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Improvement in insulin resistance is greater when infliximab is added to methotrexate during intensive treatment of early rheumatoid arthritis - results from the IDEA study

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Running header: Improvement in insulin resistance is greater when infliximab is added to methotrexate during intensive treatment of early rheumatoid arthritis

Abstract

Objectives: To determine the change in established biomarkers of cardiovascular (CV) risk, namely total cholesterol/high-density lipoprotein cholesterol ratio (TC/HDL-C), N-terminal pro-brain natriuretic peptide (NT-proBNP) and insulin resistance (IR) in patients with early rheumatoid arthritis (RA) treated with two different treat-to-target (T2T) strategies.

Methods: Fasting glucose, lipids, insulin and NT-proBNP were measured at baseline, week 26 and 78 in 79 DMARD-naïve RA patients, free of CV disease (CVD), as part of a double-blind randomised controlled trial of methotrexate (MTX) with either infliximab (IFX) or methylprednisolone (MP) as induction therapy. Homeostasis model assessment-estimated insulin resistance (HOMA-IR) (glucose*insulin/405) was used to measure IR. Multiple imputation was employed, and linear regression analyses were adjusted for baseline values.

Results: Changes in DAS44-CRP did not differ between the treatment arms at week 26 and 78. Mean TC/HDL-C, HOMA-IR and NT-proBNP improved in both groups at week 26 and 78, although change in NT-proBNP was not statistically significant at week 78. Changes in TC/HDL-C and NT-proBNP were similar between treatment arms, but HOMA-IR values in the IFX+MTX arm were 42% lower than those treated with MTX+MP at week 78 (p=0.003); difference remaining significant after adjustment for baseline body mass index, anti-citrullinated protein antibody positivity, smoking status and intra-muscular glucocorticoid use (p=0.007).

Conclusions: When implementing a T2T approach, treatment of early RA was associated with improvement in TC/HDL-C, HOMA-IR and NT-proBNP, and a greater long-term improvement in HOMA-IR was seen in those treated with IFX.

Trial registration: Eudract-2005-005013-37; ISRCTN48638981 (http://www.controlled-trials.com/ISRCTN48638981/idea)

Key words: Rheumatoid arthritis, cardiovascular risk, insulin resistance, methotrexate, infliximab, N-terminal pro-brain natriuretic peptide

INTRODUCTION:

Accelerated cardiovascular disease (CVD) is well-recognised in established rheumatoid arthritis (RA) with similar observations recently reported in early RA [1]. The utility of biomarkers of CV risk used in the general population, remains to be determined [2].

Three commonly measured biomarkers are total cholesterol/high-density lipoprotein cholesterol (TC/HDL-C) [3], the homeostasis model assessment-estimated insulin resistance (HOMA-IR) [4, 5] and N-terminal pro-brain natriuretic peptide (NT-pro BNP) [6]. In RA, the levels of these biomarkers are raised [1, 7, 8], and TC/HDL-C and NT-proBNP have been associated with future CV events [9, 10]. HOMA-IR, a measure of insulin resistance (IR), is an independent predictor of CVD in the general population.

The effect of RA disease suppression on biomarkers of CV risk has not been extensively explored, particularly in early disease. It is clear that CV morbidity and mortality are reduced with the use of disease-modifying anti-rheumatic drugs (DMARDs) [11] and tumour necrosis factor inhibitors (TNFi) [12]. DMARDS appear to reduce TC/HDL-C [13, 14], however, meta-analyses report conflicting results [15, 16], suggesting a complex relationship. IR can be improved with DMARDs in established RA [17], but the effect of TNFi is unclear [18-24]. The limited data on NT-proBNP suggest improvement with TNFi [25].

Few studies have compared the change in biomarkers of CV risk with different treatment strategies in the context of a randomised controlled trial (RCT). Cross-sectional and small open-label studies have found no differences in lipid profile when comparing TNFi to DMARDs [26-28]. The TEAR study is the only previous RCT to assess change in TC/HDL-C. A

similar decrease in TC/HDL-C at week 24 was observed in early RA patients randomised to MTX+etanercept (ETN), triple DMARD therapy or aggressively titrated MTX [29]. No superiority of TNFi over DMARDs was found on changes in HOMA-IR in cross-sectional studies [30]; however, one unblinded RCT of 40 early RA patients given MTX or infliximab (IFX)+MTX reported a lower fasting glucose at 12 months in the IFX arm [27]. Recent observational studies have reported up to 50% reduction in the incidence of diabetes mellitus (DM) in RA patients treated with TNFi compared to DMARDs [31, 32]. To our knowledge, there has not been a double-blinded RCT study, to date, comparing the change in HOMA-IR with TNFi versus non-TNFi in early DMARD-naive RA.

Our first objective was to assess the change in biomarkers of CV risk in DMARD-naïve early RA patients, treated with either IFX+MTX or MTX+methylprednisolone (MP) within the framework of a RCT. Our endpoints of interest included the change in TC/HDL-C, HOMA-IR and NT-proBNP. Our secondary exploratory objective was to determine whether any change seen in biomarkers of CV risk differed depending on treatment strategy.

METHODS

The IDEA study

Infliximab as Induction therapy for Early rheumatoid Arthritis (IDEA) was a multicentre double-blind RCT performed within the Yorkshire network [33], with full ethical approval (RR05/7092, Eudract-2005-005013-37 and ISRCTN48638981).

The study details and results have been recently reported [33], but in brief, consecutive DMARD-naïve patients with 3-12 months symptom duration meeting the 1987 American

College of Rheumatology (ACR) criteria, were recruited into the study. Participants were randomised to receive either IFX+MTX or MTX and a pulse of 250mg IV MP as induction therapy. 120mg intra-muscular (IM) MP was given at weeks 6, 14, 22, 38, 50 and 62 if DAS>2.4. Patients were unblinded at week 26 and subsequently treatment was guided by disease activity according to a pre-determined therapeutic regime.

At baseline, weeks 26 and 78, the presence of CV co-morbidity and traditional risk factors were documented in addition to disease phenotype and activity. Blood pressure, height, weight, hip and waist circumference, and the use of lipid-lowering and antihypertensive therapy were recorded. Patients completed the Rose Angina Questionnaire [34] and Edinburgh Claudication questionnaire [35] at baseline and week 78.

The subset of patients recruited in Leeds, underwent fasting blood collection at baseline, weeks 26 and 78. Glucose, TC, HDL-C, apolipoproteins A (Apo-A) and B (Apo-B), and Lipoprotein A (Lp(a)), NT-proBNP and insulin were determined in serum, LDL-C, HOMA-IR and TC/HDL-C ratio were calculated according to known formulas (see supplementary methods).

Statistical analysis

Analyses were performed in SPSS (version 21, IBM, NY, USA) and Stata (version 13.0, Statacorp, Texas, USA) (details in the online supplementary section). Missing data were managed using multiple imputation by chained equations.

Biomarkers HOMA and NT-proBNP were found to be highly skewed; values were ln-transformed prior to parametric analyses. The exponentiated differences between values on a log scale represent the ratio of one value to another. Therefore, changes between visits have been expressed as the ratio of the follow-up values to the baseline values, and differences between groups represent the ratio of values in the MTX+IFX group to those in the MTX+MP group.

Multiple linear regression was used to show whether changes in biomarkers differed between the treatment groups, controlling for baseline values, and then repeated, controlling for baseline BMI, anti-citrullinated peptide antibody (ACPA) positivity, glucocorticoid dose and smoking status (current vs. ex-/non). Initially interaction terms between treatment group and each covariate were included in each model; however, if they were not significant at $p<0.1$ these terms were subsequently removed before estimating the adjusted treatment effect.

RESULTS

Baseline characteristics

Biomarkers of CV risk data were available for 86/112 patients recruited into the IDEA study. Of these 86, 7 patients (8%) had existing CVD at baseline; 4 (5%) had ischaemic heart disease, 3 (3.5%) cerebrovascular disease and 1 (1%) peripheral vascular disease, and were excluded from subsequent analyses (Figure 1).

In the remaining 79 patients, thirty-eight (48%) received IFX+MTX and 41 (52%) MTX+MP. Baseline clinical characteristics and biomarkers of CV risk are presented in Table 1. When compared to subjects with no biomarker data or those excluded from the analysis due to existing CVD (n=33 in total), those within the CV sub-study were younger (mean (SD) age 51.6 (12.7) vs. 57.3 (12.5) years, p=0.031) and had a lower SJC44 (median (IQR) 8.0 (5.5, 13.0) vs. 12 (6.5, 21), p=0.034). No differences in gender, serology or CRP were recorded.

An extreme outlier with a history of hypertension was identified on analysis of NT-proBNP (3343pg/ml). This subject also had a low HDL-C (34.13mg/dL), a TC/HDL-C ratio of 5.71 and relatively high HOMA-IR (2.94). Data for NT-proBNP with this patient excluded are presented.

Relationship of biomarkers of CV risk with baseline variables

Correlation analyses at baseline revealed no association between TC/HDL-C, HOMA-IR or NT-proBNP and CRP or SJC44 (Table 2). However, HAQ-DI correlated positively with NT-proBNP (rho=0.332, p=0.004), and BMI correlated positively with TC/HDL-C (rho=0.312, p=0.006) and HOMA-IR (rho=0.574, p<0.001). No association was seen between BMI and NT-proBNP, or between WHR and TC/HDL-C, HOMA-IR and NT-proBNP.

There was no difference in TC/HDL-C, HOMA-IR or NT-proBNP according to RF or current smoking status at baseline. Those who were ACPA positive were more likely to have a lower NT-proBNP (median (IQR): 55.25pg/ml (34.02, 93.90) compared to 105.70pg/ml (49.84, 253.10) when ACPA negative (p=0.016); significance was sustained after removal of the

ACPA negative NT-proBNP outlier (p=0.031). ACPA status was not associated with TC/HDL-C or HOMA-IR at baseline

HOMA-IR was higher in those with a raised TC/HDL-C (median (IQR) HOMA-IR if TC/HDL>6: 2.28 (1.79, 3.41) vs. 1.82 (1.16, 3.66) if TC/HDL<6, p=0.017). NT-proBNP was not associated with either HOMA-IR or TC/HDL-C.

Follow-up

Of the patients included in this sub-study, 14/79 (6 IFX+MTX, 8 MTX+MP) did not complete the study treatment schedule for various reasons including failure to suppress disease activity (37). Three patients had missing data at baseline; data on TC/HDL-C, NT-proBNP and HOMA-IR were available for 76 patients at baseline and week 26, and 66 patients at week 78. Values of TC/HDL-C, natural log-transformed HOMA-IR & NT-proBNP, and DAS44-CRP were imputed at weeks 26 and 78, whilst BMI and WHR were imputed at week 78 only. In addition to baseline values of each variable, gender, smoking status, ACPA positivity and mean glucocorticoid requirement were included in the imputation models. One patient developed ischaemic heart disease by week 78, but there were no new cases of DM or peripheral/cerebrovascular disease.

Differences between treatment groups

Disease activity: Consistent with the reported findings, DAS44-CRP in patients within the CV sub-study did not differ between treatment groups at weeks 26 or 78 [adjusted mean difference -0.17 (-0.54, 0.19), t=-0.95, p=0.345, and 0.32 (-0.10, 0.74), t=1.50, p=0.137, respectively].

Biomarkers: Substantive reductions in all three biomarkers were observed at week 26, irrespective of treatment, with no significant differences between the groups at week 26; TC/HDL-C decreased by 0.7-0.9 units, HOMA-IR decreased by 28-29%, whilst NT-proBNP decreased by 16-17% (Table 3). At week 78, TC/HDL-C continued to improve in both groups, whilst NT-proBNP values were similar to week 26. However, the IFX+MTX group showed further improvement in HOMA-IR at week 78 (by 55% relative to baseline), whilst there was some loss of the early week 26 improvements in HOMA-IR in the MTX+MP group. On average at week 78, IFX+MTX HOMA-IR values were 0.58 times as high as those treated with MTX+MP (p=0.003). Findings were similar when restricted to observed data only (see supplementary Table S3). Results for HDL-C, low-density lipoprotein cholesterol (LDL-C), Apo A and B, and Lp(a) are shown in Tables S4-S6.

At week 26 the proportions of patients with at risk ratio of TC/HDL-C were 20.1% and 13.2% in the MTX+MP and IFX+MTX groups, respectively [adjusted OR 0.89 (0.21, 3.78), t=-0.16, p=0.876); at week 78 the proportions were 21.5% and 17.1%, respectively [adjusted OR 1.14 (0.24, 5.28), p=0.870]. At week 26 the proportions of patients with at risk levels of NT-proBNP were 8.0% and 13.2% in the MTX+MP and IFX+MTX groups, respectively [adjusted OR 0.95 (0.15, 6.14), p=0.959]); at week 78 the proportions in the observed data were 0% and 12.9%, thus in some of the imputed datasets (n=5), none of the patients in the MTX+MP group had at risk levels of NT-proBNP at week 78, causing the individual models to fail and making it impossible to obtain a combined estimate of the effect for all 20 sets. This potential difference would need to be confirmed in a future larger study.

Adjusting for potential confounders: BMI, ACPA and smoking

Adjusting for baseline BMI, ACPA and smoking status did not substantively affect the differences in TC/HDL-C between the groups, identify any substantive interactions or associations between the covariates and changes in TC/HDL-C at either time-point.

Associations between ACPA and both HOMA-IP and NT-proBNP were complex, with interactions identified between ACPA and treatment group at one or both time-points (see supplementary material).

In both groups, baseline BMI was positively associated with change in HOMA-IR at week 26 [6.5% increase per unit of BMI (95% CI 2.3%, 10.9%)], but this association was not evident at week 78 (p=0.189). No association with smoking was found at either time-point. Neither baseline BMI nor smoking status was associated with change in NT-proBNP.

Substituting WHR for BMI in the above analyses did not substantially alter the outcomes. Controlling for baseline BMI, there was no substantive difference between the groups in the mean change in BMI at 78 weeks; there was a slight increase in both groups [mean MTX+MP=0.93, IFX+MTX =0.36, adjusted mean difference (95% CI) -0.12 (-0.26, 0.048), t=-1.45, p=0.156]. Change in WHR at week 78 was negligible in both groups.

Additional glucocorticoid requirements

The groups did not differ in the median (IQR) intra-articular (IA)/IM glucocorticoid injection dose received per month [MTX+MP 20.1mg (6.7, 26.8), IFX+MTX 13.4mg (0.0, 20.4); Mann-Whitney U z=1.31, p=0.189]. Adjusting for the total IA/IM glucocorticoid received per month did not affect the overall results; for example, having adjusted for baseline BMI, smoking

status, ACPA positivity and glucocorticoid dose, the between-group ratio of HOMA-IR values at week 78 was 0.61 [95% CI (0.43, 0.87), t=-2.82, p=0.007]. For patients with medication data available throughout the 78 week follow-up there were no statistically significant differences between the groups in the cumulative doses of IA/IM glucocorticoid injections received during the first 26 weeks and between weeks 27-78 (Table S7); this is further illustrated in cumulative distribution plots of total steroid dose at 26 and 78 weeks (Figure S1). There were no substantive correlations between the change in HOMA-IR and the total IA/IM steroid received, at 26 or 78 weeks, in combined treatment groups or separately within each group (all rho<0.3).

Seventeen patients (6 MTX+MP, 11 IFX+MTX) received no additional IM glucocorticoid during the follow-up; although this subgroup was small; the results were comparable to those reported for the full cohort [mean ratio without adjusting for BMI, smoking or ACPA 0.39 (0.18, 0.85); with adjustment for additional covariates 0.48 (0.19, 1.23)]. A small number of patients received oral glucocorticoids; 3 in the IFX group [total doses 1320mg, 560mg, 150mg], 7 in the MP group [doses 916mg, 816mg, 1418mg, 952mg, 560mg, 280mg and another who received a short course of 30mg prednisolone daily for a respiratory infection]. Excluding these patients and those who received any IA/IM glucocorticoid, revealed there was still a difference between the groups for change in HOMA-IR at week 78 (IFX+MTX value 0.39 times as high as MTX+MP group value (95% CI 0.17, 0.88), p=0.027 (n= 16, 10 IFX+MTX, 6 MTX+MP). Full details of escalation therapy received by patients in each treatment group are presented in Table S8.

Patients with a history of diabetes mellitus (DM) or who were receiving statins

There were 3 patients in each group with DM; there were 5 in the MTX+MP group and 8 in the MTX+IFX group who had received statins at any point during follow-up. In a subgroup analysis that excluded these patients, the differences in HOMA-IR at week 78 remained (ratio 0.58 (0.40, 0.84), t=-2.93, p=0.005; 35 MTX+MP, 32 MTX+IFX; Table S9).

Analysis according to treatment response (ACR20) at 26 and 78 weeks

In the observed data, splitting the patients according to ACR20 response at 26 and 78 weeks (Table 4) revealed that in non-responders at week 26, greater reductions were seen in the MTX+IFX group in HOMA-IR (ratio 0.62 [0.33, 1.17]) and NT-proBNP (ratio 0.70 [0.40, 1.25]). These differences were substantive, although not statistically significant in these small subgroups. There was no substantive difference in TC/HDL-C (difference 0.11 [-0.95, 1.17]). In patients who had achieved an ACR20 response at week 26, there was no difference in HOMA-IR (ratio 1.00 [0.73, 1.38]) as this had decreased in both groups to a similar degree; the decrease in NT-proBNP was slightly greater in the MTX+MP group (ratio 1.23 [0.86, 1.76]). There was some indication of a greater reduction in TC/HDL-C in the MTX+IFX group (difference -0.22 [-0.91, 0.48]. However, none of the differences were statistically significant.

At week 78, there was only a handful of patients in either group (8 MTX+MP, 6 MTX+IFX) that had not achieved ACR20 response, which limits the accuracy of the estimates in these subgroups. In non-responders HOMA-IR had decreased in both groups (ratio 0.97 [0.55, 1.71]), whilst NT-proBNP had decreased in the MTX+MP group and remained stable in MTX+IFX (ratio 1.81 [0.80, 4.11]). Decrease in TC/HDL-C was descriptively greater in the MTX+IFX group (difference -0.25 [-1.66, 1.16]).

Amongst ACR20 responders at week 78, HOMA-IR did not change in the MTX+MP group, but decreased in the MTX+IFX group (between-group ratio 0.48 [0.33, 0.71]); this difference was highly significant. It is interesting to note that the reduction in HOMA-IR at 78 weeks in the MTX+IFX group was around 40% irrespective of ACR20 response.

In ACR20 responders there was no difference at week 78 between treatment groups in NT-proBNP (ratio 0.97 [0.65, 1.43]). There was not a statistically significant difference in TC/HDL-C (-0.31 [-0.89, 0.26]); the difference between groups was similar irrespective of ACR20 response.

Combined group analysis

Controlling for baseline values, and irrespective of treatment strategy, there was no evidence that changes in TC/HDL-C, HOMA-IR or NT-proBNP during 78 weeks of follow-up were associated with changes in DAS44-CRP over the same period (Table 5). However, patients achieving ACR70 responses had lower TC/HDL-C (differences between the means: 0.68 units, p=0.012) and their HOMA-IR values were 31% lower on average (p=0.042) than those who did not achieve a response. Change in BMI at week 78 was not associated with changes in TC-HDL-C, HOMA-IR or NT-proBNP, but HOMA-IR increased by 35.2% for each additional 10% of WHR (p=0.033).

Use of CVD screening questionnaires

Eleven of 76 patients, who completed the Rose Angina questionnaire at baseline, declared they had chest pain. However, 9 patients mapped the pain to joints, and 8 were thought not to be angina-related when assessed by the sub-investigator. Of 76 patients who completed the Edinburgh claudication questionnaire at baseline, 39 reported leg pain, however, 30

mapped the pain to joints and 31 were marked by sub-investigator as not related to intermittent claudication. Similar results were seen at week 78.

DISCUSSION

This RCT demonstrated that treatment of DMARD naïve RA, with either IFX+MTX or MTX+MP induction therapy, combined with a T2T approach, can improve biomarkers of CV risk. In addition, despite similar end-of-study disease activity levels, we demonstrated a superiority of IFX+MTX over MTX+MP in the margin of improvement in HOMA-IR, independent of BMI and IA/IM glucocorticoid use.

Our baseline analysis revealed no association of TC/HDL-C with markers of disease activity, similar to reports from established RA cohorts [36], supporting the opinion TC/HDL-C may be more reliable in calculating long-term CV risk than other lipid measurements such as LDL-C which decreases with inflammation ('lipid paradox'). There is evidence to support the synthesis of NT-proBNP following inflammatory cytokine release [37]. We, however, failed to identify an association of NT-proBNP with inflammation and disease activity (excluding HAQ-DI); this is in contrast to several studies that included patients with longer disease durations [7, 38]. In one early RA study, NT-proBNP correlated with baseline CRP, predicting NT-proBNP with repeated measures at 10 years [39], however, CV co-morbidity data was not collected limiting its application to those without clinical CVD. Given that NT-proBNP reflects the final stages in the pathogenesis of CVD, its utility in early RA could be limited. We found no evidence to support higher NT-proBNP levels in early RA.

An improvement was seen in TC/HDL-C and IR in both treatment groups after 26 weeks, sustained at week 78. The improvement in TC/HDL-C occurred due to an increase in both HDL-C and LDL-C (Tables S5-6). Similar magnitudes of change have been reported previously [13]. The effect of therapy on HOMA-IR has been less well studied [40], with most reporting the effect of TNFi alone, involving small established RA cohorts [19, 20] or short-term follow-up [18]. Our study provides valuable longer-term data. NT-proBNP also improved at weeks 26 and 78, although the change was not statistically significant at the latter time point. The prospective studies reporting improvement in NT-proBNP with TNFi are in established RA cohorts with mean disease durations of at least 7 years and higher baseline NT-proBNP values [25, 41, 42], with perhaps a greater cumulative burden of disease. Longer term follow-up data is now required from inception cohorts.

We determined that meeting ACR70 response criteria was associated with lower values of TC/HDL-C and HOMA-IR at week 78; suggesting aggressive treatment can lead to a more favourable lipid profile and improved IR in the long-term. Our findings are supported by Park *et al* who showed that the improvement in HDL-C and LDL-C/HDL-C in 42 early RA patients after treatment with glucocorticoids and DMARDs for one year was significantly improved in ACR20 responders than non-responders. They did not report the results for TC/HDL-C [8]. The COBRA study similarly revealed greater improvement in disease activity and TC/HDL-C in the combination DMARD group compared to sulphasalazine group after 16 weeks of therapy [14]. Improvements in HOMA-IR have been associated with a reduction in DAS28 following TNFi in other studies [20].

We found no difference in improvement in TC/HDL-C between the treatment regimes, in line with previous cross-sectional studies [26, 28] and the TEAR trial, where a similar fall in non-fasting TC/HDL-C was seen in all treatment arms [29]. Unlike our study, however, it is not clear if disease activity was similar across the groups, making comparisons between therapeutic regimes difficult. NT-proBNP did not differ between the groups, but longer follow-up may be needed to identify any differences.

The major finding from our study was that TNFi appears to provide additional benefit in the improvement in IR above the use of MTX+MP when using a T2T approach. IR improved by nearly half as much in comparison. This is an important finding as although patients with RA do not appear to have a greater prevalence of DM [43]; with the prevalence of DM in our study similar to that found in the general population [44], patients with RA, however, are at higher risk of IR.

This is the first RCT, to our knowledge, to compare the change in HOMA-IR between treatment regimes in early RA. This supports the emerging evidence that TNFi therapy improves insulin sensitivity and reduces IR in RA [40]. One cross-sectional study reported no difference in HOMA-IR in 37 RA patients treated with either i) TNFi, ii) MTX or iii) no treatment, but disease durations and activity varied across the groups [30]. In the open label study by Tam *et al*, the higher fasting plasma glucose in the non-TNFi arm could be explained a higher proportion of patients in TNFi group achieving remission; with the difference seen reflecting the degree of systemic inflammation [27]. In our study disease activity at week 78 was similar in both treatment groups and controlling for IM glucocorticoid use produced comparable results.

The metabolic role of adipose tissue may underlie our observations. Visceral (central) obesity is associated with a chronic, low-grade inflammatory state (including TNF production) and has been implicated in the development of IR [45]. Adipokines secreted by adipose tissue play a significant role in the development of metabolic syndrome (MetS) and were recently recognised as novel biomarkers and regulators of MetS [46]. We observed that HOMA-IR positively correlated with BMI. Central abdominal rather than gluteo-femoral adipose tissue has been shown to secrete higher levels of inflammatory cytokines [47] strengthening the argument that fat distribution (i.e. WHR) is important in determining future CV risk. We found no relationship between WHR and baseline HOMA-IR, although an increase in WHR over time was associated with an increasing IR.

The use of the Rose angina and Edinburgh claudication questionnaires proved unreliable in our study; primarily because synovitis led to many false positive results. Although both validated screening methods for CVD in the general population, their use may be limited in RA, and more specific tools are required.

This study has several limitations. Firstly, it was not designed nor powered to investigate the change in biomarkers of CV risk. However, we feel that the magnitude of difference between the treatment groups for IR is an important finding and should encourage larger more focussed studies. Secondly, only a subset of patients had samples collected for biomarker analysis due to the practicalities of sample processing and storage in peripheral hospitals. However, we would argue no selection bias was encountered as each hospital cohort was independently randomised. Finally, we recognise that long-term data is required

to validate the improvement in lipid profiles and IR found, and to detect any reduction in CV outcomes and DM. This data would also help determine the biomarker that best predicts CVD in the context of systemic inflammation.

In conclusion, this study confirms the improvement of soluble biomarkers of CV risk with suppression of disease activity in early RA using a T2T approach. TNFi appeared to show additional benefit over MTX+MP in measures of IR. This raises the question of whether TNFi may confer additional protection in the prevention of CVD over and above the suppression of inflammation. Our conclusions should encourage similar, but more long-term studies, employing overt CV outcomes, or validated surrogate measures of CVD (in the general population) such as arterial stiffness or carotid intima-media thickness, as end-points.

Key message:

- Treat to target approach in early RA improves soluble biomarkers of CV risk
- TNF inhibition may provide additional advantage over methotrexate and methlyprednisolone in improving insulin resistance measures.

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Competing interests: AWM received grant funding from Merck, as outlined above and has received consultancy fees from GSK. EV has received consultancy fees from AbbVie, Amgen, Bristol-Myers-Squibb, Janssen and UCB. HK has received consultancy fees from UCB. JLN has received speaker bureau fees for UCB. MHB has received honoraria and been on advisory boards for AbbVie, BMS, Roche-Chugai, Pfizer and UCB. PE has been on advisory boards and received honoraria from AbbVie, BMS, Merck, Pfizer, Roche-Chugai and UCB. PGC has done speaker bureaus and been on advisory boards for BMS, Janssen and Pfizer.

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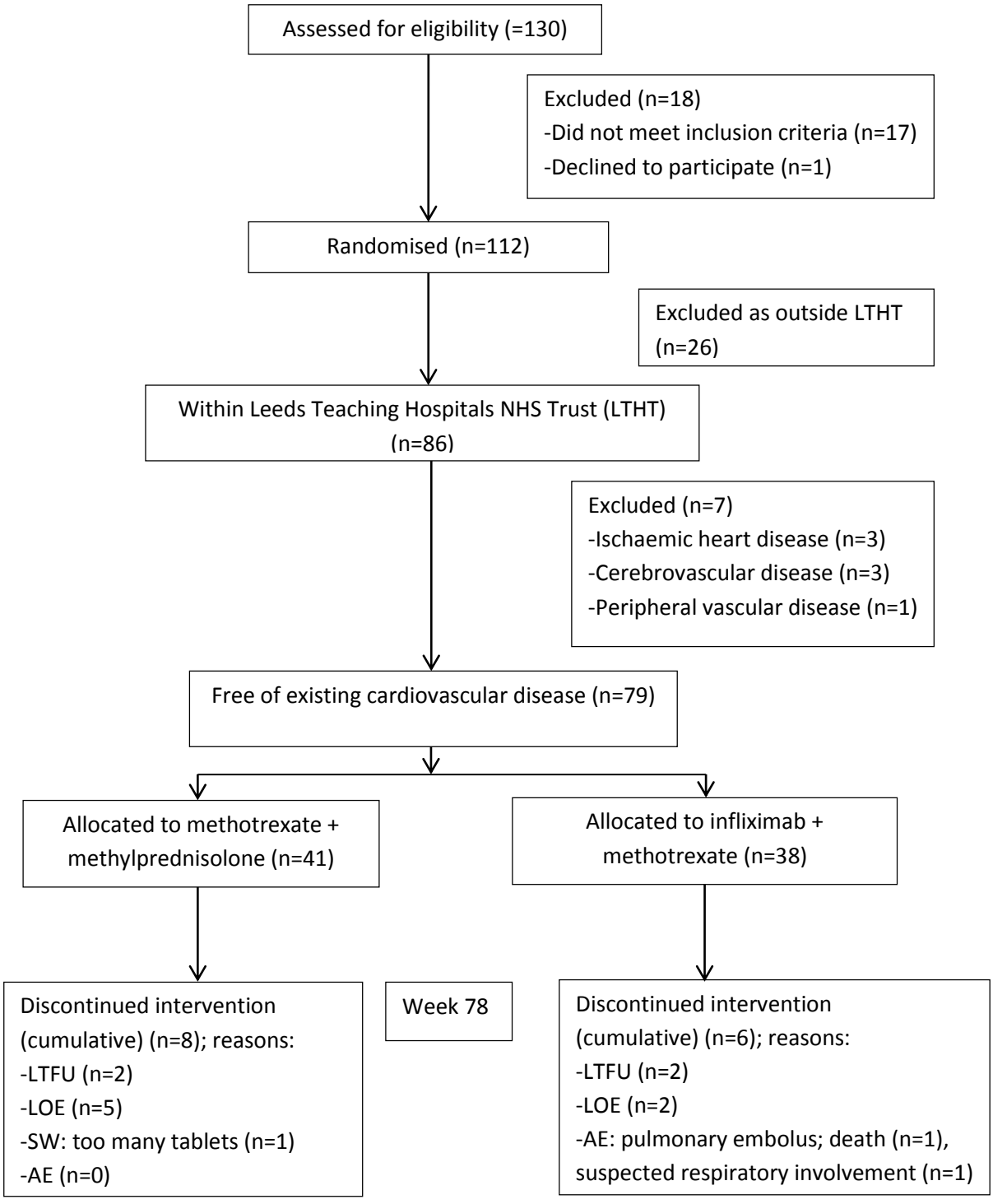
Figure 1: Flowchart of participants within the cardiovascular sub-study of IDEA.



LTFU, lost to follow-up; LOE, loss of efficacy; AE, adverse events; SW, self-withdrawal.

Table 1: Baseline clinical characteristics

		MTX+MP (n=41)	IFX+MTX (n=38)
Demographics			
Age (years):	mean (SD), range	50.9 (12.6), 19 to 69	52.3 (13.0), 28 to 75
Female:	n (%)	30 (73)	26 (68)
RA characteristics			
Disease duration (months):	median (IQR)	1.01 (0.69, 1.71)	1.00 (0.72, 1.45)
Symptom duration (months): median (IQR)		7.98 (5.03, 9.82)	7.01 (5.03, 10.38)
ESR:	median (IQR)	46 (20, 80)	34 (19, 51)
CRP (mg/L):	median (IQR)	14 (0, 35)	13 (0, 25)
DAS44:	mean (SD)	3.45 (0.91)	3.87 (1.03)
RF positive (≥40iu/ml):	n (%)	26 (63)	19 (50)
ACPA positive (≥10U/ml):	n (%)	31/39 (80)	24/37 (65)
HAQ-DI:	mean (SD)	1.37 (0.53) (n=40)	1.46 (0.51)
Co-morbidity			
Systolic BP (mmHg)	mean (SD)	122 (16)	125 (15)
Diastolic BP (mmHg)	mean (SD)	77 (11)	76 (10)

BMI	mean (SD), range	26.2 (4.2), 14.7 to 35.0	27.1 (6.0), 18.8 to 48.8
Waist/Hip circumference ratio	mean (SD)	0.89 (0.09) (n=36)	0.89 (0.15) (n=35)
Current smoker	n (%)	14 (34)	10 (26)
PMH Hypertension	n (%)	4 (10)	5 (13)
PMH Hyperlipidaemia	n (%)	6 (15)	1 (3)
PMH Diabetes Mellitus	n (%)	3 (7)	3 (8)
Family history of CVD*	n (%)	8/40 (20)	9 (24)
On anti-hypertensive therapy	n (%)	7 (17)	5 (13)
On lipid-lowering therapy	n (%)	5 (12)	0 (0)
Biomarkers of CV risk			
TC/HDL-C ratio	mean (SD)	5.71 (2.26)	5.12 (1.67)
TC/HDL-C ratio >6	n (%)	17 (42)	9 (26) (n=35)
HOMA-IR	geometric		
mean**		2.54	2.06
NT-pro-BNP (pg/ml)	geometric		
mean**		62.92	78.33 (70.15***)
High NT-pro-BNP (pg/ml)	n (%)	9/41 (22.0%)	3/35 (8.6%) [2/34 (5.9%)***]

ACPA, anti-citrullinated protein antibody; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; CVD, cardiovascular disease; DAS44, disease activity score (44 joints); ESR, erythrocyte sedimentation rate; HAQ-DI, Rasch-transformed health assessment

questionnaire disability index score; HOMA-IR, homeostasis model assessment-estimated insulin resistance index; IFX+MTX, infliximab + methotrexate; MTX+MP, methotrexate and intravenous methylprednisolone; NT-proBNP, N-terminal pro-brain natriuretic peptide, PMH, past medical history; RF, rheumatoid factor; TC/HDL-C, total cholesterol/high-density lipoprotein cholesterol ratio.

* defined as first degree relative less than 60 years old if relative is female, and 55 years old if relative is male

**It was not possible to calculate SD in original units for log-transformed variables

***minus extreme outlier

Table 2: Spearman's rank correlations of biomarkers with variables at baseline

	TC/HDL-C		HOMA-IR		NT-proBNP	
	Rho	**P value**	**Rho**	**P value**	**Rho**	**P value**
CRP	0.15	0.195	-0.035	0.765	0.182	0.116
SJC44	0.189	0.117	-0.159	0.189	0.12	0.918
HAQ-DI	0.107	0.362	0.093	0.426	0.332	0.004
BMI	0.312	0.006	0.574	<0.001	0.174	0.134
Waist/Hip circumference	0.162	0.188	0.076	0.538	-0.177	0.149

BMI, body mass index; CRP, C-reactive protein; HAQ-DI, Rasch-transformed health assessment questionnaire disability index score; HOMA-IR, homeostasis model assessment-estimated insulin resistance index; NT-proBNP, N-terminal pro-brain natriuretic peptide; SJC44, 44 swollen joint count; TC/HDL-C, total cholesterol/high-density lipoprotein cholesterol ratio.

Table 3: Differences between treatment arms in TC/HDL-C, HOMA-IR and NT-proBNP changes after 26 and 78 weeks, adjusting for baseline values

Change	MTX+MP (n=41)	IFX+MTX (n=38)	Unadjusted difference (95% CI)	Adjusted* difference (95% CI), p-value
Week 26				
TC/HDL-C mean	-0.89	-0.67	0.23 (-0.47, 0.93)	0.13 (-0.43, 0.69), t=0.48, p=0.635
HOMA-IR mean ratio	FU/BL 0.72	FU/BL 0.71	IFX/MP 0.99 (0.64, 1.53)	IFX/MP 0.84 (0.62, 1.14), t=-1.14, p=0.259
NT-proBNP mean ratio	FU/BL 0.83	FU/BL 0.84	IFX/MP 1.06 (0.76, 1.49)	IFX/MP 1.18 (0.85, 1.62), t=1.01, p=0.314
				**1.15 (0.84, 1.58), t=0.89, p=0.378
Week 78				
TC/HDL-C mean	-1.00	-0.89	0.11 (-0.64, 0.87)	-0.09 (-0.70, 0.51), t=-0.31, p=0.758
HOMA-IR mean ratio	FU/BL 0.84	FU/BL 0.55	IFX/MP 0.66 (0.40, 1.08)	IFX/MP 0.58 (0.41, 0.82), t=-3.17, p=0.003
NT-proBNP mean ratio	FU/BL 0.82	FU/BL 0.86	IFX/MP 1.02 (0.68, 1.54)	IFX/MP 1.19 (0.81, 1.75), t=0.91, p=0.367
				**1.16 (0.79, 1.71), t=0.78, p=0.440

HOMA-IR, homeostasis model assessment-estimated insulin resistance index; IFX+MTX, infliximab + methotrexate; MTX+MP, methotrexate and intravenous methylprednisolone; NT-proBNP, N-terminal pro-brain natriuretic peptide; TC/HDL-C, total cholesterol/high-density lipoprotein cholesterol ratio.

*Adjusted for baseline values

**Excluding patient with extremely high NT-proBNP value

Table 4: Differences between treatment arms in TC/HDL-C, HOMA-IR and NT-proBNP changes after 26 and 78 weeks, adjusting for baseline values, split by ACR70 response (observed data only)

Change	MTX+MP	IFX+MTX (n=38)	Unadjusted difference (95% CI)	Adjusted* difference (95% CI), p-value
Week 26				
ACR20 non-responders	(n=10)	(n=11)		
TC/HDL-C mean	-1.20	-0.13	1.07 (-0.58, 2.73)	0.11 (-0.95, 1.17), t=0.21, p=0.833
HOMA-IR mean ratio	FU/BL 0.84	FU/BL 0.62 (n=10)	IFX/MP 0.74 (0.36, 1.53)	IFX/MP 0.62 (0.33, 1.17), t=-1.58, p=0.133
NT-proBNP mean ratio	FU/BL 1.09	FU/BL 0.72	IFX/MP 0.66 (0.38, 1.16)	IFX/MP 0.70 (0.40, 1.25), t=-1.27, p=0.221 **0.69 (0.39, 1.55), t=-1.37, p=0.187
ACR20 responders	(n=28)	(n=27)		
TC/HDL-C mean	-0.73	-0.89	-0.17 (-0.93, 0.60)	-0.22 (-0.91, 0.48), t=-0.62, p=0.535
HOMA-IR mean ratio	FU/BL 0.67	FU/BL 0.74	IFX/MP 1.11 (0.65, 1.91)	IFX/MP 1.00 (0.73, 1.38), t=0.01, p=0.990
NT-proBNP mean ratio	FU/BL 0.77	FU/BL 0.90	IFX/MP 1.16 (0.78, 1.72)	IFX/MP 1.23 (0.86, 1.76), t=1.16, p=0.252
Week 78				
ACR20 non-responders	(n=6)	(n=8)		
TC/HDL-C mean	-0.37	-0.43	-0.06 (-1.90, 1.78)	-0.25 (-1.66, 1.16), t=-0.40, p=0.700
HOMA-IR mean ratio	FU/BL 0.48	FU/BL 0.63	IFX/MP 1.32 (0.47, 3.74)	IFX/MP 0.97 (0.55, 1.71), t=-0.13, p=0.899
NT-proBNP mean ratio	FU/BL 0.68	FU/BL 1.07	IFX/MP 1.57 (0.75, 3.29)	IFX/MP 1.81 (0.80, 4.11), t=1.60, p=0.137 **2.01 (0.87, 4.63), t=1.87, p=0.092
ACR20 responders	(n=29)	(n=23)		
TC/HDL-C mean	-1.15 (n=28)	-1.15 (n=22)	0.00 (-0.84, 0.84)	-0.31 (-0.89, 0.26), t=-1.09, p=0.281
HOMA-IR mean ratio	FU/BL 0.99	FU/BL 0.61	IFX/MP 0.61 (0.34, 1.09)	IFX/MP 0.48 (0.33, 0.71), t=-3.79, p<0.001
NT-proBNP mean ratio	FU/BL 0.82	FU/BL 0.87	IFX/MP 1.06 (0.68, 1.67)	IFX/MP 0.97 (0.65, 1.43), t=-0.17, p=0.863

HOMA-IR, homeostasis model assessment-estimated insulin resistance index; IFX+MTX, infliximab + methotrexate; MTX+MP, methotrexate and intravenous methylprednisolone; NT-proBNP, N-terminal pro-brain natriuretic peptide; TC/HDL-C, total cholesterol/high-density lipoprotein cholesterol ratio.

*Adjusted for baseline values

**Excluding patient with extremely high NT-proBNP value

Table 5: Associations between changes in disease activity and BMI and changes in biomarkers over 78 weeks in the combined treatment groups (n=79), adjusting for baseline values

	Biomarker change over 78 weeks		
Covariate:	**TC/HDL-C**	**HOMA-IR**	**NT-proBNP**
DAS44-CRP, per unit	0.39 (-0.05, 0.84), p=0.081	11.2% (-12.5%, 41.5%), p=0.376	10.2% (-14.9%, 42.7%), p=0.452
ACR70 response	-0.68 (-1.20, -0.15), p=0.012	-31.2% (-52.1%, -1.4%), p=0.042	8.8% (-25.8%, 59.7%), p=0.660
BMI, per unit	0.11 (-0.10, 0.32), p=0.273	10.6% (-2.0%, 24.9%), p=0.096	-4.0% (-12.0%, 4.7%), p=0.342
WHR, per 10%	0.35 (-0.10, 0.80), p=0.121	35.2% (2.5%, 78.1%), p=0.033	-14.9% (-35.1%, 11.7%), p=0.238

ACR, American College of Rheumatology; BMI, body mass index; DAS44-CRP, 3-variable disease activity score based on CRP, RAI and SJC44; HOMA-IR, homeostasis model assessment-estimated insulin resistance index; IFX+MTX, infliximab + methotrexate; TC/HDL-C, total cholesterol/high-density lipoprotein cholesterol ratio; WHR, waist/hip circumference