI, did not improve prognostic accuracy over the base model (from 0.729 to 0.737, p=0.461). Since the AUC change in response to inclusion of a novel predictor in a model is generally sensitive only to very large independent effects of that predictor, we further calculated the NRI and IDI to explore additional discrimination rendered by the inclusion of hs-cTnI towards baseline plaque prediction. Indeed, addition of hs-cTnI to the clinical risk score improved the precision of plaque prediction vs. the FRS-CVD alone [(NRI) =0.538 (95% CI 0.143-0.895) and IDI 0.035 (95% CI 0.001 to 0.128), p=0.040]. Notably, addition of hs-cTnI to the clinical risk score improved the precision of extensive or obstructive plaque prediction at baseline vs. the FRS-CVD alone [(NRI) =0.764 (95% CI 0.387-1.097) and IDI 0.066 (95% CI 0.008 to 0.186), p=0.007]. In contrast, no difference in precision of baseline plaque prediction was observed by addition of anti-b2GPI IgA status to either a base model with FRS-CVD alone [NRI 0.106 (95% CI -0.060 to 0.477) and IDI 0.001 (-0.001 to 0.042), p=0.678], or one with FRS-CVD and Hs-cTnI [NRI 0.115 (95% CI -0.149 to 0.478) and IDI 0.005 (-0.001 to 0.058), p=0.440 respectively].

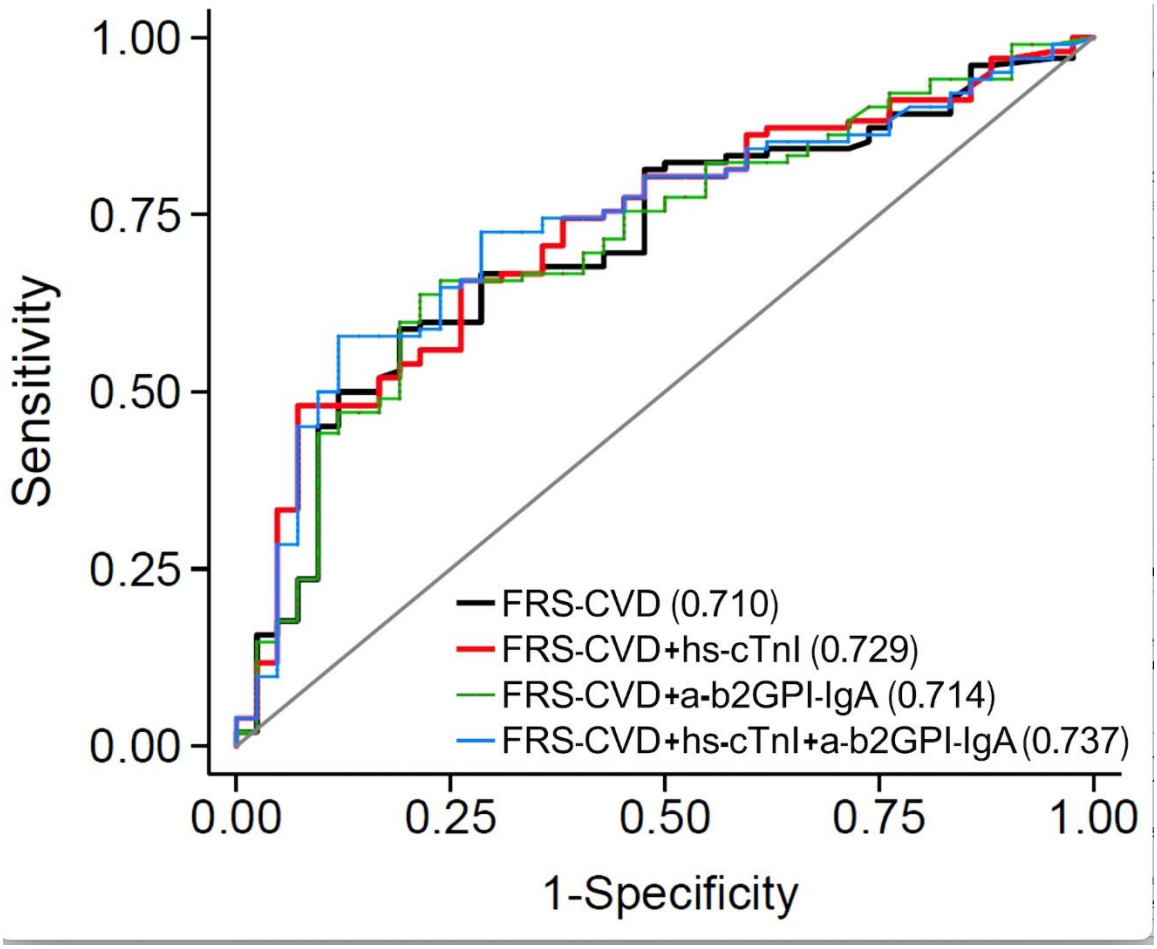

Figure 2. AUC assessments of improvement in prognostic accuracy of atherosclerosis presence at baseline by addition of hs-cTnI or anti-β2GPI IgA information or both to a base model including the Framingham D'Agostino 2008 (FRS-CVD) clinical risk score. AUCs compared with the De Long method. Hs-cTnI: highly sensitive cardiac troponin I, anti-b2GPI IgA: IgA antibodies against beta 2 glycoprotein 1

Anti-b2GPI IgA presence improves prediction of developing extensive or obstructive coronary artery disease on follow-up

Ninety-five of 144 (66%) patients with evaluable baseline data had follow-up atherosclerosis assessments. Of the remaining 49, four had no follow-up after baseline evaluation, two expired, six migrated, and 37 declined reassessment. Patients without a follow-up CCTA had higher average age, RA disease activity and FRS-CVD, though the difference in FRS-CVD was no longer significant after adjusting for age (Supplementary Table S2). Overall, 10/48 (20.8%) participants with non-extensive, non-obstructive disease at baseline developed extensive or obstructive disease at follow-up. Hs-cTnI did not associate with transition from non-extensive, non-obstructive to extensive or obstructive disease [OR 4.07 (95% CI 0.79 to 20.94), p=0.093]. In contrast, 6/13 (46.2%) participants with anti-b2GPI IgA antibodies developed extensive or obstructive disease at follow-up compared to 4/35 (11.4%) of those without (Figure 3A, Pearson X^2=6.93, p=0.008). In fact, anti-b2GPI IgA presence associated with 11 times greater likelihood of transition from non-extensive non-obstructive to extensive or obstructive disease, independently of FRS-CVD [OR 11.15 (95% CI 2.08 to 59.69), p=0.005].

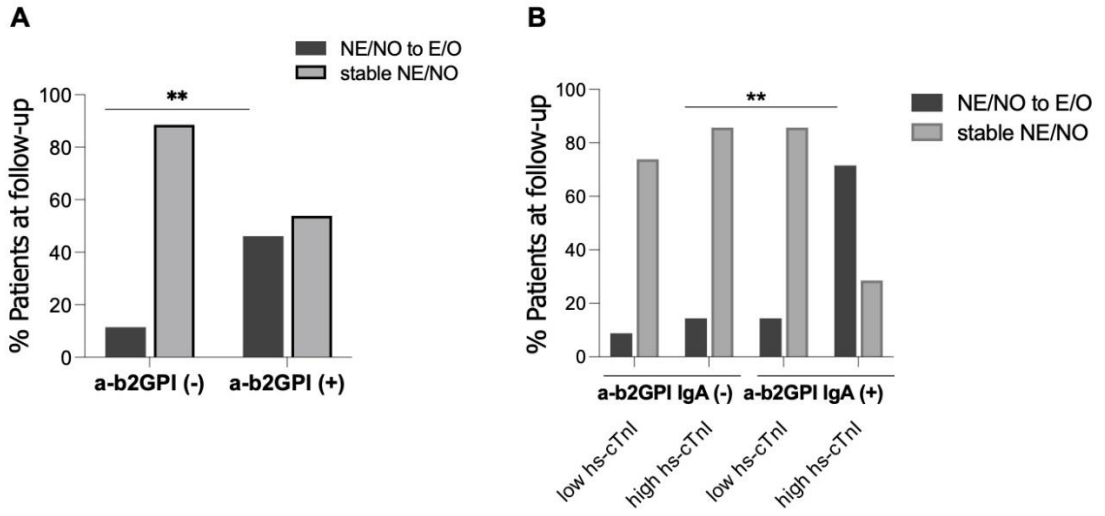

Figure 3. Plaque change on follow-up evaluation by anti-β2GPI IgA status. A. Greater transition from non-extensive non-obstructive disease to extensive or obstructive plaque in patients with vs. without anti-β2GPI IgA antibodies. B. Greater transition from non-extensive non-obstructive disease to extensive or obstructive plaque in high hs-cTnI/ anti-β2GPI IgA positive vs. high hs-cTnI/ anti-β2GPI IgA negative patients. Comparisons made with Pearson's X^2 test. Hs-cTnI: highly sensitive cardiac troponin I, anti-b2GPI IgA: IgA antibodies against beta 2 glycoprotein 1, NE/NO: Non-extensive/non-obstructive disease, E/O: extensive or obstructive disease.
**p<0.01

Anti-b2GPI IgA positivity predicted transition of non-extensive, non-obstructive to extensive or obstructive disease in patients with high hs-cTnI [OR 14.41 (95% CI 1.67 to 124.16), p=0.015] but not lower hs-cTnI (OR 4.57 (95% CI 0.24 to 87.98), p=0.314). Among patients with high hs-cTnI, 5/7 (71.4%) anti-b2GPI IgA positive patients developed extensive or obstructive plaque at follow-up compared to 2/14 (14.3%) anti-b2GPI IgA negative ones (Figure 3B, Pearson X^2=6.86, p=0.009). In incremental AUC analysis adding anti-b2GPI IgA status to a base model of FRS-CVD increased predictive accuracy for transition from non-extensive, non-obstructive to extensive or obstructive atherosclerosis in patients with high hs-cTnI (from 0.796 to 0.878, p=0.403, Figure 4). NRI and IDI analysis showed that the addition of anti-b2GPI IgA status to the FRS-CVD improved the precision of predicting transition to extensive or obstructive atherosclerosis [1.143 (95% CI -0.143 to 2.000) and 0.277 (95% CI 0.011 to 0.946), p=0.014, respectively].

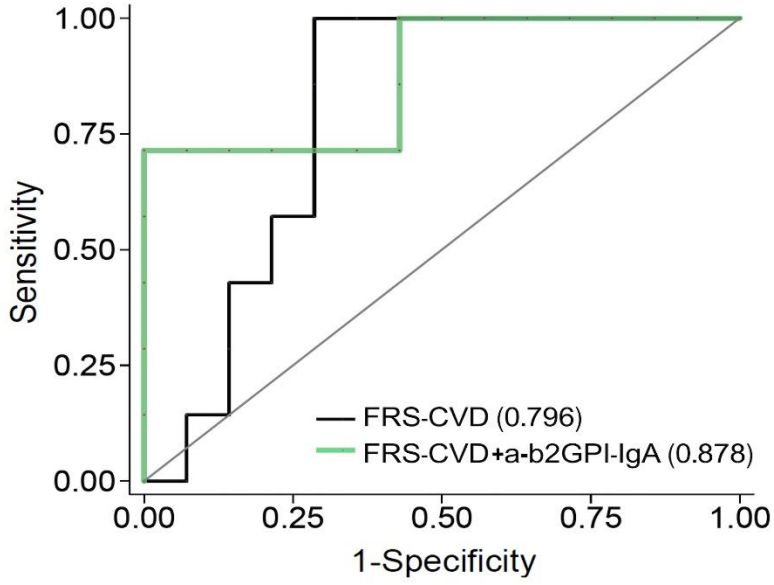

Figure 4. AUC assessments of improvement in prognostic accuracy for transition from non-extensive and non-obstructive disease at baseline to extensive and/ or obstructive disease at follow-up by addition of anti-β2GPI IgA information to a base model including the Framingham D'Agostino 2008 (FRS-CVD) clinical risk score. AUCs compared with the De Long method. Anti-b2GPI IgA: IgA antibodies against beta 2 glycoprotein 1

Discussion

Despite increasing evidence and support for the utility of noninvasive coronary atherosclerosis evaluation with CCTA in asymptomatic general patients,[21,22] there is currently no clear guidance or recommendation for its application in that setting, especially in RA.[23,24] Beyond a higher risk for atherosclerotic cardiovascular disease, which is largely underestimated by risk calculators in clinical use, RA patients additionally incur greater likelihood of silent myocardial infarction or sudden cardiac death as a first manifestation of it.[25] Hence, early identification of atherosclerosis, accurate counseling and intervention and regular follow-up are paramount in the care of patients with RA.[26] We hypothesized that serum levels of structural myocardial and immunologic biomarkers may help identify RA patients at higher risk of coronary atherosclerosis presence and progression and therefore inform the recommendation of a screening and/ or follow-up CCTA.

We demonstrated that high serum hs-cTnI improved the prediction of coronary plaque presence over cardiovascular risk score alone in RA patients without symptoms or prior diagnosis of coronary artery disease. Higher hs-cTnI may reflect latent cardiomyocyte damage underlying intermittent, chronic and clinically silent remodeling and/ or rupture and microembolization of unstable coronary plaques.[27–29] This is clinically relevant since the presence of even a singular coronary plaque in general patients was linked to increased event risk.[21] Likewise, we previously reported that RA patients without coronary atherosclerosis suffered no events at 5 years, whereas 45% of those with extensive or obstructive disease and 3-4% of those with non-extensive or non-obstructive disease experienced cardiovascular events over the same period.[5,6] Importantly, large prospective studies in general patients with chest pain indicated that initiation of preventive therapies based on CCTA evidence of atherosclerosis significantly decreased ischemic cardiovascular risk, streamlined appropriate downstream investigations and fostered patient adherence.[9–11] Although no similar prospective, interventional studies exist for asymptomatic individuals, the presence of coronary atherosclerosis on CCTA, as a risk-modifying tool, may certainly incentivize adherence to preventive therapy. Specifically in the case of RA, identification of extensive or obstructive disease would reclassify patients as very high-risk and might therefore compel initiation and/ or escalation of preventive therapy—irrespective of clinical risk score—that would have otherwise not been implemented. In the absence of atherosclerosis on a screening evaluation, and therefore of discernible risk, recommendations may be restricted to putative traditional risk factor management according to the clinical risk score level assigned by the composite calculator. In contrast, the presence of non-extensive and non-obstructive disease on a screening evaluation did not meaningfully reclassify risk in our patients, nor did it inform treatment decisions beyond those dictated by the clinical risk score magnitude. Since progression to extensive or obstructive disease is associated with very high-risk for incident cardiovascular events, it would be beneficial to identify which patients with non-extensive and non-obstructive disease might be at higher risk for evolution to extensive or obstructive atherosclerosis. Indeed, atherosclerosis progression on CCTA was shown to optimize outcome prediction above and beyond baseline plaque burden in general patients.[30,31]

Baseline hs-cTnI was not associated with coronary atherosclerosis progression on follow-up evaluation. However, high hs-cTnI predicted plaque progression from non-extensive and non-obstructive to extensive or obstructive disease at follow-up in patients with anti-b2GPI IgA antibodies. Presence and persistence of this autoantibody subclass was common in our cohort in contrast to other antiphospholipid antibody specificities. Anti-b2GPI IgA antibodies bind b2GPI or complexes of b2GPI with oxidized LDL and may promote uptake of oxidized LDL in macrophages within atherosclerotic plaque.[32,33] We recently reported that presence of anti-b2GPI IgA associated with a higher number of new coronary plaques, greater likelihood of new higher-risk plaque formation and effectively delayed their transition to more stable and lower-risk fully calcified plaques.[12] Additionally, anti-b2GPI IgA antibody presence influenced the impact of inflammation on cardiovascular event risk; higher cumulative inflammation associated with atherosclerosis progression in anti-b2GPI IgA positive patients but not in negative ones.[12] Likewise, their presence was linked to increased risk of myocardial infarction, stroke and symptomatic peripheral arterial disease in general patients.[34] The presence therefore of anti-b2GPI IgA may compel a future re-evaluation of coronary atherosclerosis and adaptation of preventive therapies as informed by the findings.

Our observations therefore outline the theoretical framework for a testable algorithm to optimize cardiovascular risk prediction and outcomes in RA (Figure 5). As part of an initial cardiovascular risk stratification, serum hs-cTnI could be measured. If high, a screening CCTA may be entertained; this could concretely guide therapeutic

decisions in the absence of atherosclerosis or in the presence of extensive or obstructive disease. If non-extensive, non-obstructive disease is found, the presence of anti-b2GPI IgA antibodies may compel a follow-up CCTA and preventive therapies be initiated and/ or escalated based on the results. Although concrete timing for serial evaluation is not yet established, a five-to-seven-year time frame—similar to the current report—appears reasonable.[21]

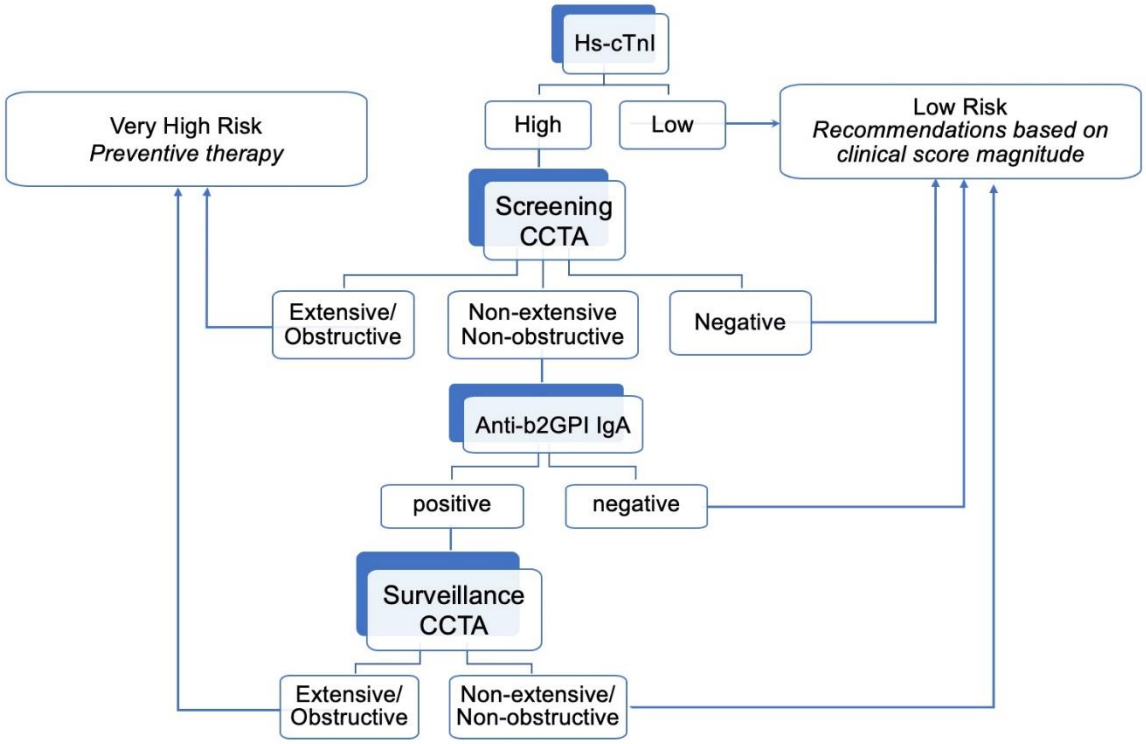

Figure 5. Proposed algorithm for the use of screening and follow-up coronary atherosclerosis evaluation with CCTA in patients with RA. CCTA: coronary computed tomography angiography, hs-cTnI: highly sensitive cardiac troponin I, anti-b2GPI IgA: IgA antibodies against beta 2 glycoprotein 1

Our study has several limitations; first, although biomarker associations with plaque presence and progression were prespecified, they were not powered for in our original study design. Our results should therefore be considered exploratory and validated in prospective, adequately powered studies. Secondly, patients with atherosclerosis or calcifications on baseline CCTA had lipid-lowering and or antiplatelet therapies initiated or intensified, irrespective of clinical indication; this may have certainly attenuated plaque progression and therefore the strength of the prediction optimization, especially in the anti-b2GPI IgA positive patients.[35,36] Lastly, our study represents the experience of a single center with little racial and ethnic variation among patients; our results may therefore not be generalizable to more ethnically and racially diverse patient cohorts.

Conclusion

Hs-cTnI improves the prediction of coronary plaque presence above and beyond that of a clinical risk score and may therefore prompt a screening coronary atherosclerosis evaluation with CCTA. This may decisively inform therapeutic decisions in the absence of atherosclerosis or in the presence of extensive and/or obstructive disease. In patients with non-extensive, non-obstructive disease at baseline, presence of anti-b2GPI IgA antibodies significantly increases the risk of progression to extensive or obstructive disease and may compel a surveillance coronary atherosclerosis evaluation as a guide for additional therapeutic decisions.

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Conflict of Interest Statement

This study was supported by grants from American Heart Association and Pfizer to GAK. The authors have no conflict of interest to declare.

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Data Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Naranjo A, Sokka T, Descalzo MA, et al. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. *Arthritis Res Ther*. 2008;10(2):R30.
2. Crowson CS, Gabriel SE, Semb AG, et al. Rheumatoid arthritis-specific cardiovascular risk scores are not superior to general risk scores: a validation analysis of patients from seven countries. *Rheumatology (Oxford)*. 2017;56(7):1102-1110.
3. Colaco K, Ocampo V, Ayala AP, et al. Predictive utility of cardiovascular risk prediction algorithms in inflammatory rheumatic diseases: a systematic review. *J Rheumatol*. 2020;47(6):928-938.
4. Karpouzas GA, Malpeso J, Choi TY, Li D, Munoz S, Budoff MJ. Prevalence, extent and composition of coronary plaque in patients with rheumatoid arthritis without symptoms or prior diagnosis of coronary artery disease. *Ann Rheum Dis*. 2014;73(10):1797-1804.
5. Karpouzas GA, Estis J, Todd J, Budoff MJ. Occult coronary plaque presence and burden predict cardiovascular events in patients with rheumatoid arthritis. *Arthritis Rheumatol*. 2017;69 (suppl 10).
6. Karpouzas GA, Estis J, Rezaeian P, Todd J, Budoff MJ. High-sensitivity cardiac troponin I is a biomarker for occult coronary plaque burden and cardiovascular events in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2018;57(6):1080-1088.
7. Karpouzas GA, Ormseth SR, Hernandez E, Budoff MJ. Biologics may prevent cardiovascular events in rheumatoid arthritis by Inhibiting coronary plaque formation and stabilizing high-risk lesions. *Arthritis Rheumatol*. 2020;72:1467-1475.
8. Nakazato R, Gransar H, Berman DS, et al. Statins use and coronary artery plaque composition: results from the International Multicenter CONFIRM Registry. *Atherosclerosis*. 2012;225(1):148-153.
9. SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet*. 2015;385(9985):2383-2391.
10. SCOT-HEART Investigators, Newby DE, Adamson PD, et al. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med*. 2018;379(10):924-933.
11. Douglas PS, Hoffmann U, Lee KL, et al. PROspective Multicenter Imaging Study for Evaluation of chest pain: rationale and design of the PROMISE trial. *Am Heart J*. 2014;167(6):796-803.e1.
12. Karpouzas GA, Ormseth SR, Hernandez E, Bui VL, Budoff MJ. Beta-2-glycoprotein-I IgA antibodies predict coronary plaque progression in rheumatoid arthritis. *Semin Arthritis Rheum*. 2020;51(1):20-27.
13. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4(2):295-306.
14. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol*. 2008;52(21):1724-1732.
15. Leipsic J, Abbara S, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr*. 2014;8(5):342-358.
16. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;15(4):827-832.
17. Pagali SR, Madaj P, Gupta M, et al. Interobserver variations of plaque severity score and segment stenosis score in coronary arteries using 64 slice multidetector computed tomography: a substudy of the ACCURACY trial. *J Cardiovasc Comput Tomogr*. 2010;4(5):312-318.
18. Bittencourt MS, Hulten E, Ghoshhajra B, et al. Prognostic value of nonobstructive and obstructive coronary artery disease detected by coronary computed tomography angiography to identify cardiovascular events. *Circ Cardiovasc Imaging*. 2014;7(2):282-291.
19. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117(6):743-753.
20. Swainson MG, Batterham AM, Tsakirides C, Rutherford ZH, Hind K. Prediction of whole-body fat percentage and visceral adipose

tissue mass from five anthropometric variables. *PLoS One*. 2017;12(5):e0177175.

21. Plank F, Friedrich G, Dichtl W, et al. The diagnostic and prognostic value of coronary CT angiography in asymptomatic high-risk patients: a cohort study. *Open Heart*. 2014;1(1):e000096.
22. Cho I, Al'Aref SJ, Berger A, et al. Prognostic value of coronary computed tomographic angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective multicentre international CONFIRM study. *Eur Heart J*. 2018;39(11):934-941.
23. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2016;37(29):2315-2381.
24. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol*. 2010;56(22):1864-1894.
25. Maradit-Kremers H, Crowson CS, Nicola PJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum*. 2005;52(2):402-411.
26. Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis*. 2017;76(1):17-28.
27. Korosoglou G, Lehrke S, Mueller D, et al. Determinants of troponin release in patients with stable coronary artery disease: insights from CT angiography characteristics of atherosclerotic plaque. *Heart*. 2011;97(10):823-831.
28. Seifarth H, Schlett CL, Lehman SJ, et al. Correlation of concentrations of high-sensitivity troponin T and high-sensitivity C-reactive protein with plaque progression as measured by CT coronary angiography. *J Cardiovasc Comput Tomogr*. 2014;8(6):452-458.
29. Altintas S, Cardinaels EPM, Versteylen MO, et al. Unstable coronary plaque characteristics are associated with high-sensitivity cardiac troponin T and N-terminal Pro-Brain Natriuretic Peptide. *J Cardiovasc Comput Tomogr*. 2016;10(1):82-88.
30. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol*. 2015;66(4):337-346.
31. Gu H, Gao Y, Wang H, et al. Sex differences in coronary atherosclerosis progression and major adverse cardiac events in patients with suspected coronary artery disease. *J Cardiovasc Comput Tomogr*. 2017;11(5):367-372.
32. Moore KJ, Tabas I. Macrophages in the pathogenesis of atherosclerosis. *Cell*. 2011;145(3):341-355. doi:10.1016/j.cell.2011.04.005
33. Matsuura E, Kobayashi K, Koike T, Shoenfeld Y. Autoantibody-mediated atherosclerosis. *Autoimmun Rev*. 2002;1(6):348-353.
34. Staub HL, Franck M, Ranzolin A, Norman GL, Iverson GM, von Mühlen CA. IgA antibodies to beta2-glycoprotein I and atherosclerosis. *Autoimmun Rev*. 2006;6(2):104-106.
35. Karpouzas GA, Ormseth SR, Hernandez E, Budoff MJ. Impact of cumulative inflammation, cardiac risk factors, and medication exposure on coronary atherosclerosis progression in rheumatoid arthritis. *Arthritis Rheumatol*. 2020;72(3):400-408.
36. Karpouzas GA, Ormseth SR, Hernandez E, Budoff MJ. The impact of statins on coronary atherosclerosis progression and long-term cardiovascular disease risk in rheumatoid arthritis. *Rheumatology (Oxford)*. 2022;61(5):1857-1866.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Prevalence of antiphospholipid antibody classes and isotypes (N=144)

	Number (%)
Unique	
Anticardiolipin	
IgG	0 (0)
IgM	0 (0)
IgA	1 (0.7)
Lupus anticoagulant	5 (3.5)
Anti-beta-2 glycoprotein I	
IgG	2 (1.4)
IgM	3 (2.1)
IgA	46 (31.9)
In Combination	
Anti-beta-2 glycoprotein I IgG + Anti-beta-2 glycoprotein I IgA	2 (1.4)
Lupus anticoagulant+ Anti-beta-2 glycoprotein I IgA	1 (0.7)

Supplementary Table 2. Baseline characteristics by follow-up CCTA status

	No Follow-up CCTA (n=49)	Follow-up CCTA (n=95)	P-value
Age (years)	56.57 10.20	51.37 10.41	0.005
Female	44 (89.8%)	81 (85.3%)	
Hs-cTnI>median (1.5 pg/mL)	27 (55.1%)	47 (49.5%)	
b2GPI-IgA positive	13 (26.5%)	33 (34.7%)	
RA duration	11.52 8.64	9.97 7.18	
RF positive	38 (77.6%)	86 (90.5%)	0.033
ACPA positive	40 (81.6%)	82 (86.3%)	
Erosions	35 (71.4%)	59 (62.1%)	
CRP (mg/dL), median (IQR)	4.20 (1.8, 10.4)	4.10 (2.0 10.1)	
Tender joint counts	2.55 4.66	1.15 2.56	0.021
Swollen joint counts	1.98 2.64	1.54 2.56	
DAS28-CRP	2.85 1.19	2.44 0.94	0.028
Hypertension	27 (55.1%)	44 (46.3%)	
Cholesterol (mg/dL)	174.63 34.32	168.45 34.49	
LDL-c (mg/dL)	99.08 27.34	94.74 27.47	
HDL-c (mg/dL)	51.37 16.70	51.46 12.84	
Diabetes	12 (24.5%)	13 (13.7%)	
Current smoking	5 (10.2%)	7 (7.4%)	
Waist-to-height ratio	0.61 0.09	0.59 0.08	
FRS-CVD	11.38 8.94	7.32 6.58	0.002
Prednisone	19 (38.8%)	33 (34.7%)	
N-conc csDMARDs	2.18 0.86	1.91 0.79	
bDMARD	26 (53.1%)	61 (64.2%)	
Statins	19 (38.8%)	38 (40.0%)	
Any plaque (SIS>0)	37 (75.5%)	65 (68.4%)	

SIS total	2.35 2.35	1.86 2.27
CAC>0	23 (46.9%)	31 (32.6%)
CAC score, median (IQR)	0 (0, 29)	0 (0, 11)

Values are n (%) or mean ± standard deviation unless indicated otherwise.
CCTA: Coronary computed tomography angiography, Hs-cTnI: Highly-sensitive cardiac troponin-I, anti-b2GPI-IgA: Anti-Beta-2-Glycoprotein-I IgA antibodies, RA: Rheumatoid arthritis, RF: Rheumatoid factor, ACPA: Anti-cyclic citrullinated peptide antibodies, CRP: C-reactive protein, DAS28-CRP: Disease Activity Score in 28 joints CRP, HDL-c: High density lipoprotein, LDL-c: Low-density lipoprotein, FRS-CVD: Framingham 2008 modified cardiovascular risk score, csDMARDs: Conventional synthetic DMARDs, bDMARD: Biologic disease modifying anti-rheumatic drug, SIS: Segment involvement score, CAC: Coronary artery calcium.