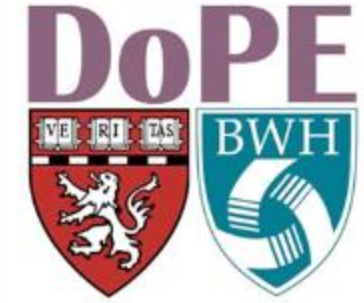


Interplay between observational and randomized perspectives on drug safety and efficacy

- Robert J Glynn
- Divisions of Pharmacoepidemiology & Pharmacoeconomics & Preventive Medicine, Brigham & Women's Hospital, Boston

- Disclosure: I will present perspectives on medication safety and efficacy and have received funding from grants to BWH from AstraZeneca, Bristol-Myers Squibb, Kowa and Novartis, as well as the NIH

Outline: observations within trials, and a trialist perspective in observations

1. A surprising side effect in a trial: diabetes in JUPITER

2. Observations motivating trials: was CIRT built on poor epidemiology?

3. What to make of an unexpected benefit: cancer in CANTOS

4. Trials as the paradigm for observations: is a placebo referent coherent?

5. Building observations into trials: mediation in CANTOS

The JUPITER trial

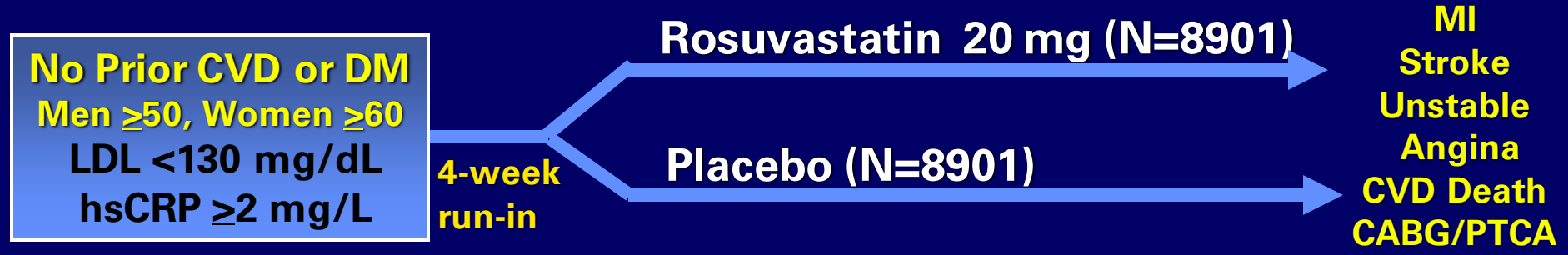
The primary objective was to investigate whether long-term treatment with rosuvastatin 20 mg decreases the rate of first major cardiovascular events compared with placebo in patients with low to normal LDL-C but at increased cardiovascular risk as identified by elevated CRP levels

Ridker PM. *Circulation* 2003; **108**: 2292–2297

JUPITER
Trial Design

JUPITER

Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP



Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Circulation 2003;108:2292-2297.

Statins and diabetes: the JUPITER surprise

- Elevated levels of high sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6) independently predict incident diabetes mellitus*
- Statin treatment reduces levels of inflammatory markers†
- The JUPITER trial pre-specified evaluation of the risk of diabetes as a secondary endpoint
- Almost no prior evidence was available from statin trials on this outcome

*Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001; 286(3):327-34.

† Albert MA, Danielson E, Rifai N, Ridker PM; PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001; 286(1):64-70.

JUPITER timeline

First randomization: March 14, 2003

Last randomization: December 15, 2006

Pre-specified stopping boundary crossed: September 7, 2007

Termination for efficacy: March 30, 2008

Last patient visit: August 20, 2008

Incident DM and HgbA1c change in JUPITER

September 7, 2007 DSMB meeting			
Treatment	Rosuvastatin	Placebo	P-value
HgbA1c 2-yr change, median (IQR)	0.2% (0.1-0.4)	0.1% (0.0-0.3)	<0.001
Incident diabetes cases, rate/1,000 pyrs	39, 2.8	22, 1.6	0.037
March 30, 2008 DSMB meeting			
HgbA1c 2-yr change, median (IQR)	0.3% (0.1-0.4)	0.2% (0.0-0.3)	<0.001
HgbA1c 3-yr change, median (IQR)	0.3% (0.1-0.4)	0.2% (0.0-0.3)	<0.001
Incident diabetes (cases/pyrs) rate	71, 3.7	40, 2.1	0.004

Diabetes in JUPITER: implications

- After final database closure, the diabetes risk associated with rosuvastatin was somewhat attenuated, but still present: HR 1.25; 95% CI: 1.09-1.45*
- A subsequent meta-analysis, including previous statin trials without reported diabetes effects, confirmed the signal from JUPITER, and showed apparently higher risk with more intensive statin regimens†
- Follow-up analyses in JUPITER showed the diabetes risk was mostly confined to those with multiple diabetes risk factors at baseline, and these individuals had strong cardiovascular benefits††

*Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359(21):2195-207.

†Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 2011;305(24):2556-64.

††Ridker PM, Pradhan A, MacFadyen JG, et al. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet 2012; 380(9841):565-71.

Diabetes in JUPITER: follow-up of potential causes

- Follow-up biomarker analyses found no strong predictors of diabetes in statin initiators
- Rosuvastatin treatment was associated with an average weight gain of 0.85 pounds over the mean 2-year treatment period relative to placebo (95% CI: 0.47-1.24)
- Perhaps some subjects are particularly susceptible to weight gain on statins: 13.4% of randomized subjects gained 10+ pounds during follow-up, and the odds of this gain were higher in statin treated subjects: OR 1.25; 95% CI: 1.14-1.38

Trials are built on observations: the example of CIRT

- Both basic science and clinical evidence are needed to justify a trial
- Often the epidemiologic evidence is key
- Numerous pharmacoepidemiological studies supported a trial of methotrexate to reduce inflammation and thereby CVD risk
- Was the Cardiovascular Inflammation Reduction Trial built on sand?

CIRT | Cardiovascular Inflammation Reduction Trial

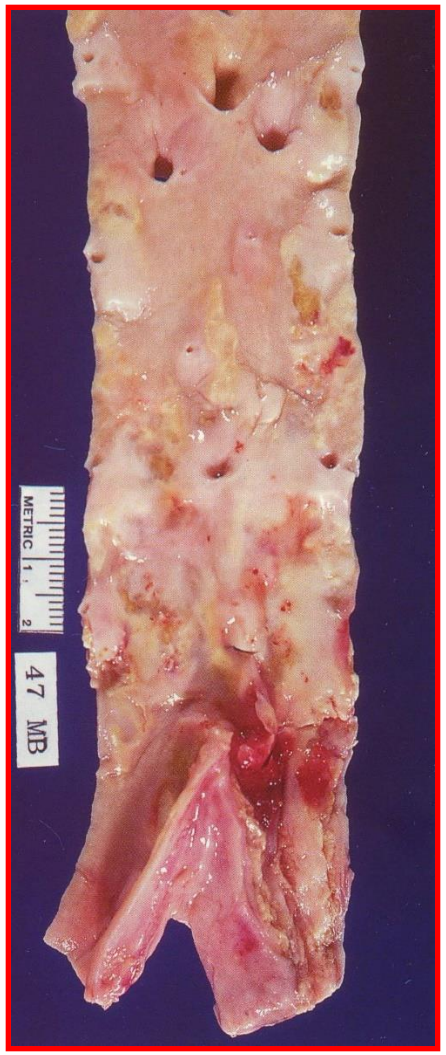
NIH National Heart, Lung, and Blood Institute

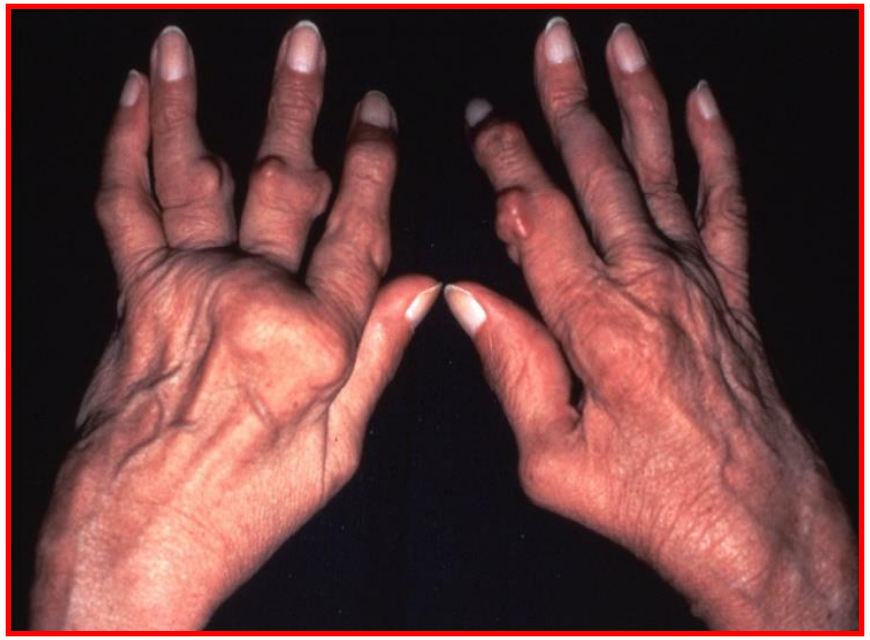
A Randomized, Double-Blind, Placebo-Controlled Trial of Low-Dose Methotrexate for the Prevention of Atherosclerotic Events

Paul Ridker, Brendan Everett*, Aruna Pradhan, Jean MacFadyen,
Daniel Solomon, Elaine Zaharris, Virak Mam, Ahmed Hasan, Yves Rosenberg,
Erin Iturriaga, Milan Gupta, Michelle Tsigoulis, Subodh Verma, Michael Clearfield,
Peter Libby, Samuel Goldhaber, Roger Seagle, Cyril Ofori,
Mohammad Saklayen, Samuel Butman, Narendra Singh, Michel Le May,
Olivier Bertrand, James Johnston, Nina Paynter*, and Robert Glynn*
for the **C**ardiovascular **I**nflammation **R**eduction **T**rial (**CIRT**) Investigators.

*these authors contributed equally to this project

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

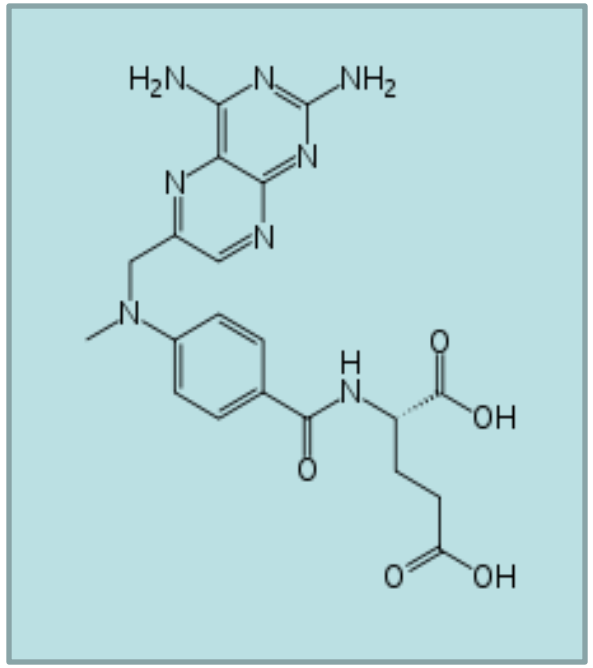




Courtesy of Ed Yeh, MD

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.**

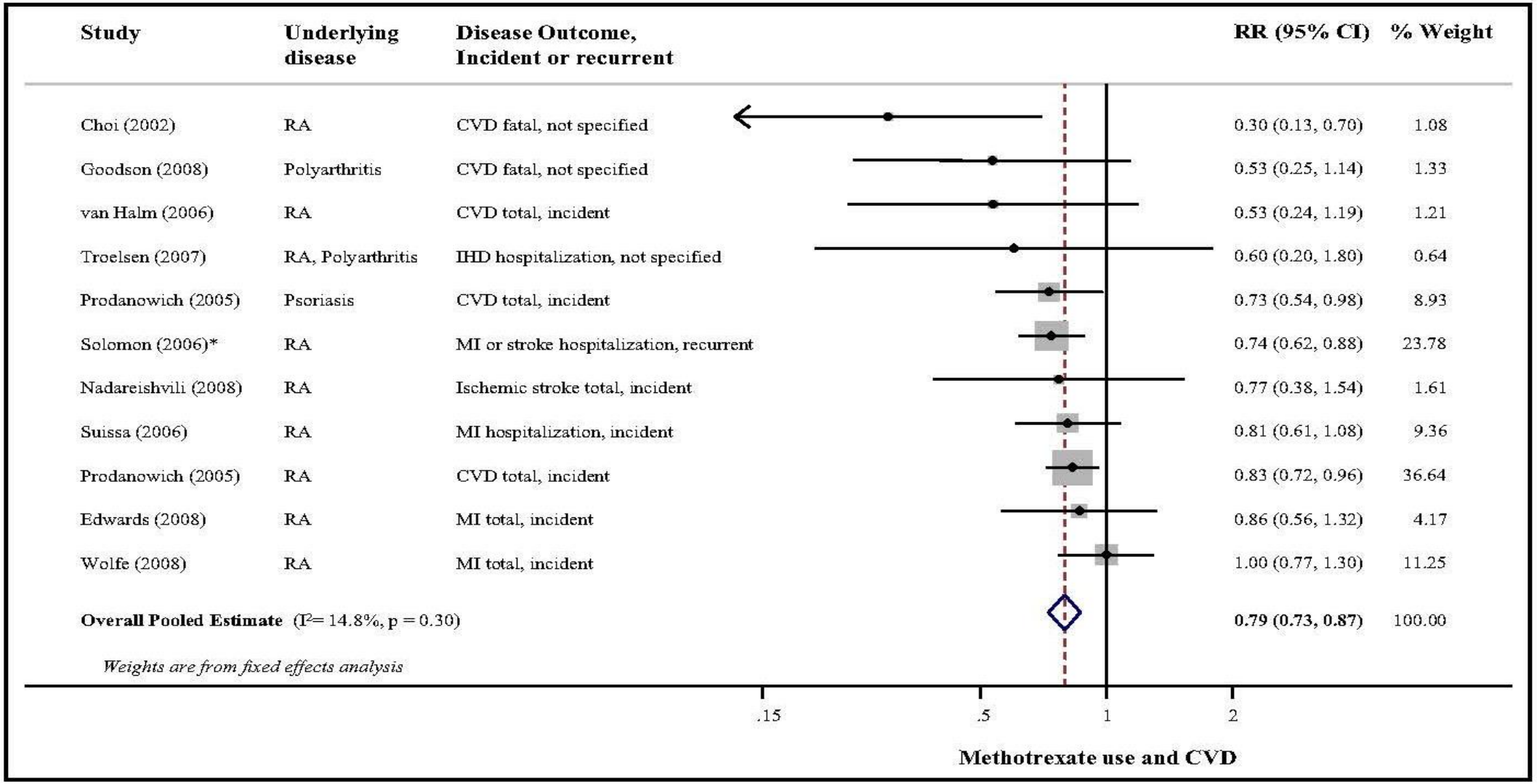
Cardiovascular Inflammation Reduction Trial (CIRT)

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)

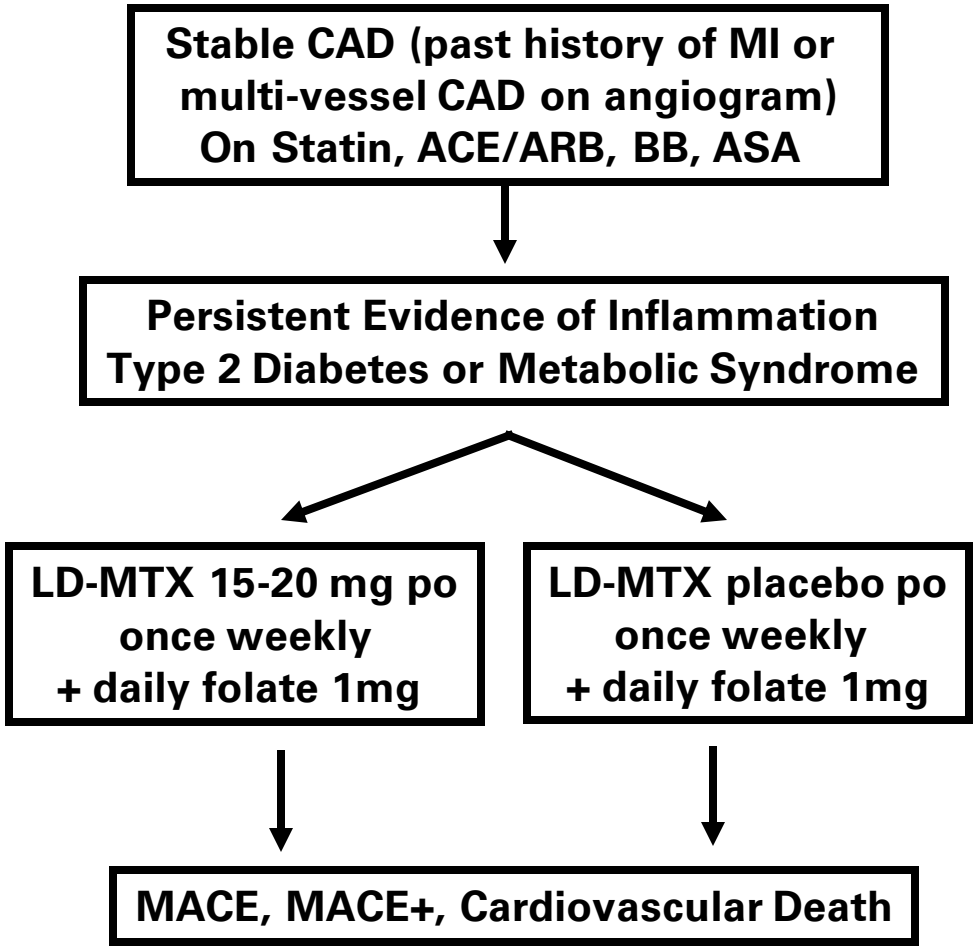
Observational non-randomized evidence suggests a reduction in vascular events among patients with RA and Psoriasis treated with low-dose methotrexate



Micha et al. Am J Cardiol 2011

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

CIRT timeline

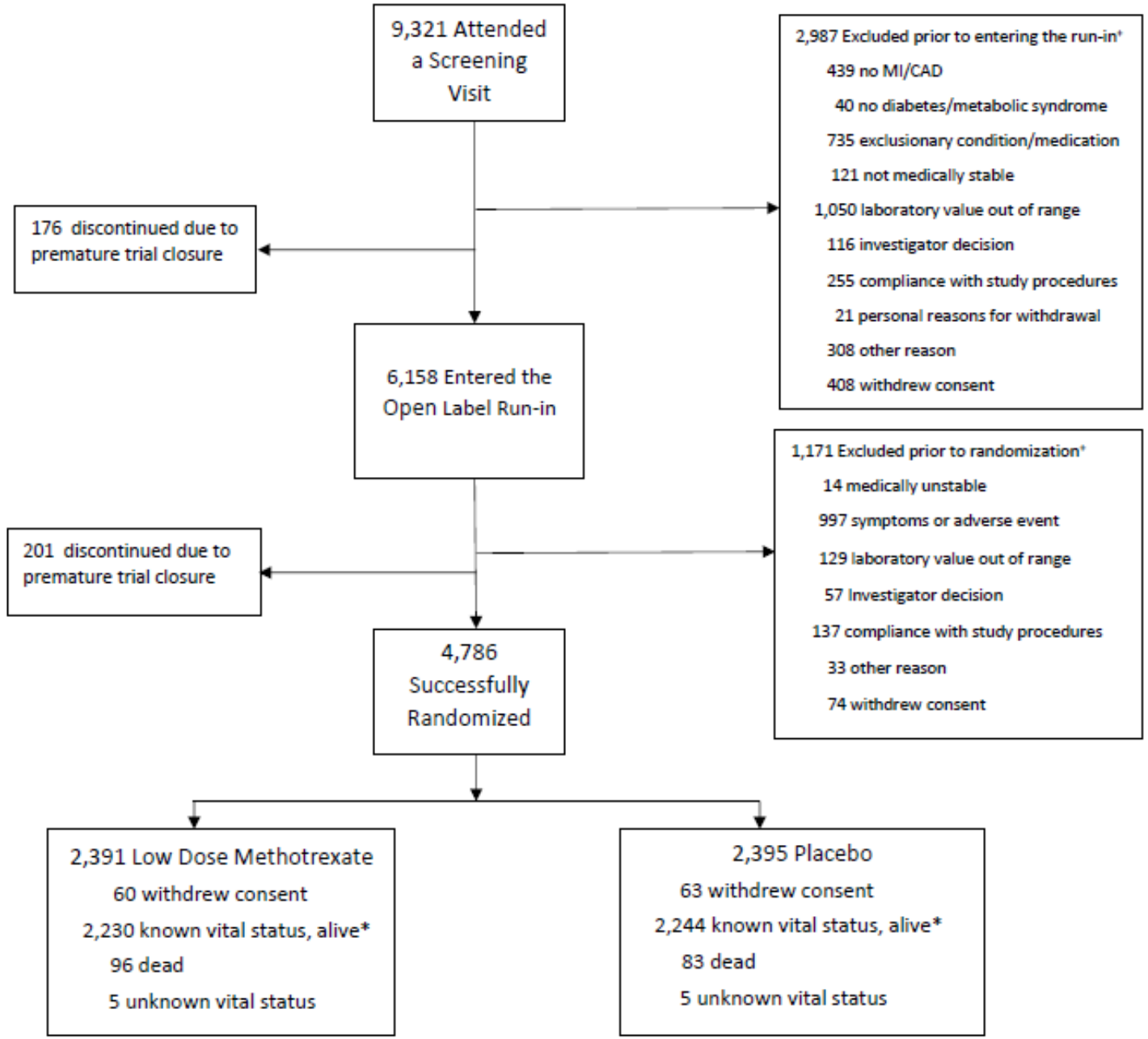
- **NHLBI approval of LOI: December 17, 2008**
- **First enrollment visit: April 4, 2013**
- **First randomization: May 17, 2013**
- **Vanguard feasibility* evaluation: May 7, 2015**
- **Interim futility analysis: March 13, 2018**
- **Termination: April 2, 2018**
- **Primary endpoint: PM Ridker et al; NEJM 2018**

*Evaluation of recruitment and compliance after 1,000 randomized patients have 6 months of follow-up

Cardiovascular Inflammation Reduction Trial (CIRT)

Baseline Characteristics

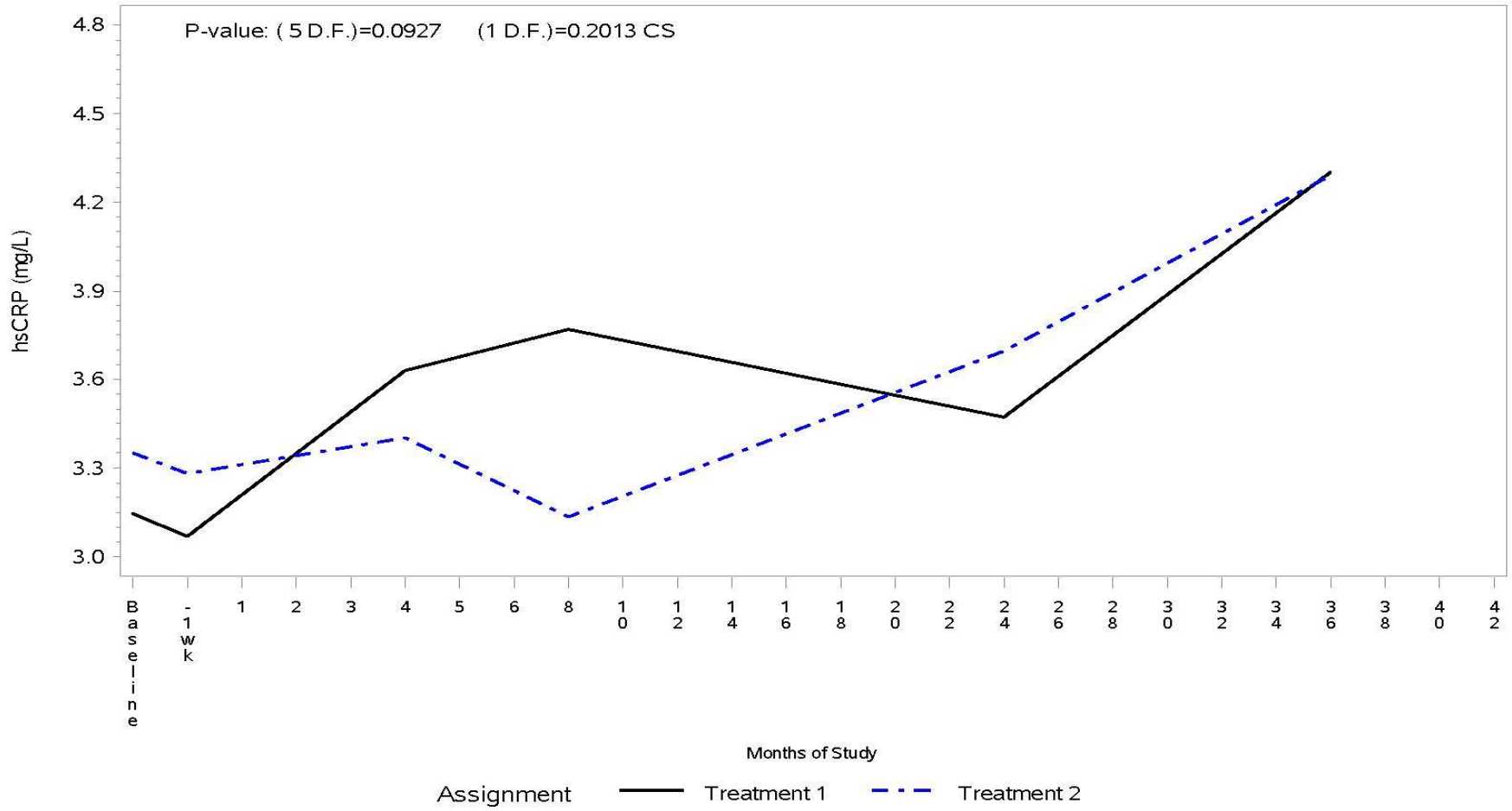
Characteristic	LD-MTX (N = 2391)	Placebo (N = 2395)
Age, years	65.6	66.0
Female gender, %	19.3	18.2
Current smokers, %	11.2	11.3
Qualifying event, %		
Myocardial infarction	60.7	60.9
Multi-vessel CAD	39.3	39.1
Qualifying comorbidity, %		
Diabetes	33.0	34.4
Metabolic syndrome	32.2	32.6
Diabetes and Metabolic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


9,321 Attended a Screening Visit
2,987 Excluded prior to entering the run-in†
439 no MI/CAD
40 no diabetes/metabolic syndrome
735 exclusionary condition/medication
121 not medically stable
1,050 laboratory value out of range
116 investigator decision
255 compliance with study procedures
21 personal reasons for withdrawal
308 other reason
408 withdrew consent
176 discontinued due to premature trial closure
6,158 Entered the Open Label Run-in
1,171 Excluded prior to randomization†
14 medically unstable
997 symptoms or adverse event
129 laboratory value out of range
57 Investigator decision
137 compliance with study procedures
33 other reason
74 withdrew consent
201 discontinued due to premature trial closure
4,786 Successfully Randomized
2,391 Low Dose Methotrexate
60 withdrew consent
2,230 known vital status, alive*
96 dead
5 unknown vital status
2,395 Placebo
63 withdrew consent
2,244 known vital status, alive*
83 dead
5 unknown vital status

Rationale for stopping CIRT

- Absence of benefit on the primary endpoint, meeting a prespecified criterion for futility
- No heterogeneity of effect by category of baseline hsCRP level, or treatment effect on hsCRP
- Adherence below that assumed in the baseline power calculation
- Safety concern related to skin cancer

Time trends in biomarker levels by treatment



CIRT Report March 2018

Confirmed endpoints by treatment group

	Treatment 1 N=2318		Treatment 2 N=2320		
	N	Rate	N	Rate	RR (95% CI)
Primary Aim					
MACE+Hosp for Unstable Angina Requiring Urgent Coronary Revasc	165	3.52	166	3.54	1.00 (0.81, 1.24)
Secondary Aims					
MACE	139	2.93	128	2.69	1.10 (0.87, 1.40)
All Death	66	1.34	59	1.20	1.13 (0.80, 1.61)

CIRT Report II-222

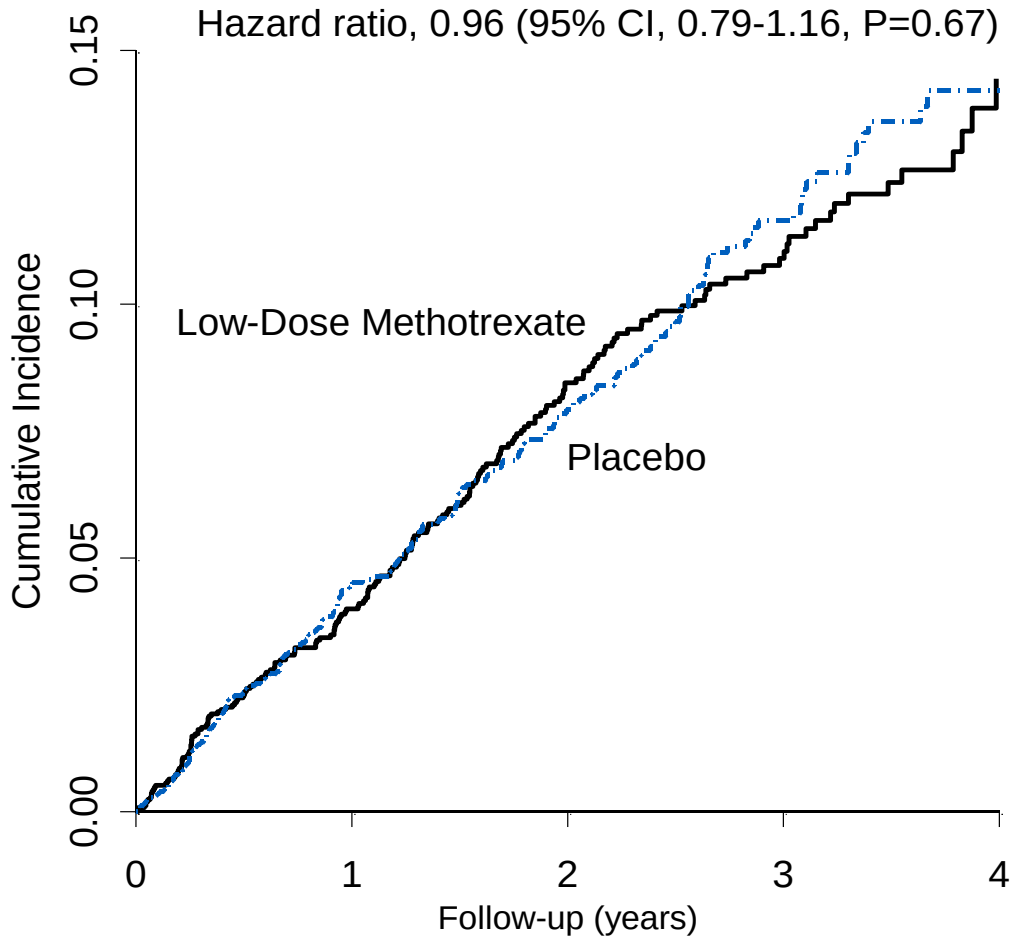
Confirmed endpoints by treatment group and baseline hsCRP

	Treatment 1 N=2318		Treatment 2 N=2320		
	N	Rate	N	Rate	RR (95% CI)
Primary Aim					
MACE+Hosp for Unstable Angina Requiring Urgent Coronary Revasc					
hsCRP <2.0 mg/L	81	2.91	98	3.51	0.83 (0.62, 1.12)
hsCRP ≥2.0 mg/L	83	4.49	67	3.67	1.22 (0.88, 1.68)
Secondary Aims					
MACE					
hsCRP <2.0 mg/L	67	2.38	75	2.64	0.91 (0.65, 1.27)
hsCRP ≥2.0 mg/L	71	3.79	52	2.81	1.32 (0.92, 1.89)

CIRT Report II-226

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)

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

What to make of an unexpected benefit: cancer in CANTOS

The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) tested whether drug treatment to lower inflammation without affecting lipid levels would reduce rates of cardiovascular events in patients with stable CVD

The trial's DSMB had almost no external evidence on the safety and side effects of the drug

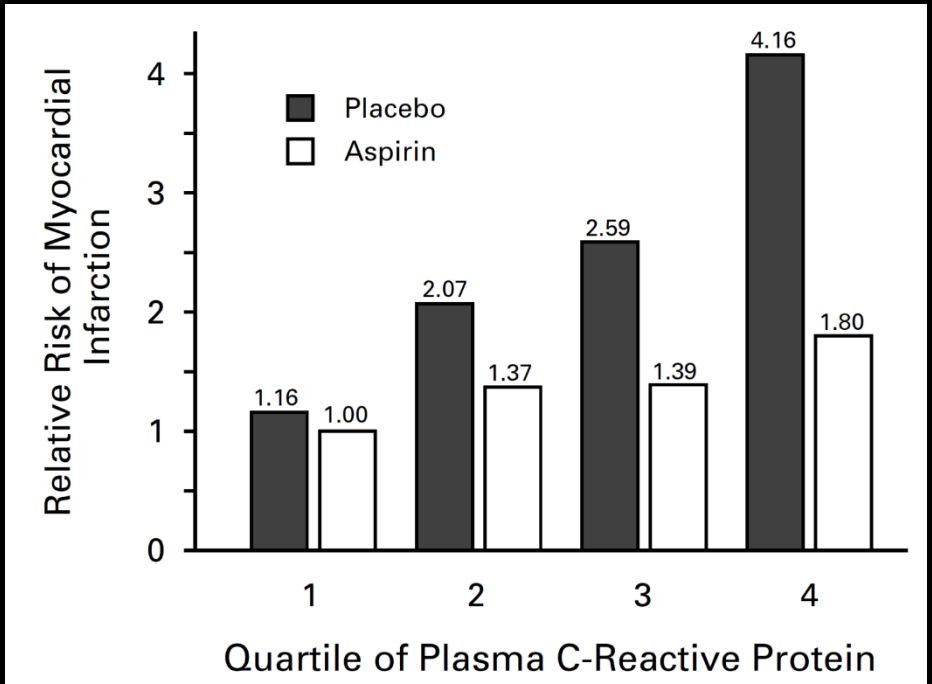
Integration of risks and benefits during interim monitoring is challenging

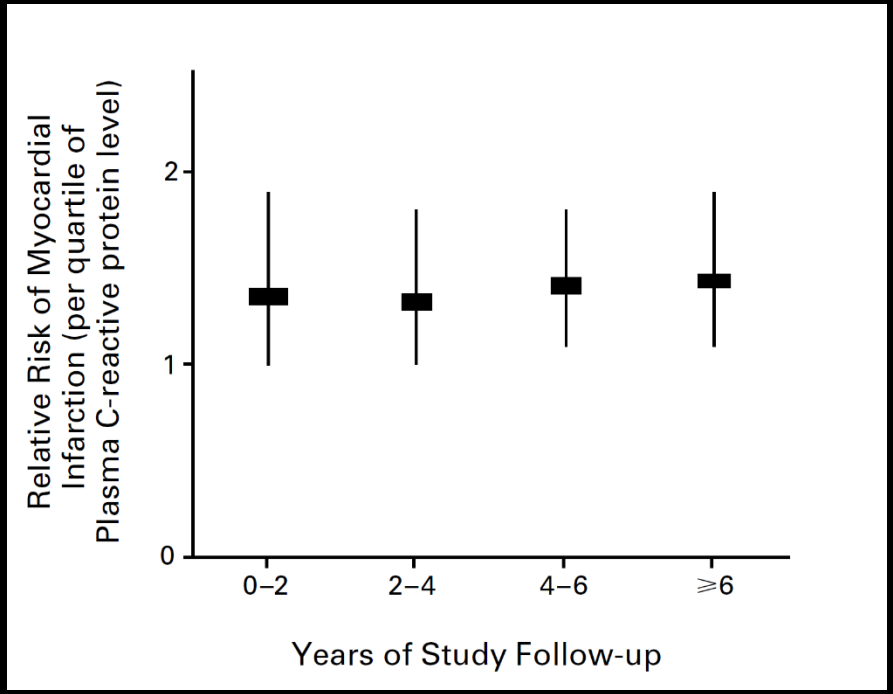
The New England
Journal of Medicine

VOLUME 336 APRIL 3, 1997 NUMBER 14

INFLAMMATION, ASPIRIN, AND THE RISK OF CARDIOVASCULAR DISEASE IN APPARENTLY HEALTHY MEN

PAUL M. RIDKER, M.D., MARY CUSHMAN, M.D., MEIR J. STAMPFER, M.D., RUSSELL P. TRACY, PH.D., AND CHARLES H. HENNEKENS, M.D.





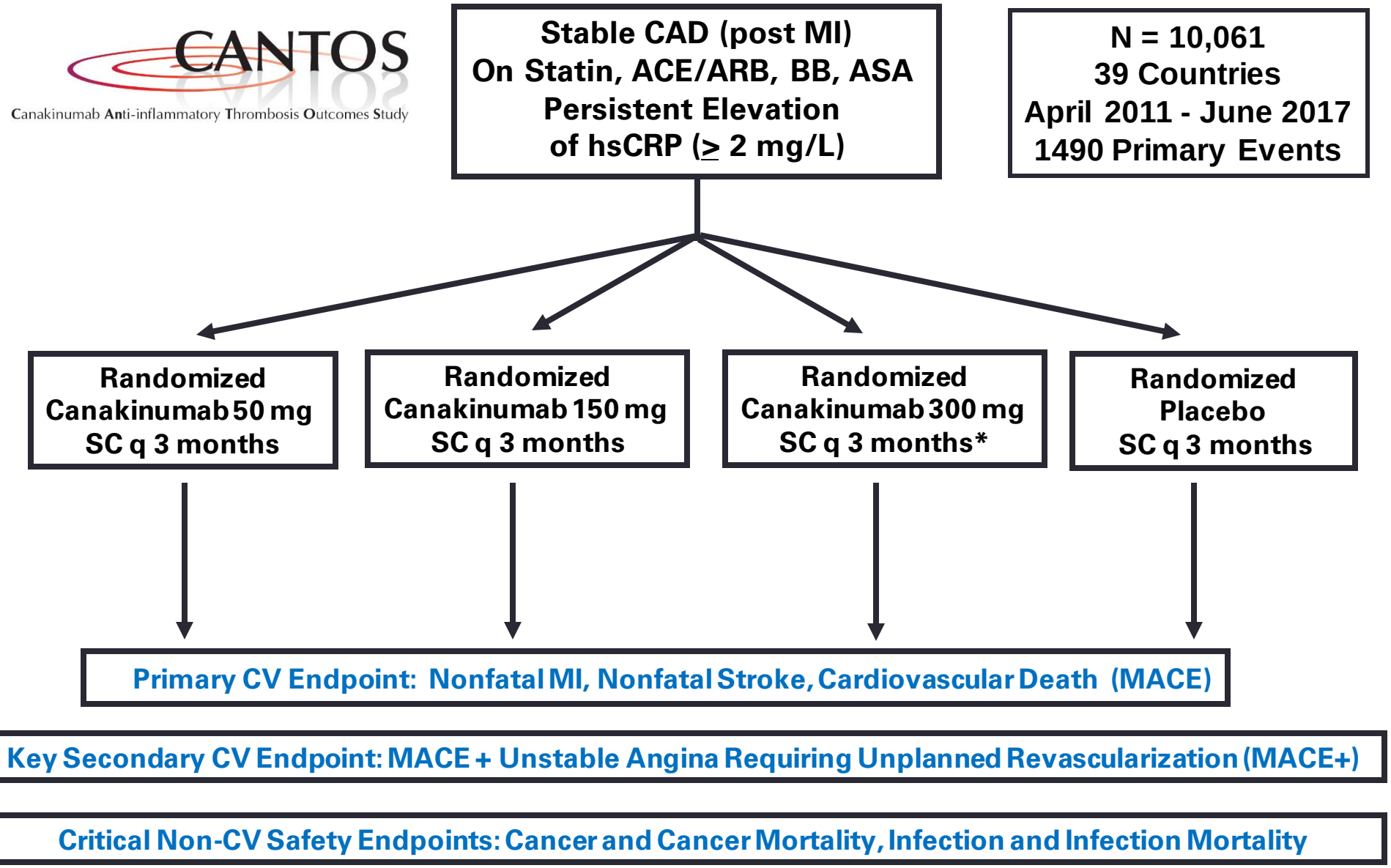
Ridker et al NEJM 1997; 336:973-9

Canakinumab (Novartis)

- **high-affinity human monoclonal anti-human interleukin-1β (IL-1β) antibody currently indicated for the treatment of IL-1β driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)**
- **designed to bind to human IL-1β and functionally neutralize the bioactivity of this pro-inflammatory cytokine**
- **long half-life (4-8 weeks) with CRP and IL-6 reduction for up to 3 months**

Ridker ESC 2017

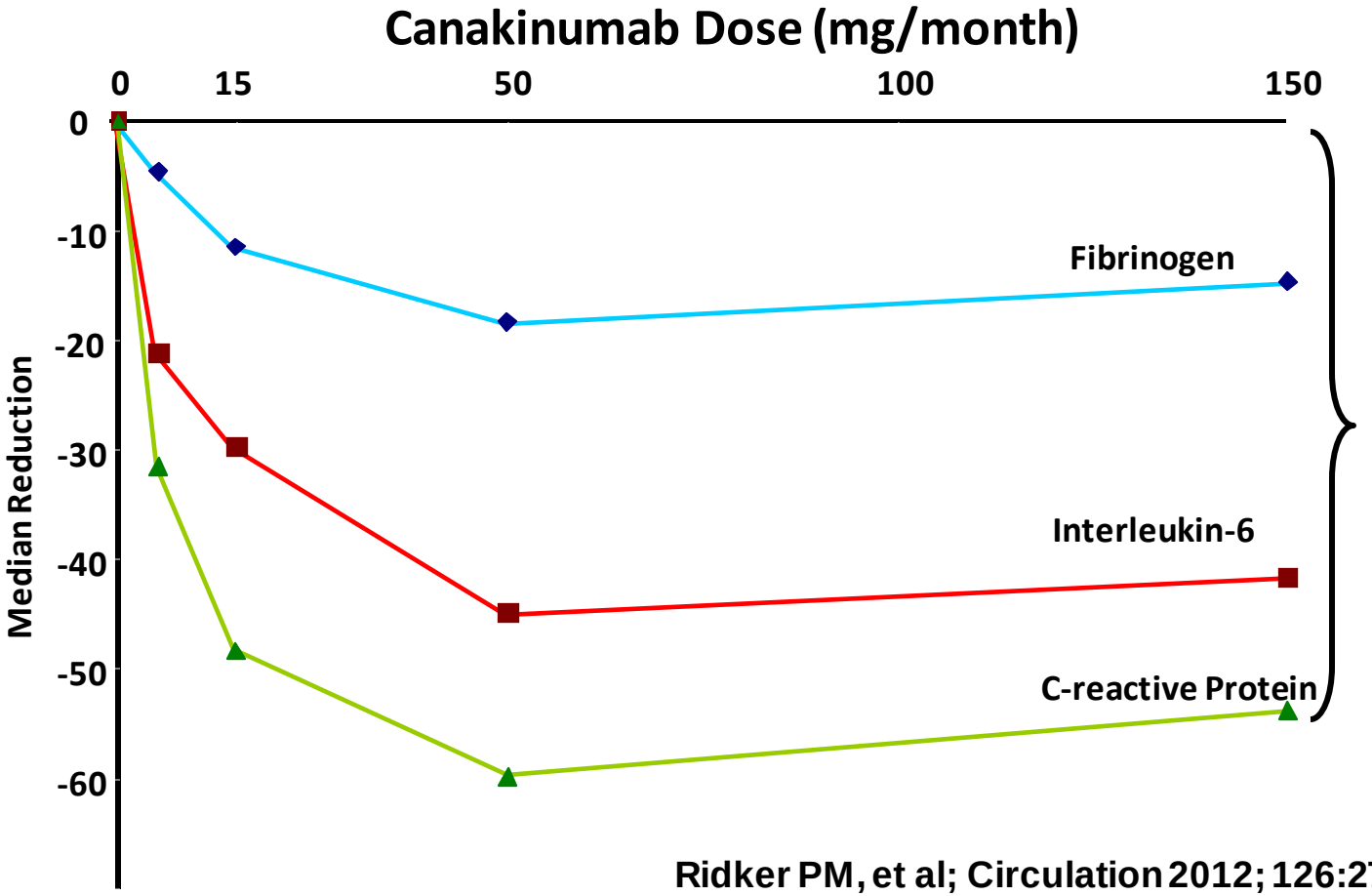
Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)



Ridker NEJM 2017

Effects of Interleukin-1β Inhibition With Canakinumab on Hemoglobin A1c, Lipids, C-Reactive Protein, Interleukin-6, and Fibrinogen

A Phase IIb Randomized, Placebo-Controlled Trial



Ridker PM, et al; Circulation 2012; 126:2739-2748

CANTOS monitoring plan

- **CANTOS designed to compare each active dose (50, 150, or 300 mg quarterly) to placebo**
- **Alpha allocated (40%, 40%, 20%) to the separate tests of the (50, 150, 300 mg) doses**
- **Secondary endpoints only tested if the primary hypothesis was rejected for that dose**
- **Futility analyses scheduled upon accrual of 25, 50 and 75% of targeted 1,400 primary endpoints**
- **Efficacy analyses upon accrual of 50 and 75% of targeted endpoints**
- **Alpha of .002 and .008 spent at interim analyses, so that .0490 remained for final analysis**

CANTOS timeline

- **First randomization: April 28, 2011**
- **Last (of 10,061) randomization: March 3, 2014**
- **Interim futility analysis: June 30, 2014**
- **Interim efficacy/futility analyses: June 26, 2015 and July 21, 2016**
- **Last patient visit: June 2017**
- **Trial results:**
- **Primary endpoint: PM Ridker et al; NEJM 2017 Cancer findings: PM Ridker et al; Lancet 2017**
- **Mediation through achieved hsCRP levels: PM Ridker et al; Lancet 2018**

Ridker ESC 2017

CANTOS - Baseline Clinical Characteristics

		Canakinumab SC q 3 months		
Characteristic	Placebo (N=3347)	50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)
Age (years)	61.1	61.1	61.2	61.1
Female (%)	25.9	24.9	25.2	26.8
Current smoker (%)	22.9	24.5	23.4	23.7
Diabetes (%)	39.9	39.4	41.8	39.2
Lipid lowering therapy (%)	93.7	94.0	92.7	93.5
Renin-angiotensin inhibitors (%)	79.8	79.3	79.8	79.6
Prior Revascularization (%)	79.6	80.9	82.2	80.7
LDL cholesterol (mg/dL)	82.8	81.2	82.4	83.5
HDL cholesterol (mg/dL)	44.5	43.7	43.7	44.0
Triglycerides (mg/dL)	139	139	139	138
hsCRP (mg/L)	4.1	4.1	4.2	4.1

Ridker NEJM 2017

CANTOS first futility analysis (>25% endpoints)

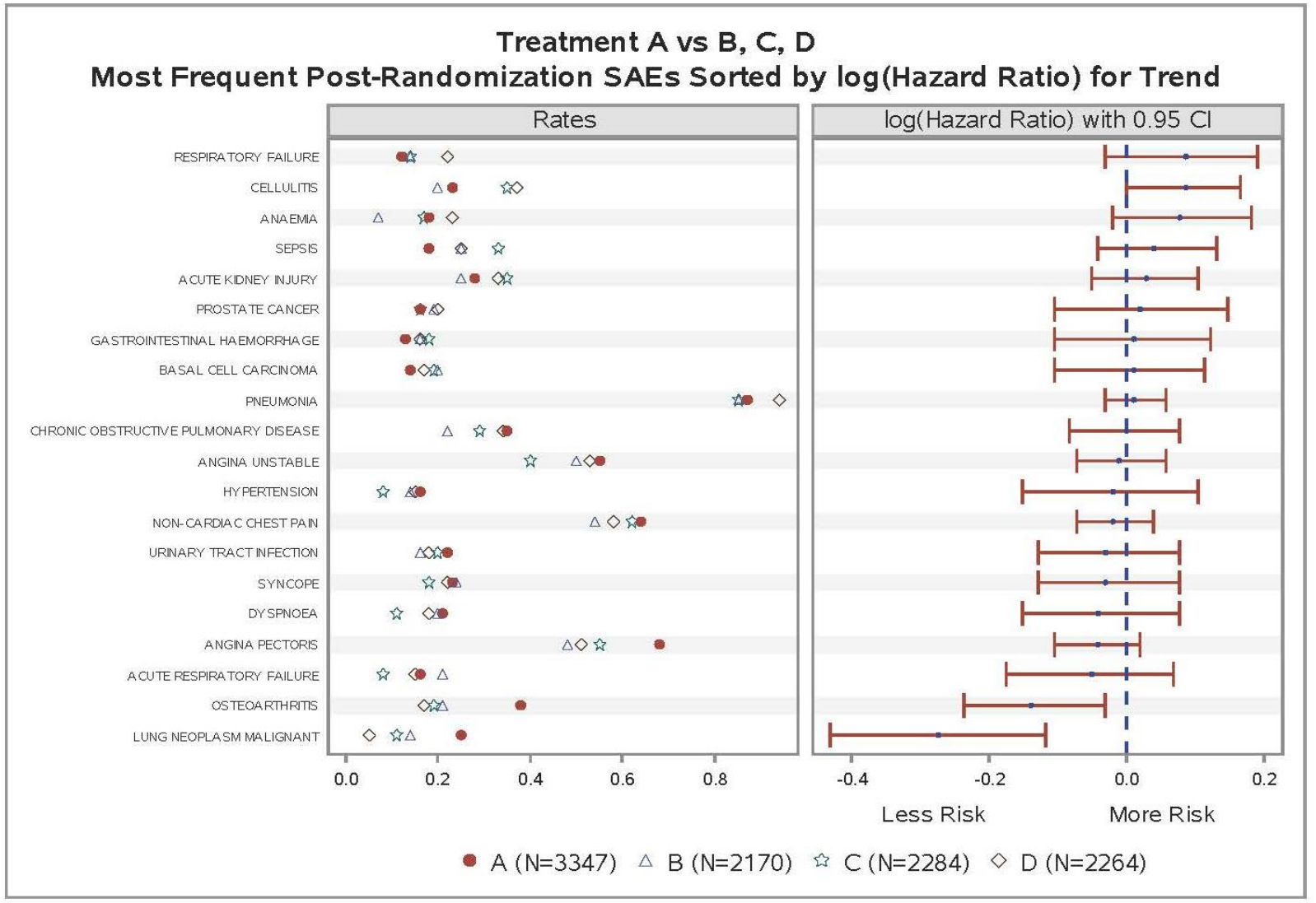
395 confirmed endpoints (28.2% of target) in 6/30/2014 DSMB report						
		Canakinumab SC every 4 months				
	Placebo	50 mg	150 mg	300 mg	Active vs plac.	P_{trend}
Event	N (rate*)	N (rate)	N (rate)	N (rate)	HR (95% CI)	
MACE	140 (33.2)	64 (25.2)	96 (32.3)	95 (31.9)	0.91 (.74-1.1)	.92
MACE+	163 (38.9)	71 (28.1)	106 (35.8)	108 (36.5)	0.87 (.72-1.1)	.78
Death	63 (15.1)	30 (11.6)	48 (15.8)	58 (19.0)	1.04 (.78-1.4)	.09
CV death	40 (9.3)	21 (8.1)	35 (11.5)	39 (12.8)	1.19 (.82-1.7)	.08
Cancer death	16 (3.7)	7 (2.7)	5 (1.6)	2 (0.7)	0.43 (.2-0.88)	.004
Sepsis/infect. death	1 (0.2)	0	5 (1.6)	9 (3.0)	7.1 (.94-54.3)	.001
Respiratory death	4 (0.9)	1 (0.4)	2 (0.7)	6 (2.0)	1.13 (.35-3.7)	.11

*Rates are per 1,000 person years; hazard ratios compare pooled active groups vs placebo; trend test uses scores 0, 1, 3, 6 for placebo, 50, 150, 300 mg, respectively

Cancer concerns in monitoring CANTOS

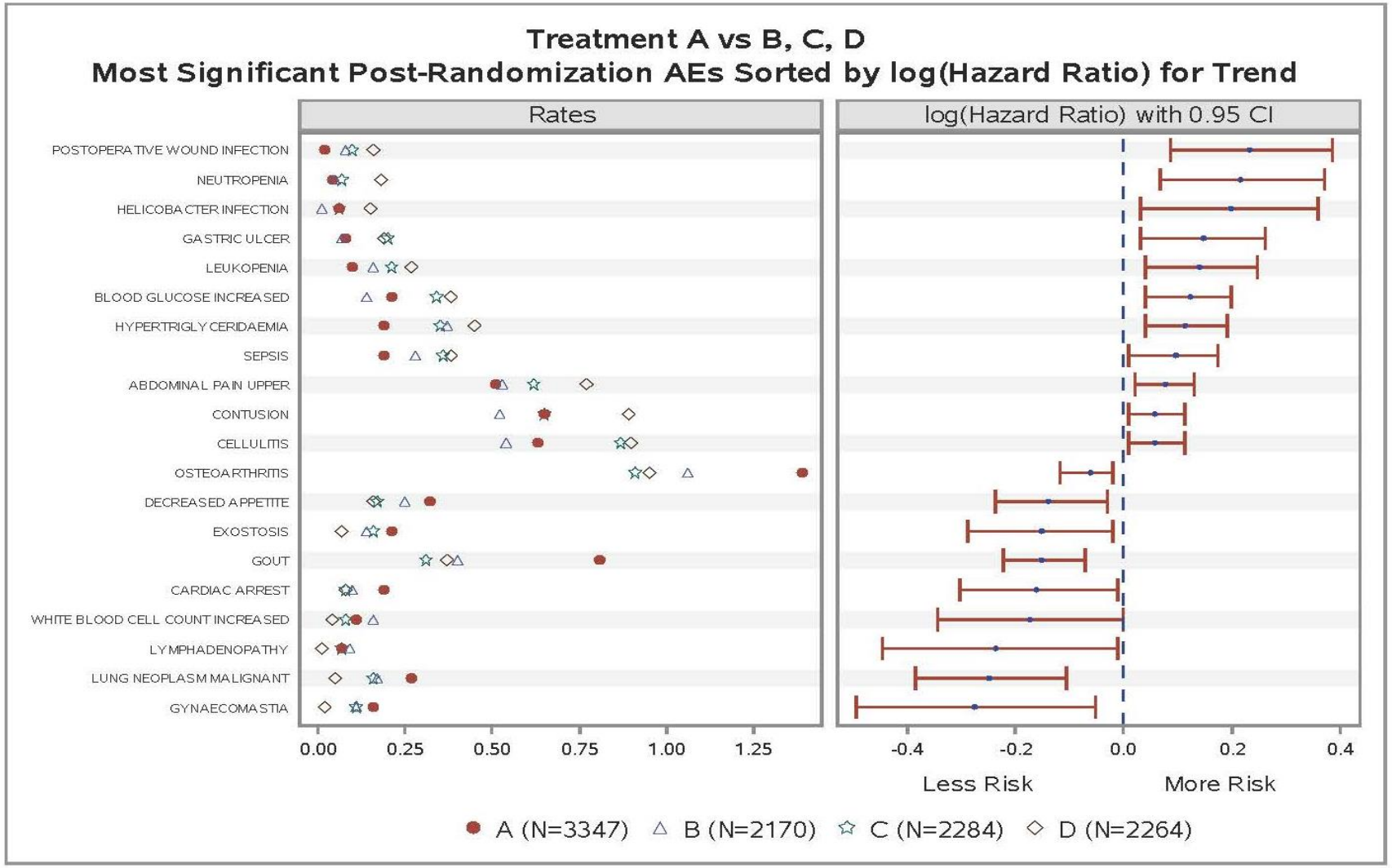
- The CANTOS protocol was mute on cancer protection or risks
- The DSMB had no experience with canakinumab
- Some concern was expressed that an anti-inflammatory drug might also be immunosuppressive
- International regulatory agencies requested careful trial monitoring for cancer risk

CANTOS final DSMB report SAEs



Final CANTOS DSMB report: 3/31/2017

CANTOS final DSMB report AEs



Final CANTOS DSMB report: 3/31/2017

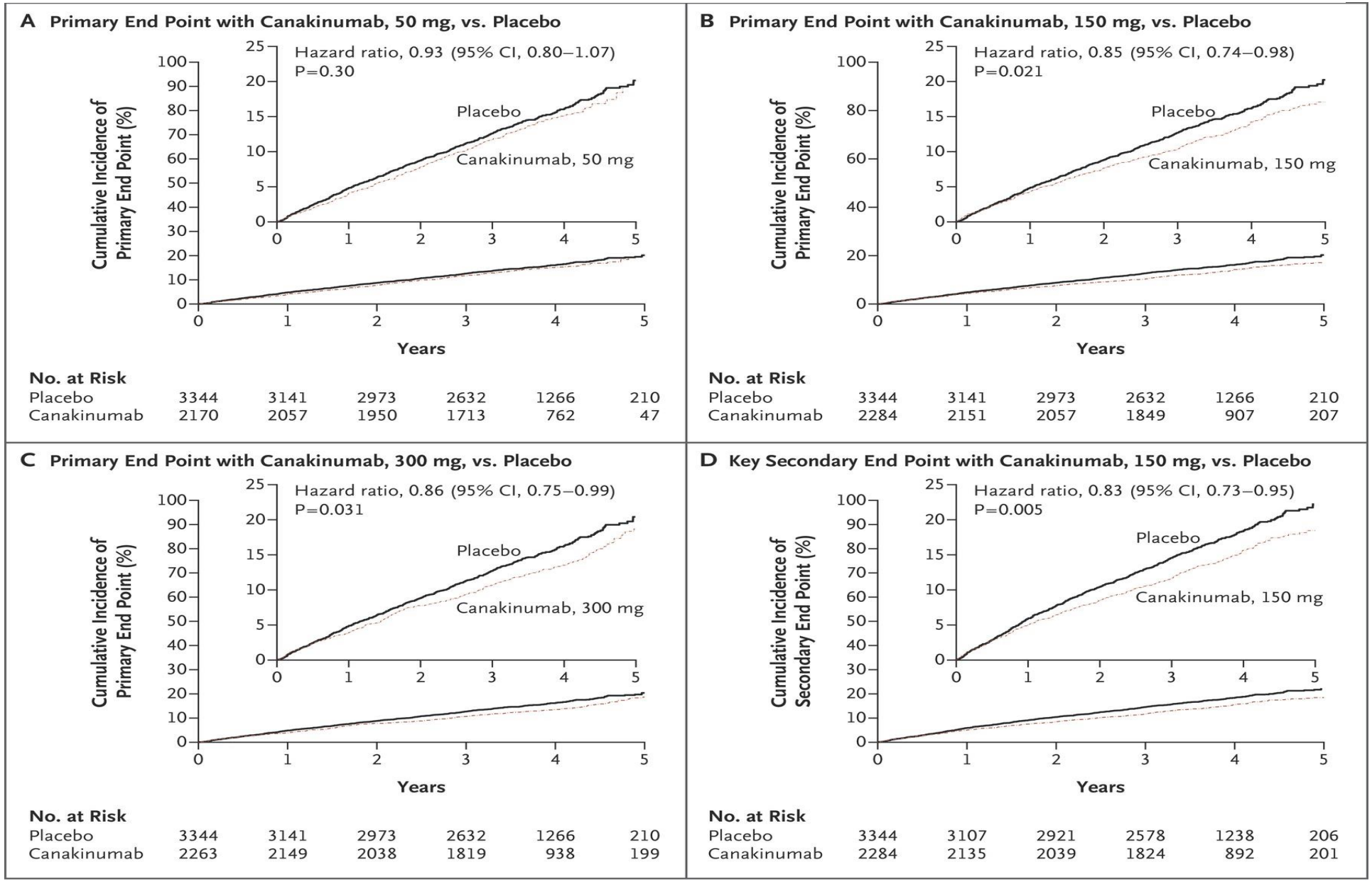
CANTOS: Primary Clinical Outcome Effects on MACE and MACE +

		Canakinumab SC q 3 months			
	Placebo (N=3347)	50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)	P-trend
Primary Endpoint					
IR (per 100 person years)	4.5	4.1	3.9	3.9	0.020
HR	1.0	0.93	0.85	0.86	
95%CI	(referent)	0.80-1.07	0.74-0.98	0.75-0.99	
P	(referent)	0.30	0.021*	0.031	
Secondary Endpoint					
IR (per 100 person years)	5.1	4.6	4.3	4.3	0.003
HR	1.00	0.90	0.83	0.83	
95%CI	(referent)	0.78-1.03	0.73-0.95	0.72-0.94	
P	(referent)	0.11	0.005*	0.004	

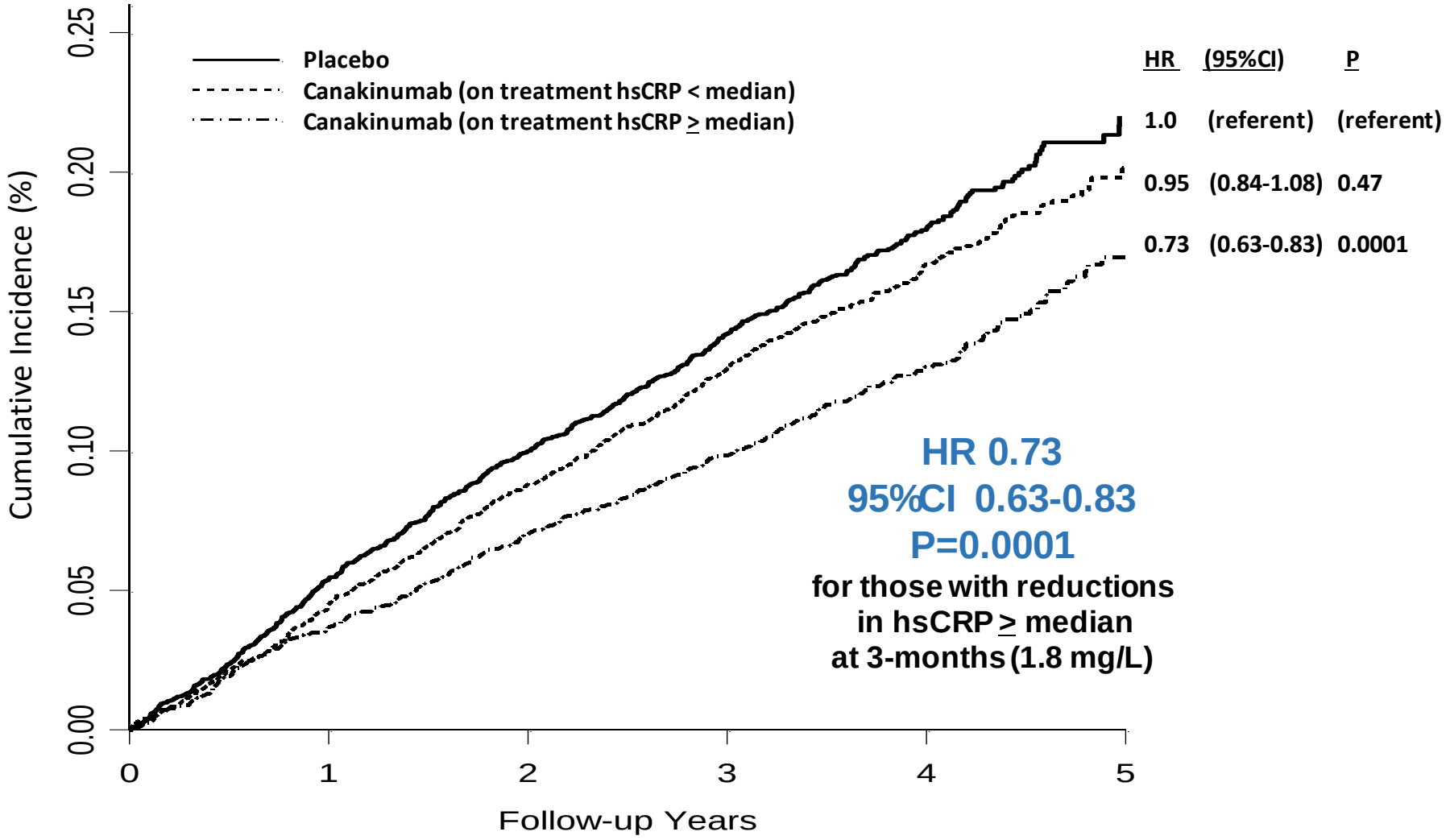
*Statistically significant, adjusted for multiplicity, in accordance with the pre-specified closed-testing procedures

Ridker NEJM 2017

CANTOS: Primary Cardiovascular Endpoint (MACE)



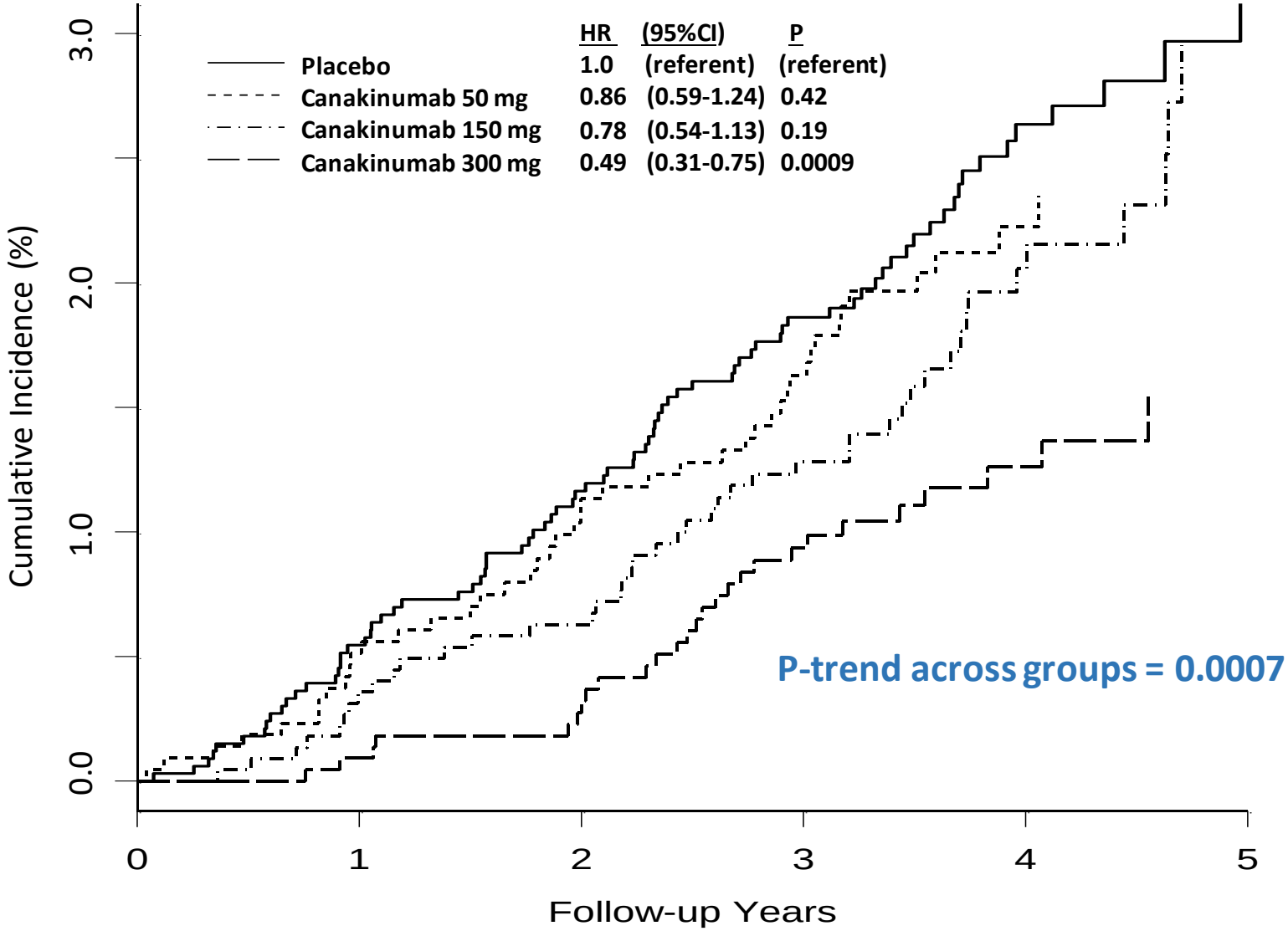
CANTOS: Greater Risk Reduction Among Those With Greater hsCRP Reduction (MACE+)



Ridker Lancet 2018

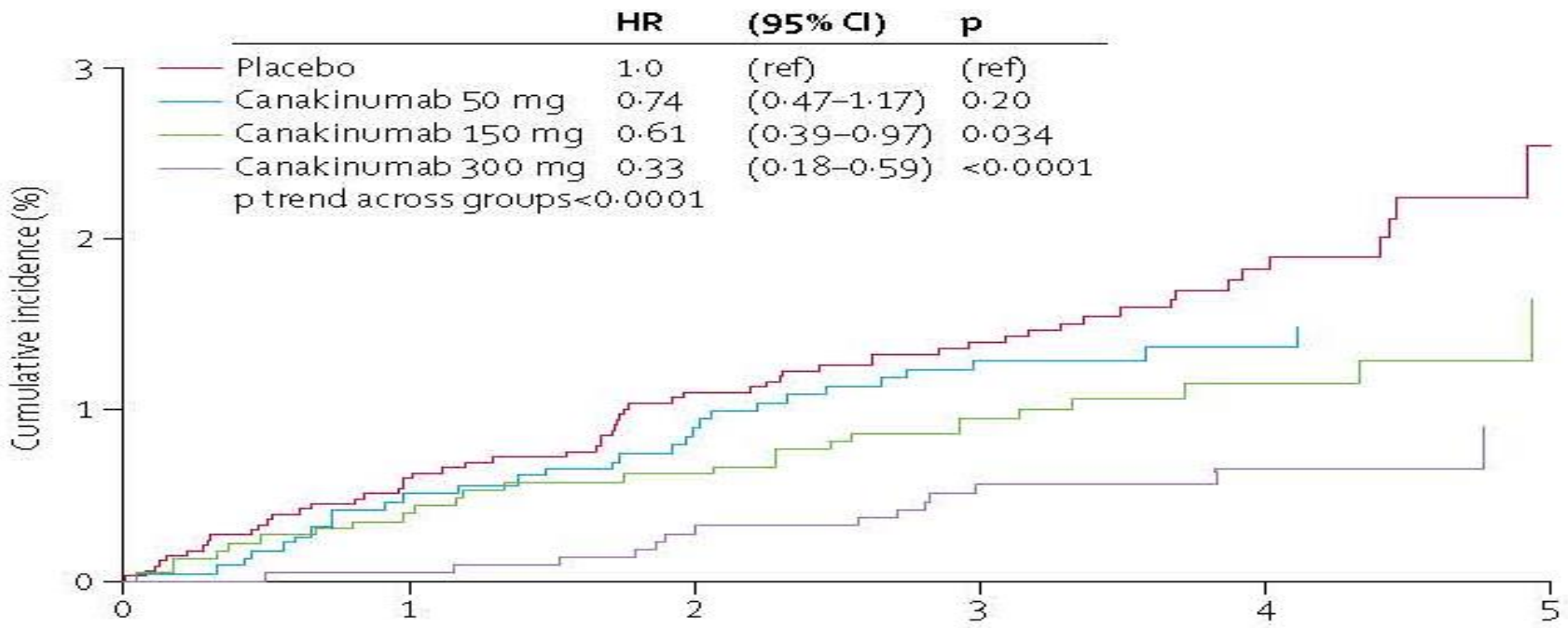
CANTOS: Additional Non-Cardiovascular Clinical Benefits

Cancer Mortality



Ridker Lancet 2017

Cumulative incidence of lung cancer by treatment in CANTOS



Number at risk

Placebo	3344	3241	3142	2835	1401	251
Canakinumab 50 mg	2170	2110	2047	1825	827	53
Canakinumab 150 mg	2284	2207	2148	1950	982	233
Canakinumab 300 mg	2263	2201	2128	1928	1002	222

PM Ridker et al. Lancet 2017

RCT as paradigm for causal efficacy, safety, and comparative effectiveness research

- Observational CER studies should parallel randomized trials, with background information used to focus on similar, but alternatively treated patients before outcome evaluation*
- Valid causal inference requires clear articulation of the treatment assignment mechanism and that subjects have non-zero probability of each treatment (positivity assumption)
- Double-blind design equalizes expectations of participants and their evaluators, visit frequency, and assessment at visits
- When placebo controls are warranted, these subjects are fully evaluated and willing to initiate therapy at baseline

*DB Rubin. The design vs the analysis of observational studies for causal effects: parallels with the design of randomized trials. Stat Med 2007

JSPE16 & ACPE5
October 31, 2010

Healthy starters, sick stoppers, and the value of new user designs with active referents in pharmacoepidemiology

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Outline

Discrepant findings for preventive therapies in observational vs randomized studies

Parallel selection and survival bias concerns arise in studies of preventive drugs and healthy workers

Potential selection occurs throughout follow-up: healthy starters and sick stoppers

Optimal time scales in pharmacoepidemiology

New user designs and the value of active referent groups

Distinguish placebo controls and non-user referents

- Placebo controls are often natural, appropriate referents for evaluation of safety and efficacy in randomized trials
- Non-user referents in observational studies differ in important ways:
- Not clearly eligible or willing to initiate therapy
- No clear date of initiation
- No comparable assessment of treatment duration
- Questionable comparability in covariate and perhaps outcome assessment

Three paradoxes with non-user referents

Among hospitalized, older people enrolled in state-sponsored drug benefits programs, diabetes diagnosis and treatment were associated with enhanced survival vs no dx or rx

Across 20 commonly used classes of drugs, users vs non-users of several classes had markedly reduced death rates, of a magnitude inconsistent with randomized evidence

Focused analysis (e.g. propensity score matching) did little to reduce the magnitude of the incredible reduction in the hazard of death in users vs non-users of lipid-lowering drugs

Selective recording and treatment of DM

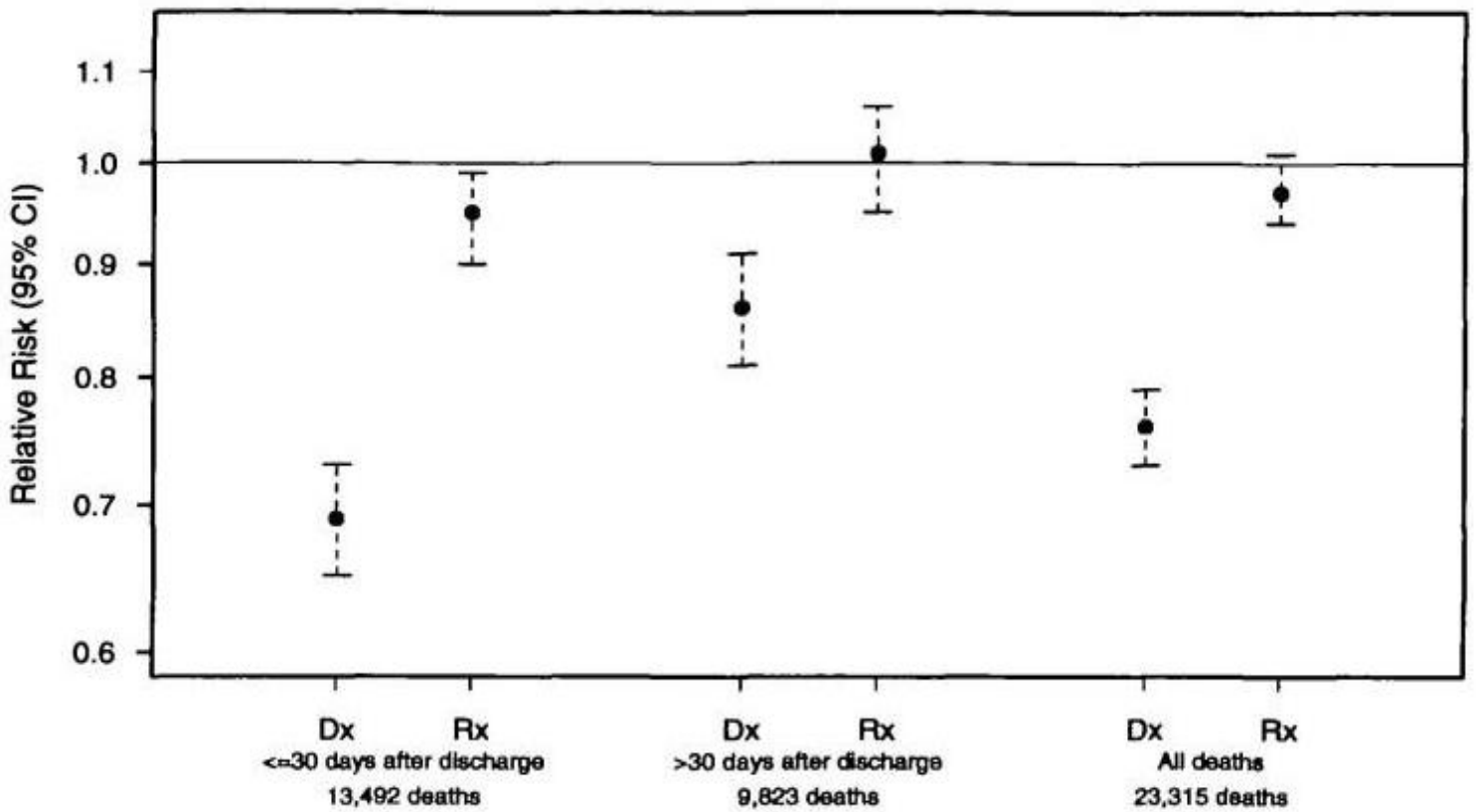
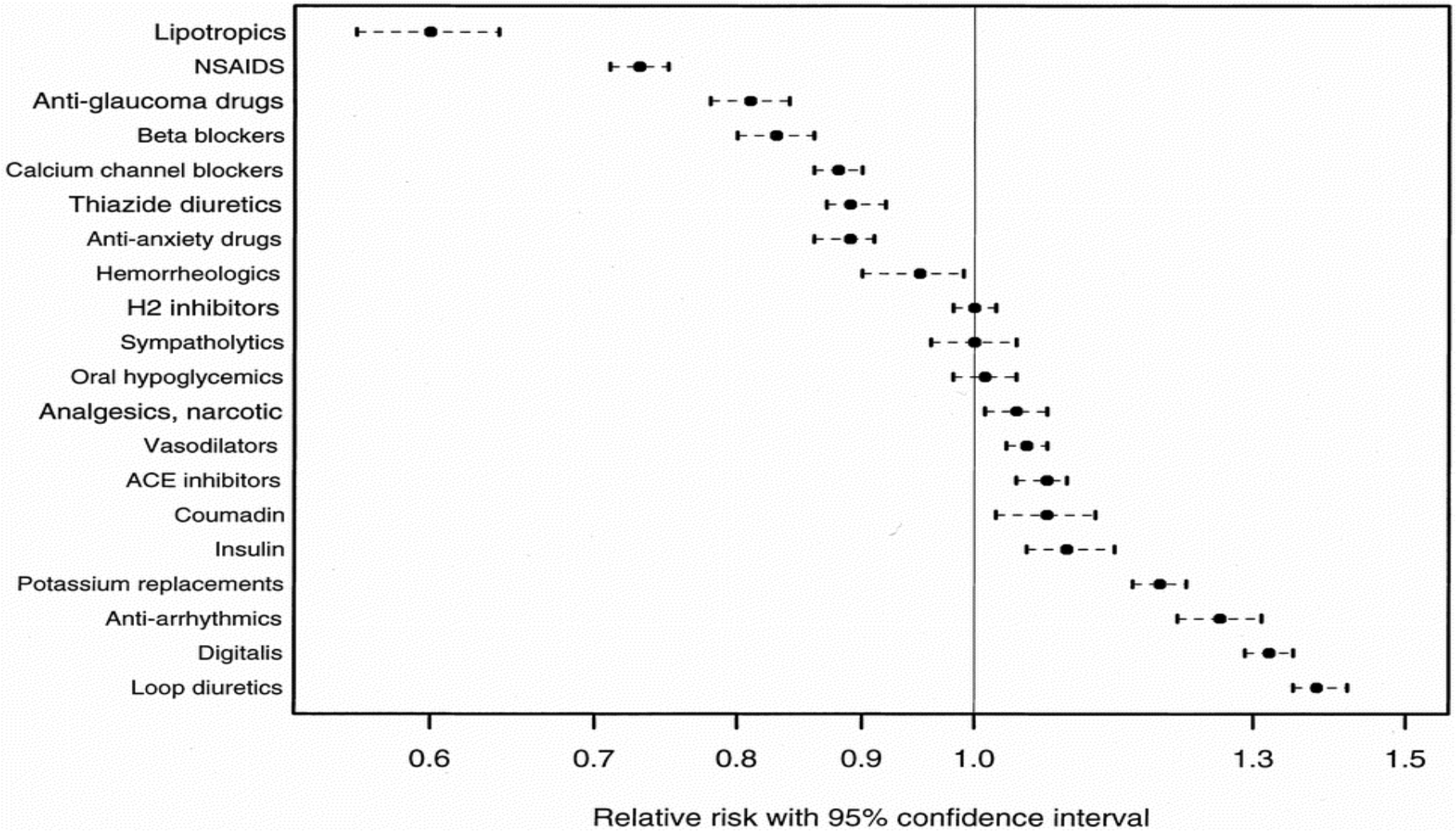


FIGURE 1. Relative risk of death associated with a diagnosis or treatment of diabetes among 81,700 elderly residents of New Jersey, 1989–1991, adjusted for age, sex, race, nursing home residence, reimbursement program, number of different drugs, and the modified Charlson index. Dx, incidence rate ratio and 95% confidence interval comparing those with a diagnosis of diabetes with those without this diagnosis; Rx, incidence rate ratio and 95% confidence interval comparing those using hypoglycemic drugs with those not using these drugs.

RJ Glynn et al. Agreement between drug treatment data and a discharge diagnosis of diabetes mellitus in the elderly. Am J Epidemiol 1999

LI Iezzoni et al. Comorbidities, complications, and coding bias. Does the number of diagnosis codes matter in predicting in-hospital mortality? JAMA 1992

Observational data on mortality with non-user referent



Glynn et al. Paradoxical relations of drug treatment with mortality in older persons. Epidemiology 2001

Observational data on mortality with non-user referent

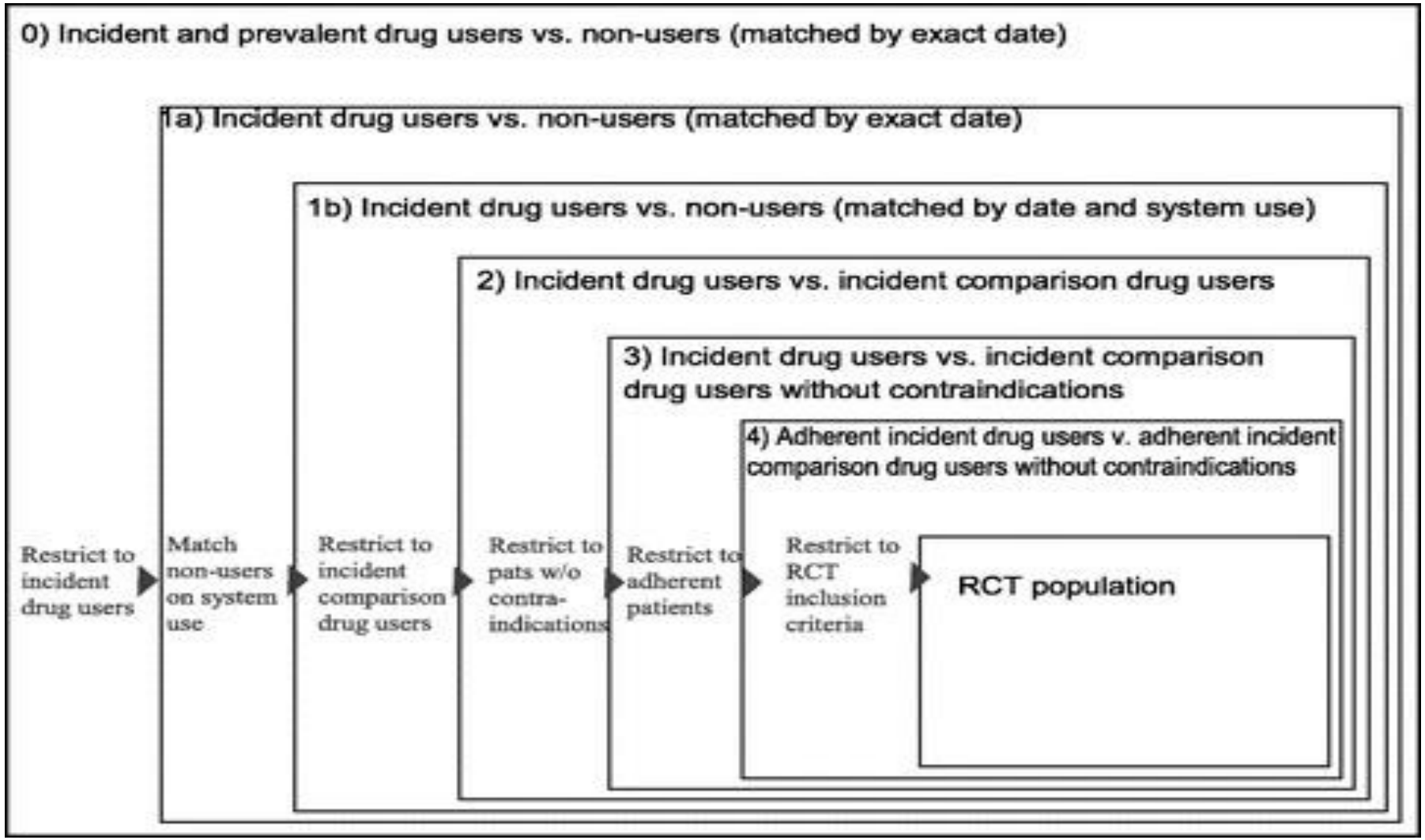
Use of lipid-lowering drugs and the hazard of death in the community sample

	Hazard ratio	95% CI	Change in hazard ratio from base estimate
Unmatched design: proportional hazards analysis with 17,524 deaths among 106,838 beneficiaries			
Adjusted for age and sex	0.44	0.40–0.49	Base estimate
Further adjusted for demographics and comorbidity indices	0.49	0.44–0.54	11%
Further adjusted for propensity quintile	0.54	0.48–0.60	23%
Further adjusted for use of other drugs and comorbidity	0.61	0.55–0.68	40%
Matched design: Proportional hazards analysis with 966 deaths in 6,466 users of lipotropics and propensity-matched nonusers			
Adjusted for age and sex	0.60	0.53–0.69	
Further adjusted for use of other drugs and comorbidity	0.60	0.52–0.68	
Based on McNemar's matched analysis			

Abbreviations: CI, confidence interval.

Glynn et al. Selective prescribing led to overestimation of the benefits of lipid lowering drugs. J Clin Epidemiol 2006

Design restrictions to enhance comparability



Schneeweiss et al. Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. Med Care 2007

Value of new user designs*

Effects of a drug may vary by duration of use, e.g. for hormone therapy or coxibs

RCTs control precisely for time on therapy

Confounders affecting initiation may differ from those affecting persistence

With prevalent users, need to consider propensity to start and propensity to persist: these may differ

Stoppers of preventive drugs are often sick (healthy starter/sick stopper bias)

Risk factors may be affected by use of study drugs

May not be possible to control for these factors on the causal pathway if measured long after initiation

*WA Ray. Am J Epidemiol 2003; 158: 915-920

Emulation of RCTs with placebo controls

- Results of the ongoing RCT-DUPLICATE program*
- “Overall, agreement between RCT and RWE estimates was good for all antidiabetic trials except those that compared a DPP-4 inhibitor with placebo.”
- Emulations of these trials used second-generation sulfonylureas as a proxy for placebo. Active comparators can decrease confounding if they are used interchangeably, but are not a perfect emulation of a placebo add-on group.
- If patients with unmeasured frailty and lower socioeconomic status more often used the older and less expensive sulfonylureas, then bias toward a protective effect for DPP-4 inhibitors would be expected, as was found in the emulations

*Franklin JM, Patorno E, Desai RJ, et al. Emulating Randomized Clinical Trials With Nonrandomized Real-World Evidence Studies: First Results From the RCT DUPLICATE Initiative. Circulation 2021; 143(10):1002-1013.

Observations in trials to elucidate mechanisms: mediation of the cancer effects in CANTOS by inflammatory markers

1. Can we illuminate the pathway whereby canakinumab appears to reduce rates of cancer death and incident lung cancer in the CANTOS trial?

2. A previous mediation analysis examined the role of inflammation reduction on reduced rates of anemia in this trial

*Vallurupalli M, MacFadyen JG, Glynn RJ, et al. Effects of Interleukin-1β Inhibition on Incident Anemia: Exploratory Analyses From a Randomized Trial. Ann Intern Med. 2020; 172(8):523-532.

Rationale for mediation analysis in RCTs

- Mediation analysis in an RCT aims to elucidate the mechanism whereby the assigned treatment achieves its effect
- Specifically aims to partition the treatment effect into its indirect (mediated) effect through the mediator and its residual direct effect
- Can identify treatment responders at an early time point
- And point to the best targets for refined future interventions

Challenges to causal mediation analysis in RCTs

- Variables measured after randomization may be affected by measured and unmeasured baseline factors
- Treatment nonadherence can affect both mediator and outcome
- Early drop-outs and those with missed visits have missing mediator levels
- Likely sensitivity of estimates to mediator measurement and assumed forms of the treatment-mediator and mediator-outcome models
- Many trialists are skeptical of control for post-randomization variables
- Subgroups defined after randomization by a variable influenced by treatment are called “improper” and such subgroup analyses can mislead*
- Related to skepticism of surrogate markers†

*S Yusuf et al. JAMA 1991; †RL Prentice Stat Med 1989; TR Fleming and DL DeMets Ann Intern Med 1996

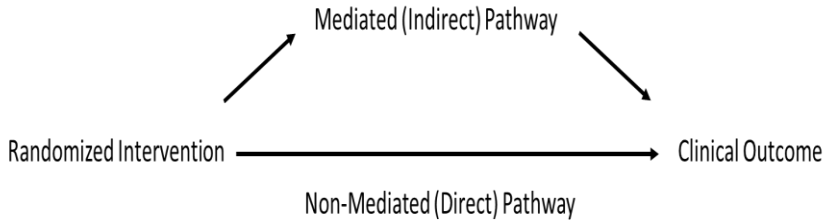
Assumptions required for causal mediation analysis

1. No unmeasured treatment-outcome confounders
2. No unmeasured treatment-mediator confounders
3. No unmeasured mediator-outcome confounders
4. No mediator-outcome confounder that is also affected by treatment*

*TJ Vanderweele Annu Rev Public Health 2016

Graphical depiction of causal mediation analysis in a trial setting

A



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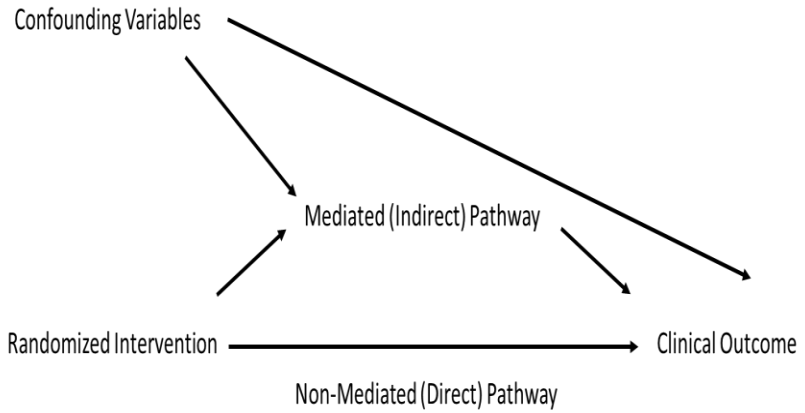

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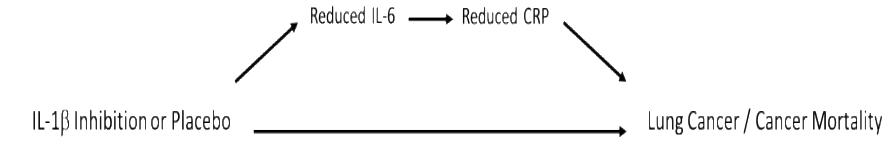

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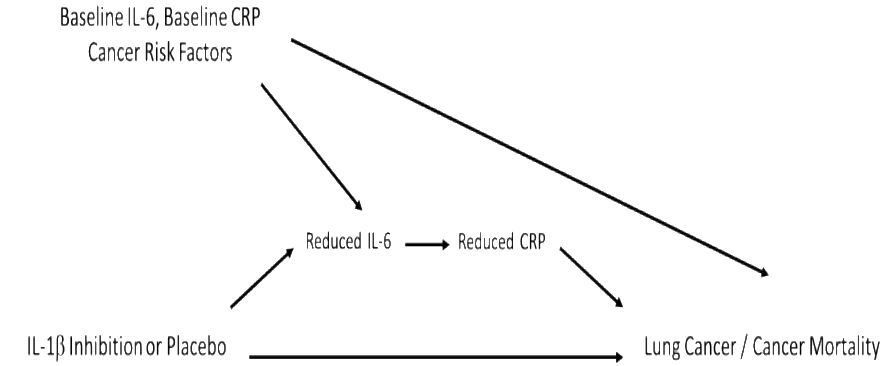

Design of mediation analyses in CANTOS

- Population: the 10,061 randomized subjects in CANTOS
- Outcomes (2 correlated cancer events): time to incident lung cancer (n=129) and fatal cancer (n=196)
- Exposure: active canakinumab (pooling 3 dose groups) vs placebo
- Mediators (Six considered): 1) hsCRP < 2 mg/L; or 2) ≤ 1.8 mg/L at 3 months; or 3) 100*(log(hsCRP at 3 months) – log(hsCRP at baseline)); or 4) log(hsCRP) at 3 months; or 5) IL6 <1.65 ng/L at 3 months; or 6) 100*(log(IL6 at 3 months)-log(IL6 at baseline))
- Confounders (assumed the same for both prediction of mediator and control of mediator-outcome association): age, gender, baseline log(hsCRP) or log(IL6), current and former smoking, BMI, waist circumference, height, exercise, alcohol consumption, DM, COPD, HF, Afib, PAD, statin, aspirin, other anticoagulants, EGFR, HgbA1c, and Albumin.
- Also consider exposure by mediator interaction in prediction of time to outcomes

Mediation definitions

- Controlled direct effect: $Y_{a,m} - Y_{a^*,m}$
- This effect is the contrast between the counterfactual outcome if the individual were exposed at A = a and the counterfactual outcome if the same individual were exposed at A = a*, with the mediator set to a fixed level M=m.
- Natural direct effect: $Y_{a,M(a^*)} - Y_{a^*,M(a^*)}$
- This effect is the contrast between the counterfactual outcome if the individual were exposed at A = a and the counterfactual outcome if the same individual were exposed at A = a*, with the mediator assuming whatever value it would have taken at the reference value of the exposure A = a*.

Richiardi L, Rellocco R, Zugna D. Int J Epidemiol 2013; 42: 1511-1519.

Mediation definitions (cont.)

- Natural indirect effect: $Y_{a,M(a)} - Y_{a,M(a^*)}$
- This effect is the contrast, having set the exposure at level A = a, between the counterfactual outcome if the mediator assumed whatever value it would have taken at a value of the exposure A = a and the counterfactual outcome if the mediator assumed whatever value it would have taken at a reference value of the exposure A = a*.

Richiardi L, Rellocco R, Zugna D. Int J Epidemiol 2013; 42: 1511-1519.

Estimation of confounder adjusted mediation effects

- Use the SAS macro of Valeri and VanderWeele
- Fit a model for the expected value of the mediator, given exposure and confounders

$$E(M|A,C) = \beta_0 + \beta_1 a + \beta'_2 c$$

- We use linear regression for continuous mediators, and logistic regression for a dichotomous mediator
- Fit a proportional hazards model for time to the cancer outcome, given exposure, mediator, and confounders

$$\lambda_T(t|a,m,c) = \lambda_T(t|0,0,0)\exp(\gamma_1 a + \gamma_2 m + \gamma_3 am + \gamma'_4 c)$$

- Make a rare disease assumption; with more common outcomes we would use an accelerated failure time model

L Valeri & T VanderWeele; Epidemiology 2015

Estimation of mediation effects (continued)

- Assuming no unmeasured confounding and correctly specified models, obtain estimates on the hazard ratio scale
- Estimate the controlled direct effect by:

$$\lambda_{Tam}(t|c)/\lambda_{Ta*m}(t|c) = \exp\{(\gamma_1+\gamma_3 m)(a-a*)\}$$

- Estimate the natural direct effect by:

$$\lambda_{TaMa*}(t|c)/\lambda_{Ta*Ma*}(t|c) \approx \exp[\{\gamma_1+\gamma_3(\beta_0+\beta_1 a^*+\beta'_2 c+\gamma_2\sigma^2)\}(a-a^*) + 0.5\gamma^2_3\sigma^2(a^2-a^{*2})],$$

where σ^2 is the mediation regression model error variance

- Estimate the natural indirect effect by:

$$\lambda_{TaMa}(t|c)/\lambda_{TaMa*}(t|c) \approx \exp\{(\gamma_2\beta_1+\gamma_3\beta_1 a)(a-a^*)\}$$

Linear regression predicting log_CRP change

- **Parameter Estimates (continued next slide)**

Variable	Label	Estimate	Std. Err.	t Value	Pr > |t|
Intercept	Intercept	74.78735	28.22355	2.65	0.0081
actpla	Active(1) vs Placebo(0)	-65.49169	1.87899	-34.85	<.0001
lncrpb	Log baseline hsCRP	-50.16479	1.28824	-38.94	<.0001
AAGE	Age (years) at randomization	0.09212	0.10652	0.86	0.3871
Male		-0.27507	2.61085	-0.11	0.9161
DM	Baseline diabetes	1.11972	2.42862	0.46	0.6448
bmi	Body Mass Index at Baseline	0.85179	0.22283	3.82	0.0001
HF	History of Heart Failure	1.92699	2.23962	0.86	0.3896
COPD	COPD at Baseline	9.33407	3.19073	2.93	0.0034
csmok	Current cigarette smoker	18.67166	2.63057	7.10	<.0001
psmok	Past cigarette smoker	3.39722	2.17513	1.56	0.1184

Linear regression predicting log_CRP change (cont.)

- **Parameter Estimates (continued from previous slide)**

Variable	Label	Estimate	Std. Err.	t Value	Pr > |t|
exercdaily	Exercise daily at baseline	-2.07120	2.33159	-0.89	0.3744
ATRFIB	Atrial Fibrillation History	0.40013	3.36667	0.12	0.9054
alcGT1daily	Alcohol 2+ drinks/day	6.81327	4.54994	1.50	0.1343
Egfr	GFR est baseline SI units	-0.06207	0.04477	-1.39	0.1657
hba1c	HbA1c baseline SI units	2.33415	0.84947	2.75	0.0060
height_b	Height at baseline	-0.10192	0.12106	-0.84	0.3999
waist_b	Waist at baseline	0.22992	0.07810	2.94	0.0032
alb	Albumin baseline	-1.56445	0.32002	-4.89	<.0001
statin1	Statin at baseline	-5.30767	2.77631	-1.91	0.0559
ASPRN	Baseline Aspirin Therapy	-4.05577	3.63609	-1.12	0.2647
P2Y12FN	Baseline P2Y12 Therapy (N)	-0.15193	5.04314	-0.03	0.9760
pad_b	PAD at baseline	9.44478	3.18051	2.97	0.0030

Proportional hazards model predicting time to fatal cancer

- **Parameter Estimates (continued next slide)**

Parameter	Estimate	Std. Err.	Chi-square	P-value	Hazard ratio
actpla	-0.09359	0.16346	0.3278	0.5669	0.911
lncrp3mchg	0.00556	0.00125	19.8630	<.0001	1.006
int	-0.00103	0.00149	0.4811	0.4879	0.999
lncrpb	0.55412	0.10968	25.5251	<.0001	1.740
AAGE	0.06935	0.01011	47.0416	<.0001	1.072
Male	0.00648	0.23840	0.0007	0.9783	1.006
DM	0.38712	0.19726	3.8512	0.0497	1.473
BMI	-0.02474	0.01908	1.6827	0.1946	0.976
Heartfail	0.27763	0.17757	2.4447	0.1179	1.320
COPD	-0.30992	0.24653	1.5805	0.2087	0.734
Cursmok	1.28676	0.25146	26.1855	<.0001	3.621
Pstsmok	0.69595	0.22934	9.2087	0.0024	2.006

Proportional hazards model predicting fatal cancer (cont.)

- **Parameter Estimates**

Parameter	Estimate	Std. Err.	Chi-square	P-value	Hazard ratio
Exerdaily	-0.27671	0.22599	1.4992	0.2208	0.758
ATRFIBFN	-0.72322	0.29933	5.8377	0.0157	0.485
AlcGT1daily	-0.10313	0.39058	0.0697	0.7917	0.902
EGFR	-0.00464	0.00395	1.3851	0.2392	0.995
Hba1c	-0.01825	0.07145	0.0653	0.7984	0.982
Height	0.02498	0.01050	5.6619	0.0173	1.025
Waistcirc	0.00408	0.00627	0.4241	0.5149	1.004
Albumin	-0.02906	0.02795	1.0808	0.2985	0.971
Statin	0.36919	0.27148	1.8493	0.1739	1.447
Aspirin	-0.15340	0.29227	0.2755	0.5997	0.858
P2Y12 inhib.	-0.77405	0.35895	4.6501	0.0311	0.461
PAD	-0.03524	0.23330	0.0228	0.8800	0.965

Estimated causal effects: fatal cancer (continuous CRP mediator)

Mediator: 100*(log(hsCRP at 3 months) - log(hsCRP at baseline))

Effect	Estimate	p_value	95% CI	
cde	0.97076	0.86814	0.68381	1.37811
nde	0.89855	0.51844	0.64942	1.24324
nie	0.74332	0.00000	0.66280	0.83362
total effect	0.66791	0.00987	0.49155	0.90754
proportion mediated	0.69450			

Mediator: log(hsCRP at 3 months)

Effect	Estimate	p_value	95% CI	
cde	0.97124	0.87530	0.67460	1.39832
nde	0.91841	0.60592	0.66467	1.26902
nie	0.73996	0.00000	0.66083	0.82858
total effect	0.67959	0.01684	0.49509	0.93285
proportion mediated	0.74536			

Estimated causal effects: fatal cancer (categorical CRP mediator)

Mediator: Achieved hsCPR at 3 months <2 mg/L

Effect	Estimate	p_value	95% CI	
cde	0.73009	0.11916	0.49151	1.08447
nde	0.86140	0.36678	0.62301	1.19102
nie	0.78231	0.00002	0.69845	0.87625
total effect	0.67389	0.01143	0.49631	0.91500
proportion mediated	0.57501			

Mediator: Achieved hsCRP at 3 months ≤ 1.8 mg/L

Effect	Estimate	p_value	95% CI	
cde	0.72817	0.12955	0.48316	1.09740
nde	0.84733	0.31370	0.61388	1.16956
nie	0.79735	0.00004	0.71603	0.88792
total effect	0.67562	0.01195	0.49765	0.91725
proportion mediated	0.52935			

Summary

- We used mediation analysis to clarify pathways whereby IL-1β treatment with canakinumab might reduce rates of lung cancer and other fatal cancers
- Each of several measures of achieved level or change in hsCRP or IL-6 strongly mediated the effect of canakinumab, as reflected by substantial and significant estimates of indirect effects of treatment through these pathways
- While active canakinumab treatment was associated with reduced rates of both outcomes, direct effects of canakinumab were considerably weaker and non-significant upon control for the mediation effects
- For both outcomes, continuous measures of mediators showed stronger mediation effects, likely reflecting more precise control relative to dichotomous measures
- While measures of hsCRP showed stronger mediation relative to IL-6 for fatal cancer, the converse was true for lung cancer, although smaller sample size for IL-6 analyses limited such comparisons