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RESEARCH ARTICLE

The Influence of Abdominal Obesity on the Accuracy of Cardiovascular Risk Prediction in Rheumatoid Arthritis

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ABSTRACT

Objectives. Underweight patients with rheumatoid arthritis incur greater total and cardiovascular mortality compared to overweight or obese. We explored whether obesity confounded cardiovascular risk estimates and the potential utility of noninvasive coronary atherosclerosis assessment and cardiac damage biomarkers in optimizing risk prediction in obese patients with rheumatoid arthritis.

Methods. We evaluated 150 participants undergoing screening atherosclerosis evaluation with coronary computed tomography angiography and follow-up over 6.0±2.4 years. Framingham 2008 modified general cardiovascular risk score was computed at baseline. Obesity was defined as waist circumference >88 cm in females and >102 cm in males. Serum highly-sensitive cardiac troponin I (hs-cTnI) and leptin were measured at baseline.

Results. An interaction between the Framingham risk score and obesity on cardiovascular risk was observed (p=0.032); lower estimates were seen in obese (area under the curve-AUC 0.660, 95% CI 0.487-0.832) vs. non-obese patients (AUC 0.952, 95% CI 0.897-1.007, p=0.002). Likewise, risk estimates were inferior in patients with high (>22.1 ng/ml) vs. low leptin (AUC 0.618, 95% CI 0.393-0.842 vs. 0.874, 95% CI 0.772-0.976, p=0.042). In obese patients, sequential addition of the top highly-sensitive cardiac troponin I tertile values and extensive atherosclerotic plaque (>5 segments) information to a base model including the Framingham risk score alone significantly improved risk estimates, based on changes in net reclassification index (1.093 95% CI 0.517-1.574), integrated discrimination improvement (0.188, 95% CI 0.060-0.526), and AUC (0.179, 95% CI 0.058-0.378, p=0.02). The final, combined model accurately predicted 83.9% of incident cardiovascular events.

Conclusion. Obesity attenuated cardiovascular risk estimate accuracy in patients with rheumatoid arthritis. Risk optimization employing non-invasive assessment of coronary atherosclerosis burden and serum cardiac damage biomarkers may warrant further study.

Keywords: Rheumatoid arthritis, cardiovascular disease, obesity, computed tomography, highly-sensitive cardiac troponin-I, leptin

Introduction

Patients with rheumatoid arthritis (RA) experience higher cardiovascular morbidity and mortality compared to the general population.[1] Published guidelines call for regular and systematic cardiovascular risk screening and stratification;[2] therefore, accurate risk assessment is essential in the routine care of patients with RA. Obesity is an established risk factor for cardiovascular disease[3] and associates with a proinflammatory state.[4] Obesity is more prevalent in RA[5,6] and represents a risk factor for the development of RA itself.[7,8] Interestingly, recent reports indicate that non-obese patients with RA—as defined by body mass index (BMI)—may incur higher all-cause mortality[9] and that low BMI may further associate with higher cardiovascular mortality.[10] Notably, BMI encompasses both fat and lean body mass[11] and does not account for fat distribution or body composition;[12] in contrast, indices such as waist circumference (WC) or waist-to-height ratio (WHtR) consider fat distribution and better associate with abdominal obesity and visceral adiposity on quantitative imaging[13,14] and linked to cardiometabolic risk in RA.[12,15] Leptin is an adipokine produced by fat cells;[4] central obesity is linked to high leptin levels, peripheral and central leptin resistance and reduced leptin transport through the blood-brain barrier to the hypothalamus and hippocampus where it regulates body weight and feeding behaviors.[16,17] Leptin polymorphisms have been further associated with obesity and cardiovascular disease.[18]

General cardiovascular risk calculators used in clinical practice reportedly underperform in RA and also do not account for obesity.[19,20] RA patients exhibit greater coronary atherosclerosis burden and plaque vulnerability compared to age and gender-matched ones without autoimmune disease as a proxy for greater cardiovascular risk.[21] Indeed, coronary atherosclerosis presence on non-invasive screening with coronary computed tomography angiography (CCTA) optimized cardiovascular risk estimates beyond traditional risk factors, inflammation and immunomodulatory treatments.[22–24] No ischemic events were observed in the absence of coronary atherosclerosis at five years; in contrast, 45% of patients with extensive or obstructive plaque suffered cardiovascular events over the same period of time.[22] Importantly, CCTA-based initiation of primary preventive therapies improved cardiovascular outcomes in large prospective trials in general patients.[25–27] At the same time, several serum candidate biomarkers are rigorously tested for their ability to optimize risk prediction.[28,29] Highly-sensitive cardiac troponin-I (hs-cTnI) is a structural cardiac biomarker shown to associate with coronary atherosclerosis burden, plaque vulnerability and cardiovascular events in RA above and beyond traditional cardiac risk factors.[23]

The aim of this study was to evaluate the influence of abdominal obesity on cardiovascular risk estimates in RA patients without known history of cardiovascular disease. A secondary aim was to investigate whether a combination of structural cardiac biomarker measurements such as hs-cTnI with non-invasive evaluation of coronary atherosclerosis burden may optimize risk estimates in RA patients with abdominal obesity.

Materials and Methods

PATIENT RECRUITMENT

One hundred-fifty participants in the *PR*O*spec*T*ive* E*valuation of Latent Coronary A*t*herosclerosis in* R*heumatoid* A*rthritis* [PROTECT RA] observational cohort underwent a screening atherosclerosis evaluation with CCTA between March 2010 and March 2011. Patients were between the ages of 18 and 75, fulfilled 2010 classification criteria for RA and reported no history of established cardiovascular disease including angina, myocardial infarction, stroke, transient ischemic attack, claudication, revascularization, or heart failure. Presence of concurrent systemic autoimmune disease (other than Sjogren's syndrome), malignancy within 5 years, active or chronic infections, weight exceeding 147.7 kg (weight limit for scanner bed), glomerular filtration rate <60 mL/min, or allergy to iodine were considered exclusionary. The local Institutional Review Board approved the study and all patients signed informed consent according to the Declaration of Helsinki.

MULTI-DETECTOR CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY

Assessments were performed with a 64-multidetector row scanner between March 2010 and March 2011. Detailed protocols describing image acquisition and processing and scoring reproducibility have been previously reported.[30,31] Coronary atherosclerosis was evaluated on contrast-enhanced scans employing a standardized 17-segment model from the American Heart Association.[31] Images were read in random order by a single, senior and blinded interpreter (MJB). Segment involvement score (SIS) described the number of segments with plaque (0-17) on cardiac CTA. Plaque composition was reported as noncalcified, partially and fully calcified as previously described.[32] Extensive atherosclerotic disease was defined as ≥5 segments with plaque.

Extensive plaque associated with significantly higher cardiovascular risk.[23,33]

LABORATORY EVALUATIONS

Comprehensive metabolic panel including fasting lipids, complete blood counts, erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) were completed on the day of CCTA assessments. Serum for biomarker studies was also collected on the day of both CCTA assessments and aliquots frozen to -80^{0}C until processing. Serum leptin was measured by electrochemiluminescence in Quest diagnostics (Nichols Institute, San Juan Capistrano, CA) by technicians blinded to clinical data. Hs-cTnI was measured with a micro-particle immunoassay and single-molecule counting at Singulex Inc. (Alameda, CA) by technicians blinded to patient information.[23]

DEFINITIONS OF COVARIATES AND OUTCOMES

Ten-year cardiovascular risk was estimated at baseline using the Framingham 2008 modified general cardiovascular risk score (FRS-CVD).[34] Height, weight and abdominal circumference were measured. For the main analysis, abdominal obesity was defined as WC >88 cm in females and >102 cm in males.[12] In a sensitivity analysis obesity was defined as a WHtR >0.58 in females and >0.62 in males[13] and as a BMI ≥30 kg/m^2 in both males and females. Disease activity score based on a 28-joint exam for tenderness, swelling and CRP (DAS28-CRP) was calculated upon enrollment. 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.

The prespecified composite end point of cardiac death, non-fatal myocardial infarction, unstable angina, stroke, transient ischemic attack, peripheral arterial disease, revascularization and heart failure was the outcome of interest.

STATISTICAL ANALYSIS

Categorical variables were summarized as frequencies and percentages and continuous variables as the mean and standard deviations or the median and interquartile range (IQR). A Cox regression model with an obesity by FRS-CVD interaction term evaluated whether obesity moderated the effect of FRS-CVD on cardiovascular event risk. Area under the receiver operating curve (AUC) assessed the accuracy of FRS-CVD in non-obese and obese subgroups. Change in AUC, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) assessed the added predictive values of the highest hs-cTnI tertile and extensive coronary plaque beyond FRS-CVD. Incremental predictive analyses were performed using the Stata *incrisk* module with 10-fold cross-validation and 95% bootstrap confidence intervals using 1000 resamples. P values < 0.05 were considered significant.

Results

Patients were predominantly female with a mean age of 53 years. Most had long-standing, seropositive and erosive RA with well-controlled disease at baseline. A third of patients were prescribed corticosteroids at screening, all received csDMARDs and 90/150 (60%) additionally received bDMARDs (Table 1). One hundred two (70.8%) patients had coronary atherosclerosis and 21 (14%) had extensive plaque at baseline (Table 1). In contrast, cardiac risk score was high (FRS-CVD>20) in 11 (7.6%).

Table 1 Participant characteristics (N=150)

	Mean ± SD or No. (%)
Age (years)	53.15 ± 10.51
Female	131 (87.33)
RA duration (years)	10.64 ± 7.69
RF positive	129 (86.00)
ACPA positive	127 (84.67)
Erosions	99 (66.00)
CRP (mg/L)	8.87 ± 12.92
Tender joint count	1.59 ± 3.41
Swollen joint count	1.69 ± 2.57
DAS28-CRP	2.58 ± 1.03
Hypertension	72 (48.00)
Cholesterol (mg/dL)	168.73 ± 34.74
LDL-c (mg/dL)	96.33 ± 29.64
HDL-c (mg/dL)	50.97 ± 14.23
Diabetes	26 (17.33)
Current smoking	13 (8.67)

	Mean ± SD or No. (%)
Framingham-CVD risk score	8.85 ± 8.13
Waist circumference (cm)	93.99 ± 12.09
Waist circumference-defined obesity*	92 (61.33)
Waist-to-height ratio	0.60 ± 0.08
Waist-to-height ratio-defined obesity†	76 (50.67)
BMI (kg/m^2)	29.12 ± 5.55
BMI-defined obesity (BMI ≥30 kg/m^2)	57 (38.00)
Prednisone	52 (34.67)
Methotrexate	121 (80.67)
No. concurrent conventional synthetic DMARDs	1.99 ± 0.82
Biologic DMARDs	90 (60.00)
Statins	59 (39.33)
High hs-cTnI (upper tertile)	56 (37.33)
Any plaque	107 (71.33)
Number of segments with plaque	2.02 ± 2.28
Extensive plaque (>5 segments)	14 (9.33)
Cardiovascular events	16 (10.67)

RA: Rheumatoid arthritis, RF: Rheumatoid factor, ACPA: Anti-citrullinated peptide antibodies, CRP: C-reactive protein, DAS28-CRP: Disease activity score based on 28 joint counts and CRP, LDL-c: Low-density lipoprotein cholesterol, HDL-c: High-density lipoprotein cholesterol, BMI: Body mass index, DMARD: Disease modifying anti-rheumatic drugs, hs-cTnI: Highly-sensitive cardiac troponin I.
*Waist circumference-defined obesity is ≥102 cm for males and ≥88 cm for females.
†Waist-to-height ratio-defined obesity is ≥0.62 for males and ≥0.58 for females.

OBESITY MAY CONFOUND CARDIOVASCULAR RISK ESTIMATES IN RA

Sixteen patients suffered 19 cardiovascular events over 6.0±2.4 years of follow-up, with an incident rate of 2.1 events/100PY. Obesity defined by WC was present in 92 (61.3%) participants at baseline. Six patients without WC-defined obesity and 10 patients with suffered cardiovascular events. The strength of the association between the FRS-CVD and cardiovascular event risk varied according to WC-defined obesity (p-for-interaction=0.032); accuracy of the FRS-CVD was higher in nonobese (mean AUC 0.952, 95% confidence interval [95% CI] 0.897-1.007) compared to patients with obesity (AUC 0.660, 95% CI 0.487-0.832). Difference in AUC was 0.292 (95% CI 0.111-0.473), p=0.002 (Figure 1).

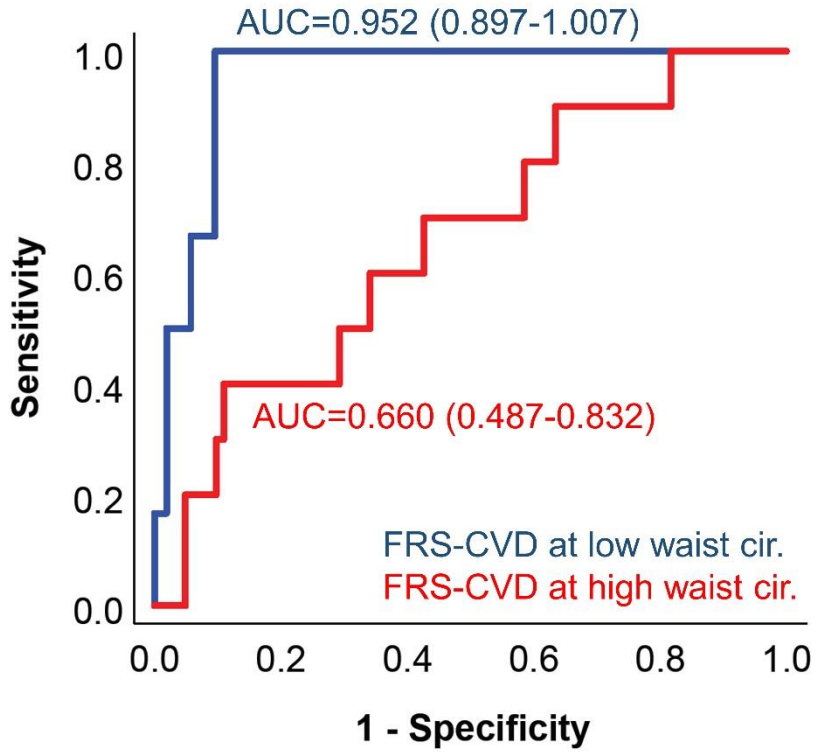

Figure 1. Receiver operating characteristic curve of Framingham Risk Score-Cardiovascular Disease (FRS-CVD) stratified by low and high waist circumference (male < or ≥ 102 cm, female < or ≥ 88 cm). Values are area under the receiver operating curve (AUC) estimates (95% confidence intervals).

In a sensitivity analysis with obesity defined by WHtR, the accuracy of the FRS-CVD was similarly greater for nonobese patients (AUC 0.925, 95% CI 0.854-0.997) compared to ones with obesity (AUC 0.662 95% CI 0.467-0.856; difference in AUC 0.264, 95% CI 0.056-0.471, p=0.013, Figure 2A). However, for BMI-defined obesity, the accuracy of FRS-CVD was not different in nonobese patients (AUC 0.860 95% CI 0.759-0.962) versus ones with obesity (AUC 0.712, 95% CI 0.442-0.983; difference in AUC 0.148, 95% CI -0.141 to 0.437, p=0.316, Figure 2B).

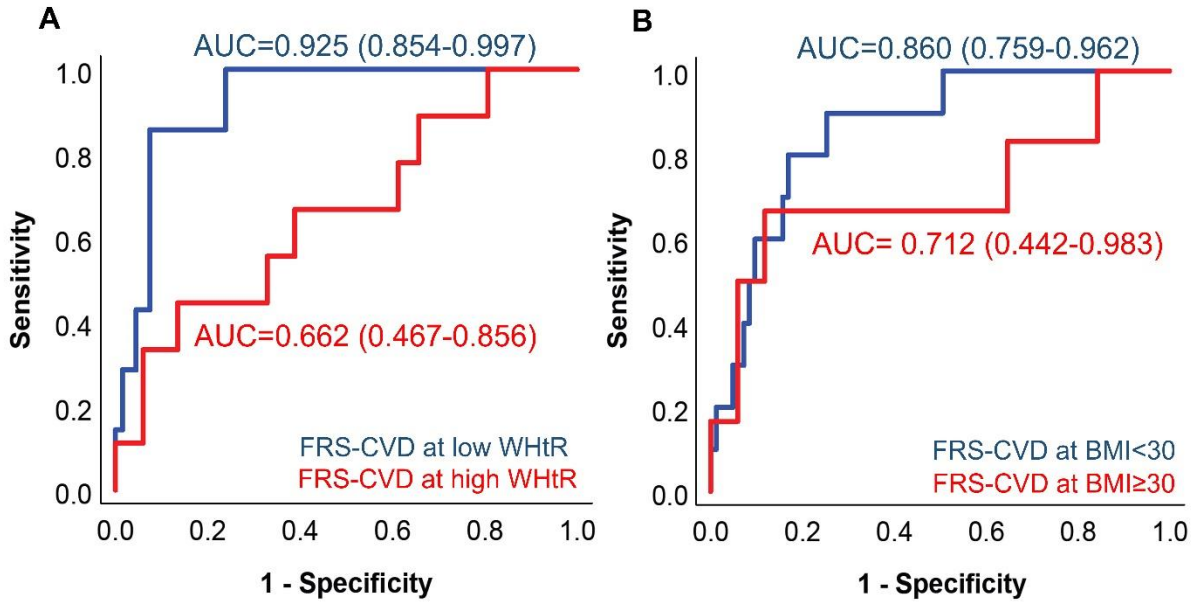

Figure 2. Receiver operating characteristic curve of Framingham Risk Score-Cardiovascular Disease (FRS-CVD) stratified by **A.** Low and high waist-to-height ratio (WHtR) (male < or ≥ 0.62, female < or ≥ 0.58) and **B.** Low and high body mass index (BMI) (<30 and ≥30 kg/m^2). Values are area under the receiver operating curve (AUC) estimates (95% confidence intervals).

Serum leptin was higher in patients with WC-defined obesity (29.20 [95% CI 25.78-32.62] ng/mL) versus non-obese patients (17.20 [95% CI 13.04-21.37] ng/mL, p<0.001). Presence of obesity by all three measures associated with leptin levels independently of age, gender, hypertension, CRP, prednisone, and hydroxychloroquine use (not shown). The accuracy of the FRS-CVD was greater in patients with below-median leptin (AUC 0.874, 95% CI 0.772-0.976) than those with above-median leptin (AUC 0.618, 95% CI 0.393-0.842) with difference in AUC of 0.256 (95% CI 0.009-0.503), p=0.042 (Figure 3).

Similarly, to cardiovascular event risk estimates, the accuracy of extensive coronary plaque (SIS≥5) prediction by FRS-CVD was higher in patients without WC-defined obesity (AUC 0.923, 95% CI 0.848-0.998) compared to patients with obesity (AUC 0.662, 95% CI 0.494-0.831; difference in AUC 0.261, 95% CI 0.077-0.445, p=0.006).

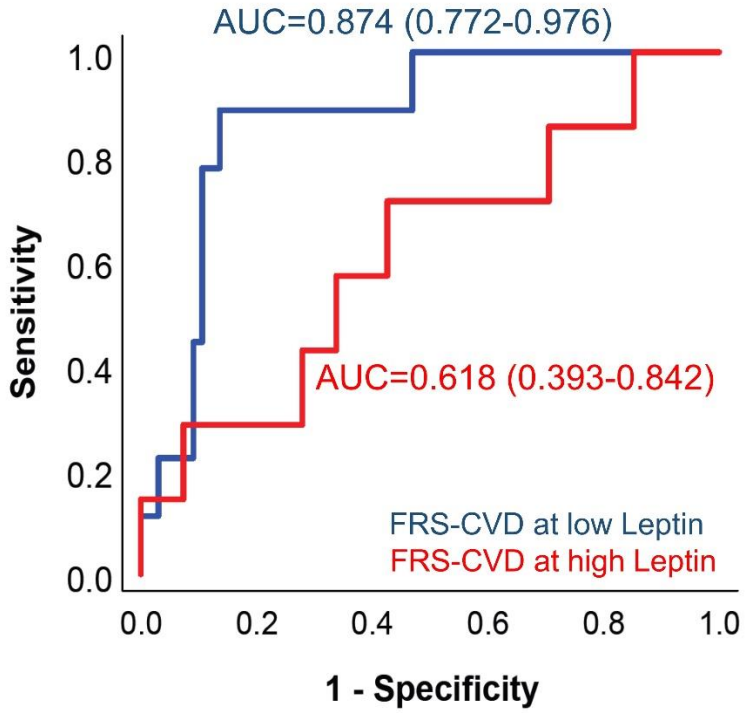

Figure 3. Receiver operating characteristic curve of Framingham Risk Score-Cardiovascular Disease (FRS-CVD) stratified by low and high leptin levels (<22.1 and ≥22.1 ng/mL). Values are area under the receiver operating curve (AUC) estimates (95% confidence intervals).

HIGHLY-SENSITIVE CARDIAC TROPONIN I AND CORONARY ATHEROSCLEROSIS ENHANCE CARDIOVASCULAR RISK ESTIMATES

Highly-sensitive cardiac troponin I was detectable in all patients with a median of 1.5 (IQR 1.1-2.6) pg/mL. hs-cTnI was higher in patients with atherosclerosis (1.8 [IQR 1.1-2.6] pg/ml) than those without (1.3 [IQR 0.9-1.8] pg/ml), p=0.02. In patients with WC-defined obesity, sequential addition of high hs-cTnI (upper tertile versus lower tertiles) and extensive coronary plaque burden (SIS≥5) to a base model with the FRS-CVD score alone significantly improved risk prediction based on changes in AUC, NRI and IDI (Table 2). The combined model with all three predictors accurately identified 83.9% of incident cardiovascular events (AUC 0.839, 95% CI 0.696-0.982), significantly higher than the base model with FRS-CVD alone (AUC 0.660, 95% CI 0.480-0.839) with a difference in AUC of 0.179 (95% CI 0.058-0.378), p<0.05 (Figure 4).

Table 2 Increase in precision of cardiovascular event risk prediction after addition of hs-cTnI and extensive coronary plaque in patients with obesity (n=92)

CVD Risk Models	AUC (95% CI)	Δ AUC (95% CI)	NRI (95% CI)	IDI (95% CI)
Base model (FRS-CVD alone)	0.660 (0.480-0.839)	—	—	—
Base + high hs-cTnI	0.783 (0.610-0.956)	0.123 (0.011-0.274)*	0.917 (0.309-1.474)*	0.095 (0.012-0.323)*
Base + SIS>5	0.742 (0.552-0.930)	0.082 (-0.009-0.290)	0.702 (0.098-1.407)*	0.150 (0.005-0.431)*
Base + high hs-cTnI + SIS>5	0.839 (0.696-0.982)	0.179 (0.058-0.378)*	1.093 (0.517-1.574)*	0.188 (0.060-0.526)*

AUC: Area under the Receiver Operator Curve, NRI: Net Reclassification Index, IDI: Integrated Discrimination Improvement, CI: Confidence interval, FRS-CVD: Framingham Risk Score for cardiovascular disease, High hs-cTnI: Upper tertile of highly-sensitive cardiac troponin I, SIS: Segment involvement score.
*p<0.05

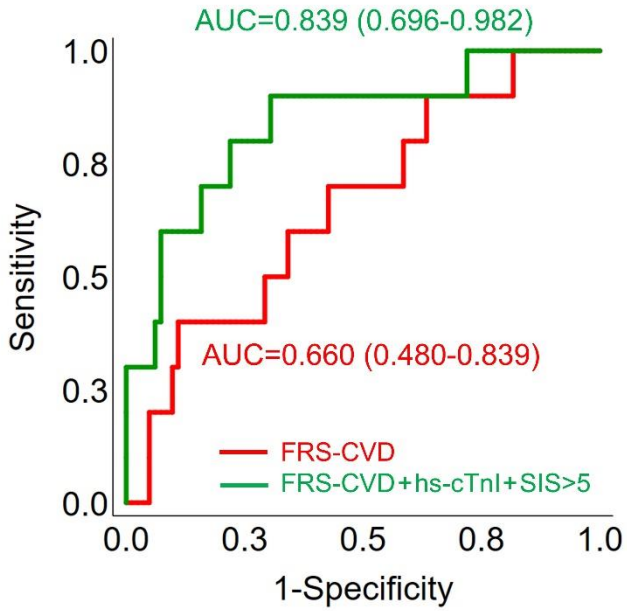

Figure 4. Receiver operating characteristic curve of base model with FRS-CVD, and base model with high hs-cTnI (upper tertile) plus extensive plaque (≥5 coronary segments) in predicting cardiovascular event risk in waist circumference male/female ≥102/88 cm subgroup. Values are area under the receiver operating curve (AUC) estimates (95% confidence intervals). FRS-CVD: Framingham Risk Score-Cardiovascular Disease, hs-cTnI: highly sensitive cardiac troponin I, SIS: Segment Involvement Score.

Discussion

The influence of obesity on cardiovascular risk in RA, much like that of lipid levels and lipoprotein function appears more complex than in the broader population.[35,36] While obesity is well characterized as a cardiovascular risk factor in general patients, it was reported to associate with cardiovascular and overall survival benefits in RA.[9,10] Cardiovascular risk calculators used in general practice reportedly underperform in RA; additionally, they do not account for obesity. We therefore hypothesized that obesity may further confound the accuracy of cardiovascular risk estimates generated by broadly used calculators. Indeed, we demonstrated that obesity and specifically abdominal adiposity as defined by WC or WHtR significantly attenuated the accuracy of cardiovascular risk estimates (66% with both) while obesity as defined by BMI did not. In contrast, in nonobese RA patients, at least in our hands, the clinical risk estimates were generally accurate (95.2% and 92.5% for models with WC or WHtR respectively). One explanation may be that in nonobese patients, abdominal visceral adipose tissue is not expanded and therefore the additional adverse metabolic and inflammatory contributions from that depot on cardiovascular risk are negligible. Instead, the risk here is largely conferred by traditional cardiac risk factors which are ostensibly accurately captured by the composite risk calculator. Likewise, we observed that abdominal obesity similarly associated with worse estimates for presence of extensive or obstructive atherosclerosis: 65.1% in obese vs. 94.6% in nonobese RA patients.

Obesity refers to excessive fat accumulation throughout the body–under the skin, body cavities and around or within organs–resulting in adverse metabolic, biomechanical, and psychosocial consequences.[37] An increasing abdominal girth measured via WC as an index of abdominal adiposity therefore reflects both subcutaneous and visceral fat accumulation, which display highly diverse metabolic activity and health risk profiles.[11] Yet, in general patients, both WC and WHtR are good predictors specifically of abdominal visceral adipose tissue burden by quantitative imaging in both males and females.[13,14,38] Obesity and in particular abdominal obesity and visceral adiposity are more prevalent in RA.[5,6] Expanding visceral fat is highly active metabolically and immunologically and a pivotal source of proinflammatory cytokines, including TNFa, IL-1, IL-6 and leptin.[38] Excess accumulation of visceral fat associates with insulin resistance, diabetes, dyslipidemia and hypertension.[39] Not surprisingly, visceral fat expansion is an independent predictor of all-cause mortality in men and women[40,41] and of cardiovascular risk in both general as well as RA patients.[39,42] Visceral fat expansion has also been linked to coronary atherosclerosis presence and burden in both general[13,39,42,43] and RA patients.[43,44]

Body mass index on the other hand measures average body weight against average body height. Therefore BMI reflects both lean muscle mass and fat mass[11] and does not consider fat distribution or body composition.[12] Unsurprisingly, BMI was a weak predictor of total body fat in both males and females and of visceral fat in males.[45] Accordingly we showed that increasing BMI did not significantly confound cardiovascular risk estimates in RA. Another reason BMI-defined obesity might not associate with a significant difference by AUC analysis in our study is that the independent effect of a new predictor would have to be rather large in order to cause significant change by AUC analysis, when added to a base model. Alternatively, the small number of CV events in our cohort may have not allowed sufficient power for the analysis in question.

Leptin is a hormone produced by adipocytes and regulates the balance between food intake and energy expenditure.[16,17] Acting in the hypothalamus and brain stem, leptin inhibits hunger and regulates energy balance. It directly reflects white adipose tissue mass. Higher leptin levels in obesity lead to secondary leptin resistance which further contributes to obesity through appetite stimulation and decreased metabolism. We here showed that hyperleptinemia, as a proxy for obesity, similarly confounds cardiovascular risk estimates in RA.

Given the increasing prevalence of obesity, including in patients with RA, there is a growing unmet need for accurate cardiovascular risk stratification. We previously reported that presence and burden of subclinical coronary atherosclerosis on noninvasive evaluation optimized cardiovascular risk estimates beyond traditional risk factors, inflammation and immunomodulatory treatments.[22–24] Likewise, we showed that the structural cardiac biomarker hs-cTnI associated with coronary atherosclerosis burden, plaque vulnerability and cardiovascular events in RA above and beyond standard risk factors.[23] So, we here asked whether the combination of hs-cTnI and coronary plaque burden information may enhance the accuracy of cardiovascular risk estimates in obese patients with RA. Indeed, this was the case; the accuracy of risk estimates by AUC increased significantly from 66% to 83.9% upon addition of the highest tertile values of hs-cTnI and presence of extensive disease to a base model of clinical risk score alone, and this was also true for both net reclassification index (NRI) and integrated discrimination improvement (IDI) index.

Several limitations of our study should be acknowledged: first, participants originated from a single center with largely homogeneous racial and ethnic distribution; our findings may therefore not be generalizable to more ethnically and racially diverse cohorts. Secondly, this was not a study of natural history; 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 subsequent cardiovascular risk and additionally confounded risk estimates.[44,46] Lastly, only baseline obesity and FRS-CVD estimates were considered. The effects of longitudinal variability of obesity and FRS-CVD may be assessed in future studies.

Conclusion

The accuracy of clinical cardiovascular risk estimates was significantly lower in obese RA patients compared to nonobese ones. Improved cardiac risk stratification in this patient group by considering serum biomarkers of cardiac damage and non-invasive assessment of coronary atherosclerosis burden may warrant further validation in prospective, adequately powered studies.

Acknowledgements

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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.

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