Anti-inflammatory therapy in cardiovascular disease

2019 ACP Oklahoma Chapter Scientific Meeting
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Relevant Disclosures and Resolution

Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

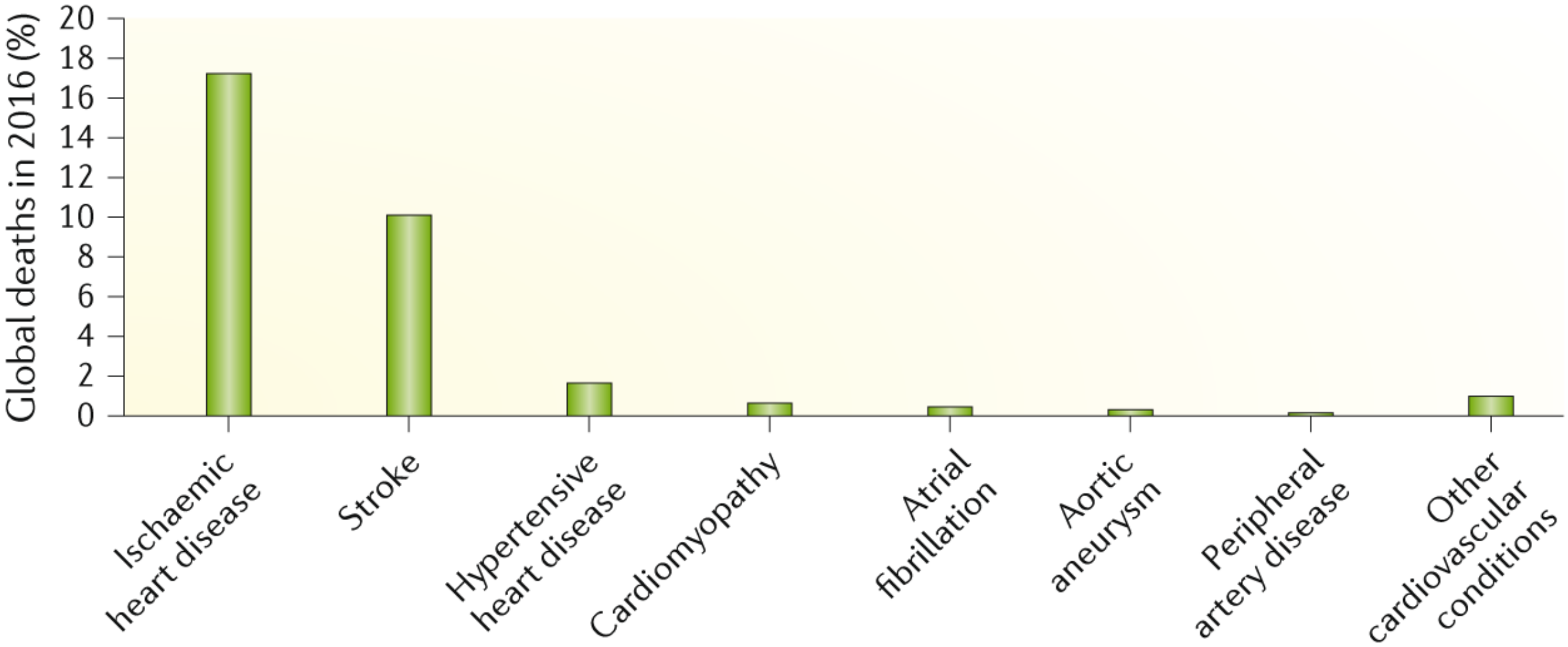
- No financial disclosures

Learning Objectives

Upon completion of this session, participants will improve their competence and performance by being able to:

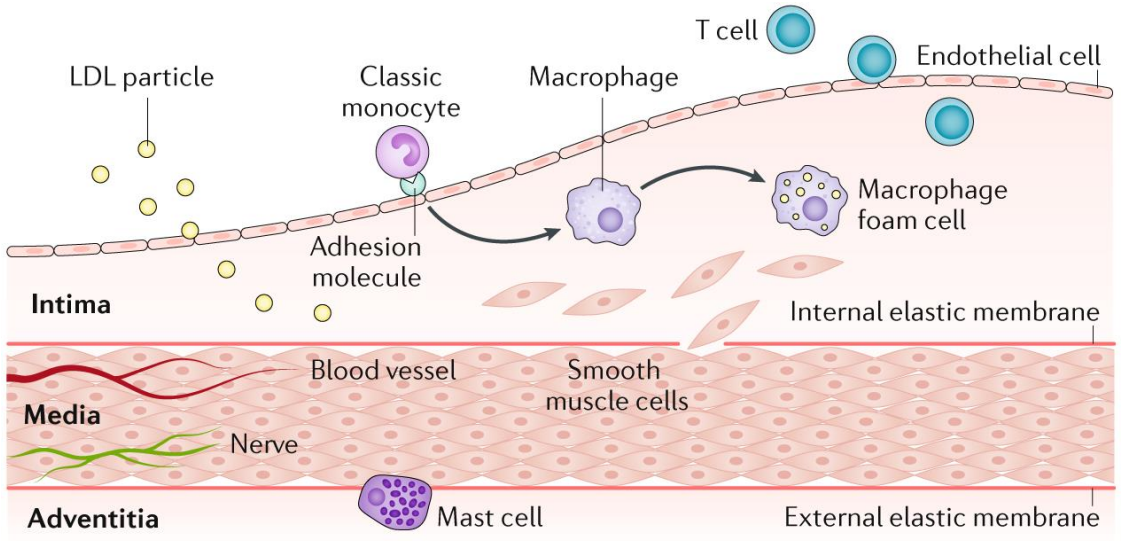
- Describe the role of inflammation in the pathogenesis of atherosclerosis
- Describe the role of anti-inflammatory therapy in the prevention of cardiovascular events

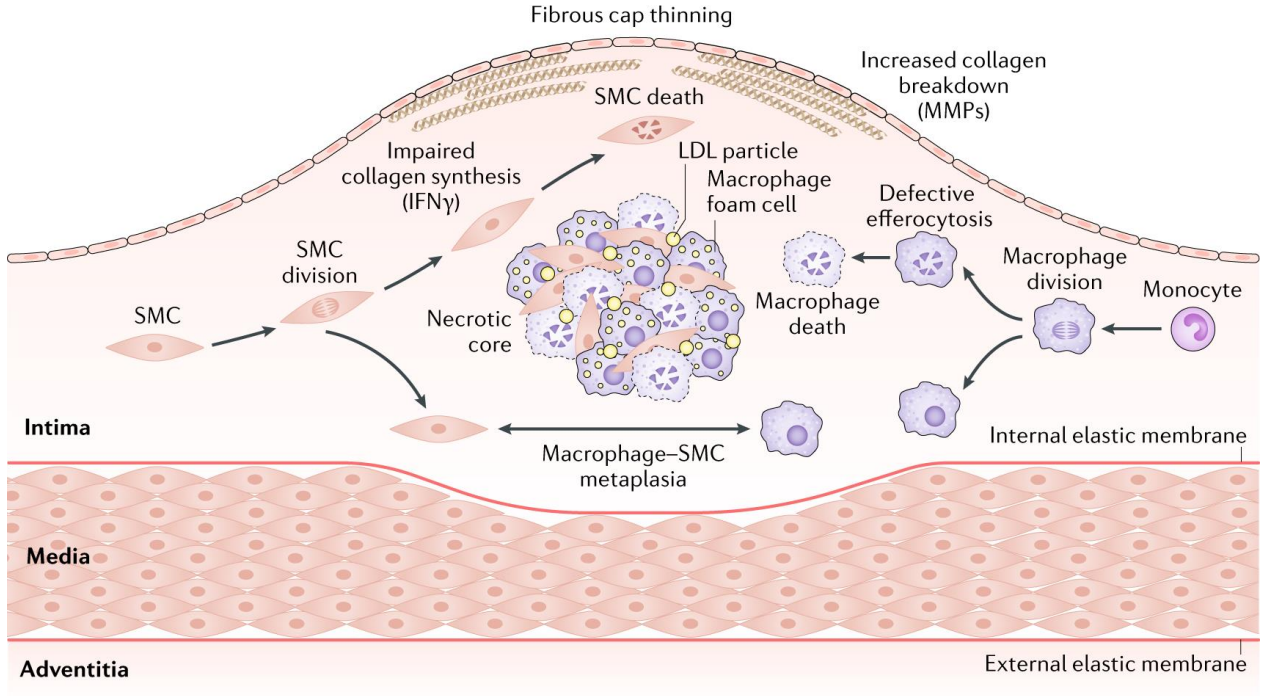
The burden of atherosclerotic cardiovascular disease



Libby P et al. Nat Rev Dis Primers 2019

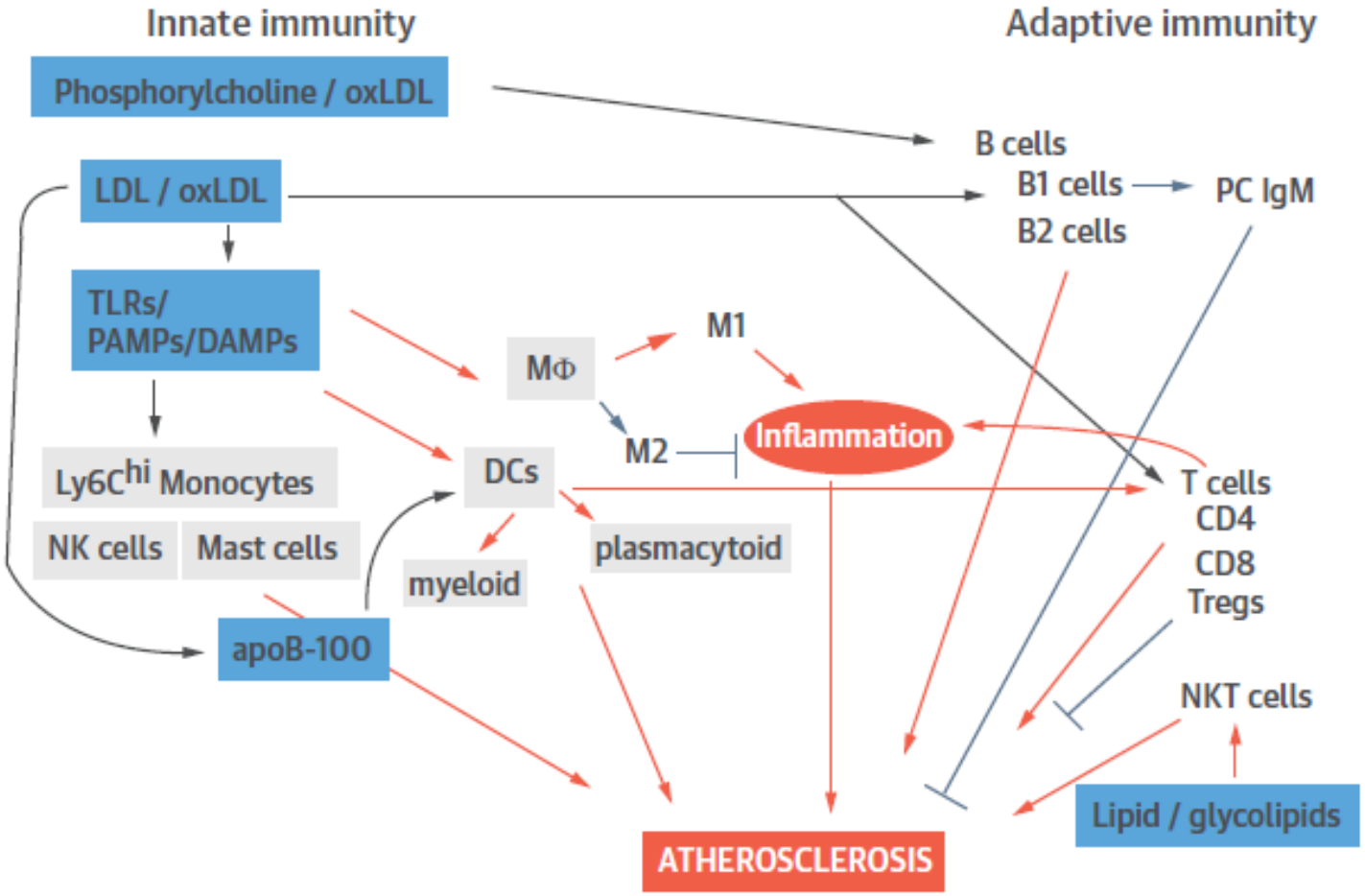
Pathogenesis of atherosclerotic lesions





Libby P et al. Nat Rev Dis Primers 2019

Complex interactions among components of the innate and adaptive immunity in atherogenesis



Shah PK et al. JACC 2014

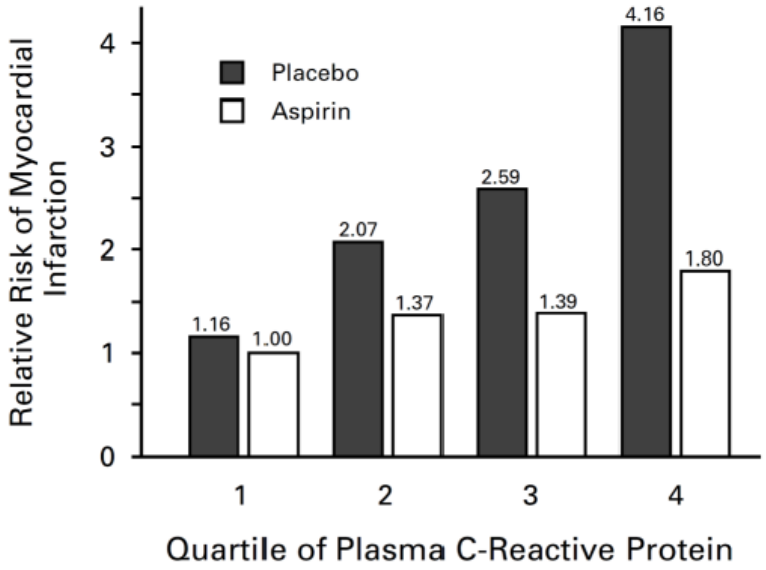
Low Grade Systemic Inflammation *Precedes* By Many Years the Onset of Vascular Events

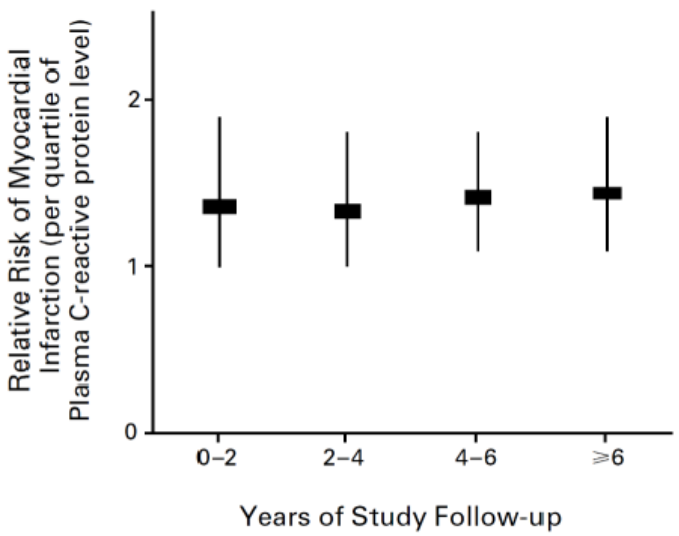
The New England
Journal of Medicine

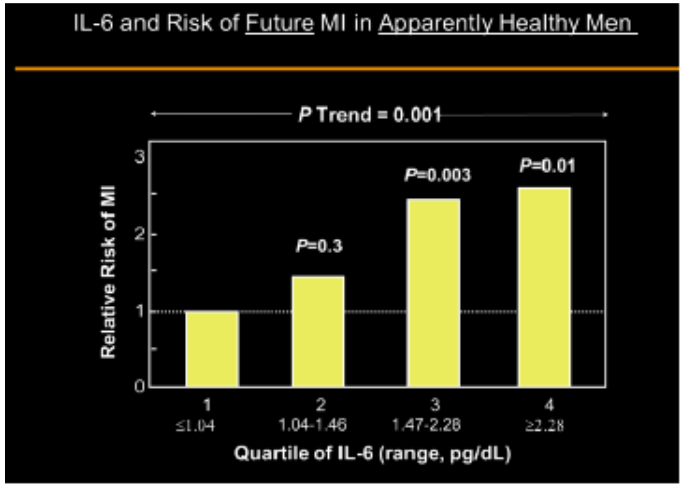
VOLUME 336 APRIL 3, 1997 NUMBER 14

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 PM et al. Circulation 2000

The NEW ENGLAND JOURNAL of MEDICINE

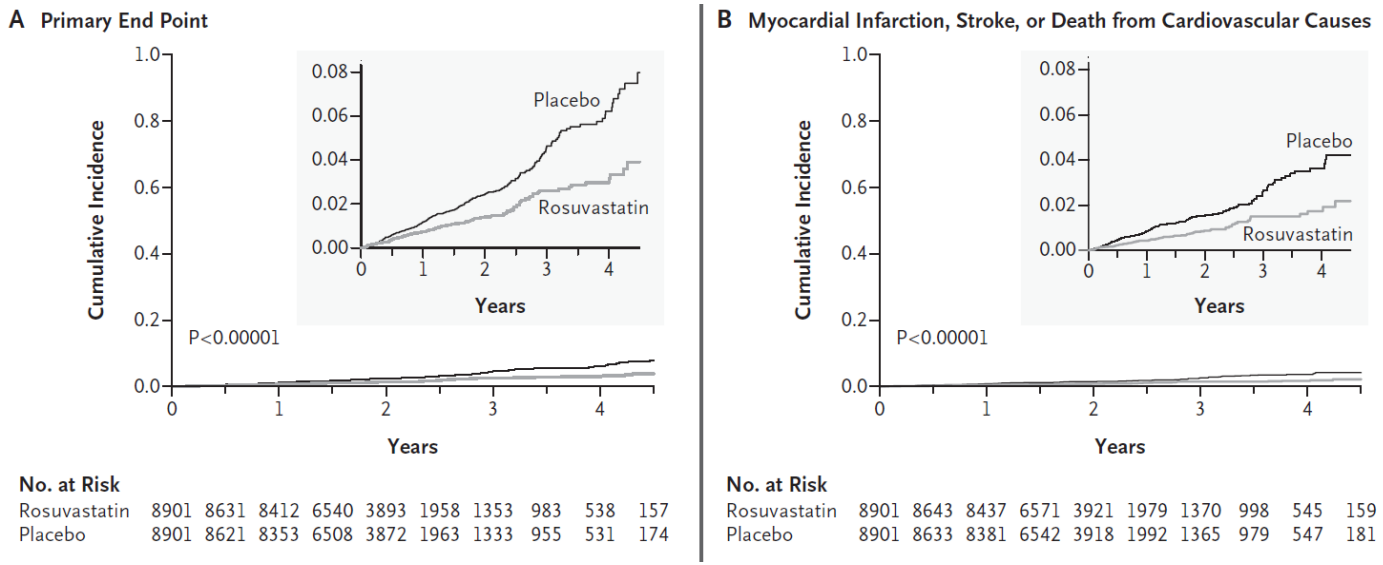
ESTABLISHED IN 1812 NOVEMBER 20, 2008 VOL. 359 NO. 21

CRP>2mg/L

LDL<130mg/dL

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

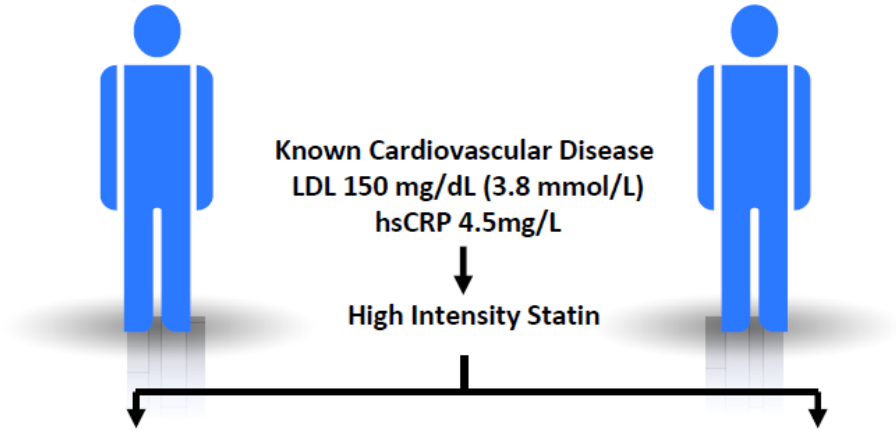
Paul M Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Robert J. Glynn, Sc.D., for the JUPITER Study Group*



Statins are both lipid lowering and anti-inflammatory, and the greatest benefits of statin therapy accrue to those who not only lower LDLC, but who also lower hsCRP.

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"

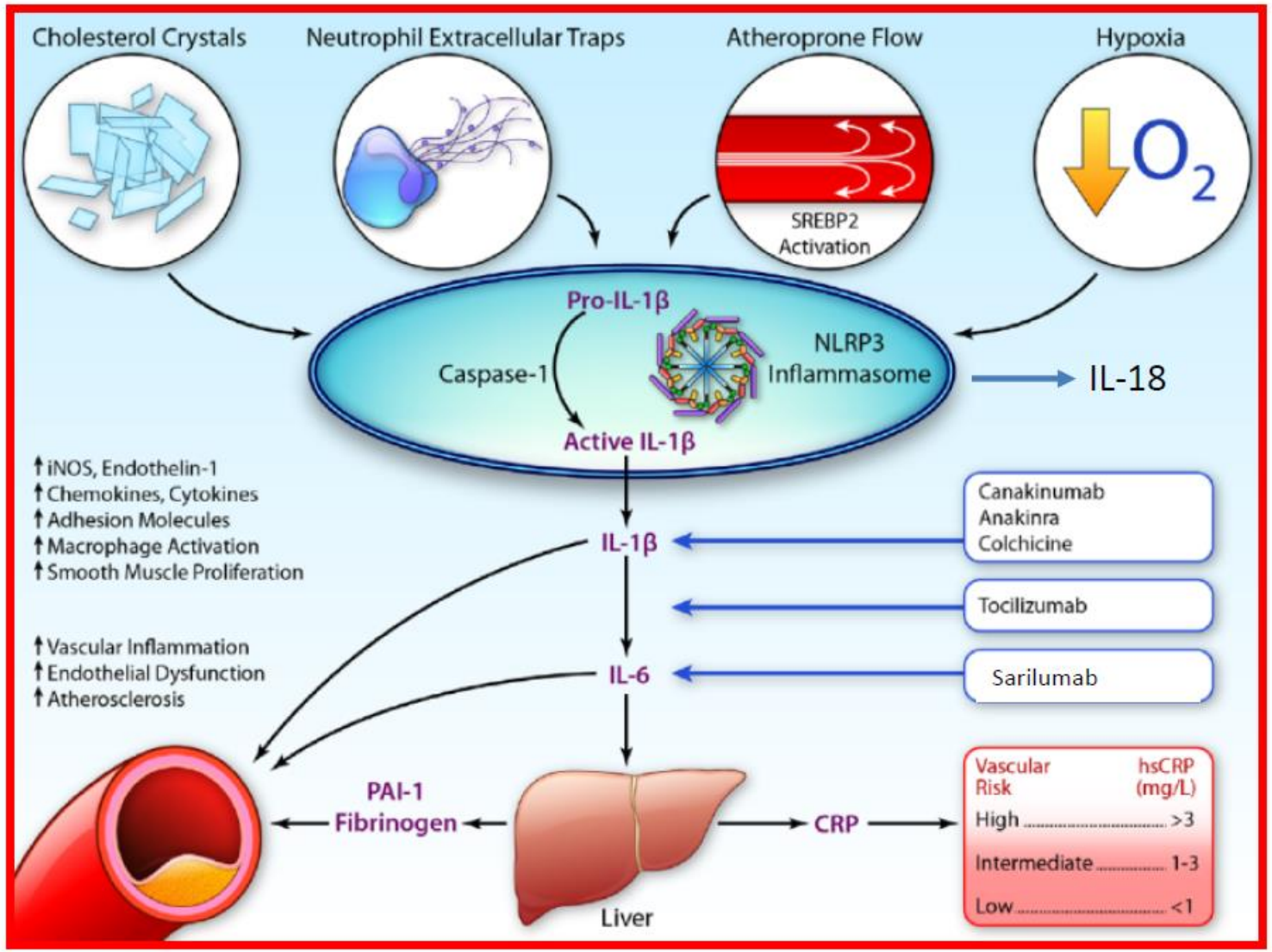
LDL 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L

Additional
Inflammation Reduction

No Prior Proof of Concept

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

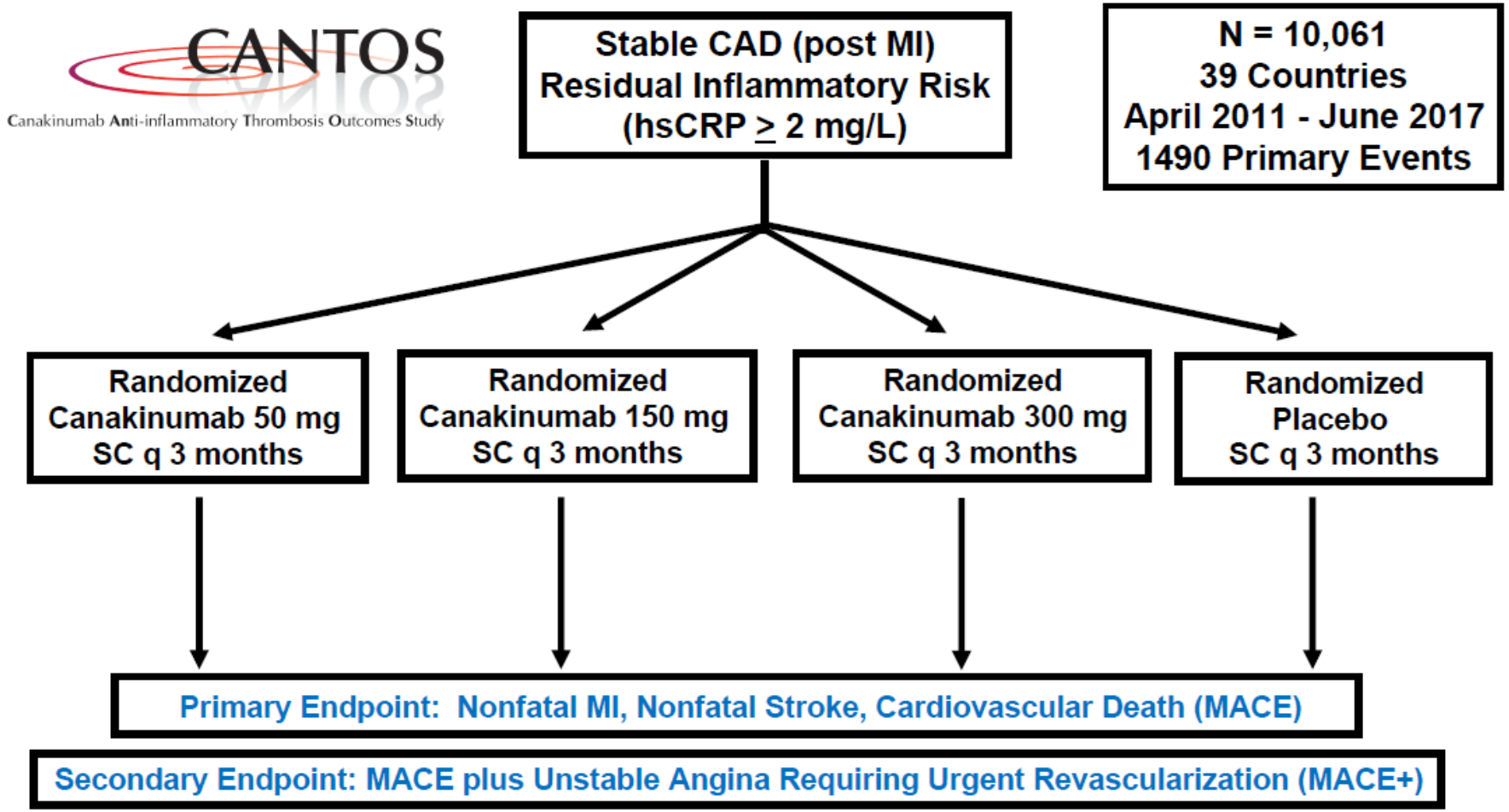


Ridker PM. Circ Res 2016;118:145-156.

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

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

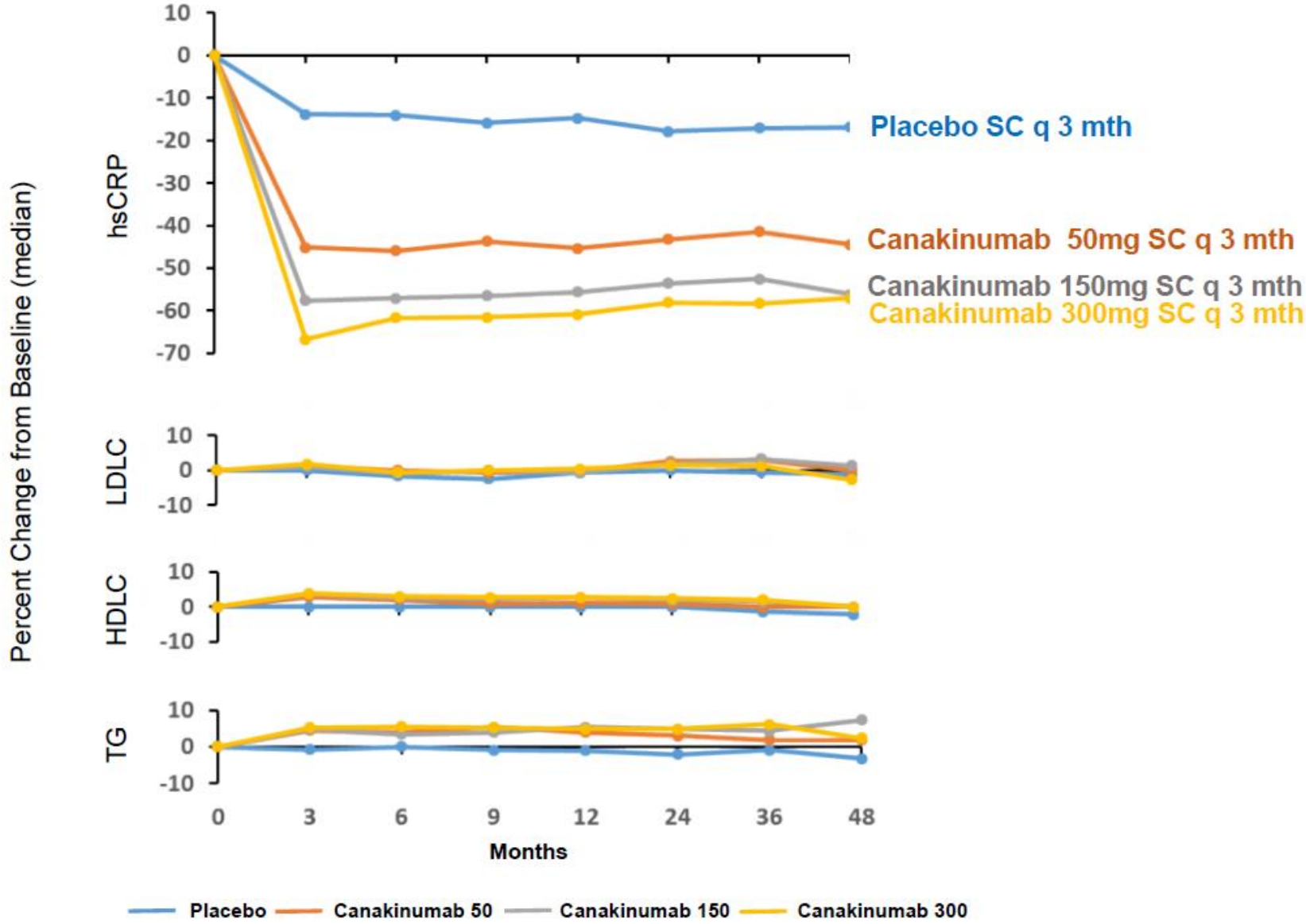


"Residual Inflammatory Risk"

Baseline LDLC 82mg/dL (2.1mmol/L) but hsCRP 4.1 mg/L

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

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

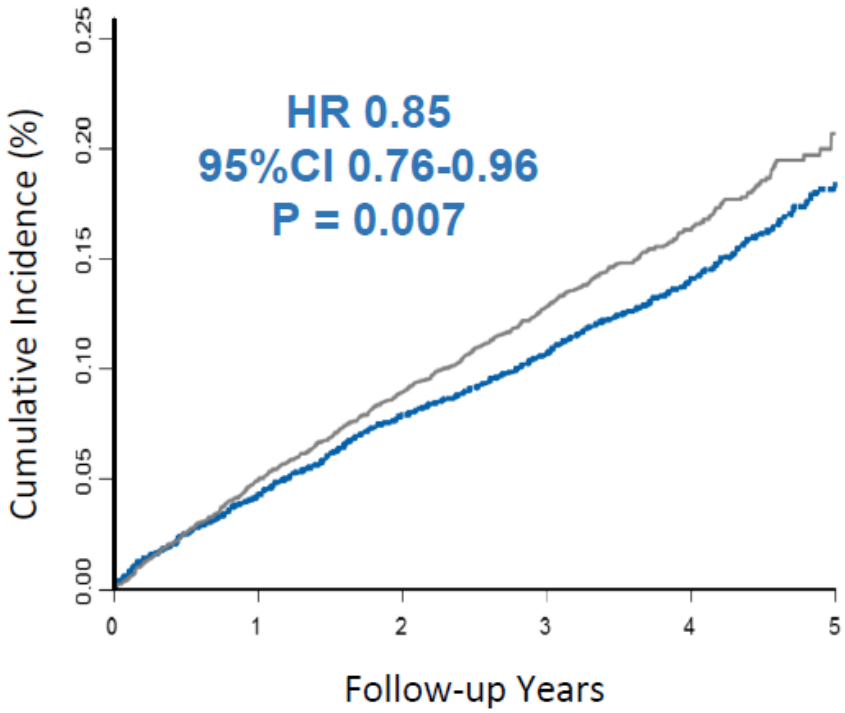


Ridker PM et al. N Engl J Med. 2017;377:1119-31

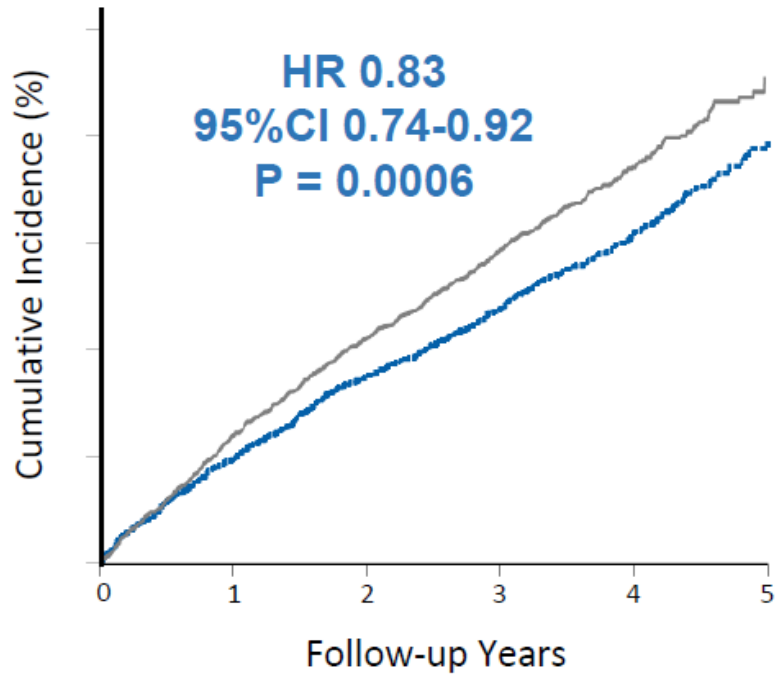
CANTOS: Primary Cardiovascular Endpoints

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

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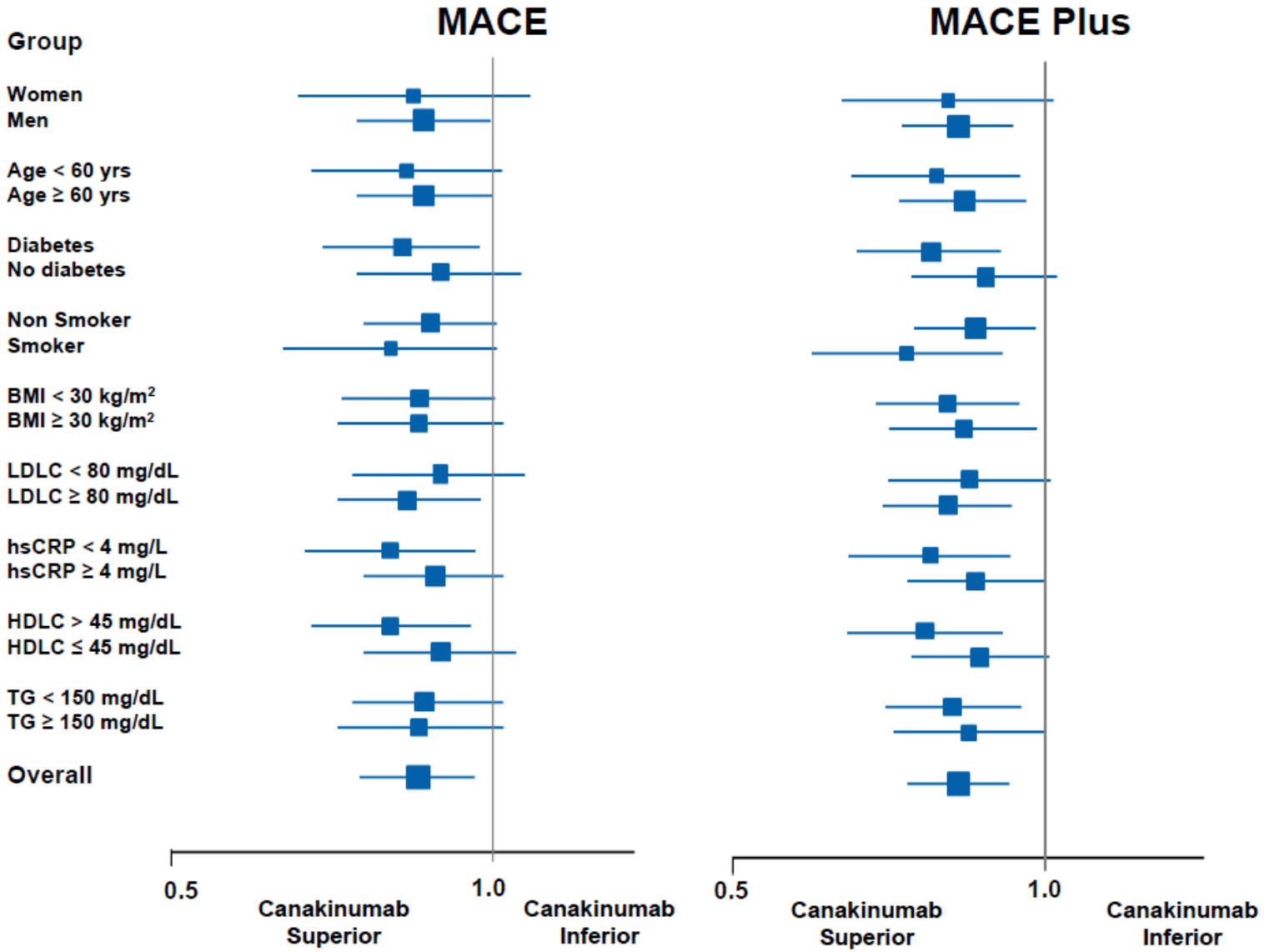
CANTOS : Consistency of Effect Across All patient Groups Defined By Baseline Clinical Characteristics



Ridker et al Lancet 2018;391:319-328

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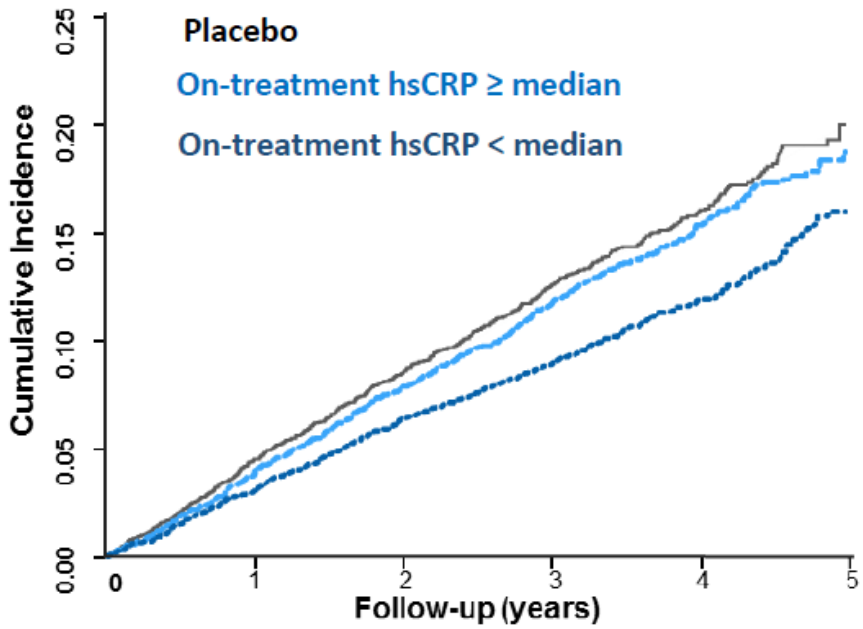
CANTOS: Greater Risk Reduction With Greater Cytokine Inhibition (MACE)

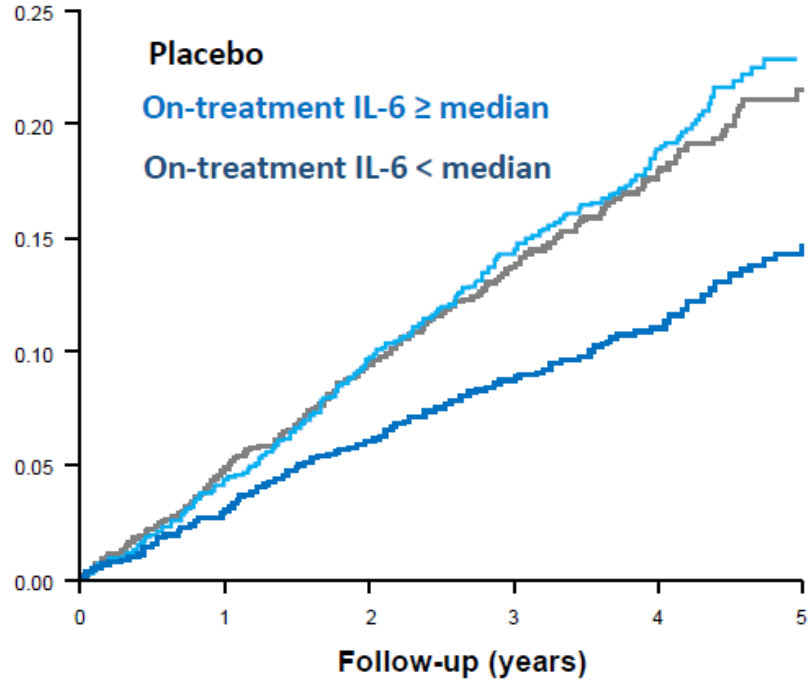
On-Treatment hsCRP



MACE
25% reduction in risk for those achieving hsCRP below median
5 % reduction in risk for those achieving hsCRP above median
(No change in LDL cholesterol)

Lancet 2018;391:319-328

On-Treatment IL-6

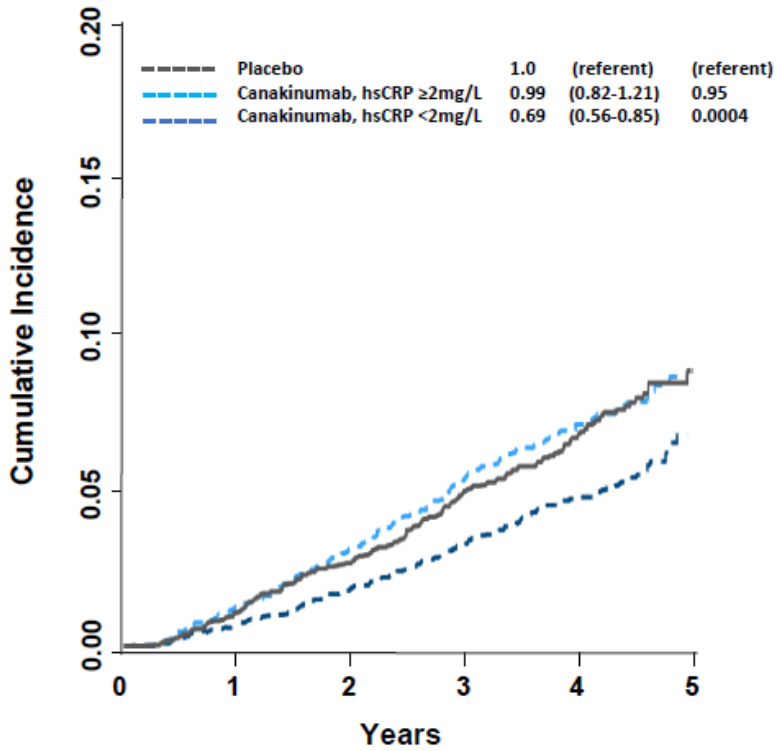


MACE
36% reduction for those achieving IL-6 below median
No benefit for those achieving IL-6 above median
(No change in LDL cholesterol)

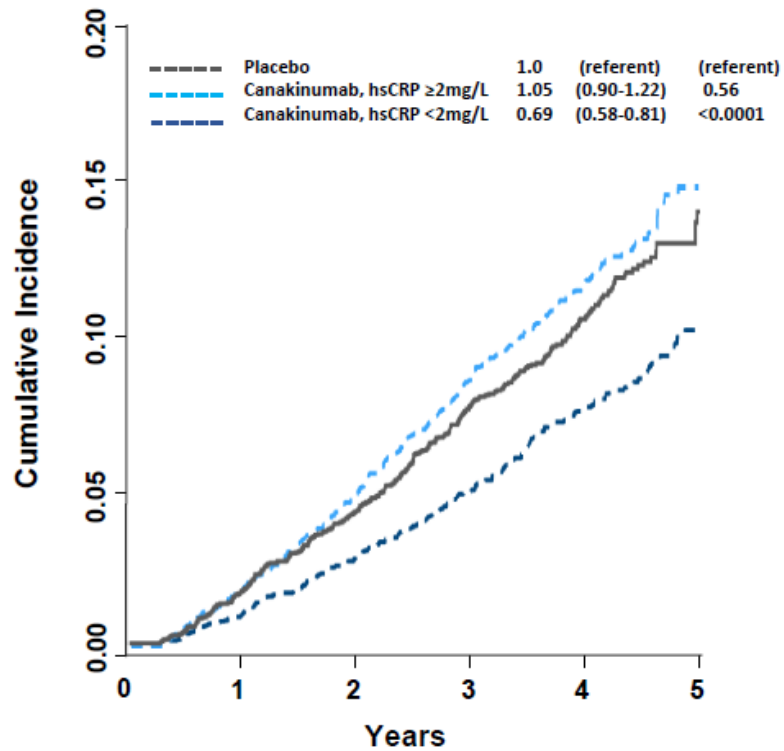
Eur Heart J 2018;39:3499-3507

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

Circulation 2018;137:1763-1766

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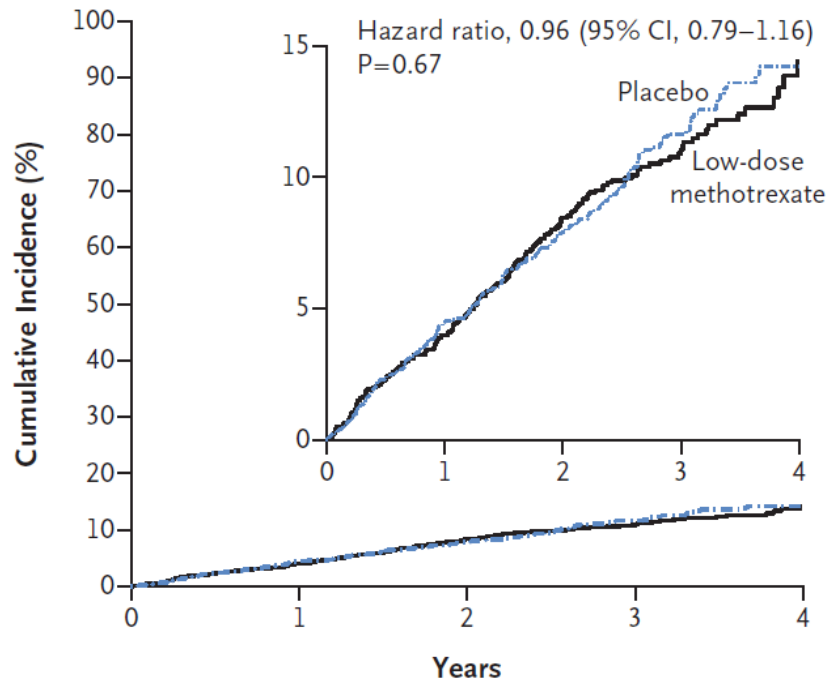
CIRT: low dose methotrexate for the prevention of atherosclerotic events

CIRT | CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

Ridker et al, N Engl J Med. 2019; 380:752-762

- 4786 patients with prior MI with DM or metabolic syndrome
- Methotrexate 15mg to 20mg weekly vs. placebo



No. at Risk					
Low-dose methotrexate	2391	1754	1175	611	153
Placebo	2395	1722	1167	593	143

Interleukin-1β Inhibition

CANTOS

Canakinumab Anti-inflammatory Thrombosis Outcomes Study

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

- ↓ IL-1β
- ↓ IL-6
- ↓ hsCRP
- ↓ 15-17% reduction in MACE and MACE+
- ↓ 50-70% reduction in Lung Cancer

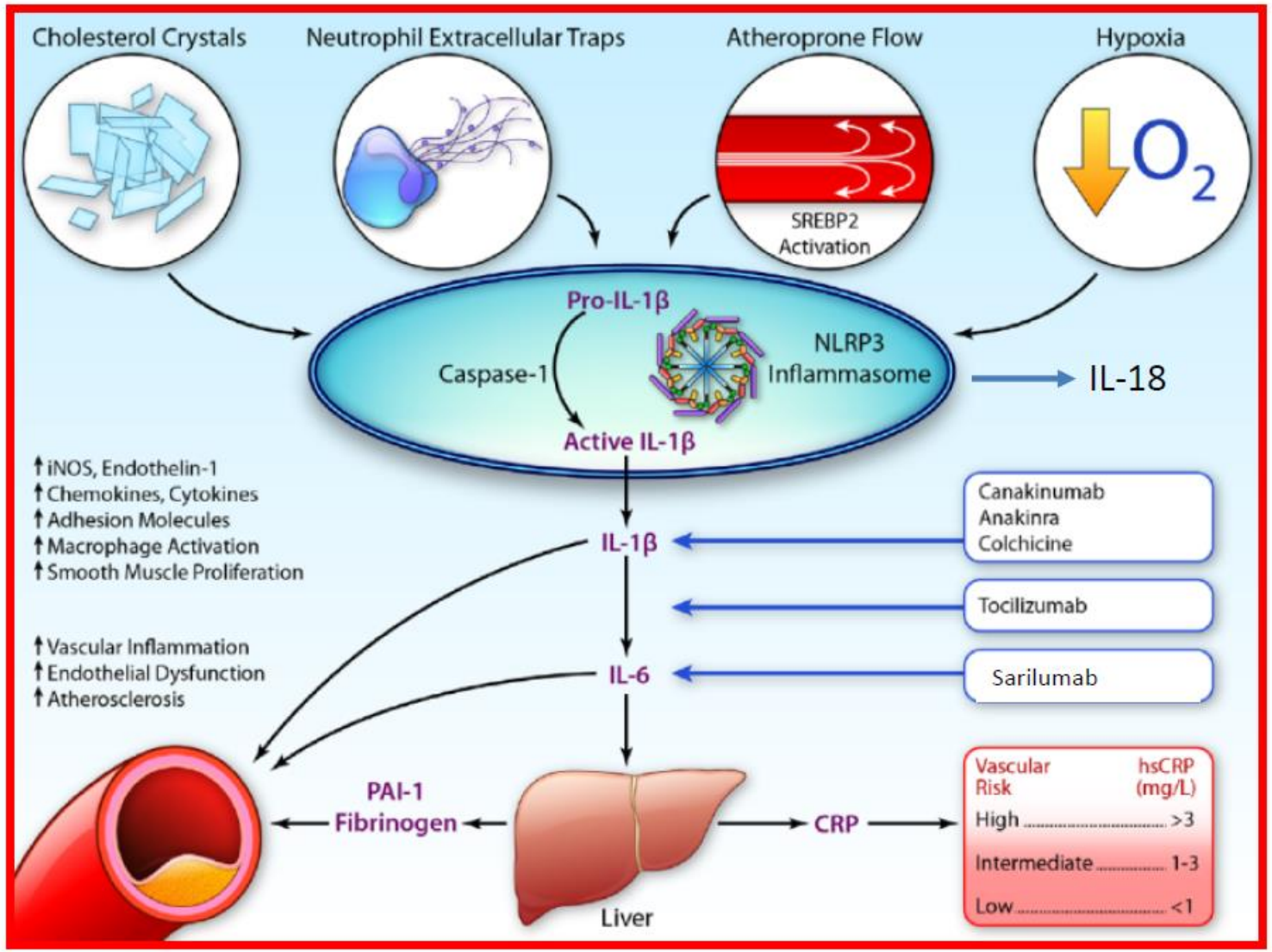
Low-Dose Methotrexate

CIRT | Cardiovascular Inflammation Reduction Trial

Ridker et al, N Engl J Med. 2019; 380:752-762

- ↔ IL-1β
- ↔ IL-6
- ↔ hsCRP
- ↔ No reduction in MACE and MACE+
- ↔ No reduction in Lung Cancer
- ↑ Non-basal cell Skin Cancer

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



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

Alternative Agents For Anti-Inflammatory Approaches to Atherosclerosis

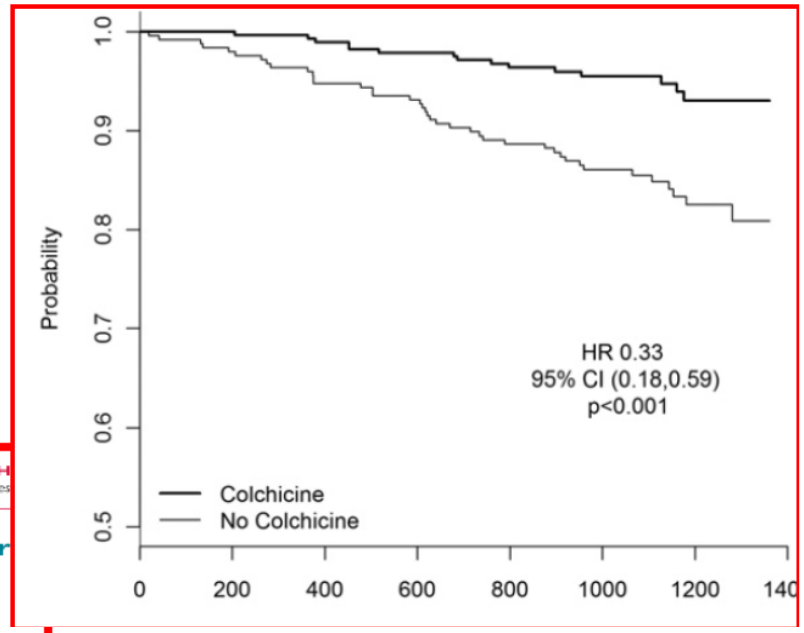
CLINICAL RESEARCH — Clinical Trial

Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease

Stefan M. Nidorf, MD, MBBS,* John W. Eikelboom, MBBS,† Charley A. Budgeon, BSc (Hons),‡ Peter L. Thompson, MD§

Colchicine

Prevented cardiovascular events



European Heart Journal (2015) 36, 377–384
doi:10.1093/eurheartj/ehu272

CLINICAL RESEARCH
Acute coronary syndromes

The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study

Allison C. Morton[1†], Alexander M. K. Rothman[1,2†], John P. Greenwood[3], Julian Gunn[1,2], Alex Chase[4], Bernard Clarke[5], Alistair S. Hall[3], Keith Fox[6], Claire Foley[7], Winston Banya[7], Duolao Wang[8], Marcus D. Flather[7,9], and David C. Crossman[10*]

European Heart Journal
doi:10.1093/eurheartj/ehw171

CLINICAL RESEARCH
Acute coronary syndromes

Effect of a single dose of the interleukin-6 receptor antagonist tocilizumab on inflammation and troponin T release in patients with non-ST-elevation myocardial infarction: a double-blind, randomized, placebo-controlled phase 2 trial†

Ola Kleveland[1,2*], Gabor Kunszt[4,6], Marte Bratlie[4,5,6], Thor Ueland[5,6,7,8], Kaspar Broch[4,8], Espen Holte[1,2], Annika E. Michelsen[5,6], Bjørn Bendz[4], Brage H. Amundsen[1,2], Terje Espevik[3], Svend Aakhus[2,4], Jan Kristian Damås[3‡], Pål Aukrust[5,6,7‡], Rune Wiseth[1,2‡], and Lars Gullestad[4,6,8,9‡]

European Heart Journal
doi:10.1093/eurheartj/ehw247

BASIC SCIENCE

The selective NLRP3-inflammasome inhibitor MCC950 reduces infarct size and preserves cardiac function in a pig model of myocardial infarction

Gerardus P.J. van Hout[1‡*], Lena Bosch[1‡], Guilielmus H.J.M. Ellenbroek[1], Judith J. de Haan[1], Wouter W. van Solinge[2], Matthew A. Cooper[3], Fatih Arslan[1], Saskia C.A. de Jager[1], Avril A.B. Robertson[3], Gerard Pasterkamp[1,2], and Imo E. Hoefer[1,2]

NLRP3 Inhibitors

Reduced infarct size

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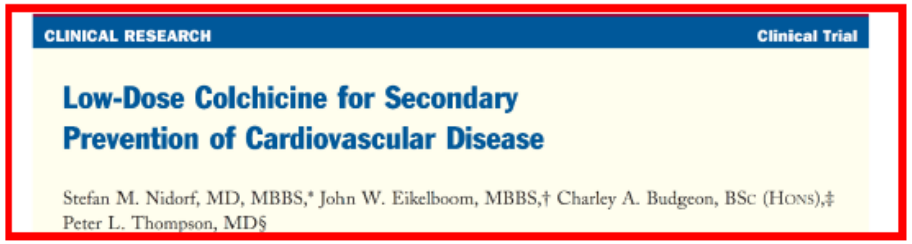
Alternative Agents For Anti-Inflammatory Approaches to Atherosclerosis



CLINICAL RESEARCH — Clinical Trial

Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease

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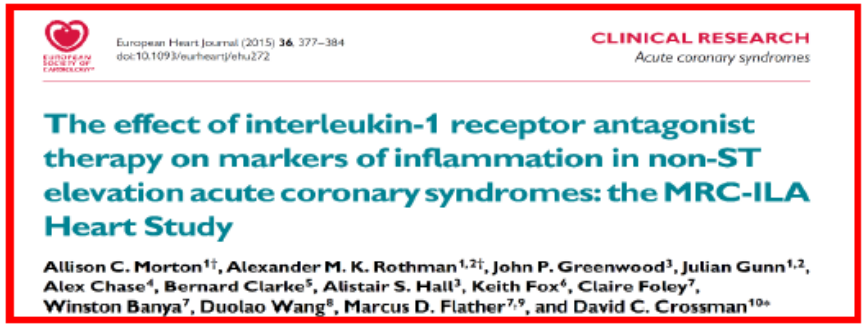
Colchicine — Prevented cardiovascular events



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IL-1Ra — Decreased CRP

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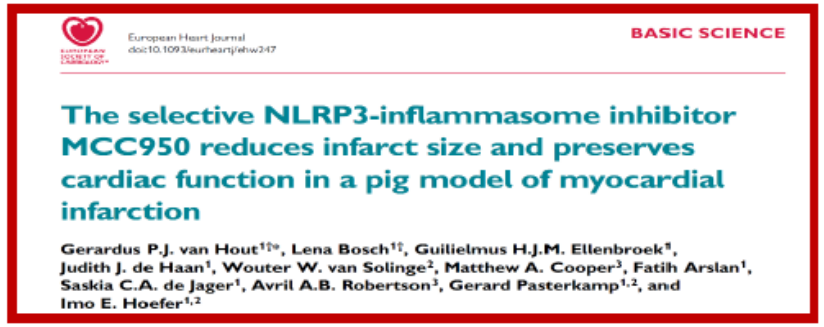
IL-6 Inhibitors — Decreased CRP and TnI



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NLRP3 Inhibitors — Reduced infarct size

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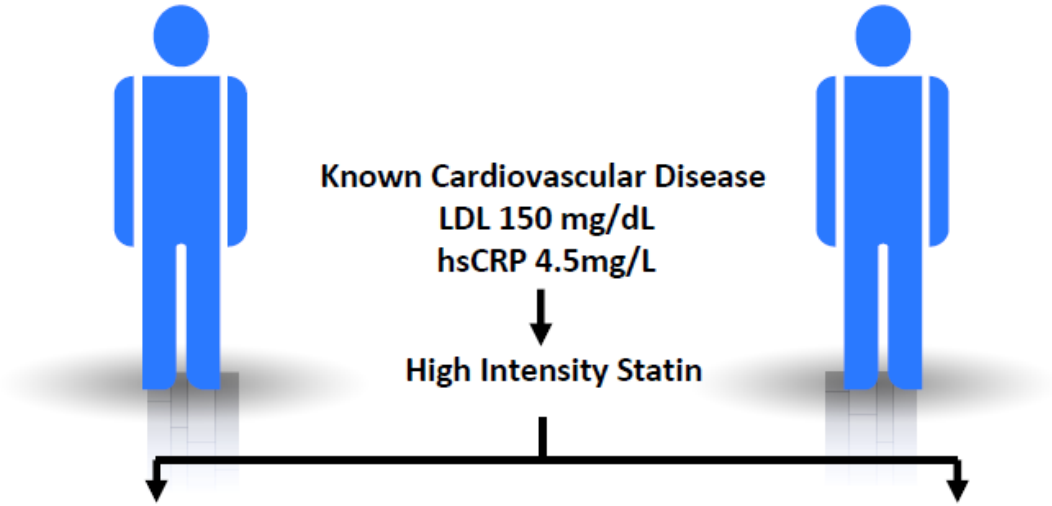
Residual Inflammatory Risk:
Addressing the Obverse Side of the Atherosclerosis Prevention Coin

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

FOURIER/SPIRE/ODYSSEY
PCSK9 Inhibition SC q 2 weeks 15% RRR

"Residual Inflammatory Risk"

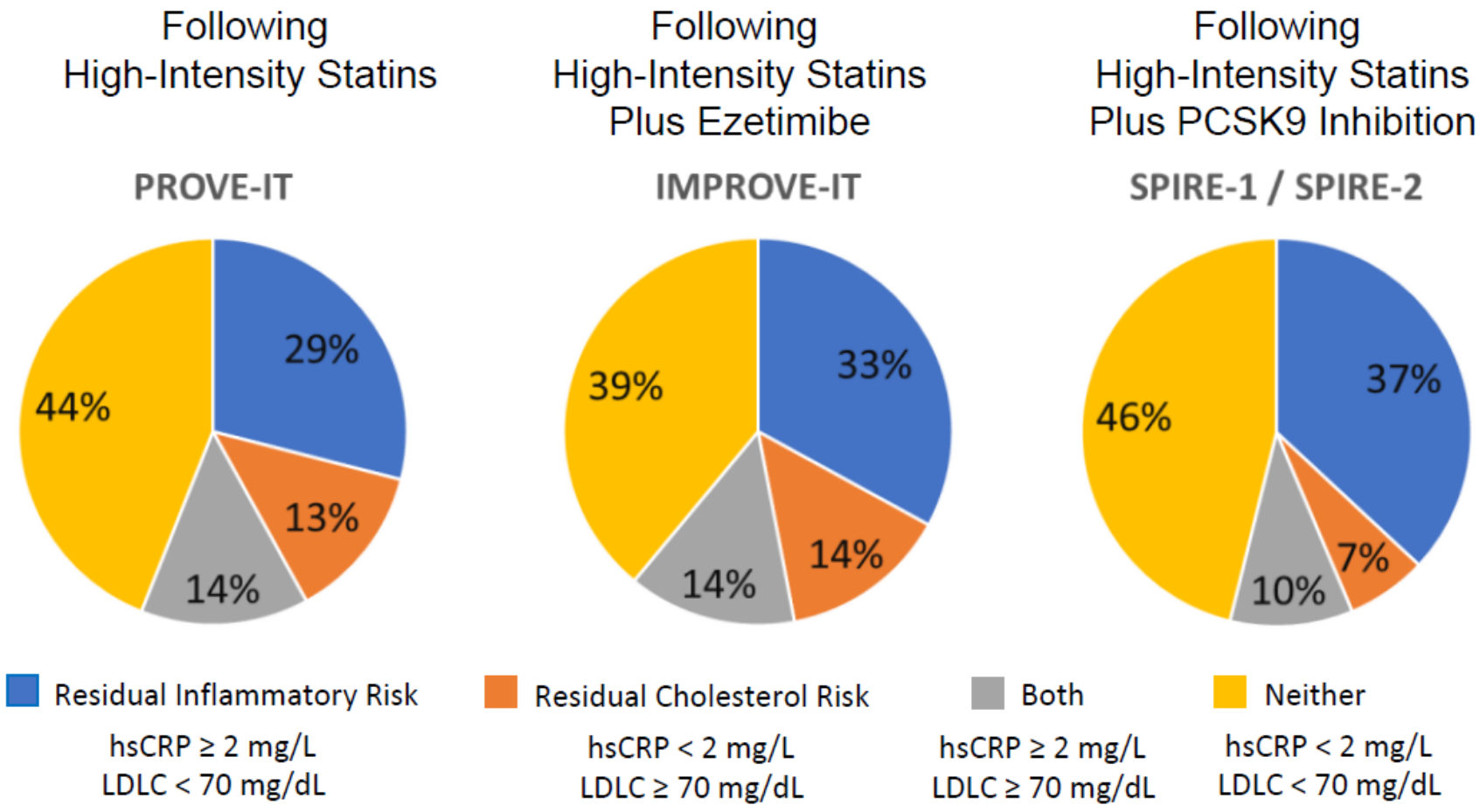
LDL 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L

↓

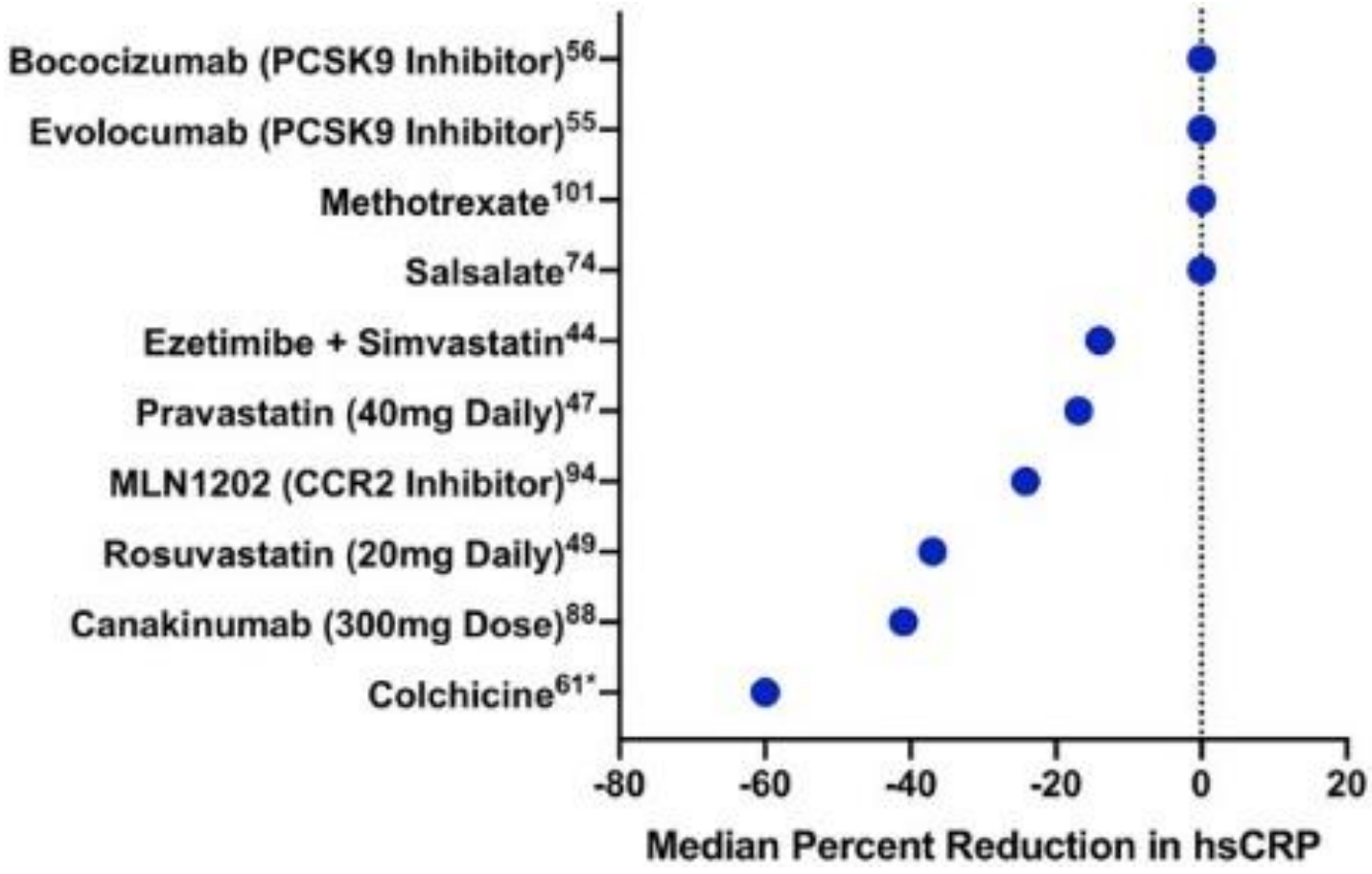
Additional
Inflammation Reduction

CANTOS
Canakinumab 150-300mg SC q 3 months 15%RRR

How common is residual inflammatory risk?



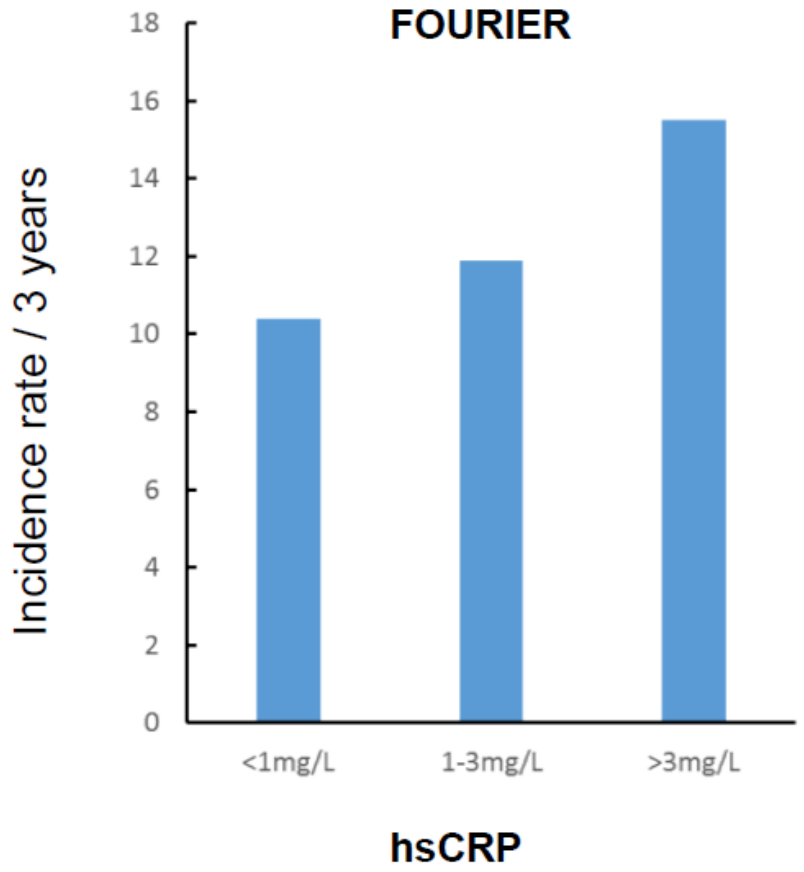
Strategies to improve inflammatory risk

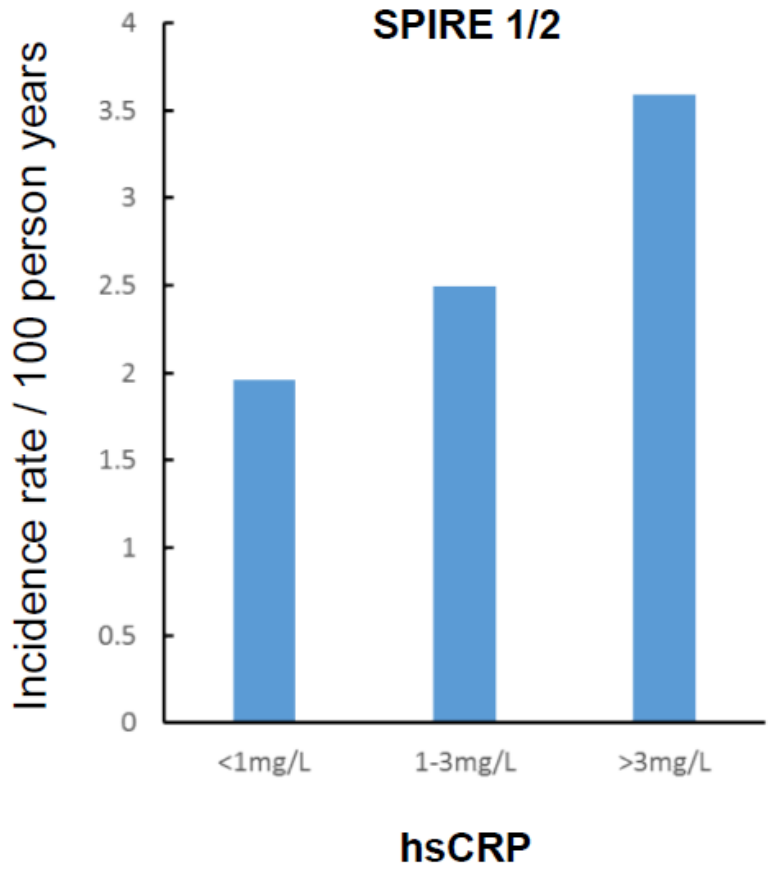


Ridker PM et al. Front Cardiovasc Med 2019

LDL Reduction Alone Does Not Address Residual Inflammatory Risk

Relationships of hsCRP Levels With Future Cardiovascular Events
Among High-Risk Patients Treated with Both Statins and PCSK9 Inhibitors





Bohula et al, Circulation 2018;138:131-140

Pradhan et al, Circulation 2018;138:141-149

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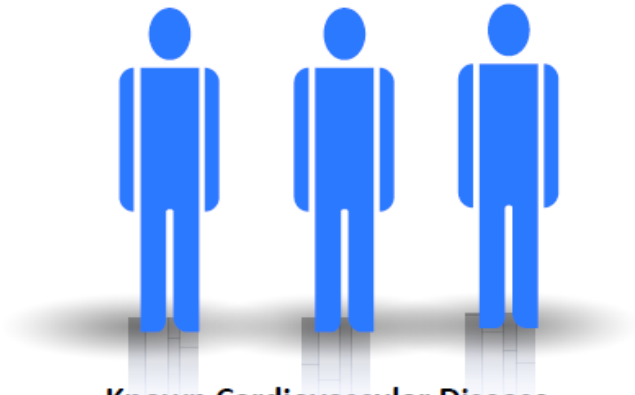
Strategies to improve residual risk for secondary prevention



Known Cardiovascular Disease
LDL 150 mg/dL
hsCRP 4.5mg/L
TG 240 mg/dL

↓

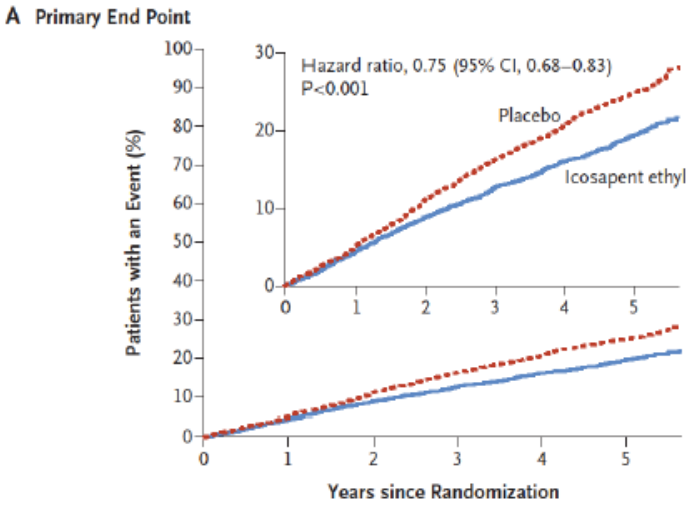
High Intensity Statin

Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Triglyceride Risk
LDL 110 mg/dL	LDL 60 mg/dL	LDL 60 mg/dL
hsCRP 1.8 mg/L	hsCRP 3.8 mg/L	hsCRP 1.8 mg/L
TG 180 mg/dL	TG 180 mg/dL	TG 220 mg/dL
↓	↓	↓
Additional LDL Reduction	Additional Inflammation Reduction	Additional TG Reduction

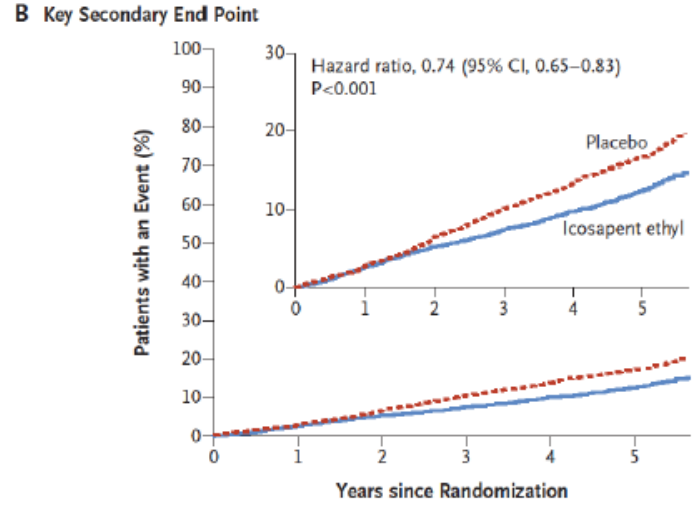
J Am Coll Cardiol 2018;72:3320-3331

REDUCIE-IT: EPA vs. placebo

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



CV Death, MI, Stroke



Baseline triglycerides				0.45
≥200 mg/dl	430/2481 (17.3)	559/2469 (22.6)	0.73 (0.64–0.83)	
<200 mg/dl	275/1605 (17.1)	342/1620 (21.1)	0.79 (0.67–0.93)	
Baseline triglycerides				0.83
≥150 mg/dl	640/3674 (17.4)	811/3660 (22.2)	0.75 (0.68–0.83)	
<150 mg/dl	65/412 (15.8)	90/429 (21.0)	0.79 (0.57–1.09)	
Baseline triglycerides ≥200 mg/dl and HDL cholesterol ≤35 mg/dl				0.04
Yes	149/823 (18.1)	214/794 (27.0)	0.62 (0.51–0.77)	
No	554/3258 (17.0)	687/3293 (20.9)	0.79 (0.71–0.88)	

No Impact of BL TG

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018.

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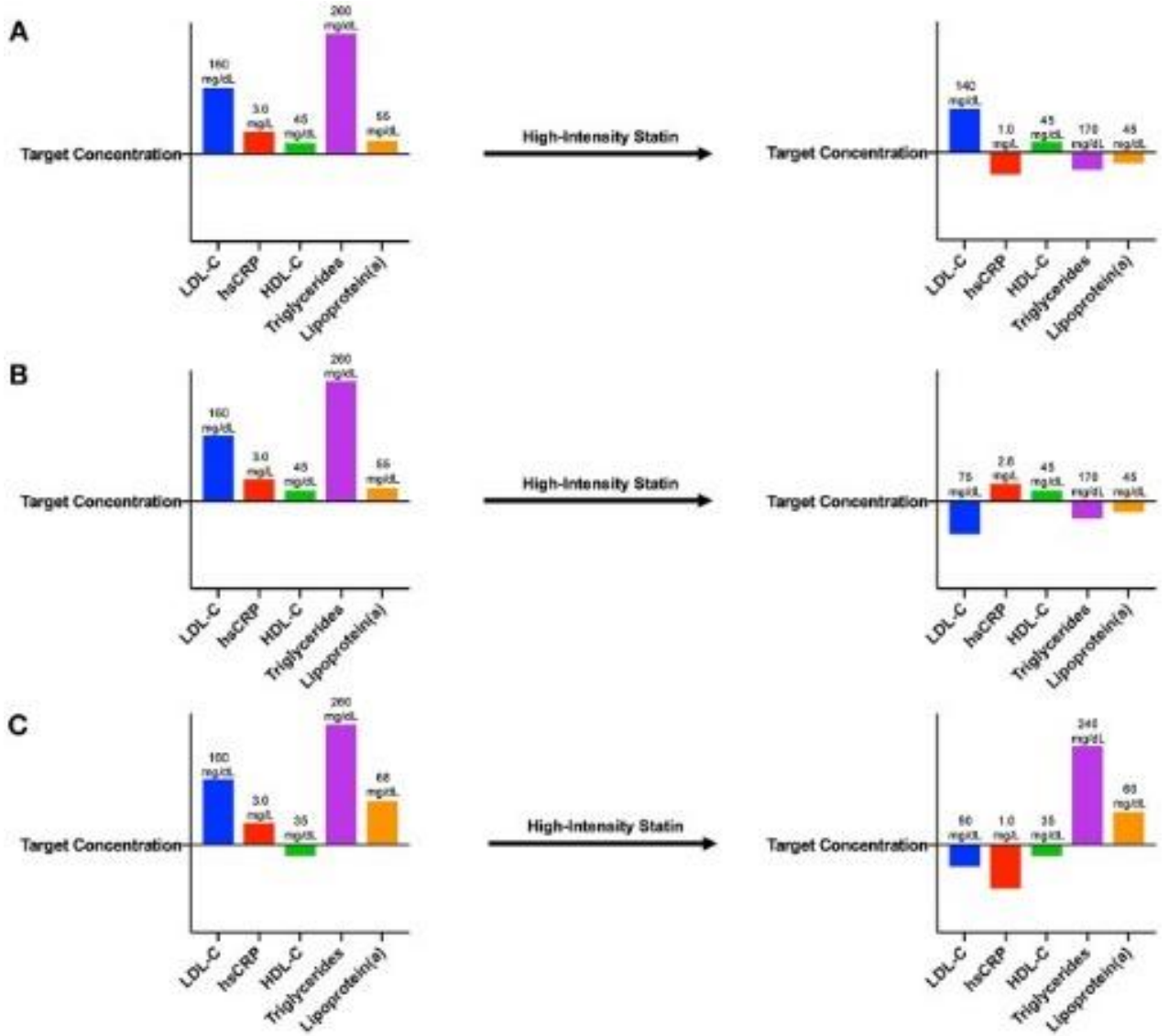
Residual Inflammatory Risk:
Addressing the Obverse Side of the Atherosclerosis Prevention Coin



Residual cholesterol risk: PCSK9 inhibitor

Residual inflammatory risk: Canakinumab, colchicine

Residual triglyceride risk: EPA

Ridker PM et al. Front Cardiovasc Med 2019

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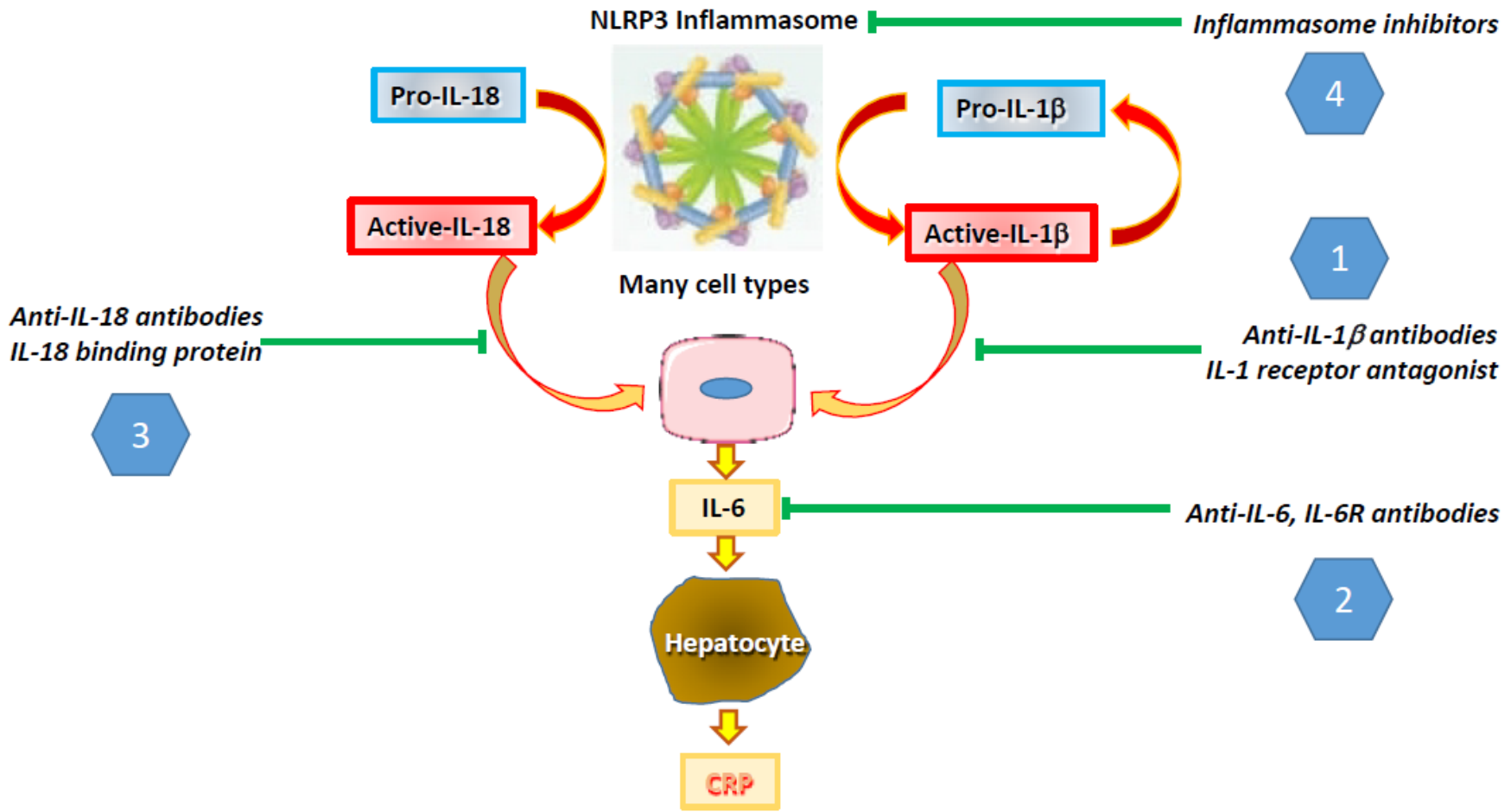
Directions for the Development of Future Anti-Cytokine Therapies for Atherothrombosis



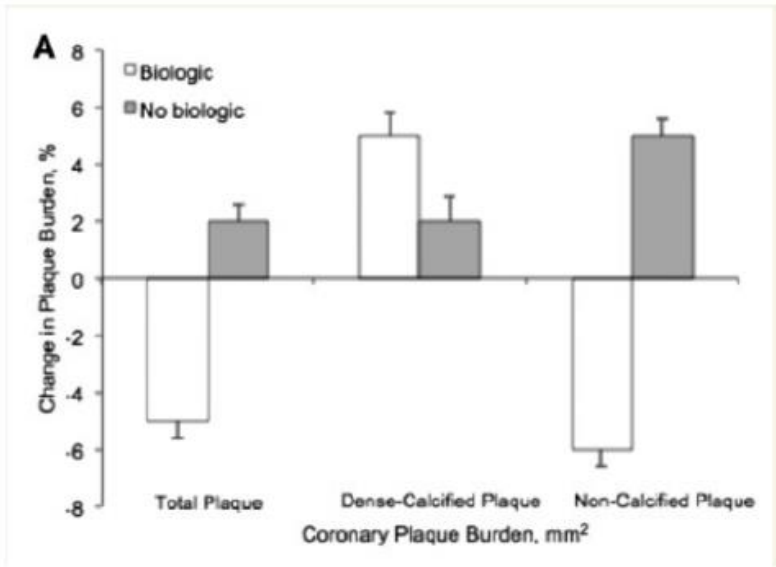
Ridker ESC 2019

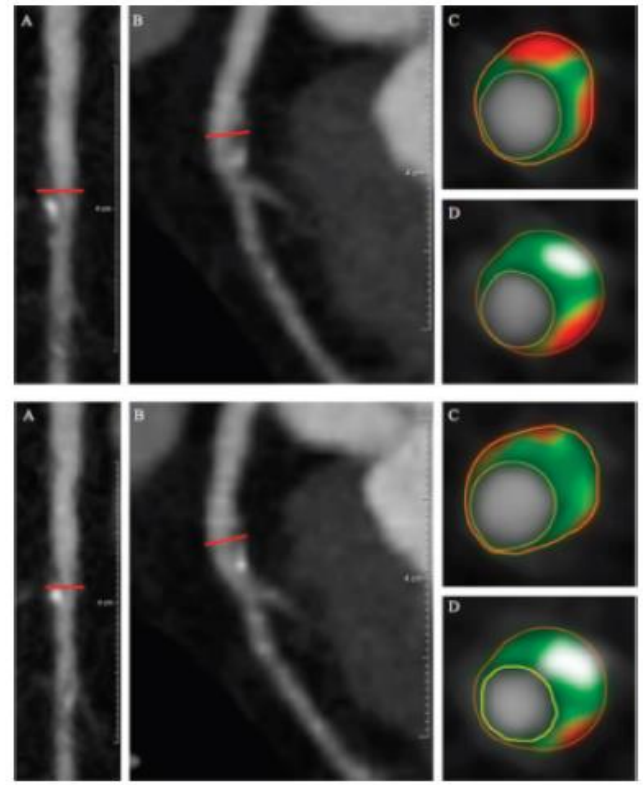
Inflammatory and Cardiovascular Disease - Lessons From Psoriasis

ESC European Society of Cardiology
Cardiovascular Research (2019) 115, 721–728
doi:10.1093/cvr/cvz009
FAST-TRACK COMMUNICATION

Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study

Youssef A. Elnabawi[1], Amit K. Dey[1], Aditya Goyal[1], Jacob W. Groenendyk[1], Jonathan H. Chung[1], Agastya D. Belur[1], Justin Rodante[1], Charlotte L. Harrington[1], Heather L. Teague[1], Yvonne Baumer[1], Andrew Keel[1], Martin P. Playford[1], Veit Sandfort[1], Marcus Y. Chen[1], Benjamin Lockshin[2], Joel M. Gelfand[3], David A. Bluemke[4], and Nehal N. Mehta[1]*





Elnabawi YA., et al; Cardiovasc Res. 2019;115(4):721-728.

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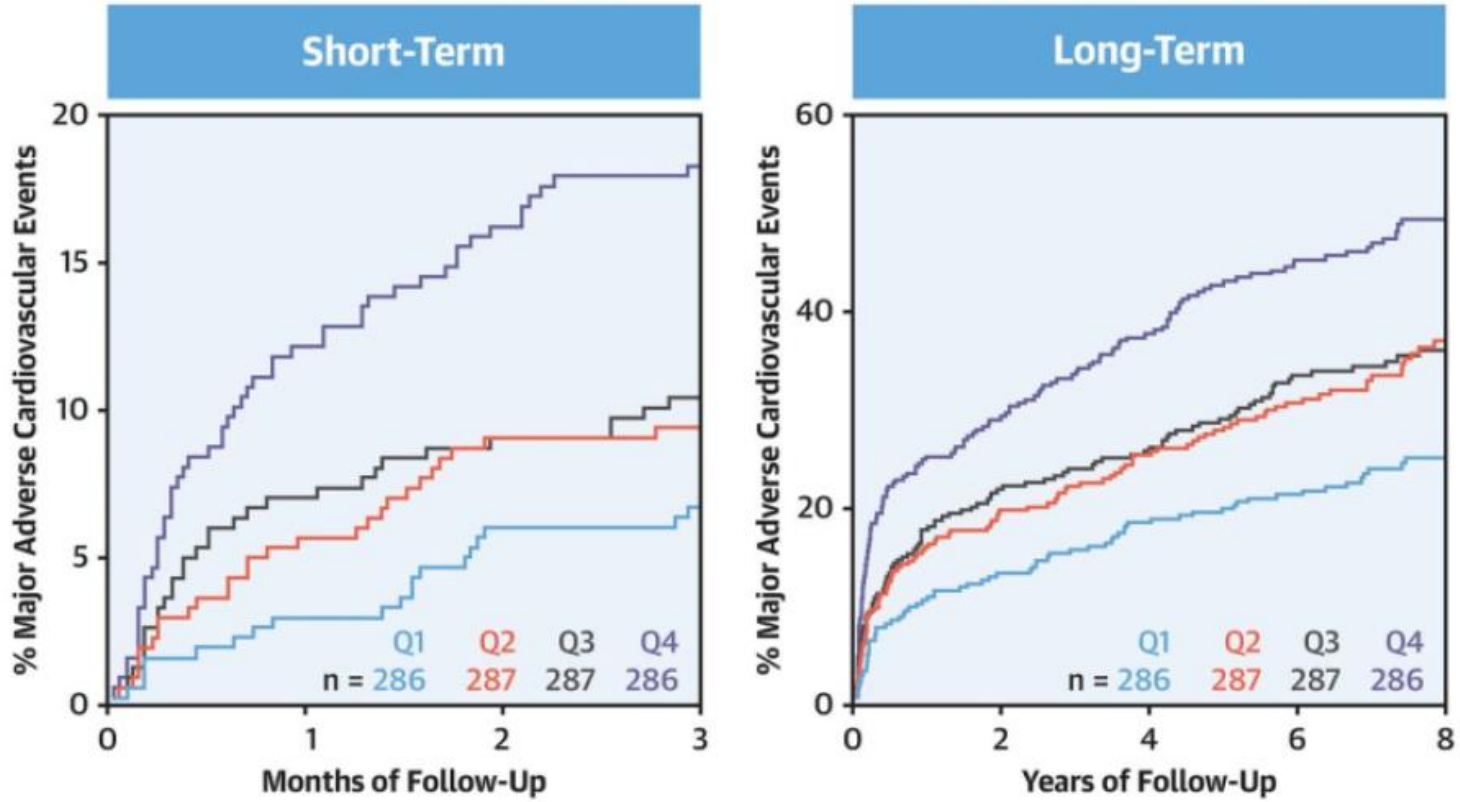
Potential New Targets: Chemokine CCL21 in ACS

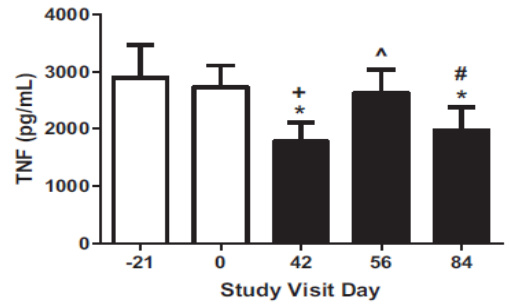
CENTRAL ILLUSTRATION: Admission Levels of CCL21 and Prognosis in Acute Coronary Syndrome



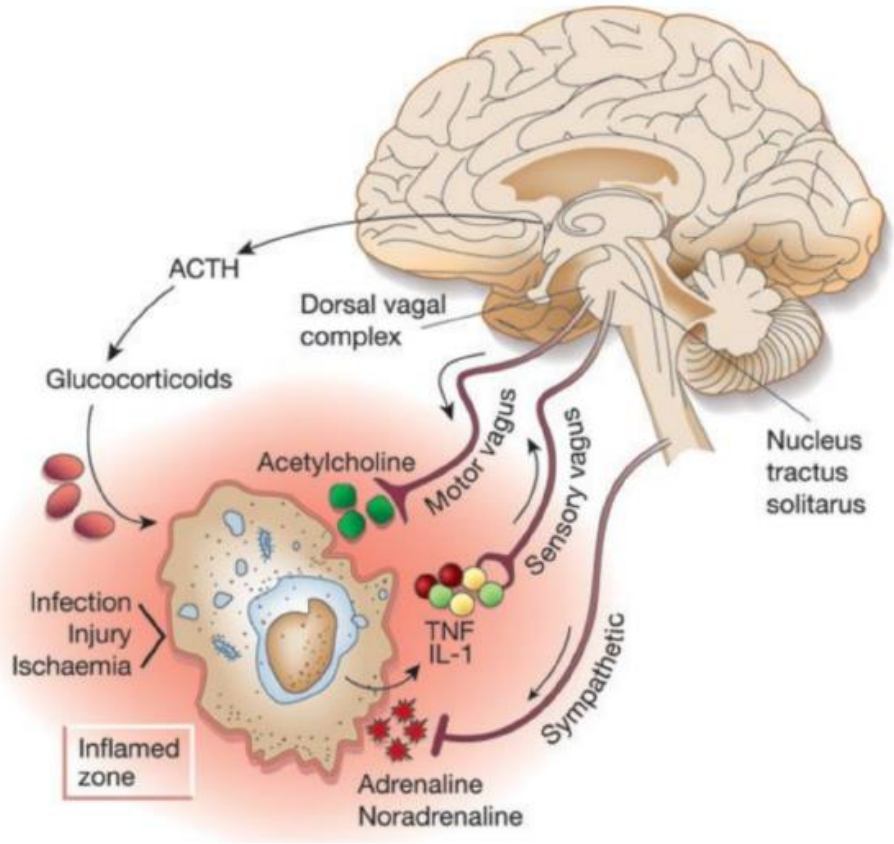
Caidahl, K. et al. J Am Coll Cardiol. 2019;74(6):774-82.

Non-Pharmacologic Approaches to Inflammation Inhibition

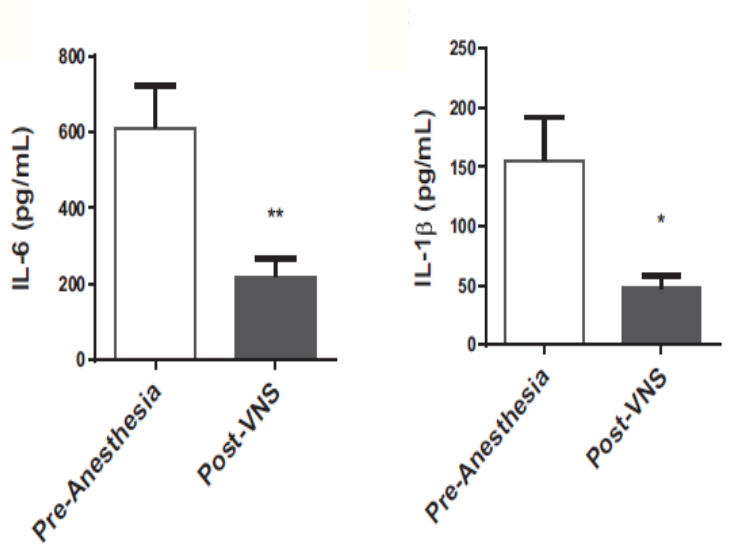
Vagal Regulation of Innate Immunity: The Neuro-Inflammatory Reflex



Koopman FA et al. PNAS 2016;113:8284-9



30 s of VNS ➡ 4 hours of anti-inflammatory effect



Koopman FA et al. PNAS 2016;113:8284-9

Tracey KJ. Nature. 2002 Dec 19-26;420(6917):853-9.

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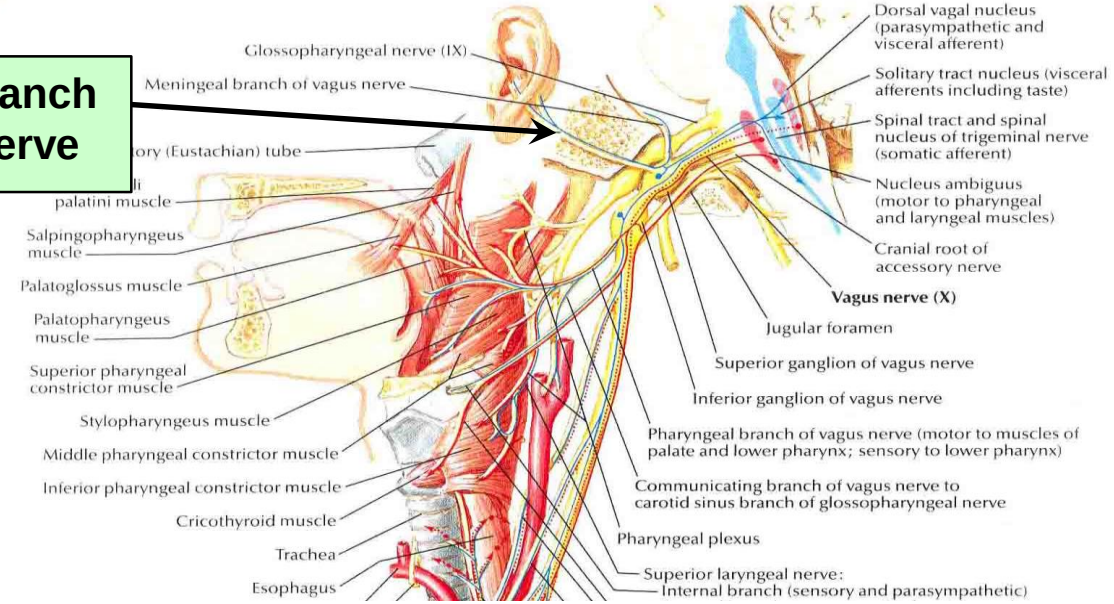
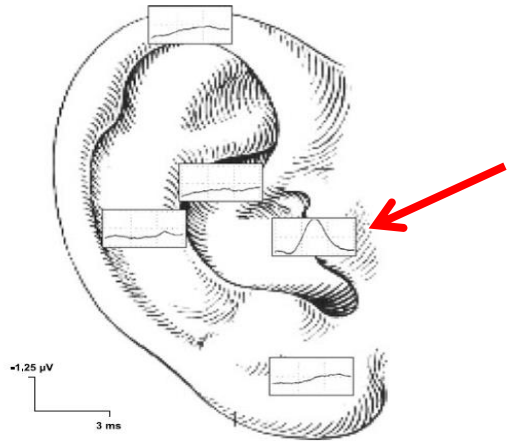
Non-Pharmacologic Approaches to Inflammation Inhibition

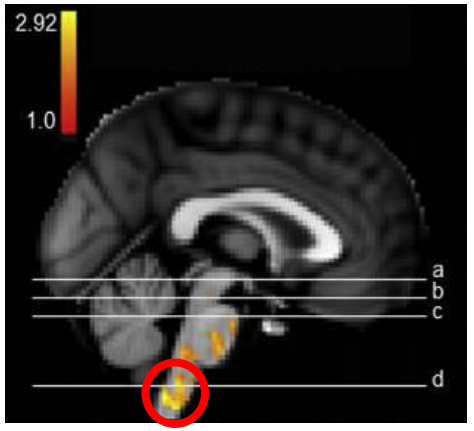
Vagal Regulation of Innate Immunity: The Neuro-Inflammatory Reflex

Auricular Branch of Vagus Nerve





Fallgatter AJ et al. J Neural Transm 2003



Brain Stim 2015;8:624-36

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Non-Pharmacologic Approaches to Inflammation Inhibition

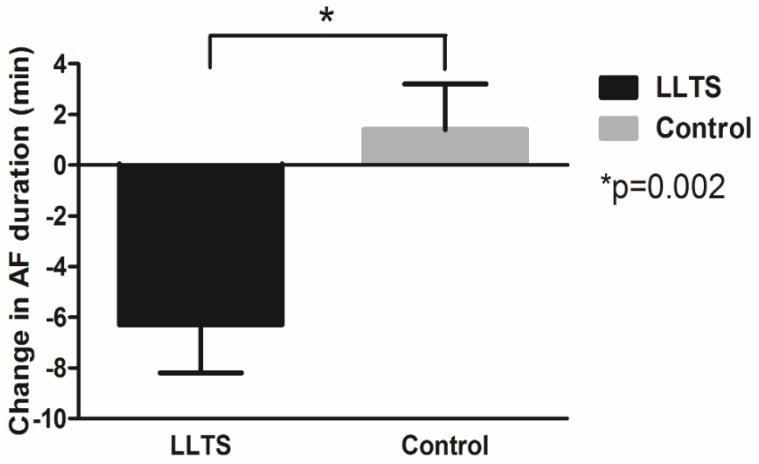
Vagal Regulation of Innate Immunity: The Neuro-Inflammatory Reflex

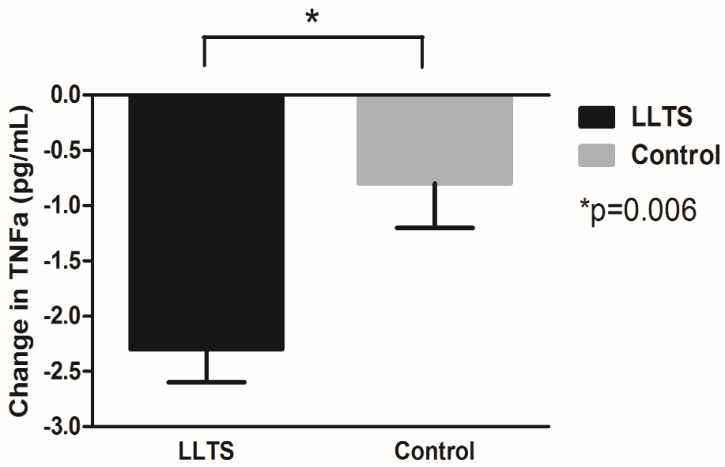
ORIGINAL INVESTIGATIONS

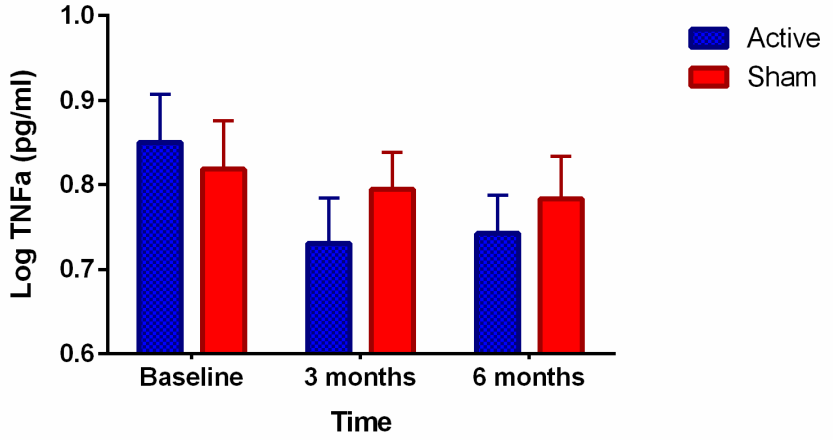
Low-Level Transcutaneous Electrical Vagus Nerve Stimulation Suppresses Atrial Fibrillation

Stavros Stavrakis, MD, PhD,* Mary Beth Humphrey, MD, PhD,† Benjamin J. Scherlag, PhD,* Yanqing Hu, PhD,† Warren M. Jackman, MD,* Hiroshi Nakagawa, MD, PhD,* Deborah Lockwood, MD,* Ralph Lazzara, MD,* Sunny S. Po, MD, PhD*

TRanscutaneous Electrical vAgus nerve sTimulation to suppress Atrial Fibrillation (TREAT-AF): A Randomized Clinical Trial







Stavrakis, S. et al. J Am Coll Cardiol. 2015; 65(9):867-75.

Active vs. Sham: ratio of medians 0.77, 95% CI: 0.63 to 0.94, p=0.0093

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JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 15, 2017

ISSN 1936-8798/$36.00
http://dx.doi.org/10.1016/j.jcin.2017.04.036

Low-Level Tragus Stimulation for the Treatment of Ischemia and Reperfusion Injury in Patients With ST-Segment Elevation Myocardial Infarction

A Proof-of-Concept Study

Lilei Yu, MD, PhD,[a] Bing Huang, MD, PhD,[a] Sunny S. Po, MD, PhD,[b] Tuantuan Tan, MD, PhD,[c] Menglong Wang, MD,[a] Liping Zhou, MD,[a] Guannan Meng, MD,[a] Shenxu Yuan, MD,[a] Xiaoya Zhou, MD, PhD,[a] Xuefei Li, MD,[a] Zhuo Wang, MD,[a] Songyun Wang, MD,[a] Hong Jiang, MD[a]

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Yu L et al. JACC Cardiovasc Interv 2017

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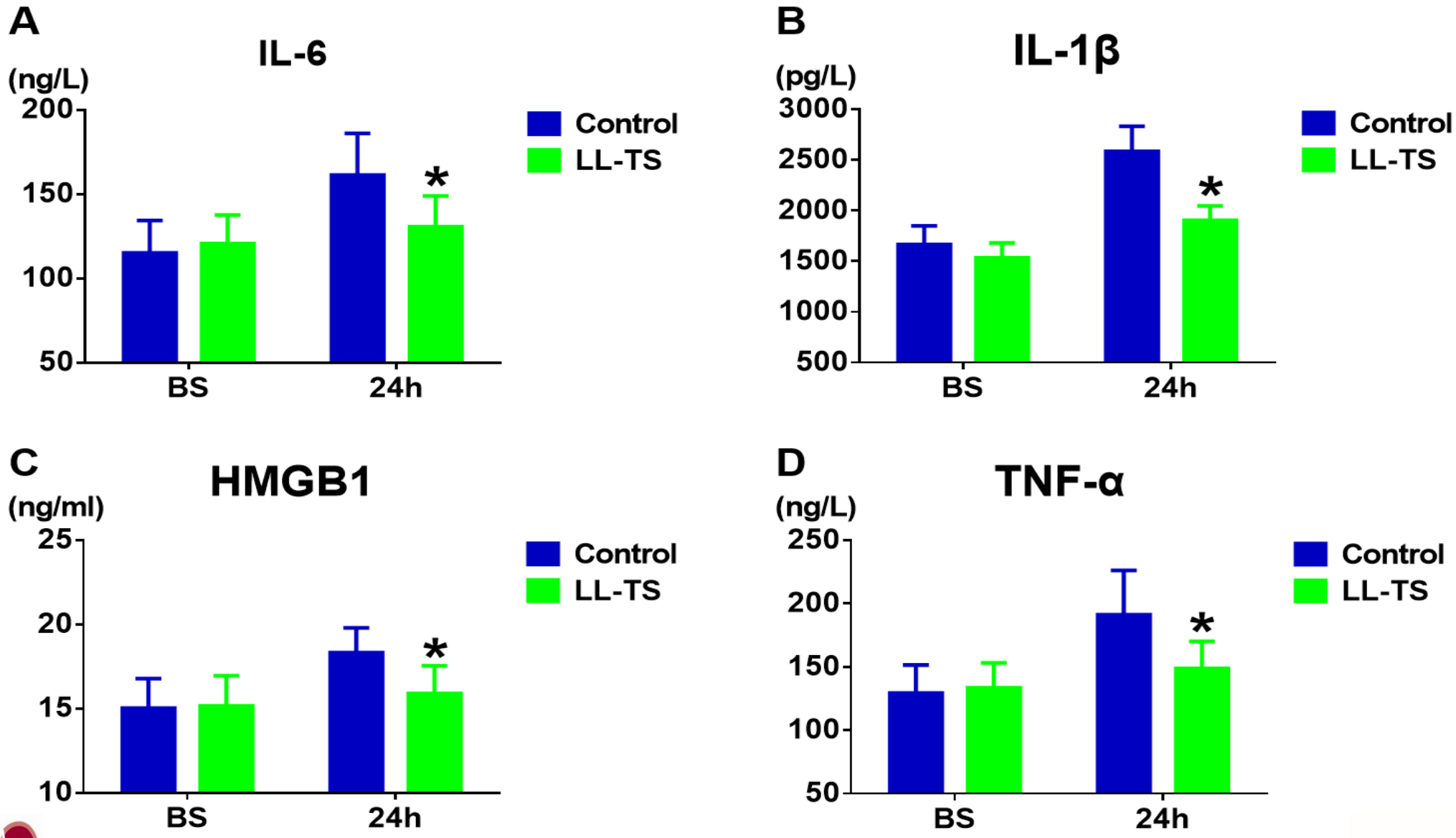
Low level vagal stimulation in STEMI decreases inflammation



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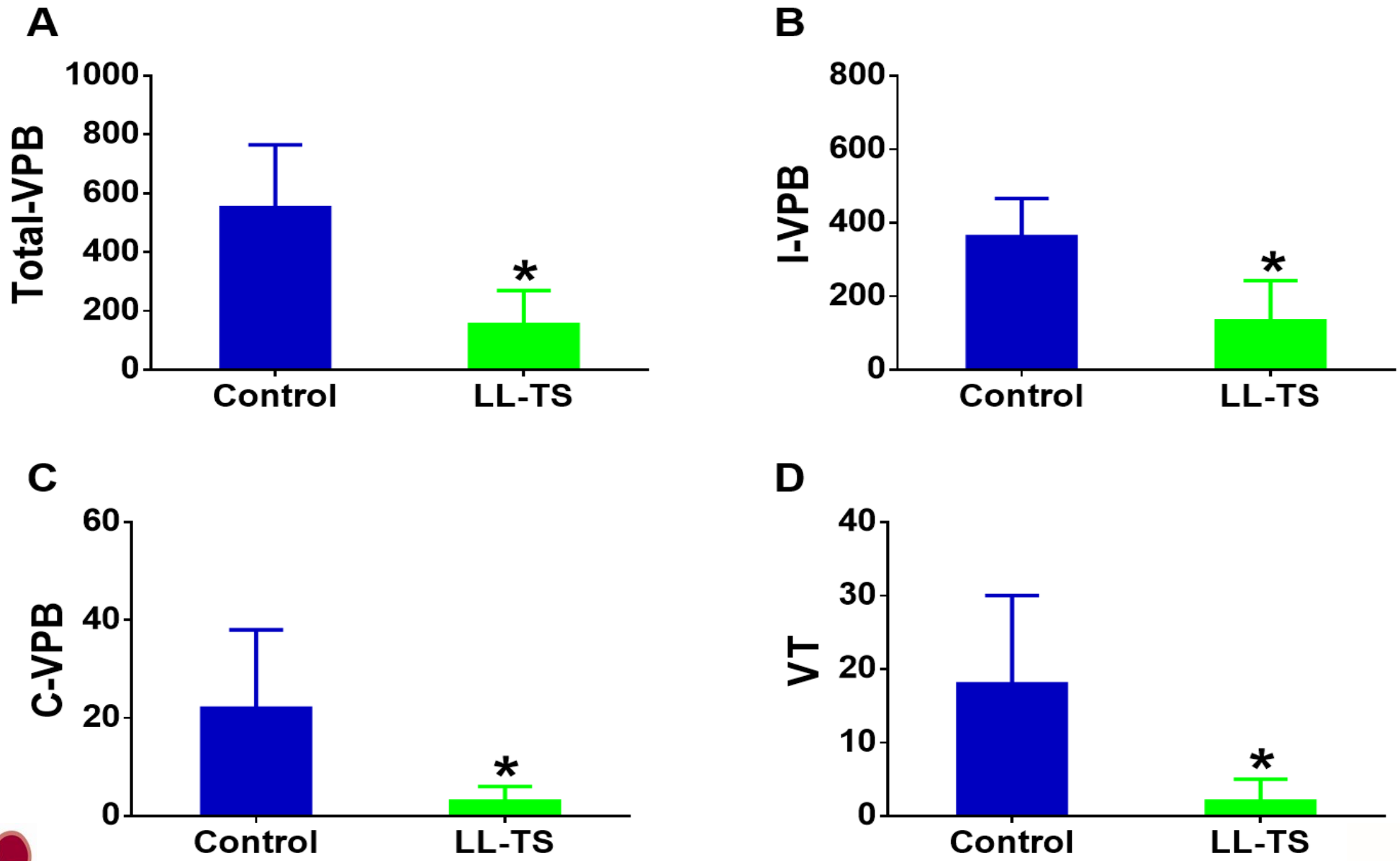
Low level vagal stimulation in STEMI decreases ventricular arrhythmias



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Non-Pharmacologic Approaches to Inflammation Inhibition

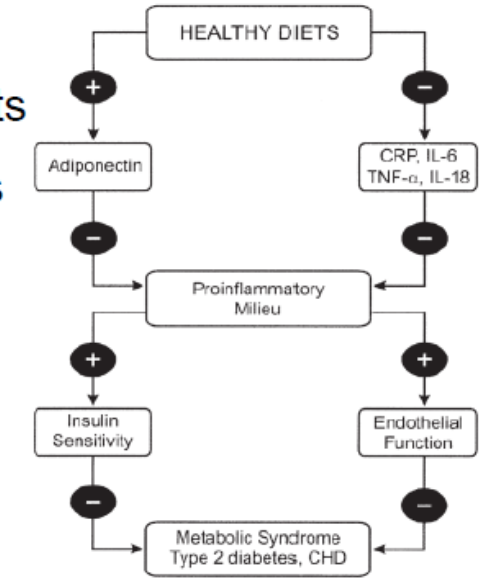
STATE-OF-THE-ART PAPER

The Effects of Diet on Inflammation

Emphasis on the Metabolic Syndrome

Dario Giugliano, MD, PhD,* Antonio Ceriello, MD,† Katherine Esposito, MD, PhD*
Naples, Italy; and Coventry, United Kingdom

- ↑ omega-3, fish
- ↓ saturated and trans fats
- ↑ fruits, vegetables, nuts
- ↑ whole grains
- ↓ sugar
- ↑ exercise
- ↑ alcohol
- ↓ smoking



Diet, Exercise, Smoking Cessation
AHA/ACC Simple Seven

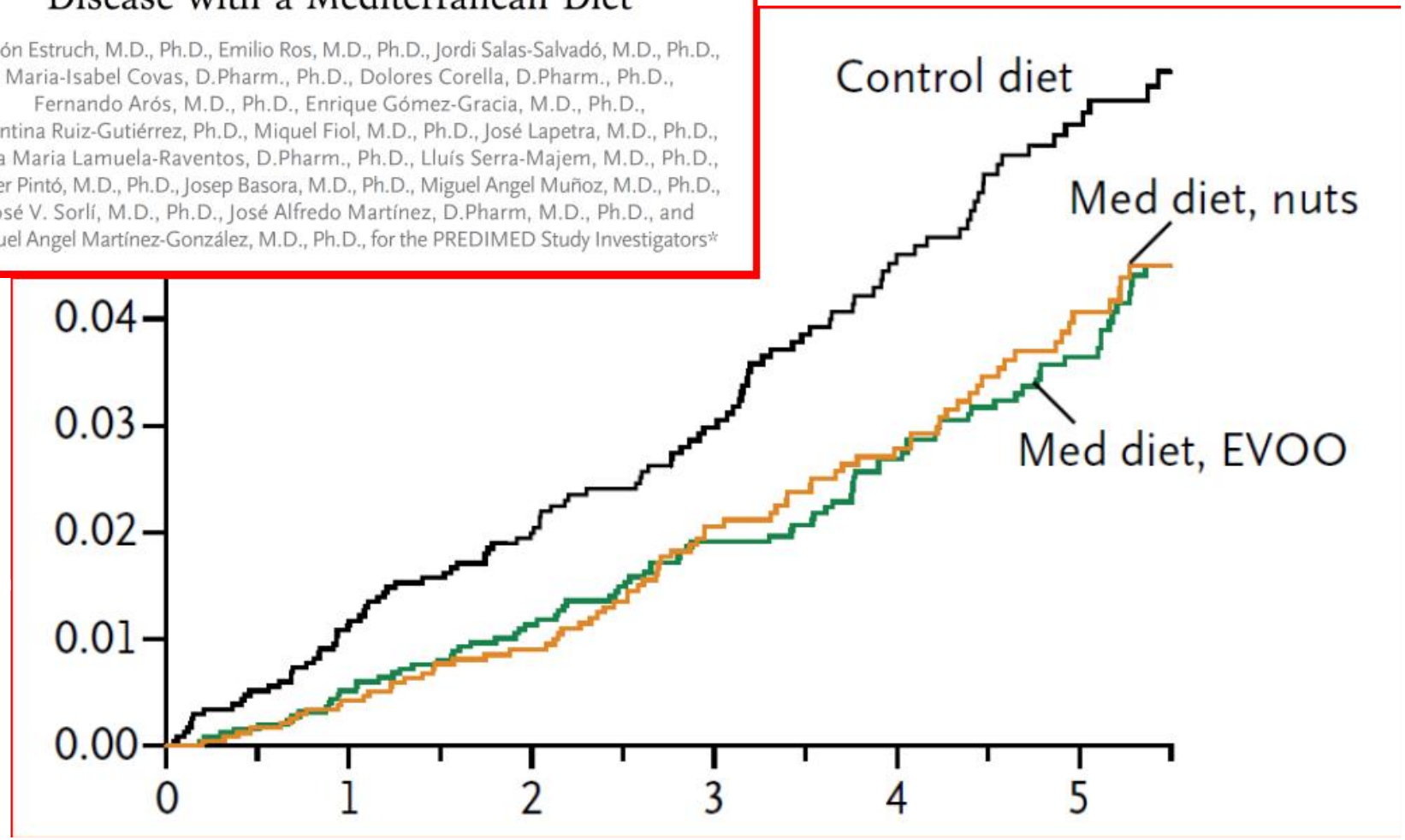
Giugliano D, et al; JACC 2006;48677-85.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

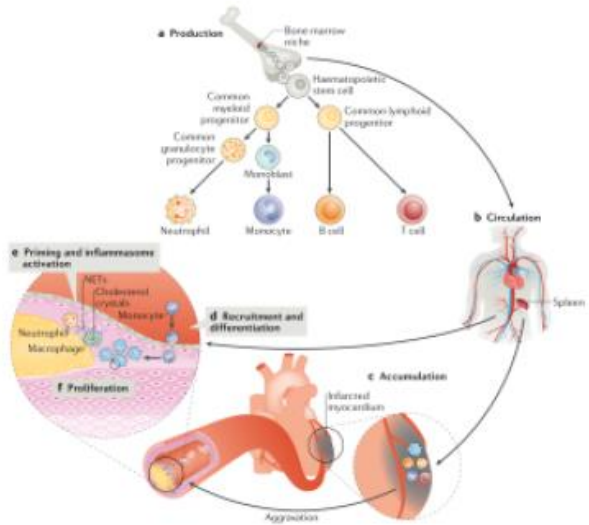
Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

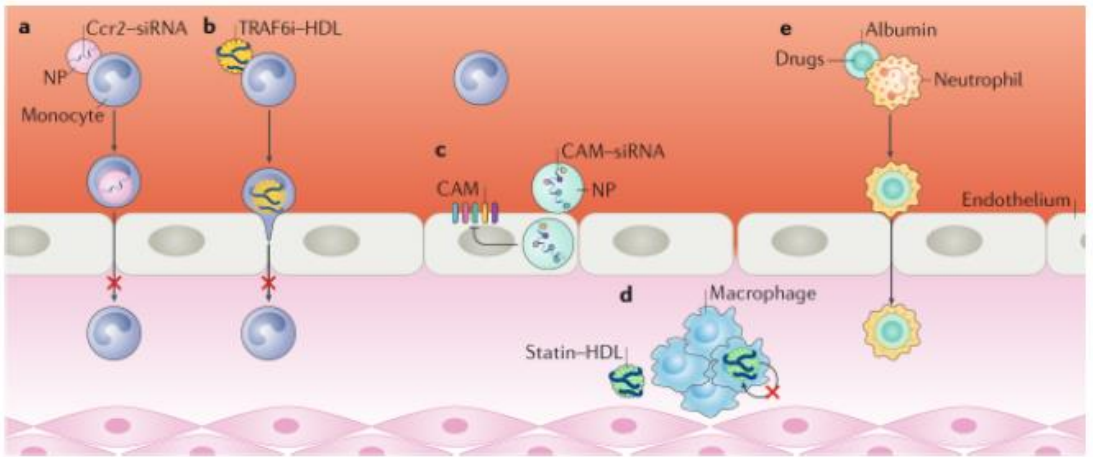
Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*



Nanoimmunotherapy to treat ischaemic heart disease

Raphaël Duivenvoorden[1,2,3], Max L. Senders[3,4], Mandy M. T. van Leent[3,4], Carlos Pérez-Medina[3], Matthias Nahrendorf[5], Zahi A. Fayad[3] and Willem J. M. Mulder[3,4,6,7]**





- **The therapeutic focus in atherosclerosis has shifted from lipid lowering to treating inflammation**
- **Novel nanoimmunotherapies, aimed at modulating innate immune responses in cardiovascular diseases**

Duivenvoorden R., et al; Nat Rev Cardiol. 2019;16(1):21-32.

Conclusions

- Atherosclerosis is driven by lipid accumulation and inflammation
- hsCRP is a strong risk factor for cardiovascular disease
- In primary prevention, targeting patients with high hsCRP with a statin reduces cardiovascular outcomes even in the presence of normal LDL
- In secondary prevention, inflammation inhibition, without lipid lowering reduces cardiovascular outcomes
- Patients with residual inflammatory risk and residual cholesterol risk have distinct etiology of recurrent events
- Neuroimmunomodulation (vagus nerve stimulation) may be a novel way to improve cardiovascular outcomes

Thank you

“Science begets knowledge; opinion, ignorance”

Hippocrates