

CARDIOVASCULAR INFLAMMATION
REDUCTION TRIAL

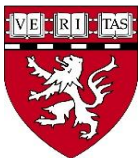


National Heart, Lung,
and Blood Institute

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

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for the **C**ardiovascular **I**nflammation **R**eduction **T**rial (**CIRT**) Investigators.

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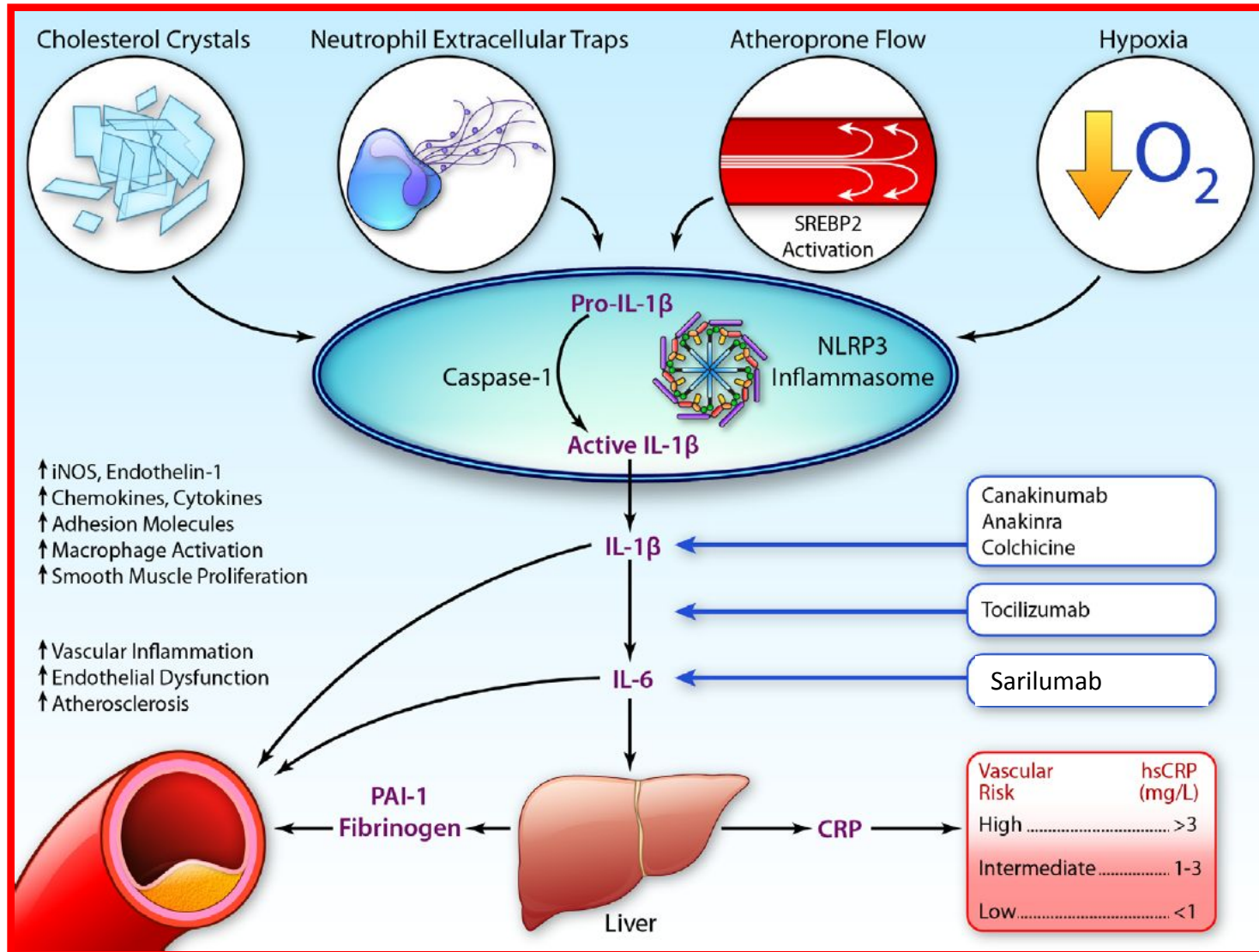


Can Inflammation Reduction, in the Absence of Lipid Lowering, Reduce Cardiovascular Event Rates?



Courtesy of Ed Yeh, MD

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



CANTOS

Canakinumab **A**nti-inflammatory **T**hrombosis **O**utcomes **S**tudy

2011 - 2017

Interleukin-1 β Inhibition

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



CARDIOVASCULAR INFLAMMATION
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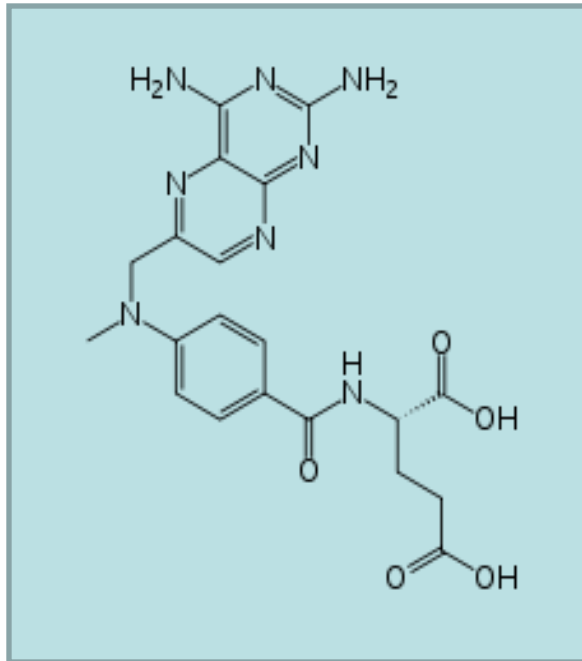
2013 - 2018

Low-Dose Methotrexate

- ? IL-1 β
- ? 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.**
- **Enviably safe 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.**



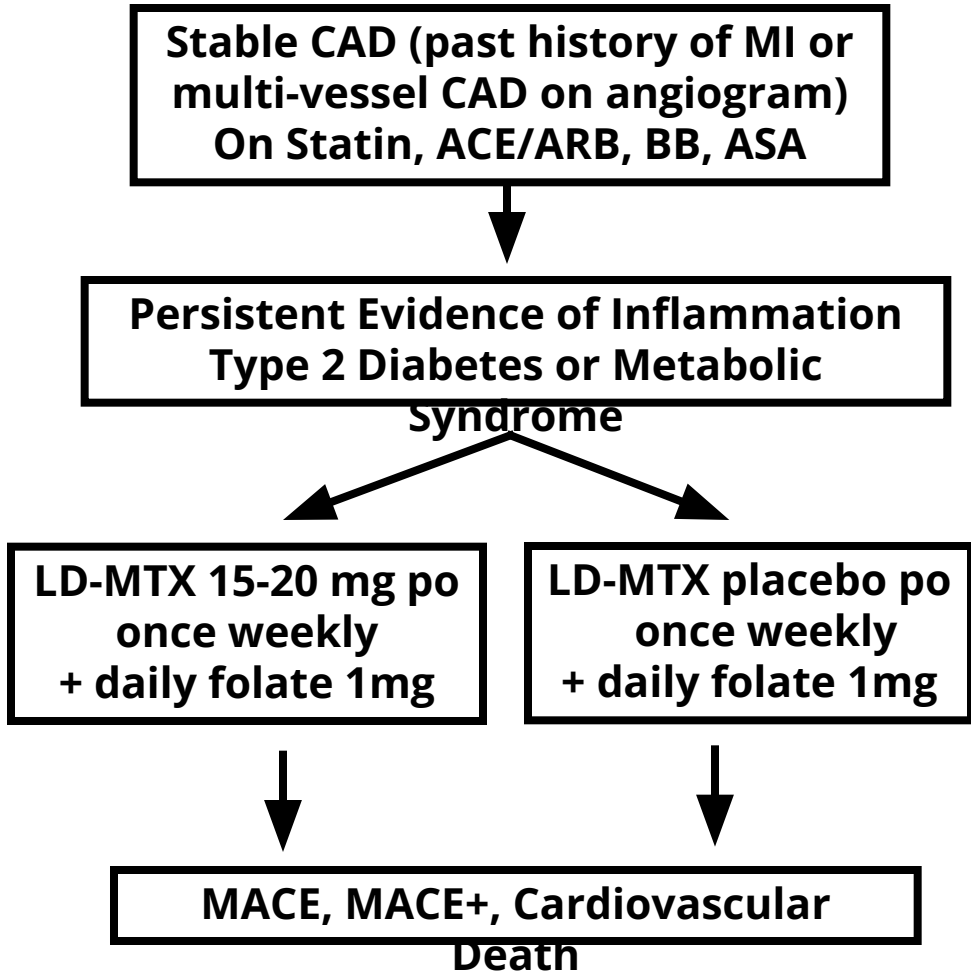
Cardiovascular Inflammation Reduction Trial (CIRT)

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

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

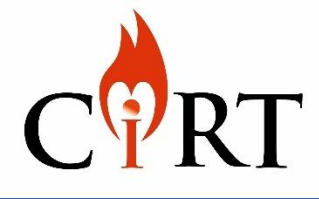


Cardiovascular Inflammation Reduction Trial (CIRT) Flow Diagram



- 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)

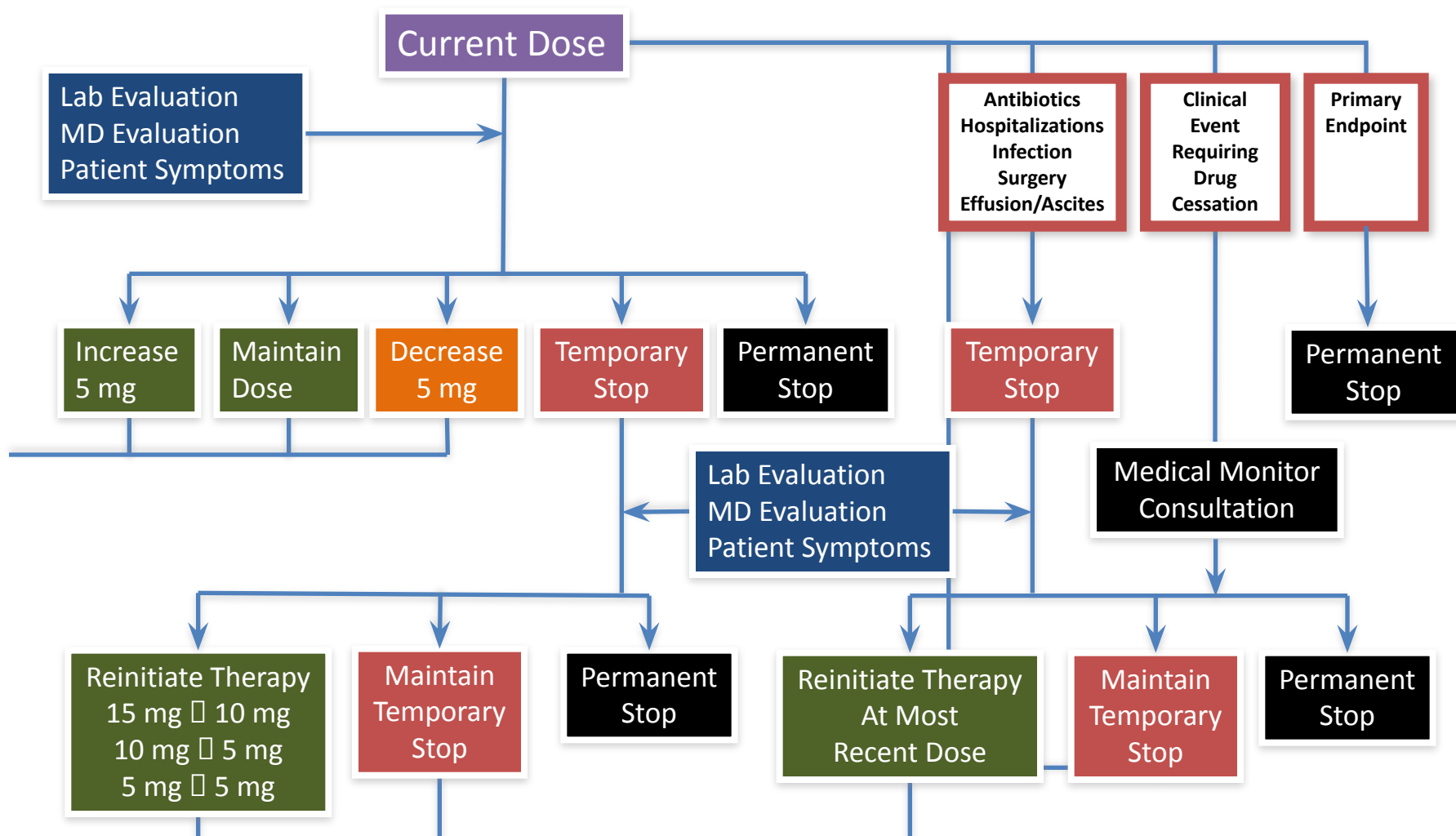


Cardiovascular Inflammation Reduction Trial (CIRT)

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 Methotrexate Titration Algorithm



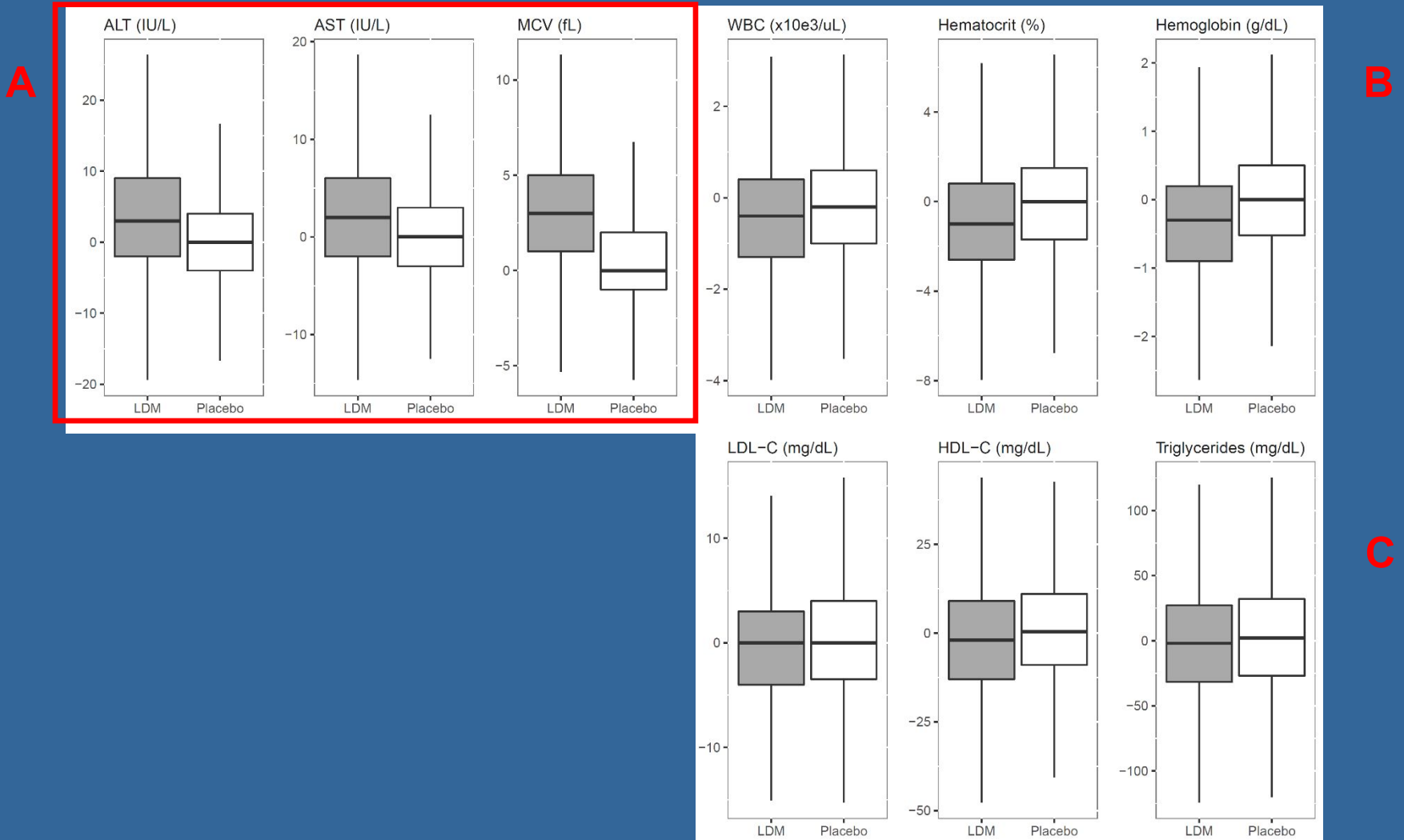


Cardiovascular Inflammation Reduction Trial (CIRT)

Baseline Characteristics

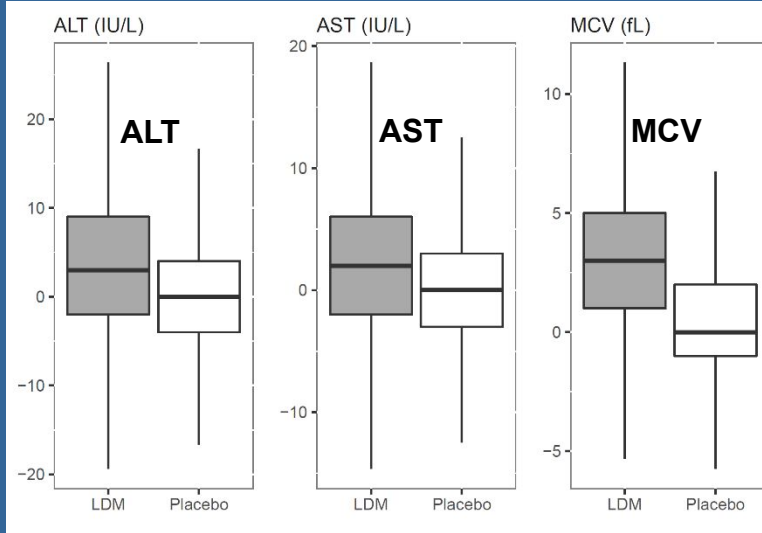
Characteristic	LD-MTX (N = 2391)	Placebo (N = 2395)
Age, years	65.6	66.0
Female gender, %	19.3	18.2
Current smokers, %	11.2	11.3
Qualifying event, %		
Myocardial infarction	60.7	60.9
Multi-vessel CAD	39.3	39.1
Qualifying comorbidity, %		
Diabetes	33.0	34.4
Metabolic syndrome	32.2	32.6
Diabetes and Metabolic 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

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**).

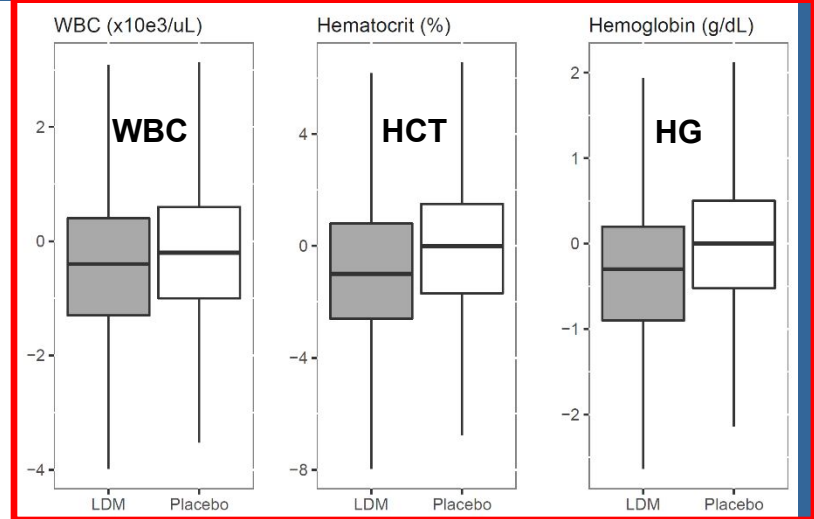


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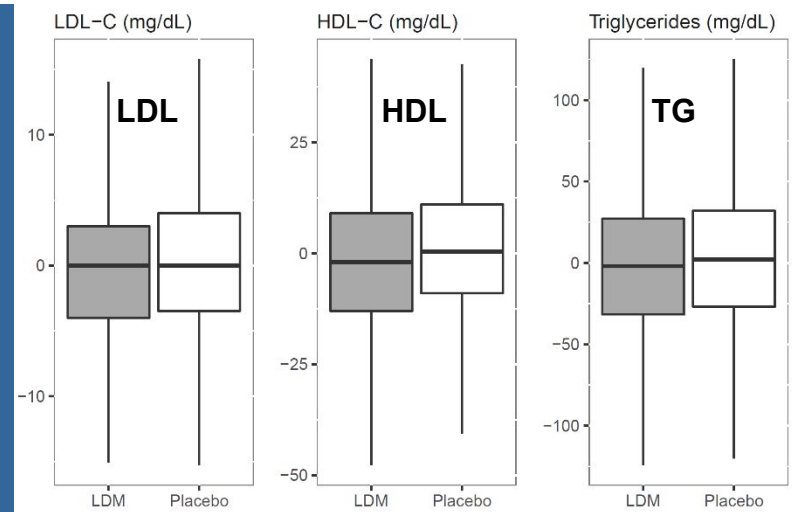
A



B

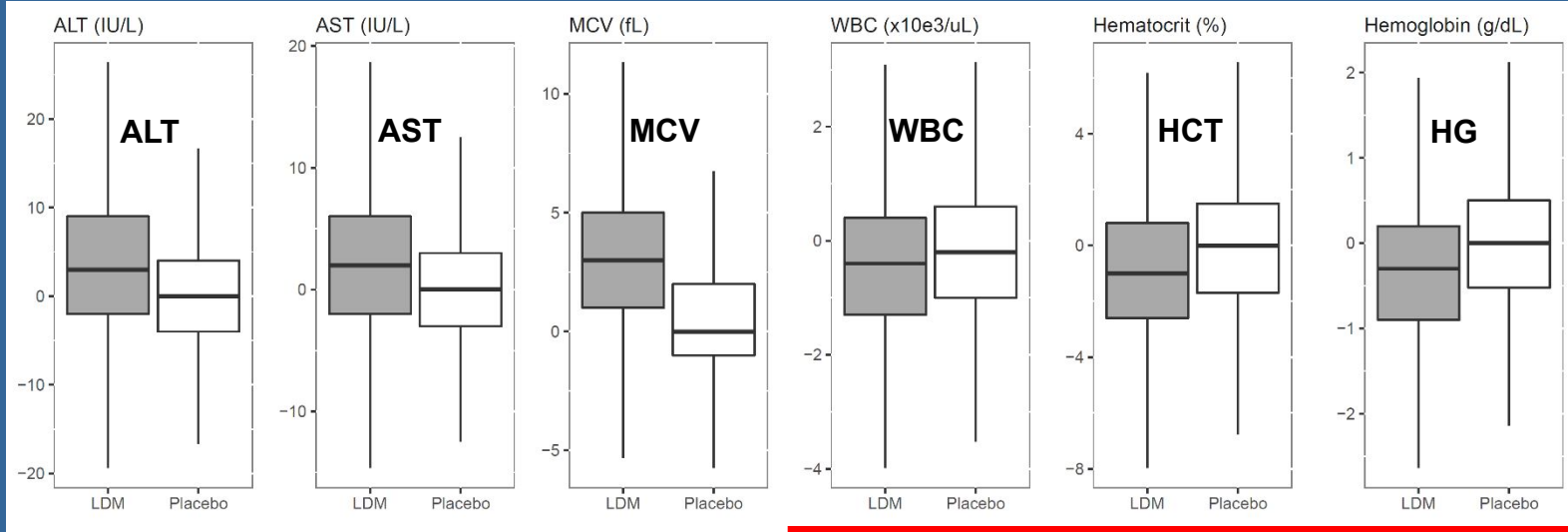


C

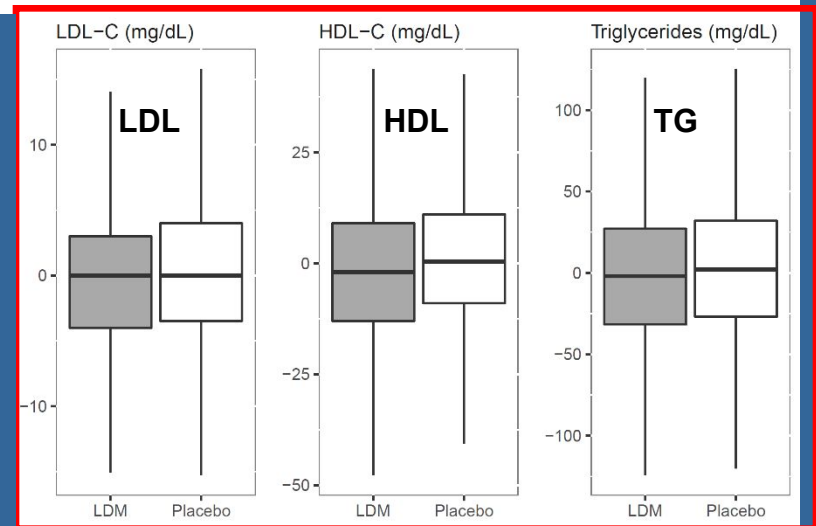


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A



B

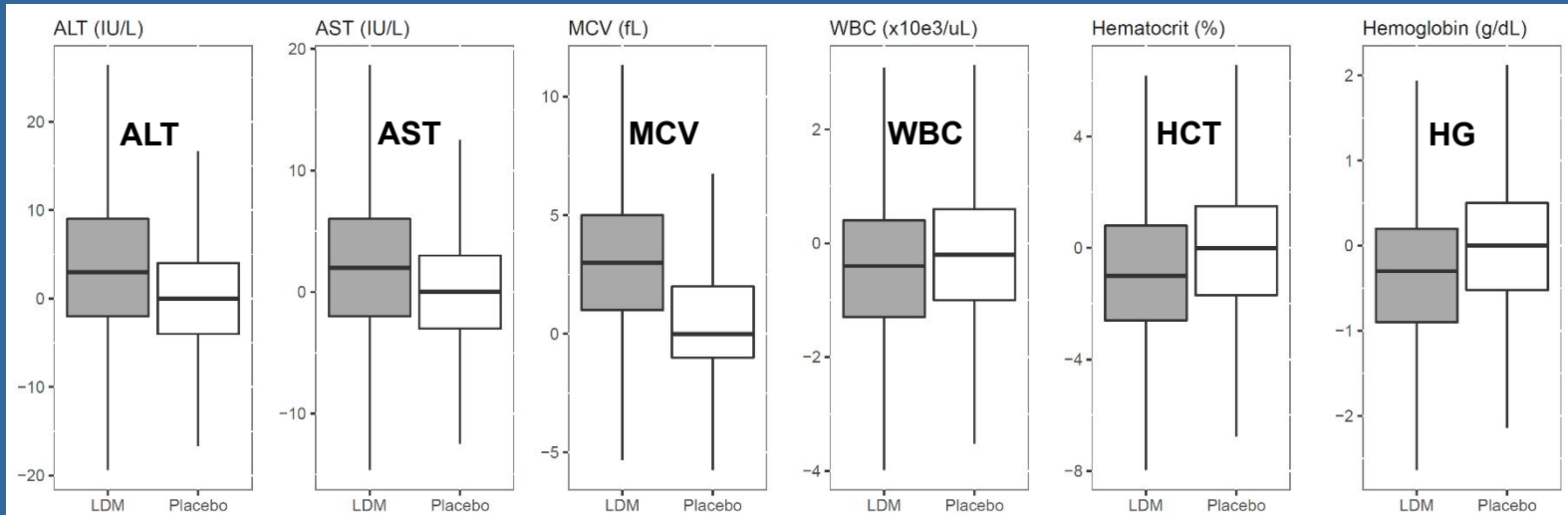


C

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

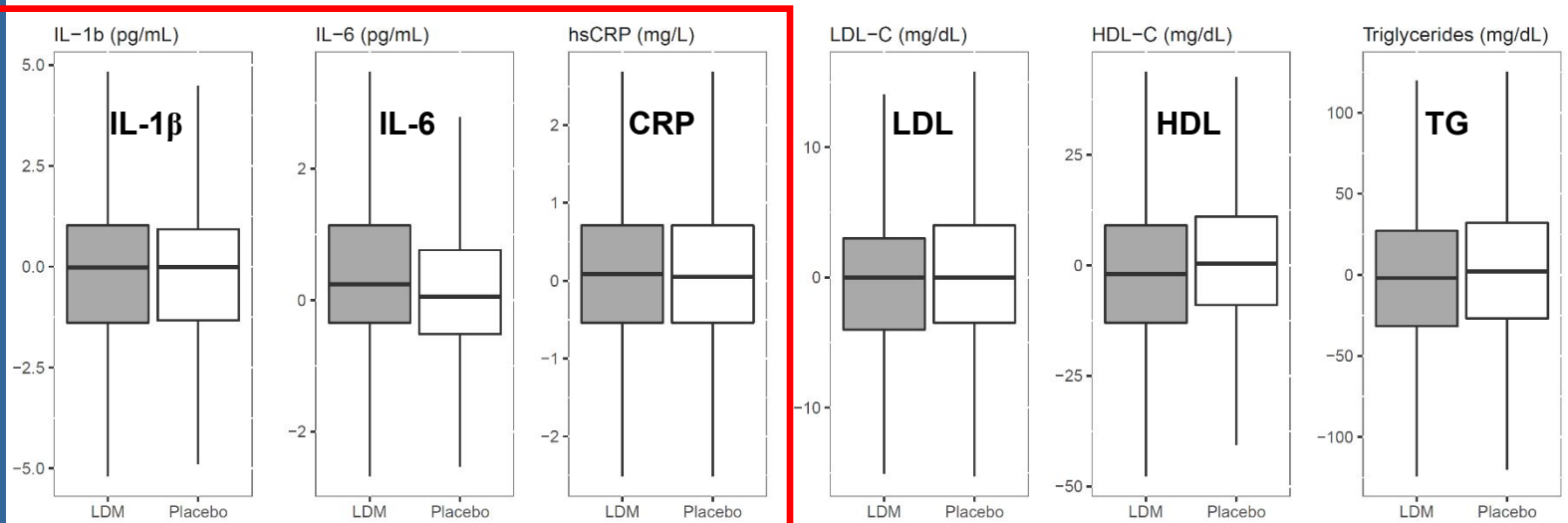
A

B



D

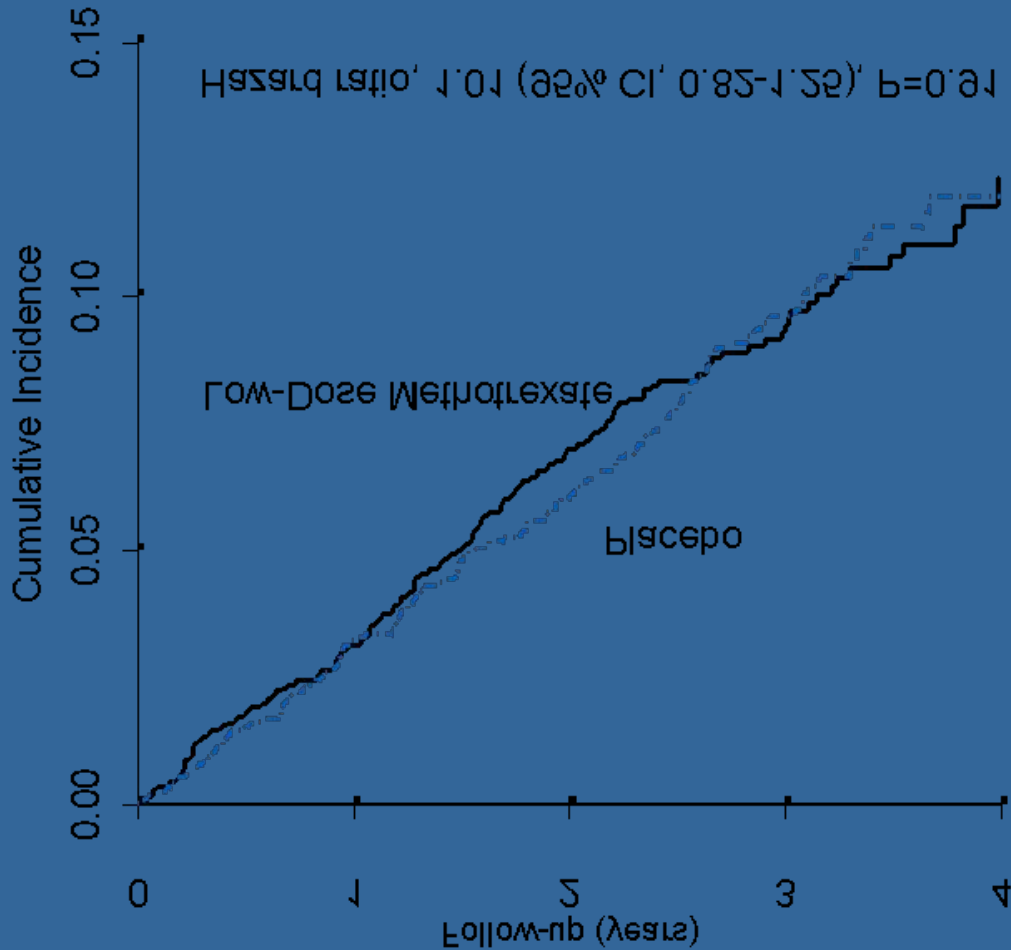
C





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
 Placebo

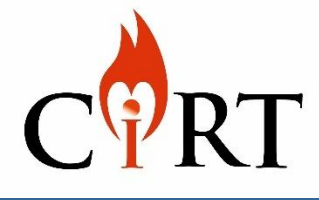
2381
 2382

1771
 2477

1183
 1817

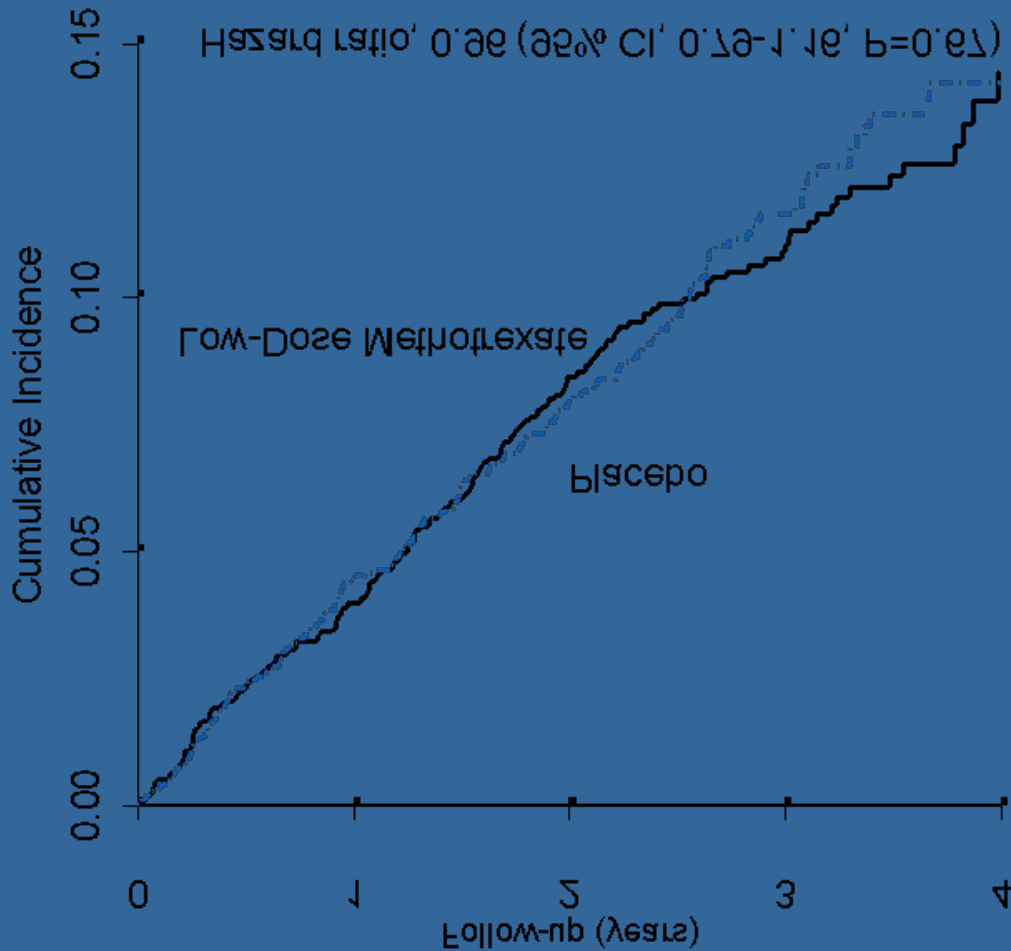
851
 1288

751
 847



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:

	0	1	2	3	4
Low-Dose Methotrexate	5381	4324	3377	2411	1423
Placebo	5382	4377	3407	2483	1443



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		49 (0.97)	17 (0.34)	0.0001
AST > 3x ULN		39 (0.77)	21 (0.42)	0.029
Leukopenia		241 (5.14)	172 (3.63)	0.0006

CANTOS

Canakinumab **A**nti-inflammatory **T**hrombosis **O**utcomes **S**tudy

Interleukin-1 β Inhibition

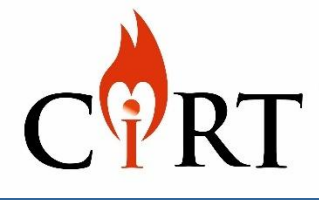
- ▼ IL-1 β
- ▼ IL-6
- ▼ hsCRP
- ▼ 17% reduction in MACE+



CARDIOVASCULAR INFLAMMATION
REDUCTION TRIAL

Low-Dose Methotrexate

- ↔ IL-1 β
- ↔ 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-1 β 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.



ORIGINAL ARTICLE

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