New York City Cardiovascular Symposium December 10, 2017

Reducing Inflammation to Reduce Cardiovascular Risk: The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

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Inflammation, Atherothrombosis, and Vascular Prevention: Three Translational Questions 1997-2017

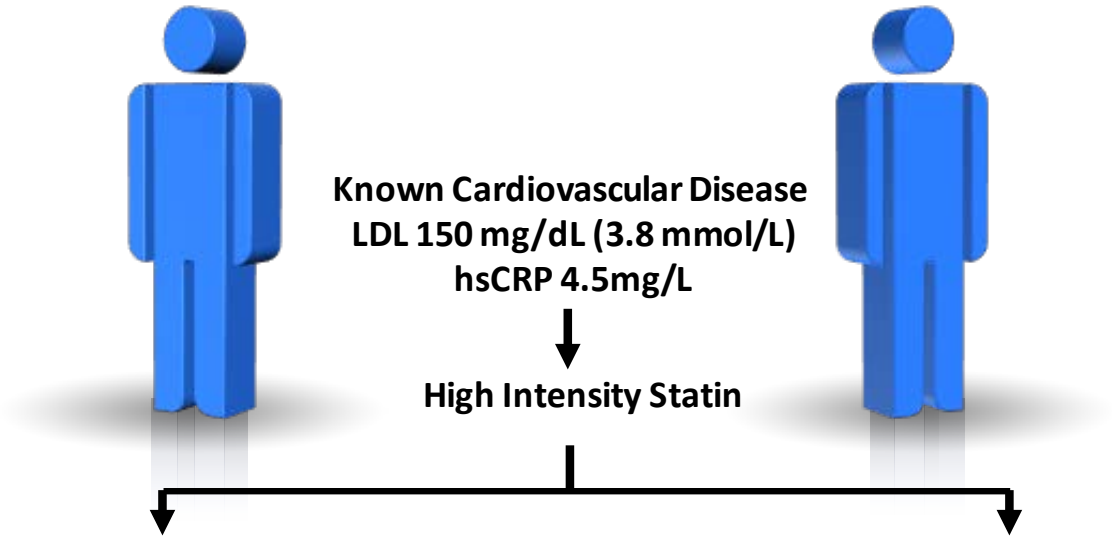
Is there evidence that individuals with elevated levels of inflammatory biomarkers are at high vascular risk even when other risk factors are acceptable?

Is there evidence that individuals identified at increased risk due to inflammation benefit from a therapy they otherwise would not have received?

Is there evidence that reducing inflammation per se will reduce vascular events?

Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Ridker PM. Eur Heart J 2016;37:1720-22



"Residual Cholesterol Risk"

LDL 110 mg/dL (2.8 mmol/L)
hsCRP 1.8 mg/L

↓

Additional
LDL Reduction

IMPROVE-IT : Ezetimibe 6% RRR
FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR

"Residual Inflammatory Risk"

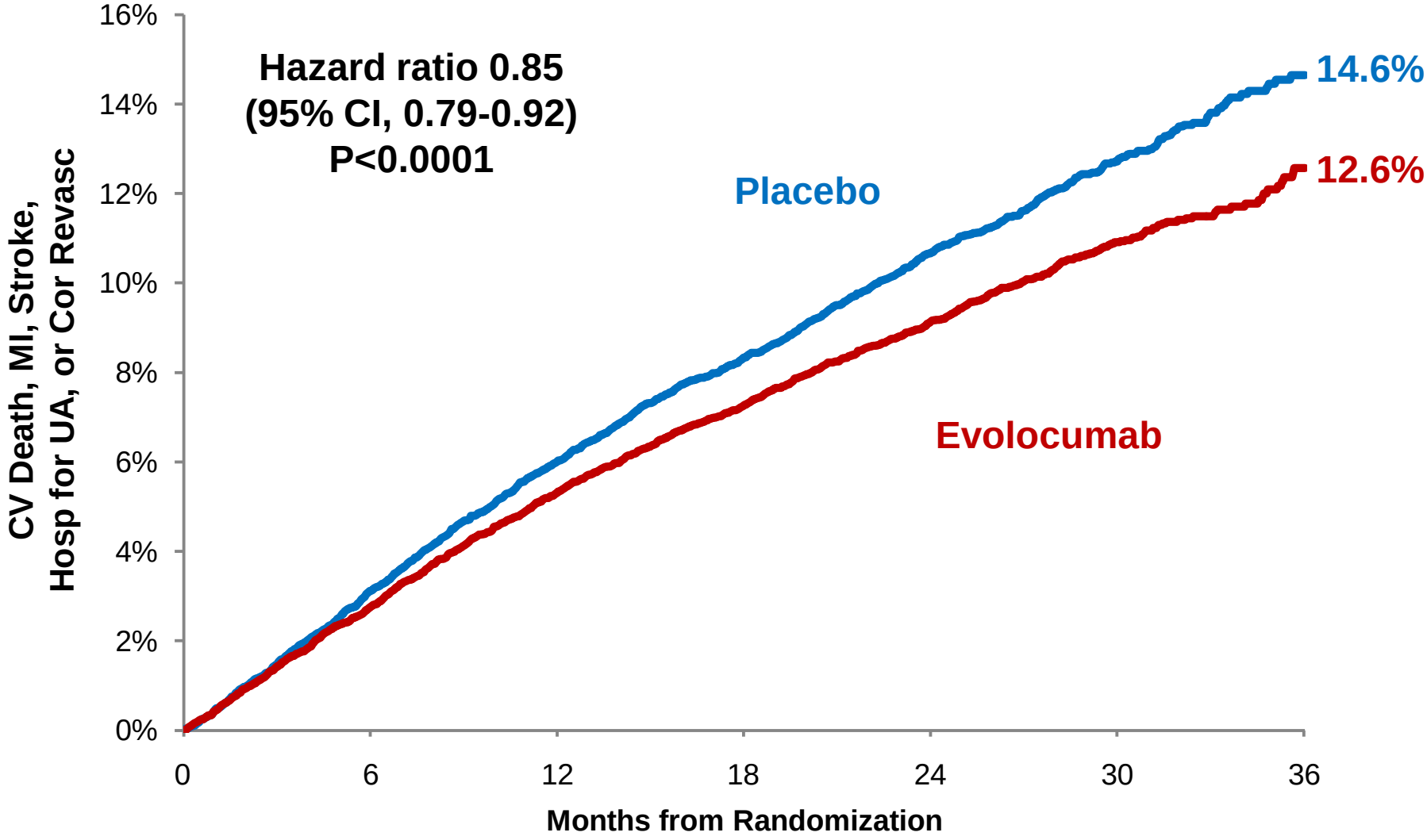
LDL 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L

↓

Additional
Inflammation Reduction

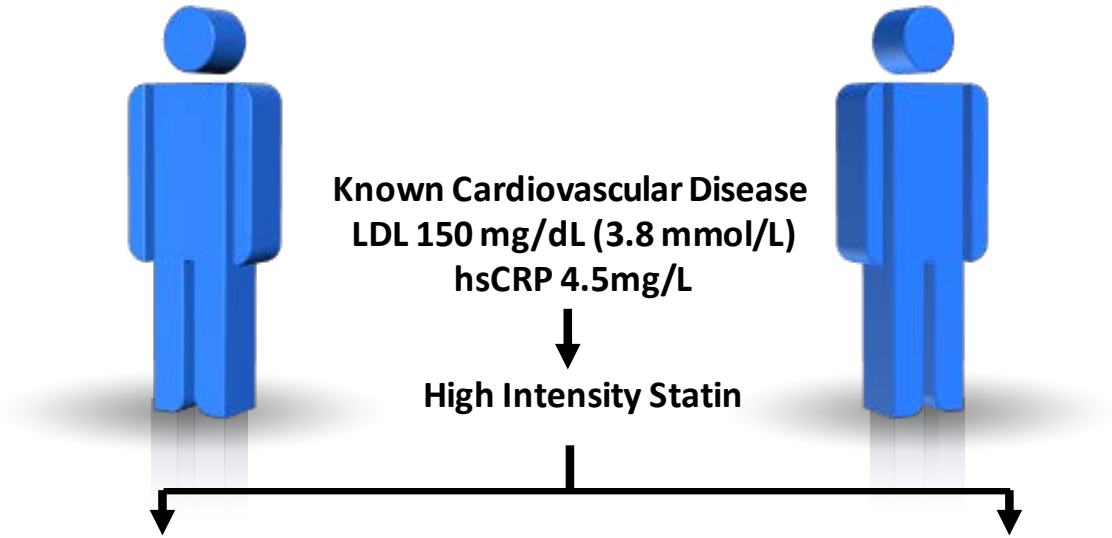
No Prior Proof of Concept

Primary Endpoint



Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Ridker PM. Eur Heart J 2016;37:1720-22



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"Residual Inflammatory Risk"

LDL 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L

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Additional
Inflammation Reduction

No Prior Proof of Concept

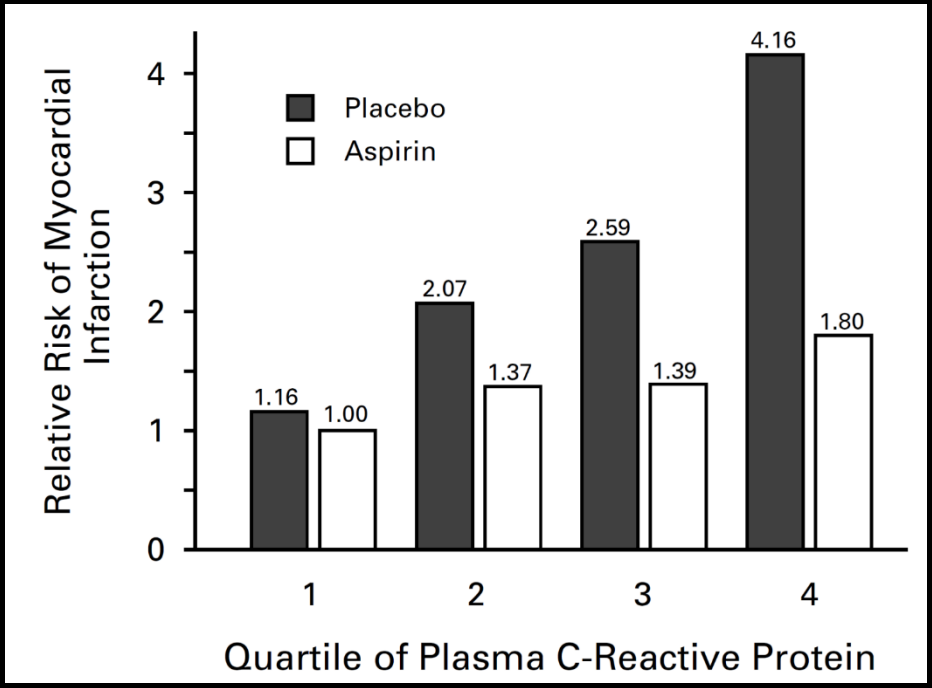
Low Grade Systemic Inflammation *Precedes* By Many Years the Onset of Vascular Events

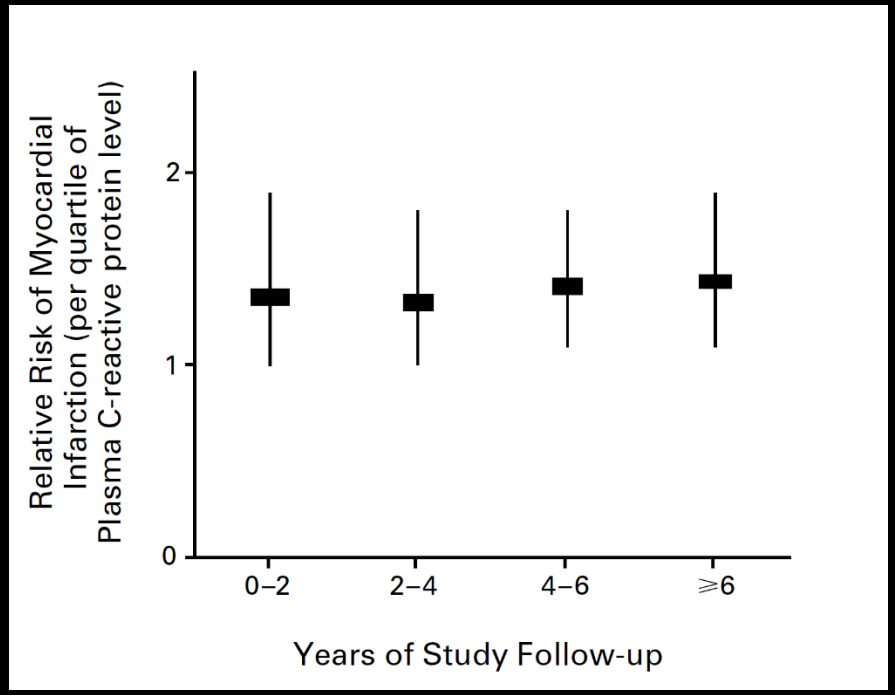
The New England
Journal of Medicine

VOLUME 336 APRIL 3, 1997 NUMBER 14

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

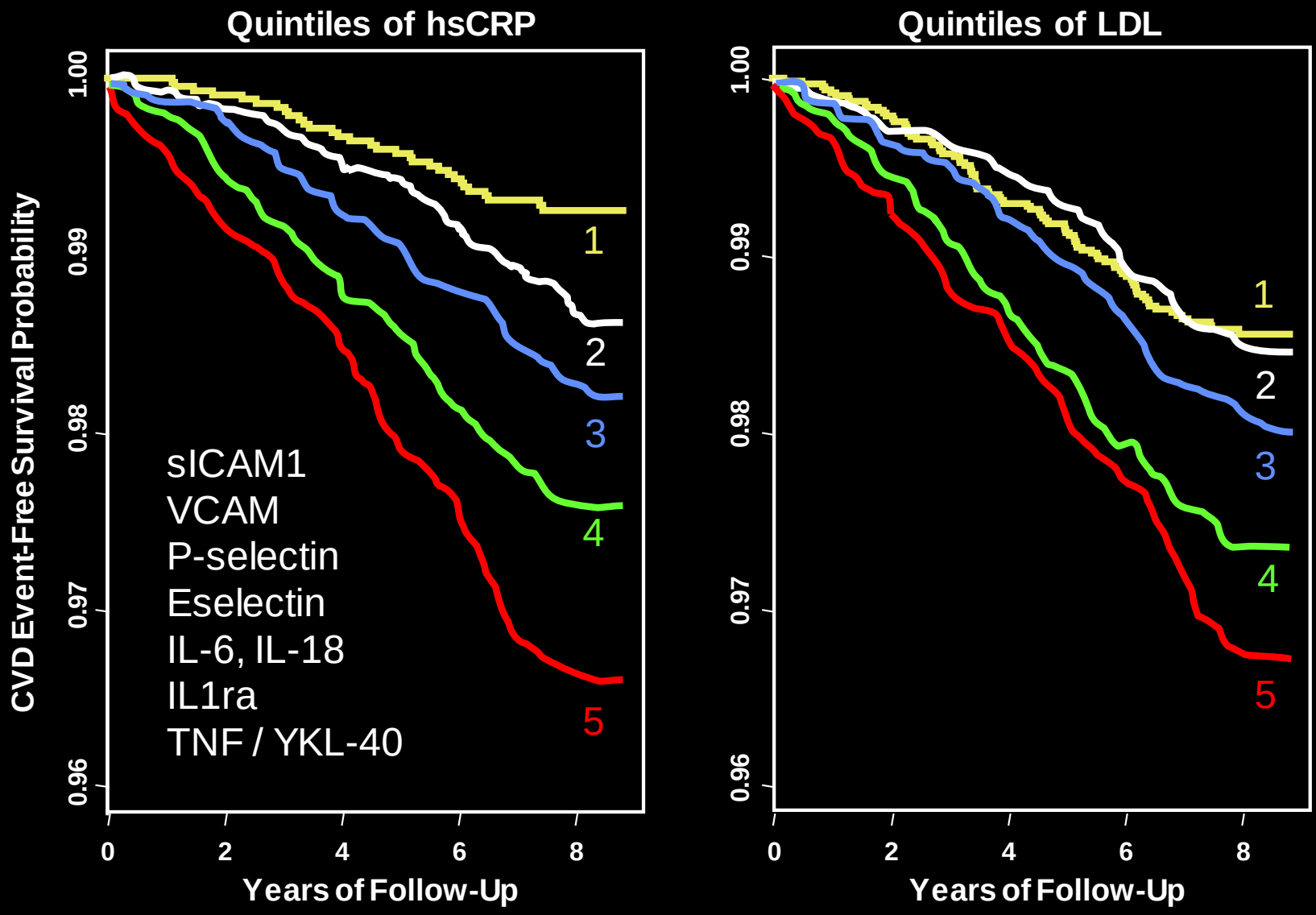
PAUL M. RIDKER, M.D., MARY CUSHMAN, M.D., MEIR J. STAMPFER, M.D., RUSSELL P. TRACY, PH.D., AND CHARLES H. HENNEKENS, M.D.





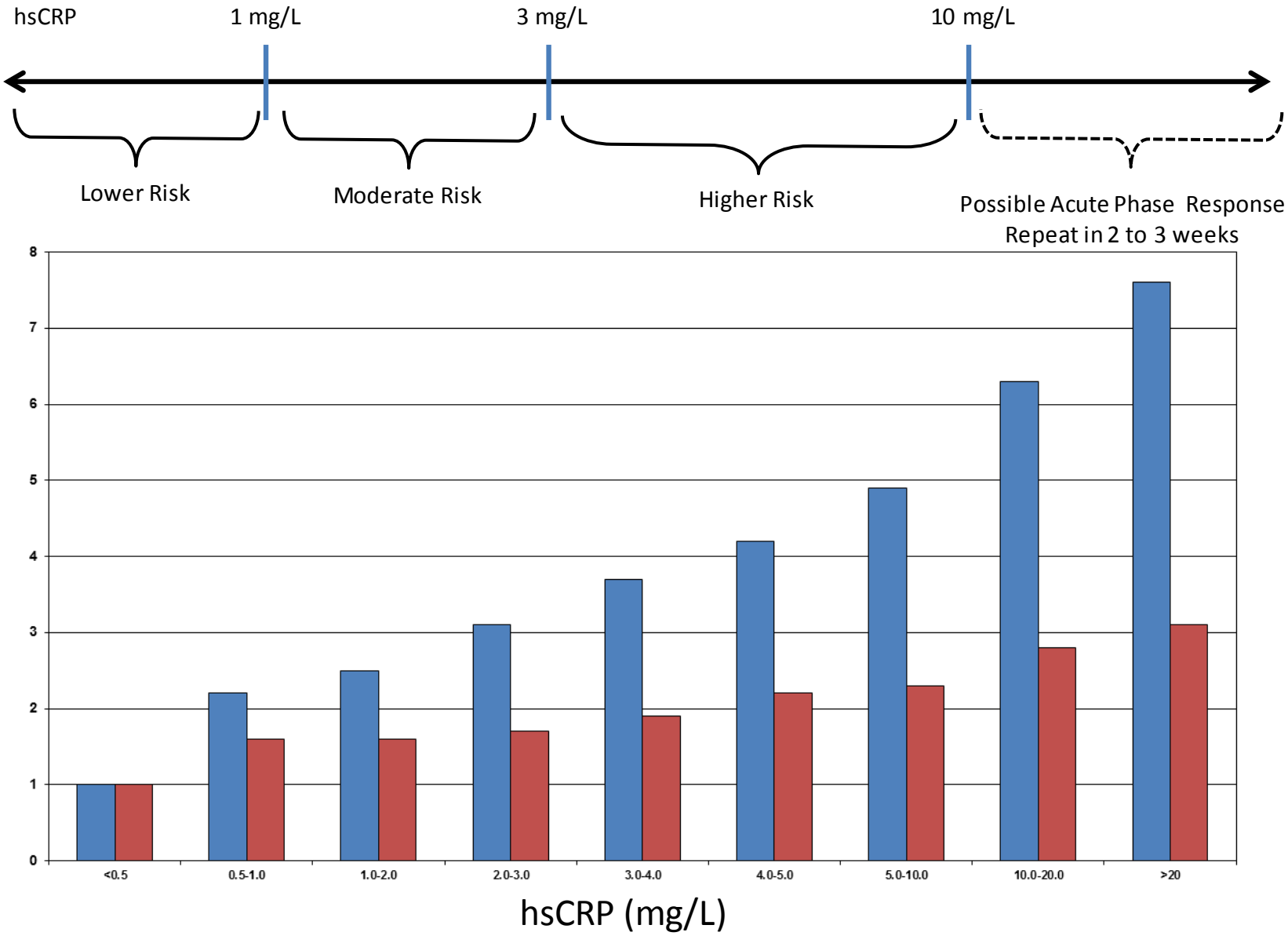
Ridker et al NEJM 1997; 336:973-9

Event-Free Survival According to Baseline Quintiles of hs-CRP and LDL Cholesterol



Ridker et al N Engl J Med. 2002;347:1157-1165.

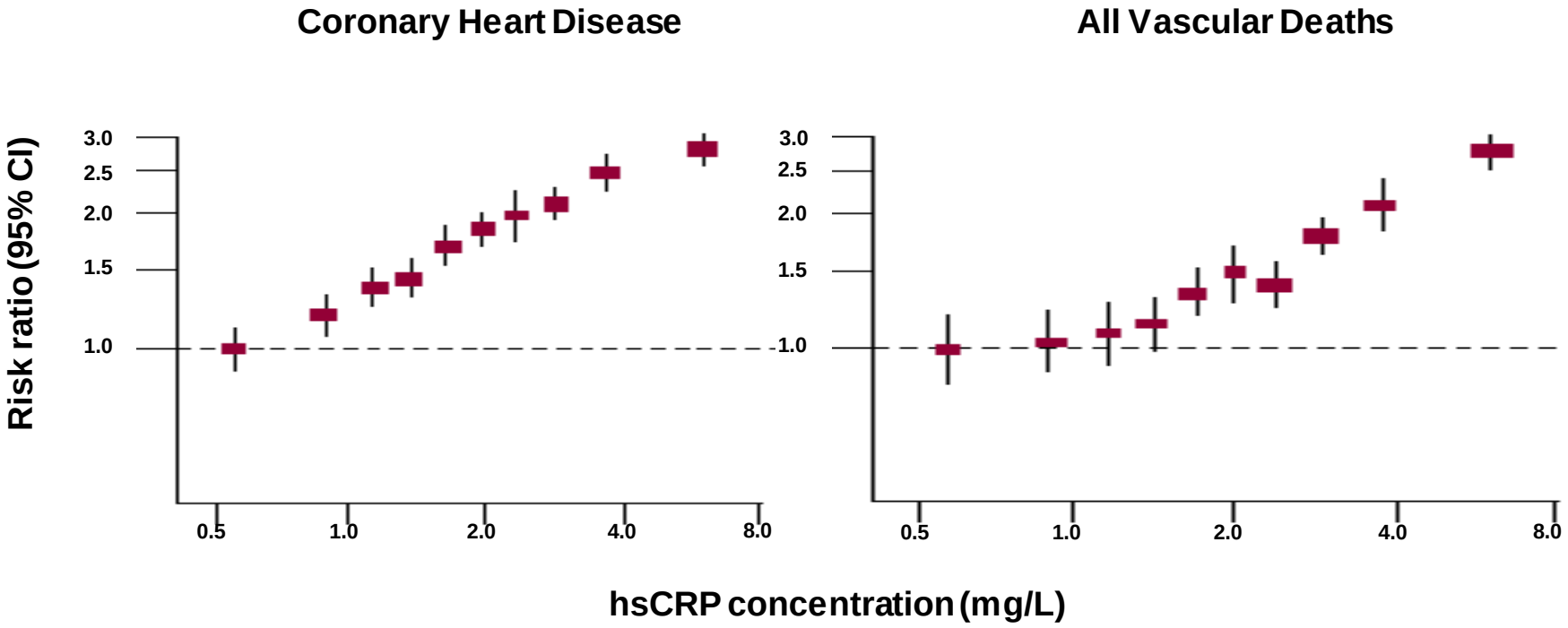
High Sensitivity C-Reactive Protein (hsCRP) : A Test In Context



Ridker PM. JACC 2016;16:67:712-23

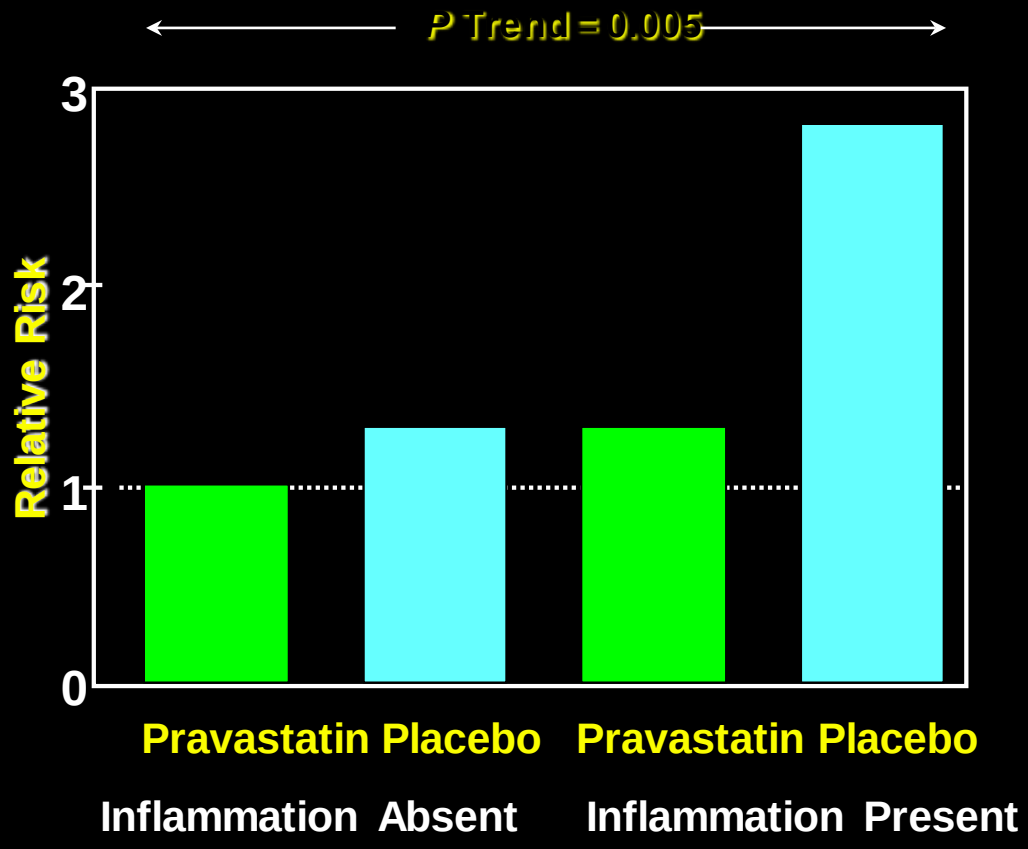
Inflammation is a Strong and Consistent Predictor of CV Risk

Meta-analysis of 54 Prospective Cohort Studies
hsCRP concentration and risk of cardiovascular events : 2010

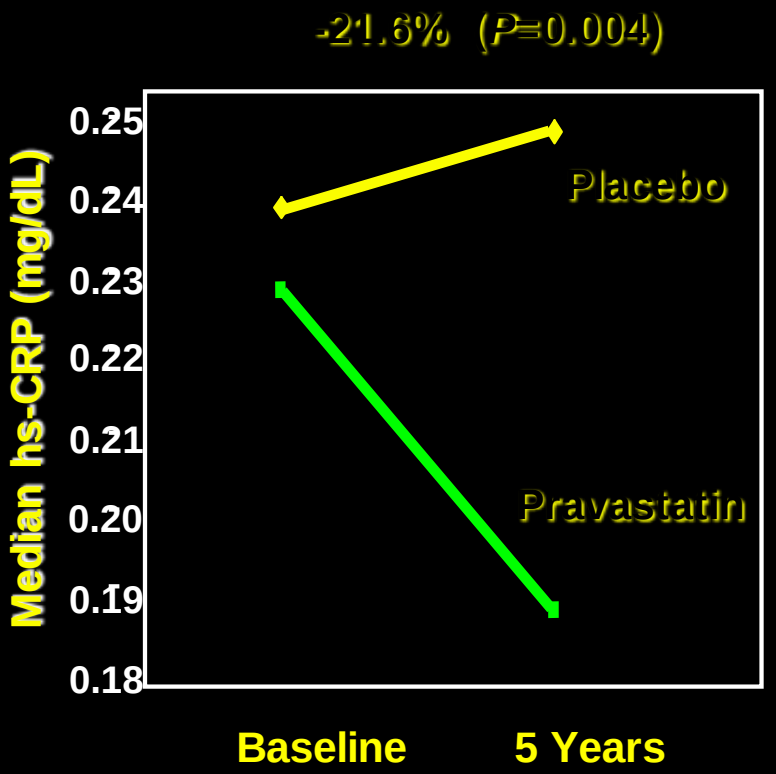


Emerging Risk Factor Collaborators, Lancet January 2010

Inflammation, Statin Therapy, and hsCRP: Initial Observations

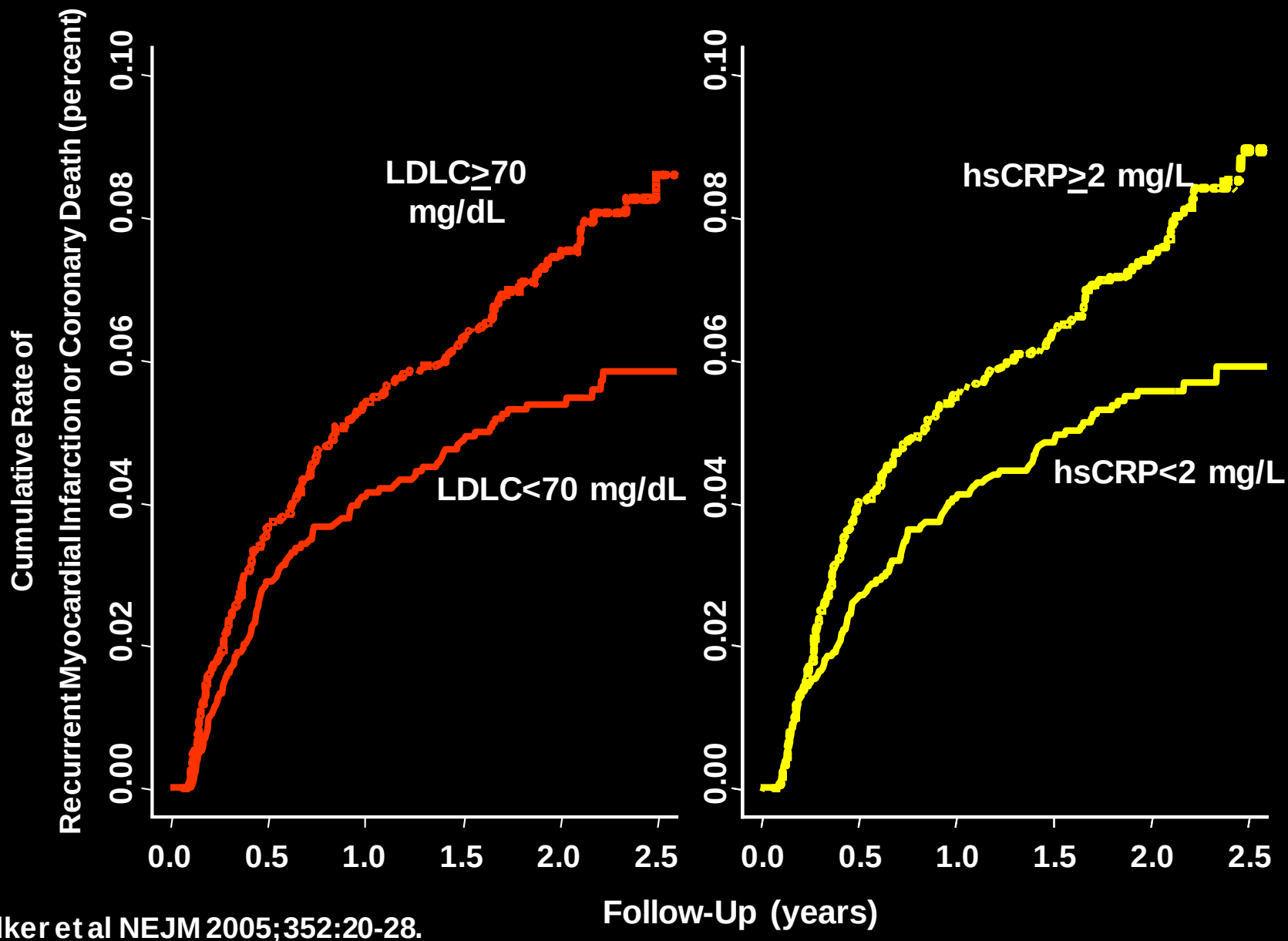


Ridker et al Circulation. 1998;98:839–844.

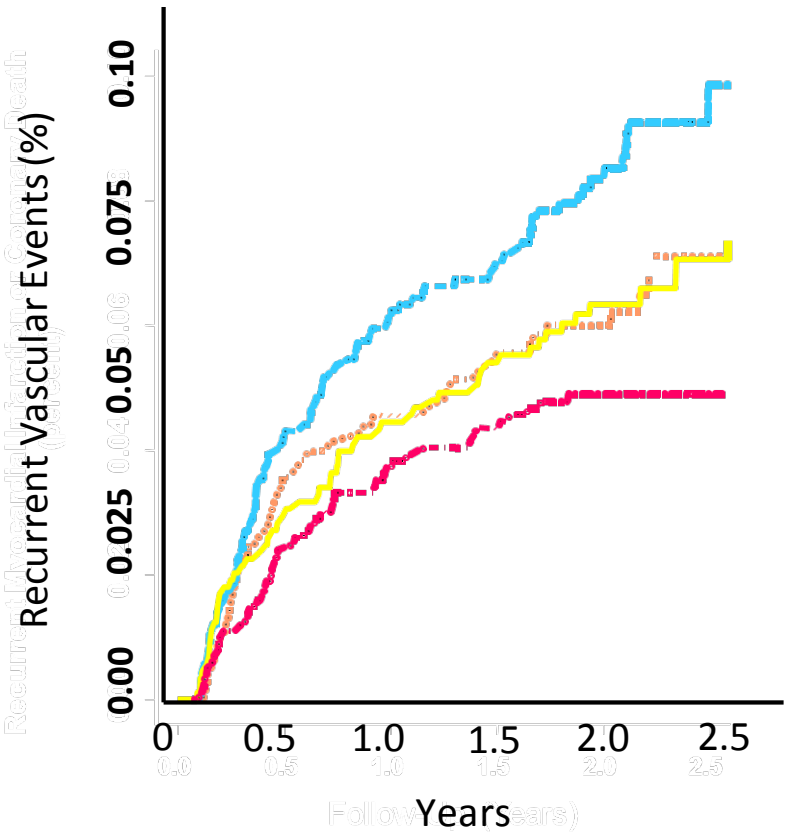


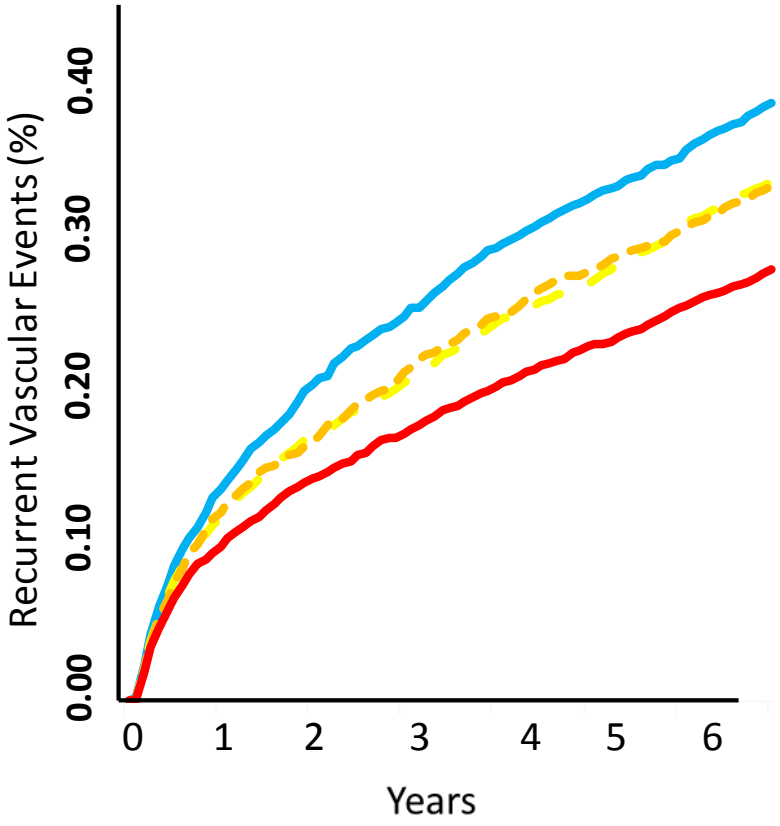
Ridker et al Circulation. 1999;100:230-235.

Clinical Relevance of Achieved LDL and Achieved CRP After ACS Treated with Statin Therapy



Ridker et al NEJM 2005;352:20-28.





PROVE-IT

Ridker et al, NEJM 2005;352:20-8

IMPROVE-IT

Bohula et al, Circulation 2015;132:1224-33

LDL >70 mg/dL hsCRP > 2mg/L	LDL <70 mg/dL hsCRP > 2mg/L	LDL > 70 mg/dL hsCRP < 2mg/L	LDL <70 mg/dL hsCRP < 2mg/L
Neither Goal Achieved	LDL Goal Achieved	hsCRP Goal Achieved	Dual Goals Achieved

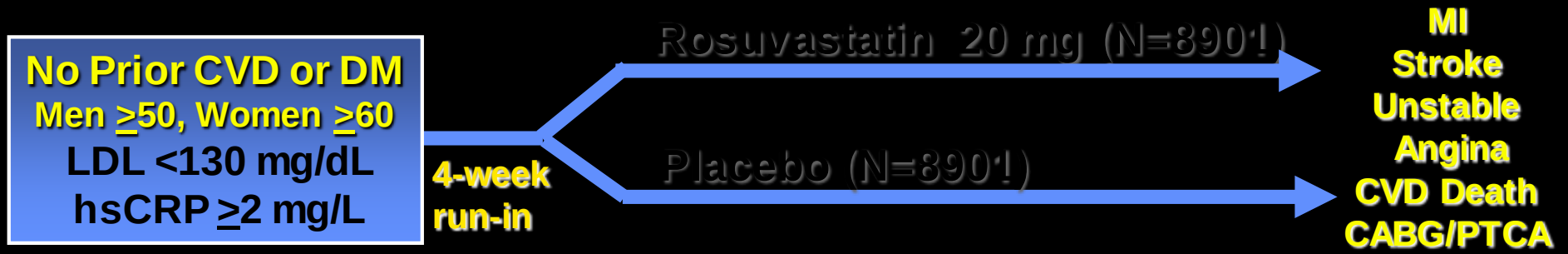
Ridker et al, Eur Heart J 2016;37:1729-22

JUPITER Trial Design

Ridker et al NEJM 2008;359:2195-2207

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



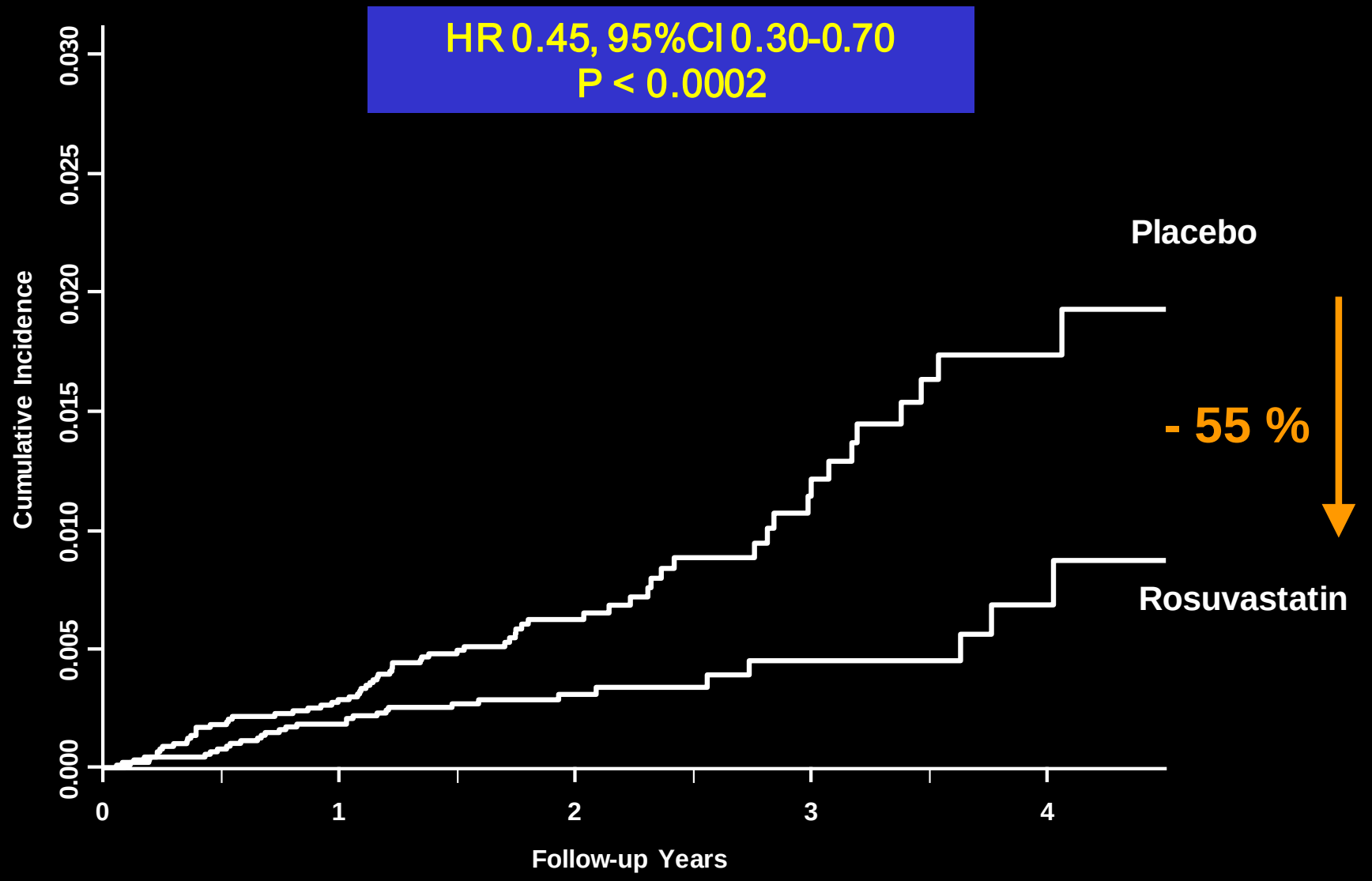
Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Mean LDLC 104 mg/dL, Mean HDLC 50 mg/dL, hsCRP 4 mg/L

JUPITER

Ridker et al NEJM 2008;359:2195-2207

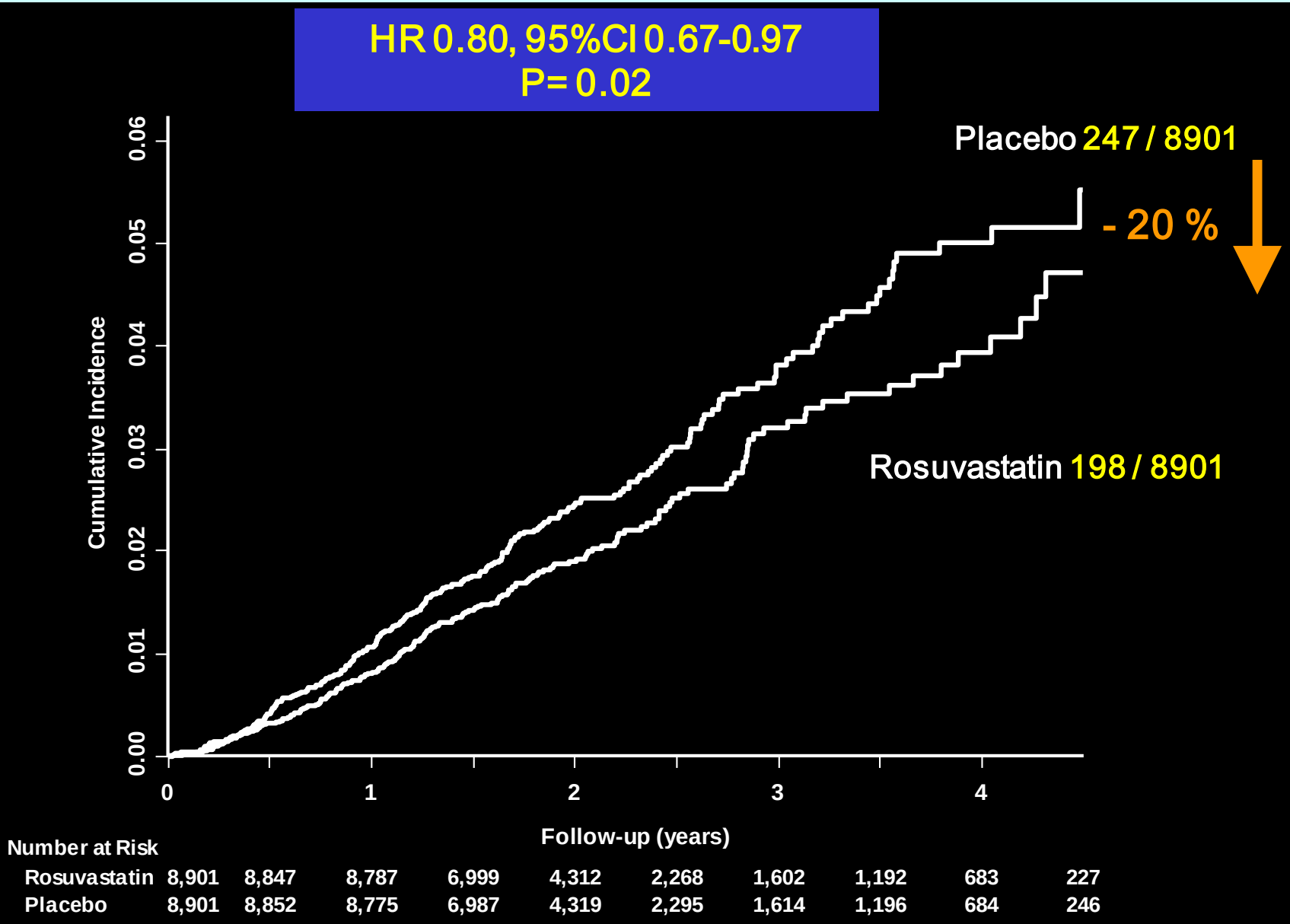
Fatal or Nonfatal Myocardial Infarction



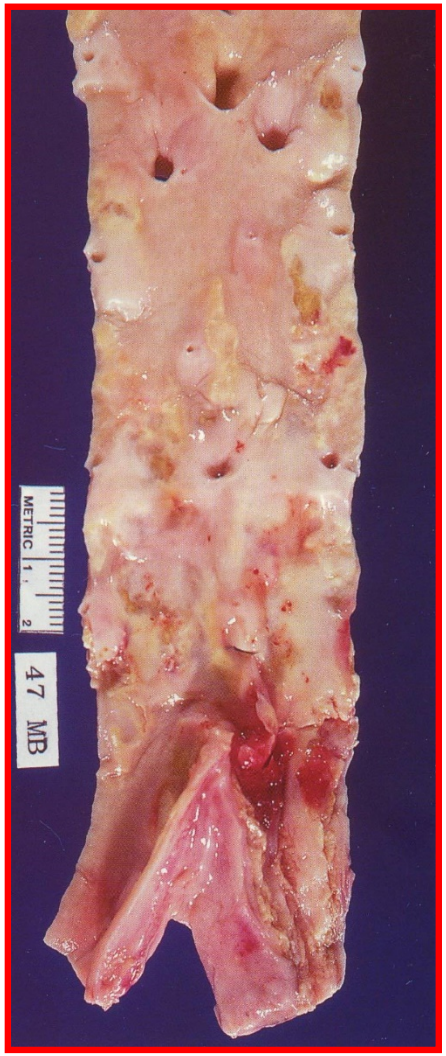
JUPITER

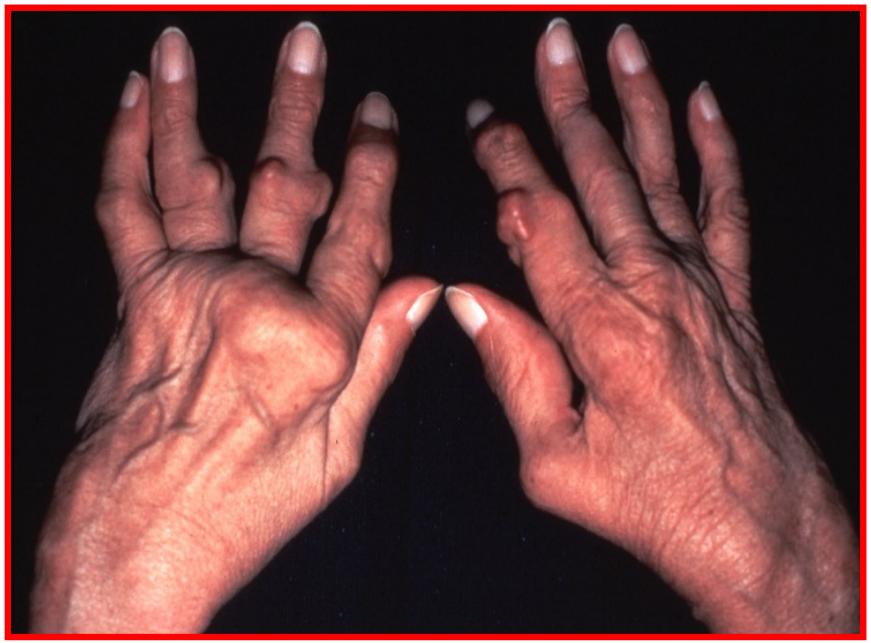
NEJM 2008;359:2195-2207

Secondary Endpoint – All Cause Mortality

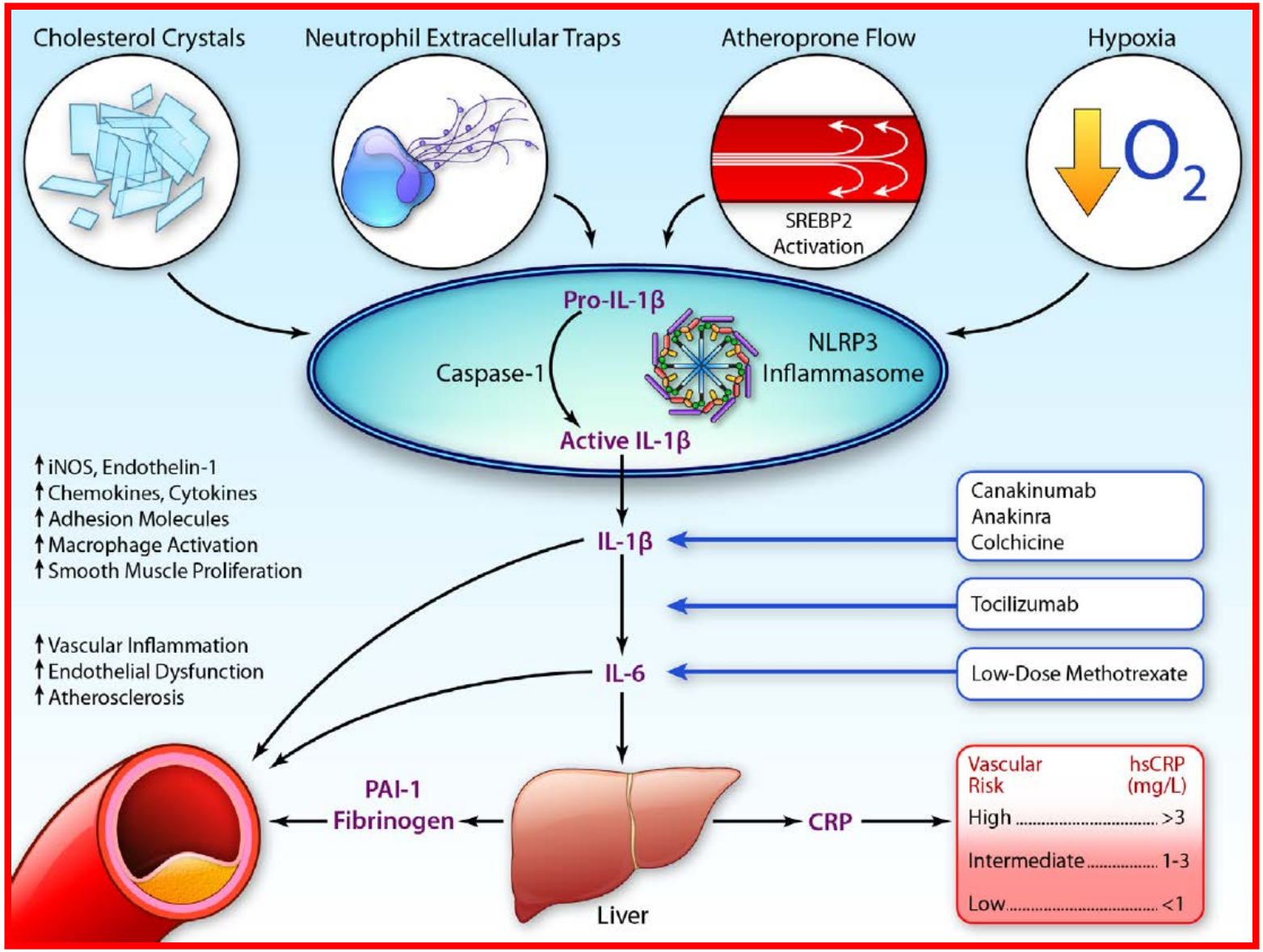


Can Inflammation Reduction, in the Absence of Lipid Lowering, Reduce Cardiovascular Event Rates?

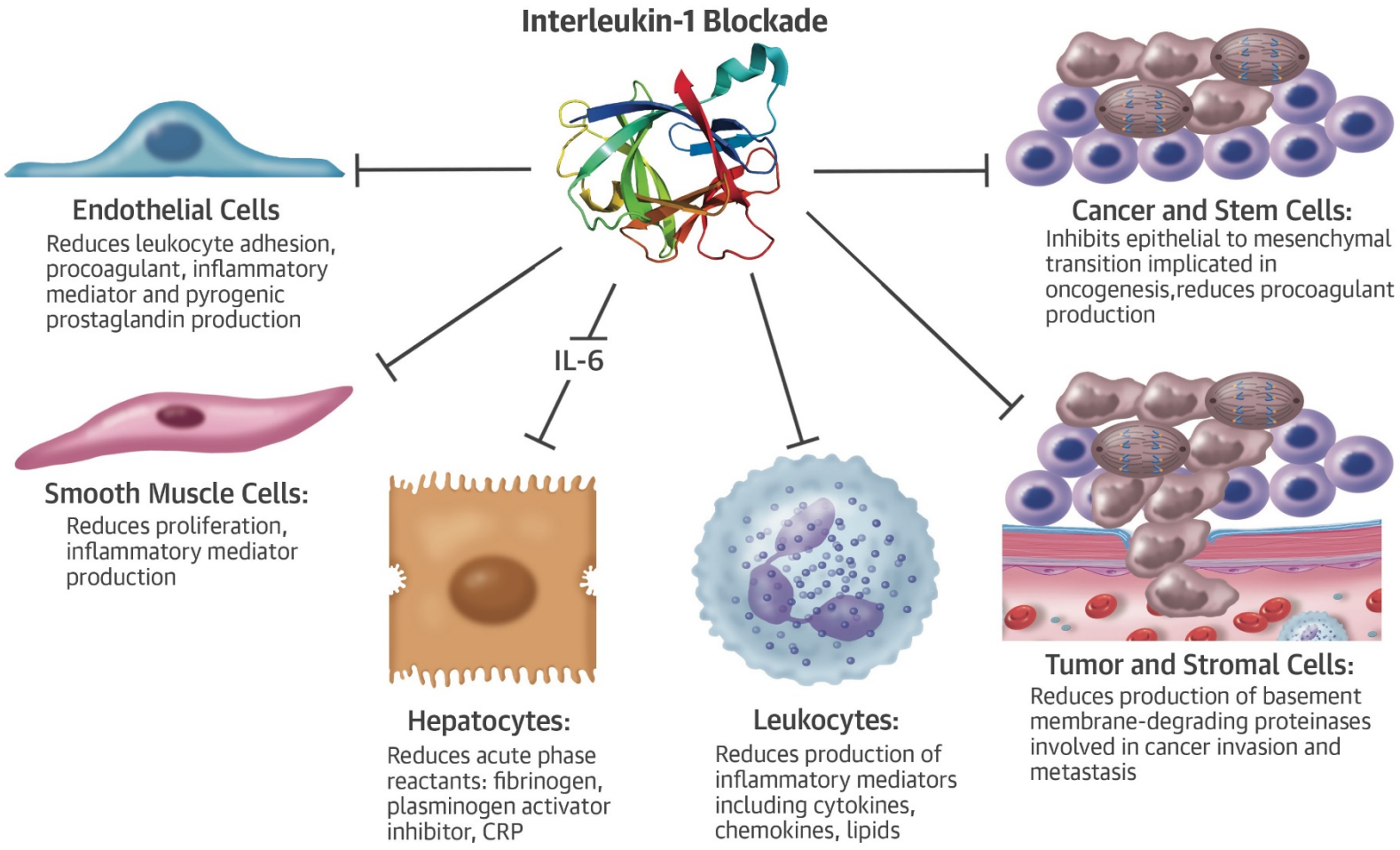




From CRP to IL-6 to IL-1: Moving Upstream to Identify novel Targets for Atheroprotection



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



Libby P. Interleukin-1 Beta as a Target for Atherosclerosis: Biologic Basis for CANTOS and Beyond. JACC 2017;70:2278-89

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Stable CAD (post MI)
Residual Inflammatory Risk
(hsCRP ≥ 2 mg/L)

N = 10,061
39 Countries
April 2011 - June 2017
1490 Primary Events

Randomized
Canakinumab 50 mg
SC q 3 months

Randomized
Canakinumab 150 mg
SC q 3 months

Randomized
Canakinumab 300 mg
SC q 3 months

Randomized
Placebo
SC q 3 months

Primary Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)

Secondary Endpoint: MACE plus Unstable Angina Requiring Urgent Revascularization (MACE+)

Additional Adjudicated Endpoints: Cancer, Infection

Ridker PM et al. N Engl J Med. 2017;377:1119-31

Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

39 countries
> 1000 investigators

17482 Screened

7377 Excluded Prior to Entering Randomization Process
- 146 refused consent
- 71 child-bearing potential
- 44 age out of range
- 251 no documented MI
- 3390 hsCRP < 2 mg/L
- 728 exclusionary concomitant disease
- 1873 tuberculosis risk factors
- 104 infectious disease
- 76 immunocompromised state
- 27 life threatening condition
- 574 withdrew consent
- 137 site closure
- 81 physician decision
- 49 unable to contact
- 7 adverse event
- 11 died
- 139 other reasons

10105 Entered Into Randomization Process

44 Failed Randomization Process
- 41 Invalid randomization
- 3 major GCP violations

10061 Successfully Randomized

3344 placebo
- 18.1% discontinued study drug
- 3335 known final vital status
- 9 unknown final vital status

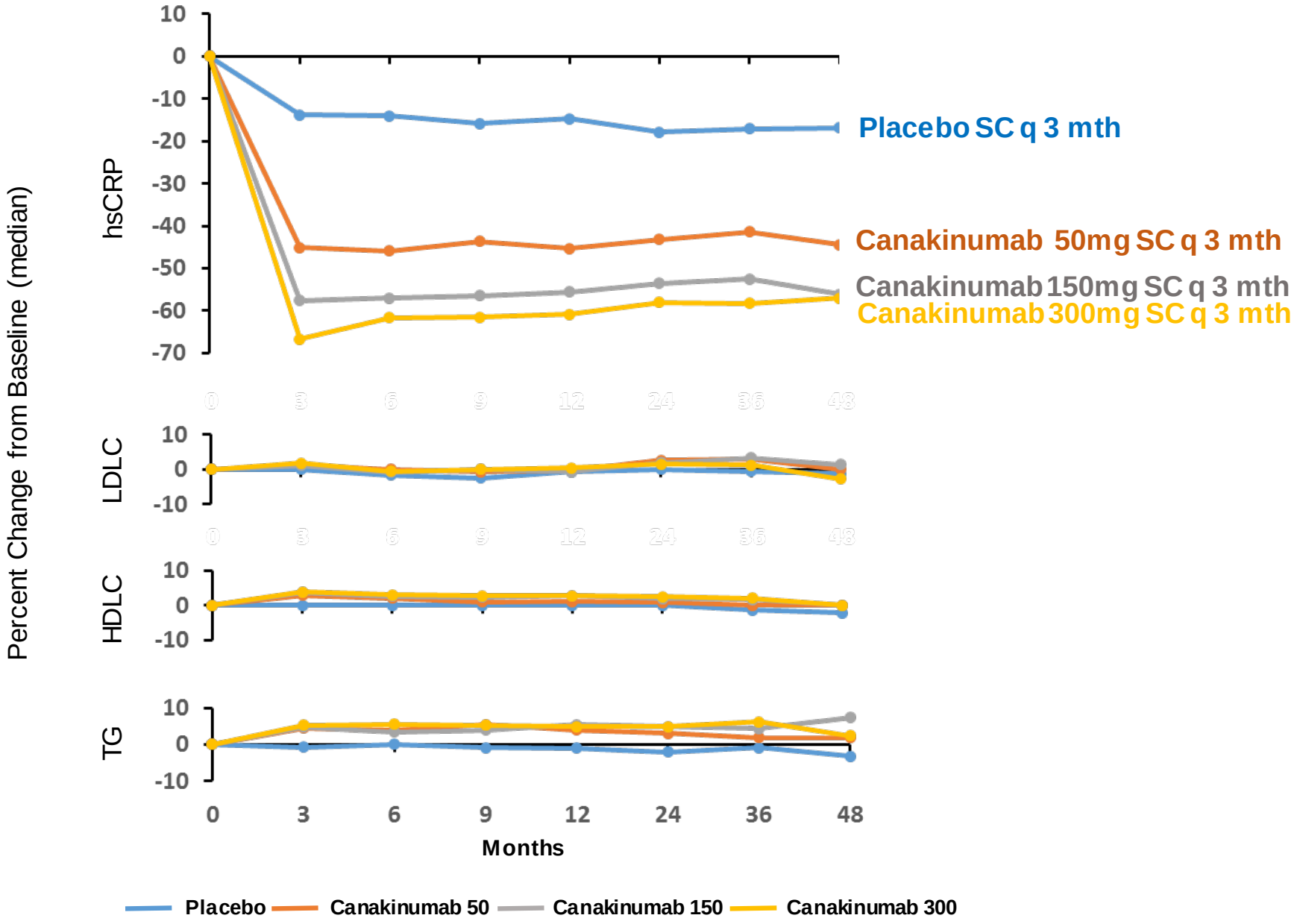
2170 canakinumab 50mg
- 16.7% discontinued study drug
- 2161 known final vital status
- 9 unknown final vital status

2284 canakinumab 150mg
- 19.2% discontinued study drug
- 2279 known final vital status
- 5 unknown final vital status

2263 canakinumab 300mg
- 20.1% discontinued study drug
- 2259 known final vital status
- 4 unknown final vital status

Ridker PM et al. N Engl J Med. 2017;377:1119-31

CANTOS: Dose-Dependent Effects on Inflammatory Biomarkers and Lipids (48 Months)

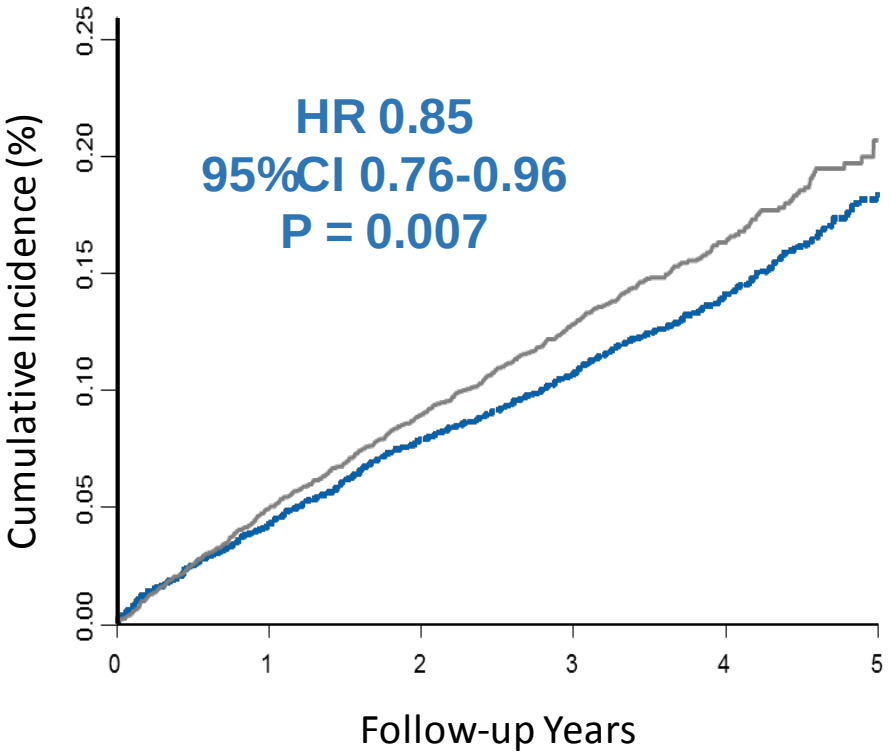


Ridker PM et al. N Engl J Med. 2017;377:1119-31

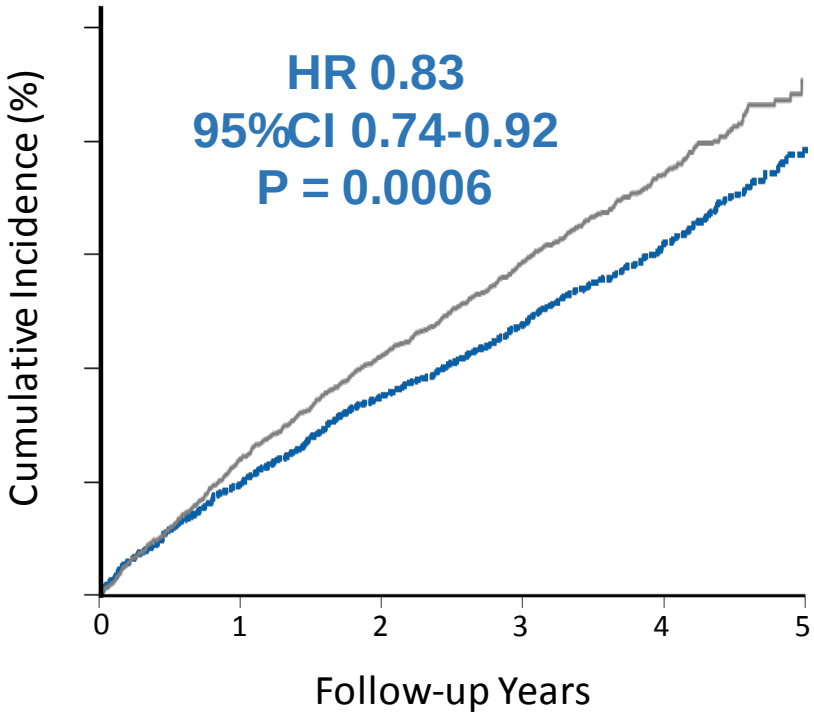
CANTOS: Primary Cardiovascular Endpoints

Placebo SC q 3 months
Canakinumab 150/300 mg SC q 3 months

MACE



MACE - Plus



35 - 40% reductions in hsCRP and IL-6
No change in LDLC

Ridker PM et al. N Engl J Med. 2017;377:1119-31

CANTOS: Critical Unanswered Clinical Questions

Monoclonal Antibodies and the Era of Personalized Medicine
Can we predict who benefits the most from effective but expensive treatments?

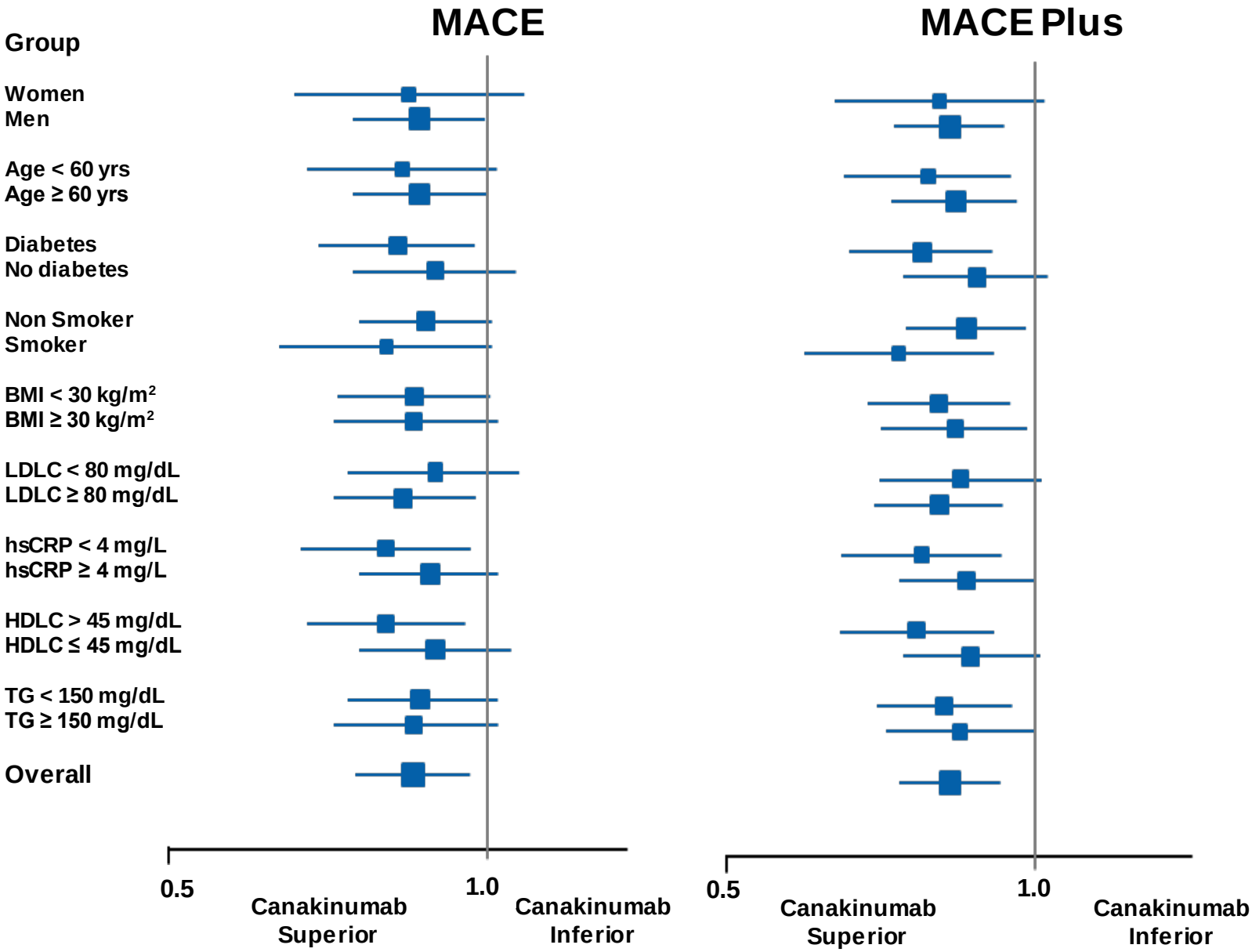
Is there an easily identified clinical subgroup for whom benefits are large and might clearly outweigh hazards?

Is there an easily identifiable subgroup where there is evidence not only of reduced MACE, but also of reduced cardiovascular mortality and reduced all-cause mortality?

Is there an easily identified clinical subgroup for whom benefits are small and may not justify the hazards?

These biologically directed questions have broad implications for patient selection, for cost-effectiveness, for calculations of the number-needed-to-treat (NNT), and ultimately for personalized medicine, allowing us to get the right drug to the right patient, thus maximizing benefits while reducing costs as well as hazards.

CANTOS : Consistency of Effect Across All patient Groups Defined By Baseline Clinical Characteristics



Ridker PM, et al. Lancet. 2017. http://dx.doi.org/10.1016/S0140-6736(17)32814-3

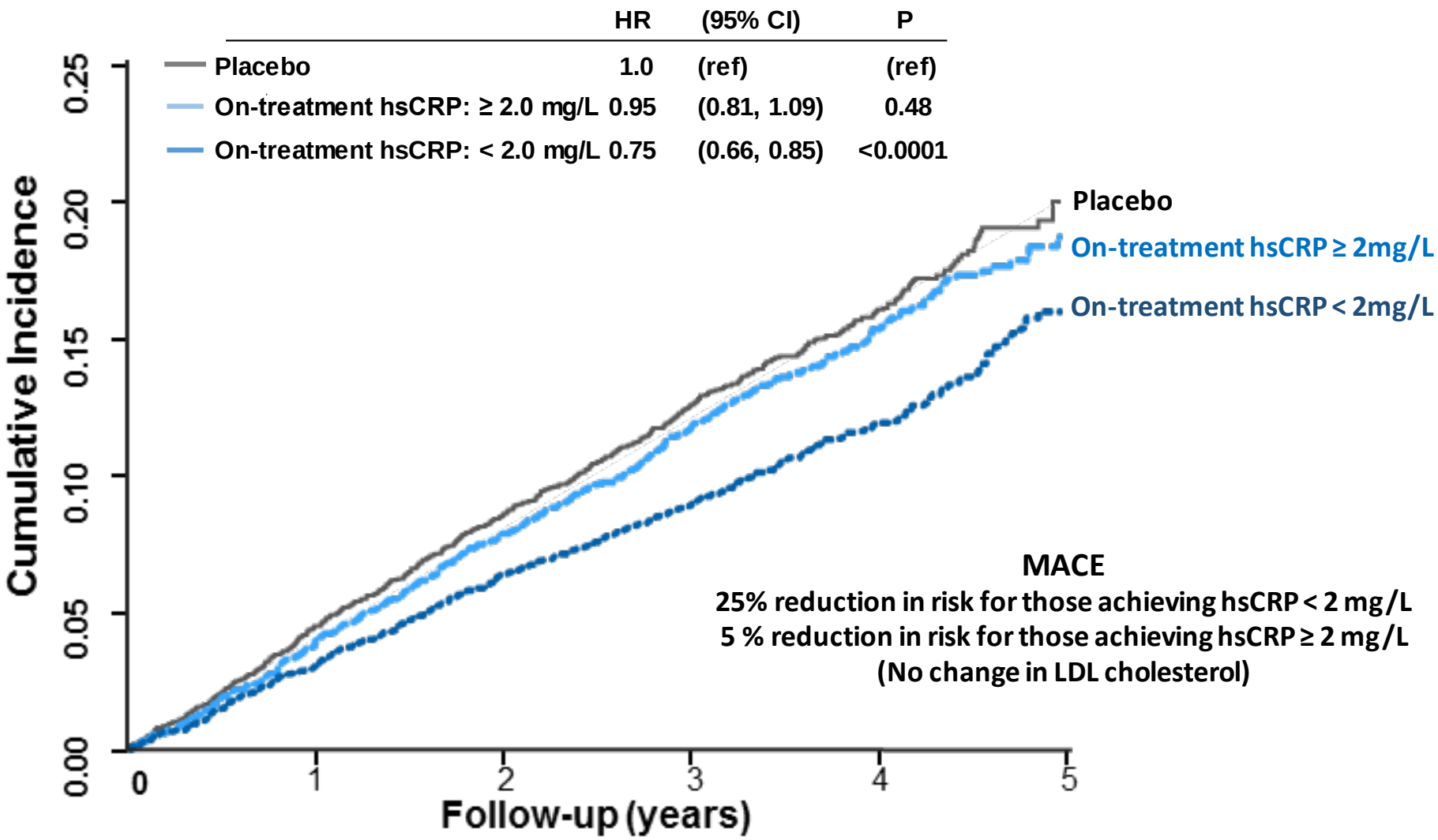
Interleukin-1β Inhibition with Canakinumab

Can we use evidence of individual biologic drug response to define patient groups more or less likely to benefit from treatment with canakinumab?

Can we use the magnitude of reduction (or level achieved) of hsCRP or interleukin-6 following treatment with canakinumab to identify individual patients most likely to benefit?

Perform a series of sensitivity analyses to address the robustness of any informative findings.

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



Ridker PM, et al. Lancet. 2017. http://dx.doi.org/10.1016/S0140-6736(17)32814-3

CANTOS Sensitivity Analysis I : Multivariate Adjustment* for Potential Confounding Factors Related to On-Treatment hsCRP Has Minimal Impact

On-treatment hsCRP Threshold		Placebo	Canakinumab On-treatment hsCRP above threshold	Canakinumab On-treatment hsCRP below threshold
hsCRP < or > clinical cutpoint (2 mg/L)	HR (adjusted) 95% CI P	1.0 Referent Referent	0.90 0.79-1.02 0.11	0.75 0.66-0.85 <0.0001

*HRs adjusted for age, gender, smoking, HTN, diabetes, BMI, baseline hsCRP, Baseline LDLC

Ridker PM, et al. Lancet. 2017. http://dx.doi.org/10.1016/S0140-6736(17)32814-3

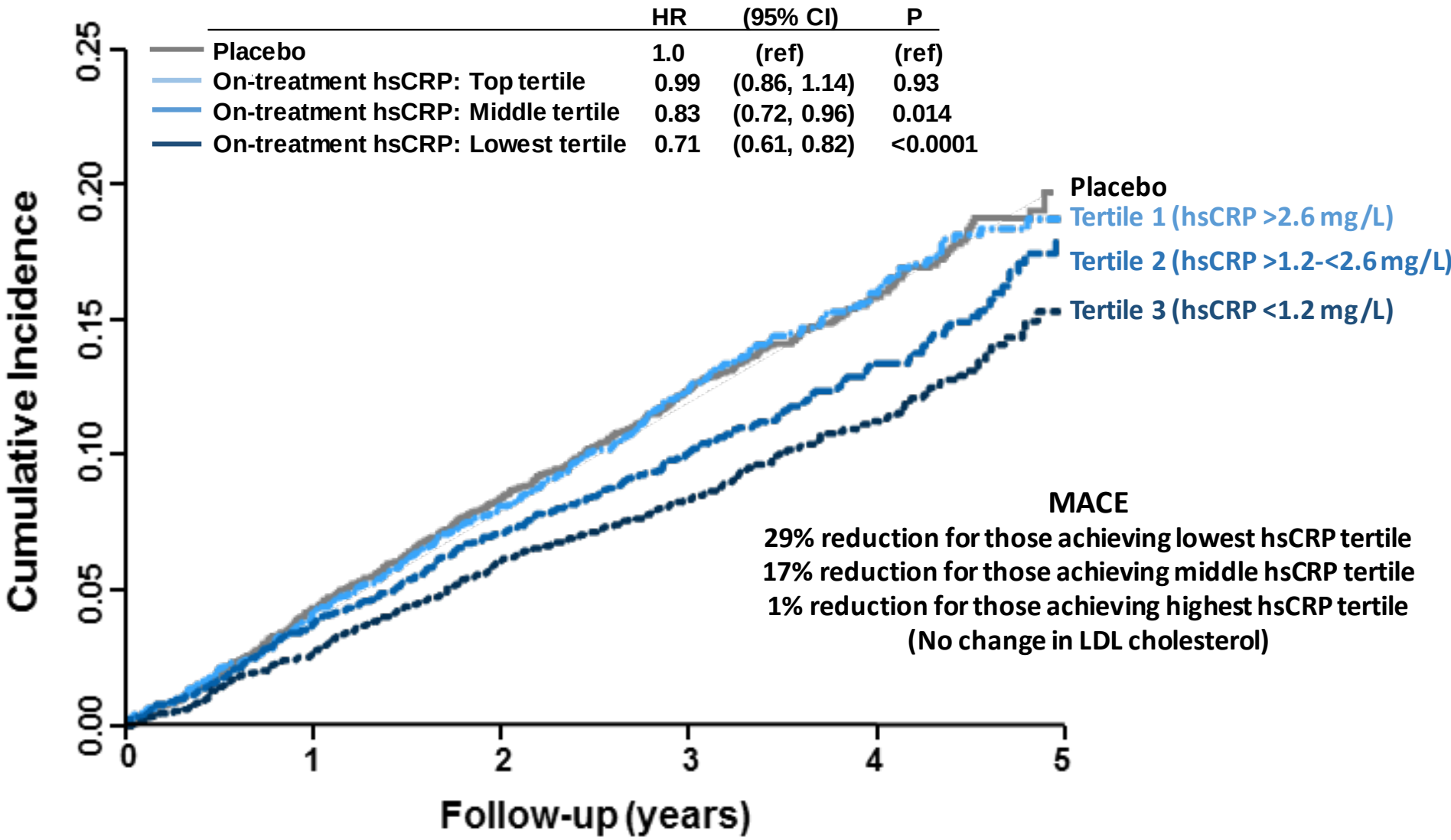
CANTOS Sensitivity Analysis II : Choice of Alternative Thresholds for On-treatment hsCRP Has Minimal Impact

On-treatment hsCRP Threshold		Placebo	Canakinumab On-treatment hsCRP above threshold	Canakinumab On-treatment hsCRP below threshold
hsCRP < or > clinical cutpoint (2 mg/L)	HR (adjusted) 95% CI P	1.0 Referent Referent	0.90 0.79-1.02 0.11	0.75 0.66-0.85 <0.0001
hsCRP < or > median (1.8 mg/L)	HR (adjusted) 95% CI P	1.0 Referent Referent	0.90 0.79-1.02 0.10	0.73 0.64-0.84 <0.0001
hsCRP > or < 50 % reduction	HR (adjusted) 95% CI P	1.0 Referent Referent	0.87 0.76-1.00 0.05	0.81 0.71-0.91 0.0008
hsCRP > or < Median % reduction	HR (adjusted) 95% CI P	1.0 Referent Referent	0.86 0.75-0.98 0.02	0.80 0.70-0.92 0.001

HRs adjusted for age, gender, smoking, HTN, diabetes, BMI, baseline hsCRP, Baseline LDLC

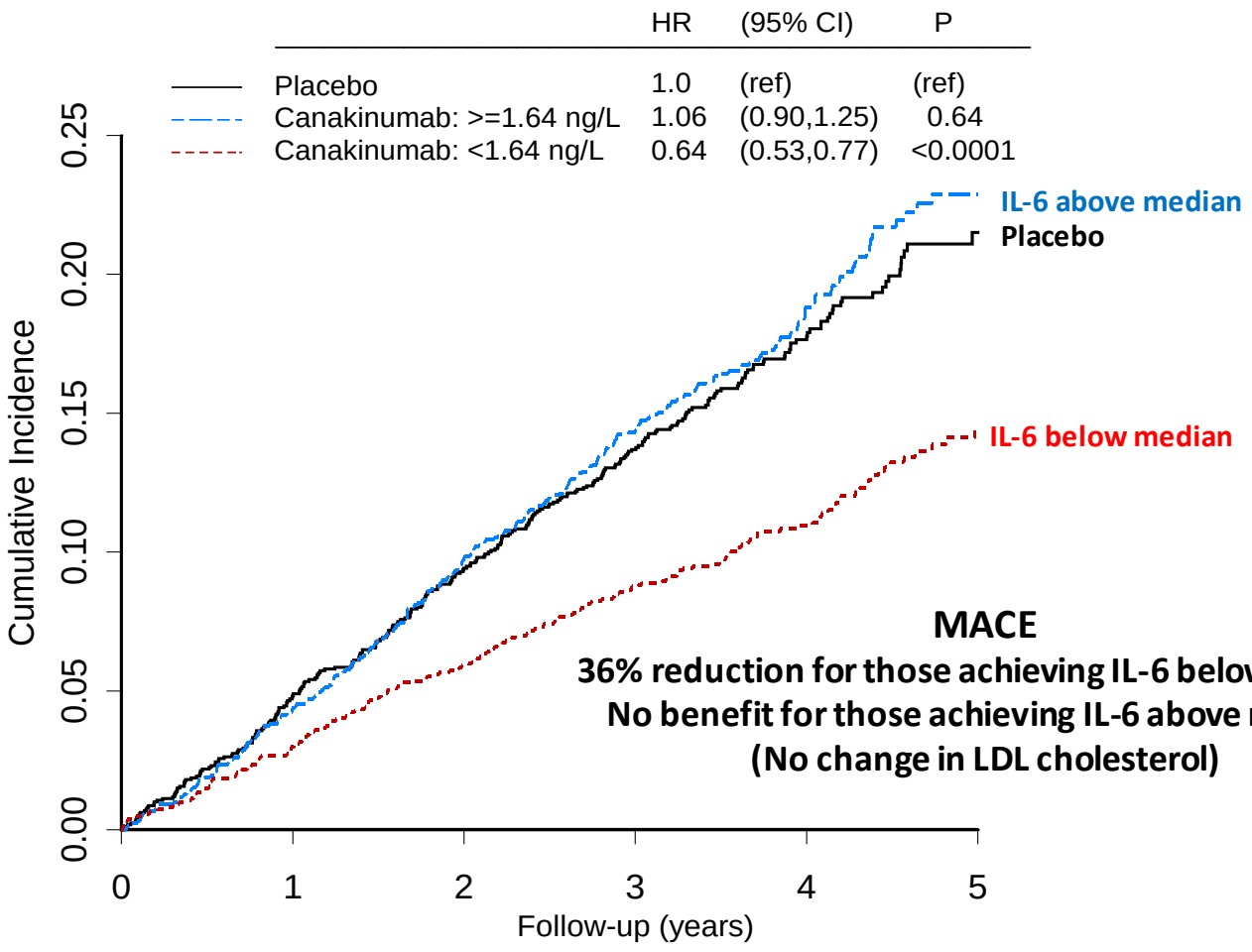
Ridker PM, et al. Lancet. 2017. http://dx.doi.org/10.1016/S0140-6736(17)32814-3

CANTOS Sensitivity Analysis III: Cardiovascular Outcomes According to On-treatment Tertiles of hsCRP Measured After the Initial dose of Canakinumab (MACE)



Ridker PM, et al. Lancet. 2017. http://dx.doi.org/10.1016/S0140-6736(17)32814-3

CANTOS Sensitivity Analysis IV. Cardiovascular Outcomes According to On-Treatment Levels of Interleukin-6 Above or Below the Study Median After the Initial Dose of Canakinumab (MACE)



No. at risk:

Placebo	1597	1501	1411	1254	635	153
Canakinumab:						
Interleukin-6 >=1.64 ng/L	1638	1542	1427	1227	569	124
Interleukin-6 <1.64 ng/L	1598	1541	1485	1355	765	210

Ridker AHA 2017

CANTOS Sensitivity Analysis V: Multivariable Adjusted Hazard Ratios for Additional Pre-Specified Cardiovascular Outcomes According to On-treatment hsCRP Levels Above or Below 2 mg/L After Drug Initiation

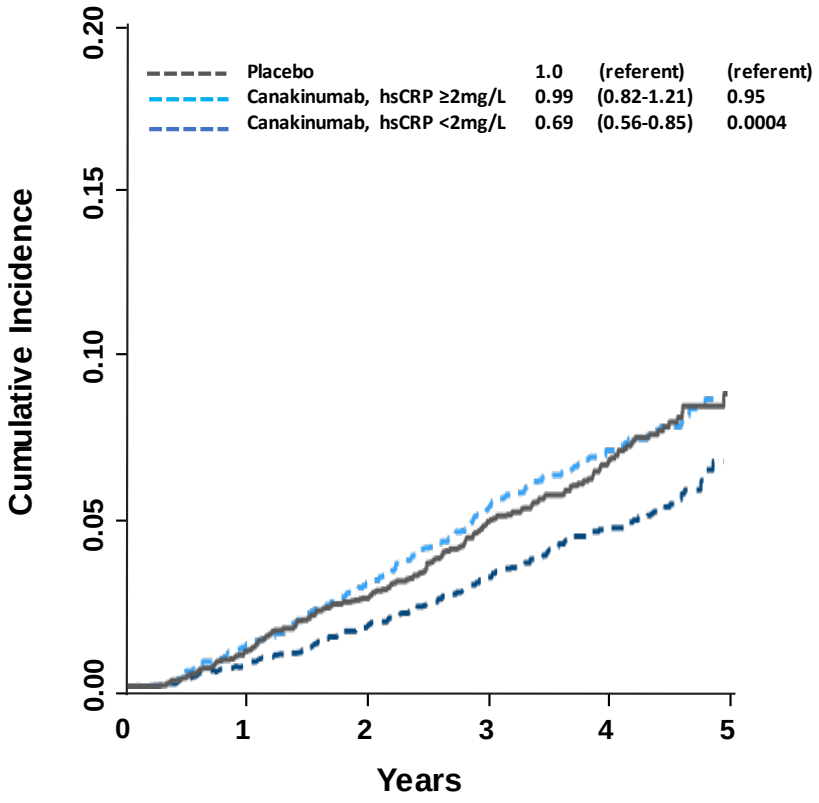
Clinical Outcome		Placebo (N = 3182)	Canakinumab On-treatment hsCRP ≥ 2mg/L (N = 2868)	Canakinumab On-treatment hsCRP < 2 mg/L (N = 3484)
MACE	HR (adjusted) 95% CI P	1.0 Referent Referent	0.90 0.79-1.02 0.11	0.75 0.66-0.85 <0.0001
MACE - Plus	HR (adjusted) 95% CI P	1.0 Referent Referent	0.91 0.81-1.03 0.14	0.74 0.66-0.83 <0.0001
CV Death	HR (adjusted) 95% CI P	1.0 Referent Referent	0.99 0.82-1.21 0.95	0.69 0.56-0.85 0.0004
All-Cause Mortality	HR (adjusted) 95% CI P	1.0 Referent Referent	1.05 0.90-1.22 0.56	0.69 0.58-0.81 <0.0001

HRs adjusted for age, gender, smoking, HTN, diabetes, BMI, baseline hsCRP, Baseline LDLC

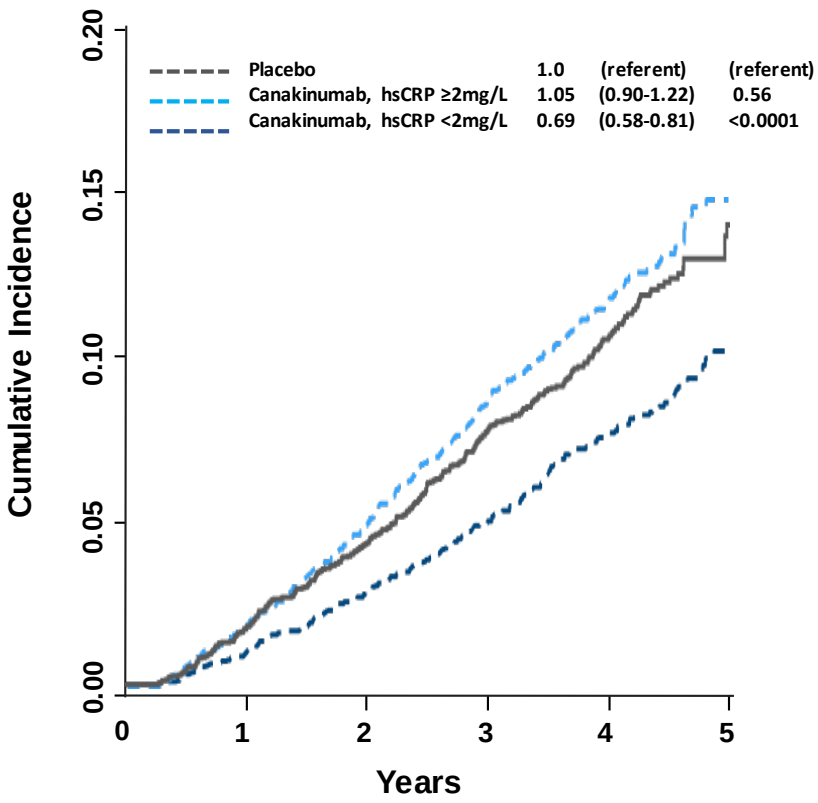
Ridker PM, et al. Lancet. 2017. http://dx.doi.org/10.1016/S0140-6736(17)32814-3

CANTOS : 31% Reduction in Cardiovascular Mortality and All-Cause Mortality Among Participants with Robust Inhibition of the Inflammatory Response

CANTOS - Cardiovascular Mortality



CANTOS - All Cause Mortality



35 - 40% reductions in hsCRP and IL-6
No change in LDLC

CANTOS Sensitivity Analysis VI: Consistent Effects at All Doses of Canakinumab (MACE)

Canakinumab Dose		Placebo	Canakinumab On-treatment hsCRP ≥ 2mg/L	Canakinumab On-treatment hsCRP < 2 mg/L
50 mg SC q 3 months	HR (adjusted) 95% CI P	1.0 Referent Referent	0.96 0.80-1.14 0.63	0.78 0.63-0.96 0.02
150 mg SC q 3 months	HR (adjusted) 95% CI P	1.0 Referent Referent	0.86 0.71-1.04 0.11	0.75 0.62-0.91 0.003
300 mg SC q 3 months	HR (adjusted) 95% CI P	1.0 Referent Referent	0.87 0.71-1.07 0.18	0.74 0.62-0.88 0.0009

HRs adjusted for age, gender, smoking, HTN, diabetes, BMI, baseline hsCRP, Baseline LDLC

The proportions of those treated who achieved hsCRP levels < 2 mg/L were 44%, 55%, and 65% in the 50mg, 150mg, and 300mg canakinumab groups, respectively.

Ridker PM, et al. Lancet. 2017. http://dx.doi.org/10.1016/S0140-6736(17)32814-3

CANTOS Sensitivity Analysis VII:

Similar Results Observed in a Causal Inference Analysis Which Modelled Potential Outcomes Using Baseline Covariates for Individual Patients Treated With Canakinumab Had They Counterfactually Been Allocated to Placebo (and then Comparing the Modelled Effects to the Observed Effects)

Canakinumab Dose		Canakinumab On-treatment hsCRP ≥ 2mg/L	Canakinumab On-treatment hsCRP < 2 mg/L
150 mg SC q 3 months	HR (counterfactually modelled) 95% CI	0.90 0.75-1.07	0.76 0.64-0.91
300 mg SC q 3 months	HR (counterfactually modelled) 95% CI	0.93 0.74-1.04	0.80 0.69-0.96

Ridker PM, et al. Lancet. 2017. http://dx.doi.org/10.1016/S0140-6736(17)32814-3

CANTOS: Additional Outcomes (per 100 person years of exposure)

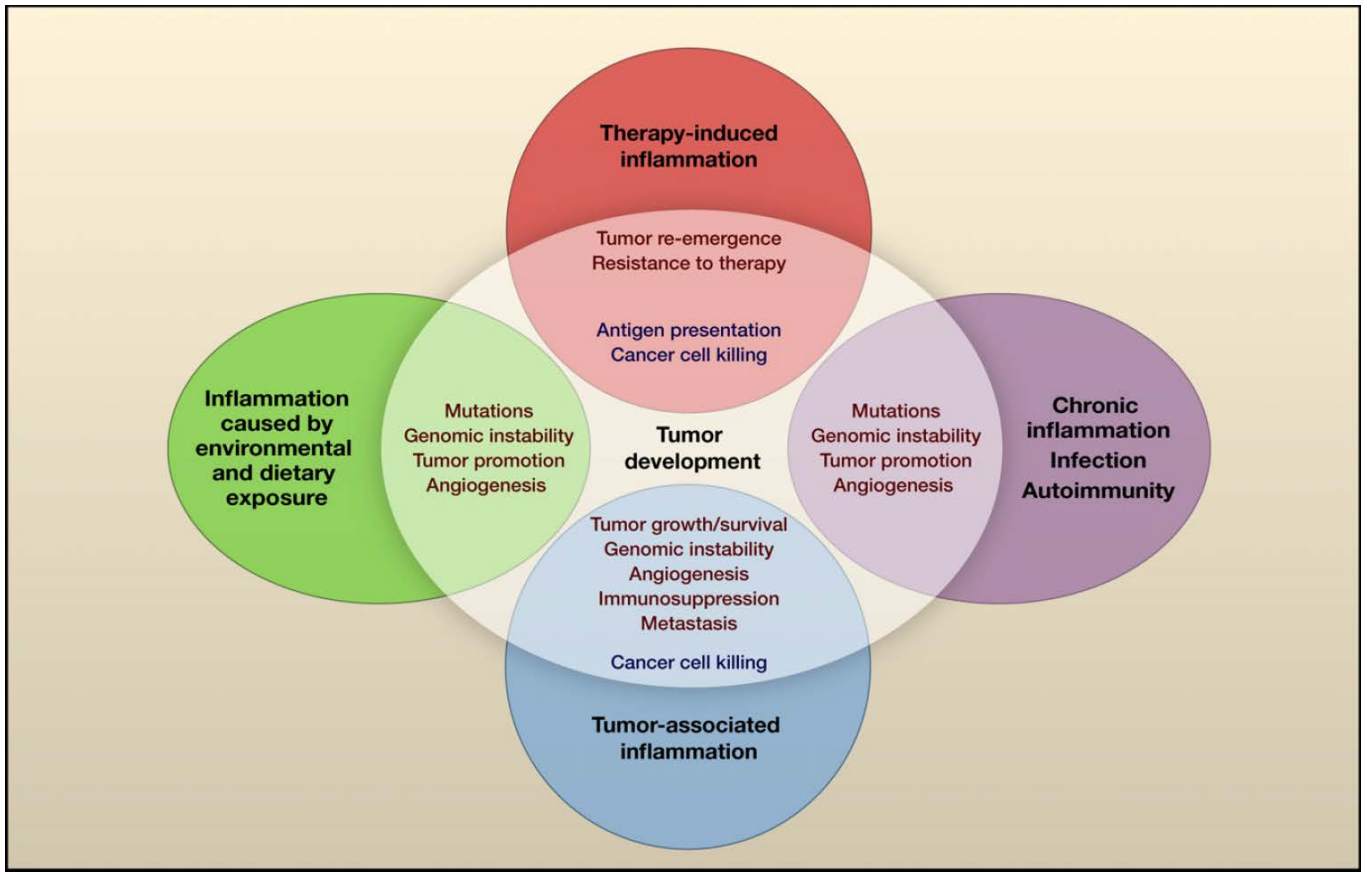
		Canakinumab SC q 3 months			
Adverse Event	**Placebo (N=3347)**	**50 mg (N=2170)**	**150 mg (N=2284)**	**300 mg (N=2263)**	**P-trend**
Any SAE	12.0	11.4	11.7	12.3	0.43
Leukopenia	0.24	0.30	0.37	0.52	0.002
Any infection	2.86	3.03	3.13	3.25	0.12
Fatal infection	0.18	0.31	0.28	0.34	0.09/0.02*
Injection site reaction	0.23	0.27	0.28	0.30	0.49
Any Malignancy	1.88	1.85	1.69	1.72	0.31
Fatal Malignancy	0.64	0.55	0.50	0.31	0.0007
Arthritis	3.32	2.15	2.17	2.47	0.002
Osteoarthritis	1.67	1.21	1.12	1.30	0.04
Gout	0.80	0.43	0.35	0.37	0.0001
ALT > 3x normal	1.4	1.9	1.9	2.0	0.19
Bilirubin > 2x normal	0.8	1.0	0.7	0.7	0.34

* P-value for combined canakinumab doses vs placebo

ALT, alanine aminotransferase;
SAE, serious adverse event; SC, subcutaneous

Ridker PM et al. N Engl J Med. 2017;377:1119-31

Immunity, Inflammation, and Cancer



Sub-clinical chronic inflammation increases cancer risk (hsCRP is also a risk factor for certain cancers, in particular lung cancer)

Inflammation in the tumor micro-environment impacts upon tumor initiation, progression, invasiveness, and metastatic progression

Grivennikov, Greten, Karin. Cell 2010;140:883-99.

Chronic Inflammation, Tumor Progression, and IL-1 Inhibition

Cancer Metastasis Rev (2006) 25:387–408
DOI 10.1007/s10555-006-9004-4

The involvement of IL-1 in tumorigenesis, tumor invasiveness, metastasis and tumor-host interactions

Ron N. Apte · Shahar Dotan · Moshe Elkabets · Malka R. White · Eli Reich · Yaron Carmi · Xiaping Song · Tatyana Dvozkin · Yakov Krelin · Elena Voronov

Ron Apte, et al;
Cancer Metastasis Rev.
2006;25:387-408.

Journal of Translational Medicine BioMed Central

Review Open Access

Interleukin-1 and cancer progression: the emerging role of interleukin-1 receptor antagonist as a novel therapeutic agent in cancer treatment

Anne M Lewis[1,2], Sheelu Varghese[1,3], Hui Xu[1] and H Richard Alexander*[1,3]

Anne Lewis, et al;
J Transl Med.
2006;4:48.

Cancer Metastasis Rev (2010) 29:317–329
DOI 10.1007/s10555-010-9229-0

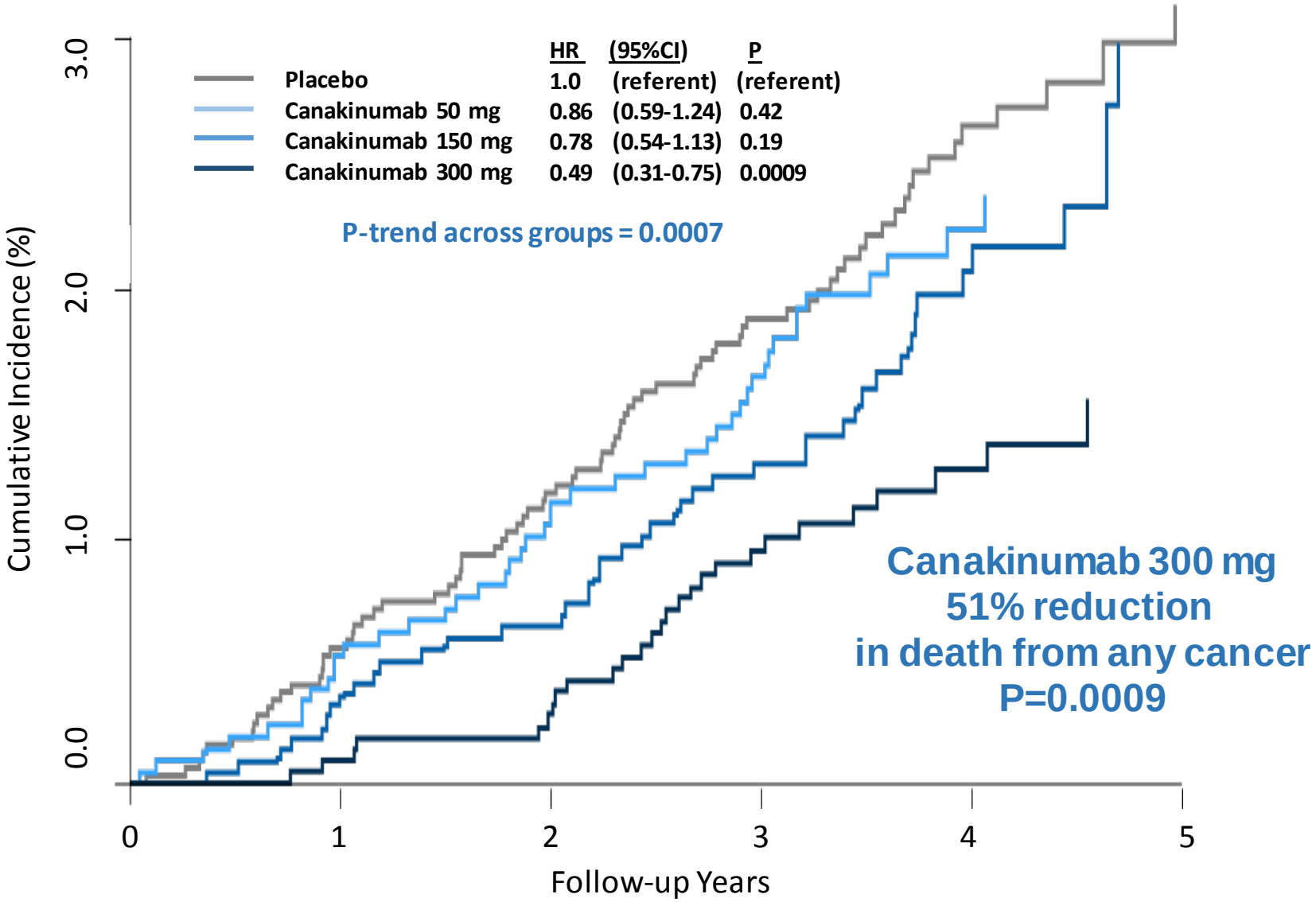
Why not treat human cancer with interleukin-1 blockade?

Charles A. Dinarello

Charles A. Dinarello.
Cancer Metastasis
Rev
2010;29:317-329.

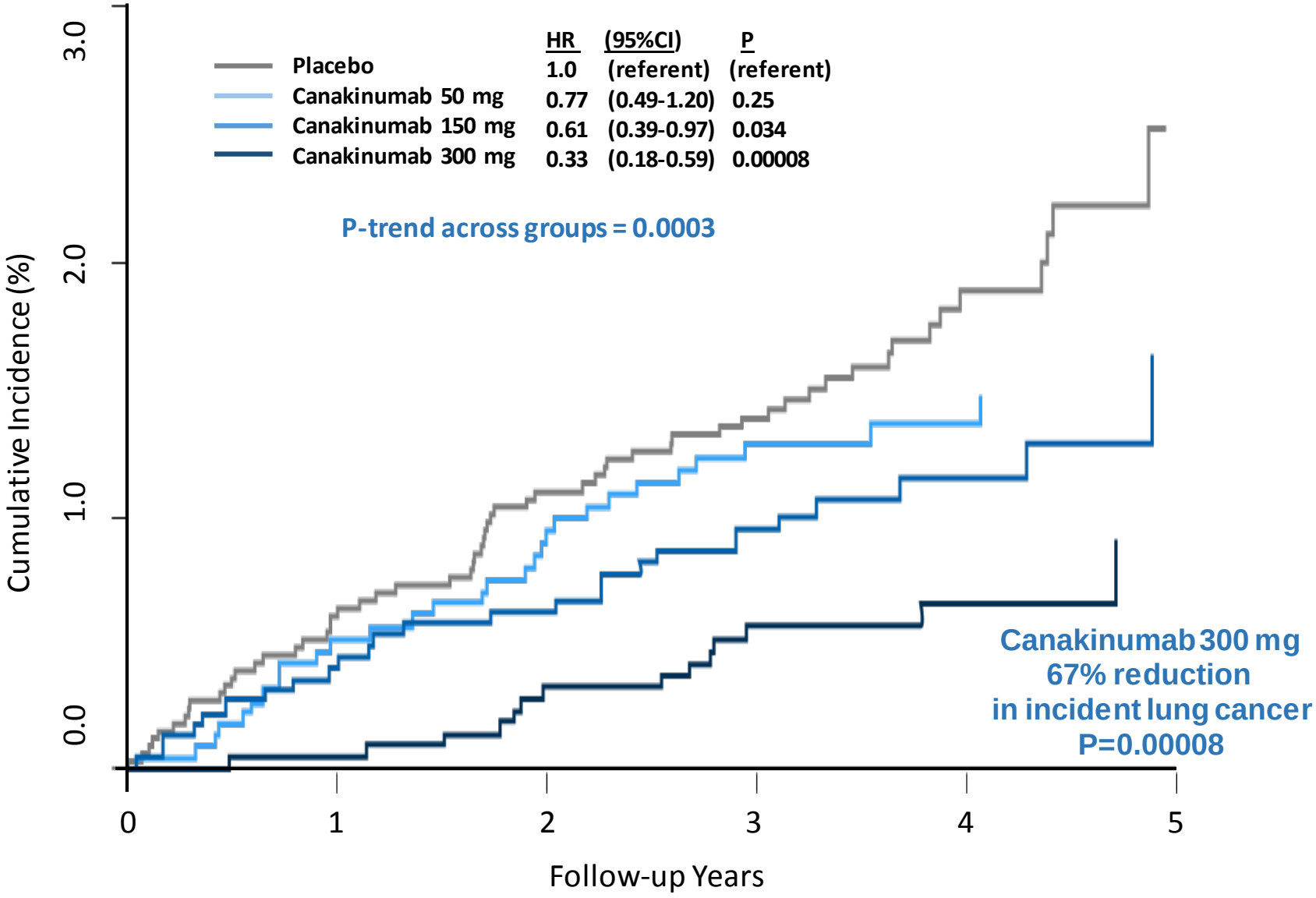
CANTOS: Additional Non-Cardiovascular Clinical Benefits

Cancer Mortality



Ridker PM et al. Lancet. 2017;390:1833-1842

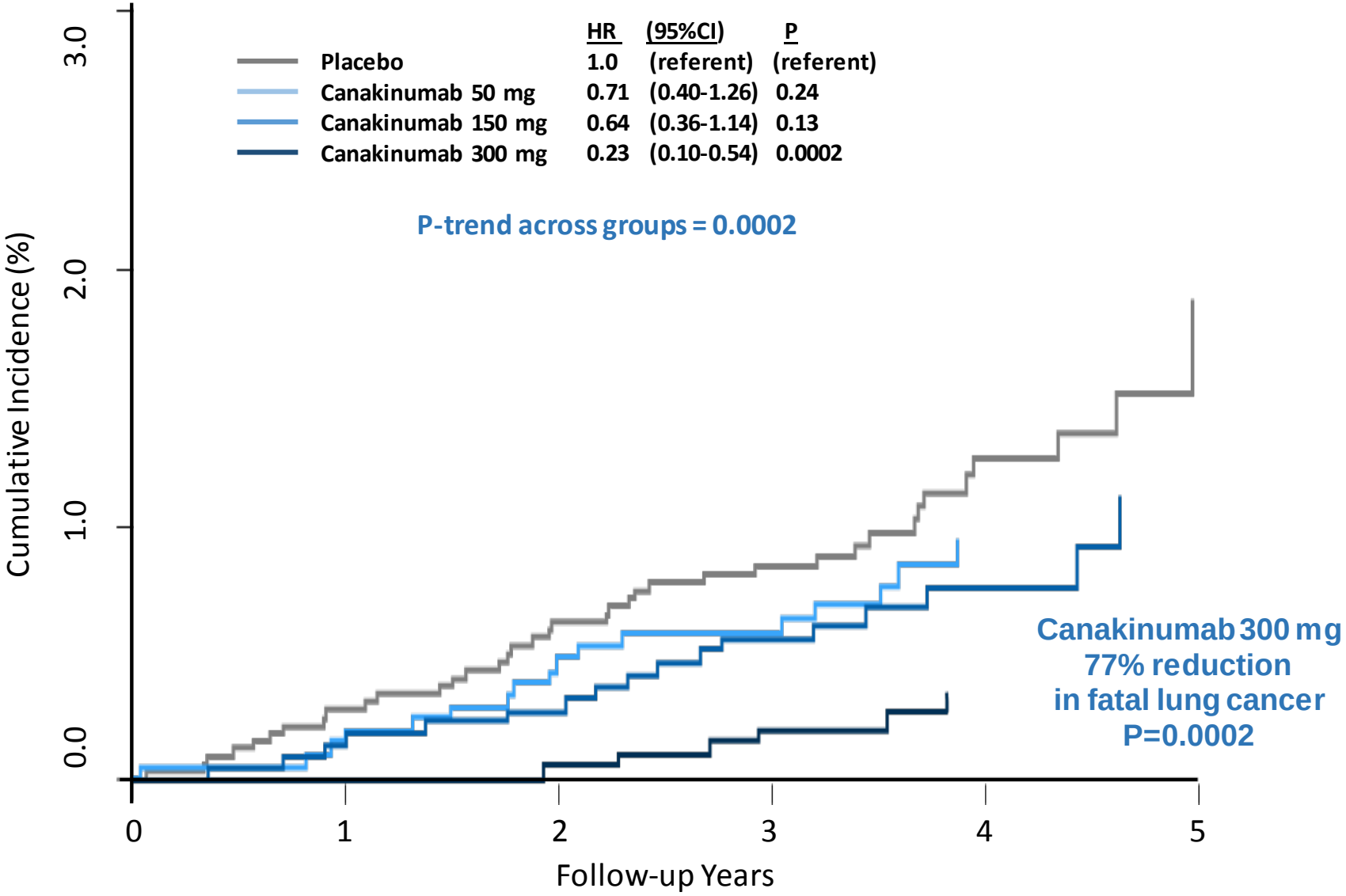
CANTOS: Additional Non-Cardiovascular Clinical Benefits
Incident Lung Cancer



Ridker PM et al. Lancet. 2017;390:1833-1842

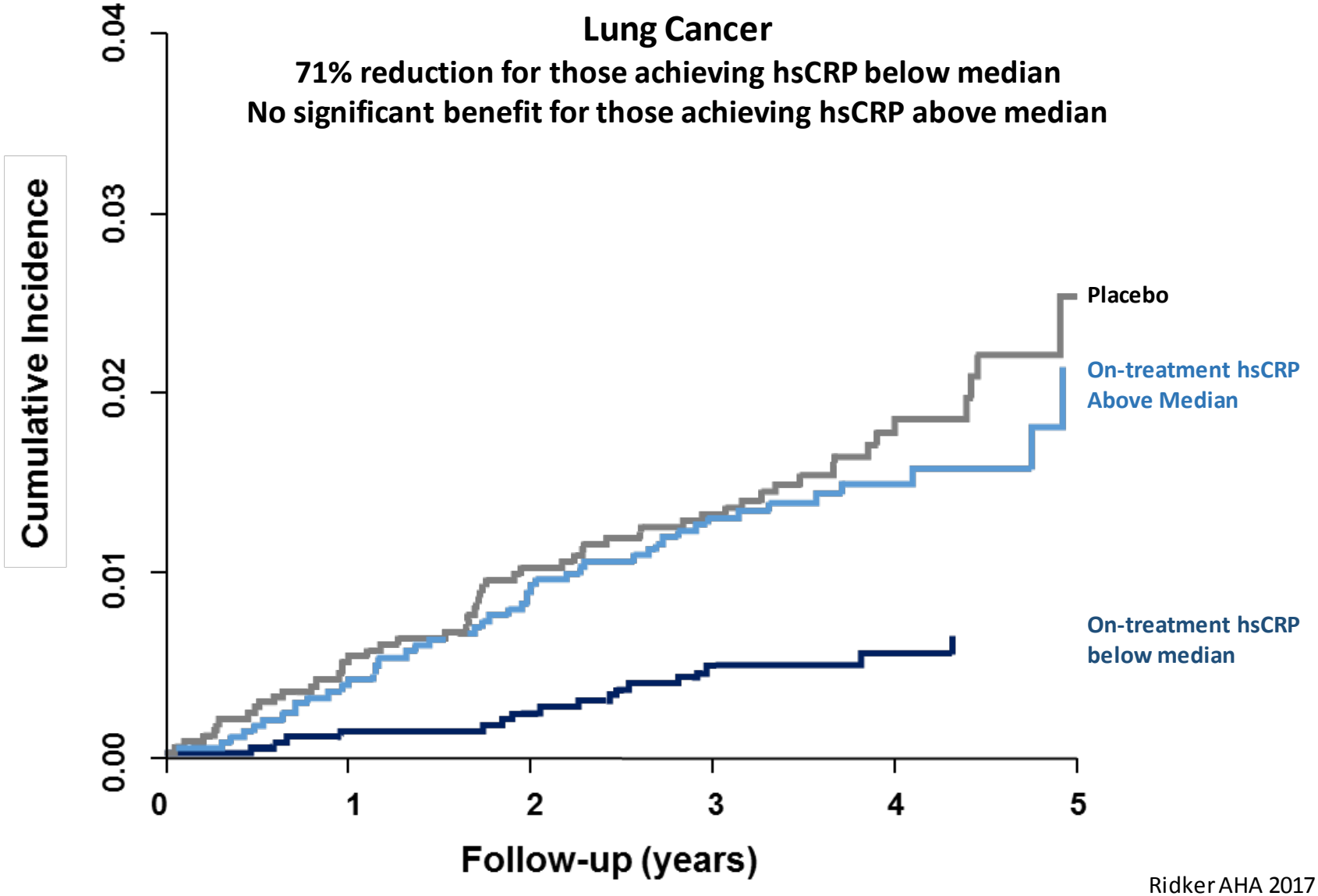
CANTOS: Additional Non-Cardiovascular Clinical Benefits

Fatal Lung Cancer



Ridker PM et al. Lancet. 2017;390:1833-1842

CANTOS: Greater Risk Reduction for Incident Lung Cancer With Greater hsCRP Reduction



Ridker AHA 2017

CANTOS : Adverse Effects

Incidence Rates of Fatal Infection are Not Related to On-Treatment Levels of hsCRP

Clinical Outcome	Placebo (N = 3182)	Canakinumab On-treatment hsCRP ≥ 2mg/L (N = 2868)	Canakinumab On-treatment hsCRP < 2 mg/L (N = 3484)
Fatal Infection Incidence rate (per 100 person years)	**0.18**	**0.35**	**0.27**

Conclusions:

The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

1. CANTOS demonstrates that targeting the IL-1b to IL-6 pathway of innate immunity with canakinumab reduces cardiovascular event rates and potentially reduces rates of incident lung cancer and lung cancer mortality.

2. CANTOS thus provides critical proof-of-concept that inflammation inhibition, in the absence of lipid lowering, can improve atherothrombotic outcomes.

3. The magnitude of hsCRP reduction following a single dose of canakinumab may provide a simple clinical method to identify individuals most likely to accrue the largest cardiovascular and cancer benefits from continued treatment.

Conclusions:

The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

4. For example, among those who achieved levels of hsCRP <2mg/L after a single dose of canakinumab, continued long-term treatment was associated with a 25% reduction in MACE (P<0.0001), a 31% reduction in cardiovascular mortality (P=0.0004) and a 31% reduction in all-cause mortality (P<0.0001). By contrast, effects were smaller in magnitude and non-significant for all of these endpoints among those with a less profound inflammatory response.

5. The differential outcomes observed in CANTOS on the basis of achieved hsCRP concentration were robust to the choice of on-treatment measures, were minimally affected by adjustment for baseline clinical characteristics, were observed at all individual canakinumab doses, and were consistent in causal inference analyses.

Conclusions:

The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

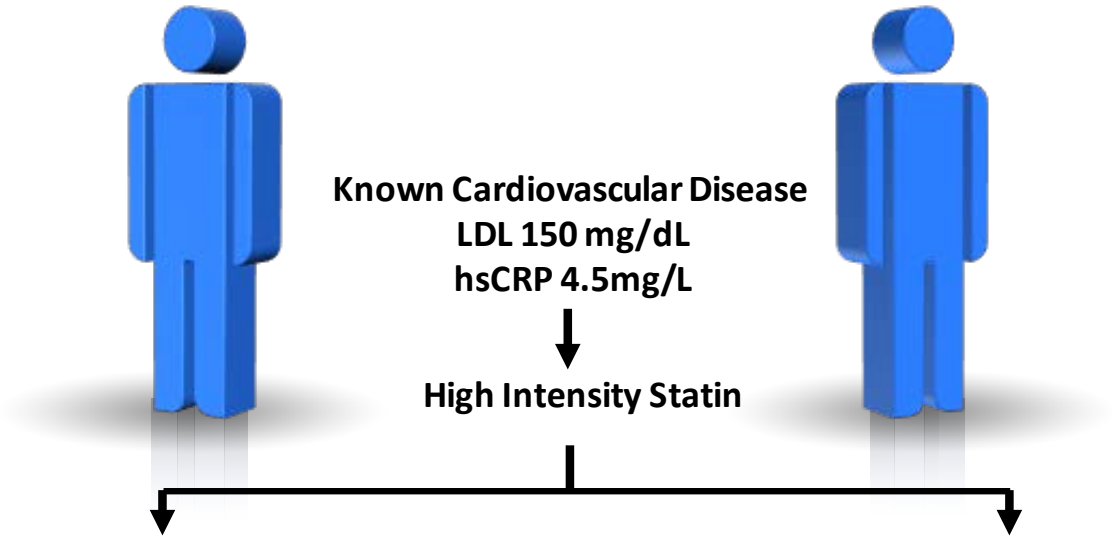
6. The CANTOS data have clinical importance not only for the pathophysiology of inflammation and future drug development, but also for patient selection, cost-effectiveness, and personalized medicine.

7. The 5-year number-needed-to-treat (NNT) for the endpoint of myocardial infarction, stroke, coronary revascularization, or death from any cause was 16 among those with on-treatment concentrations of hsCRP <2mg/L. By contrast, the 5-year NNT was 57 for those treated with canakinumab who did not achieve this inflammation threshold.

8. The main hazard of canakinumab – a small but statistically significant increase in fatal infection – was not related to on-treatment hsCRP levels. As such, the use of biologic response to canakinumab may also provide a simple selection tool to maximize benefit without increasing clinical hazard.

Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Ridker PM. Eur Heart J 2016;37:1720-22



"Residual Cholesterol Risk"

LDL 110 mg/dL
hsCRP 1.8 mg/L

Additional LDL Reduction

IMPROVE-IT : Ezetimibe 6% RRR
FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR

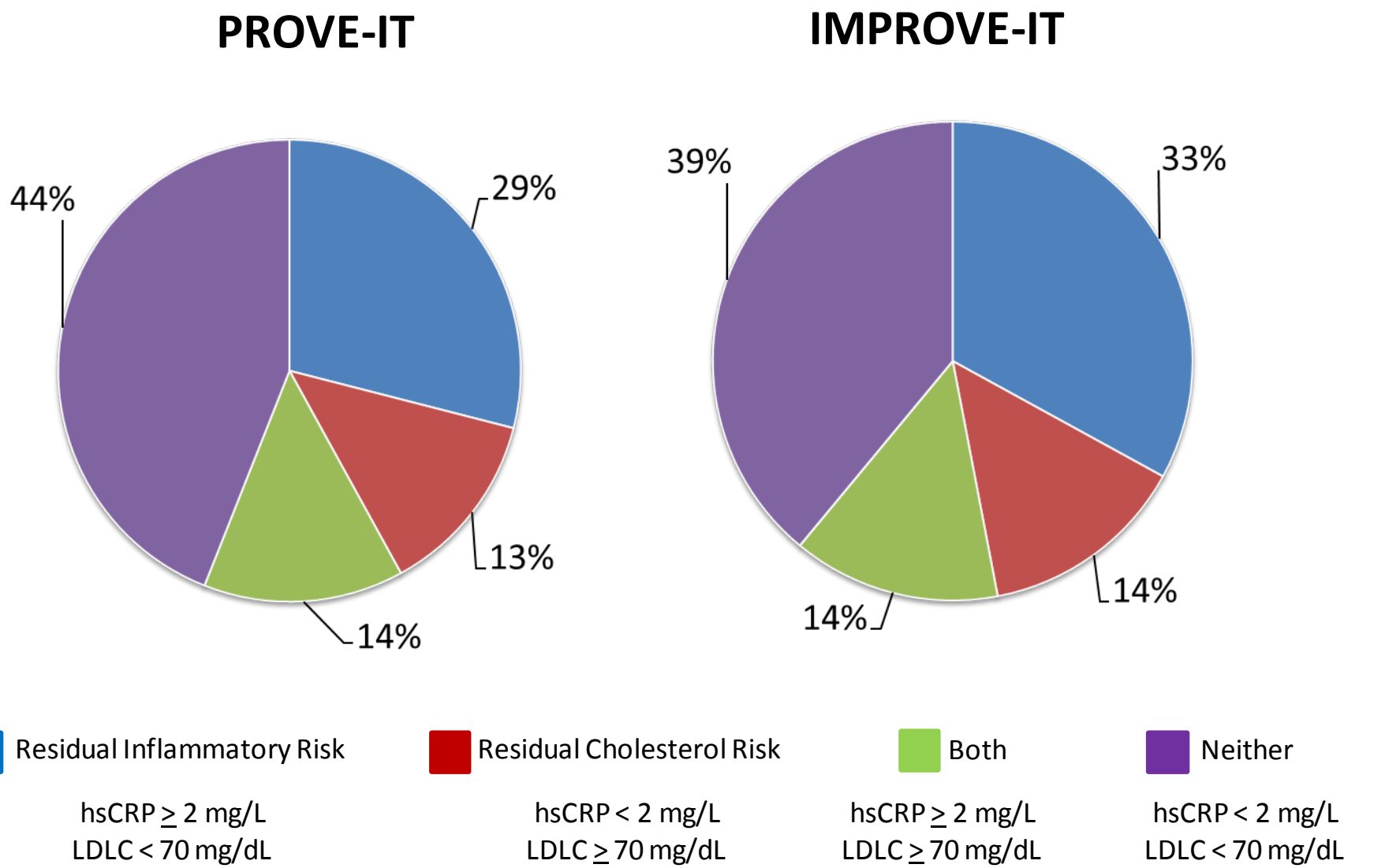
"Residual Inflammatory Risk"

LDL 80 mg/dL
hsCRP 3.8 mg/L

Additional Inflammation Reduction

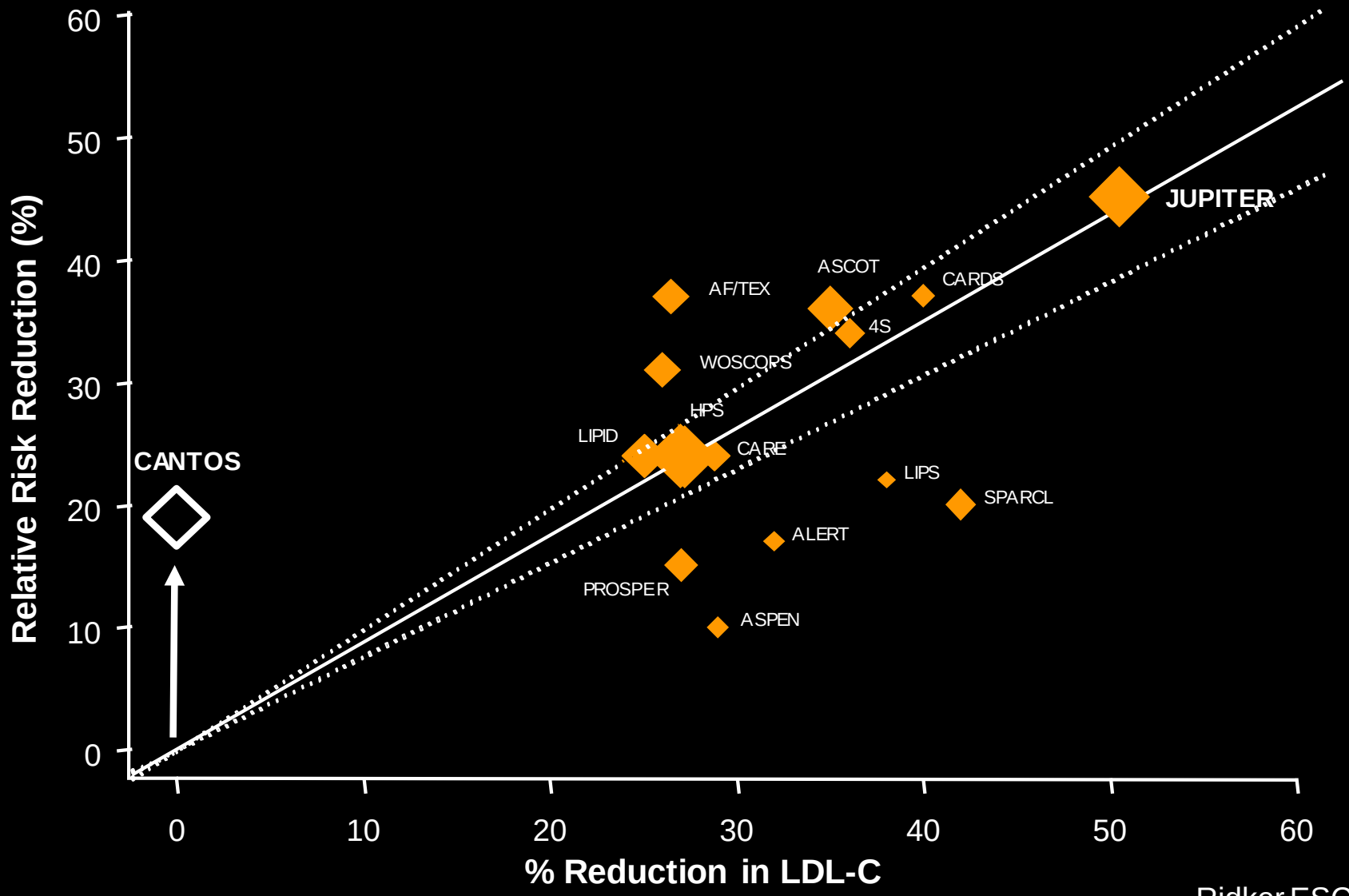
CANTOS
Canakinumab 150mg SC q 3 months 15%RRR

How Common is Residual Inflammatory Risk?



Ridker PM. Circulation Res 2017;120:617-9.

CANTOS : Adding a New Axis to the Oxford LDL Lowering Line



Ridker ESC 2017


Targeting Inflammation in Coronary Artery Disease

Robert A. Harrington, M.D.

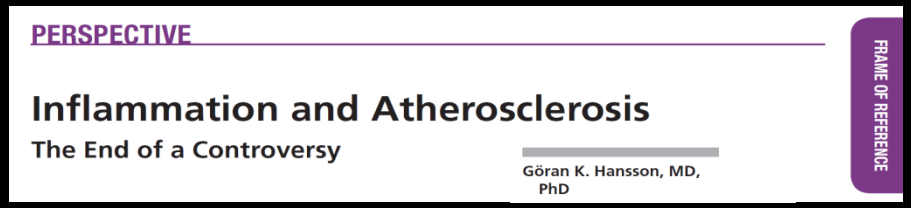
Harrington R.
NEJM 2017;377:1197-8


Interleukin-1 Beta as a Target for Atherosclerosis Therapy

Biological Basis of CANTOS and Beyond

Peter Libby, MD

Libby P.
JACC 2017;18:2278-89


PERSPECTIVE

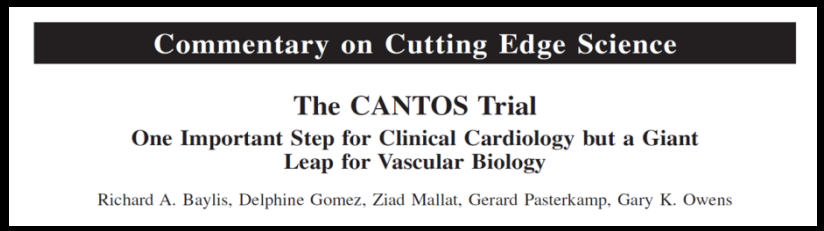
Inflammation and Atherosclerosis

The End of a Controversy

Göran K. Hansson, MD, PhD

FRAME OF REFERENCE

Hansson GK.
Circulation 2017;136:1875-1877


Commentary on Cutting Edge Science

The CANTOS Trial

One Important Step for Clinical Cardiology but a Giant Leap for Vascular Biology

Richard A. Baylis, Delphine Gomez, Ziad Mallat, Gerard Pasterkamp, Gary K. Owens

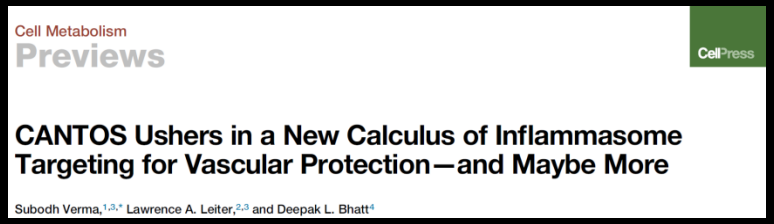
Baylis RA, Gomez D, Mallat Z, Pasterkamp G, Owens GK.
ATVB 2017;11:


Cardiovascular Pharmacology

Inflammation Revisited: Atherosclerosis in The Post-CANTOS Era

Wolfgang Koenig[1,2]

Koenig W.
Cardiovasc Pharmacol 2017


Cell Metabolism

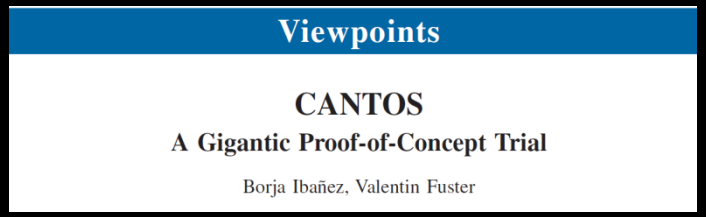
Previews

CellPress

CANTOS Ushers in a New Calculus of Inflammasome Targeting for Vascular Protection—and Maybe More

Subodh Verma,[1,3,*] Lawrence A. Leiter,[2,3] and Deepak L. Bhatt[4]

Verma S, Leiter LA, Bhatt DL.
Cell Metabolism 2017


Viewpoints

CANTOS

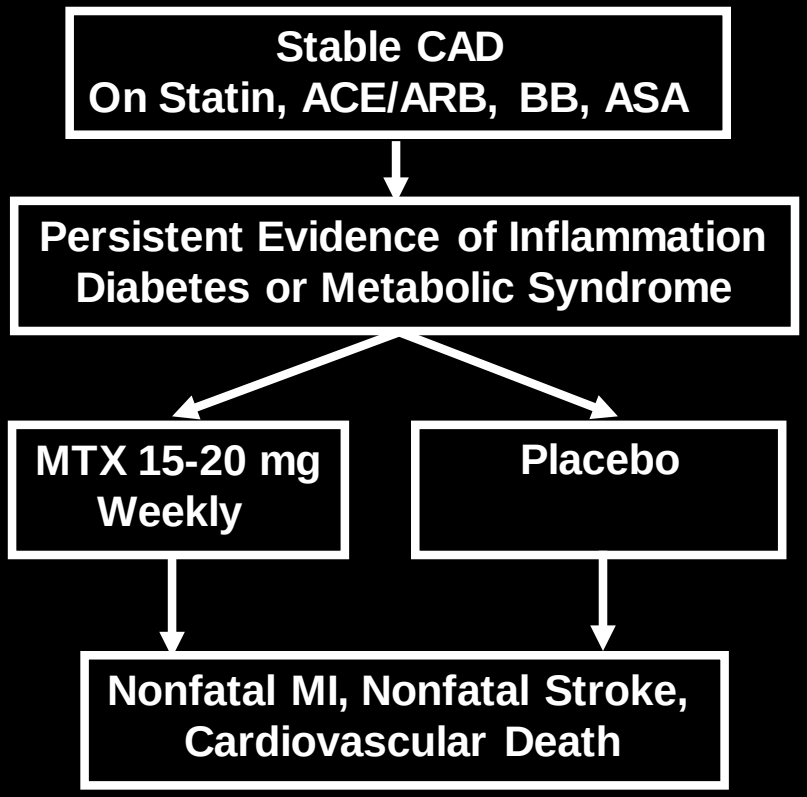
A Gigantic Proof-of-Concept Trial

Borja Ibañez, Valentin Fuster

Ibanez, Fuster
JACC 2017

Cardiovascular Inflammation Reduction Trial (CIRT)

Primary Aims (NHLBI - Ridker PI)



- To directly test the inflammatory hypothesis of atherothrombosis
- To evaluate in a randomized, double-blind, placebo-controlled trial whether MTX given at a target dose of 20 mg po weekly over a three year period will reduce rates of recurrent myocardial infarction, stroke, or cardiovascular death among patients with a prior history of atherosclerosis and either type 2 diabetes or metabolic syndrome.

CIRT | CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

N = 7,000 NHLBI-Sponsored
350 US and Canadian Sites

1932

Arthur Eisner 1907-1956

Frances Eisner 1909-1974