Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ridker PM, Everett BM, Pradhan A, et al. Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med 2019;380:752-62. DOI: 10.1056/NEJMoa1809798

SUPPLEMENTARY APPENDIX

Low-Dose Methotrexate for the Prevention of Atherosclerotic Events

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Data from September 19, 2018 Closure

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Section B. Trial Inclusion and Exclusion Criteria

Inclusion Criteria	• Age ≥ 18 years • Myocardial infarction in the past *and/or* multivessel coronary artery disease by angiography • Type 2 diabetes *and/or* metabolic syndrome • Completed all planned revascularization procedures • Medically stable for 60 days from index MI, surgical procedure or other significant illness (including newly diagnosed diabetes)
Exclusion Criteria	• Chronic liver disease • Chronic inflammatory condition such as lupus or rheumatoid arthritis, ulcerative colitis or Crohn's disease • Chronic infectious disease • Interstitial lung disease or pulmonary fibrosis • Myeloproliferative disease in past 5 years • HIV positive • Requirement for, or intolerance to, methotrexate or folate • History of non-basal cell malignancy or treatment for lymphoproliferative disease in past 5 years • Requirement for use of drugs that alter folate metabolism • History of alcohol abuse or unwillingness to limit consumption to < 4 drinks per week • Women of childbearing potential (even if using oral contraceptive agents) or intention to breastfeed • Men who plan to father children during the study period or are unwilling to use contraception • Life expectancy < 3 years or unlikely to comply in judgment of investigator • Chronic use of oral or IV steroid therapy or other immunosuppressive or biologic response modifiers (see drug list in Manual of Operations) • History of hepatitis B or C • Chronic pericardial effusion, pleural effusion or ascites • New York Heart Association Class IV heart failure

Additional criteria used to exclude patients from continuing in the trial after the active treatment run-in phase:	• Willingness to continue with trial
	• Patient was not deemed appropriate for randomization in the opinion of the investigator
	• New symptoms indicting low-dose methotrexate intolerance and/or laboratory assay changes indicating intolerance to low-dose methotrexate
	  ○ WBC <3.5 x 10^3/uL
	  ○ Hematocrit < 32 percent
	  ○ AST/ALT >1.5 upper limit of normal
	  ○ Platelet<75 x 10^3/uL
	  ○ Albumin < lower limit of normal
	  ○ Creatinine <40ml/min (as estimated with the Cockcroft-Gault equation)

Section C. Randomization Scheme

Randomized treatment assignment was done by the Electronic Data Capture (EDC) system at the time of qualification and neither the sequence nor the allocation could be obtained in advance. Dynamic allocation was used to assign participants across the strata maintaining the minimum imbalance. At each dispensing visit by a participant, the EDC directed the site regarding the blinded drug pack to allocate. All participants, sites, investigators, staff, and endpoint adjudicators, except for the Data Coordinating Center staff preparing the unblinded DCC reports, were blinded to individual treatment assignment until the end of study visit occurred. This was accomplished through use of the placebo medication, the concealment of treatment assignment in the EDC system, and the potential for sham dose adjustments.

Section D. Study-Drug Dose Adjustment

A computerized algorithm based upon blinded levels of centrally measured laboratory parameters and reported symptoms assessed every 2 months was used to adjust the dose of methotrexate or placebo in a standardized manner at all sites. For example, the algorithm could reduce study drug by 5-mg increments (or hold dosing altogether) in response to a decline in the white blood cell or platelet count, an increase in liver function tests, or following the development of an intercurrent illness such as infection or hospitalization for non-trial clinical events. Board certified rheumatologists served as medical monitors for the trial, sending email notices to all sites when a change in medication was required, when a potentially unsafe laboratory value became apparent, or when temporary or permanent discontinuation of study drug was required. Sites were blind to all routine laboratory evaluations except in circumstances where an extreme abnormality was observed requiring clinical intervention. The medical monitors also reminded sites by email to re-start study drug when transient risks had subsided, when laboratory abnormalities had normalized, or reported symptoms resolved.

Section E. Good Clinical Practice Violations

During the conduct of the trial, it was discovered through careful record review by staff at the Clinical Coordinating Center that a small cluster of clinical sites in Miami, Florida appeared to be randomizing the same patient into the trial on multiple occasions, such that an individual patient might represent two, three or four separate randomizations. Once this violation of Good Clinical Practice was identified, the trial leadership brought concerns regarding patient safety and data quality from these sites to the relevant Institutional Review Boards, the Data and Safety Monitoring Board, the National Heart Lung and Blood Institute, the Office for Human Research Protections at Health and Human Services, and the US Food and Drug Administration. After extensive consultation with all regulatory parties involved, a decision was unanimously made to protect the integrity of trial data and patient safety; as such, participant data (representing 174 randomizations) in the greater Miami area were excluded from data analysis and 17 sites where concern had been raised were terminated from further participation. This decision was further reviewed by the trial Data and Safety Monitoring Board and approved by the NHLBI. All of the above events occurred prior to trial unblinding.

Figure S1. Trial Diagrammatic Overview

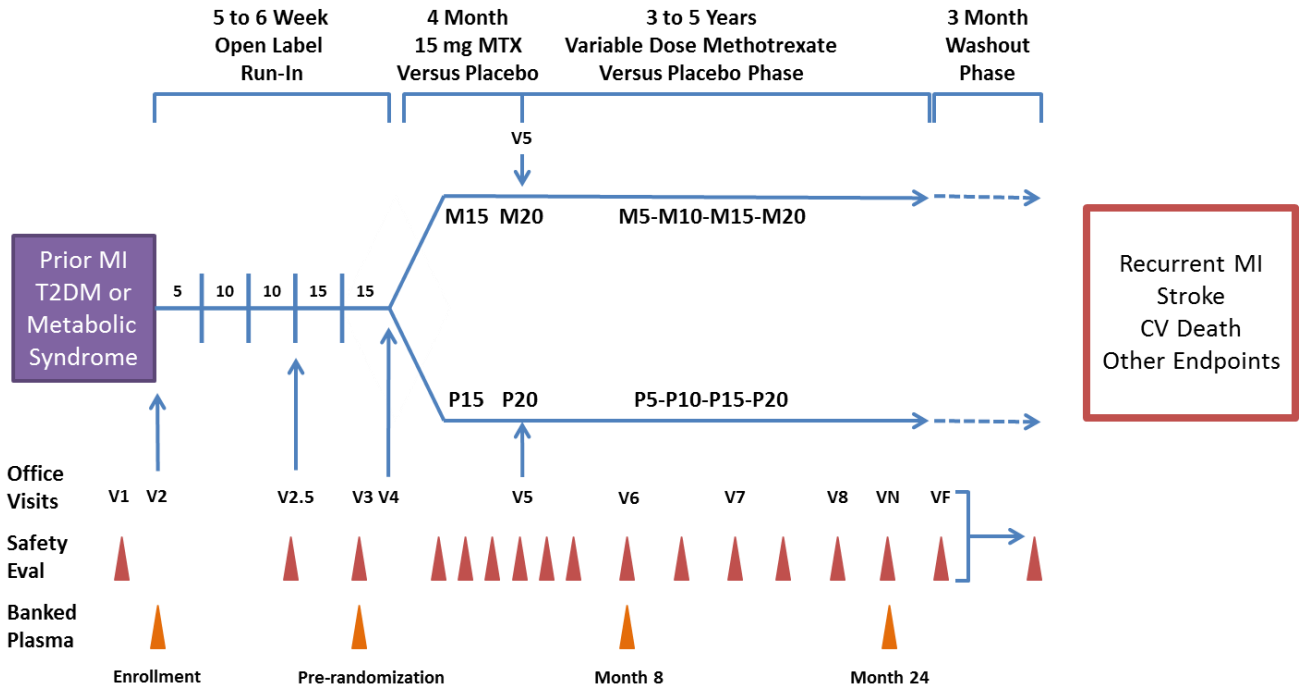


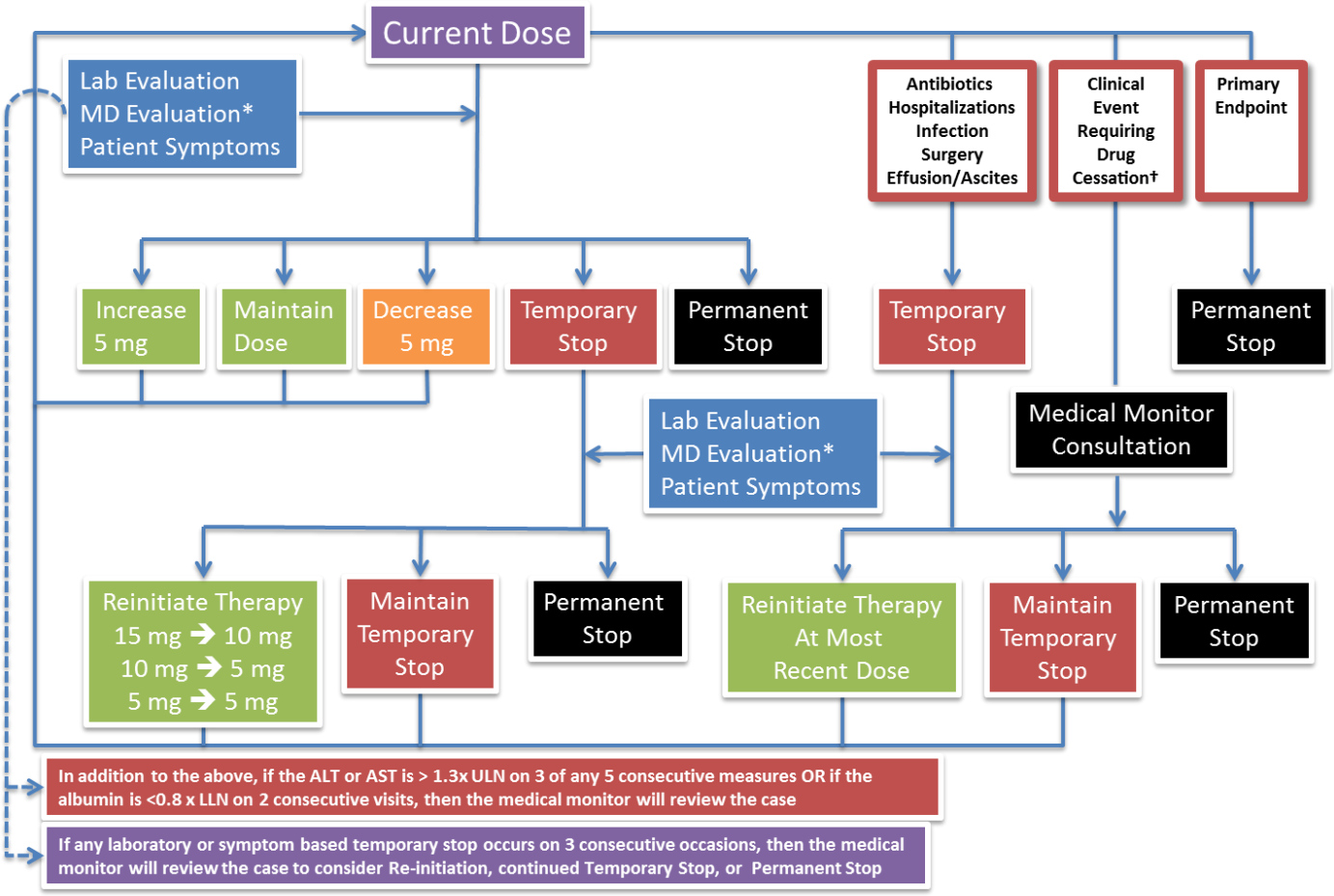
Figure S2. Algorithm for low-dose methotrexate management (Part 1)

Lab	Value	5mg	10mg	15mg	20 mg
WBC (n/uL)	≥ 3,500	↑ to 10mg if all conditions met	↑ to 15 mg if all conditions met	↑ to 20 mg if all conditions met	Maintain if all conditions met
	≥ 3,000 to <3,500	Do not increase	Do not increase	↓ to 10 mg	↓ to 15 mg
	< 3,000	Temporary stop	Temporary stop	Temporary stop	Temporary stop
Platelets (n/uL)	≥75,000	↑ to 10mg if all conditions met	↑ to 15 mg if all conditions met	↑ to 20 mg if all conditions met	Maintain if all conditions met
	50,000 to <75,000	Do not increase	Do not increase	Do not increase	↓ to 15 mg
	<50,000	Temporary stop	Temporary stop	Temporary stop	Temporary stop
Creatinine Clearance (mL/min)	≥40	↑ to 10mg if all conditions met	↑ to 15 mg if all conditions met	↑ to 20 mg if all conditions met	Maintain if all conditions met
	≥30 to <40	Do not increase	Do not increase	Do not increase	↓ to 15 mg
	<30	Temporary stop	Temporary stop	Temporary stop	Temporary stop
AST, ALT	≤1.5x ULN	↑ to 10mg if all conditions met	↑ to 15 mg if all conditions met	↑ to 20 mg if all conditions met	Maintain if all conditions met
	1.5 to ≤2.0x ULN	Do not increase	↓ to 5 mg	↓ to 10 mg	↓ to 15 mg
	>2.0x ULN	Temporary stop	Temporary stop	Temporary stop	Temporary stop
Hematocrit	≥27%	↑ to 10mg if all conditions met	↑ to 15 mg if all conditions met	↑ to 20 mg if all conditions met	Maintain if all conditions met
	<27%	Temporary stop	Temporary stop	Temporary stop	Temporary stop
Clinically important symptoms*	No	↑ to 10mg if all conditions met	↑ to 15 mg if all conditions met	↑ to 20 mg if all conditions met	Maintain if all conditions met
	Yes	Temporary stop	Temporary stop	Temporary stop	Temporary stop

*New and persistent stomatitis, vomiting, diarrhea, unexplained cough with fever or shortness of breath

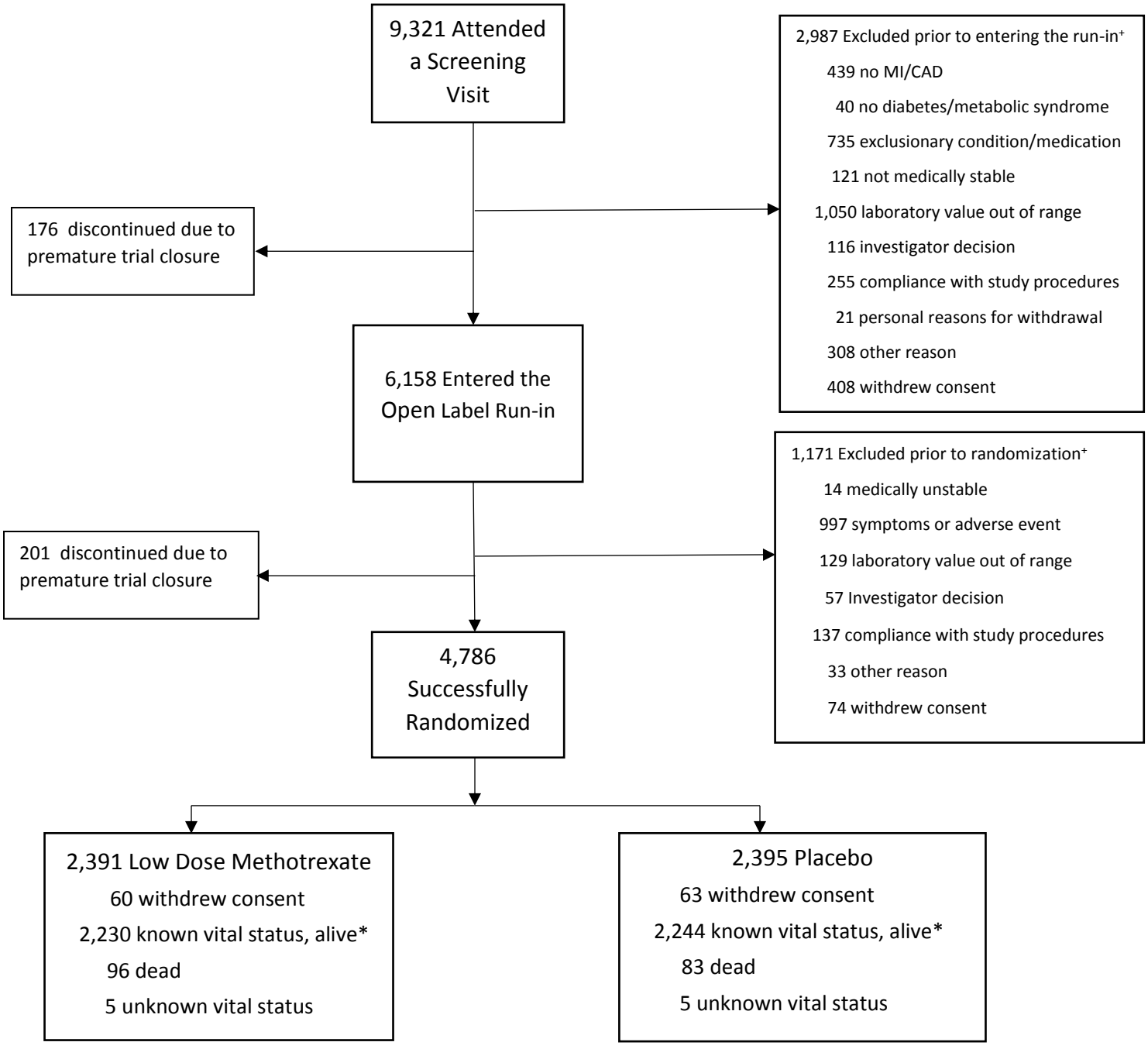
In addition to the above, if the ALT or AST is > 1.3x ULN on 3 of any 5 consecutive measures OR if the albumin is <0.8 x LLN on 2 consecutive visits, then the medical monitor will review the case
Further, if any laboratory or symptom based temporary stop occurs on 3 consecutive measures then the medical monitor will review the case to consider Re-Initiation, a continued Temporary Stop, or a Permanent Stop

Figure S3. Algorithm for low-dose methotrexate management (Part 2)



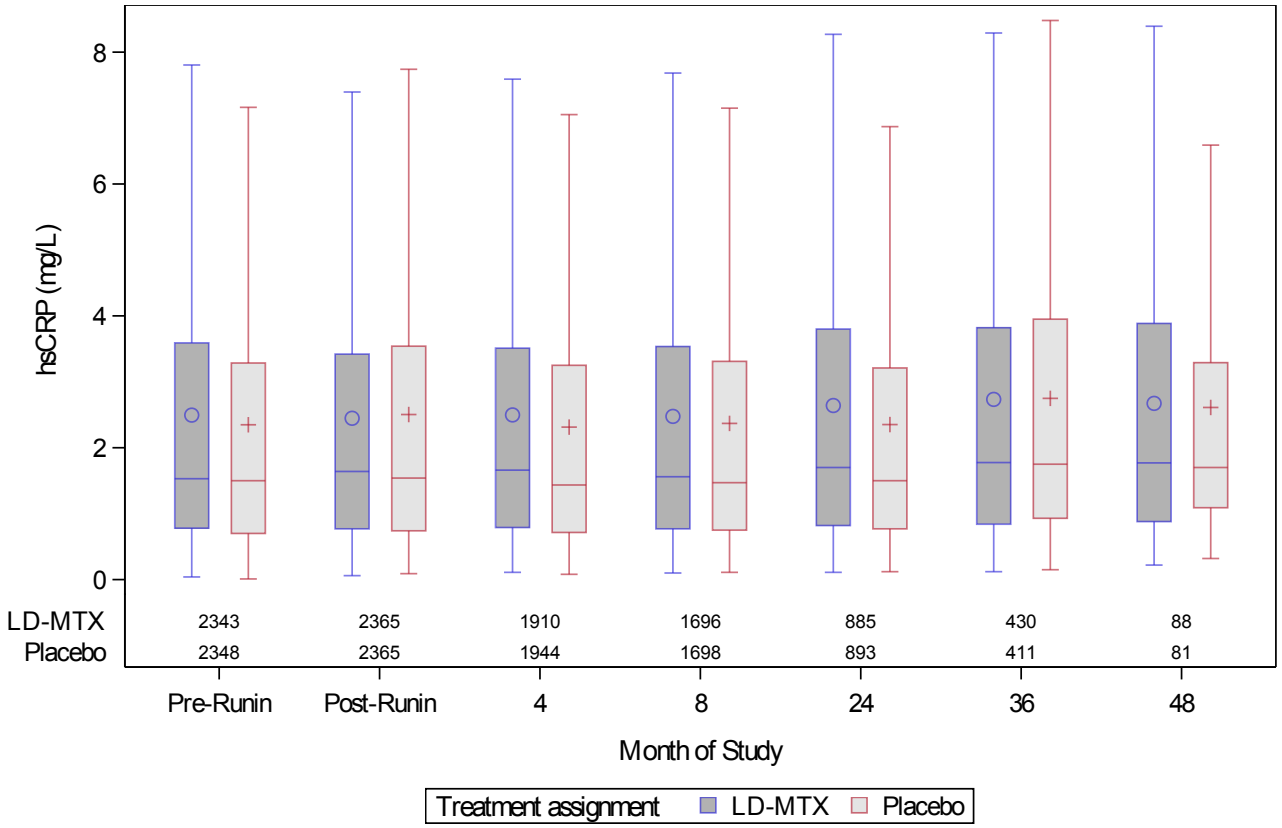
†Cancer (except non-melanoma skin cancer), chronic infection (e.g. HIV, hepatitis B or C, tuberculosis), cirrhosis, chronic need for exclusionary medication, life threatening fungal infection

Figure S4. Participant flow in CIRT



* Within 3 months of trial end. +Participants may have multiple reasons for exclusion.

Figure S5. hsCRP over time by treatment assignment



Data are presented as the median(line), mean(circle) and interquartile range; whiskers extend to the extremes of the data or to one and a half times the interquartile range, whichever was closer

Table S1. Effects of LD-MTX on biochemical measures during open label run-in among randomized participants. All data reported as median (Interquartile Range).

Biochemical Measure				
	Enrollment	Post Run-in	Change	P-value for change*
ALT (IU/L)	21.0(16.0,28.0)	24.0(18.0,31.0)	2.0(-1.0,7.0)	<0.0001
AST (IU/L)	20.0(17.0,24.0)	22.0(18.0,26.0)	1.0(-2.0,4.0)	<0.0001
Mean Corpuscular Hemoglobin (pg)	30.0(28.8,31.1)	30.3(29.0,31.4)	0.2(-0.1,0.7)	<0.0001
Mean Corpuscular Volume (fl)	90.0(87.0,93.0)	91.0(88.0,94.0)	1.0(0.0,2.0)	<0.0001
WBC (x10E3/uL)	7.0(6.0,8.3)	6.7(5.6,7.9)	-0.4(-1.1,0.4)	<0.0001
Hematocrit (%)	42.3(39.6,44.9)	41.8(39.0,44.3)	-0.7(-2.0,0.9)	<0.0001
Hemoglobin (g/dL)	14.1(13.0,15.0)	13.9(12.8,14.8)	-0.2(-0.7,0.2)	<0.0001
hsCRP (mg/L)	1.51(0.74,3.44)	1.60(0.76,3.50)	0.04(-0.50,0.61)	0.0003
LDL-C (mg/dL)	68.0(54.0,87.0)	67.0(52.0,86.0)	-1.9(-10.8,7.0)	<0.0001
HDL-C (mg/dL)	41.0(35.0,48.0)	41.0(34.7,48.0)	0.0(-3.0,3.0)	0.025
Triglycerides (mg/dL)	135.4(98.0,191.2)	135.0(97.0,187.0)	-1.0(-28.0,24.0)	0.0064

* Wilcoxon signed-rank test. Data are from randomized subjects with enrollment and post run-in measures.

Table S2. Effects of LD-MTX on biochemical measures (change from enrollment to 8 months post randomization). All data are reported as median (Interquartile Range).

Biochemical Measure	LD-MTX			Placebo			
	Enrollment	8-Months	Change	Enrollment	8-Months	Change	P-value for change*
ALT (IU/L)	22.0(16.0,28.0)	25.0(18.0,34.0)	3.0(-2.0,9.0)	21.0(16.0,28.0)	21.0(16.0,27.0)	0.0(-4.0,4.0)	<0.0001
AST (IU/L)	20.0(17.0,25.0)	22.0(18.0,28.0)	2.0(-2.0,6.0)	21.0(17.0,25.0)	20.0(17.0,25.0)	0.0(-3.0,3.0)	<0.0001
Corpuscular Hemoglobin	30.0(28.9,31.0)	31.0(29.9,32.1)	1.0(0.4,1.7)	30.0(28.8,31.2)	30.0(29.0,31.2)	0.0(-0.6,0.6)	<0.0001
Corpuscular Volume (fl)	90.0(87.0,93.0)	94.0(90.0,97.0)	3.0(1.0,5.0)	90.0(87.0,93.0)	91.0(87.0,94.0)	0.0(-1.0,2.0)	<0.0001
WBC (x10E3/uL)	7.0(5.9,8.4)	6.7(5.5,7.9)	-0.4(-1.3,0.4)	7.0(5.9,8.3)	6.8(5.6,8.0)	-0.2(-1.0,0.6)	<0.0001
Hematocrit (%)	42.5(39.7,45.0)	41.8(38.5,44.1)	-1.0(-2.6,0.8)	42.2(39.7,44.8)	42.3(39.8,44.9)	0.0(-1.7,1.5)	<0.0001
Hemoglobin (g/dL)	14.1(13.1,15.0)	13.8(12.7,14.8)	-0.3(-0.9,0.2)	14.0(13.1,15.0)	14.1(13.0,15.0)	0.0(-0.6,0.5)	<0.0001
Interleukin-1β (pg/mL)	1.51(0.40,3.16)	1.00(0.21,2.49)	-0.24(-1.74,0.69)	1.39(0.47,3.06)	0.80(0.16,2.09)	-0.31(-1.79,0.58)	0.62
Interleukin-6 (pg/mL)	2.24(1.48,3.55)	2.68(1.78,4.12)	0.30(-0.32,1.22)	2.18(1.51,3.35)	2.29(1.53,3.75)	0.04(-0.56,0.80)	0.001
hsCRP (mg/L)	1.45(0.73,3.40)	1.56(0.77,3.53)	0.09(-0.54,0.71)	1.43(0.67,3.07)	1.47(0.75,3.31)	0.05(-0.54,0.71)	0.83
LDL-C (mg/dL)	69.0(54.8,87.0)	67.0(51.7,85.0)	-2.0(-13.0,9.0)	68.0(54.0,86.0)	69.0(53.7,86.0)	0.4(-9.0,11.0)	<0.0001
HDL-C (mg/dL)	41.0(35.0,48.6)	40.0(34.0,48.0)	0.0(-4.0,3.0)	41.0(35.0,48.0)	41.0(35.0,48.3)	0.0(-3.5,4.0)	0.0028
Triglycerides (mg/dL)	135.0(97.0,187.0)	132.4(94.0,182.	-2.0(-31.9,27.0)	135.0(99.0,190.0)	139.0(98.0,193.0)	2.0(-27.0,32.0)	0.0051

* Wilcoxon ranked sum test comparing the LD-MTX change with the Placebo change. Data are from subjects with 8 Month assessments.