

Efficacy and Mechanism Evaluation

Volume 8 • Issue 4 • March 2021

ISSN 2050-4365

Using cardiovascular magnetic resonance to define mechanisms of comorbidity and to measure the effect of biological therapy: the CADERA observational study

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Declared competing interests of authors: Maya H Buch reports grants and personal fees from Pfizer Inc. (New York, NY, USA), grants from Roche-Chugai (Tokyo, Japan) and UCB (Brussels, Belgium) and personal fees from AstraZeneca plc (Cambridge, UK), Bristol-Myers Squibb Co. (New York, NY, USA), Mitsubishi Tanabe Pharma Corp. (Osaka, Japan), Sandoz (Holzkirchen, Germany), R-Pharm (Moscow, Russia), Sanofi (Paris, France), Merck Serono (Darmstadt, Germany) and Roche-Chugai outside the submitted work. Elizabeth M Hensor reports grants from the National Institute for Health Research (NIHR) and grants from Versus Arthritis [formerly Arthritis Research UK (London, UK)] outside the submitted work. Sue Pavitt is NIHR Clinical Research Network (CRN) National Specialty Lead for Oral and Dental Health. She also reports non-financial support from NIHR CTU Standing Advisory Committee and from NIHR EME outside the submitted work. In addition, the NIHR CRN Specialty Leadership role attracts one programmed activity of funding outside the submitted work. Graham Fent reports support from Novartis International AG (Basel, Switzerland) outside the submitted work.

Published March 2021

DOI: 10.3310/eme08040

This report should be referenced as follows:

Plein S, Erhayiem B, Fent G, Andrews J, Greenwood J, Baxter P, *et al.* Using cardiovascular magnetic resonance to define mechanisms of comorbidity and to measure the effect of biological therapy: the CADERA observational study. *Efficacy Mech Eval* 2021;**8**(4).

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

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The EME programme is funded by the Medical Research Council (MRC) and the National Institute for Health Research (NIHR), with contributions from the Chief Scientist Office (CSO) in Scotland and National Institute for Social Care and Health Research (NISCHR) in Wales and the Health and Social Care Research and Development (HSC R&D), Public Health Agency in Northern Ireland.

This report

The research reported in this issue of the journal was funded by the EME programme as project number 11/117/27. The contractual start date was in April 2013. The final report began editorial review in November 2018 and was accepted for publication in August 2019. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Using cardiovascular magnetic resonance to define mechanisms of comorbidity and to measure the effect of biological therapy: the CADERA observational study

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Background: The VEDERA (Very Early vs. Delayed Etanercept in Rheumatoid Arthritis) randomised controlled trial compared the effect of conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) therapy with biologic DMARD (bDMARD) therapy using the tumour necrosis factor inhibitor etanercept in treatment-naive, early rheumatoid arthritis patients. The CADERA (Coronary Artery Disease Evaluation in Rheumatoid Arthritis) trial was a bolt-on study in which VEDERA patients underwent cardiovascular magnetic resonance imaging to detect preclinical cardiovascular disease at baseline and following treatment.

Objectives: To evaluate whether or not patients with treatment-naive early rheumatoid arthritis have evidence of cardiovascular disease compared with matched control subjects; whether or not this is modifiable with DMARD therapy; and whether or not bDMARDs confer advantages over csDMARDs.

Design: The VEDERA patients underwent cardiovascular magnetic resonance imaging at baseline and at 1 and 2 years after treatment.

Setting: The setting was a tertiary centre rheumatology outpatient clinic and specialist cardiovascular magnetic resonance imaging unit.

Participants: Eighty-one patients completed all assessments at baseline, 71 completed all assessments at 1 year and 56 completed all assessments at 2 years. Patients had no history of cardiovascular disease, had had rheumatoid arthritis symptoms for ≤ 1 year, were DMARD treatment-naive and had a minimum Disease Activity Score-28 of 3.2. Thirty control subjects without cardiovascular disease were approximately individually matched by age and sex to the first 30 CADERA patients. Patients with a Disease Activity Score-28 of ≥ 2.6 at 48 weeks were considered non-responders.

Interventions: In the VEDERA trial patients were randomised to group 1, immediate etanercept and methotrexate, or group 2, methotrexate \pm additional csDMARD therapy in a treat-to-target approach, with a switch to delayed etanercept and methotrexate in the event of failure to achieve clinical remission at 6 months.

Main outcome measures: The primary outcome measure was difference in baseline aortic distensibility between control subjects and the early rheumatoid arthritis group and the baseline to year 1 change in aortic distensibility in the early rheumatoid arthritis group. Secondary outcome measures were myocardial perfusion reserve, left ventricular strain and twist, left ventricular ejection fraction and left ventricular mass.

Results: Baseline aortic distensibility [geometric mean (95% confidence interval)] was significantly reduced in patients ($n = 81$) compared with control subjects ($n = 30$) [$3.0 \times 10^{-3}/\text{mmHg}$ ($2.7 \times 10^{-3}/\text{mmHg}$ to $3.3 \times 10^{-3}/\text{mmHg}$) vs. $4.4 \times 10^{-3}/\text{mmHg}$ ($3.7 \times 10^{-3}/\text{mmHg}$ to $5.2 \times 10^{-3}/\text{mmHg}$), respectively; $p < 0.001$]. Aortic distensibility [geometric mean (95% confidence interval)] improved significantly from baseline to year 1 across the whole patient cohort ($n = 81$, with imputation for missing values) [$3.0 \times 10^{-3}/\text{mmHg}$ ($2.7 \times 10^{-3}/\text{mmHg}$ to $3.4 \times 10^{-3}/\text{mmHg}$) vs. $3.6 \times 10^{-3}/\text{mmHg}$ ($3.1 \times 10^{-3}/\text{mmHg}$ to $4.1 \times 10^{-3}/\text{mmHg}$), respectively; $p < 0.001$]. No significant difference in aortic distensibility improvement between baseline and year 1 was seen in the following comparisons (geometric means): group 1 ($n = 40$ at baseline) versus group 2 ($n = 41$ at baseline): $3.8 \times 10^{-3}/\text{mmHg}$ versus $3.4 \times 10^{-3}/\text{mmHg}$, $p = 0.49$; combined groups 1 and 2 non-responders ($n = 38$) versus combined groups 1 and 2 responders ($n = 43$): $3.5 \times 10^{-3}/\text{mmHg}$ versus $3.6 \times 10^{-3}/\text{mmHg}$, $p = 0.87$; group 1 non-responders ($n = 17$) versus group 1 responders ($n = 23$): $3.6 \times 10^{-3}/\text{mmHg}$ versus $3.9 \times 10^{-3}/\text{mmHg}$, $p = 0.73$. There was a trend towards a 10–30% difference in aortic distensibility between (group 1) responders who received first-line etanercept ($n = 23$) and (group 2) responders who never received etanercept ($n = 13$): $3.9 \times 10^{-3}/\text{mmHg}$ versus $2.8 \times 10^{-3}/\text{mmHg}$, $p = 0.19$; ratio 0.7 (95% confidence interval 0.4 to 1.2), $p = 0.19$; ratio adjusted for baseline aortic distensibility 0.8 (95% confidence interval 0.5 to 1.2), $p = 0.29$; ratio fully adjusted for baseline characteristics 0.9 (95% confidence interval 0.6 to 1.4), $p = 0.56$.

Conclusions: The CADERA establishes evidence of the vascular changes in early rheumatoid arthritis compared with controls and shows improvement of vascular changes with rheumatoid arthritis DMARD therapy. Response to rheumatoid arthritis therapy does not add further to modification of cardiovascular disease but, within the response to either strategy, etanercept/methotrexate may confer greater benefits over standard methotrexate/csDMARD therapy.

Trial registration: Current Controlled Trials ISRCTN89222125 and ClinicalTrials.gov NCT01295151.

Funding: This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership, and will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 8, No. 4. See the NIHR Journals Library website for further project information. Pfizer Inc. (New York, NY, USA) supported the parent study, VEDERA, through an investigator-sponsored research grant reference WS1092499.

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List of abbreviations

| | | | |
|-----------|--|--------|---|
| ACPA | anti-citrullinated peptide antibody | EULAR | European League Against Rheumatism |
| AD | aortic distensibility | | |
| ANCOVA | analysis of covariance | Hct | venous haematocrit |
| AUC | area under the curve | LGE | late gadolinium enhancement |
| bDMARD | biologic disease-modifying anti-rheumatic drug | LV | left ventricular |
| | | LVEF | left ventricular ejection fraction |
| CADERA | Coronary Artery Disease Evaluation in Rheumatoid Arthritis | LVLS | left ventricular longitudinal strain |
| | | LVM | left ventricular mass |
| CI | confidence interval | MECV | myocardial extracellular volume |
| CMR | cardiovascular magnetic resonance | MTX | methotrexate |
| CRP | C-reactive protein | NIHR | National Institute for Health Research |
| csDMARD | conventional synthetic disease-modifying anti-rheumatic drug | PLVTw | peak left ventricular twist |
| CV | cardiovascular | RA | rheumatoid arthritis |
| CVD | cardiovascular disease | RF | rheumatoid factor |
| DAS28-ESR | Disease Activity Score-28-erythrocyte sedimentation rate | TNF | tumour necrosis factor |
| | | TNFi | tumour necrosis factor inhibitor |
| DMARD | disease-modifying anti-rheumatic drug | VAS | visual analogue scale |
| ECV | extracellular volume | VEDERA | Very Early vs. Delayed Etanercept in early Rheumatoid Arthritis |
| ETN | etanercept | | |

Plain English summary

Rheumatoid arthritis is mainly known for the disabling joint changes that it causes, such as stiffness and pain. Patients with rheumatoid arthritis also have a higher rate of heart and blood vessel abnormalities, including a higher risk of heart attack and stroke, than the general population. This is thought to be caused by widespread inflammation affecting not only the joints but also the heart and blood vessels. Newer treatments for rheumatoid arthritis work well to control inflammation in the joints. The aim of the CADERA (Coronary Artery Disease Evaluation in Rheumatoid Arthritis) study was to find out whether or not these treatments also improve the health of the blood vessels.

The CADERA study was carried out alongside a larger, randomised study in which patients with newly diagnosed rheumatoid arthritis received either standard treatment or more effective anti-inflammatory treatment called 'biologics', which directly target the substances that cause inflammation.

Eighty-one patients with newly diagnosed rheumatoid arthritis were randomly started on standard treatment or biologics. At 1 and 2 years after treatment was started, magnetic resonance imaging was used to provide detailed images that can be used to detect the presence and extent of heart and blood vessel problems.

We found that, before any treatment, rheumatoid arthritis patients showed changes of blood vessel function compared with a group of 30 control subjects without rheumatoid arthritis of similar age and sex. Both types of rheumatoid arthritis treatment improved blood vessel function but there was no significant benefit of the newer biologic treatment compared with the standard treatment, although small differences were seen.

The results show that rheumatoid arthritis patients, even at an early stage of their disease, have changes in blood vessel function and that this can be improved with rheumatoid arthritis treatment. Whether or not these improvements lead to lower rates of heart attacks and strokes needs to be established in future studies.

Scientific summary

Background

Rheumatoid arthritis is a chronic, systemic, inflammatory arthritis affecting over 400,000 (0.8%) of the UK population. Rheumatoid arthritis has considerable health and socioeconomic impacts. The life expectancy of patients with rheumatoid arthritis is reduced and the mortality rate is increased up to threefold compared with the general population. This is largely because of the increased frequency of premature cardiovascular disease, which accounts for up to 40% of mortality in rheumatoid arthritis patients and is independent of and incremental to traditional cardiovascular disease risk factors.

According to current guidelines, patients with newly diagnosed rheumatoid arthritis should be treated with conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) therapy in combination with short-term glucocorticoids in a 'treat-to-target' (with the target of remission) approach. Biologic disease-modifying anti-rheumatic drug (bDMARD) therapy, including tumour necrosis factor inhibitor therapy, is recommended in patients with inadequate disease control with csDMARDs [in the UK, National Institute for Health and Care Excellence guidelines permit bDMARD after failure of at least after two conventional agents, including methotrexate and in the presence of high disease activity].

Treatment of rheumatoid arthritis with methotrexate and tumour necrosis factor inhibitors has been shown to have beneficial effects on cardiovascular disease in epidemiological studies, with relative risks in the range of 0.72 and 0.46–0.70, respectively, in patients with established rheumatoid arthritis. It is not clearly known if patients with a new diagnosis of very early rheumatoid arthritis already have signs of cardiovascular disease, if disease-modifying anti-rheumatic drug (DMARD) therapy confers benefits in this patient group and if DMARD therapy reduces the incidence of cardiovascular disease, including whether or not bDMARD therapy has additional benefits over csDMARDs.

The VEDERA (Very Early vs. Delayed Etanercept in early Rheumatoid Arthritis) study was a phase IV, pragmatic, single-centre, open-label randomised controlled trial with the aim of determining the effect of bDMARD therapy with tumour necrosis factor inhibitor in patients with new-onset, treatment-naïve early rheumatoid arthritis compared with standard methotrexate \pm additional csDMARD therapy in a treat-to-target approach (with escalation to tumour necrosis factor inhibitor if clinical remission was not achieved). Participants were randomised to one of two first-line therapeutic strategies: (1) group 1 – immediate tumour necrosis factor inhibitor (etanercept) and methotrexate or (2) group 2: methotrexate \pm additional csDMARD therapy in a treat-to-target approach, with switch to delayed etanercept and methotrexate in the event of failure to achieve clinical remission at 6 months. The primary end point of the VEDERA trial was a comparison of the proportion of patients in each treatment arm achieving Disease Activity Score-28 remission at 1 year. Secondary end points included evaluation of the response to first-line etanercept compared with delayed etanercept (following methotrexate).

The CADERA (Coronary Artery Disease Evaluation in Rheumatoid Arthritis) study was a bolt-on study to the VEDERA trial in which patients randomised in the VEDERA trial underwent additional multiparametric cardiovascular magnetic resonance imaging to assess cardiovascular disease at baseline and after initiation of either of the two treatment strategies.

Objectives

Primary objectives

- To determine if cardiovascular abnormalities, as assessed by cardiovascular magnetic resonance imaging, are present in a treatment-naïve inception cohort of early rheumatoid arthritis patients compared with control subjects.

- To establish whether or not (any) rheumatoid arthritis DMARD strategy is associated with improvement in cardiovascular abnormalities, as measured by cardiovascular magnetic resonance imaging, in a treatment-naïve inception cohort of early rheumatoid arthritis patients over a 1-year period.
- To establish whether or not tumour necrosis factor inhibitor therapy confers a quantitative difference in cardiovascular disease, as measured by cardiovascular magnetic resonance imaging, compared with standard therapy in a treatment-naïve inception cohort of early rheumatoid arthritis patients over a 1-year period.

Secondary objectives

- To determine cardiovascular changes, as assessed by cardiovascular magnetic resonance imaging, in a treatment-naïve inception cohort of early rheumatoid arthritis patients over a 2-year period.
- In additional analysis (in line with the VEDERA parent study), following a protocol amendment, to evaluate the response relative to Disease Activity Score-28 control (Disease Activity Score-28 category of remission-defined clinical response/non-response status) and therapeutic intervention (tumour necrosis factor inhibitor/methotrexate and csDMARD including methotrexate).

Methods

Design

The CADERA study was a bolt-on study to the VEDERA parent randomised controlled trial. Patients recruited to the VEDERA trial and randomised to the csDMARD or bDMARD treatment group underwent cardiovascular resonance imaging at baseline and at 1 year and 2 years following initiation of therapy.

Setting

Participants were recruited from a single tertiary centre, an early rheumatoid arthritis rheumatology outpatient clinic (Chapel Allerton Hospital, Leeds, UK), and underwent cardiovascular magnetic resonance imaging at the Multidisciplinary Cardiovascular Research Centre (MCRC) at the Leeds Institute of Cardiovascular and Metabolic Medicine.

Participants

The methods used in the VEDERA and CADERA studies have been published previously. Patients were recruited between February 2012 and November 2015. Consecutive patients diagnosed with new-onset rheumatoid arthritis according to American College of Rheumatology/European League Against Rheumatism 2010 criteria were invited to enrol into the VEDERA randomised controlled trial and parallel CADERA substudy. Thirty control subjects (free of cardiovascular disease) were recruited through advertisements, e-mail and word of mouth and were approximately individually matched by age and sex to the first 30 CADERA patients.

Outcome measures

The primary outcome measure was difference in aortic distensibility between patients and control subjects at baseline and in patients from baseline to 1 year of follow-up.

Secondary outcome measures were myocardial perfusion reserve, left ventricular strain and twist, left ventricular ejection fraction and left ventricular mass.

The exploratory outcome measure was myocardial extracellular volume.

Sample size

The sample size estimation for the primary end point aortic distensibility was based on previous published studies showing improved aortic distensibility in rheumatoid arthritis patients in response to interleukin-1-directed therapy. Thirty-three patients in each treatment group would equate to 80% power to detect a difference in aortic distensibility between the two treatment groups at a 5% significance level.

Interventions

All recruited patients were randomised into two groups according to the VEDERA protocol.

1. Group 1: experimental treatment arm – etanercept group: immediate etanercept and methotrexate treatment.
2. Group 2: control treatment arm – standard treatment group: initial myocardial extracellular volume monotherapy with treat-to-target regimen; escalation to combination DMARD therapy at or after 8 weeks (up to week 24) if failing to meet the predefined target at 4-weekly assessments, and if failing to meet the predefined target of clinical remission at week 24, step up to bDMARD, etanercept and methotrexate.

Etanercept (Enbrel®, Pfizer Inc. New York, NY, USA) is a human tumour necrosis factor receptor p75Fc fusion protein produced by recombinant deoxyribonucleic acid (DNA) technology. Methotrexate and/or additional csDMARDs include sulfasalazine and hydroxychloroquine.

Study procedures

All patients underwent screening within the 4 weeks prior to the baseline visit for the VEDERA trial. At the baseline visit eligibility for the study was confirmed, patients were randomised to one of the treatment groups and study treatment was initiated. Further visits, which included assessment of disease activity, took place at weeks 4, 12 and every 12 weeks thereafter, up to week 96, for both treatment arms, with additional visits (for group 2) at week 8, 16 and 20 for safety and efficacy within a treat-to-target protocol.

At baseline and at 1 and 2 years following initiation of therapy, patients recruited to the CADERA study were invited for cardiovascular magnetic resonance imaging. The cardiovascular magnetic resonance imaging protocol included aortic cine imaging, cine imaging in left ventricular short- and long-axis orientations, myocardial tissue tagging, adenosine stress and rest first-pass perfusion imaging using a dual-bolus technique, with intravenous infusion of 0.01 and 0.1 mmol/kg gadopentetate dimeglumine (Magnevist®, Bayer, Berlin, Germany), myocardial T1 mapping pre and post contrast and late gadolinium enhancement imaging.

Analysis

All post-processing analysis of cardiovascular magnetic resonance scans was performed by experienced blinded assessors using CVI 42 software (Circle Cardiovascular Imaging, Calgary, Canada). Aortic distensibility was calculated from aortic cine images according to previously described methods. Left ventricular contours were drawn manually at both end-diastole and end-systole on the left ventricular short-axis cine stack and left ventricular volumes and mass derived. Left ventricular strain and peak left ventricular twist were derived from tissue tagging images and myocardial extracellular volume was derived from pre- and post-contrast T1 mapping.

Patients were compared with control subjects for the primary outcome, aortic distensibility, using matched pairs analysis and regression analysis. The objective was to determine if a significant difference ($p < 0.05$) existed between patients and control subjects and to estimate the magnitude of this difference as a 95% confidence interval. The patients as a whole group and the two randomised treatment groups were compared at baseline to 1 year with primary outcome aortic distensibility and aforementioned secondary outcomes on 1-year follow-up.

Myocardial perfusion analysis is not included in this report.

Following a protocol amendment, further analyses were conducted for patients stratified as responders or non-responders to therapy according to Disease Activity Score-28 remission status.

All analyses were adjusted for baseline aortic distensibility, age, sex, systolic blood pressure and pack-years smoking (\pm baseline Disease Activity Score-28-erythrocyte sedimentation rate as applicable). All analyses were performed on 81 patients, with imputation of missing baseline and follow-up outcomes.

Results

A total of 82 patients were enrolled into the CADERA study and underwent baseline cardiovascular magnetic resonance imaging. In one participant no aortic distensibility data could be acquired. Of the remaining 81 patients at baseline, 71 underwent a 1-year cardiovascular magnetic resonance scan. A total of four patients were withdrawn from the study during the first year of follow-up, one because of treatment non-compliance and the other three because of serious adverse events relating to treatment. The reasons for the remaining six patients not undergoing a 1-year cardiovascular magnetic resonance scan were refusal or claustrophobia (five patients) and moved away and not able to attend a repeat scan (one patient). In total, 56 patients attended for a 2-year cardiovascular magnetic resonance scan.

Early rheumatoid arthritis patients and control subjects were of similar median [interquartile range] age [51 (21) and 54 (23) years, respectively] and systolic blood pressure [121 (26) mmHg and 121 (14) mmHg, respectively]. Median (interquartile range) erythrocyte sedimentation rate, C-reactive protein and Disease Activity Score-28 in early rheumatoid arthritis patients were 30 (30) mm/hour, 8 (23) mg/l and 5.3 (1.4), respectively. In total, 64 (84%) and 57 (75%) patients were anti-citrullinated peptide antibody and rheumatoid factor positive, respectively. A total of 17 (22%), 25 (33%) and 34 (45%) patients in the rheumatoid arthritis group were current, former and never smokers, respectively, and 4 (13%), 5 (17%) and 21 (70%) patients in the control group were current, former and never smokers, respectively.

Primary objectives

Primary outcome

The primary outcome measure aortic distensibility [geometric mean (95% confidence interval)] was significantly reduced in patients ($n = 81$) compared with control subjects ($n = 30$) [$3.0 \times 10^{-3}/\text{mmHg}$ ($2.7 \times 10^{-3}/\text{mmHg}$ to $3.3 \times 10^{-3}/\text{mmHg}$) vs. $4.4 \times 10^{-3}/\text{mmHg}$ ($3.7 \times 10^{-3}/\text{mmHg}$ to $5.2 \times 10^{-3}/\text{mmHg}$), respectively; $p < 0.01$]. Aortic distensibility improved significantly from baseline to 1 year across the whole patient cohort [$3.0 \times 10^{-3}/\text{mmHg}$ ($2.7 \times 10^{-3}/\text{mmHg}$ to $3.4 \times 10^{-3}/\text{mmHg}$) vs. $3.6 \times 10^{-3}/\text{mmHg}$ ($3.1 \times 10^{-3}/\text{mmHg}$ to $4.1 \times 10^{-3}/\text{mmHg}$), respectively; $p < 0.01$].

All differences remained significant when adjusted for age, sex, systolic blood pressure and pack-years smoked.

Secondary outcomes

Of the secondary outcome measures, left ventricular mass [geometric mean (95% confidence interval)] was significantly lower in patients ($n = 81$) than in control subjects ($n = 30$) [78.2 g (74.0 to 82.7 g) vs. 92.9 g (84.8 to 101.7 g), respectively; $p < 0.01$]. Left ventricular mass in patients increased from baseline to 1 year, from 78.2 g (95% confidence interval 73.7 to 83.0 g) to 81.4 g (95% confidence interval 76.3 to 86.9 g; $p = 0.01$). All differences remained significant when adjusted for age, sex, systolic blood pressure and pack-years smoked.

Myocardial extracellular volume [geometric mean (95% confidence interval)] was significantly increased at baseline in patients ($n = 78$) compared with control subjects ($n = 30$) [27.1% (26.4% to 27.9%) vs. 24.9% (23.8% to 26.1%), respectively; $p < 0.01$]. This difference remained significant when adjusted for age, sex, systolic blood pressure and pack-years smoked. Myocardial extracellular volume in patients ($n = 81$) decreased from baseline to 1 year [geometric mean (95% confidence interval)], from 27.2% (26.4% to 28.1%) to 26.4% (25.6% to 27.3%), but this difference was not statistically significant ($p = 0.06$).

Matched pairs analyses corroborated the significant differences between the control group and the rheumatoid arthritis group for aortic distensibility, myocardial extracellular volume and left ventricular mass (with left ventricular mass showing a consistent magnitude of change).

No significant differences were seen in the other secondary outcome measures between patients and control subjects at baseline or in patients between baseline and 1 year of follow-up.

Secondary objectives

At the 2-year follow-up time point, differences in the primary end point of aortic distensibility and in the secondary end point of left ventricular mass were maintained. In addition, peak left ventricular twist significantly increased from baseline to the 2-year follow-up, from a geometric mean of 14.9° (95% confidence interval 14.0° to 15.9°) to a geometric mean of 16.6° (95% confidence interval 15.5° to 17.8°; $p = 0.02$).

As part of the additional analyses (following the protocol amendment), no significant differences in aortic distensibility improvement were seen in the following comparisons (geometric means):

- group 1 ($n = 40$ at baseline) versus group 2 ($n = 41$ at baseline): $3.8 \times 10^{-3}/\text{mmHg}$ versus $3.4 \times 10^{-3}/\text{mmHg}$; $p = 0.49$
- combined group 1 and 2 non-responders ($n = 38$) versus combined group 1 and 2 responders ($n = 43$): $3.5 \times 10^{-3}/\text{mmHg}$ versus $3.6 \times 10^{-3}/\text{mmHg}$; $p = 0.87$
- group 1 non-responders ($n = 17$) versus group 1 responders ($n = 23$): $3.6 \times 10^{-3}/\text{mmHg}$ versus $3.9 \times 10^{-3}/\text{mmHg}$; $p = 0.73$.

There was a trend towards a 10–30% difference between treatment strategies comparing group 1 responders ($n = 23$) with group 2 responders ($n = 13$): geometric mean $3.9 \times 10^{-3}/\text{mmHg}$ versus $2.8 \times 10^{-3}/\text{mmHg}$; ratio 0.7 (95% confidence interval 0.4 to 1.2; $p = 0.19$); ratio adjusted for baseline aortic distensibility 0.8 (95% confidence interval 0.5 to 1.2; $p = 0.29$); ratio fully adjusted for baseline characteristics 0.9 (95% confidence interval 0.6 to 1.4; $p = 0.56$).

Discussion

The CADERA study presents the first evidence from a randomised controlled trial of the effects of DMARD therapy on cardiovascular magnetic resonance imaging markers of cardiovascular disease in patients with early, treatment-naïve rheumatoid arthritis. The CADERA study has demonstrated that aortic distensibility, a measure of aortic stiffness and a surrogate marker of cardiovascular disease risk, is lower in patients with new-onset early rheumatoid arthritis than in control subjects. This finding suggests that cardiovascular disease abnormalities are an early manifestation of rheumatoid arthritis, with potential implications for the routine care of these patients.

The CADERA study has further shown that aortic distensibility improves at the 1- and 2-year follow-ups after the initiation of DMARD therapy. Although there was no significant difference between the two treatment regimes, first-line etanercept/methotrexate responders had a higher aortic distensibility at 1 year than first-line methotrexate/csDMARD responders. This finding suggests that, in those patients who respond well to first-line therapy, bDMARD treatment may be of further benefit. However, these preliminary findings are based on modest patient numbers and require corroboration in future prospective studies.

Among the other cardiovascular magnetic resonance measures, we have demonstrated elevated myocardial extracellular volume in patients compared with control subjects, which shows a trend towards improvement after therapy. Myocardial extracellular volume is a marker of diffuse interstitial fibrosis and the elevated values may relate to myocardial inflammation in early rheumatoid arthritis.

We have also observed lower baseline left ventricular mass in patients compared with control subjects and an increase in left ventricular mass in patients from baseline to the 1- and 2-year follow-ups. This observation may relate to the phenomenon of 'rheumatoid cachexia' caused by the reduced physical activity in rheumatoid arthritis patients prior to the initiation of therapy.

Conclusion

These randomised controlled trial data show changes in vascular function and myocardial composition in treatment-naïve early rheumatoid arthritis of < 12 months' symptom duration compared with control subjects. Optimal DMARD therapy (whether csDMARDs or bDMARDs) to control rheumatoid arthritis disease activity is associated with significant improvements in aortic distensibility at 1 year. However, aortic distensibility improvement appears not to be associated with response status per se (whether within a treatment arm strategy or not). Exploratory evaluation suggests greater aortic distensibility improvement with etanercept/methotrexate than with methotrexate (when controlling for response status).

Trial registration

This trial is registered as ISRCTN89222125 and ClinicalTrials.gov NCT01295151.

Funding

This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership, and will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 8, No. 4. See the NIHR Journals Library website for further project information. Pfizer supported the parent study, VEDERA, through an investigator-sponsored research grant reference WS1092499.

Chapter 1 Introduction

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Background

Rheumatoid arthritis and cardiovascular disease

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease that affects approximately 400,000 people in the UK. The life expectancy of patients with RA is reduced and the mortality rate is increased up to threefold compared with the general population. This is largely because of the increased frequency of premature cardiovascular disease (CVD), which accounts for up to 40% of mortality in RA patients and is as high as that in patients with other major CVD risk factors, such as type 2 diabetes mellitus.^{2,3} It is now widely accepted that CVD risk in RA is independent of and incremental to traditional cardiovascular (CV) risk factors.⁴⁻⁶ European guidelines therefore suggest that, pending more definitive evidence, estimates of CVD risk are multiplied by a factor of 1.5 for patients with RA.^{7,8}

Rheumatoid arthritis time course and excess cardiovascular disease

Surrogate markers have been extensively applied to investigate CVD risk and outcomes in RA, partly because of the challenges of delivering hard CV event end-point studies. Several studies have evaluated subclinical and clinical evidence of atherosclerosis at the start of a RA diagnosis, although these are often limited by modest participant numbers and the use of a variety of surrogate tools (endothelium-dependent vasodilatory response and mainly ultrasound carotid intima-media thickness). One review concluded that subclinical evidence of atherosclerosis and CV risk appear to exist at the time of diagnosis and overt events gradually increase in incidence over time.^{9,10} A meta-analysis confirmed increased CVD mortality in RA but not in a subgroup analysis of an inception cohort.¹¹ Although the rate of CV events is low in the early stages of RA, delayed diagnosis is associated with higher rates of CV events, with hypertension a strong independent predictor of CV events.¹²

Rheumatoid arthritis-related inflammation and disease activity over time are associated with increased CVD risk in patients with RA, which further highlights the importance of ensuring optimal and effective disease control.¹²⁻¹⁵

Traditional CVD risk factors, systemic inflammation and RA-specific factors, and an interplay of this triad, play a role in the increased risk. Although RA-specific factors have been implicated in the increased risk, cumulative disease activity appears to be the strongest contributor to excess CVD risk.¹³

Therapeutic strategies in new-onset early rheumatoid arthritis

Current European League Against Rheumatism (EULAR) guidelines recommend that patients with newly diagnosed RA are commenced on conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) therapy in combination with short-term glucocorticoids, with remission the ideal target (low disease activity acceptable if remission is not considered achievable), as part of the 'treat-to-target' guidelines.^{14,15}

Biologic disease-modifying anti-rheumatic drug (bDMARD) therapy, including tumour necrosis factor inhibitors (TNFis), is recommended only if csDMARDs, including methotrexate (MTX) (and, in the UK, at least two csDMARDs), are tried and fail to confer adequate disease control, with escalation to bDMARD therapy particularly advised in poorer prognostic groups. Strategy studies comparing first-line csDMARD therapy in a treat-to-target approach with TNFi therapy show variable results, demonstrating equivalence or superiority of first-line TNFi therapy. Improvements in radiographic evidence of joint disease and higher rates of drug-free remission have been demonstrated with bDMARD therapy, as well as similar or slightly greater remission induction rates.^{16–18} Long-term registry data have demonstrated a significant reduction in the incidence of acute myocardial infarction in patients receiving TNFi compared with csDMARD therapy.^{19,20}

Effect of rheumatoid arthritis disease-modifying anti-rheumatic drug therapy on cardiovascular disease outcomes

There is significant focus on the extent to which effective RA disease control can also improve comorbidity, especially CVD. Epidemiological studies have confirmed that RA disease-modifying anti-rheumatic drugs (DMARDs) reduce CV events in RA patients. Systematic reviews have evaluated the reduction in CV events with the use of MTX and TNFis, in particular, with relative risks in the range of 0.72 and 0.46–0.70, respectively.^{21,22} Evaluation of any differential benefit of MTX as the anchor csDMARD and TNFi bDMARD therapy has provided conflicting results, with some studies suggesting an equivalent benefit and others indicating an additional benefit of a TNFi.^{19–21}

Cardiovascular magnetic resonance studies in rheumatoid arthritis

Cardiovascular magnetic resonance (CMR) imaging is the most accurate test for detecting abnormalities in myocardial and vascular function. CMR imaging studies of patients with RA have demonstrated abnormalities in left ventricular (LV) remodelling.^{23–25} No studies have evaluated changes in LV myocardial and vascular function in treatment-naïve early RA. Furthermore, aside from the earlier mentioned cohort studies, the impact of csDMARD and bDMARD therapy on the structure and function of the CV system in RA has not been studied.

The VEDERA trial

The VEDERA (Very Early vs. Delayed Etanercept in early Rheumatoid Arthritis) trial was a phase IV, pragmatic, single-centre, open-label randomised controlled trial of new-onset, treatment-naïve early RA. Participants were randomised to one of two first-line therapeutic strategies: (1) immediate TNFi therapy (etanercept, ETN) and MTX or (2) MTX ± additional csDMARD therapy in a treat-to-target approach,²⁶ with switch to delayed ETN and MTX in the event of failure to achieve clinical remission at 6 months. The primary end point of the VEDERA trial was the difference in the proportion of patients in each treatment arm achieving Disease Activity Score-28-erythrocyte sedimentation rate (DAS28-ESR) remission at 1 year. Secondary end points included evaluation of the response to first-line ETN compared with delayed ETN (following MTX).

The CADERA study rationale

The CADERA (Coronary Artery Disease Evaluation in Rheumatoid Arthritis) study was a bolt-on study to the VEDERA trial.²³ The overarching objective was to evaluate whether or not patients with treatment-naïve early RA demonstrate myocardial and vascular changes on CMR imaging compared with matched control subjects; whether or not such changes are modifiable with RA DMARD therapy; and whether or not bDMARD (TNFi) therapy confers additional advantages over MTX/csDMARD therapy in modifying CV abnormalities.

The clinical unmet need

Individuals with RA are known to have an excess risk of CVD, equivalent to individuals with type 2 diabetes mellitus. Large epidemiological studies indicate that RA treatment improves CVD risk. No clinical studies using accurate imaging have been performed on a controlled cohort of RA (early or established) to determine the presence, extent and type of CV abnormalities compared with control subjects, whether or not RA disease control using DMARDs improves these CV abnormalities and whether or not RA treatment type is relevant. The CADERA study was the first study to use CMR imaging to address these questions and, in doing so, will help to inform future management of patients with early RA.

Chapter 2 Clinical trial methods

Objectives

Primary objectives

- To determine if CV abnormalities, as assessed by CMR imaging, are present in a treatment-naive inception cohort of early RA patients compared with control subjects.
- To establish whether or not (any) RA DMARD strategy is associated with improvement in CV abnormalities, as measured by CMR imaging, in a treatment-naive inception cohort of early RA patients over a 1-year period.
- To establish whether or not TNFi therapy confers a quantitative difference in the incidence of CVD compared with standard therapy, as measured by CMR imaging, in a treatment-naive inception cohort of early RA patients over a 1-year period.

Secondary objectives

- To determine changes in CV abnormalities, as assessed by CMR imaging, in a treatment-naive inception cohort of early RA patients over a 2-year period.
- Improvement in CV abnormalities relative to RA disease control (based on response status) and also each treatment strategy (initial TNFi/MTX vs initial csDMARD including MTX). This was an additional analysis undertaken as part of a protocol amendment.

Exploratory objectives (not included in this report and subject to separate funding)

- To undertake bolt-on studies on biological samples (blood) collected from all patients recruited into the study to identify RA patients with a high-risk profile for preclinical CVD and identify candidate markers and shared mechanisms.
- To link CMR imaging findings to clinical outcomes through long-term follow-up in a longitudinal observational registry.

Design

The study was a longitudinal, observational CMR imaging study that bolted onto the parent VEDERA trial, a phase IV, pragmatic, single-centre, open-label randomised controlled trial of new-onset, treatment-naive early RA comparing the clinical effectiveness of two different first-line therapeutic strategies.²³ Participants were randomised to one of two first-line therapeutic strategies: (1) immediate TNFi therapy (ETN) and MTX or (2) MTX ± additional csDMARD therapy in a treat-to-target approach, with a switch to delayed ETN and MTX in the event of failure to achieve clinical remission at 6 months. The primary end point was the comparison of the proportion of patients in each treatment arm to achieve DAS28-ESR remission. Secondary end points included evaluation of the response to first-line ETN compared with delayed ETN (following MTX).

The VEDERA trial participants who also consented to the CADERA substudy underwent CMR scans at baseline (prior to the commencement of randomised RA treatment) and at 1 and 2 years after enrolment.

The study was reviewed and approved by the National Research Ethics Service Research Ethics Committee Leeds (West) (reference 10/H1307/138).

Patient and public involvement

Mrs Ailsa Bosworth, Chief Executive and founder of the National Rheumatoid Arthritis Society (NRAS), was the patient and public involvement (PPI) contributor on the Trial Steering Group. Through membership of the Trial Steering Committee, the PPI contributor also provided input into the conduct of the trial as needed; this ensured a patient-centred approach to maximise the chance of obtaining patient therapeutic benefits.

Participants

Patients were recruited between February 2012 and November 2015 from a single tertiary centre, an early RA rheumatology outpatient clinic (Chapel Allerton Hospital, Leeds, UK). Consecutive patients diagnosed with new-onset RA according to American College of Rheumatology (ACR)/EULAR 2010 criteria²⁷ were invited to enrol into the VEDERA randomised controlled trial²³ and the parallel CADERA CVD substudy.²⁴

Thirty control subjects (free of CVD) were recruited through local advertisements, e-mail shots and word of mouth. From the responders, those of similar age and sex distribution to the study subjects were selected. Exclusion criteria were any history of rheumatological and/or CVD.

Eligibility

The VEDERA inclusion criteria

The VEDERA inclusion criteria were no previous use of DMARD therapy, a symptom duration of ≤ 1 year, a DAS28-ESR of ≥ 3.2 and at least one poor prognostic factor [positive for anti-citrullinated peptide antibody (ACPA) \pm rheumatoid factor (RF) or, in ACPA- and RF-negative individuals, the presence of abnormal power Doppler in any joint].

The VEDERA exclusion criteria

The VEDERA exclusion criteria were previous use of DMARD therapy, contraindications to TNFi therapy or patients considered clinically unsuitable for TNFi therapy by the treating physician.

Additional CADERA exclusion criteria

Additional CADERA exclusion criteria were renal failure (estimated glomerular filtration rate < 30 ml/minute/1.73 m²), contraindications to intravenous adenosine (asthma or high-grade atrioventricular block), a known allergy to gadolinium-based contrast agent, claustrophobia, a weight of ≥ 120 kg and a metallic implant/foreign body deemed unsafe for CMR imaging.

Interventions

This observational study bolted onto the parent VEDERA trial, which included the following 1-year duration randomised intervention treatment arms:

- experimental treatment arm (group 1) – ETN group: immediate ETN and MTX treatment
- control treatment arm (group 2) – standard treatment group: initial MTX monotherapy with a treat-to-target regimen – escalation to combination conventional synthetic DMARD therapy at or after 8 weeks (up to week 24) if failing to meet the predefined target at 4-weekly assessments, and if failing to meet the predefined target of clinical remission at week 24, step up to bDMARD, ETN and MTX.

Etanercept (Enbrel®, Pfizer Inc., New York, NY, USA) is a human tumour necrosis factor (TNF) receptor p75Fc fusion protein produced by recombinant deoxyribonucleic acid (DNA) technology. MTX and/or additional csDMARDs include sulfasalazine and hydroxychloroquine.

After week 48, participants on ETN stopped therapy and standard of care treatment was maintained for the year 2 observational period.

Study procedures

Following written informed consent (to participate in the VEDERA and the CADERA studies) and prior to any trial-related procedures for the CADERA study, patients were registered into the CADERA study. All patients underwent screening within the 4 weeks prior to the baseline visit for the VEDERA trial. At the baseline visit eligibility for the study was confirmed, patients were randomised to one of the treatment groups and study treatment was initiated. Further visits, which included assessment of disease activity, took place at weeks 4, 12 and every 12 weeks thereafter, up to week 96, for both treatment arms, with additional visits (for group 2) at weeks 8, 16 and 20 for safety and efficacy evaluation within a treat-to-target protocol.

At baseline and at 1 and 2 years following initiation of therapy, all patients recruited to the CADERA study also underwent comprehensive CMR imaging.

Cardiovascular magnetic resonance imaging protocol

Each CMR imaging study was conducted using the same protocol. Imaging took approximately 1 hour. The CMR imaging protocol included:

- cine imaging in a stack of LV short-axis sections covering the entire heart for measurement of ventricular volumes and LV mass (LVM)
- MR tagging in three LV short-axis sections to derive LV longitudinal strain and twist
- cine imaging of the thoracic aorta to allow measurement of aortic distensibility (AD)
- adenosine stress and rest first-pass perfusion imaging using a dual-bolus technique, with intravenous infusion of 0.01 and 0.1 mmol/kg gadopentate dimeglumine (Magnevist®, Bayer, Berlin, Germany) – this part of the protocol was optional for patients and the results are not reported here
- T1 mapping (modified look-locker inversion recovery method) pre and 10 minutes post contrast to derive the myocardial extracellular volume (MECV) fraction
- late gadolinium enhancement (LGE) imaging.

Outcome measures

Primary outcome measure

The primary outcome measure for the study was AD, a measure of aortic stiffness. This was chosen because of its dynamic nature, high reproducibility and ability to predict major CV events independently of traditional clinical risk scoring models in patients with no known CVD.³² The normality of data were tested using a Shapiro–Wilk test.

Secondary outcome measures

- Left ventricular ejection fraction (LVEF).
- Left ventricular longitudinal strain (LVLS).
- Left ventricular twist.
- Left ventricular mass.
- Myocardial perfusion reserve (not reported here).

Exploratory outcome measures

- Myocardial extracellular volume fraction from T1 mapping.
- Biomarkers of CVD (as part of future biological studies; not reported here).

Patient withdrawal

Patients could withdraw from the study at any time without explanation and continue to receive treatment as per standard clinical practice. Patient withdrawal was categorised as withdrawing consent for further study follow-up evaluation only, but willing to have CMR imaging data to date kept and used.

Sample size and power calculation

The sample size estimation for the primary end point AD was based on previous work by Ikonomidis *et al.*,²³ which showed improved AD in RA patients in response to interleukin-1 therapy. We calculated that 33 patients in each treatment group would equate to an 80% power to detect a difference in AD between the two treatment groups at a 5% significance level.

Blinding

The CMR fellows analysing the CMR scans were blinded to the VEDERA treatment allocation.

Analysis

Statistical analysis

The first 30 CADERA patients (cases) were approximately matched by age and sex to control subjects, who were invited for a CMR scan. Matched pairs analysis was conducted on the primary outcome (AD), secondary outcomes [LVEF, LVLS, peak left ventricular twist (PLVTw)] and exploratory outcome (MECV) at baseline. To reflect the approximate matching, additional linear regression analyses are presented for each of the primary, secondary and exploratory outcomes at baseline including the 30 control subjects and all cases when data are available. Each analysis is presented unadjusted (with a single independent variable case/control) and adjusted (with dependent variables of case/control, age, sex, systolic blood pressure and pack-years smoked). Outcomes are natural log transformed to achieve normality assumptions (an approach favoured over non-parametric analysis to allow straightforward adjustment in the additional regression analyses and consistency with the analyses at the 1-year and 2-year follow-ups. Back-transformation is performed when presenting results [thus, geometric mean ratios and associated 95% confidence intervals (CIs) are reported]. To assess the balance of demographic characteristics across all cases and the 30 control subjects, summary statistics are presented for age, sex, systolic blood pressure and pack-years smoked.

For analysis of the primary, secondary and exploratory outcomes in the CADERA patients at the 1-year and 2-year follow-ups, an analysis of covariance (ANCOVA) method has been adopted. The outcome at follow-up is linearly regressed on a grouping variable (defined below) as the dependent variable, first as an unadjusted analysis (exploring differences in the outcome by group at 1 year or 2 years), second, additionally adjusted for baseline outcome (an ANCOVA approach to analysis of change, replacing the differences from baseline method originally proposed) and, third, additionally adjusted for baseline outcome, age, sex, systolic blood pressure, pack-years smoked and, where appropriate (see below), baseline DAS28-ESR (again, an ANCOVA approach to analysis of change, replacing the differences from baseline method originally proposed). The change of approach compared with the CADERA study protocol, from differences from baseline to an

ANCOVA approach, was undertaken to enhance the power, given the additional grouped analyses to be undertaken (see below). Outcomes are naturally log transformed to achieve normality assumptions. Back-transformation is performed when presenting results and thus estimates are geometric means or ratios across groups.

Groups were defined as follows, in which group 1 patients received first-line ETN/MTX and group 2 patients received first-line MTX \pm additional csDMARD therapy that either continued (2a) or escalated to delayed ETN/MTX (2b) at week 24. The intention of these subgroup analyses was to determine any differences between patients who were treated with first-line ETN and those who never received ETN:

- (a) group 1 (all patients) compared with group 2 (all patients)
- (b) combined group 1 and group 2 responders compared with combined group 1 and group 2 non-responders, adjusting for baseline DAS28-ESR
- (c) group 1 responders compared with group 1 non-responders, adjusting for baseline DAS28-ESR
- (d) group 1 responders compared with group 2a responders, adjusting for baseline DAS28-ESR.

Patients with a DAS28-ESR of ≥ 2.6 at 48 weeks were considered non-responders. Patients with DAS28-ESR of < 2.6 at week 48 for reasons other than withdrawal for lack of efficacy were assumed to be responders in the initial analysis. The data were then reanalysed assuming that they were non-responders.

For an intention-to-treat analysis, multiple imputation by chained equations was used to create 50 complete data sets per outcome analysed, the results from which were combined in accordance with Rubin's rules. The imputation model included the following variables at weeks 0, 12, 24, 36 and 48: Swollen Joint Count-28 joints (SJC44), Ritchie Articular Index (RAI), C-reactive protein (CRP), ESR, physician visual analogue scale (VAS), patient general health VAS, patient pain VAS, patient disease activity VAS and early morning stiffness. Outcome values at 1 or 2 years were included (dependent on outcome analysed) in addition to baseline values. The model also included age, sex, systolic blood pressure, pack-years smoked, symptom duration, treatment and an indicator for whether or not a patient was a responder (as defined above). Multiple imputation chain mixing and distribution diagnostics were checked for plausibility of imputations.

For the primary outcome (AD) at 1 year only, an analysis adjusted for area under the curve (AUC) disease activity is reported. A trapezoid rule is used based on DAS28-ESR at weeks 0, 12, 24, 36 and 48 to calculate the AUC. The imputation model for this analysis excluded the indicator variable for whether or not a patient was a responder.

For comparison, demographics are presented for those CADERA patients who have at least one primary, secondary or exploratory outcome missing at the 1-year or 2-year follow-up and those CADERA patients who have complete data for all outcomes at 1 year and 2 years.

Where relevant, protocol amendments (see *Appendix 4*) informed any change and/or additional analyses.

Cardiovascular magnetic resonance analysis

All post-processing analysis of CMR scans was performed using CVI 42 software (Circle Cardiovascular Imaging, Calgary, Canada) except for tagging analysis by assessors with > 2 years' experience in CMR imaging reporting blinded to all patient details.

- AD was calculated from cross-sectional cine images of the thoracic aorta at the level of the pulmonary artery bifurcation. The endocardial aortic border was delineated in both diastole and systole. AD was calculated as follows: Δ relative aortic cross-sectional area/ Δ systolic and diastolic blood pressure.
- The LV endocardial and epicardial borders were manually traced from the short-axis LV cine stack at both end-systole and end-diastole. The LV end-systolic and end-diastolic volumes were generated by summation of discs and the LVEF calculated. The LVM was calculated from the end-diastolic myocardial volume, with trabeculation and papillary muscles excluded.

- Tagged images were analysed with inTag software version 1.0 (Creatis, Lyon, France). Endocardial and epicardial borders were outlined. Peak circumferential strain and rotation were calculated for three slices. PLVTw was calculated by subtracting basal from apical rotation. LVLS was defined as peak LV systolic annular velocity ('Mid LV S prime').
- Pre-contrast and post-contrast T1 was measured in a region of interest in the interventricular septum of the midventricular slice. The venous haematocrit (Hct) was used to calculate the MECV fraction according to the following equation:

$$\text{MECV} = (1 - \text{Hct}) \times ((1/\text{myocardial post contrast T1(millisecond)} - (1/\text{myocardial native T1(millisecond)})) / ((1/\text{blood post-contrast T1(millisecond)} - (1/\text{blood pre-contrast T1(millisecond)})). \quad (1)$$

Chapter 3 Clinical trial results

Patient recruitment

Patient numbers

A total of 82 patients were enrolled into the CADERA study and underwent the baseline CMR scan. In one patient, no AD data could be acquired (but all other assessments were completed). Of the 81 patients with complete baseline data, 71 underwent a 1-year CMR scan (Figure 1) and 56 underwent a 2-year scan. In total, the 30 control subjects matched for sex and age to the first 30 CADERA patients were recruited.

Withdrawals

A total of four patients were withdrawn from the study between baseline and 1 year of follow-up; one patient withdrew because of treatment non-compliance and the other three patients withdrew because of serious adverse events relating to treatment. The reasons for the remaining six patients not undergoing a 1-year CMR scan included refusal or claustrophobia (five patients) and moving away and not able to attend a repeat scan (one patient).

Baseline demographic data

Demographic data for the control subjects and the CADERA study cohort are presented in Table 1. The baseline characteristics were balanced across the two treatment groups with the exception of median pack-years of smoking. Patients and control subjects were matched for age and sex.

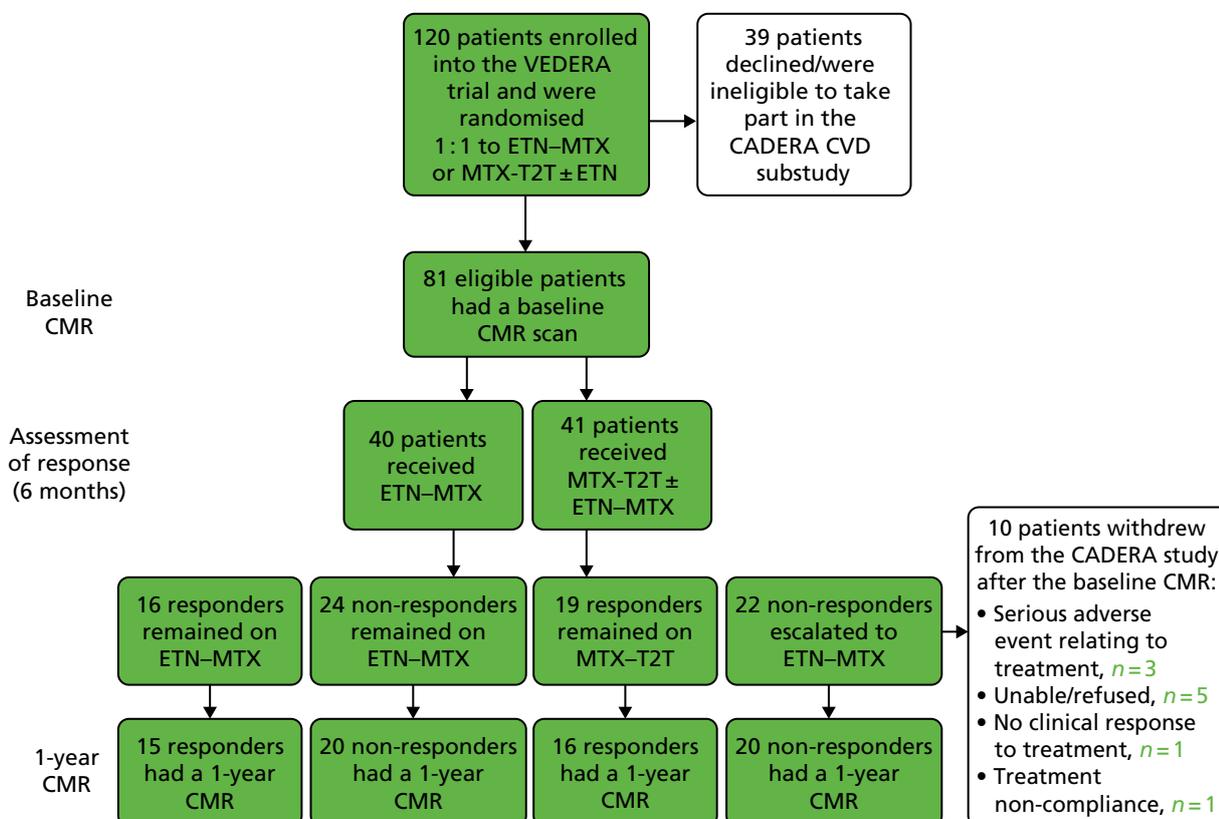


FIGURE 1 Study recruitment flow chart.

TABLE 1 Summary of baseline demographic, disease activity and comorbidity data for control subjects and patients

| Demographic variable | Control, <i>n</i> (%) or <i>n</i> (median, interquartile range) | All early RA patients, <i>n</i> (%) or <i>n</i> (median, interquartile range) | Group 1, ^a <i>n</i> (%) or <i>n</i> (median, interquartile range) | Group 2, ^a <i>n</i> (%) or <i>n</i> (median, interquartile range) |
|--------------------------------|---|---|--|--|
| Sex | Male 11 (37), female 19 (63) | Male 25 (31), female 55 (69) | Male 15 (38), female 24 (62) | Male 10 (24), female 31 (76) |
| Age (years) | 30 (54, 23) | 81 (51, 21) | 40 (48.5, 13.5) | 41 (54, 23) |
| BMI (kg/m ²) | 30 (27.0, 7.1) | 81 (24.9, 5.4) | 40 (25.6, 5.5) | 41 (24.6, 5.2) |
| ESR (mm/hr) | N/A | 77 (30, 30) | 39 (31, 33.5) | 38 (30, 28.3) |
| CRP (mg/l) | N/A | 77 (8, 23) | 39 (8, 27) | 38 (8, 17.8) |
| CCP positive | N/A | Yes 64 (84), no 12 (16) | Yes 31 (82), no 7 (18) | Yes 33 (87), no 5 (13) |
| RF positive | N/A | Yes 57 (75), no 19 (25) | Yes 26 (68), no 12 (32) | Yes 31 (82), no 7 (18) |
| Baseline DAS28-ESR | N/A | 76 (5.3, 1.4) | 38 (5.5, 1.6) | 38 (5.3, 1.4) |
| Hypertension | N/A | Yes 6 (7), no 75 (93) | Yes 1 (3), no 39 (97) | Yes 5 (12), no 36 (88) |
| Hypercholesterolaemia | N/A | Yes 2 (2), no 79 (98) | Yes 0 (0), no 40 (100) | Yes 2 (5), no 39 (95) |
| Diabetes mellitus | Yes 0 (0), no 30 (100) | Yes 0 (0), no 81 (100) | Yes 0 (0), no 40 (100) | Yes 0 (0), no 41 (100) |
| Family history of IHD | N/A | Yes 4 (5), no 77 (95) | Yes 2 (5), no 38 (95) | Yes 2 (5), no 39 (95) |
| Systolic blood pressure (mmHg) | 30 (120.5, 13.5) | 81 (121, 26) | 40 (122, 24.5) | 41 (120, 23) |
| Pack-years smoking | 30 (0, 0.4) | 81 (0.1, 10) | 40 (0, 5.3) | 41 (3, 17.5) |
| Smoking status | Current 4 (13), former 5 (17), never 21 (70) | Current 17 (22), former 25 (33), never 34 (45) | Current 6 (16), former 11 (29), never 21 (55) | Current 11 (29), former 14 (37), never 13 (34) |

BMI, body mass index; CCP, cyclic-citrullinated peptide; IHD, ischaemic heart disease; N/A, not applicable.

^a Group 1: immediate ETN and MTX treatment; group 2: first-line MTX ± additional csDMARD therapy.

As detailed earlier, 71 patients attended for the 1-year scan and 56 attended for the 2-year scan. *Table 2* details the key demographic data relevant for the primary outcome, split by those with complete data for all outcomes and those who had at least one missing outcome. No notable differences were observed between these two groups.

TABLE 2 Key demographics split by patients with at least one missing outcome at 1 year or 2 years

| Demographic variable | At least one missing outcome, <i>n</i> (%) or <i>n</i> (median, interquartile range) | Complete data for all outcomes, <i>n</i> (%) or <i>n</i> (median, interquartile range) |
|--------------------------------|--|--|
| Age (years) | 37 (45, 18) | 44 (53, 18.25) |
| Sex | Male 9 (25), female 27 (75) | Male 16 (36), female 28 (64) |
| Systolic blood pressure (mmHg) | 37 (115, 21) | 44 (123, 26) |
| Pack-years smoking | 37 (1, 15) | 44 (0.1, 8.1) |

Primary objectives

Patients compared with control subjects

The primary objective of the CADERA study was to determine if CV abnormalities, as assessed by CMR imaging, are present in a treatment-naïve inception cohort of early RA patients compared with control subjects.

The primary outcome measure AD [geometric mean (95% CI)] was significantly lower in patients ($n = 81$) than in control subjects ($n = 30$) [$3.0 \times 10^{-3}/\text{mmHg}$ ($2.7 \times 10^{-3}/\text{mmHg}$ to $3.3 \times 10^{-3}/\text{mmHg}$) vs. $4.4 \times 10^{-3}/\text{mmHg}$ ($3.7 \times 10^{-3}/\text{mmHg}$ to $5.2 \times 10^{-3}/\text{mmHg}$), respectively; $p < 0.01$] (Table 3). This difference remained significant when adjusted for age, sex, systolic blood pressure and pack-years smoked.

Of the secondary outcome measures, LVM [geometric mean (95% CI)] was significantly lower in patients ($n = 81$) than in control subjects ($n = 30$) [78.2 g (74.0 to 82.7 g) vs. 92.9 g (84.8 to 101.7 g), respectively; $p < 0.01$]. MECV [geometric mean (95% CI)] was significantly increased at baseline in patients ($n = 78$) compared with control subjects ($n = 30$) [27.1% (26.4% to 27.9%) vs. 24.9% (23.8% to 26.1%), respectively; $p < 0.01$]. These differences remained significant when adjusted for age, sex, systolic blood pressure and pack-years smoked. No significant differences between patients and control subjects were seen in the other secondary outcome measures.

Matched pairs analyses corroborated the significant differences between the control group and the early RA group for AD, MECV and LVM (with a consistent magnitude and direction in the difference for LVM) (Table 4). Three patients were excluded because of screen failure for the VEDERA trial; thus, a maximum of 27 matched pairs were available for analysis.

These data were partly presented at the American College of Rheumatology meeting.²⁸

Early rheumatoid arthritis cohort: baseline to 1 year

All analyses were performed on 81 patients, with imputation of missing baseline and follow-up outcomes as described in Chapter 2.

A further primary objective of the CADERA study was to establish whether or not (any) RA DMARD strategy is associated with improvement in CV abnormalities over a 1-year period (Table 5).

TABLE 3 Unadjusted and adjusted CMR imaging variables in control subjects and early RA patients at baseline

| Outcome | <i>n</i> | Unadjusted geometric mean (control) (95% CI) | Unadjusted geometric mean (cases) (95% CI) | Unadjusted geometric mean ratio (control/case) (95% CI) | <i>p</i> -value | Adjusted ^a geometric mean ratio (control/case) (95% CI) | <i>p</i> -value |
|------------------------------|----------|--|--|---|-----------------|--|-----------------|
| AD ($10^{-3}/\text{mmHg}$) | 111 | 4.4 (3.7 to 5.2) | 3.00 (2.7 to 3.3) | 1.5 (1.2 to 1.8) | <0.01 | 1.5 (1.3 to 1.7) | <0.01 |
| LVEF (%) | 111 | 61.6 (59.7 to 63.7) | 60.3 (59.2 to 61.5) | 1.0 (1.0 to 1.1) | 0.27 | 1.0 (1.0 to 1.1) | 0.38 |
| LVLS (cm/second) | 106 | 1.1 (1.1 to 1.2) | 1.1 (1.1 to 1.2) | 1.0 (1.0 to 1.1) | 0.76 | 1.0 (0.9 to 1.1) | 0.95 |
| PLVTw (°) | 106 | 15.3 (13.9 to 16.9) | 15.1 (14.1 to 16.0) | 1.0 (0.9 to 1.2) | 0.71 | 1.0 (0.9 to 1.2) | 0.69 |
| LVM (g) | 111 | 92.9 (84.8 to 101.7) | 78.2 (74.0 to 82.6) | 1.2 (1.1 to 1.3) | <0.01 | 1.2 (1.1 to 1.3) | 0.03 |
| MECV (%) | 108 | 24.9 (23.8 to 26.1) | 27.2 (26.4 to 27.9) | 0.9 (0.9 to 1.0) | <0.01 | 0.9 (0.9 to 1.0) | <0.01 |

a Adjusted for age, sex, systolic blood pressure and pack-years smoked.

TABLE 4 Matched pairs analyses of outcomes at baseline

| Outcome | <i>n</i> | Ratio (control/case), geometric mean (95% CI) | <i>p</i> -value |
|-----------------------------|----------|---|-----------------|
| AD (10 ⁻³ /mmHg) | 27 | 1.5 (1.15 to 2.00) | <0.01 |
| LVEF (%) | 27 | 1.0 (1.0 to 1.1) | 0.23 |
| LVLS (cm/second) | 25 | 1.0 (1.0 to 1.1) | 0.35 |
| PLVTw (°) | 25 | 1.0 (0.9 to 1.2) | 0.78 |
| LVM (g) | 27 | 1.2 (1.0 to 1.3) | 0.07 |
| MECV (%) | 25 | 0.9 (0.8 to 0.9) | <0.01 |

TABLE 5 Summary of baseline to year 1 outcomes for the whole early RA group

| Outcome | Geometric mean (95% CI), baseline | Geometric mean (95% CI), 1 year | Ratio (95% CI); <i>p</i> -value |
|-----------------------------|-----------------------------------|---------------------------------|---------------------------------|
| AD (10 ⁻³ /mmHg) | 3.0 (2.7 to 3.4) | 3.6 (3.1 to 4.1) | 1.2 (1.1 to 1.3); 0.01 |
| LVEF (%) | 60.3 (59.1 to 61.6) | 59.9 (58.5 to 61.5) | 1.0 (1.0 to 1.0); 0.54 |
| LVLS (cm/second) | 1.1 (1.1 to 1.2) | 1.1 (1.1 to 1.2) | 1.0 (1.0 to 1.1); 0.84 |
| PLVTw (°) | 14.9 (13.9 to 15.8) | 14.6 (13.7 to 15.7) | 1.0 (0.9 to 1.1); 0.69 |
| LVM (g) | 78.2 (73.7 to 82.9) | 81.4 (76.3 to 86.9) | 1.0 (1.0 to 1.1); 0.01 |
| MECV (%) | 27.2 (26.4 to 28.1) | 26.4 (25.6 to 27.1) | 1.0 (0.9 to 1.0); 0.06 |

N = 81, with imputation for missing baseline or follow-up values.

The primary outcome measure, AD [geometric mean (95% CI)], improved significantly from baseline to 1 year across the whole patient cohort [3.0×10^{-3} /mmHg (2.7 $\times 10^{-3}$ /mmHg to 3.4 $\times 10^{-3}$ /mmHg) vs. 3.6 $\times 10^{-3}$ /mmHg (3.1 $\times 10^{-3}$ /mmHg to 4.1 $\times 10^{-3}$ /mmHg), respectively; $p < 0.01$]. This difference remained significant when adjusted for age, sex, systolic blood pressure and pack-years smoked.

Left ventricular mass in the combined groups 1 and 2 cohort increased from baseline to the 1-year follow-up, from a geometric mean of 78.2 g (95% CI 73.7 to 83.0 g) to 81.4 g (95% CI 76.3 to 86.9 g; $p = 0.01$), but no significant between group differences were observed. This difference remained significant when adjusted for age, sex, systolic blood pressure and pack-years smoked.

Myocardial extracellular volume decreased from baseline to 1 year, from a geometric mean of 27.2% (95% CI 26.4% to 28.1%) to 26.4% (95% CI 25.6% to 27.3%), but this difference was not statistically significant ($p = 0.06$).

There were no significant changes in the other secondary outcome measures between baseline and the 1-year follow-up.

Early compared with delayed etanercept and methotrexate

A third primary objective of the CADERA study was to establish whether or not TNFi therapy confers a quantitatively superior difference (improvement) in CVD, as measured by CMR imaging, compared with standard therapy in a treatment-naive inception cohort of early RA patients over a 1-year period. There was no statistically significant difference in AD change at 1 year when comparing the two treatment groups (Table 6).

TABLE 6 Change in AD between baseline and 1 year: differences between groups

| Comparison ^a | AD (10 ⁻³ /mmHg), geometric mean (unadjusted) (95% CI) | Ratio (95% CI); <i>p</i> -value | | |
|--|--|---------------------------------|---------------------------|---------------------------|
| | | Unadjusted | Adjusted 1 ^b | Adjusted 2 ^c |
| Combined groups 1 and 2 (<i>n</i> = 81): baseline, 1 year | 3.0 (2.7 to 3.4), 3.6 (3.1 to 4.1) | 1.2 (1.1 to 1.3); < 0.01 | N/A | N/A |
| Group 1 at 1 year (all, <i>n</i> = 40) vs. group 2 at 1 year (all, <i>n</i> = 41) | 3.8 vs. 3.4 | 0.9 (0.7 to 1.2); 0.49 | 0.9 (0.7 to 1.2); 0.42 | 0.9 (0.8 to 1.2); 0.56 |
| Combined groups 1 and 2 at 1 year (non-responders, <i>n</i> = 38) vs. combined groups 1 and 2 at 1 year (responders, <i>n</i> = 43) | 3.5 vs. 3.6 | 1.0 (0.8 to 1.4); 0.87 | 1.0 (0.8 to 1.2); 0.79 | 1.0 (0.8 to 1.2); 0.86 |
| Group 1 at 1 year (non-responders, <i>n</i> = 17) vs. group 1 at 1 year (responders, <i>n</i> = 23) | 3.6 vs. 3.9 | 1.1 (0.7 to 1.6); 0.73 | 1.0 (0.7 to 1.3); 0.84 | 1.0 (0.7 to 1.3); 0.82 |
| Group 1 at 1 year (responders, <i>n</i> = 23) vs. group 2a at 1 year (responders, <i>n</i> = 13) | 3.9 vs. 2.8 | 0.7 (0.4 to 1.2); 0.19 | 0.8 (0.5 to 1.2); 0.29 | 0.9 (0.6 to 1.4); 0.56 |

N/A, not applicable.

a Group 1: immediate ETN and MTX treatment; group 2: first line MTX ± additional csDMARD therapy; group 2a: group 2 patients who continued csDMARD therapy and did not escalate to delayed ETN/MTX at week 24; non-responders: patients with a DAS28-ESR ≥ 2.6 at 48 weeks; responders: patients with DAS28-ESR of < 2.6 at 48 weeks.

b Adjusted 1: adjusted for baseline AD.

c Adjusted 2: adjusted for baseline AD, age, sex, systolic blood pressure and pack-years smoking (± baseline DAS28-ESR as applicable).

Response assumed for patients whose responder status at 48 weeks was unknown.

Secondary objectives

Disease activity

A secondary objective of the CADERA study was to explore whether or not the DAS28-ESR²⁹ control and associated response status (DAS28-ESR remission-defined clinical response/non-response) affects changes in CV abnormalities over a 1-year period.

There were no differences when all responders were compared with non-responders and when group 1 responders were compared with non-responders (all adjusted for baseline AD, age and sex) (see *Table 6*). To clarify this apparent absence of effect of disease activity as represented by response status, correlation analyses between AUC disease activity and AD at year 1 in the combined groups 1 and 2 (*Table 7*) and between group 1 and group 2 (*Table 8*) were carried out; these also did not identify an association.

TABLE 7 Regression analyses between AD at 1 year and AUC disease activity^a

| Patient group | AD-to-AUC disease activity ratio (95% CI); <i>p</i> -value | | |
|----------------------------------|--|-------------------------|-------------------------|
| | Unadjusted | Adjusted 1 ^b | Adjusted 2 ^c |
| All RA patients (<i>n</i> = 81) | 1.1 (0.8 to 1.5); 0.60 | 1.0 (0.8 to 1.3); 0.70 | 1.1 (0.8 to 1.3); 0.69 |

a Coefficients presented per 100-unit increase in AUC.

b Adjusted 1: additionally adjusted for baseline AD.

c Adjusted 2: additionally adjusted for baseline AD, age, sex, systolic blood pressure and pack-years smoking.

TABLE 8 Regression analyses between AD at 1 year and differences between RA groups

| Comparison ^a | AD (10 ⁻³ /mmHg), geometric mean (unadjusted) | Ratio (95% CI); <i>p</i> -value | | |
|---|--|---------------------------------|---------------------------|---------------------------|
| | | Unadjusted | Adjusted 1 ^b | Adjusted 2 ^c |
| Group 1 (all, <i>n</i> = 40) vs. group 2 (all, <i>n</i> = 41) | 3.8 vs. 3.4 | 0.9 (0.7 to 1.2); 0.48 | 0.9 (0.7 to 1.1); 0.41 | 0.9 (0.7 to 1.2); 0.45 |

a Group 1: immediate ETN and MTX treatment; group 2: first-line MTX ± additional csDMARD therapy.

b Adjusted 1: adjusted for baseline AD.

c Adjusted 2: adjusted for baseline AD, age, sex, systolic blood pressure, pack-years smoking and AUC disease activity.

Comparison of (group 1) responders who received ETN as first-line therapy and (group 2) responders who never received ETN (group 2a) showed an unadjusted difference of 30% (ratio 0.7, 95% CI 0.4 to 1.2); the difference was 19% when adjusted for baseline AD (ratio 0.8, 95% CI 0.5 to 1.2) and 10% when adjusted for possible confounders (ratio 0.9, 95% CI 0.60 to 1.18), although these differences are not statistically significant (see *Table 6*).

Two-year follow-up

A further secondary objective of the CADERA study was to establish if any treatment effects of RA therapy are sustained over a 2-year period. The difference in the primary outcome measure, AD, was maintained at the 2-year follow-up [geometric mean (95% CI): 3.0 × 10⁻³/mmHg (2.7 × 10⁻³/mmHg to 3.4 × 10⁻³/mmHg) vs. 3.6 × 10⁻³/mmHg (3.1 × 10⁻³/mmHg to 4.1 × 10⁻³/mmHg), respectively; *p* = 0.05] (*Table 9*). As in the year 1 analysis, there were no differences between responders and non-responders. The comparison of group 1 responders and group 2a responders showed a smaller difference than in year 1 (see *Table 9*).

TABLE 9 Change in AD between baseline and 2 years: differences between groups

| Comparison ^a | AD (10 ⁻³ /mmHg), geometric mean (unadjusted) | Ratio (95% CI), <i>p</i> -value | | |
|--|--|---------------------------------|---------------------------|---------------------------|
| | | Unadjusted | Adjusted 1 ^b | Adjusted 2 ^c |
| Combined groups 1 and 2 (<i>n</i> = 81): baseline, 2 years | 3.0 (2.7 to 3.4), 3.6 (3.1 to 4.1) | 1.1 (1 to 1.4), 0.05 | N/A | N/A |
| Group 1 at 2 years (all, <i>n</i> = 40) vs. group 2 at 2 years (all, <i>n</i> = 41) | 3.7 vs. 3.4 | 0.9 (0.7 to 1.2), 0.59 | 0.9 (0.7 to 1.2), 0.6 | 0.9 (0.7 to 1.2), 0.65 |
| Combined groups 1 and 2 at 2 years (non-responders, <i>n</i> = 38) vs. combined groups 1 and 2 at 2 years (responders, <i>n</i> = 43) | 3.5 vs. 3.6 | 1.0 (0.8 to 1.4), 0.83 | 1.0 (0.8 to 1.4), 0.91 | 1.0 (0.7 to 1.4), 0.95 |
| Group 1 at 2 years (non-responders, <i>n</i> = 17) vs. group 1 at 2 years (responders, <i>n</i> = 23) | 3.5 vs. 3.8 | 1.1 (0.7 to 1.7), 0.75 | 1.1 (0.6 to 1.7), 0.83 | 1.1 (0.6 to 1.8), 0.83 |
| Group 1 at 2 years (responders, <i>n</i> = 23) vs. group 2a at 2 years (responders, <i>n</i> = 13) | 3.8 vs. 3.4 | 0.9 (0.6 to 1.4), 0.56 | 0.9 (0.6 to 1.5), 0.70 | 0.9 (0.5 to 1.6), 0.70 |

N/A, not applicable.

a Group 1: immediate ETN and MTX treatment; group 2: first-line MTX ± additional csDMARD therapy; group 2a: group 2 patients who continued csDMARD therapy and did not escalate to delayed ETN/MTX at week 24; non-responders: patients with DAS28-ESR ≥ 2.6 at 48 weeks; responders: patients with DAS28-ESR of < 2.6 at 48 weeks.

b Adjusted 1: adjusted for baseline AD.

c Adjusted 2: adjusted for baseline AD, age, sex, systolic blood pressure and pack-years smoking (± baseline DAS28-ESR as applicable).

Response assumed for patients whose responder status at 48 weeks was unknown.

The difference in LVM remained significant from baseline to the 2-year follow-up [geometric mean (95% CI): 78.2 g (73.7 to 82.9 g) vs. 85.5 g (79.0 to 92.6 g), respectively; $p = 0.02$] (see *Appendix 3, Table 17*). Of the other secondary outcome measures, PLVTw showed a significant difference from baseline to the 2-year follow-up [geometric mean (95% CI): 14.9° (14.0° to 15.9°) vs. 16.6° (15.5° to 17.8°), respectively; $p = 0.02$] (see *Appendix 3, Table 15*). There were no differences between the treatment arms and no other parameters showed statistically significant differences at the 2-year follow-up. *Appendix 3 (Tables 10–20)* details all secondary measures at years 1 and 2.

Ten RA patients had abnormal findings on LGE imaging and/or follow-up CMR imaging. In eight patients inferior right ventricular insertion point enhancement was seen and in two patients there was septal enhancement.

Chapter 4 Discussion

The CADERA study was the first prospectively conducted single-centre randomised controlled trial to assess the impact of modern DMARD therapy on CMR imaging markers of subclinical CVD in patients with newly diagnosed, treatment-naive, very early RA and no previous history of CVD.

The study has demonstrated that AD, a measure of aortic stiffness and a surrogate marker for increased risk of CVD, is lower in patients with a recent new diagnosis of RA than in control subjects. Other markers of CVD, in particular those related to inflammation, including elevated native T1 and extracellular volume (ECV) in CMR imaging, were raised and LVM was reduced compared with control subjects. Treatment for RA, irrespective of strategy, improved AD at 1 and 2 years, whereas first-line treatment with TNFi bDMARD (ETN) showed the potential for additional benefits in those patients who responded to treatment.

Baseline assessment

Several previous studies have demonstrated reduced aortic stiffness using a variety of non-invasive imaging techniques in patients with established RA. A cross-sectional study of RA patients in clinical remission showed lower augmentation index values than in patients with active RA.²³ Another study showed that a high augmentation index and aortic pulse wave velocity values were predictive of CV events in 138 patients over a 6-year follow-up period.³⁰ The CADERA study is the first study to demonstrate changes in vascular function compared with control subjects in newly diagnosed RA patients with a symptom duration of < 12 months. The observation that CVD is already manifest at such an early disease stage should motivate the commencement of CVD risk modification at the time of RA diagnosis.

We used CMR imaging to detect other subclinical CVD in the CADERA cohort. CMR imaging is considered to be the most accurate test for measuring left and right ventricular dimension, function and mass, and allows non-invasive tissue characterisation using cine, LGE and parametric mapping methods. Previous studies using CMR imaging have shown a range of abnormalities in patients with established RA, including lower LVM compared with control subjects, higher native T1 and ECV, indicative of diffuse oedema and/or myocardial fibrosis, focal fibrosis on LGE imaging and lower LV strain, indicating diastolic myocardial impairment.^{31,32} Native T1, ECV and strain correlated with disease activity.

The CADERA study has shown that changes in these parameters compared with control subjects are already present in patients with new-onset early RA, suggesting that the relatively short period of generalised inflammation is sufficient to cause measurable and widespread CV changes. In effect, this refers to the period of generalised inflammation from the time of onset of symptoms, preceding presentation and the diagnosis of RA, leading to measurable CV effects at the point of diagnosis.

The observed reduced myocardial muscle mass in RA in the CADERA study and previous studies may be the consequence of myocardial collagen deposition in response to elevated TNF or a process called 'rheumatoid cachexia'. A combination of inflammation and reduced physical activity in RA patients, which leads to reduced skeletal muscle mass in combination with increased fat mass, is a key driver of rheumatoid cachexia. It is possible that the reduction in muscle mass extends beyond skeletal muscle to involve the myocardium in patients with rheumatoid cachexia.

Patients had a higher MECV than control subjects. MECV is a measure of diffuse myocardial fibrosis and has been reported to be elevated in patients with established RA.³¹ Our data suggest that, even in an inception cohort of RA, myocardial fibrosis is present. MECV has emerged as a potentially useful biomarker of disease and indicator of poor prognostic outcome in the general ischaemic heart disease population. Longitudinal studies may similarly suggest a role in RA populations. In addition, a small proportion (14%) of the CADERA patients showed non-ischaemic areas of LGE. A previous study by Ntusi *et al.*³² found

non-ischaeamic LGE in 46% of 39 established RA patients. Focal fibrosis is generally considered a later manifestation of disease, consistent with the lower rate of LGE in the CADERA study compared with this previous study.

Treatment effects

The CADERA study has shown that aortic stiffness improves following treatment initiation in a treatment-naive RA cohort. Although AD is a surrogate for risk, this finding underscores the importance of early detection and treatment of CVD in patients with RA.

Furthermore, MECV as a marker of diffuse myocardial fibrosis improved from baseline to the 1-year follow-up, suggesting that anti-inflammatory therapy can reverse some of the abnormal myocardial findings associated with even early RA. These observations provide insights into the potential underlying inflammatory (as well as fibrotic) mechanisms of myocardial fibrosis, which may offer novel therapeutic opportunities for improving the outcomes of RA patients with co-existent CVD.

The type of treatment used had no statistically significant effect in the CADERA study: ETN as first-line treatment was not superior to an initial csDMARD strategy in improving markers of CVD in the entire study population. Unexpectedly, there was also no difference in AD change between responders and non-responders from both treatment groups. To account for the dichotomous response measure 'hiding' a disease activity effect an additional analysis of cumulative disease activity burden was undertaken, which also indicated an absence of effect on AD change. Early TNFi bDMARD therapy appeared to provide additional benefits in first-line bDMARD responders compared with csDMARD responders; however, the difference was not statistically significant. If confirmed in larger studies, these data suggest that bDMARD therapy with ETN may provide specific CVD benefits.

Lastly, we have demonstrated an increase in LVM following treatment for RA in both treatment arms. Other markers of subclinical CVD, including LV strain indices, ECV and native myocardial T1 relaxation time, did not improve significantly with treatment.

Study limitations

The sample size of this study was small for some of the secondary end points and larger studies will be needed to test these end points with adequate power. Although we performed analyses to establish the effect of age, sex, smoking and blood pressure between the control and patient groups, there may have been other confounders that affected the comparisons. AD is related to CV risk but also varies with age and normal values for AD are not clearly defined. Both treatment regimens were effective for the treatment of RA, which translated into a comparable total burden of disease activity (and thus presumably inflammation). This was by design and driven by the primary trial (VEDERA), which aimed to determine whether or not initial ETN plus MTX offered greater benefit over an optimal initial csDMARD treat-to-target strategy, with 'optimal' meaning efficient switching to ETN in those not achieving remission. A primary cardiac-only study could have included continuation of csDMARD therapy in group 2 to create a greater separation of disease burden, although this would be less clinically meaningful and would probably be deemed unethical.

Conclusion

The CADERA study is the first randomised controlled trial to show changes in vascular function in treatment-naive early RA of < 12 months' symptom-duration patients compared with control subjects. Optimal DMARD therapy (whether csDMARDs or bDMARDs) to control RA disease activity is associated

with significant improvement in AD over a 48-week period. However, AD improvement over 48 weeks appears not to be associated with response status per se (whether within a treatment arm strategy or not). Exploratory evaluation suggests greater AD improvement with ETN/MTX compared with MTX (when controlling for response status).

Recommendations

The CADERA study offers new insights into the relationship between RA disease activity (reflecting systemic and local inflammation), subclinical CVD and the influence of RA-directed treatments. The presence of vascular changes at the earliest stages of RA onset deserve validation to inform future evaluation of CVD comorbidity. The ability to modify vascular and myocardial changes with RA therapy alone, with the suggestion of drug-specific benefits, also warrants confirmation in larger studies.

Multicentre studies are thus needed, both for feasibility and for generalisability. Consistency in imaging platforms, protocols and analysis approaches is crucial to deliver robust multicentre imaging studies. Utilising research networks [such as National Institute for Health Research (NIHR) Biomedical Research Centres and Clinical Research Facilities) and NIHR Translational Research Collaborations can foster such interdisciplinary experimental studies.

Acknowledgements

This research was supported by the NIHR infrastructure at Leeds. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. Pfizer supported the parent study, VEDERA, through an investigator-sponsored research grant reference WS1092499.

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Thank you to all trial patients for their essential contribution to the trial.

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Bara Erhayiem (<https://orcid.org/0000-0002-9340-6127>) was one of the principal clinical research fellows (Cardiology) analysing the CMR imaging data. He also contributed to the writing of the report and had the opportunity to critically revise it.

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Publications

Erhayiem B, McDiarmid A, Swoboda P, Kidambi A, Ripley D, Musa T, *et al.* Treatment-naïve, early rheumatoid arthritis patients demonstrate abnormalities of vascular and myocardial function on cardiac MRI. *Arthritis Rheumatol* 2015;**67**(Suppl. 10).

Dumitru RB, Horton S, Hodgson R, Wakefield RJ, Hensor EMA, Emery P, Buch MH. A prospective, single-centre, randomised study evaluating the clinical, imaging and immunological depth of remission achieved by very early versus delayed Etanercept in patients with Rheumatoid Arthritis (VEDERA). *BMC Musculoskelet Disord* 2016;**17**:61.

Plein S, Erhayiem B, Fent G, Horton S, Dumitru RB, Andrews J, *et al.* Cardiovascular effects of biological versus conventional synthetic disease-modifying antirheumatic drug therapy in treatment-naïve, early rheumatoid arthritis. *Ann Rheum Dis* 2020;**79**:1414–22.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation>.

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Appendix 1 The VEDERA trial design

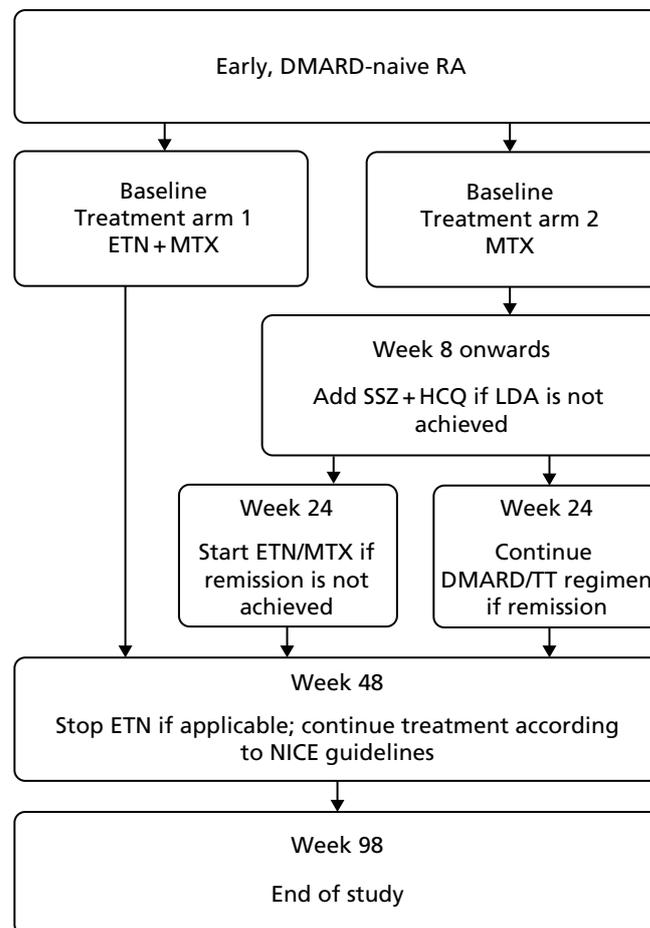


FIGURE 2 Schematic of the trial design. HCQ, hydroxychloroquine; LDA, low disease activity; NICE, National Institute for Health and Care Excellence; SSZ, sulfasalazine; TT, treat to target. Reproduced from Dumitru *et al.*²³ This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated.

Appendix 2 The CADERA study design

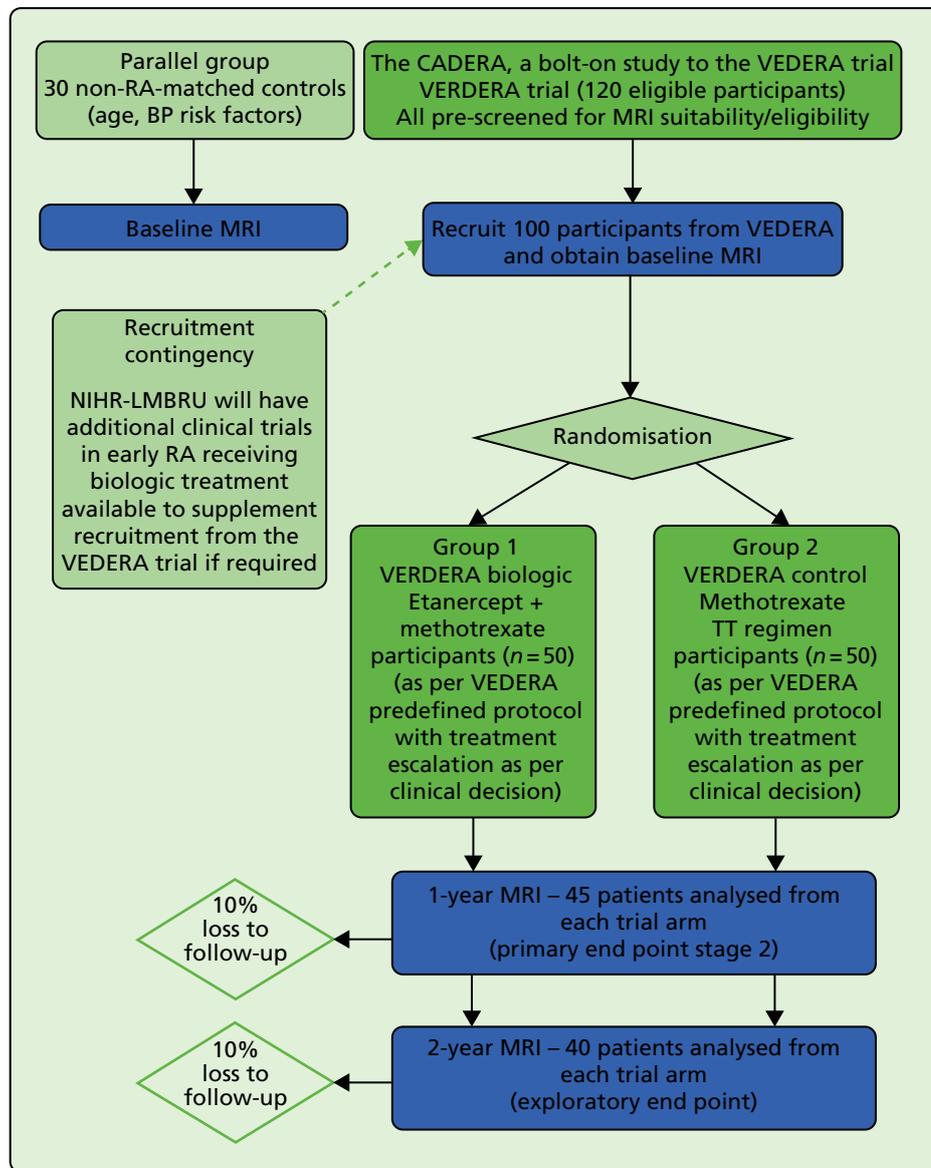


FIGURE 3 BP, blood pressure; MRI, magnetic resonance imaging, NIHR-LMBRU, National Institute for Health Research – Biomedical Research Unit; TT, treat to target.

Appendix 3 Additional tables

TABLE 10 Left ventricular ejection fraction at 1 year: differences between groups

| Comparison ^a | LVEF (%), geometric mean (unadjusted) (95% CI) | Ratio (95% CI); <i>p</i> -value | | |
|--|---|---------------------------------|---------------------------|---------------------------|
| | | Unadjusted | Adjusted 1 ^b | Adjusted 2 ^c |
| Combined groups 1 and 2 (<i>n</i> = 81): baseline, 1 year | 60.3 (59.1 to 61.6), 59.9 (58.5 to 61.5) | 1.0 (1.0 to 1.0); 0.54 | N/A | N/A |
| Group 1 at 1 year (all, <i>n</i> = 40) vs. group 2 at 1 year (all, <i>n</i> = 41) | 60.0 vs. 60.9 | 1.0 (1.0 to 1.1); 0.20 | 1.0 (1.0 to 1.1); 0.16 | 1.0 (1.0 to 1.1); 0.22 |
| Combined groups 1 and 2 at 1 year (non-responders, <i>n</i> = 38) vs. combined groups 1 and 2 at 1 year (responders, <i>n</i> = 43) | 61.1 vs. 58.9 | 1.0 (0.9 to 1.0); 0.16 | 1.0 (0.9 to 1.0); 0.13 | 1.0 (0.9 to 1.0); 0.31 |
| Group 1 at 1 year (non-responders, <i>n</i> = 17) vs. group 1 at 1 year (responders, <i>n</i> = 23) | 59.7 vs. 58.4 | 1.0 (0.9 to 1.1); 0.54 | 1.0 (0.9 to 1.0); 0.24 | 1.0 (0.9 to 1.0); 0.38 |
| Group 1 at 1 year (responders, <i>n</i> = 23) vs. group 2a at 1 year (responders, <i>n</i> = 13) | 58.4 vs. 59.4 | 1.0 (0.9 to 1.1); 0.75 | 1.0 (1.0 to 1.1); 0.29 | 1.1 (1.0 to 1.2); 0.19 |

N/A, not applicable.

a Group 1: immediate ETN and MTX treatment; group 2: first-line MTX ± additional csDMARD therapy; group 2a: group 2 patients who continued csDMARD therapy and did not escalate to delayed ETN/MTX at week 24; non-responders: patients with a DAS28-ESR of ≥ 2.6 at 48 weeks; responders: patients with DAS28-ESR of < 2.6 at 48 weeks.

b Adjusted 1: adjusted for baseline LVEF.

c Adjusted 2: adjusted for baseline AD, age, sex, systolic blood pressure and pack-years smoking (± baseline DAS28-ESR as applicable).

Response assumed for patients whose responder status at 48 weeks was unknown.

TABLE 11 Left ventricular ejection fraction at 2 years: differences between groups

| Comparison ^a | LVEF (%), geometric mean (unadjusted) (95% CI) | Ratio (95% CI); <i>p</i> -value | | |
|--|---|---------------------------------|---------------------------|---------------------------|
| | | Unadjusted | Adjusted 1 ^b | Adjusted 2 ^c |
| Combined groups 1 and 2 (<i>n</i> = 81): baseline, 2 years | 60.3 (59.1 to 61.6), 60.1 (58.1 to 62.1) | 1.0 (1.0 to 1.0); 0.82 | N/A | N/A |
| Group 1 at 1 year (all, <i>n</i> = 40) vs. group 2 at 1 year (all, <i>n</i> = 41) | 59.3 vs. 60.9 | 1.0 (1.0 to 1.1); 0.44 | 1.0 (1.0 to 1.1); 0.46 | 1.0 (1.0 to 1.1); 0.41 |
| Combined groups 1 and 2 at 1 year (non-responders, <i>n</i> = 38) vs. combined groups 1 and 2 at 1 year (responders, <i>n</i> = 43) | 61.2 vs. 59.2 | 1.0 (0.9 to 1.0); 0.31 | 1.0 (0.9 to 1.0); 0.33 | 1.0 (0.9 to 1.1); 0.54 |
| Group 1 at 1 year (non-responders, <i>n</i> = 17) vs. group 1 at 1 year (responders, <i>n</i> = 23) | 60.6 vs. 58.4 | 1.0 (0.9 to 1.1); 0.46 | 1.0 (0.9 to 1.1); 0.32 | 1.0 (0.9 to 1.1); 0.41 |
| Group 1 at 1 year (responders, <i>n</i> = 23) vs. group 2a at 1 year (responders, <i>n</i> = 13) | 58.4 vs. 59.8 | 1.0 (0.9 to 1.2); 0.67 | 1.0 (0.9 to 1.2); 0.57 | 1.1 (0.9 to 1.2); 0.45 |

N/A, not applicable.
a Group 1: immediate ETN and MTX treatment; group 2: first-line MTX ± additional csDMARD therapy; group 2a: group 2 patients who continued csDMARD therapy and did not escalate to delayed ETN/MTX at week 24; non-responders: patients with a DAS28-ESR of ≥ 2.6 at 48 weeks; responders: patients with DAS28-ESR of < 2.6 at 48 weeks.
b Adjusted 1: adjusted for baseline LVEF.
c Adjusted 2: adjusted for baseline AD, age, sex, systolic blood pressure and pack-years smoking (± baseline DAS28-ESR as applicable).
Response assumed for patients whose responder status at 48 weeks was unknown.

TABLE 12 Left ventricular longitudinal strain at 1 year: differences between groups

| Comparison ^a | LVLS (cm/second), geometric mean (unadjusted) (95% CI) | Ratio (95% CI); <i>p</i> -value | | |
|--|---|---------------------------------|---------------------------|---------------------------|
| | | Unadjusted | Adjusted 1 ^b | Adjusted 2 ^c |
| Combined groups 1 and 2 (<i>n</i> = 81): baseline, 1 year | 1.1 (1.1 to 1.2), 1.1 (1.1 to 1.2) | 1.0 (1.0 to 1.1); 0.84 | N/A | N/A |
| Group 1 at 1 year (all, <i>n</i> = 40) vs. group 2 at 1 year (all, <i>n</i> = 41) | 1.2 vs. 1.1 | 1.0 (0.9 to 1.1); 0.33 | 0.9 (0.9 to 1.0); 0.21 | 0.9 (0.9 to 1.0); 0.21 |
| Combined groups 1 and 2 at 1 year (non-responders, <i>n</i> = 38) vs. combined groups 1 and 2 at 1 year (responders, <i>n</i> = 43) | 1.1 vs. 1.2 | 1.1 (1.0 to 1.2); 0.30 | 1.1 (1.0 to 1.2); 0.29 | 1.1 (0.9 to 1.2); 0.38 |
| Group 1 at 1 year (non-responders, <i>n</i> = 17) vs. group 1 at 1 year (responders, <i>n</i> = 23) | 1.2 vs. 1.2 | 1.0 (0.9 to 1.1); 0.83 | 1.0 (0.9 to 1.1); 0.92 | 1.0 (0.9 to 1.1); 0.98 |
| Group 1 at 1 year (responders, <i>n</i> = 23) vs. group 2a at 1 year (responders, <i>n</i> = 13) | 1.2 vs. 1.2 | 1.0 (0.9 to 1.1); 0.81 | 1.0 (0.9 to 1.2); 0.97 | 1.0 (0.9 to 1.2); 0.96 |

N/A, not applicable.
a Group 1: immediate ETN and MTX treatment; group 2: first-line MTX ± additional csDMARD therapy; group 2a: group 2 patients who continued csDMARD therapy and did not escalate to delayed ETN/MTX at week 24; non-responders: patients with a DAS28-ESR of ≥ 2.6 at 48 weeks; responders: patients with DAS28-ESR of < 2.6 at 48 weeks.
b Adjusted 1: adjusted for baseline LVLS.
c Adjusted 2: adjusted for baseline AD, age, sex, systolic blood pressure and pack-years smoking (± baseline DAS28-ESR as applicable).
Response assumed for patients whose responder status at 48 weeks was unknown.

TABLE 13 Left ventricular longitudinal strain at 2 years: differences between groups

| Comparison ^a | LVLS (cm/second), geometric mean (unadjusted) (95% CI) | Ratio (95% CI); <i>p</i> -value | | |
|--|---|---------------------------------|---------------------------|---------------------------|
| | | Unadjusted | Adjusted 1 ^b | Adjusted 2 ^c |
| Combined groups 1 and 2 (<i>n</i> = 81): baseline, 2 years | 1.1 (1.1 to 1.2), 1.0 (0.9 to 1.2) | 0.9 (0.8 to 1.1); 0.27 | N/A | N/A |
| Group 1 at 1 year (all, <i>n</i> = 40) vs. group 2 at 1 year (all, <i>n</i> = 41) | 1.0 vs. 1.1 | 1.0 (0.8 to 1.3); 0.77 | 1.0 (0.8 to 1.3); 0.75 | 1.0 (0.8 to 1.3); 0.80 |
| Combined groups 1 and 2 at 1 year (non-responders, <i>n</i> = 38) vs. combined groups 1 and 2 at 1 year (responders, <i>n</i> = 43) | 1.0 vs. 1.1 | 1.0 (0.8 to 1.3); 0.91 | 1.0 (0.8 to 1.3); 0.91 | 1.0 (0.8 to 1.3); 0.75 |
| Group 1 at 1 year (non-responders, <i>n</i> = 17) vs. group 1 at 1 year (responders, <i>n</i> = 23) | 1.0 vs. 1.1 | 1.1 (0.8 to 1.6); 0.57 | 1.1 (0.8 to 1.7); 0.55 | 1.1 (0.7 to 1.7); 0.56 |
| Group 1 at 1 year (responders, <i>n</i> = 23) vs. group 2a at 1 year (responders, <i>n</i> = 13) | 1.1 vs. 1.0 | 1.0 (0.7 to 1.4); 0.87 | 1.0 (0.7 to 1.4); 0.85 | 1.0 (0.6 to 1.6); 0.97 |

N/A, not applicable.

a Group 1: immediate ETN and MTX treatment; group 2: first-line MTX ± additional csDMARD therapy; group 2a: group 2 patients who continued csDMARD therapy and did not escalate to delayed ETN/MTX at week 24; non-responders: patients with a DAS28-ESR of ≥ 2.6 at 48 weeks; responders: patients with DAS28-ESR of < 2.6 at 48 weeks.

b Adjusted 1: adjusted for baseline LVLS.

c Adjusted 2: adjusted for baseline AD, age, sex, systolic blood pressure and pack-years smoking (± baseline DAS28-ESR as applicable).

Response assumed for patients whose responder status at 48 weeks was unknown.

TABLE 14 Peak left ventricular twist at 1 year: differences between groups

| Comparison ^a | PLVTw (°), geometric mean (unadjusted) (95% CI) | Ratio (95% CI); <i>p</i> -value | | |
|--|--|---------------------------------|----------------------------|---------------------------|
| | | Unadjusted | Adjusted 1 ^b | Adjusted 2 ^c |
| Combined groups 1 and 2 (<i>n</i> = 81): baseline, 1 year | 14.9 (13.9 to 15.8), 14.6 (13.7 to 15.7) | 1.0 (0.9 to 1.1); 0.69 | N/A | N/A |
| Group 1 at 1 year (all, <i>n</i> = 40) vs. group 2 at 1 year (all, <i>n</i> = 41) | 14.5 vs. 14.8 | 1.0 (0.9 to 1.2); 0.75 | 1.0 (0.9 to 1.2); 0.80 | 1.0 (0.9 to 1.2); 0.96 |
| Combined groups 1 and 2 at 1 year (non-responders, <i>n</i> = 38) vs. combined groups 1 and 2 at 1 year (responders, <i>n</i> = 43) | 15.0 vs. 14.3 | 1.0 (0.8 to 1.1); 0.52 | 1.0 (0.83 to 1.1); 0.43 | 1.0 (0.8 to 1.1); 0.61 |
| Group 1 at 1 year (non-responders, <i>n</i> = 17) vs. group 1 at 1 year (responders, <i>n</i> = 23) | 15.0 vs. 14.1 | 1.0 (0.8 to 1.2); 0.58 | 0.9 (0.8 to 1.1); 0.50 | 1.0 (0.8 to 1.2); 0.60 |
| Group 1 at 1 year (responders, <i>n</i> = 23) vs. group 2a at 1 year (responders, <i>n</i> = 13) | 14.1 vs. 15.4 | 1.1 (0.9 to 1.4); 0.49 | 1.1 (0.9 to 1.4); 0.44 | 1.1 (0.8 to 1.4); 0.75 |

N/A, not applicable.

a Group 1: immediate ETN and MTX treatment; group 2: first-line MTX ± additional csDMARD therapy; group 2a: group 2 patients who continued csDMARD therapy and did not escalate to delayed ETN/MTX at week 24; non-responders: patients with a DAS28-ESR of ≥ 2.6 at 48 weeks; responders: patients with DAS28-ESR of < 2.6 at 48 weeks.

b Adjusted 1: adjusted for baseline PLVTw.

c Adjusted 2: adjusted for baseline AD, age, sex, systolic blood pressure and pack-years smoking (± baseline DAS28-ESR as applicable).

Response assumed for patients whose responder status at 48 weeks was unknown.

TABLE 15 Peak left ventricular twist at 2 years: differences between groups

| Comparison ^a | PLVTw (°), geometric mean (unadjusted) (95% CI) | Ratio (95% CI); <i>p</i> -value | | |
|--|--|---------------------------------|---------------------------|---------------------------|
| | | Unadjusted | Adjusted 1 ^b | Adjusted 2 ^c |
| Combined groups 1 and 2 (<i>n</i> = 81): baseline, 2 years | 14.9 (14.0 to 15.9), 16.6 (15.5 to 17.8) | 1.1 (1.0 to 1.2); 0.02 | N/A | N/A |
| Group 1 at 1 year (all, <i>n</i> = 40) vs. group 2 at 1 year (all, <i>n</i> = 41) | 16.7 vs. 16.4 | 1.0 (0.9 to 1.1); 0.78 | 1.0 (0.9 to 1.1); 0.76 | 1.0 (0.9 to 1.2); 0.75 |
| Combined groups 1 and 2 at 1 year (non-responders, <i>n</i> = 38) vs. combined groups 1 and 2 at 1 year (responders, <i>n</i> = 43) | 16.5 vs. 16.6 | 1.0 (0.8 to 1.2); 0.95 | 1.0 (0.8 to 1.2); 1.00 | 1.1 (0.9 to 1.3); 0.64 |
| Group 1 at 1 year (non-responders, <i>n</i> = 17) vs. group 1 at 1 year (responders, <i>n</i> = 23) | 16.6 vs. 17.6 | 1.1 (0.8 to 1.4); 0.61 | 1.1 (0.8 to 1.4); 0.60 | 1.1 (0.8 to 1.5); 0.44 |
| Group 1 at 1 year (responders, <i>n</i> = 23) vs. group 2a at 1 year (responders, <i>n</i> = 13) | 16.7 vs. 16.4 | 1.0 (0.9 to 1.1); 0.78 | 1.0 (0.9 to 1.1); 0.76 | 1.0 (0.9 to 1.2); 0.75 |

N/A, not applicable.
a Group 1: immediate ETN and MTX treatment; group 2: first-line MTX ± additional csDMARD therapy; group 2a: group 2 patients who continued csDMARD therapy and did not escalate to delayed ETN/MTX at week 24; non-responders: patients with a DAS28-ESR of ≥ 2.6 at 48 weeks; responders: patients with DAS28-ESR of < 2.6 at 48 weeks.
b Adjusted 1: adjusted for baseline PLVTw.
c Adjusted 2: adjusted for baseline AD, age, sex, systolic blood pressure and pack-years smoking (± baseline DAS28-ESR as applicable).
Response assumed for patients whose responder status at 48 weeks was unknown.

TABLE 16 Left ventricular mass at 1 year: differences between groups

| Comparison ^a | LVM (g), geometric mean (unadjusted) (95% CI) | Ratio (95% CI); <i>p</i> -value | | |
|--|--|---------------------------------|---------------------------|---------------------------|
| | | Unadjusted | Adjusted 1 ^b | Adjusted 2 ^c |
| Combined groups 1 and 2 (<i>n</i> = 81): baseline, 1 year | 78.2 (73.7 to 82.9), 81.4 (76.3 to 86.9) | 1.0 (1.0 to 1.1); 0.01 | N/A | N/A |
| Group 1 at 1 year (all, <i>n</i> = 40) vs. group 2 at 1 year (all, <i>n</i> = 41) | 80.9 vs. 81.9 | 1.0 (0.9 to 1.2); 0.84 | 1.0 (1.0 to 1.1); 0.68 | 1.0 (1.0 to 1.1); 0.35 |
| Combined groups 1 and 2 at 1 year (non-responders, <i>n</i> = 38) vs. combined groups 1 and 2 at 1 year (responders, <i>n</i> = 43) | 76.0 vs. 86.5 | 1.1 (1.0 to 1.3); 0.05 | 1.0 (0.9 to 1.1); 0.88 | 1.0 (0.9 to 1.1); 0.69 |
| Group 1 at 1 year (non-responders, <i>n</i> = 17) vs. group 1 at 1 year (responders, <i>n</i> = 23) | 76.9 vs. 83.9 | 1.1 (0.9 to 1.3); 0.33 | 1.0 (0.9 to 1.1); 0.80 | 1.0 (0.9 to 1.1); 0.65 |
| Group 1 at 1 year (responders, <i>n</i> = 23) vs. group 2a at 1 year (responders, <i>n</i> = 13) | 83.9 vs. 87.5 | 1.0 (0.8 to 1.3); 0.71 | 1.0 (0.9 to 1.1); 0.74 | 1.0 (0.9 to 1.2); 0.78 |

N/A, not applicable.
a Group 1: immediate ETN and MTX treatment; group 2: first-line MTX ± additional csDMARD therapy; group 2a: group 2 patients who continued csDMARD therapy and did not escalate to delayed ETN/MTX at week 24; non-responders: patients with a DAS28-ESR of ≥ 2.6 at 48 weeks; responders: patients with DAS28-ESR of < 2.6 at 48 weeks.
b Adjusted 1: adjusted for baseline LVM.
c Adjusted 2: adjusted for baseline AD, age, sex, systolic blood pressure and pack-years smoking (± baseline DAS28-ESR as applicable).
Response assumed for patients whose responder status at 48 weeks was unknown.

TABLE 17 Left ventricular mass at 2 years: differences between groups

| Comparison ^a | LVM (g), geometric mean (unadjusted) (95% CI) | Ratio (95% CI); <i>p</i> -value | | |
|--|--|---------------------------------|---------------------------|---------------------------|
| | | Unadjusted | Adjusted 1 ^b | Adjusted 2 ^c |
| Combined groups 1 and 2 (<i>n</i> = 81): baseline, 2 years | 78.2 (73.7 to 82.9), 85.5 (79.0 to 92.6) | 1.1 (1.0 to 1.2); 0.02 | N/A | N/A |
| Group 1 at 1 year (all, <i>n</i> = 40) vs. group 2 at 1 year (all, <i>n</i> = 41) | 85.1 vs. 86.0 | 1.0 (0.9 to 1.2); 0.90 | 1.0 (0.9 to 1.2); 0.90 | 1.0 (0.9 to 1.2); 0.78 |
| Combined groups 1 and 2 at 1 year (non-responders, <i>n</i> = 38) vs. combined groups 1 and 2 at 1 year (responders, <i>n</i> = 43) | 80.5 vs. 90.2 | 1.1 (1.0 to 1.3); 0.17 | 1.0 (0.9 to 1.2); 0.60 | 1.0 (0.9 to 1.2); 0.83 |
| Group 1 at 1 year (non-responders, <i>n</i> = 17) vs. group 1 at 1 year (responders, <i>n</i> = 23) | 80.8 vs. 88.4 | 1.1 (0.9 to 1.4); 0.43 | 1.0 (0.8 to 1.3); 0.79 | 1.0 (0.8 to 1.3); 0.98 |
| Group 1 at 1 year (responders, <i>n</i> = 23) vs. group 2a at 1 year (responders, <i>n</i> = 13) | 88.4 vs. 90.0 | 1.0 (0.8 to 1.3); 0.90 | 1.0 (0.8 to 1.3); 0.86 | 1.0 (0.8 to 1.4); 0.83 |

N/A, not applicable.

a Group 1: immediate ETN and MTX treatment; group 2: first-line MTX ± additional csDMARD therapy; group 2a: group 2 patients who continued csDMARD therapy and did not escalate to delayed ETN/MTX at week 24; non-responders: patients with a DAS28-ESR of ≥ 2.6 at 48 weeks; responders: patients with DAS28-ESR of < 2.6 at 48 weeks.

b Adjusted 1: adjusted for baseline LVM.

c Adjusted 2: adjusted for baseline AD, age, sex, systolic blood pressure and pack-years smoking (± baseline DAS28-ESR as applicable).

Response assumed for patients whose responder status at 48 weeks was unknown.

TABLE 18 Myocardial extracellular volume at 1 year: differences between groups

| Comparison ^a | MECV (%), geometric mean (unadjusted) (95% CI) | Ratio (95% CI); <i>p</i> -value | | |
|--|---|---------------------------------|---------------------------|---------------------------|
| | | Unadjusted | Adjusted 1 ^b | Adjusted 2 ^c |
| Combined groups 1 and 2 (<i>n</i> = 81): baseline, 1 year | 27.2 (26.4 to 28.1), 26.4 (25.6 to 27.1) | 1.0 (0.9 to 1.0); 0.06 | N/A | N/A |
| Group 1 at 1 year (all, <i>n</i> = 40) vs. group 2 at 1 year (all, <i>n</i> = 41) | 26.2 vs. 26.5 | 1.0 (1.0 to 1.1); 0.69 | 1.0 (1.0 to 1.1); 0.68 | 1.0 (0.9 to 1.1); 0.88 |
| Combined groups 1 and 2 at 1 year (non-responders, <i>n</i> = 38) vs. combined groups 1 and 2 at 1 year (responders, <i>n</i> = 43) | 26.4 vs. 26.3 | 1.0 (0.9 to 1.1); 0.90 | 1.0 (0.9 to 1.1); 0.81 | 1.0 (1.0 to 1.1); 0.72 |
| Group 1 at 1 year (non-responders, <i>n</i> = 17) vs. group 1 at 1 year (responders, <i>n</i> = 23) | 25.9 vs. 26.5 | 1.0 (0.9 to 1.1); 0.61 | 1.0 (0.9 to 1.1); 0.87 | 1.0 (0.9 to 1.1); 0.46 |
| Group 1 at 1 year (responders, <i>n</i> = 23) vs. group 2a at 1 year (responders, <i>n</i> = 13) | 26.5 vs. 26.6 | 1.0 (0.9 to 1.1); 0.91 | 1.0 (0.9 to 1.1); 0.56 | 1.0 (0.9 to 1.1); 0.68 |

N/A, not applicable.

a Group 1: immediate ETN and MTX treatment; group 2: first-line MTX ± additional csDMARD therapy; group 2a: group 2 patients who continued csDMARD therapy and did not escalate to delayed ETN/MTX at week 24; non-responders: patients with a DAS28-ESR of ≥ 2.6 at 48 weeks; responders: patients with DAS28-ESR of < 2.6 at 48 weeks.

b Adjusted 1: adjusted for baseline MECV.

c Adjusted 2: adjusted for baseline AD, age, sex, systolic blood pressure and pack-years smoking (± baseline DAS28-ESR as applicable).

Response assumed for patients whose responder status at 48 weeks was unknown.

TABLE 19 Myocardial extracellular volume at 2 years: differences between groups

| Comparison ^a | MECV (%), geometric mean (unadjusted) (95% CI) | Ratio (95% CI); <i>p</i> -value | | |
|--|---|---------------------------------|---------------------------|---------------------------|
| | | Unadjusted | Adjusted 1 ^b | Adjusted 2 ^c |
| Combined groups 1 and 2 (<i>n</i> = 81): baseline, 2 years | 27.2 (26.4 to 28.0), 27.0 (25.5 to 28.6) | 1.0 (0.9 to 1.1); 0.77 | N/A | N/A |
| Group 1 at 2 years (all, <i>n</i> = 40) vs. group 2 at 2 years (all, <i>n</i> = 41) | 26.6 vs. 27.3 | 1.0 (0.9 to 1.1); 0.60 | 1.0 (0.9 to 1.1); 0.60 | 1.0 (0.9 to 1.1); 0.67 |
| Combined groups 1 and 2 at 2 years (non-responders, <i>n</i> = 38) vs. combined groups 1 and 2 at 2 years (responders, <i>n</i> = 43) | 26.4 vs. 27.5 | 1.0 (1.0 to 1.1); 0.38 | 1.0 (1.0 to 1.1); 0.39 | 1.1 (1.0 to 1.2); 0.17 |
| Group 1 at 2 years (non-responders, <i>n</i> = 17) vs. group 1 at 2 years (responders, <i>n</i> = 23) | 25.9 vs. 27.2 | 1.1 (0.9 to 1.2); 0.43 | 1.0 (0.9 to 1.2); 0.55 | 1.1 (0.9 to 1.3); 0.29 |
| Group 1 at 2 years (responders, <i>n</i> = 23) vs. group 2a at 2 years (responders, <i>n</i> = 13) | 27.2 vs. 27.5 | 1.0 (0.9 to 1.2); 0.86 | 1.0 (0.9 to 1.2); 0.73 | 1.0 (0.8 to 1.2); 0.96 |

N/A, not applicable.

a Group 1: immediate ETN and MTX treatment; group 2: first-line MTX ± additional csDMARD therapy; group 2a: group 2 patients who continued csDMARD therapy and did not escalate to delayed ETN/MTX at week 24; non-responders: patients with a DAS28-ESR of ≥ 2.6 at 48 weeks; responders: patients with DAS28-ESR of < 2.6 at 48 weeks.

b Adjusted 1: adjusted for baseline MECV.

c Adjusted 2: adjusted for baseline AD, age, sex, systolic blood pressure and pack-years smoking (± baseline DAS28-ESR as applicable).

Response assumed for patients whose responder status at 48 weeks was unknown.

TABLE 20 Key demographics split by responders and non-responders for patients in groups 1, 2 and 2a^a

| Demographic variable | Group 1 responders, <i>n</i> (%) or <i>n</i> (median, interquartile range) | Group 1 non-responders, <i>n</i> (%) or <i>n</i> (median, interquartile range) | Group 2 responders, <i>n</i> (%) or <i>n</i> (median, interquartile range) | Group 2 non-responders, <i>n</i> (%) or <i>n</i> (median, interquartile range) | Group 2a responders, <i>n</i> (%) or <i>n</i> (median, interquartile range) | Group 2a non-responders, <i>n</i> (%) or <i>n</i> (median, interquartile range) |
|--------------------------------|--|--|--|--|---|---|
| Age (years) | 23 (45, 15.5) | 17 (49, 12) | 20 (51, 23.5) | 21 (54, 19) | 13 (59, 19) | 6 (46, 26.5) |
| Sex | Male 9 (41), female 13 (59) | Male 6 (35), female 11 (65) | Male 7 (35), female 13 (65) | Male 3 (14), female 18 (86) | Male 5 (38), female 8 (62) | Male 0 (0), female 6, (100) |
| Systolic blood pressure (mmHg) | 23 (121, 27.5) | 17 (124, 22) | 20 (118, 18.7) | 21 (121, 24) | 13 (122, 16) | 6 (125.5, 11) |
| Pack-years smoking | 23 (0, 4.8) | 17 (0, 6) | 20 (0, 20) | 21 (5 14.3) | 13 (0, 24) | 6 (2.6, 6.2) |

a Group 1: immediate ETN and MTX treatment; group 2: first-line MTX ± additional csDMARD therapy; group 2a: group 2 patients who continued csDMARD therapy and did not escalate to delayed ETN/MTX at week 24; non-responders: patients with a DAS28-ESR of ≥ 2.6 at 48 weeks; responders: patients with DAS28-ESR of < 2.6 at 48 weeks.

Response assumed for patients whose responder status at 48 weeks was unknown

Appendix 4 Protocol amendments July 2018

For analysis of primary, secondary and exploratory outcomes in CADERA patients at 1-year and 2-year follow-up, an ANCOVA method has been adopted. The outcome at follow-up is linearly regressed on a grouping variable (defined below) as dependent variable, first as an unadjusted analysis (exploring differences by group in the outcome at 1 year or 2 years), second additionally adjusted for baseline outcome (an ANCOVA approach to analysis of change, replacing the differences to baseline method originally proposed) and, third, additionally adjusted for baseline outcome, age, sex, systolic blood pressure and, where appropriate (see below), baseline DAS28-ESR (again, an ANCOVA approach to analysis of change, replacing the differences from baseline method originally proposed). The change of approach from differences to baseline to ANCOVA was undertaken for consistency with the preliminary analysis presented to the Efficacy and Mechanism Evaluation programme in 2017 and to enhance power given the additional grouped analyses to be undertaken (see below). Outcomes are naturally log transformed to achieve normality assumptions. Back-transformation is performed when presenting results, thus estimates are geometric means or ratios across groups.

Groups were defined as follows where group 1 are patients on first-line ETN/MTX and group 2 are patients on first-line ETN/MTX with possible escalation at week 24.

Group 1 (all patients) versus group 2 (all patients).

Combined group 1 and group 2 (responders) versus combined group 1 and group 2 (non-responders) adjusting for baseline DAS28-ESR.

Group 1 (responders) and group 1 (non-responders) adjusting for baseline DAS28-ESR

Group 1 (responders) and group 2a (responders) adjusting for baseline DAS28-ESR.

Patients with a DAS28-ESR of ≥ 2.6 at 48 weeks considered non-responders. Patients with missing DAS28-ESR at week 48 for reasons other than withdrawal for lack of efficacy were assumed to be responders in the initial analysis. The data were then reanalysed assuming they were non-responders.

For an intention-to-treat analysis, multiple imputation by chained equations was used to create 50 complete data sets per outcome analysed. The results from which were combined according to Rubin's rules. The imputation model included the following variables at weeks 0, 12, 24, 36 and 48: SJC44, RAI, CRP, ESR, physician VAS, patient general health VAS, patient pain VAS, patient disease activity VAS and early morning stiffness. Outcome values at 1 or 2 years were included (dependent on outcome analysed) in addition to baseline values. The model also included age, sex, systolic blood pressure, symptom duration, treatment and an indicator for whether or not the patient was a responder (as defined above). Multiple imputation chain mixing and distribution diagnostics were checked for plausibility of imputations.

For the primary outcome (AD) at 1 year only, an analysis adjusted for AUC disease activity is reported. A trapezoid rule is used based on DAS28-ESR at weeks 0, 12, 24, 36 and 48 to calculate AUC. The imputation model for this analysis excluded the indicator variable for whether or not a patient was a responder.

Amendments to analysis plan following reviewer comments.

The first 30 CADERA patients (cases) were approximately matched by age and sex to volunteers (control subjects) who were invited for a cardiac scan and matched pairs analysis conducted on the primary outcome (AD), secondary outcomes (LVEF, LVLS, PLVTw and left ventricular mass) and the exploratory outcome (MECV) at baseline. Three patients from these 30 were excluded due to screen failure for the VADERA study, thus a maximum of 27 matched pairs were available for analysis. To reflect the approximate matching, additional

linear regression analyses are presented for each of the primary, secondary and exploratory outcomes at baseline including the 30 control subjects and all cases where data are available. Each analysis is presented unadjusted (with a single independent variable case/control) and adjusted (with dependent variables case/control, age, sex, systolic blood pressure and pack-years smoked). Outcomes are natural log transformed to achieve normality assumptions (an approach favoured over non-parametric analysis to allow straightforward adjustment in the additional regression analyses and consistency with the analyses at 1-year and 2-year follow-up as described under point 2 below). Back transformation is performed when presenting results (thus, geometric mean ratios and associated 95% CIs are reported). To assess balance of demographic characteristics across all cases and the 30 control subjects, summary statistics are presented including for key demographics of age, sex, systolic blood pressure and pack-years smoked.

For comparison, key demographics are presented for those CADERA patients who have at least one primary, secondary or exploratory outcome missing at 1-year and 2-year follow-up, versus CADERA patients who have complete data for all outcomes at 1 year and 2 years.

For further comparison key demographics are presented for CADERA patients split by group 1, group 2, group 2a responders and non-responders.

Pack-years smoked was added as a variable to the analysis of primary, secondary and exploratory outcomes (as described in the protocol amendment 1 of July 2018).

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*This report presents independent research funded by the National Institute for Health Research (NIHR).
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