Baseline characteristics of the study population.	csDMARDs (n=43)	TNFi (n=64)	P value
Age, median years (IQR)	58.6 (53.0, 66.0)	58.1 (49.3, 67.0)	0.839
Female sex	33 (76.7)	54 (84.4)	0.321
Obesity	5 (11.6)	7 (10.9)	0.999
Hypertension	19 (44.2)	30 (46.9)	0.784
Anti-hypertensive drug	17 (39.5)	28 (43.8)	0.784
Smoking status, ever	18 (42.9)	30 (46.9)	0.684
Dyslipidemia	30 (40.2)	34 (59.8)	0.085
Current statin use	13 (34.2)	10 (15.9)	0.033
Diabetes mellitus	3 (7.0)	3 (4.7)	0.676
Anti-diabetic medication	1 (2.3)	1 (1.5)	0.999
CVD risk factors, median (IQR)	2 (1, 3)	2 (1, 3)	0.199
RF and/or ACPA positive	28 (65.1)	33 (51.6)	0.165
Disease duration, median years (IQR)	14.1 (11.5)	15.4 (10.5)	0.538
Methotrexate	38 (88.4)	52 (81.3)	0.192
Leflunomide	5 (17.9)	12 (19.0)	0.999
Hydroxychloroquine	9 (31.0)	5 (7.8)	0.009
Prednisone > 5 mg daily	7 (7.7)	5 (5.5)	0.823
NSAIDs	6 (20.7)	22 (34.4)	0.227

ACPA, anti-citrullinated peptides antibodies; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; RF, rheumatoid factor; TNFi, tumor necrosis factor inhibitors. All data reported as absolute numbers (percentage) otherwise specified. P-value refers to Chi-squared or Fisher test for categorical variables or ANOVA for continuous variables.

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EFFECT OF LOW-DOSE METHOTREXATE ON ESTIMATED GLOMERULAR FILTRATION RATE AND KIDNEY ADVERSE EVENTS IN THE CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

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Background: Low-dose methotrexate (LD-MTX) is a common first-line treatment for systemic rheumatic diseases, and its use is contraindicated in advanced chronic kidney disease (CKD) because it is primarily excreted by the kidneys. Among patients with preserved kidney function, the safety of LD-MTX on estimated glomerular filtration rate (eGFR) and kidney adverse events (AEs) has not been established.

Objectives: To investigate the effect of LD-MTX on eGFR and kidney AEs using data from a randomized clinical trial.

Methods: We performed a secondary analysis for eGFR and kidney AEs using the randomized double-blind, placebo-controlled Cardiovascular Inflammation Reduction Trial. Adults with known cardiovascular disease and diabetes and/or metabolic syndrome were randomly allocated to oral LD-MTX (target dose 15-20 mg/week) or placebo. All participants took folic acid 1 mg six days/week. Exclusion criteria included systemic inflammatory disease and creatinine clearance <40 mL/min (by Cockcroft-Gault). eGFR was calculated using the CKD-EPI formula. Clinical kidney AEs were blindly adjudicated. The least-squares mean change of eGFR from baseline was calculated at each study visit; the difference in eGFR slopes between LD-MTX and placebo was compared using a modified intention-to-treat approach. We also compared rates of kidney AEs for LD-MTX versus placebo using Cox proportional hazards models.

Results: A total of 2,391 subjects were randomized to LD-MTX and 2,395 to placebo. At baseline, mean age was 66 years, 19% were female, mean eGFR was 80.0 mL/min/1.73 m², and 18% had stage 3 CKD or worse. Median follow-up duration was 23 months, and median LD-MTX dose was 16 mg/week. Those randomized to LD-MTX had less decline in eGFR over the entire follow-up compared to placebo (slope difference 1.12, 95%CI 0.59-1.65, $p < 0.001$, Figure 1). Those with CKD stage 3 or worse on LD-MTX saw less eGFR decline than those with CKD stage 2 or better (slope difference among CKD stage 3 or worse: 2.46, 95%CI 1.10-3.82, $p < 0.001$; p for interaction 0.02). The LD-MTX group had higher eGFR than placebo over the first 24 months of study follow-up ($p < 0.05$ at each visit). On safety laboratory monitoring, there were 159 acute kidney injury AEs in the LD-MTX group and 187 in the placebo group (HR 0.83, 95%CI 0.67-1.02, Table 1). There were 37 clinical kidney AEs in the LD-MTX group and 42 in the placebo group (0.87, 95%CI 0.56-1.36). One subject began dialysis in the LD-MTX group compared to 3 in the placebo group.

Conclusion: These results demonstrate the kidney safety of LD-MTX among patients without advanced CKD at baseline. We observed a possible beneficial effect of LD-MTX on preserving kidney function, suggesting that inflammation may be involved in the pathogenesis of CKD in this population.

Figure. Least-squares mean change of estimated glomerular filtration rate (eGFR) from baseline to each follow-up visit according to random assignment of low-dose methotrexate (LD-MTX) or placebo in the Cardiovascular Inflammation Reduction Trial (n=4,786). eGFR was calculated using the CKD-EPI equation. A slope difference significantly above 0 denotes less decline in eGFR for the LD-MTX group.