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## CLINICAL SCIENCE

## Reducing cardiovascular risk with immunomodulators: a randomised active comparator trial among patients with rheumatoid arthritis

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## ABSTRACT

**Objective** Recent large-scale randomised trials demonstrate that immunomodulators reduce cardiovascular (CV) events among the general population. However, it is uncertain whether these effects apply to rheumatoid arthritis (RA) and if certain treatment strategies in RA reduce CV risk to a greater extent.

**Methods** Patients with active RA despite use of methotrexate were randomly assigned to addition of a tumour necrosis factor (TNF) inhibitor (TNFi) or addition of sulfasalazine and hydroxychloroquine (triple therapy) for 24 weeks. Baseline and follow-up <sup>18</sup>F-fluorodeoxyglucose-positron emission tomography/CT scans were assessed for change in arterial inflammation, an index of CV risk, measured as an arterial target-to-background ratio (TBR) in the carotid arteries and aorta.

**Results** 115 patients completed the protocol. The two treatment groups were well balanced with a median age of 58 years, 71% women, 57% seropositive and a baseline disease activity score in 28 joints of 4.8 (IQR 4.0, 5.6). Baseline TBR was similar across the two groups— $\Delta$ TNFi:  $-0.24$  (SD=0.51),  $\Delta$ triple therapy:  $-0.19$  (SD=0.51)—without difference between groups (difference in  $\Delta$ s:  $-0.02$ , 95% CI  $-0.19$  to  $0.15$ ,  $p=0.79$ ). While disease activity was significantly reduced across both treatment groups, there was no association with change in TBR ( $\beta=0.04$ , 95% CI  $-0.03$  to  $0.10$ ).

**Conclusion** We found that addition of either a TNFi or triple therapy resulted in clinically important improvements in vascular inflammation. However, the addition of a TNFi did not reduce arterial inflammation more than triple therapy.

**Trial registration number** NCT02374021.

## INTRODUCTION

Inflammation drives atherosclerosis and contributes to cardiovascular (CV) disease.<sup>1</sup> Based on human and animal data, elevated cytokine levels in coronary arteries (eg, interleukin (IL)-1 $\beta$ , TNF, IL-6) appear to lead to plaque formation and rupture,<sup>2–4</sup> and C reactive protein (CRP) elevations predict future CV events.<sup>5,6</sup> Further, several immunomodulators have led to reductions in CV events among the general population with known CV disease.<sup>7,8</sup>

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Recent large-scale randomised trials demonstrate that immunomodulators reduce cardiovascular (CV) events among the general population. However, it is uncertain whether these effects apply to rheumatoid arthritis (RA) and if certain treatment strategies in RA reduce CV risk to a greater extent.

## WHAT THIS STUDY ADDS

⇒ Statistically significant reductions in arterial inflammation were observed in patients randomised to TNF inhibitors or triple therapy, but no differences were noted between groups. While disease activity was significantly reduced across both treatment groups, there was no association with change in arterial inflammation.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Patients with RA have increased arterial inflammation that is responsive to effective treatments. However, it is unclear that different treatments impact arterial inflammation differentially.

These observations in the general population, linking inflammation to plaque rupture and atherosclerotic disease events, help explain the elevated risk of CV disease in rheumatoid arthritis (RA),<sup>9</sup> the most common systemic autoimmune inflammatory arthritis, affecting approximately 0.5%–1% of adults.<sup>10</sup> Many studies demonstrate an approximately 50% increased risk of CV events among this group.<sup>11,12</sup> While epidemiologic studies have identified associations between many aspects of RA and CV disease, including glucocorticoid use, non-steroidal anti-inflammatory drug use and dyslipidaemia,<sup>13</sup> RA disease activity appears to be strongly and independently correlated with CV events.<sup>14–17</sup> Furthermore, it may be possible to modify CV risk through various treatment strategies known to impact disease activity in RA.

Prior studies have examined the impact of immunomodulators on CV disease in the general population. Randomised controlled trials (RCTs) found IL-1 $\beta$  blockade and colchicine reduced event rates, but low-dose methotrexate had no impact in patients without RA.<sup>7 8 18</sup> Many non-randomised studies in patients with RA demonstrate a potential impact of immunomodulators on CV events; meta-analysis of observational studies of CV events suggests a 54% reduction with TNF inhibition,<sup>19</sup> a 21% reduction with low-dose methotrexate<sup>20</sup> and a 47% increase in risk with glucocorticoid use.<sup>21</sup>

Apart from two safety trials,<sup>22 23</sup> data regarding potential benefits of immunomodulators and CV disease among people with RA are largely derived from non-randomised studies. We conducted an RCT among people with RA with continued moderate disease activity despite low-dose methotrexate use to assess the impact of two anti-inflammatory strategies, measured using <sup>18</sup>F-fluorodeoxyglucose-positron emission tomography/CT (FDG-PET/CT) (a predictor of atherosclerotic disease events). The objective of the trial was to determine whether a strategy of adding a TNF inhibitor (TNFi) to low-dose methotrexate results in greater reduction in arterial inflammation than addition of hydroxychloroquine and sulfasalazine to low-dose methotrexate (triple therapy). A secondary objective was to assess the impact of disease activity reductions on arterial inflammation.

## METHODS

### Study design and participants

The Treatments Against RA and Effect on FDG-PET/CT trial was a 24-week multicentre randomised active comparator trial conducted at 41 centres in the USA between 2015 and 2021.<sup>24</sup> The key FDG-PET/CT measure used as the primary outcome was target to background ratio (TBR), which is a reproducible method for measuring arterial FDG uptake, shown to correlate with histological markers of inflammation, and used in several prior studies.<sup>25–28</sup>

Patients and their clinicians were not masked to the treatment assignment, but joint examiners and image assessors were masked. Randomisation occurred centrally in permuted blocks based on baseline use of glucocorticoids, 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (ie, statins) and prior hydroxychloroquine use.

All patients had RA and at least moderately active disease at screening (disease activity score in 28 joints, DAS28-CRP >3.2),<sup>29</sup> despite use of  $\geq 15$  mg per week of methotrexate for  $\geq 8$  weeks. Alternatively, patients could have been using  $\geq 7.5$  mg of methotrexate weekly for  $\geq 8$  weeks if they had a documented intolerance to higher methotrexate dosages and were using a stable dosage for the previous 4 weeks. These patients were potentially eligible if they additionally met all of the following inclusion criteria at screening: women  $\geq 50$  years of age or men  $\geq 45$ ; no more than moderate intensity statins with stable dosage for  $\geq 6$  weeks and no plans to change during the 6 months of the trial; a glycated haemoglobin <7%; no known CV disease;  $\leq 10$  mg of prednisone (or its equivalent) per day and no use of a targeted biologic or synthetic disease modifying antirheumatic drug in the last 6 months (see online supplemental table 1 for a complete listing of selection criteria). Subjects who provided informed consent and remained eligible after screening underwent a baseline FDG PET/CT scan, followed by randomisation to add a TNFi or triple therapy to methotrexate. Follow-up occurred every 6 weeks (see online supplemental figure 1 for a study schema) until study completion at week 24 (because of the COVID-19

pandemic, acceptable dates for the final study visit and final FDG-PET/CT scan were broadened).

The study protocol was reviewed and approved by the Mass-General Brigham Healthcare Human Subjects Committee. Several sites used a local Institutional Review Board for oversight. There was no public or patient input on the study design or interpretation.

### Procedures

Subjects remained on the baseline dosage of weekly methotrexate (not provided by study) and were randomised to a TNFi—adalimumab 40 mg every other week or etanercept 50 mg every week—or triple therapy. Triple therapy consisted of the addition of sulfasalazine 1 g two times per day and hydroxychloroquine 200 mg two times per day (not to exceed 6.5 mg/kg of body weight). Subjects who did not reach low disease activity (DAS28-CRP  $\leq 3.2$ ) by week 18 could switch to the other TNFi (if randomised to TNFi, n=19) or to leflunomide 20 mg/day (n=33) from methotrexate (if triple therapy). Sites managed folic acid supplementation according to routine clinical care. Oral glucocorticoid dosage increases or decreases of no more than 3 mg/day were allowed but not >10 mg/day; intra-articular glucocorticoid injections were allowed but not within 1 month of either FDG-PET/CT scan.

We assessed adherence to study medications by counting pills or syringes of the study medications. Subjects' use of study drug was considered adherent if they used at least 80% of dosages of randomised medicines based on pill or syringe counts.

### Outcomes

The primary outcome was the change in the mean of the maximum of the TBR in the most diseased segment (MDS) of either carotid artery or the aorta as measured by FDG-PET/CT scans conducted at baseline and after 24 weeks of randomised treatment allocation (MDS meanmaxTBR of the index vessel). The MDS of the index vessel was identified by the biostatistical team using the reads of the baseline FDG-PET/CT scan, according to a pre-specified algorithm. Cardiac FDG-PET/CT imaging was performed on different machines in this multisite study. All imaging sites underwent a standardised training, and all images had to pass quality assurance before assessment (see online supplemental methods for scan acquisition protocol and image assessment). In brief, 370 MBq (10 mCi) of FDG was administered intravenously after an overnight fast. PET images were acquired approximately 90 min later, with patients in the supine position. Images were batch-analysed by investigators blinded to patients' randomised treatment assignment as well as to imaging timepoint. FDG uptake was evaluated within the walls of ascending aorta and carotid arteries (as maximum and mean standardised FDG uptake value (standardised uptake value (SUV), max and SUVmean, respectively)) approximately every 5 mm on axial images.<sup>30</sup> The MDS meanmaxTBR (TBR) was calculated as the ratio of the average arterial SUV to blood SUV to correct for the blood compartment contribution.<sup>28 30</sup> As noted above, TBR is reproducible and correlates with markers of inflammation; it has been used in multiple prior studies.<sup>25–28</sup> During the trial, 18 scans were read twice by the same reader. We calculated intraclass correlations (ICCs) for the MDS TBR of each vessel at each time point. For all vessels and timepoints, the ICC was >0.82 indicating good reliability of intra-reader assessments of CV inflammation.

DAS28-CRP was a pre-specified secondary outcome.<sup>29</sup> This was measured at baseline, weeks 6 and 18, and then at the final

**Table 1** Baseline patient characteristics of patients included in final analyses

	All patients (n=115)	MTX+TNF inhibitor (n=58)	Triple therapy (n=57)
	n (%) or median (IQR)		
Age, years	58.0 (53.0, 65.0)	58.0 (53.0, 66.0)	59.0 (54.0, 63.0)
Sex, female	82 (71.3)	39 (67.2)	43 (75.4)
Race			
White	90 (80.4)	49 (87.5)	41 (73.2)
Black	12 (10.7)	6 (10.7)	6 (10.7)
Other	10 (8.9)	1 (1.8)	9 (16.1)
Ethnicity			
Hispanic	31 (27.0)	15 (25.9)	16 (28.1)
Non-Hispanic	84 (73.0)	43 (74.1)	41 (71.9)
RA disease duration, years	1.4 (0.5, 6.6)	1.5 (0.5, 7.2)	1.4 (0.5, 5.3)
Serologic status, positive	63 (56.8)	35 (61.4)	28 (51.9)
DAS28-CRP	4.8 (4.0, 5.6)	4.9 (4.0, 5.5)	4.6 (3.7, 5.6)
hsCRP (mg/L)	3.9 (1.6, 9.8)	3.9 (1.4, 7.6)	4.0 (1.8, 11.1)
Glucocorticoid use	38 (33.0)	20 (34.5)	18 (31.6)
NSAID use	46 (40.0)	26 (33.8)	20 (35.1)
Aspirin use	28 (24.4)	19 (32.8)	9 (15.8)
Methotrexate weekly dose (mg)	20.0 (15.0, 25.0)	20.0 (20.0, 25.0)	20.0 (15.0, 25.0)
Health assessment questionnaire	1.1 (0.5, 1.8)	1.1 (0.4, 1.8)	1.3 (0.6, 1.6)
Body mass index (kg/m <sup>2</sup> )	29.3 (25.7, 33.2)	29.5 (26.2, 34.1)	28.8 (25.7, 32.9)
Hypertension	52 (45.2)	28 (48.3)	24 (42.1)
Hyperlipidaemia	23 (20.0)	12 (20.7)	11 (19.3)
Diabetes mellitus	2 (1.7)	2 (3.5)	0 (0.0)
Tobacco use			
Current	14 (12.2)	4 (6.9)	10 (17.5)
Past	30 (26.1)	18 (31.0)	12 (21.1)
Never	71 (61.7)	36 (62.1)	35 (61.4)
Statin use			
None	93 (80.9)	47 (81.0)	46 (80.7)
Low-moderate intensity	20 (17.4)	10 (17.2)	10 (17.5)
High intensity*	2 (1.7)	1 (1.7)	1 (1.8)
Any cardiovascular risk factor†	63 (54.8)	31 (53.5)	32 (56.1)

\*High intensity statin use was an exclusion. The inclusion of these two patients was considered a protocol violation and only determined after randomisation and treatment initiation.

†Cardiovascular risk factors include the presence of hypertension, diabetes, hyperlipidaemia or current tobacco use (all self-reported at baseline). DAS28, disease activity score in 28 joints; hsCRP, high sensitivity C reactive protein; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

study visit. Biomarkers of CV risk were assessed at baseline and final study visit, including total cholesterol, high density lipoprotein, low density lipoprotein, triglycerides, high-sensitivity CRP (hsCRP) and high sensitivity troponin T (all measured using Roche assays).

### Statistical analyses

We originally proposed to enrol 200 participants based on previous data in patients with RA which observed a baseline TBR of 2.51 (SD of 0.33) and a 0.46 reduction after 8 weeks of a TNFi.<sup>31</sup> We re-estimated sample size using blinded data from 45 subjects in the trial, and determined that  $\geq 115$  participants with

two evaluable FDG-PET/CT scans would provide 99% power to detect an absolute difference in TBR of 0.17 between the two treatment groups; this change in sample size was approved by the Data Safety Monitoring Board. This difference corresponds to the effect observed in a prior study among patients with RA<sup>31</sup> and is similar in magnitude to what was observed between a low-dose versus high-dose statin,<sup>30</sup> a contrast with known clinical significance.<sup>32</sup> To account for anticipated dropout and non-evaluable FDG-PET/CT scans, we aimed to enrol at least 150 subjects.

We compared the baseline characteristics of those randomised to TNFi plus methotrexate versus triple therapy using  $\chi^2$  tests or Fisher's exact tests for categorical variables and Wilcoxon rank sum tests for continuous variables. For the analysis of the primary outcome, we estimated the change in each treatment group separately and assessed the statistical significance of those changes using a paired t-test. We then used an analysis of covariance (ANCOVA) model to estimate the change in TBR as a function of the baseline TBR, treatment group and the randomisation strata (statin use at baseline, oral steroid use at baseline and hydroxychloroquine use at baseline). A p value threshold of 0.05 for a two-sided test was used to determine statistical significance. The primary analysis only included participants with imaging data that could be evaluated at baseline and follow-up.

As described in the Statistical Analysis Plan (see online supplemental file 1), a series of pre-planned secondary outcomes and exploratory subgroup analyses were performed. The secondary outcomes included the MDS TBR or average TBR of the aorta and carotids, as well as the SUV of the index vessel. In addition, the exploratory subgroup analyses stratified treatment groups by achievement of low disease activity, serologic status, presence of CV risk factors, baseline glucocorticoid use, sex, age, disease duration and statin use. We formally tested for interaction between randomised treatment assignment and these factors by using an interaction term. The primary analyses were repeated among patients considered adherent (at least 80% of pills or syringes). An additional secondary analysis compared the primary vascular inflammation outcome (TBR) change between adalimumab and etanercept users. We examined whether the magnitude of the treatment response achieved by individuals was related to the disease activity response and treatment group. Details of this analysis are described in the online supplemental methods. We compared DAS28-CRP treatment response at the final follow-up between the two treatment groups, using ANCOVA.

Three further post hoc exploratory analyses were conducted. First, we assessed whether changes in DAS28-CRP from baseline to final follow-up were associated with changes in TBR using an ANCOVA model adjusting for randomised treatment assignment, age, gender, disease duration, smoking status, serologic status and body mass index. Second, we examined changes in CV risk factors between the two treatment groups. Finally, we examined changes in glucocorticoid use during the trial.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

### RESULTS

One hundred and fifty-nine patients were recruited and randomised between 16 March 2016 and 20 November 2021; 138 completed follow-up and 115 had paired FDG-PET/CT scans that were analysable for the primary outcome (TBR) (see online supplemental figure 2). The 44 patients not included in

**Table 2** Results of FDG-PET/CT scans target to background ratio comparing subjects randomised to TNF inhibitors versus triple therapy

Arterial location assessed	Baseline		Follow-up		Differences ( $\Delta$ =baseline to follow-up)			P value
	TNFi	Triple therapy	TNFi	Triple therapy	$\Delta$ TNFi	$\Delta$ Triple therapy	TNFi versus triple therapy $\beta$ (95% CI)	
<b>Primary outcome</b>								
MDS of index vessel*	2.72 (0.75)	2.62 (0.51)	2.47 (0.68)	2.43 (0.51)	-0.24 (0.51)	-0.19 (0.51)	-0.02 (-0.19 to 0.15)	0.79
<b>Secondary outcomes†</b>								
MDS of aorta	2.67 (0.79)	2.64 (0.50)	2.50 (0.69)	2.47 (0.42)	-0.17 (0.52)	-0.17 (0.39)	0.01 (-0.14 to 0.17)	0.87
Aorta	2.46 (0.66)	2.48 (0.43)	2.45 (0.74)	2.42 (0.38)	-0.02 (0.43)	-0.06 (0.34)	0.03 (-0.11 to 0.18)	0.64
Bilateral carotids	2.13 (0.36)	2.21 (0.44)	2.07 (0.51)	2.11 (0.46)	-0.06 (0.48)	-0.10 (0.51)	-0.003 (-0.20 to 0.19)	0.98
Index vessel	2.51 (0.62)	2.45 (0.45)	2.43 (0.74)	2.38 (0.47)	-0.09 (0.43)	-0.07 (0.47)	-0.01 (-0.17 to 0.16)	0.94

Follow-up value is at study conclusion (approximately 24 weeks). Triple therapy refers to the use of weekly methotrexate, sulfasalazine 1000 mg two times per day, and hydroxychloroquine 200–400 mg per day. Counts of the number of individuals included in each analysis: TBR MDS—TNFi=58, triple therapy=57; aorta—TNFi=56, triple therapy=52; left carotid—TNFi=44, triple therapy=41; right carotid—TNFi=43, triple therapy=42; average carotid—TNFi=45, triple therapy=43.

\*When vessel is not specified, the measurement refers to the index vessel with the most diseased segment.

†P values for the secondary outcomes are nominal and not corrected for multiple testing. All  $\beta$  estimates and p values are from ANCOVA models that estimate the change in TBR as a function of the baseline TBR, treatment group and the randomisation strata.

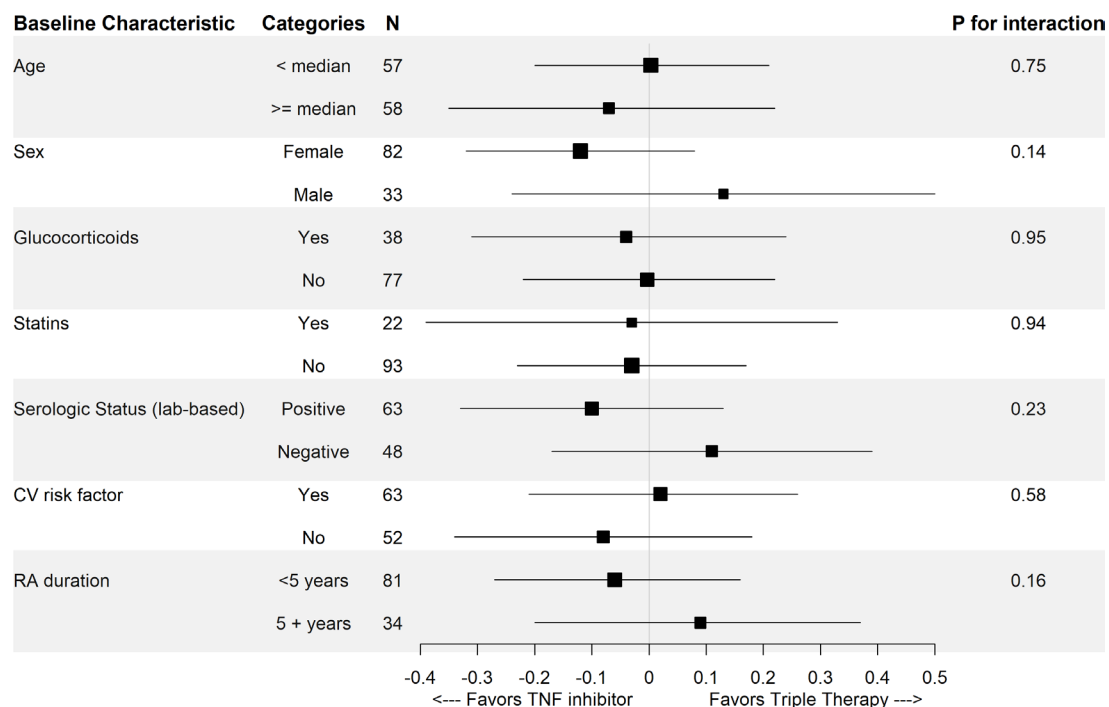
ANCOVA, analysis of covariance; FDG-PET/CT, 18F-fluorodeoxyglucose positron emission tomography/CT scan; MDS, most disease segment examining right and left carotid arteries and aorta; TBR, target to background ratio; TNFi, TNF inhibitor.

the primary analysis were similar to the 115 who were included (see online supplemental table 2). The subjects included in the main analysis were well balanced across the two treatment groups (see table 1): median age was 58.0 years, 71% were women; median RA duration 1.4 years and median baseline disease activity was moderate, DAS28-CRP 4.8. Median hsCRP was elevated (median of 3.9 mg/L). Median methotrexate dosage was 20 mg per week, and glucocorticoids were used by 33% of subjects. 1.7% of subjects were diagnosed with diabetes and 17.4% used low or moderate intensity statins. Small differences were noted between treatment arms in the distribution of race.

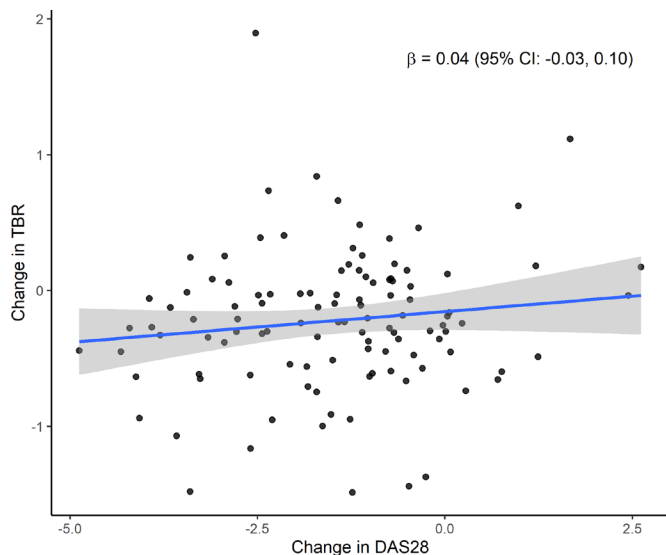
The FDG-PET/CT vascular inflammation assessments at baseline and at final follow-up (24 weeks) were similar across the two treatments groups (see table 2). Both groups experienced statistically significant reductions in TBR between baseline and

follow-up, change in TNFi -0.24 (SD 0.51; p=0.001) and change in triple therapy -0.19 (SD 0.51; p=0.001). However, the difference in the improvement in TBR between the two treatment groups was not statistically significant (baseline adjusted difference in changes: -0.02, 95% CI -0.19 to 0.15, p=0.79).

The secondary imaging outcomes agreed with the primary outcome results (see table 2). The results for the primary outcome were similar across subgroups (see figure 1); all interaction p values were non-significant. In the secondary per protocol analyses that only included subjects deemed to have >80% adherence to randomised study medications (n=65), we also observed no difference in the improvement in TBR (difference in changes: 0.03, 95% CI -0.20 to 0.26, p=0.80). More lenient definitions of adherence gave similar results (see online supplemental table 3). We observed no difference in the improvement



**Figure 1** This forest plot demonstrates subgroup results of the change in MDS TBR on the FDG-PET/CT scan. CV, cardiovascular; FDG-PET/CT, fluorodeoxyglucose positron emission tomography CT scan; MDS, most diseased segment; RA, rheumatoid arthritis; TBR, target to background ratio.



**Figure 2** This figure demonstrates the correlation between change in rheumatoid arthritis disease activity (DAS28-CRP) and vascular inflammation (MDS TBR) ( $\beta=0.05$ , 95% CI  $-0.02$  to  $0.11$ ). Additional adjustment for baseline TBR, randomised treatment assignment, age, gender, disease duration, smoking status, serologic status and body mass index did not change the results ( $\beta=0.04$ , 95% CI  $-0.03$  to  $0.10$ ). CRP, C reactive protein; DAS28, disease activity in 28 joints; MDS, most diseased segment; TBR, target to background ratio.

in TBR comparing adalimumab users to etanercept users ( $\beta$  0.09, 95% CI  $-0.15$  to  $0.34$ ,  $p=0.46$ ).

RA disease activity was significantly reduced and to the same extent between baseline and follow-up in both treatment arms (see online supplemental figure 3). Each component of the DAS28-CRP was also reduced between baseline and follow-up. Although we observed decreases in DAS28-CRP over time, these changes were not associated with improvements in TBR (figure 2 (adjusted  $\beta$  0.04, 95% CI  $-0.03$  to  $0.10$ )).

To better understand whether the effect of treatment on TBR varied by the effect of the treatment on RA disease activity, we compared changes in TBR by disease activity within treatment groups (see online supplemental table 4). None of the TBR

changes by RA disease activity groups were significant. We also examined whether there were any differences between baseline and final follow-up values for CV risk factors, including biomarkers, between the two treatment groups (see table 3). The only difference between treatment groups was for triglycerides, where we observed larger reductions for triple therapy than for TNFi, and for hsCRP, where we observed larger reductions for TNFi than for triple therapy. Finally, we examined changes in prednisone dosages during the trial (see online supplemental table 5) and found a trend towards more glucocorticoid use after randomisation among subjects in the triple therapy group.

**DISCUSSION**

This randomised active comparator trial is the first to explore the effect of disease modifying anti-rheumatic drugs (DMARDs) on vascular inflammation in RA. We compared the change in TBR, a biomarker for atherosclerotic vascular inflammation, over 24 weeks between two RA treatment strategies. Both strategies—adding a TNFi or triple therapy (sulfasalazine and hydroxychloroquine) to weekly methotrexate—resulted in significant within-group reductions in vascular inflammation as measured by FDG-PET/CT. However, the between group changes were not statistically different. While both treatments had similar statistically significant benefits on disease activity, there was no correlation between improvements in disease activity and the change in TBR.

This work builds on prior studies demonstrating the importance of inflammation and immunomodulation on CV risk.<sup>7-33</sup> FDG-PET/CT imaging was used as an intermediate endpoint of arterial inflammation based on the reproducible observation that arterial FDG uptake associates with atherosclerotic inflammation on histology.<sup>28</sup> The ability of FDG-PET to identify tissue inflammation in patients has led to guideline-level recommendations for its use for imaging in aortitis, device infections, endocarditis and sarcoidosis.<sup>34</sup> Further, the arterial FDG signal is predictive of subsequent CV risk,<sup>27,35</sup> and reductions in the arterial FDG signal may be clinically important. For drugs where there are both clinical outcomes data and FDG-PET imaging trial data, there is concordance between changes seen on imaging and apparent clinical benefits.<sup>36</sup> Notably, the 7%–9% reduction in the arterial FDG signal that was seen in both treatment

**Table 3** Changes in cardiovascular risk factors from baseline to final follow-up between treatment arms

Cardiovascular risk factor	Baseline		Follow-up		Differences ( $\Delta$ =baseline to follow-up)			P value*
	TNFi	Triple therapy	TNFi	Triple therapy	$\Delta$ TNFi	$\Delta$ Triple therapy	TNFi versus triple therapy $\beta$ (95% CI)	
Blood pressure, mm Hg	Mean (SD) unless noted							
Diastolic	77.2 (8.7)	77.4 (10.2)	78.9 (7.3)	78.7 (8.5)	1.7 (9.8)	1.3 (9.9)	0.3 (–2.5 to 3.0)	0.85
Systolic	129.1 (16.5)	130.1 (17.2)	131.6 (15.6)	132.4 (13.4)	2.5 (14.2)	2.3 (18.1)	–0.4 (–5.2 to 4.3)	0.85
Total cholesterol, mg/dL	202.2 (34.7)	206.3 (37.9)	210.4 (35.4)	205.9 (43.0)	8.1 (28.7)	–0.3 (35.8)	7.0 (–4.5 to 18.5)	0.23
Low density lipoprotein, mg/dL	104.6 (27.7)	104.1 (26.1)	107.9 (28.3)	104.1 (30.7)	3.3 (20.8)	0.01 (25.9)	3.5 (–4.8 to 11.9)	0.40
High density lipoprotein, mg/dL	58.3 (15.8)	53.8 (18.3)	58.4 (17.7)	59.8 (18.0)	0.2 (17.5)	6.0 (14.0)	–3.8 (–9.1 to 1.6)	0.16
Triglycerides, mg/dL	113.0 (46.5)	125.3 (52.8)	121.3 (55.3)	113.7 (46.3)	8.3 (35.0)	–11.6 (44.1)	16.8 (2.74 to 31.0)	0.02
Log(hsCRP), mg/L	1.4 (1.3)	1.4 (1.4)	0.6 (1.4)	1.3 (1.3)	–0.8 (1.2)	–0.1 (0.9)	–0.6 (–1.0 to 0.3)	<0.001
hsTnT, ng/L								
All participants	8.4 (5.0)	8.3 (4.2)	8.9 (6.2)	8.0 (3.2)	0.6 (2.1)	–0.3 (2.8)	0.88 (–0.05 to 1.81)	0.06
Among those with values >6.0†	11.1 (6.5)	10.9 (5.3)	12.0 (8.2)	10.2 (3.7)	1.0 (2.9)	–0.7 (3.9)	1.7 (–0.3 to 3.8)	0.10

Follow-up value is at study conclusion (approximately 24 weeks). Triple therapy refers to the use of weekly methotrexate, sulfasalazine 1000 mg two times per day and hydroxychloroquine 200–400 mg/day.

\*P values for these outcomes are nominal and not corrected for multiple testing. All  $\beta$  estimates and p values are from ANCOVA models that estimate the change in cardiovascular risk factor as a function of the baseline value, treatment group and the randomisation strata. hsCRP p value is from a Wilcoxon rank sum test.

†Lower limits of detection.

ANCOVA, analysis of covariance; hsCRP, high-sensitivity CRP; hsTnT, high-sensitivity cardiac troponin T; TNFi, TNF inhibitor.

arms is similar to the signal reduction previously achieved with 10 mg atorvastatin.<sup>30</sup> Thus, the degree of arterial inflammation reduction seen in the current study is similar to that seen with moderate intensity statin therapy,<sup>30,37</sup> which is known to significantly lower CV risk. While there have been no FDG PET/CT scan studies in patients with RA that correlated scan assessments (TBR in MDS) with CV events, or compared scan measures between RA and non-RA groups, the TBR values in patients with RA are very similar to matched controls with known CV disease, supporting the use of FDG-PET/CT as a marker of CV risk in this study.<sup>31,38</sup>

The trial results demonstrate the differences between patients with RA and the general population. In the current study, TNFi was not superior to triple therapy in reducing vascular inflammation measured by FDG-PET/CT. As noted above, we hypothesised that TNFi would be superior in reducing vascular inflammation compared with triple therapy. This theory was based on the fact that vascular endothelium is a select target for TNF where it induces pro-inflammatory, pro-coagulant and pro-apoptotic genes known to damage the endothelium.<sup>39</sup> In addition, TNF induces endothelial adhesion molecules which mediate inflammatory cell trafficking to the arterial walls where oxidised low density lipoprotein (LDL) accumulates in an early stage of atherosclerosis.<sup>40</sup> Prior trials in the general population have shown differential effects on CV risk between different immunomodulators. The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) trial performed in people with elevated hsCRPs and known CV disease demonstrated that IL-1 $\beta$  blockade reduced CV events, but the Cardiovascular Inflammation Reduction Trial performed in people with less systemic inflammation and known CV disease demonstrated no reduction in CV events with low-dose methotrexate.<sup>7,18</sup> Neither of these trials enrolled patients using baseline immunomodulators. While these trials used different immunomodulators and were event-driven, the results from the general population stand in distinction to the current trial, where two different immunomodulator treatment strategies produced similar reductions in CV risk as measured by FDG-PET/CT. It is possible that patients with RA who have a high degree of systemic inflammation achieve similar CV risk improvements measured by FDG-PET/CT with different treatment strategies. Additionally, both RA treatment strategies achieved similar benefits on disease activity. As suggested by prior observational studies, the similar improvement in RA disease activity may partially explain the lack of observed difference in vascular inflammation reduction; however, not all studies of RA disease activity have demonstrated convincing associations with CV events.<sup>15-17</sup> Future PET-CT studies investigating RA therapies with differing mechanisms than the ones used in this study (eg, IL-6 inhibitors, B cell depleting antibodies, Janus kinase inhibitors) may further inform this area of investigation.

Randomisation is a major strength of our study, which resulted in balanced treatment groups. Table 1 suggests minor imbalance in several variables, but none qualified to be included in the primary regression analysis based on the statistical analysis plan. Limitations of our methods include the lack of patient and clinician masking; this may have impacted patient's global assessments. However, all other assessments (joint counts and image assessments) were masked. Adherence to the randomised treatment assignment was poor (56.5% with >80% adherence to randomised medicines). However, per protocol analyses and more lenient definitions of adherence agreed with the primary analyses, suggesting that lower than expected adherence is unlikely to explain the null effect. Further, there were no reports of crossover between treatments. We also had to modify the

follow-up protocol because of the COVID-19 pandemic. This impacted the last year of the trial, resulting in several follow-up scans being delayed; however, controlling for these delays did not affect the results. The trial was relatively small with short duration of follow-up, limiting the statistical power for the secondary exploratory analyses. We also were encouraged to re-estimate sample size after the start of the trial by the data safety monitoring board.<sup>31</sup> While re-estimation of sample size after the start of an RCT may be considered unorthodox, the pre-trial estimation was based on data from a small observational study among patients with RA. The re-estimation of the sample size during the trial was approved by the data safety monitoring board and was performed blinded to treatment group.<sup>41</sup> Correlations between surrogate imaging markers and CV risk are not perfect; some have suggested that FDG-PET/CT may indicate hypoxia and metabolic activity broadly and not only inflammation.<sup>42</sup> While a trial with CV events as the outcome would have been preferred, this was not practical as it would have required thousands of patients with RA, larger than any prior RCT in RA.

In conclusion, we conducted a randomised active comparator trial to compare the effects of two different accepted RA treatment strategies on vascular inflammation among patients with active RA despite weekly methotrexate. Vascular inflammation, as measured by FDG-PET/CT, was significantly reduced within both treatment strategies, without differences between the two treatment groups. Future studies will explore the mechanisms by which RA therapies appear to ameliorate vascular inflammation independent of their effect on articular disease activity.

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**Contributors** DHS accessed to all data; designed the trial; wrote the first draft. JTG designed the trial; revised the paper. KPL designed the trial; revised the paper. PMRid designed the trial; revised the paper. PMRiS designed the trial; developed the statistical analysis plan; revised the paper. RJG designed the trial; developed the statistical analysis plan; revised the paper. RB collected data; revised the paper. FL collected data; revised the paper. MTM collected data; revised the paper. KV collected data; revised the paper. LMS analysed the data; revised the paper. SA analysed the data; revised the paper. PMRo analysed the data; revised the paper. VM analysed the data; revised the paper. AT designed the trial; analysed the data; revised the paper. JB accessed to all data; designed the trial; revised the paper. DHS is the guarantor.

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**Data availability statement** Data are available in a public, open access repository. Data will be deposited to the appropriate NIH repository. We anticipate that the data will become available to qualified investigators through the NIH during summer 2023.

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