CIRT | Cardiovascular Inflammation Reduction Trial

NIH National Heart, Lung, and Blood Institute

A Randomized, Double-Blind, Placebo-Controlled Trial of Low-Dose Methotrexate for the Prevention of Atherosclerotic Events

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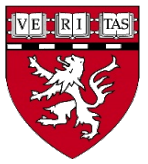
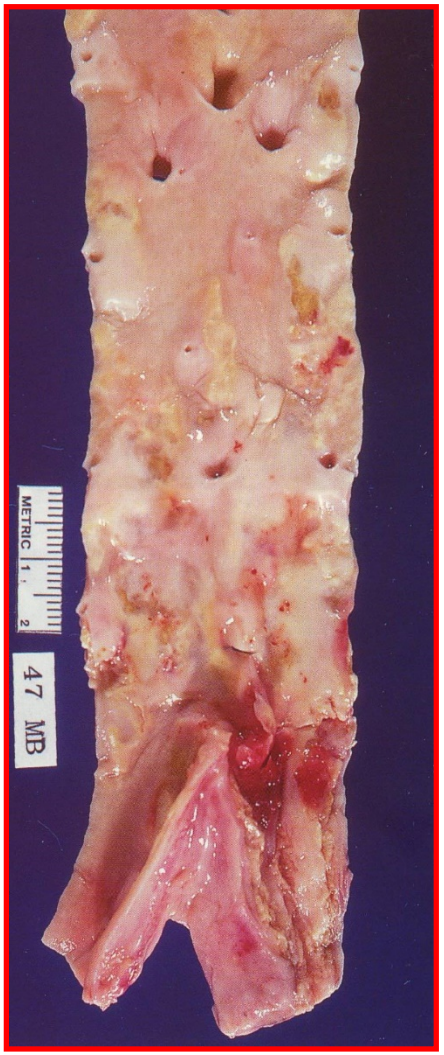
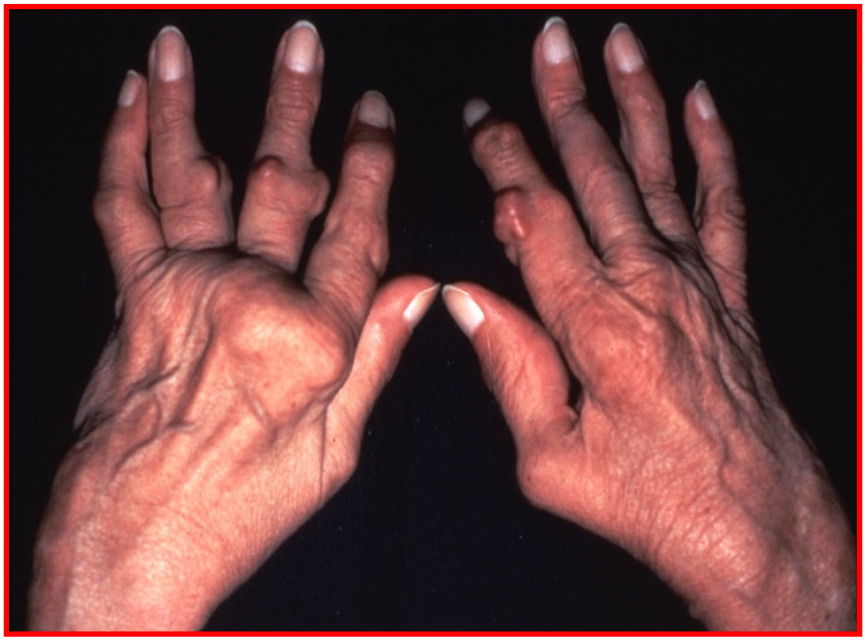
*these authors contributed equally to this project



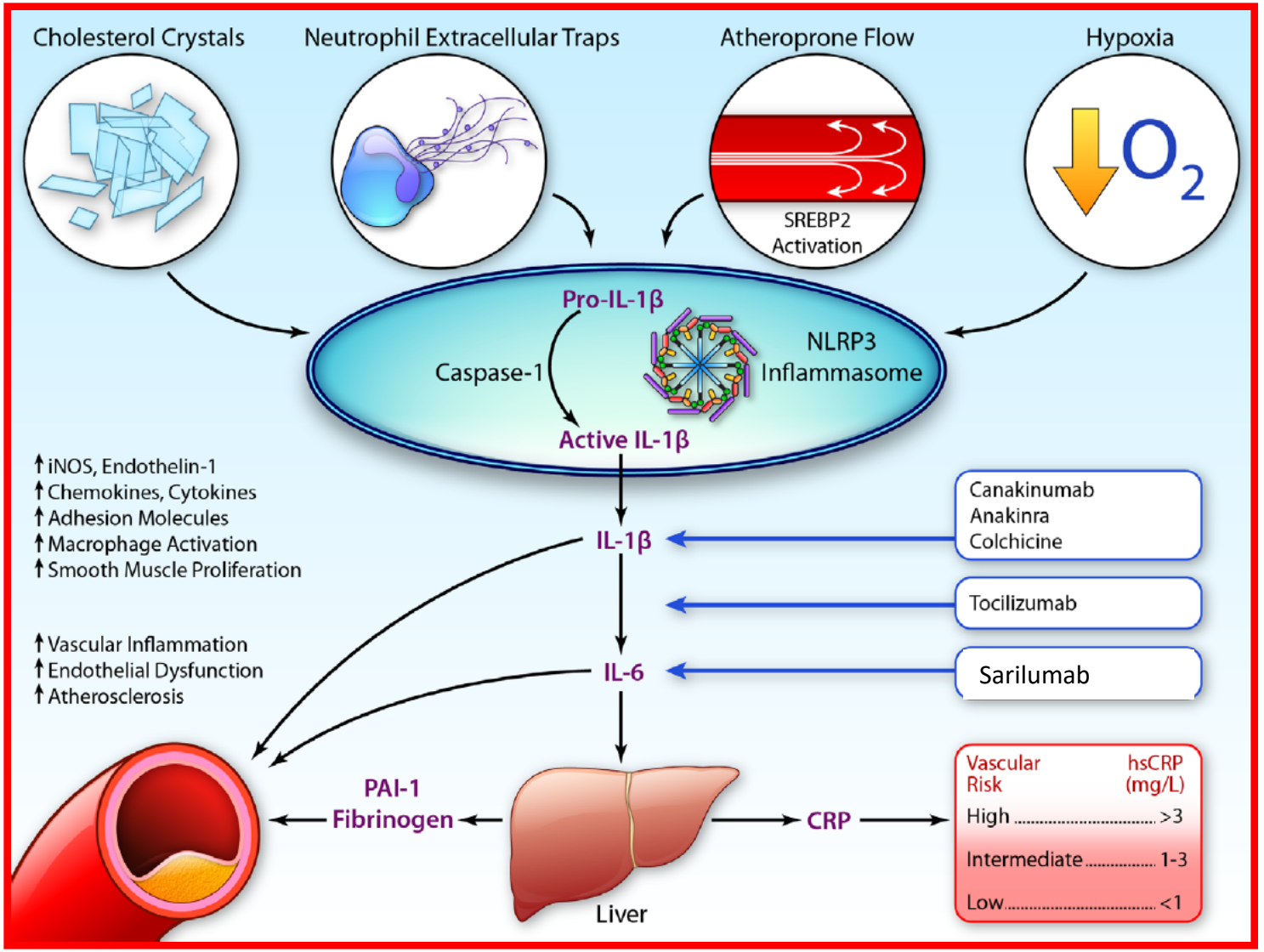
Can Inflammation Reduction, in the Absence of Lipid Lowering, Reduce Cardiovascular Event Rates?





Courtesy of Ed Yeh, MD

Critical Role of the IL-1β to IL-6 to CRP Pathway in Atherothrombosis



Ridker PM. Circ Res 2016;118:145-156.

CANTOS

Canakinumab Anti-inflammatory Thrombosis Outcomes Study

2011 - 2017

Interleukin-1β Inhibition

- ↓ IL-1β
- ↓ IL-6
- ↓ hsCRP
- ↔ LDL, BP, coagulation
- ↓ 15-17% reduction in MACE and MACE+

CIRT | CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

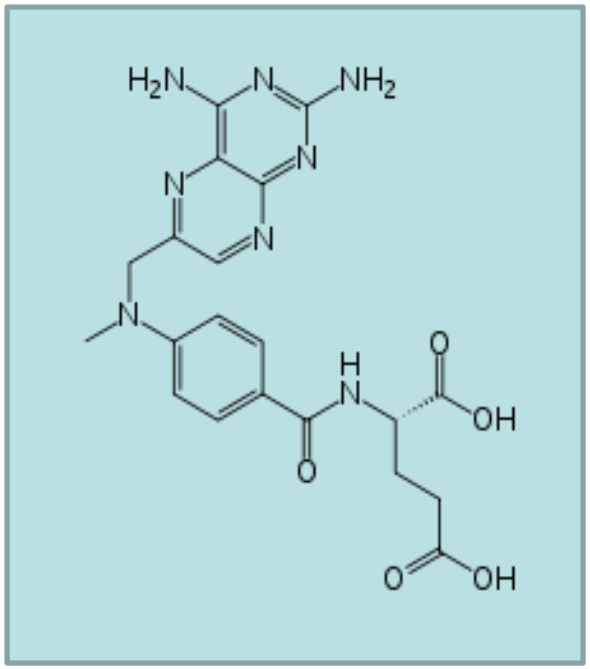
2013 - 2018

Low-Dose Methotrexate

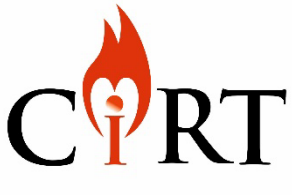
- ? IL-1β
- ? IL-6
- ? hsCRP
- ? reduction in MACE and MACE+

Cardiovascular Inflammation Reduction Trial (CIRT)

Low-Dose Methotrexate: 15 to 20 mg po weekly + folic acid



- **Used weekly as first line therapy for rheumatoid arthritis and psoriatic arthritis.**
- **Enviable safety record with over 40 years of use among older individuals with similar co-morbidities as those who have suffered a prior heart attack.**
- **Inexpensive and widely used, unlikely to have any unknown off-target effects.**
- **Guidelines for safe use already exist from the American College of Rheumatology.**
- **Mechanism of anti-inflammatory effect uncertain, likely due to adenosine mediated effects.**

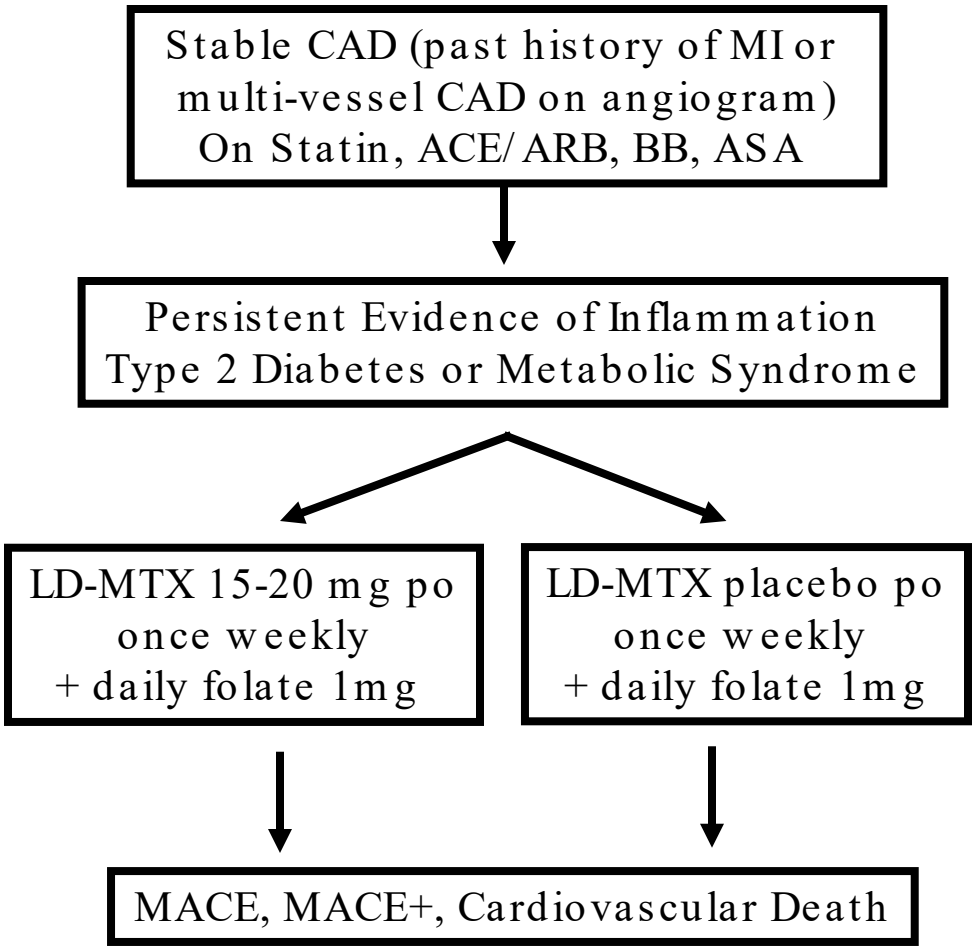


Cardiovascular Inflammation Reduction Trial (CIRT)

Observational non-randomized evidence suggests a reduction in vascular events among patients with RA and Psoriasis treated with low-dose methotrexate

Cohort	Group	HR* (95 % CI)	Endpoint	Exposure
Wichita	RA	0.4 (0.2 - 0.8)	Total Mortality	LD-MTX
Choi 2002		0.3 (0.2 - 0.7)	CV Mortality	LD-MTX
		0.4 (0.3 – 0.8)	CV Mortality	LD-MTX < 15 mg/wk
Netherlands	RA	0.3 (0.1 – 0.7)	CVD	LD-MTX only
van Helm 2006		0.2 (0.1 – 0.5)	CVD	LD-MTX + SSZ
		0.2 (0.1 – 1.2)	CVD	LD-MTX + HCQ
		0.2 (0.1 – 0.5)	CVD	LD-MTX + SSZ + HCQ
Miami VA	PsA	0.7 (0.6 – 0.9)	CVD	LD-MTX
Pradanovich 2005		0.5 (0.3 – 0.8)	CVD	LD-MTX < 15 mg/wk
	RA	0.8 (0.7 – 1.0)	CVD	LD-MTX
		0.6 (0.5 – 0.8)	CVD	LD-MTX < 15 mg/wk
CORRONARA	0.6 (0.3 – 1.2)	CVD	LD-MTX	
Solomon 2008		0.4 (0.2 – 0.8)	CVD	TNF-inhibitor
QUEST-RA	RA	0.85 (0.8 – 0.9)	CVD	LD-MTX
Narango 2008		0.82 (0.7 – 0.9)	MI	LD-MTX
		0.89 (0.8 - 1.0)	Stroke	LD-MTX
UK Norfolk	RA, PsA	0.6 (0.4 – 1.0)	Total Mortality	LD-MTX
2008		0.5 (0.3 – 1.1)	CV Mortality	LD-MTX

Cardiovascular Inflammation Reduction Trial (CIRT)
Flow Diagram



- To evaluate in a randomized, double-blind, placebo-controlled trial whether LD-MTX given at a target dose of 15 to 20 mg po weekly will reduce rates of myocardial infarction, stroke, or cardiovascular death among patients with stable coronary artery disease and either type 2 diabetes or metabolic syndrome.

417 US and Canadian Sites
4786 Patients Randomized
10 Patients Lost to Follow Up

Cardiovascular Inflammation Reduction Trial (CIRT)

Inclusion Criteria

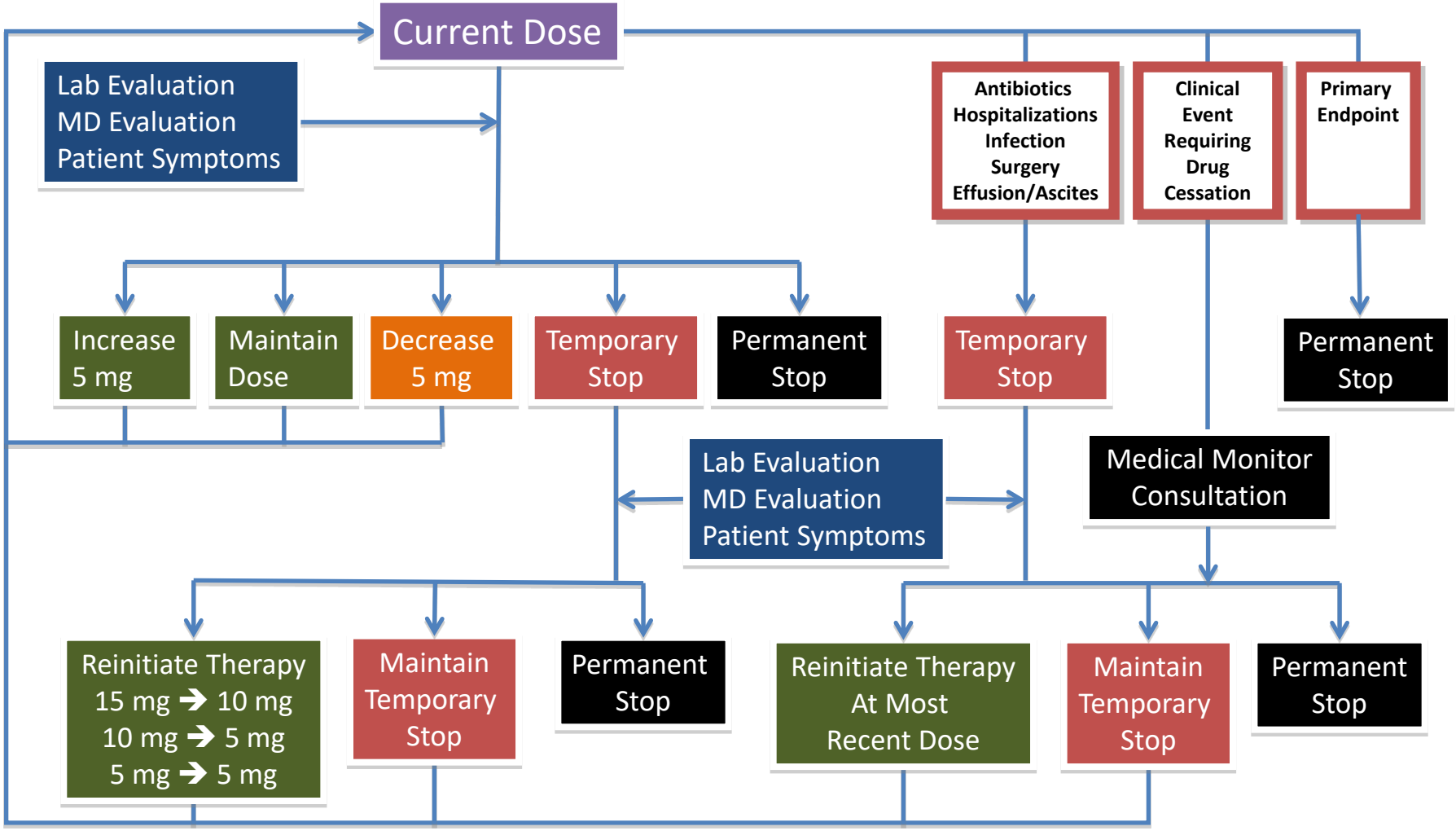
- aged 18 years and over
- have suffered a documented myocardial infarction or have multi-vessel CAD on an angiogram at any time in the past
- have completed any planned coronary revascularization procedures associated with the qualifying event
- have been on a stable secondary prevention regimen for a minimum of 60 days
- have either type 2 diabetes or metabolic syndrome
- no contraindication to LD-MTX (American College of Rheumatology 2010 guidelines)

Cardiovascular Inflammation Reduction Trial (CIRT)

Dosage adjustments based on Labs and Symptoms

Lab	Value	5mg	10mg	15mg	20 mg
WBC (n/uL)	≥ 4,000	↑ 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
	≥ 3,000 to <3,500	Do not increase	Do not increase	↓ to 10 mg	↓ to 15 mg
	< 3,500	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

Low-Dose MethotrexateTitration Algorithm



Cardiovascular Inflammation Reduction Trial (CIRT)

Baseline Characteristics

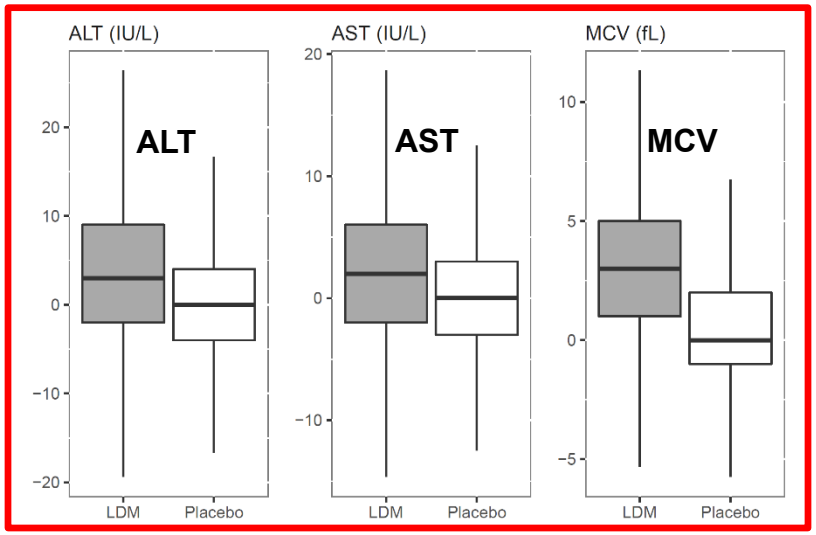
Characteristic	LD-MTX (N = 2391)	Placebo (N = 2395)
Age, years	65.6	66.0
Female gender, %	19.3	18.2
Current smokers, %	11.2	11.3
Qualifying event, %		
Myocardial infarction	60.7	60.9
Multi-vessel CAD	39.3	39.1
Qualifying comorbidity, %		
Diabetes	33.0	34.4
Metabolic syndrome	32.2	32.6
Diabetes and Metabolic Syndrome	34.8	33.1
LDL cholesterol, mg/dL	68.0	68.0
HDL cholesterol, mg/dL	41.0	41.0
hsCRP, mg/L	1.5	1.5

Cardiovascular Inflammation Reduction Trial (CIRT)

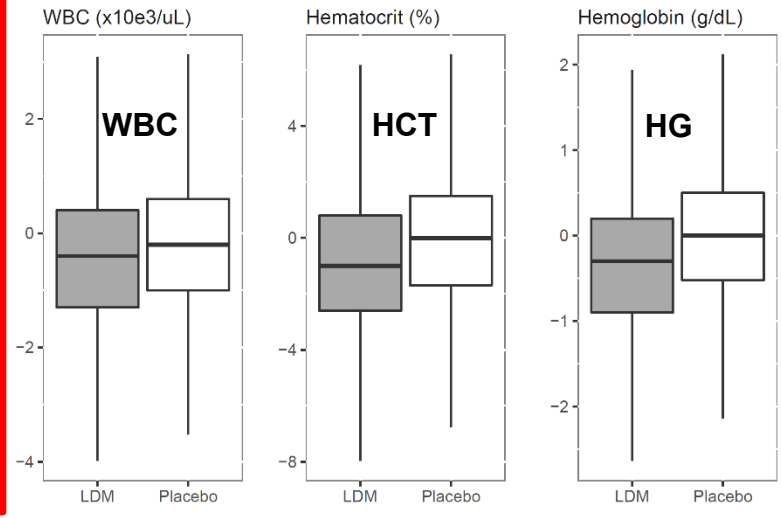
Results Part 1: Low-Dose Methotrexate vs Placebo at 8 Months

As anticipated, LD-MTX resulted in significant increases in ALT, AST, MCV (**A**); significant reductions in the WBC count, hematocrit, and hemoglobin levels (**B**), and no clinically relevant effect on lipids (**C**).

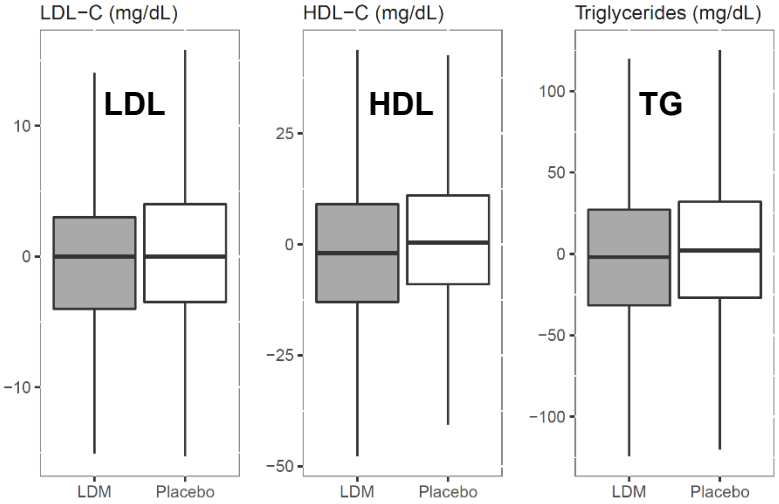
A



B



C



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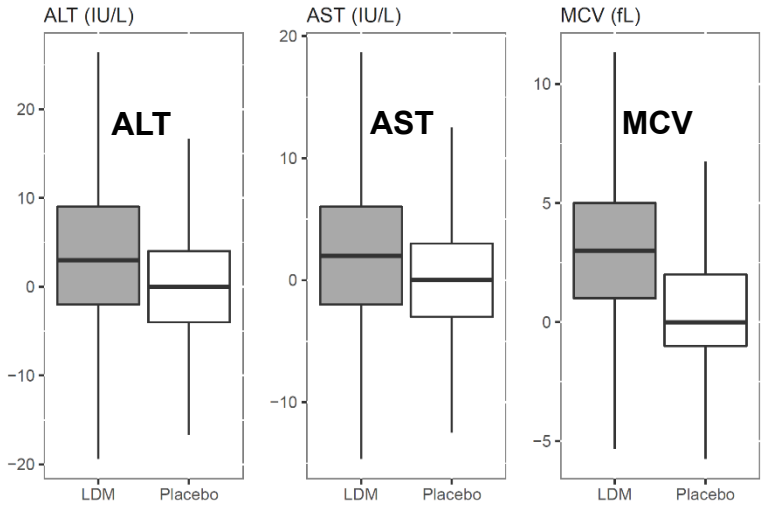
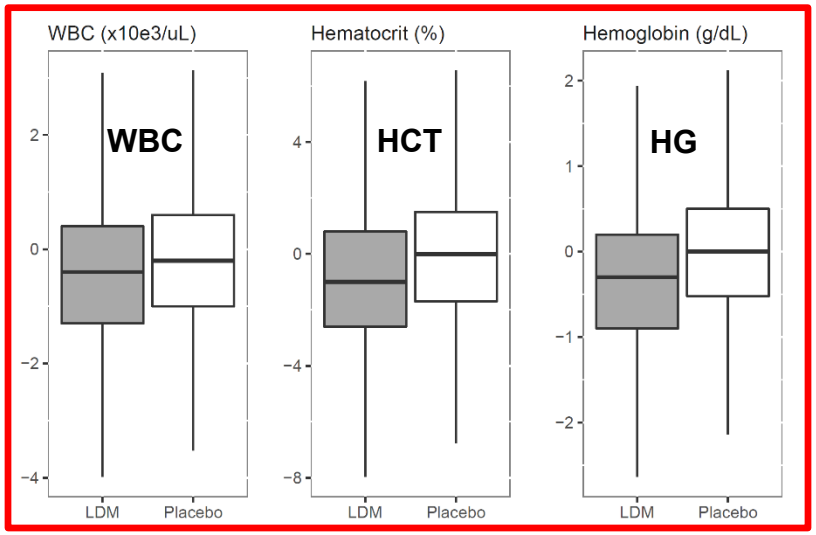
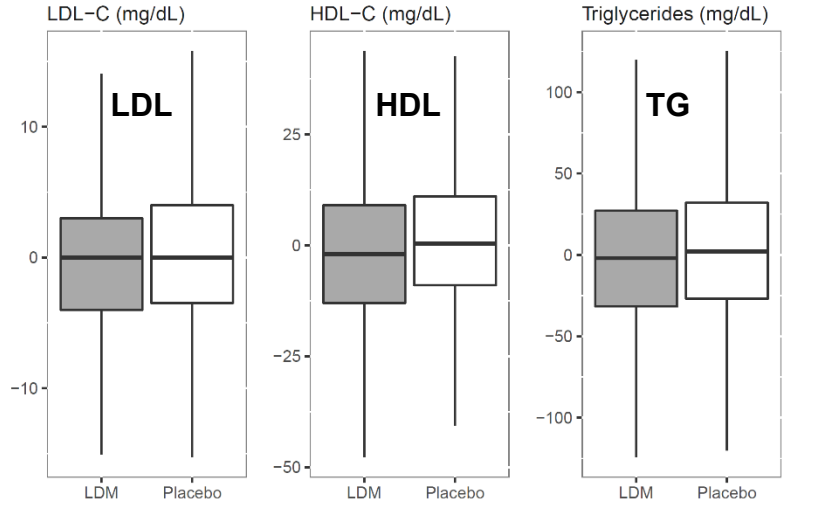


B



C



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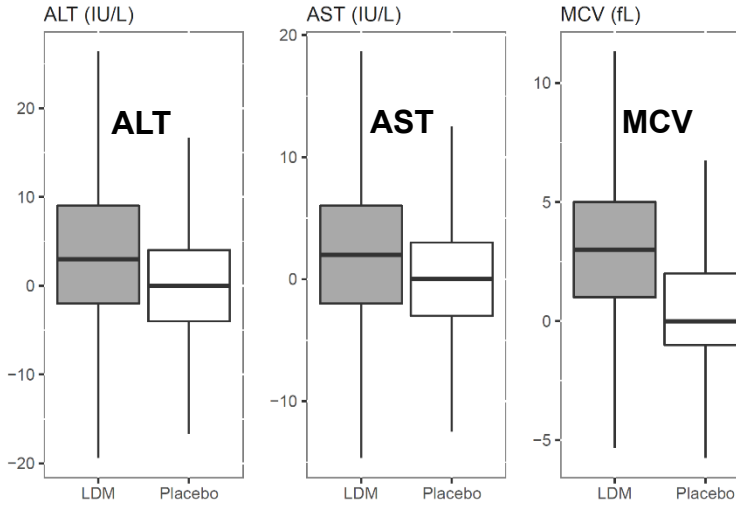

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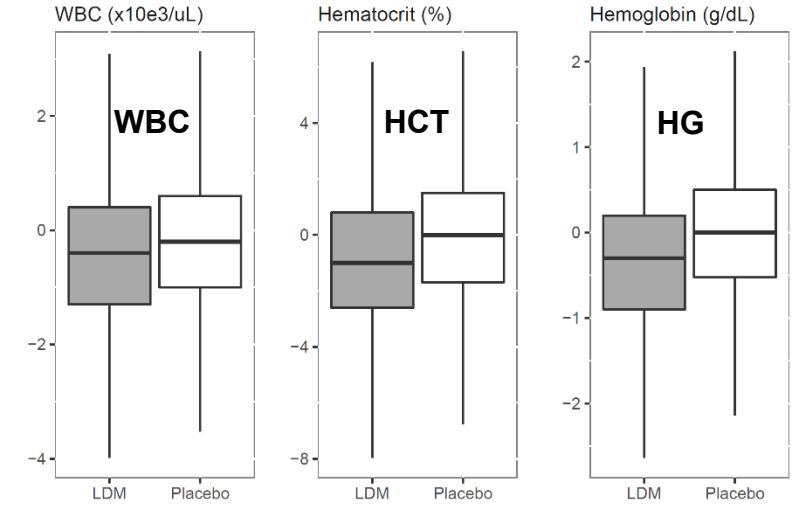

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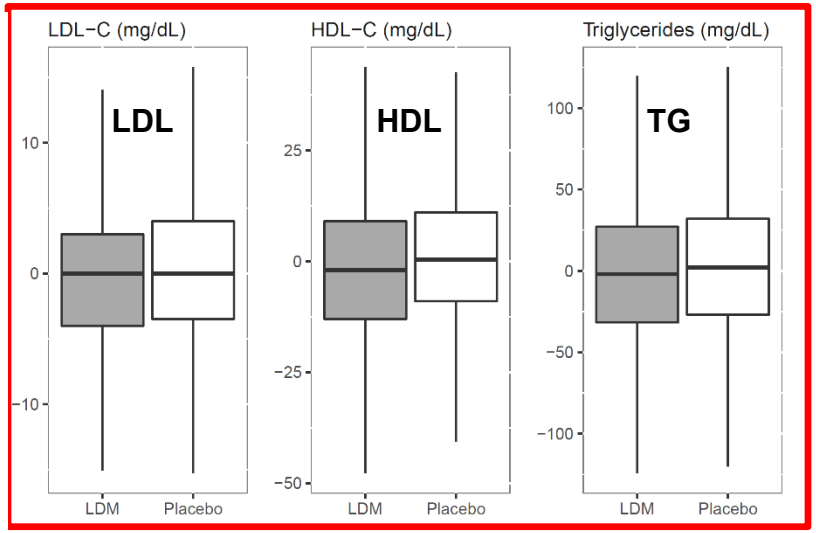
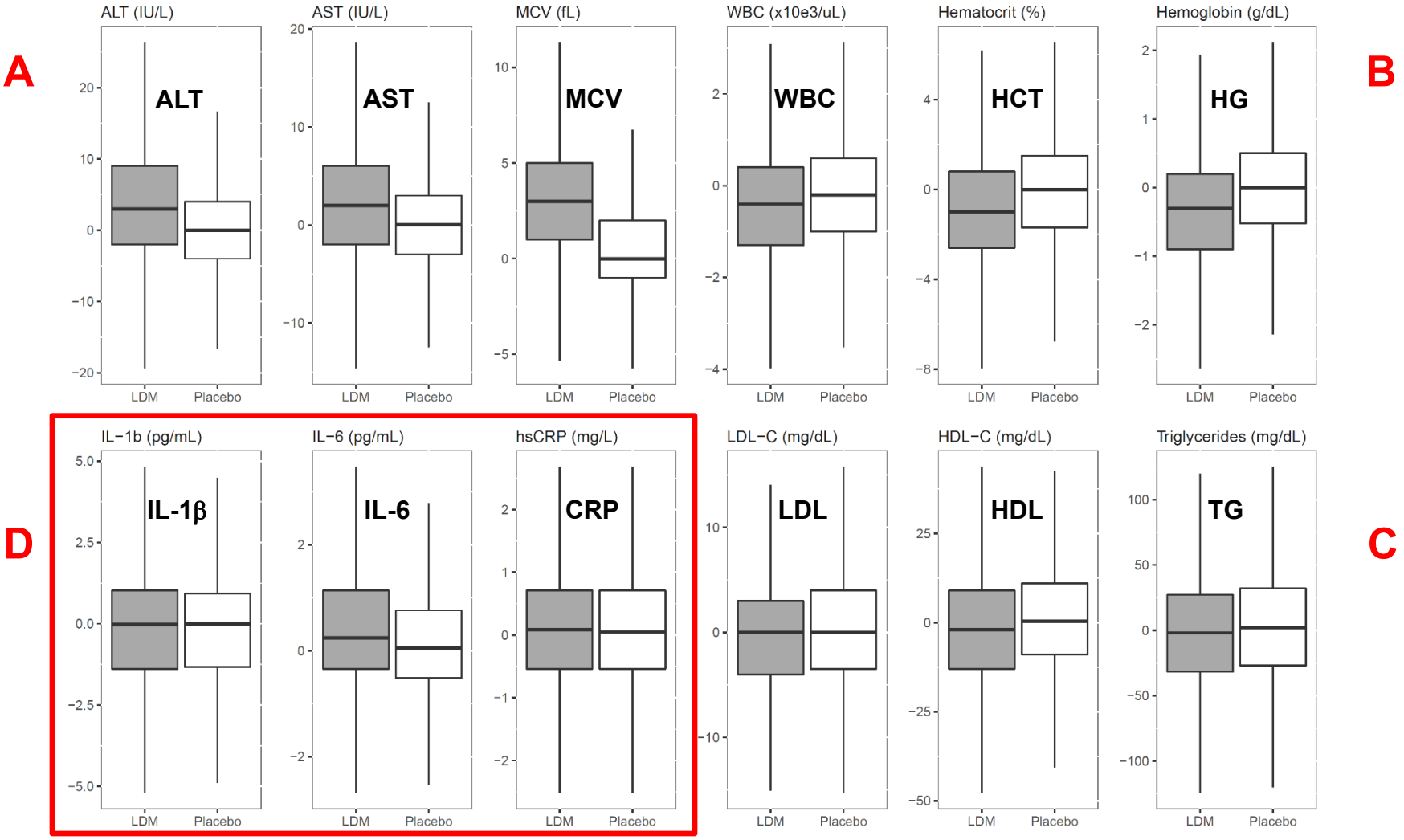


Cardiovascular Inflammation Reduction Trial (CIRT)

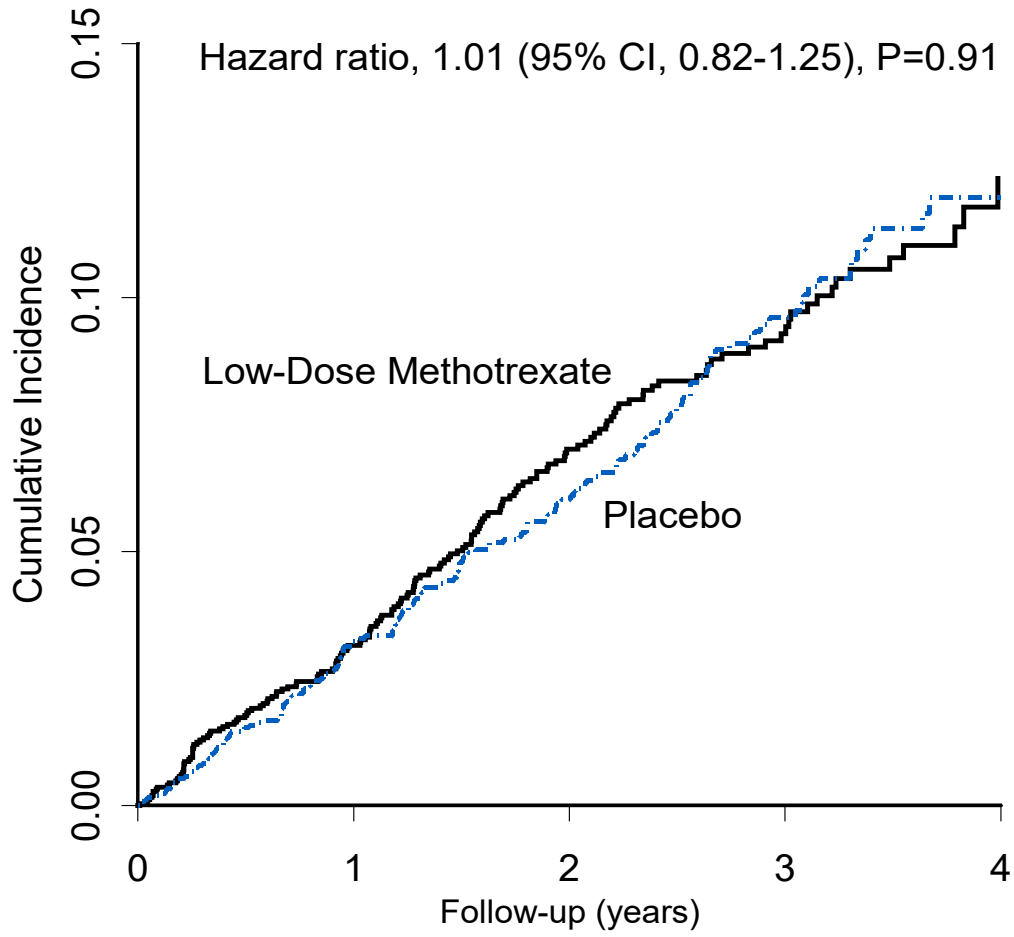
Results Part 1: Low-Dose Methotrexate vs Placebo at 8 Months

However, LD-MTX did not reduce IL-1β, IL-6, nor hsCRP (**D**), consistent with hypotheses that the anti-inflammatory effects of LD-MTX are mediated through an alternative adenosine pathway



Cardiovascular Inflammation Reduction Trial (CIRT)

Primary Result : Major Adverse Cardiovascular Events (MACE)



MACE
N (Incidence Rate Per 100 person years)

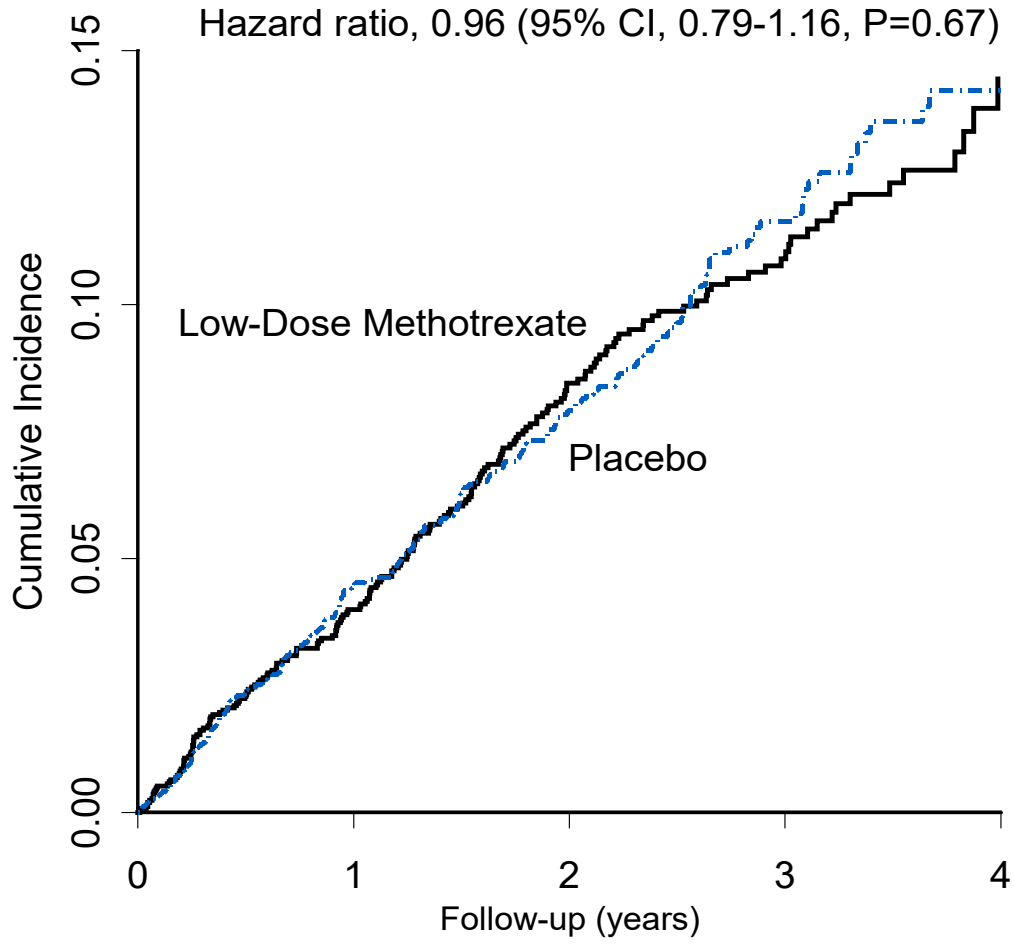
170 (3.46) LD-MTX
167 (3.43) Placebo

No. at risk:

Low-Dose Methotrexate	2391	1771	1193	621	157
Placebo	2395	1745	1194	612	148

Cardiovascular Inflammation Reduction Trial (CIRT)

Primary Result : MACE – Plus Hospitalization for UA Requiring Urgent Revascularization (MACE+)



MACE+
N (Incidence Rate Per 100 person years)

201 (4.13) LD-MTX
207 (4.31) Placebo

No. at risk:

Low-Dose Methotrexate	2391	1754	1175	611	153
Placebo	2395	1722	1167	593	143

Cardiovascular Inflammation Reduction Trial (CIRT)

Cardiovascular Outcomes, N (incidence rate per 100 person years)

Endpoint	LD-MTX N (incidence)	Placebo N (incidence)	HR	95%CI	P
PRIMARY					
MACE	170 (3.46)	167 (3.43)	1.01	0.82-1.25	0.91
MACE+	201 (4.13)	207 (4.31)	0.96	0.79-1.16	0.67
SECONDARY					
All-Cause Mortality	96 (1.80)	83 (1.55)	1.16	0.87-1.56	0.32
Hosp. for Heart Failure	48 (0.95)	53 (1.06)	0.95	0.81-1.12	0.54
MACE or Revascularization	278 (5.86)	288 (6.15)	0.95	0.81-1.12	0.57
TERTIARY					
Myocardial Infarction	113 (2.29)	114 (2.32)	0.99	0.76-1.29	0.95
Stroke	28 (0.55)	30 (0.60)	0.91	0.54-1.52	0.72
Cardiovascular Death	49 (0.92)	43 (0.80)	1.14	0.76-1.72	0.52
Coronary Revascularization					
Hospitalized, Urgent	41 (0.81)	50 (1.01)	0.81	0.53-1.22	0.31
Any	190 (3.95)	205 (4.30)	0.92	0.75-1.12	0.38

MACE = Major Adverse CV Events (nonfatal MI, nonfatal stroke, cardiovascular death)
MACE+ = MACE plus hospitalization for unstable angina requiring urgent revascularization

Cardiovascular Inflammation Reduction Trial (CIRT)

Adverse Events, N (incidence rate per 100 person years)

Adverse Event		LD-MTX N (incidence*)	Placebo N (incidence*)	P
Total	Any Serious	1488 (62.4) 569 (13.5)	1399 (56.0) 549 (13.0)	0.0042 0.52
Infections or Infestations	Any Serious	659 (16.5) 111 (2.24)	584 (14.4) 121 (2.47)	0.015 0.50
Gastrointestinal Disorders	Any	350 (7.79)	284 (6.23)	0.0058
Neurologic Disorders	Any	213 (4.53)	195 (4.12)	0.37
Malignancy	Any Skin, Non-basal Cell	106 (2.15) 33 (0.65)	95 (1.93) 12 (0.24)	0.51 0.0026
Mouth Sores or Oral Pain	Any	96 (1.95)	56 (1.13)	0.0014
Unintended Weight Loss	Any	104 (2.10)	73 (1.47)	0.022
ALT > 3x ULN AST > 3x ULN Leukopenia		49 (0.97) 39 (0.77) 241 (5.14)	17 (0.34) 21 (0.42) 172 (3.63)	0.0001 0.029 0.0006

CANTOS

Canakinumab Anti-inflammatory Thrombosis Outcomes Study

Interleukin-1β Inhibition

- ↓ IL-1β
- ↓ IL-6
- ↓ hsCRP
- ↓ 17% reduction in MACE+

CIRT | CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

Low-Dose Methotrexate

- ↔ IL-1β
- ↔ IL-6
- ↔ hsCRP
- ↔ No reduction in MACE+

Cardiovascular Inflammation Reduction Trial (CIRT)

Conclusions

- Taken together, the CANTOS and CIRT trials demonstrate that inflammation inhibition can significantly reduce cardiovascular event rates independent of lipid-lowering and blood pressure reduction.
- However, at least at this point in development, given the positive findings of CANTOS and the neutral findings of CIRT, inhibition of the IL-1β to IL-6 to CRP pathway of innate immunity appears to be important for atheroprotection.
- These two trials - CANTOS positive, CIRT a neutral control - thus point directly toward future work targeting upstream inhibition of the NLRP3 inflammasome or downstream inhibition of IL-6 as potential targets for novel cardiovascular therapeutics.

- The CIRT trial is available today on-line at NEJM.com

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Low-Dose Methotrexate for the Prevention of Atherosclerotic Events

Paul M Ridker, M.D., Brendan M. Everett, M.D., Aruna Pradhan, M.D., Jean G. MacFadyen, B.A., Daniel H. Solomon, M.D., Elaine Zaharris, B.A., Virak Mam, B.S., Ahmed Hasan, M.D., Yves Rosenberg, M.D., Erin Iturriaga, M.S.N., Milan Gupta, M.D., Michelle Tsigoulis, Subodh Verma, M.D., Michael Clearfield, D.O., Peter Libby, M.D., Samuel Z. Goldhaber, M.D., Roger Seagle, M.D., Cyril Ofori, M.D., Mohammad Saklayen, M.D., Samuel Butman, M.D., Narendra Singh, M.D., Michel Le May, M.D., Olivier Bertrand, M.D., James Johnston, M.D., Nina P. Paynter, Ph.D., and Robert J. Glynn, Sc.D., for the CIRT Investigators*