Biologie de la Plaque d'Athérosclérose

Ziad Mallat, MD, PhD

Department of Medicine, University of Cambridge, Cambridge, UK

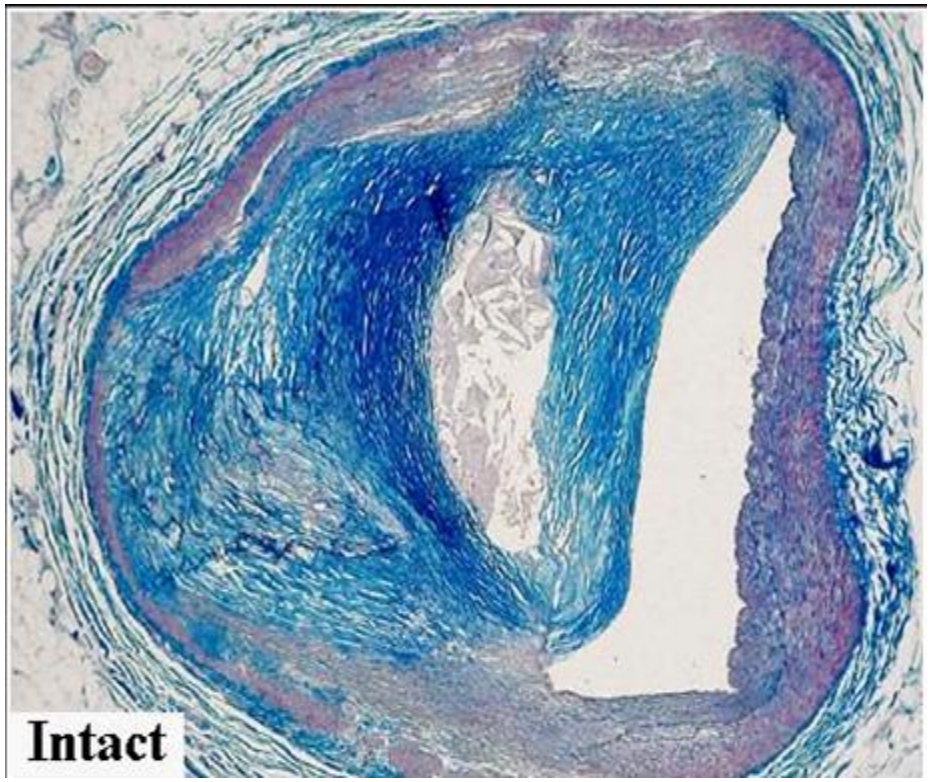
UNIVERSITY OF CAMBRIDGE

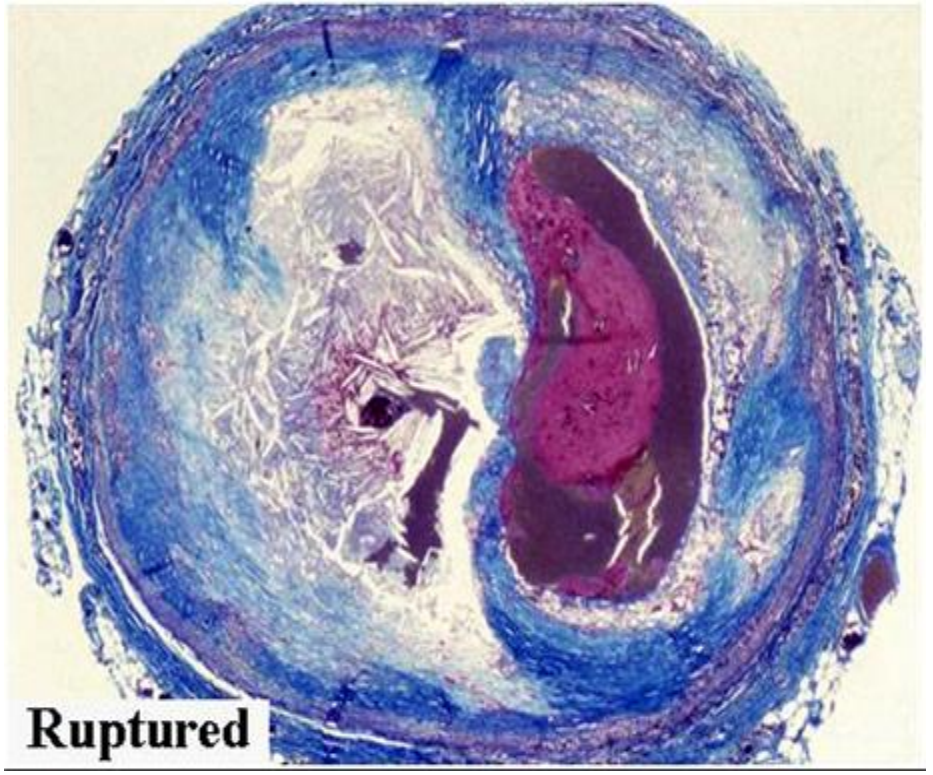
British Heart Foundation

Inserm

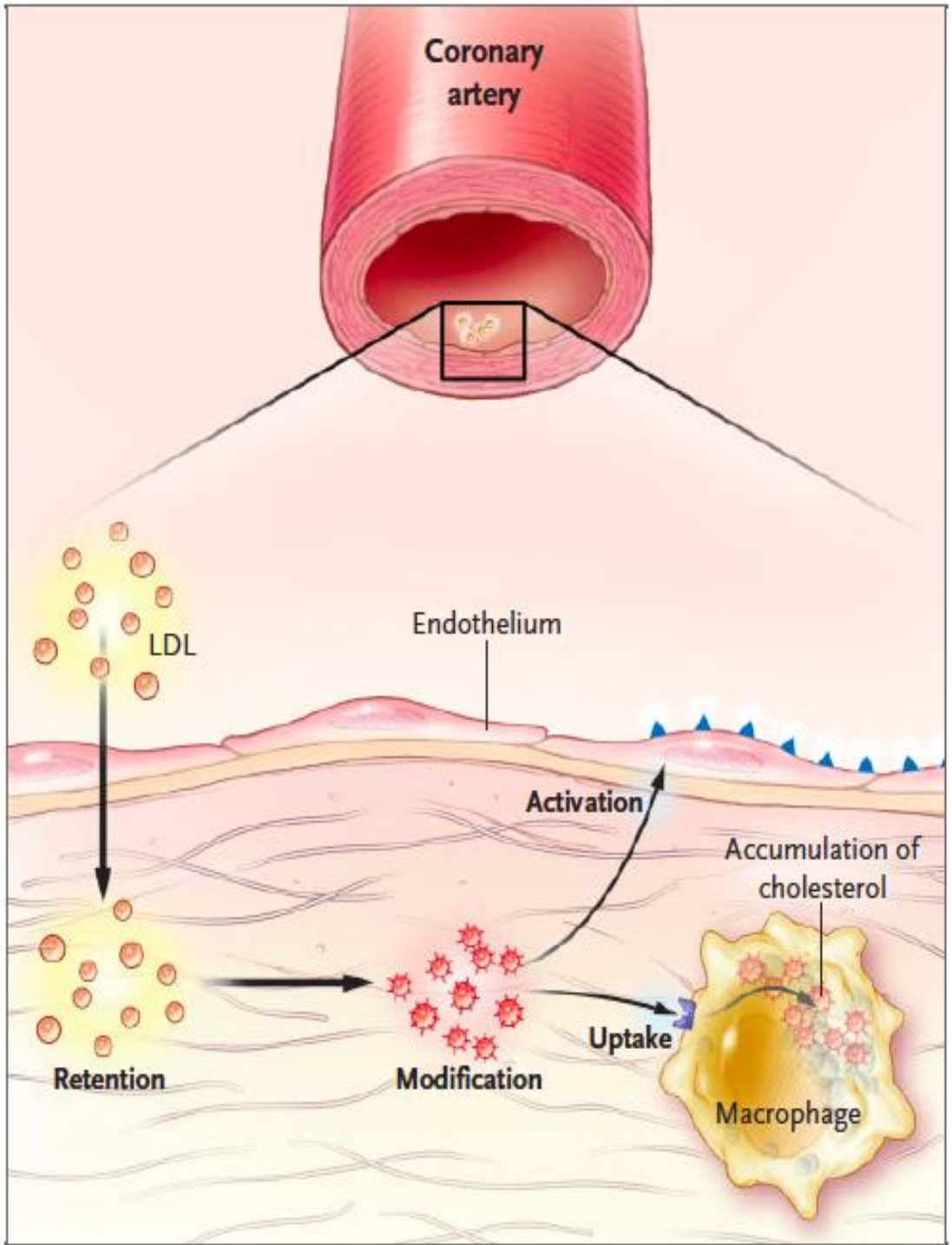
Atherosclerosis

Kolodgie, et al. Heart 2004



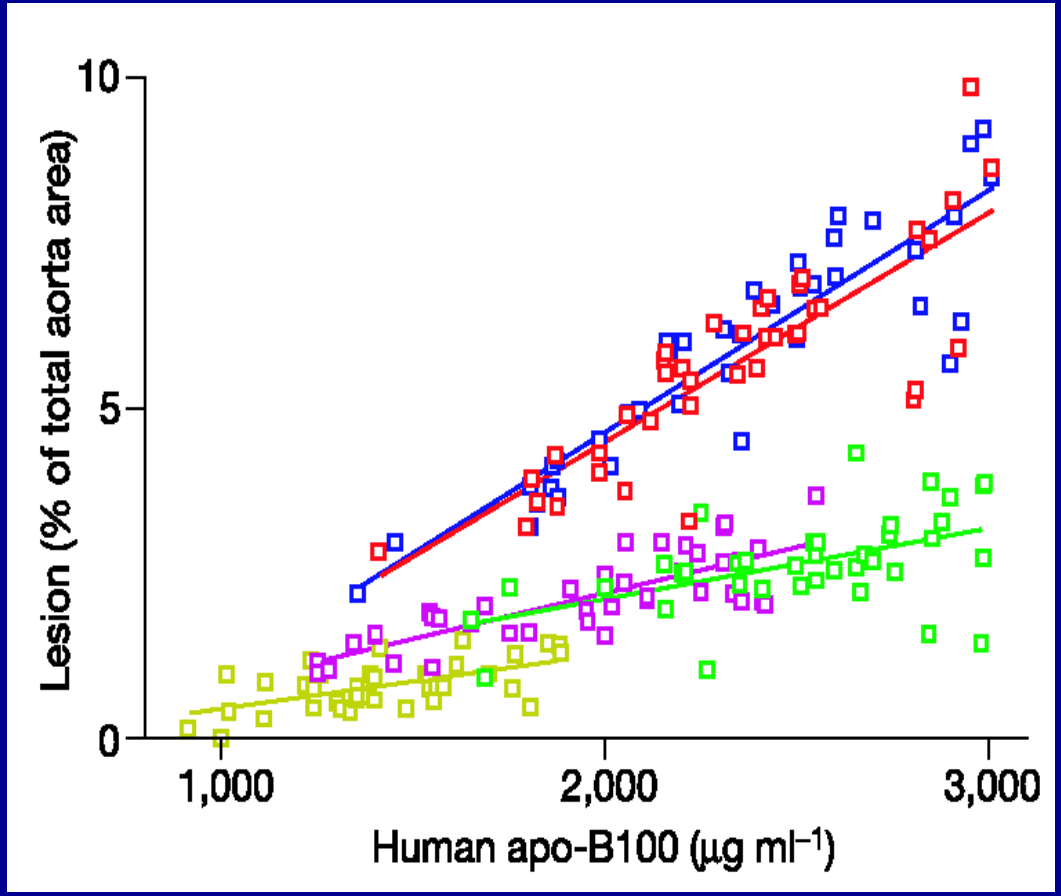


Risk factors: ApoB/apoA1 ratio, diabetes, abdominal obesity, smoking, hypertension, psychosocial index, fruits/veg., exercise, alcohol



Hanson GK.
N Engl J Med 2005

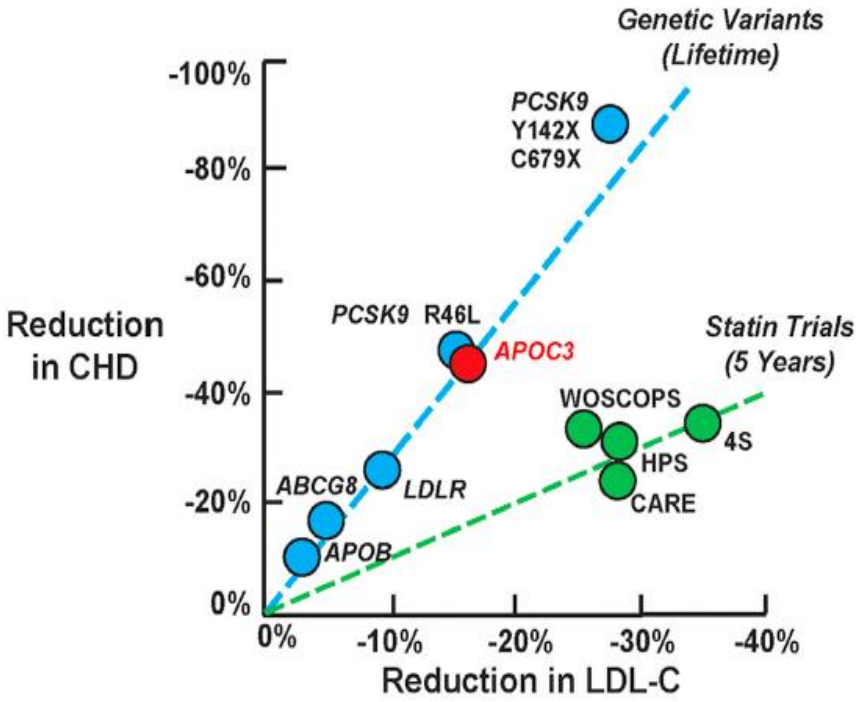
Effect of Subendothelial Retention of Atherogenic Lipoproteins on Atherosclerosis



Wild type-control LDL

Proteoglycan-binding-defective LDL

Skalen et al. Nature, 2002;417:750-754.

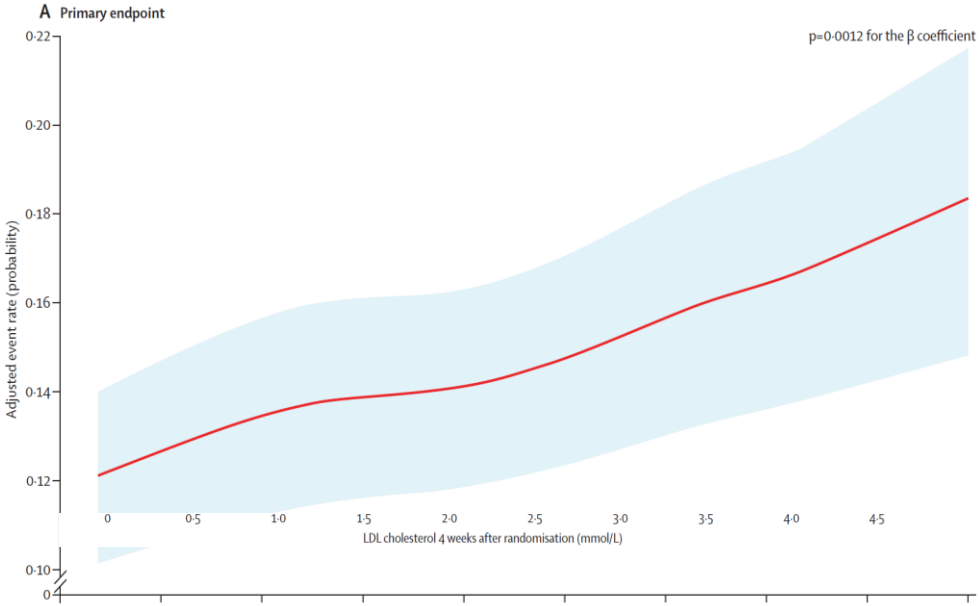


Cohen JC et al. *Cell Metab* 2014

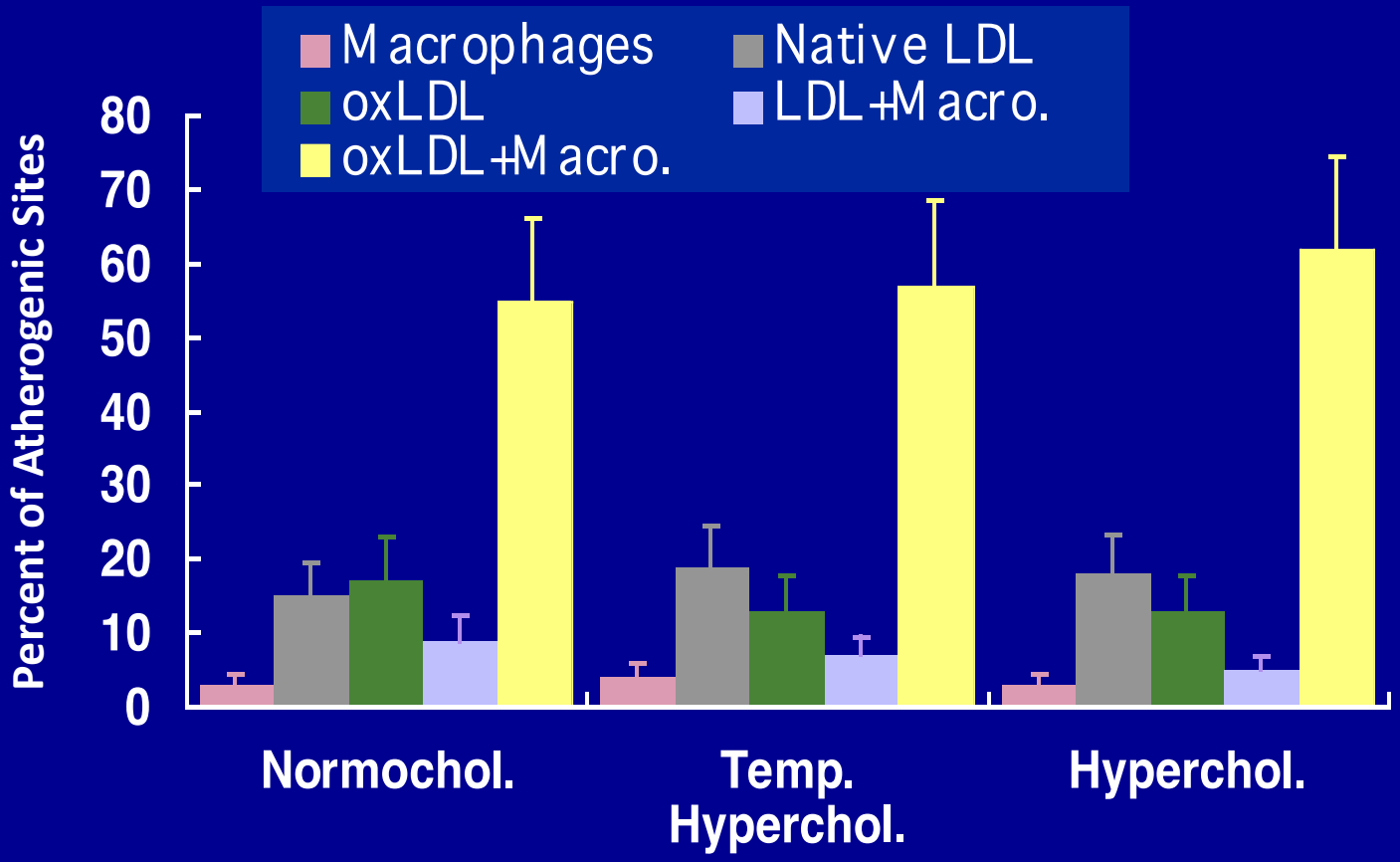
Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial

Lancet 2017; 390: 1962–71

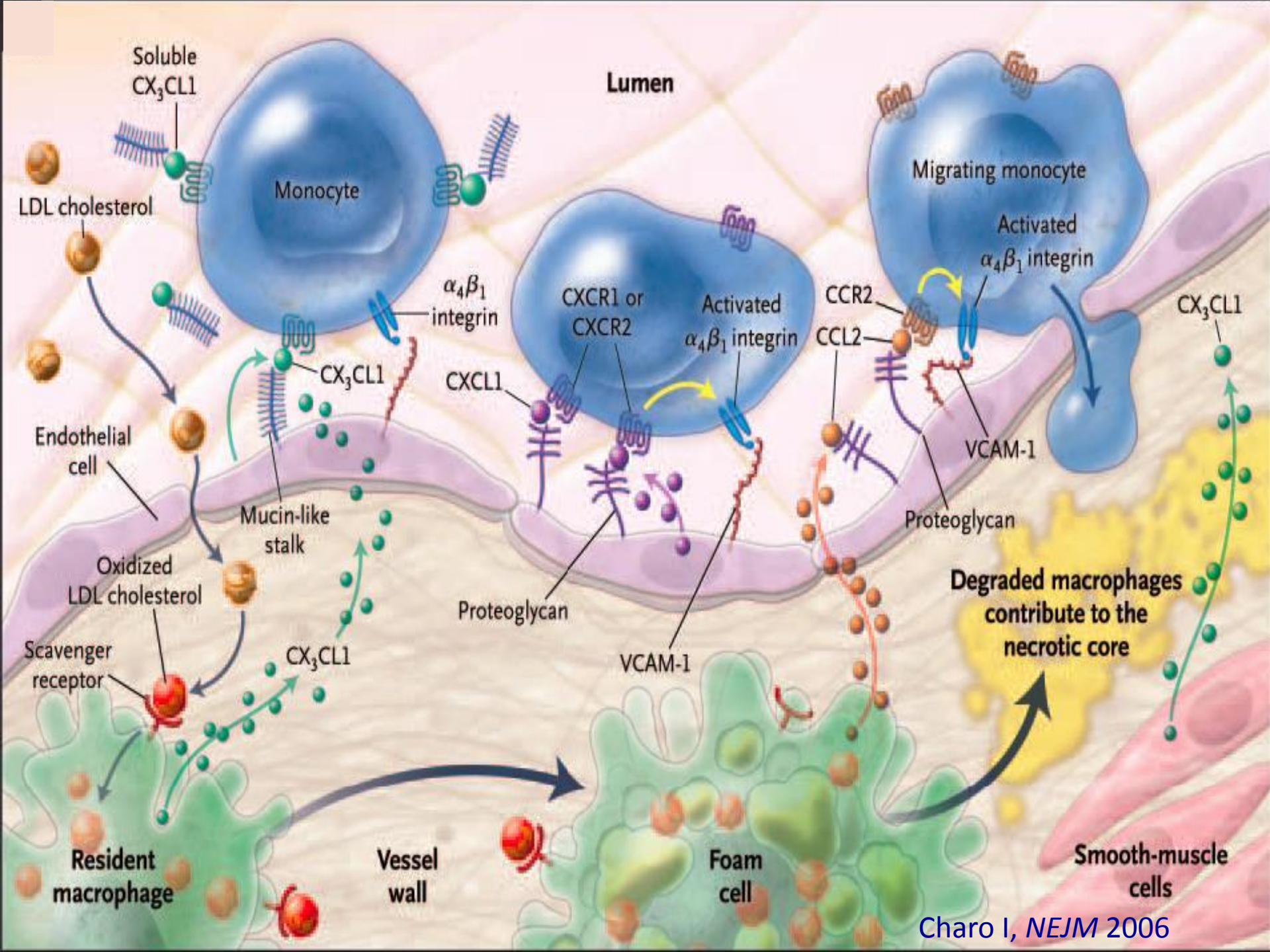
Robert P Giugliano, Terje R Pedersen, Jeong-Gun Park, Gaetano M De Ferrari, Zbigniew A Gaciong, Richard Ceska, Kalman Toth, Ioanna Gouni-Berthold, Jose Lopez-Miranda, François Schiele, François Mach, Brian R Ott, Estella Kanevsky, Armando Lira Pineda, Ransi Somaratne, Scott M Wasserman, Anthony C Keech, Peter S Sever, Marc S Sabatine, on behalf of the FOURIER Investigators



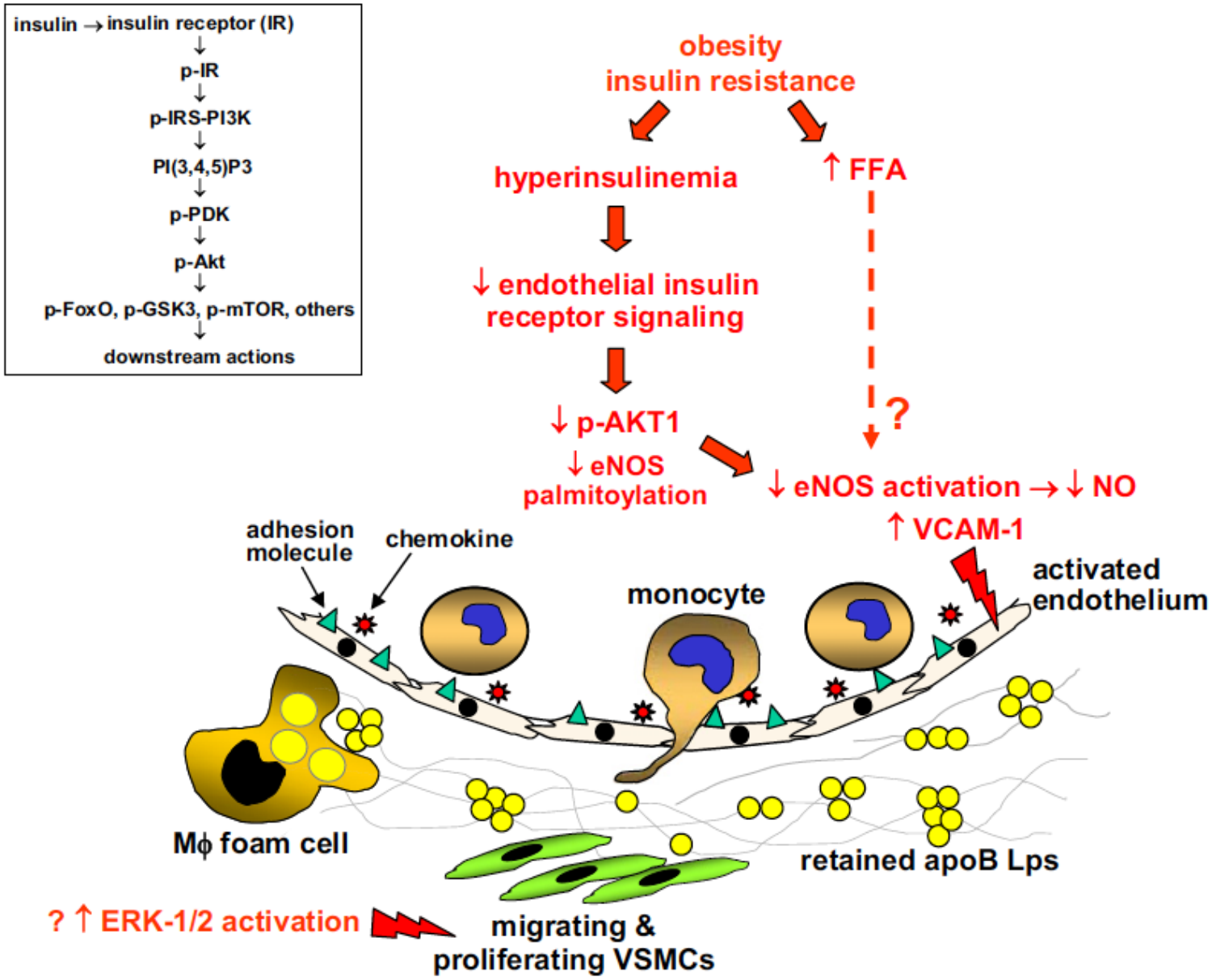
Composition of Atherogenic Sites in Fetal Aortas



Napoli et al. JCI, 1997, 100:2680-2690.

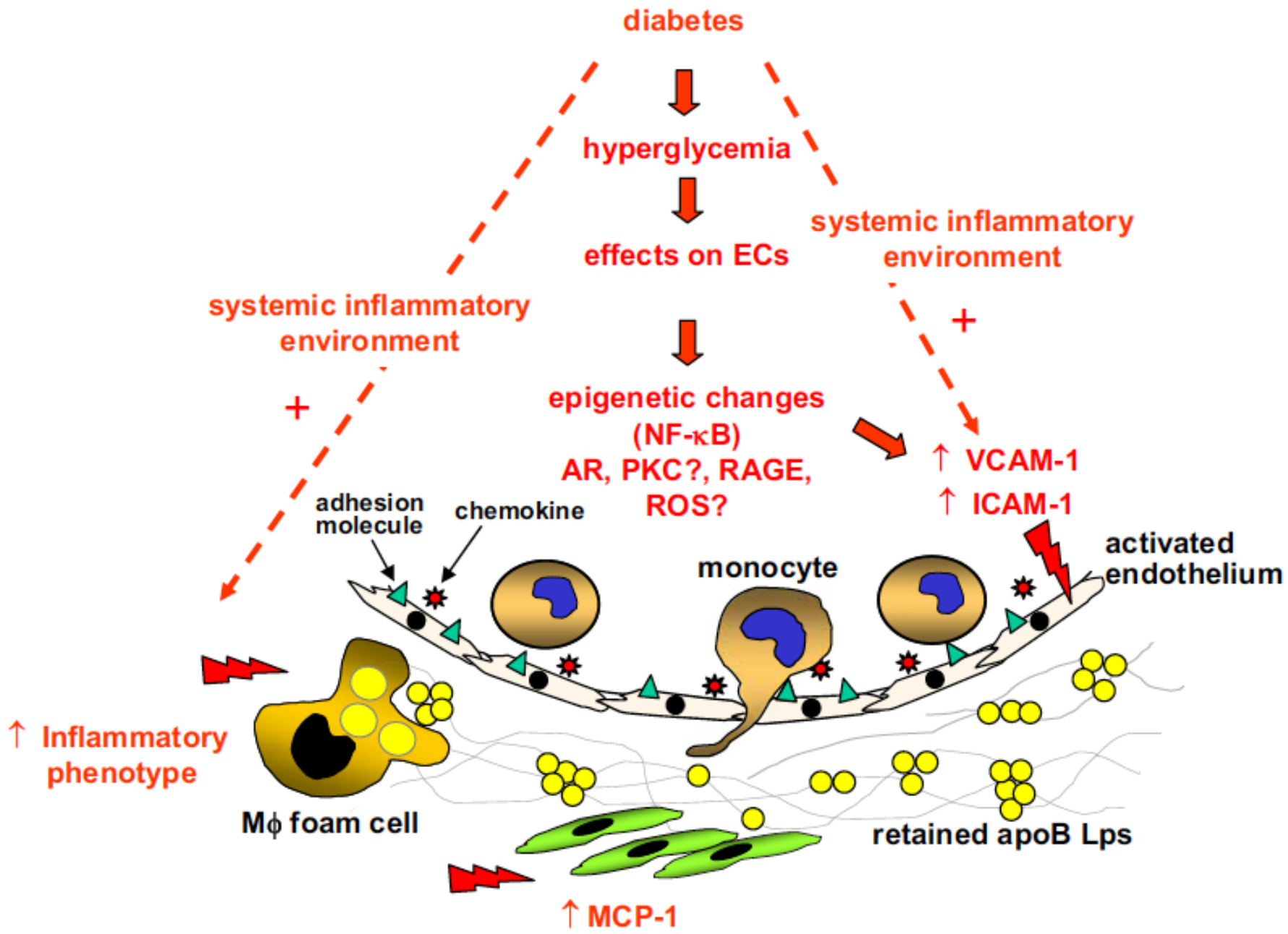


Charo I, *NEJM* 2006

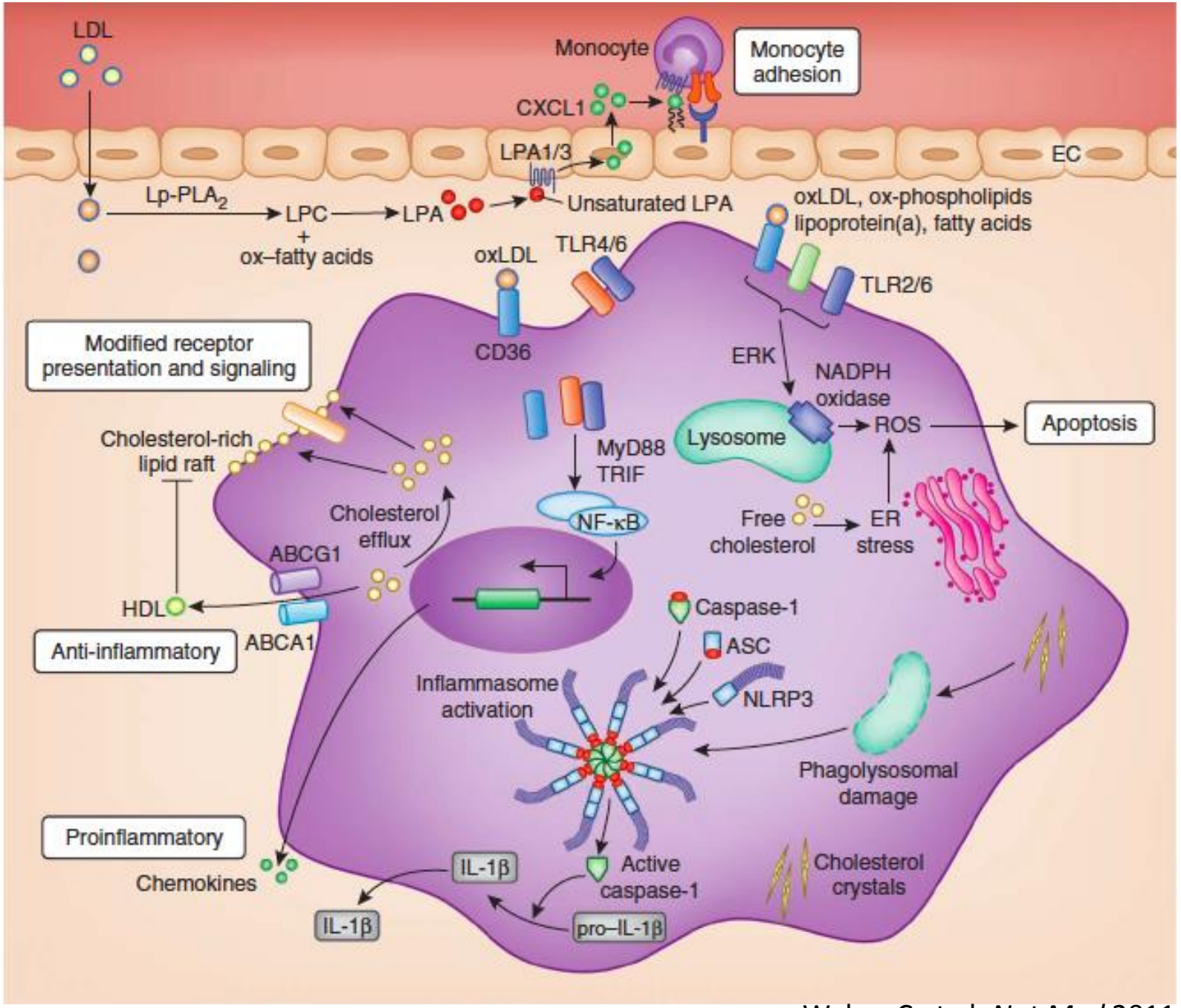


Early atherogenesis—Insulin resistance

Bornfeldt KE et al. *Cell Metab* 2011



Bornfeldt KE et al. *Cell Metab* 2011

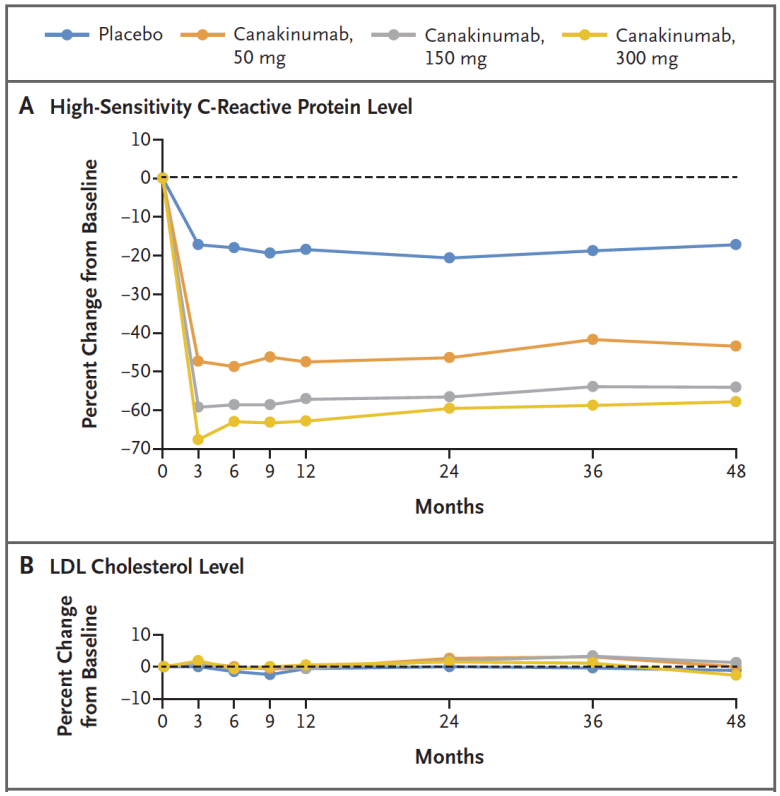


Weber C et al. *Nat Med* 2011

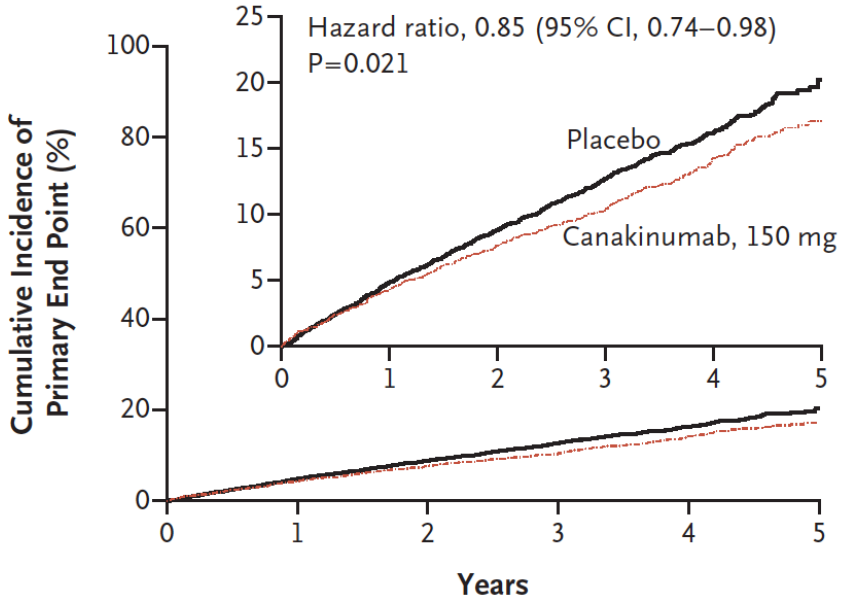
Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

The NEW ENGLAND JOURNAL of MEDICINE

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*



Primary End Point with Canakinumab, 150 mg, vs. Placebo

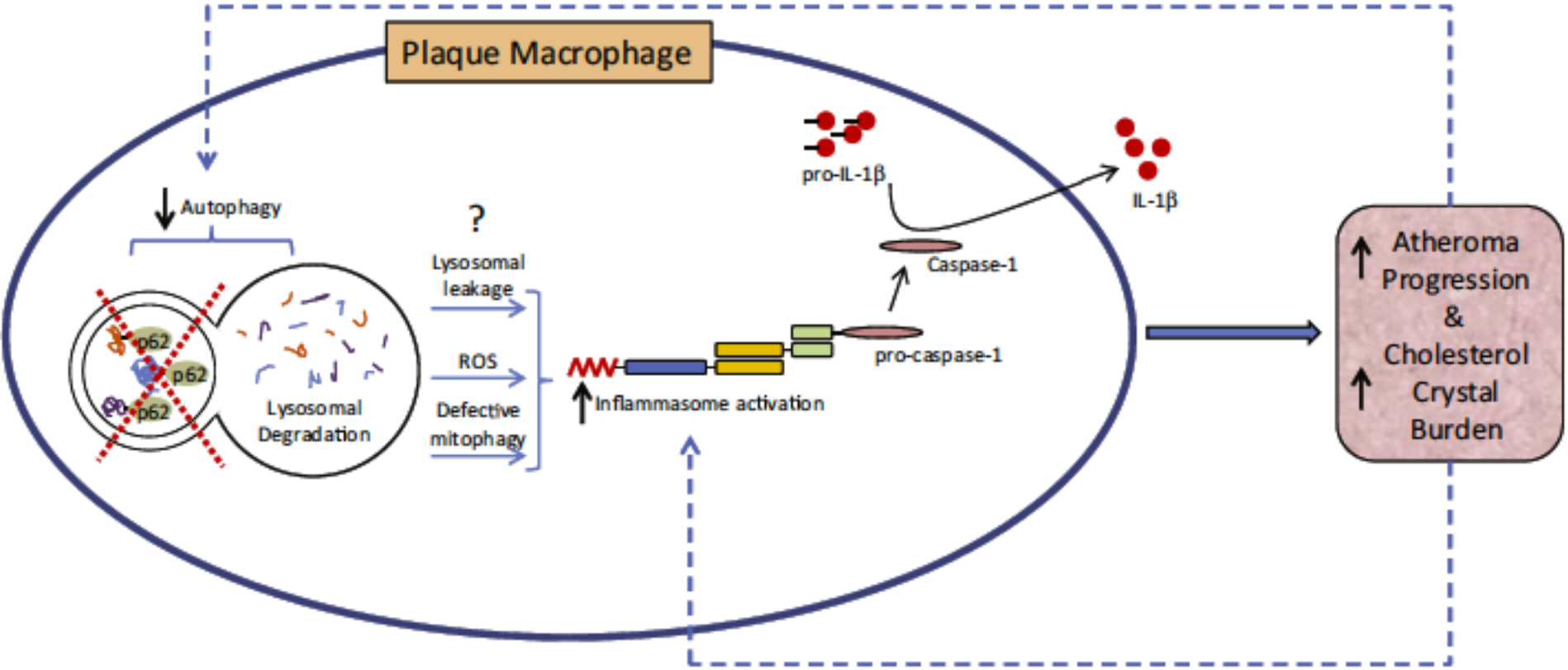


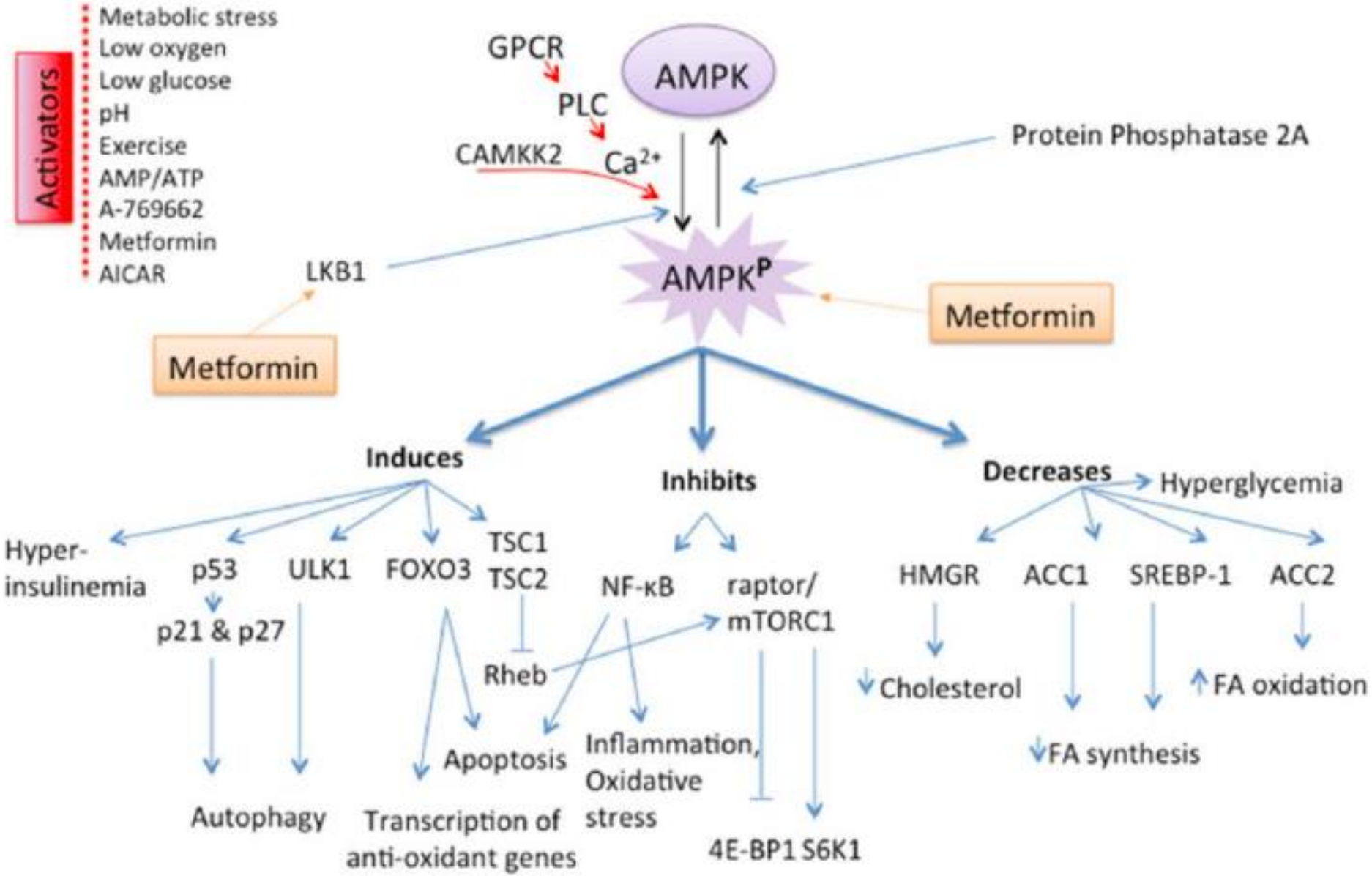
No. at Risk

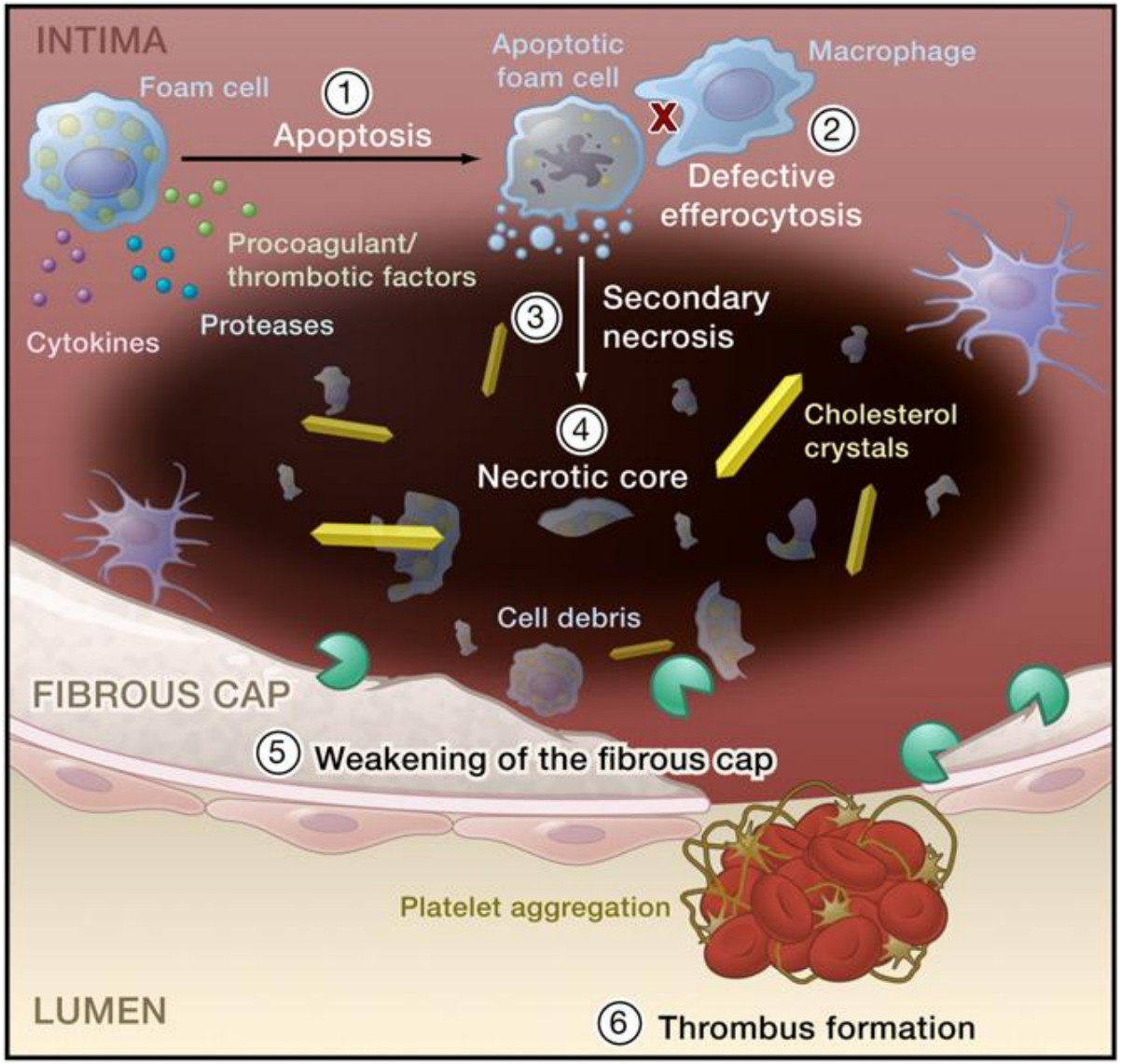
Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2284	2151	2057	1849	907	207

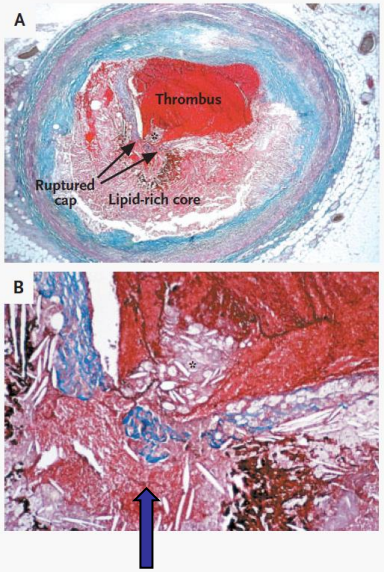
Autophagy Links Inflammasomes to Atherosclerotic Progression

Babak Razani,[1,2] Chu Feng,[1] Trey Coleman,[1] Roy Emanuel,[1] Haitao Wen,[5] Seungmin Hwang,[4] Jenny P. Ting,[5] Herbert W. Virgin,[4] Michael B. Kastan,[6] and Clay F. Semenkovich[1,3,*]




Activators
Metabolic stress
Low oxygen
Low glucose
pH
Exercise
AMP/ATP
A-769662
Metformin
AICAR
GPCR
PLC
CAMKK2
Ca2+
AMPK
Protein Phosphatase 2A
LKB1
AMPKP
Metformin
Metformin
Induces
Inhibits
Decreases
Hyperglycemia
Hyper-insulinemia
p53
p21 & p27
ULK1
FOXO3
TSC1
TSC2
Rheb
NF-κB
raptor/
mTORC1
HMGR
ACC1
SREBP-1
ACC2
Cholesterol
FA oxidation
FA synthesis
Apoptosis
Inflammation,
Oxidative
stress
Autophagy
Transcription of
anti-oxidant genes
4E-BP1 S6K1



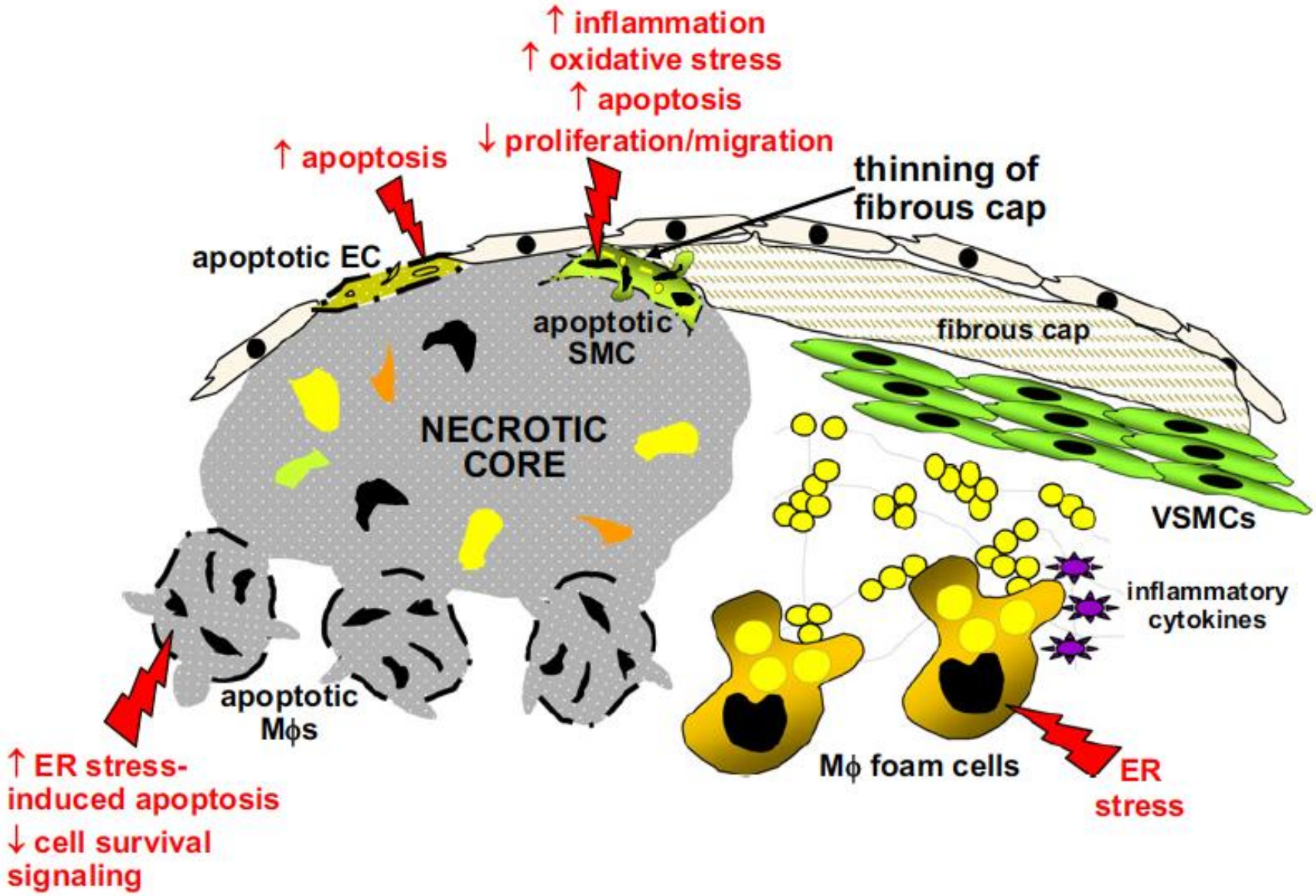


Debris of dead cells (thrombogenic)

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Mallat et al. 1999, 2000

Moore KJ & Tabas I. Cell 2011



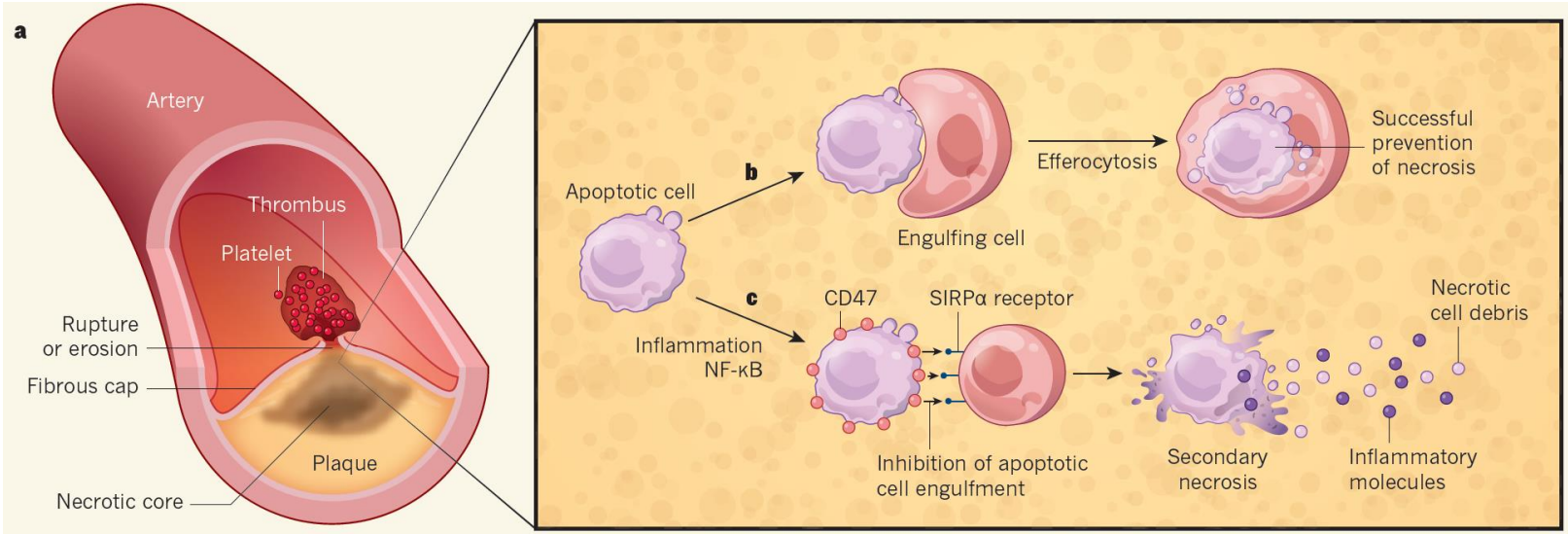
Advanced plaque progression—Insulin resistance

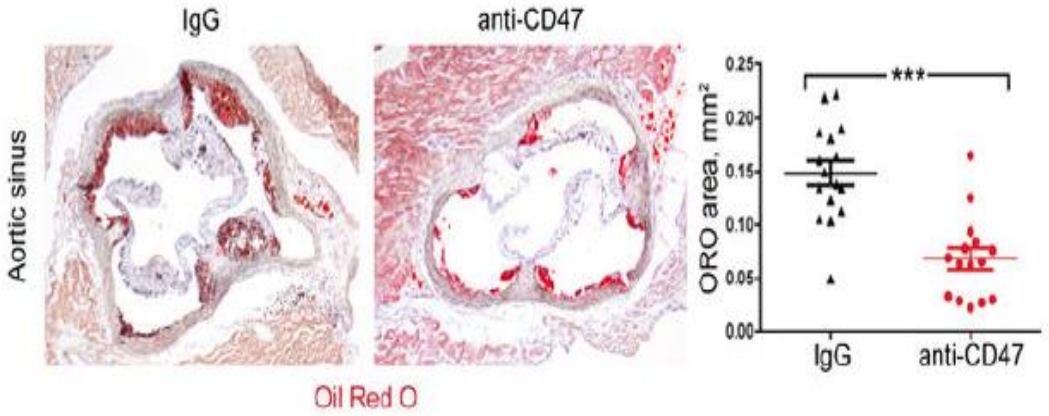
Bornfeldt KE et al. *Cell Metab* 2011

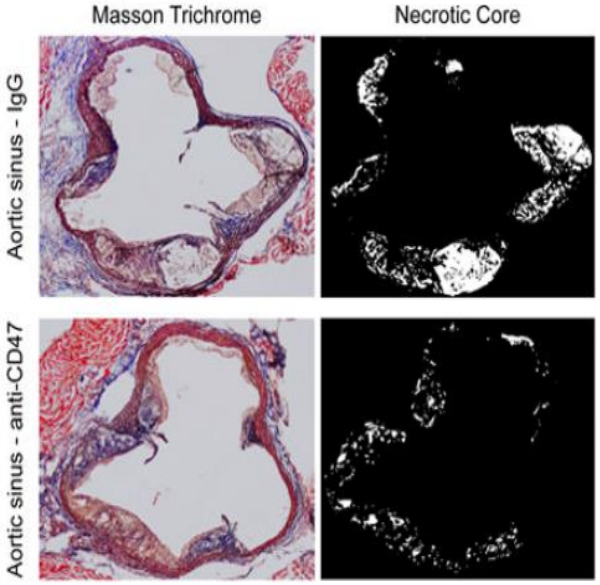
CD47–blocking antibodies restore phagocytosis and prevent atherosclerosis

Yoko Kojima[1], Jens-Peter Volkmer[2], Kelly McKenna[2], Mete Civelek[3], Aldons Jake Lusis[3], Clint L. Miller[4], Daniel Direnzo[1], Vivek Nanda[1], Jianqin Ye[1], Andrew J. Connolly[5], Eric E. Schadt[6], Thomas Quertermous[4], Paola Betancur[2], Lars Maegdefessel[7], Ljubica Perisic Matic[8], Ulf Hedin[8], Irving L. Weissman[2] & Nicholas J. Leeper[1,4]

NATURE
LETTER RESEARCH

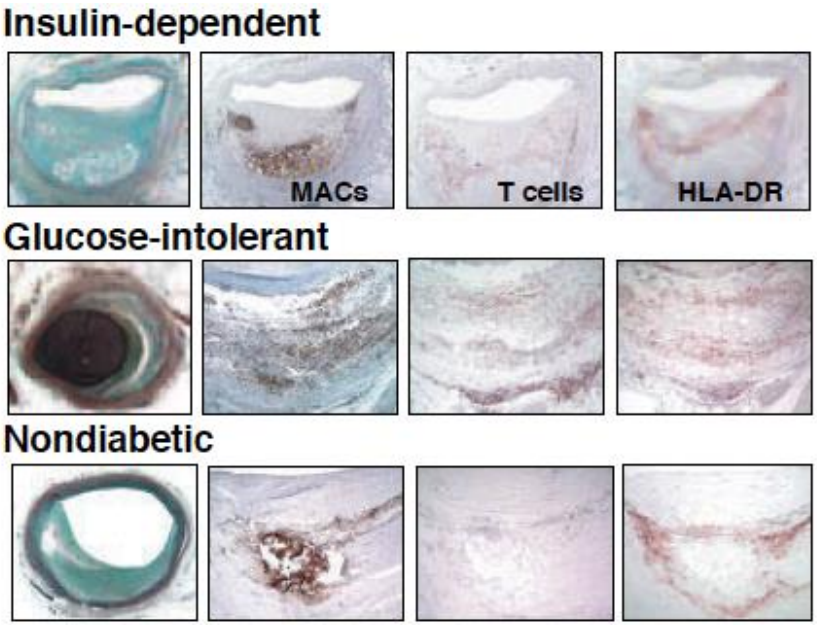


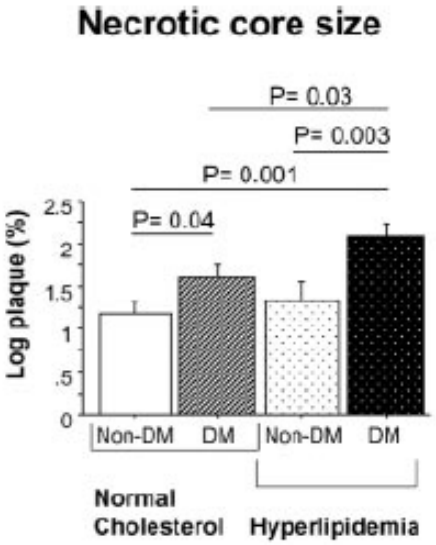


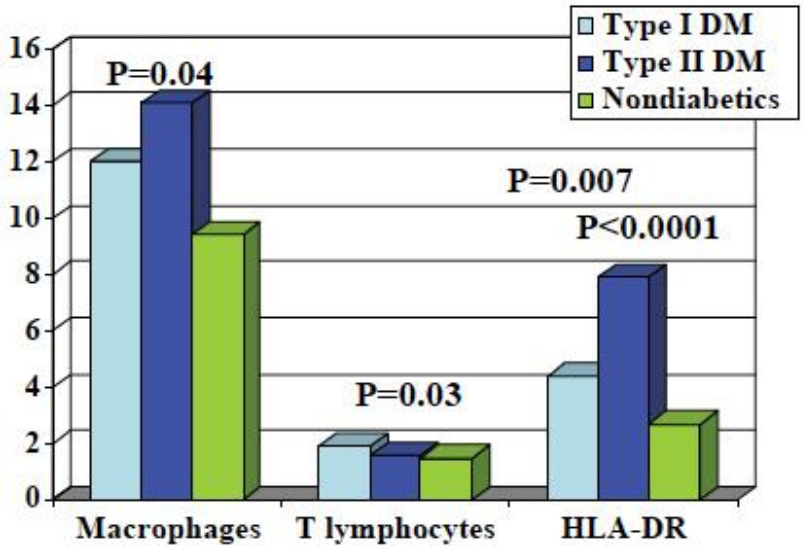


Morphological characteristics of coronary atherosclerosis in diabetes mellitus

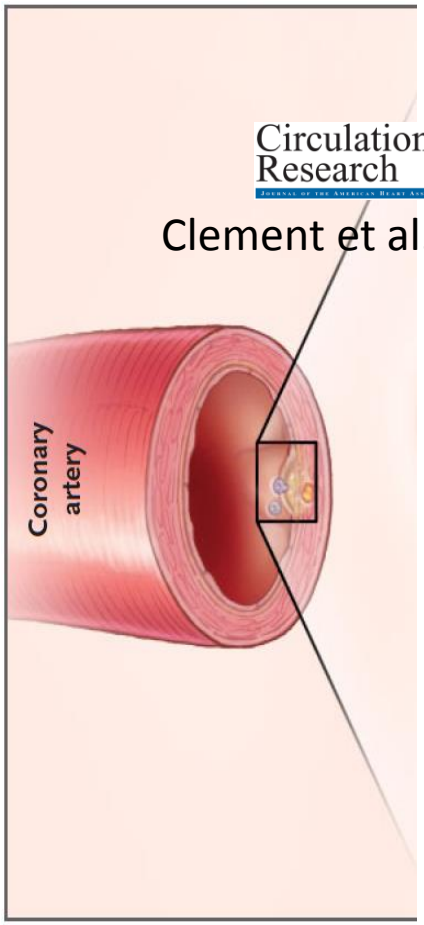
Renu Virmani MD[1], Allen P Burke MD[2], Frank Kolodgie PhD[1]







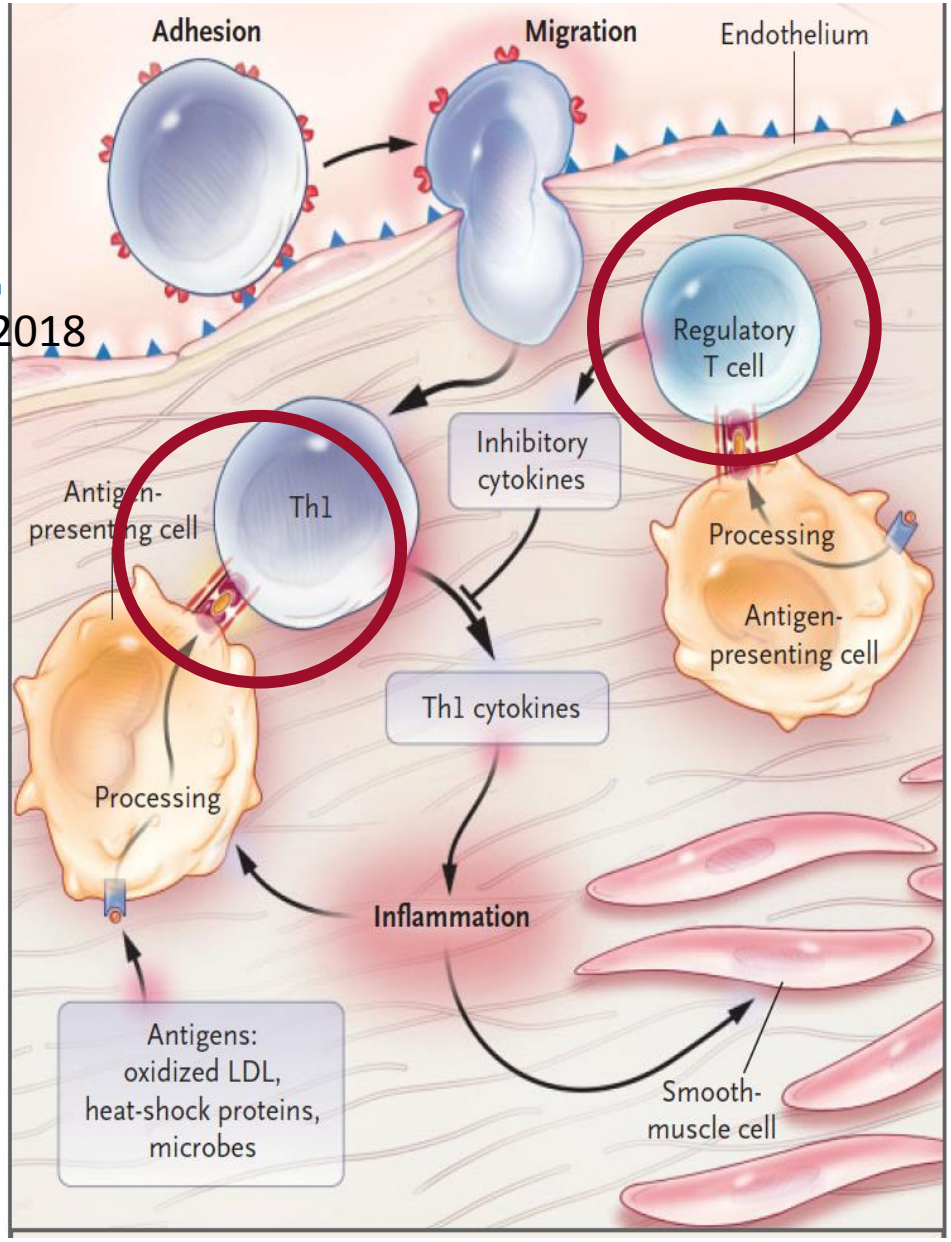
Pro-atherogenic Th1 vs atheroprotective Tregs



Circulation Research

Clement et al., 2018

Hanson GK.
N Engl J Med 2005



Circulation

Mallat et al. 2003

Tr1 cells: IL-10

nature medicine

Ait-Oufella et al. 2006

nTreg and TGF-β

Arteriosclerosis, Thrombosis, and Vascular Biology

Herbin et al. 2012

ApoB100-Tregs

Circulation Research

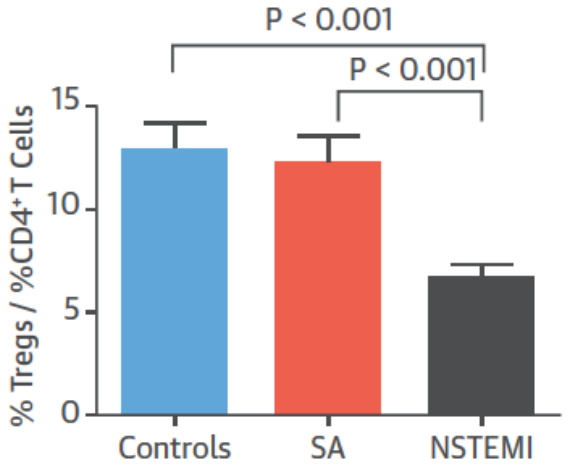
Mallat et al. 1999, 2001

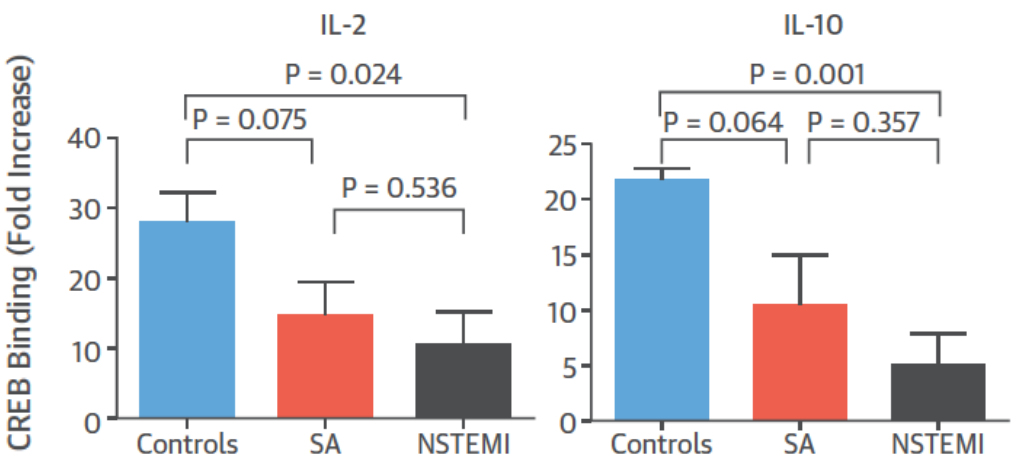
IL-10 and TGF-β

Increased PTPN22 Expression and Defective CREB Activation Impair Regulatory T-Cell Differentiation in Non-ST-Segment Elevation Acute Coronary Syndromes

JACC VOL. 65, NO. 12, 2015

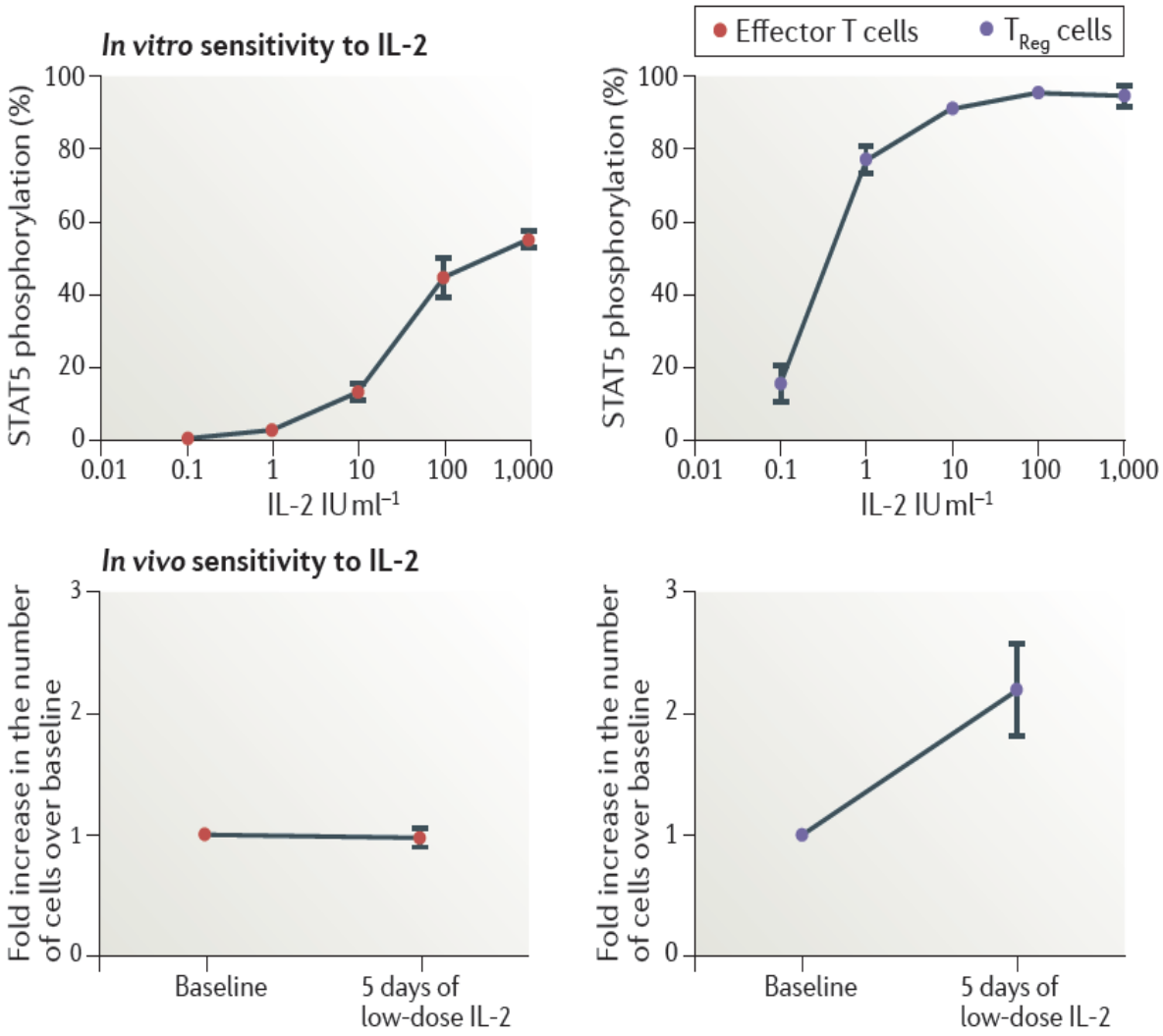
Flego D et al.



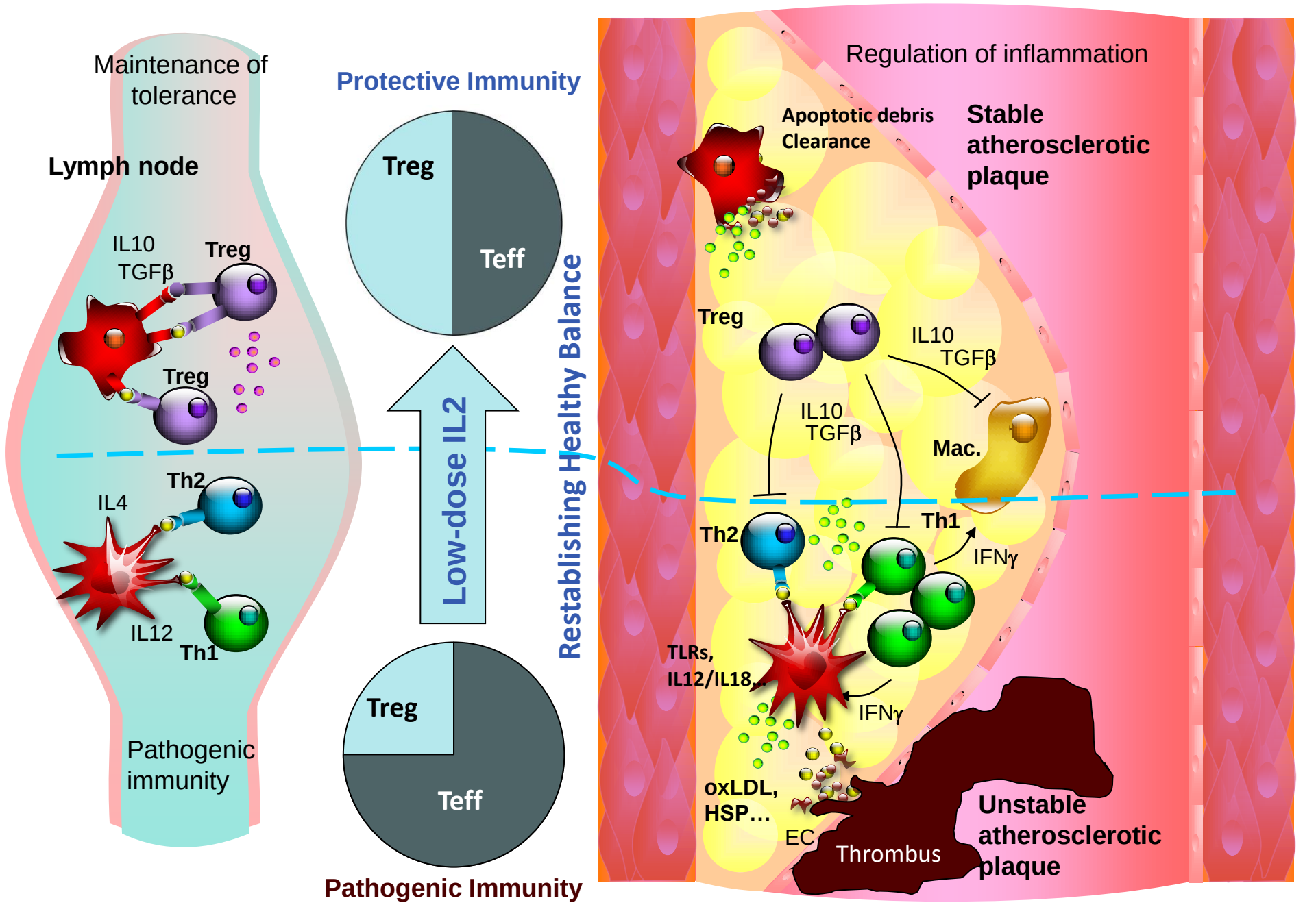


The promise of low-dose interleukin-2 therapy for autoimmune and inflammatory diseases

NATURE REVIEWS | IMMUNOLOGY
Klatzmann D & Abbas K, 2015

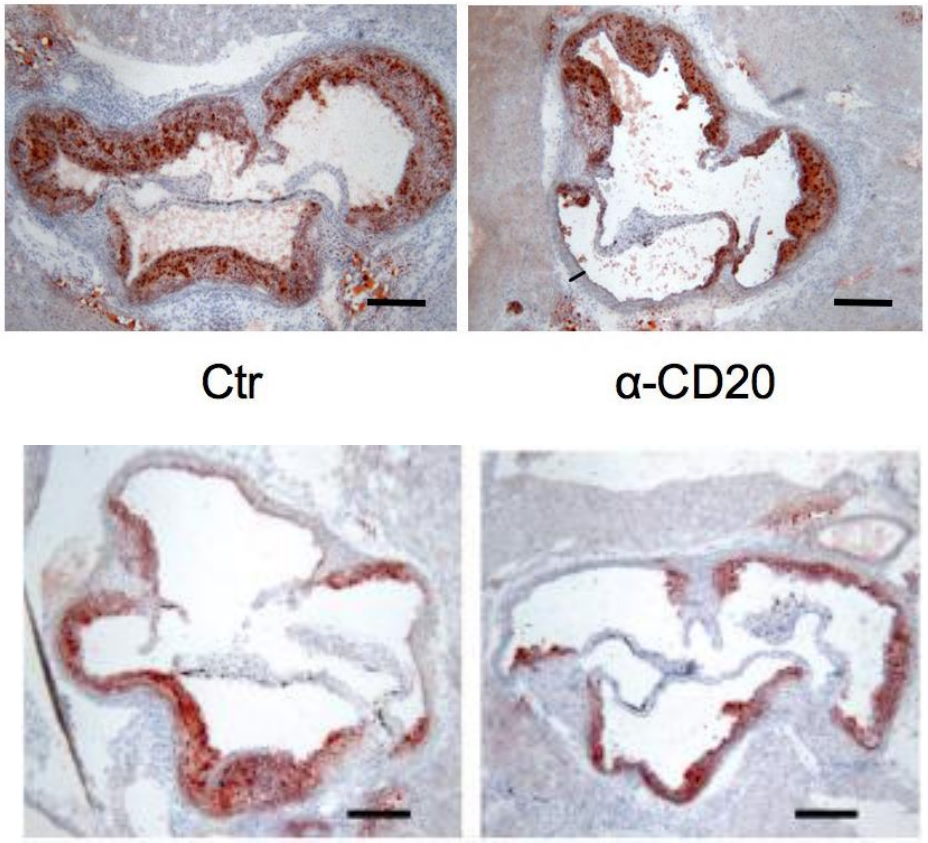


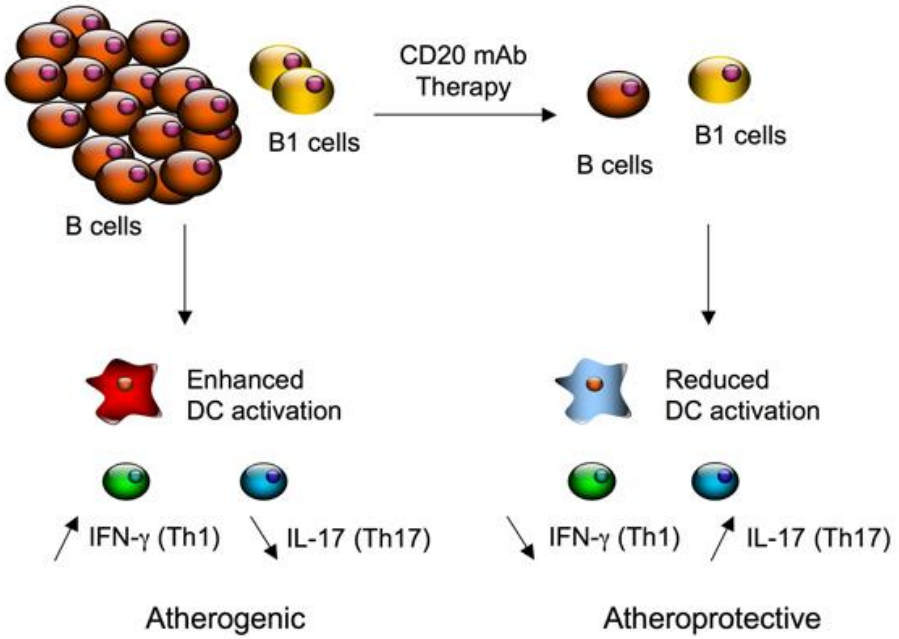
Low-dose IL-2 to limit plaque inflammation



B cell depletion reduces the development of atherosclerosis in mice

Ait-Oufella et al. JEM 2010

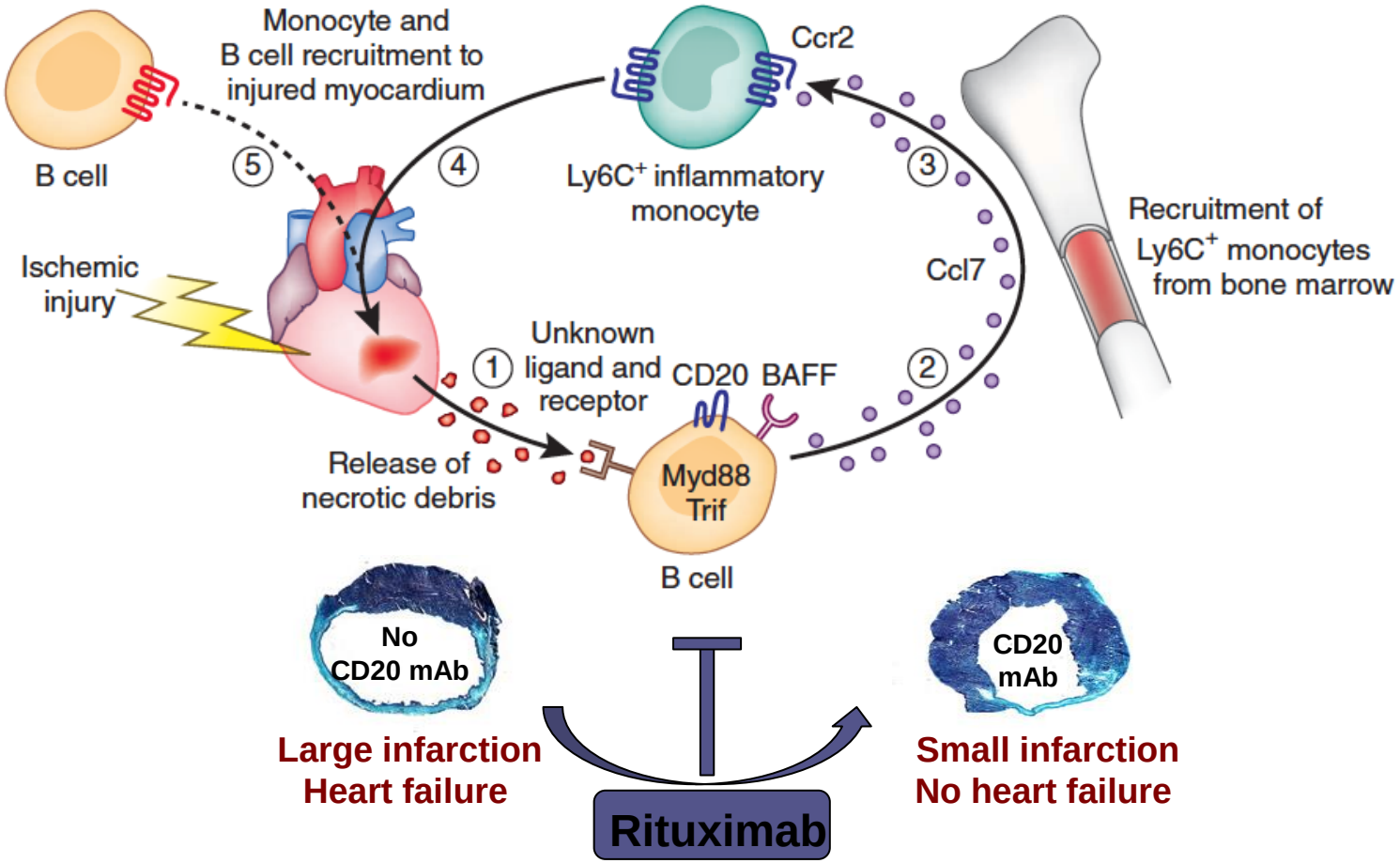




B lymphocytes trigger monocyte mobilization and impair heart function after acute myocardial infarction

nature medicine
2013

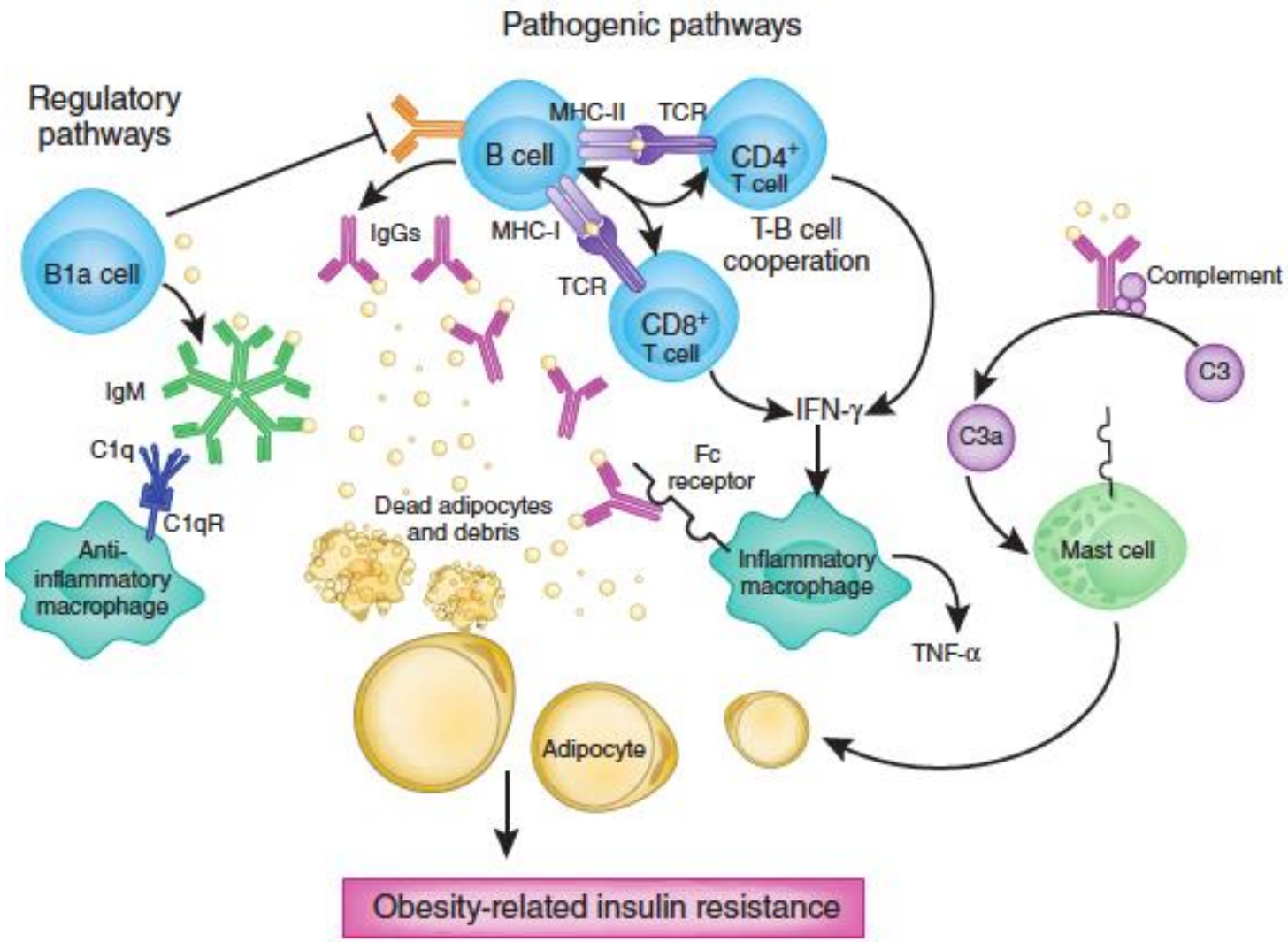
Yasmine Zouggari[1,2,13], Hafid Ait-Oufella[1–3,13], Philippe Bonnin[4], Tabassome Simon[3,5], Andrew P Sage[6], Coralie Guérin[1,2], José Vilar[1,2], Giuseppina Caligiuri[7], Dimitrios Tsiantoulas[8,9], Ludivine Laurans[1,2], Edouard Dumeau[1,2], Salma Kotti[5], Patrick Bruneval[1,2,10], Israel F Charo[11], Christoph J Binder[8,9], Nicolas Danchin[10], Alain Tedgui[1,2], Thomas F Tedder[12], Jean-Sébastien Silvestre[1,2,13] & Ziad Mallat[1,6,13]

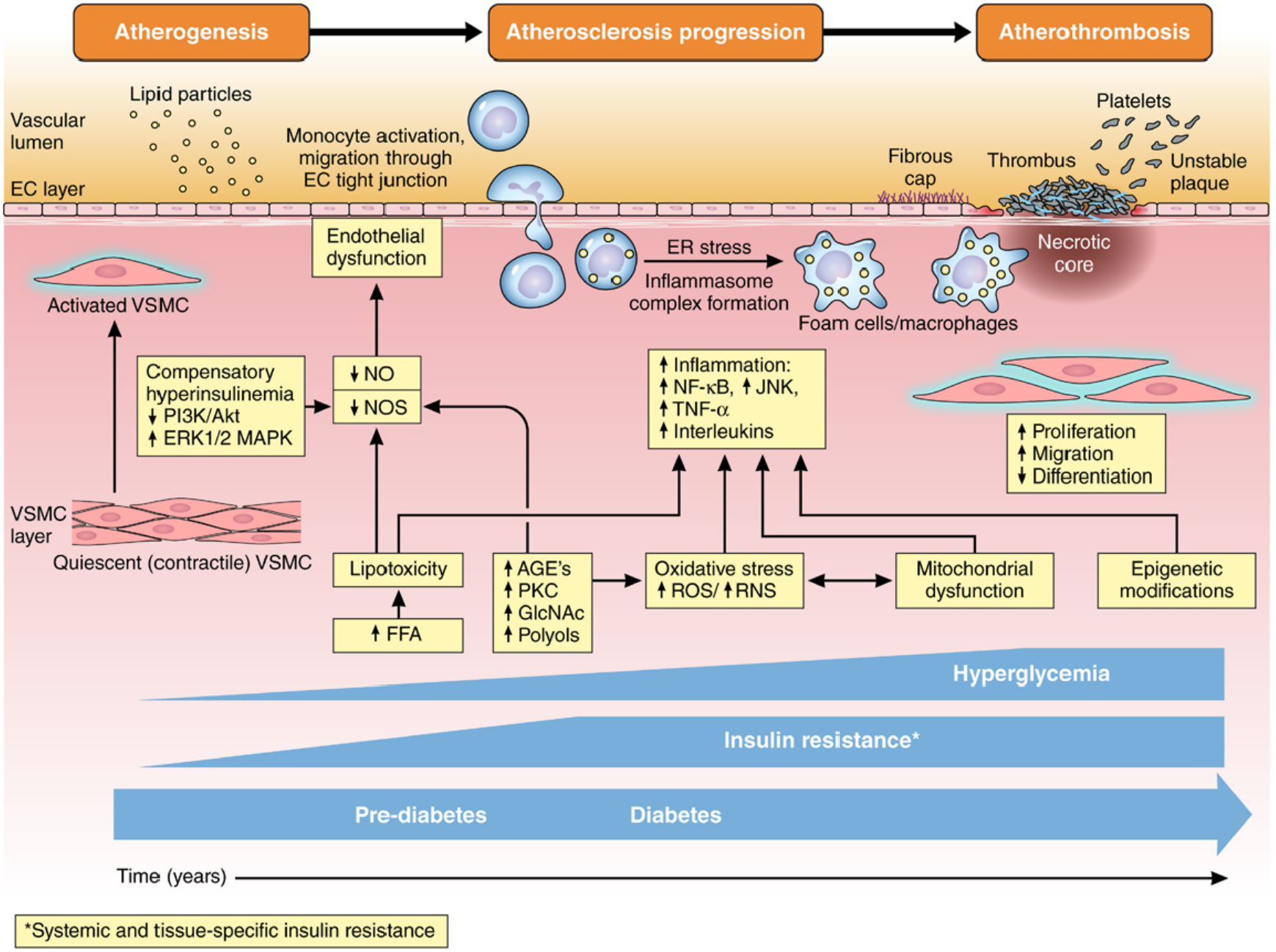


The B-side story in insulin resistance

nature medicine

Ziad Mallat





Low Wang CC et al. *Circulation* 2016

University of Cambridge
British Heart Foundation
Xuan LI
Andy SAGE
Marc CLEMENT

Inserm U970
Paris, France
Hafid AIT-OUFELLA
JS SILVESTRE
Alain TEDGUI

CeMM, Medical
University
of Vienna, Austria
CJ. BINDER

Duke University, USA
Thomas F. TEDDER

Patients with diabetes differ in atherosclerotic plaque characteristics and have worse clinical outcome after iliofemoral endarterectomy compared with patients without diabetes

Steven T. W. van Haelst, MD,[a] Saskia Haitjema, MD,[b] Jean-Paul P. M. de Vries, MD, PhD,[c] Frans L. Moll, MD, PhD,[a] Gerard Pasterkamp, MD, PhD,[b,d] Hester M. den Ruijter, PhD,[b] *and* Gert J. de Borst, MD, PhD,[a] *Utrecht and Nieuwegein, The Netherlands*

Journal of Vascular Surgery

Plaque characteristic	Beta value of DM (95% CI)	OR of DM (95% CI)	*P* value
Calcified plaque	NA	2.11 (1.43-3.12)	<.01[a]
Collagen-rich plaque	NA	1.60 (0.93-2.74)	.09
Lipid core >10%	NA	0.98 (0.63-1.53)	.92
Presence of IPH	NA	0.73 (0.51-1.04)	.08
Macrophages[b]	−0.13 (−0.46 to 0.20)	NA	.44
Smooth muscle cells[b]	−0.06 (−0.35 to 0.22)	NA	.67
Vessel density[c]	0.08 (−0.17 to 0.33)	NA	.52

CI, Confidence interval; *DM*, diabetes mellitus; *IPH*, intraplaque hemorrhage; *NA*, not applicable; *OR*, odds ratio.

Model corrected for body mass index, hypercholesterolemia, current smoking, hypertension, history of coronary artery disease, total cholesterol, low-density lipoprotein cholesterol, glucose, and statin use.

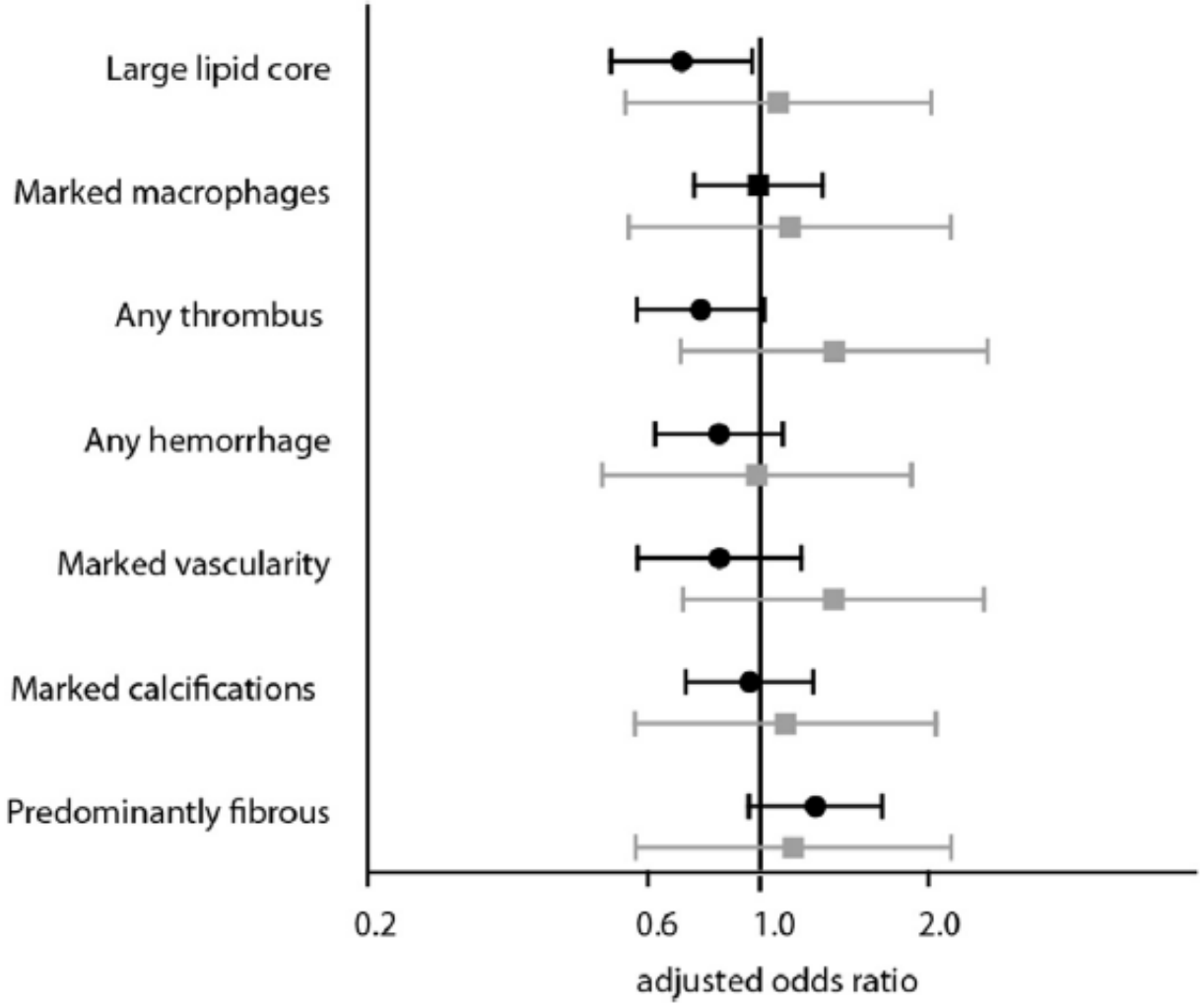
[a] $P < .05$.

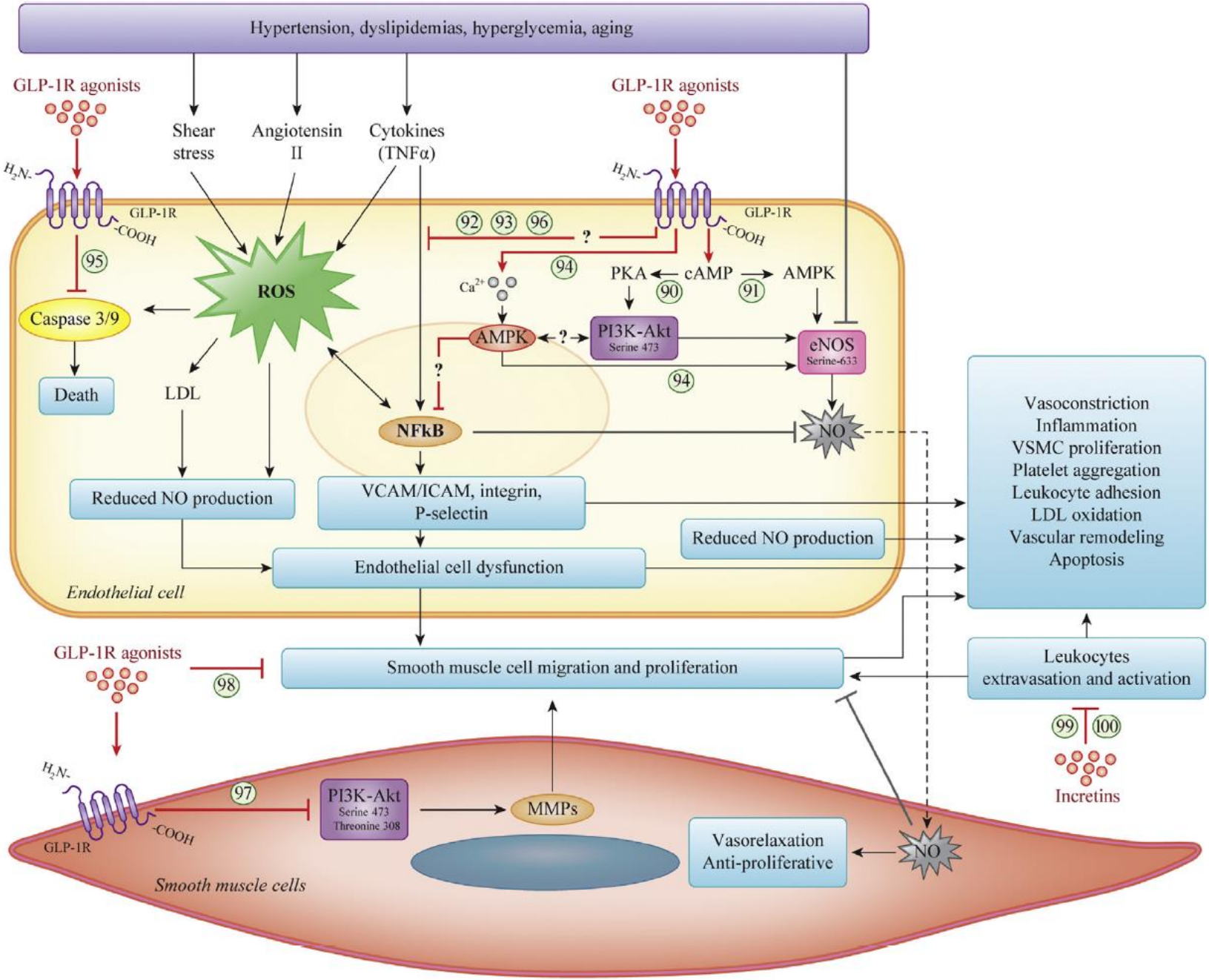
[b] Log-transformed % of plaque area.

[c] Log-transformed number of vessels per hotspot.

Type 2 diabetes is not associated with an altered plaque phenotype among patients undergoing carotid revascularization. A histological analysis of 1455 carotid plaques

Vincent P.W. Scholtes [a], Wouter Peeters [a], Guus W. van Lammeren [a], Dominic P.J. Howard [b], Jean-Paul P.M. de Vries [c], Gert Jan de Borst [d], Jessica N. Redgrave [b], Hans Kemperman [e], Casper G. Schalkwijk [f,g], Hester M. den Ruijter [a,h], Dominique P.V. de Kleijn [a], Frans L. Moll [d], Peter M. Rothwell [b], Gerard Pasterkamp [a,*]

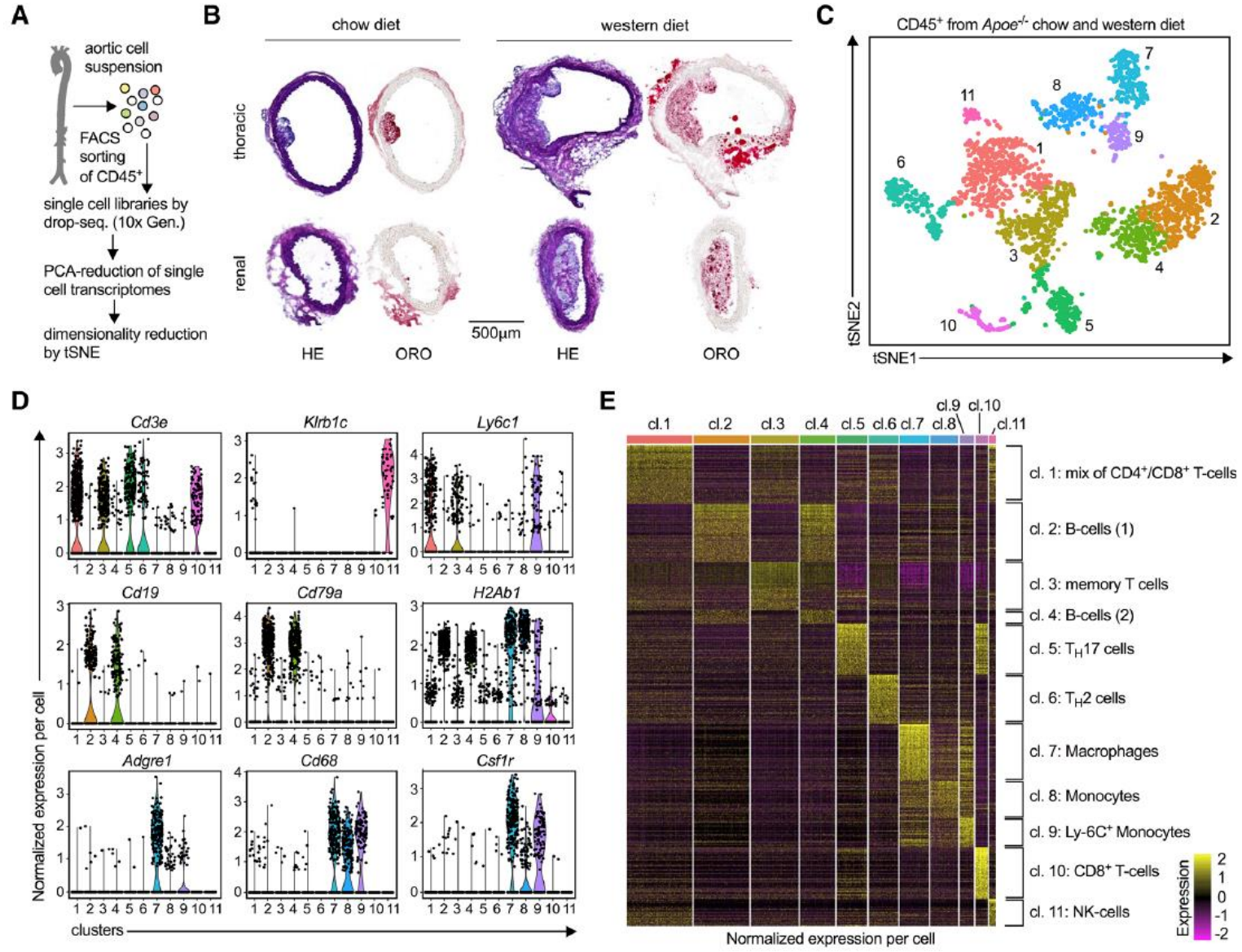




Gallego-Colon E et al. *Atherosclerosis* 2018

Atlas of the Immune Cell Repertoire in Mouse Atherosclerosis Defined by Single-Cell RNA-Sequencing and Mass Cytometry

Circulation Research
Journal of the American Heart Association

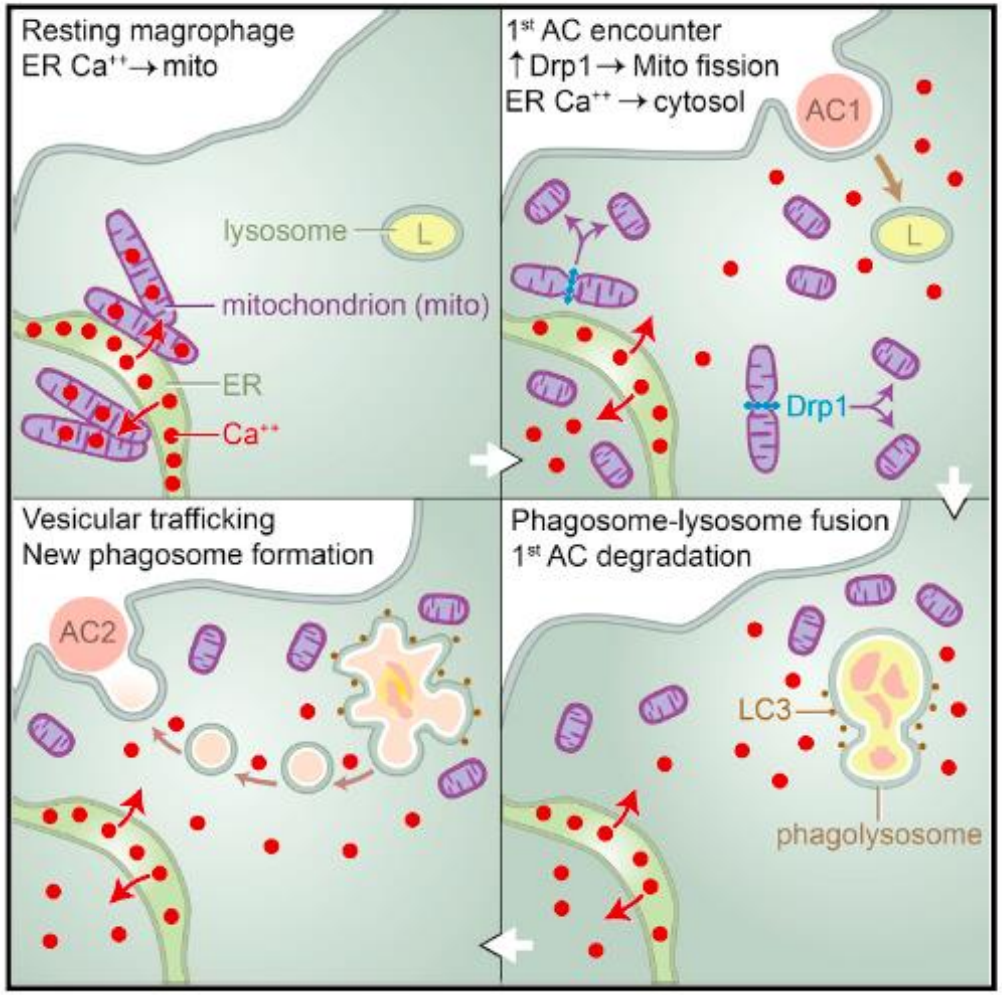


Winkels H et al, Circ Res 2018

Cell

Mitochondrial Fission Promotes the Continued Clearance of Apoptotic Cells by Macrophages

Graphical Abstract



Authors

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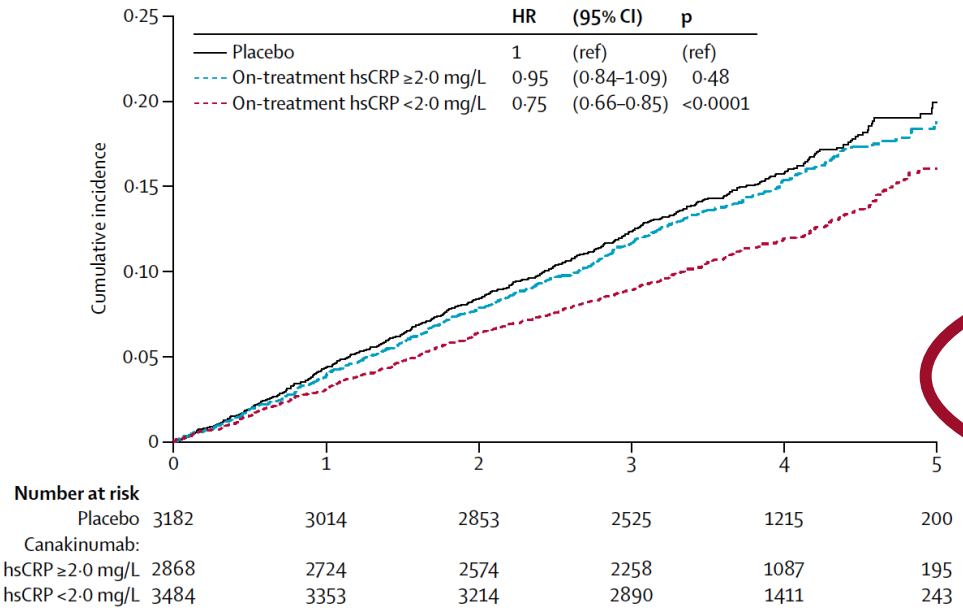
In Brief

How are dead cells in our bodies rapidly cleared by phagocytes in order to avoid inflammation and necrosis?

Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial

Lancet 2018; 391: 319–28

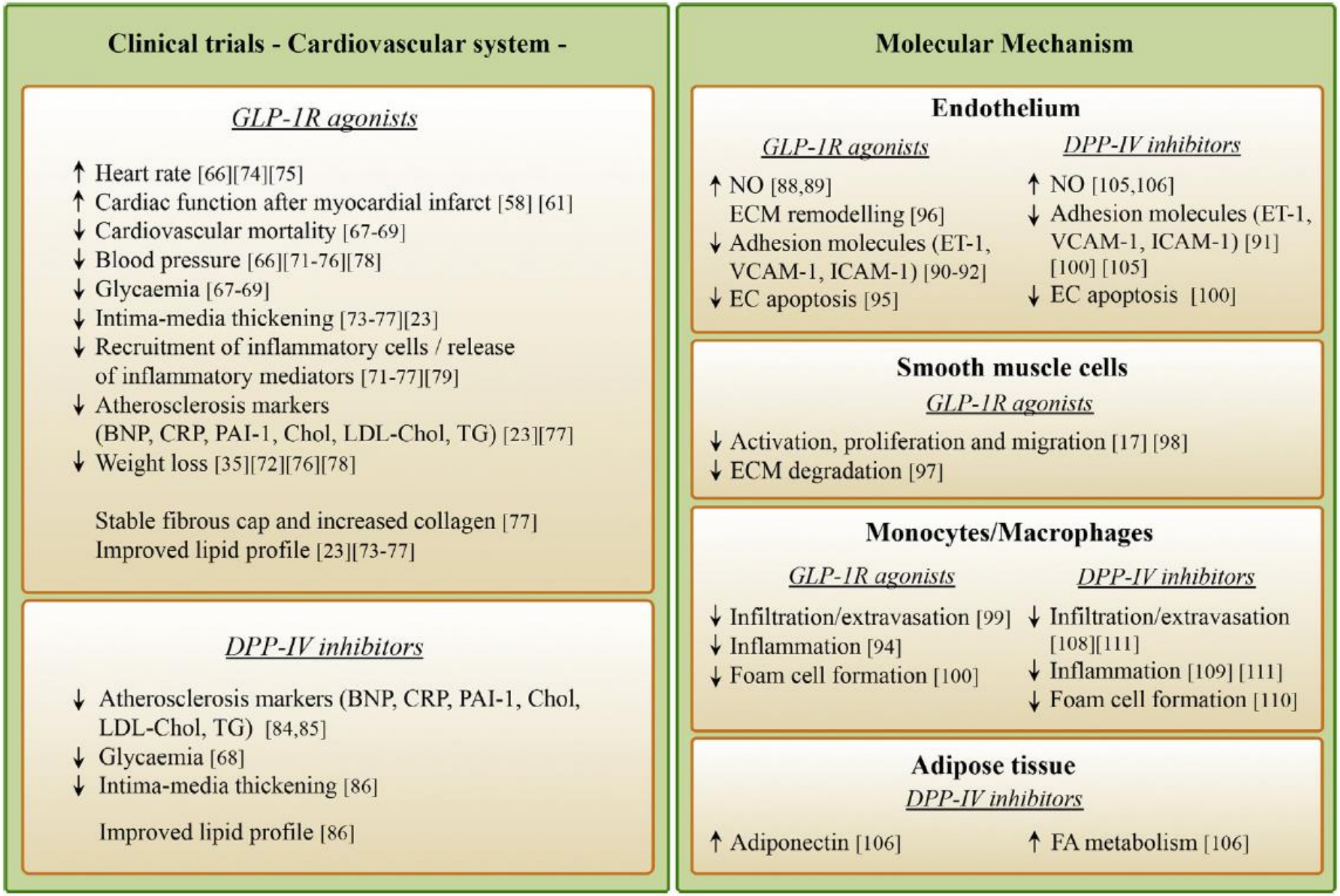
*Paul M Ridker, Jean G MacFadyen, Brendan M Everett, Peter Libby, Tom Thuren, Robert J Glynn, on behalf of the CANTOS Trial Group**



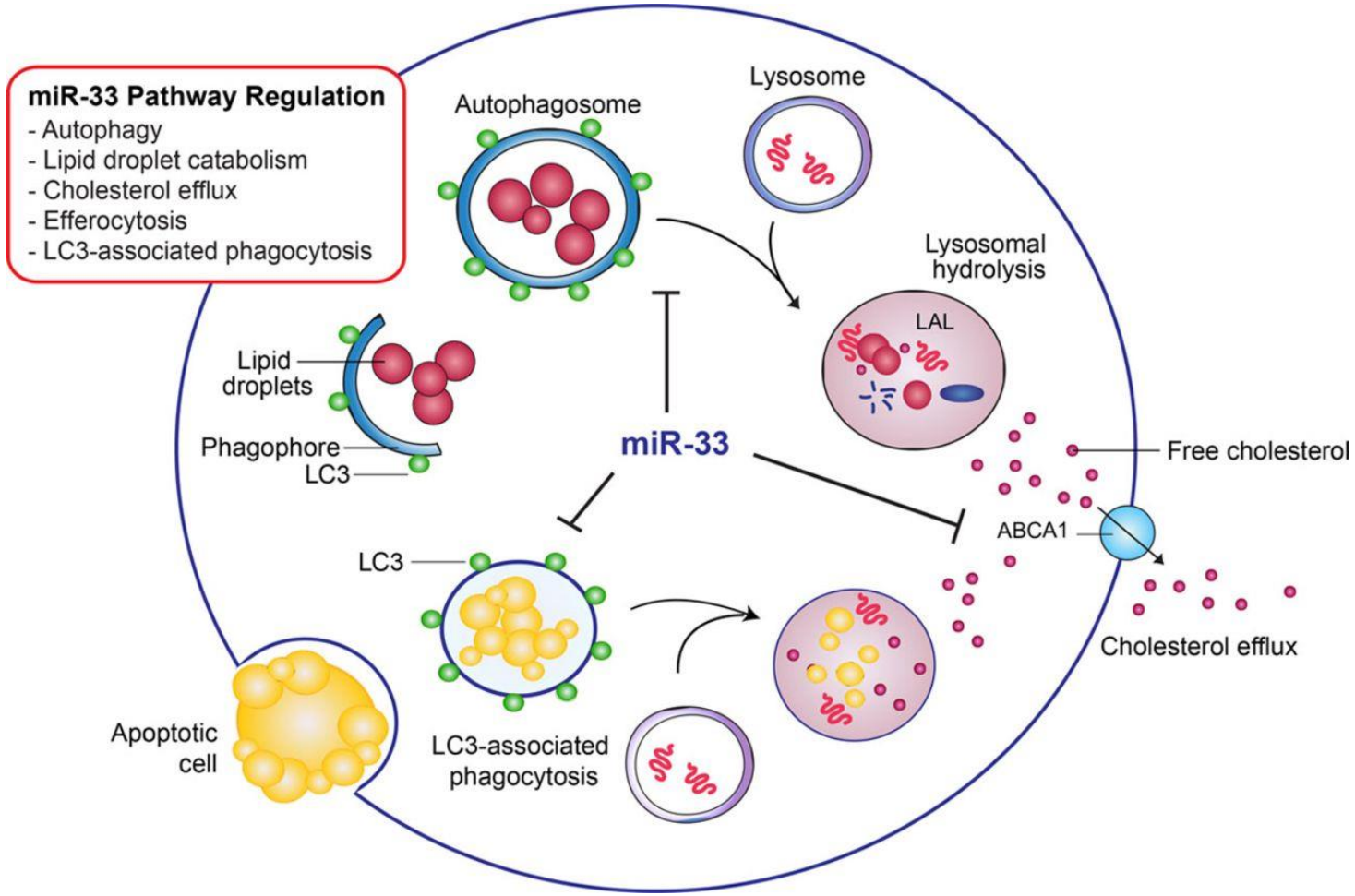
	Placebo (n=3182)	Canakinumab, hsCRP ≥2 mg/L at 3 months (n=2868)	Canakinumab, hsCRP <2 mg/L at 3 months (n=3484)	p_{trend} across categories
Myocardial infarction, stroke, or death from any cause				
Incidence rate (n)	5·39 (614)	5·38 (553)	3·96 (508)	..
HR^{adj} (95% CI)	1 (ref)	0·93 (0·83–1·05)	0·73 (0·65–0·82)	..
p value	Ref	0·25	<0·0001	<0·0001
Cardiovascular death				
Incidence rate (n)	[illegible]	1·83 (198)	[illegible]	..
HR^{adj} (95% CI)	1 (ref)	0·99 (0·82–1·21)	0·69 (0·56–0·85)	..
p value	Ref	0·95	0·0004	0·0004
All-cause mortality				
Incidence rate (n)	2·79 (338)	3·14 (339)	1·96 (264)	..
HR^{adj} (95% CI)	1 (ref)	1·05 (0·90–1·22)	0·69 (0·58–0·81)	..
p value	Ref	0·56	<0·0001	<0·0001

Incidence rates calculated per 100 person-years of exposure. Covariates included in the adjusted multivariable model include age, sex, smoking status, hypertension, diabetes, body mass index, baseline concentration of hsCRP, and baseline concentration of LDL cholesterol. HR^{adj}=adjusted hazard ratio. hsCRP=high-sensitivity C-reactive protein.

***Table 3*: Incidence rates and adjusted hazard ratios for additional prespecified cardiovascular endpoints in CANTOS, according to on-treatment hsCRP concentrations at 3 months, <2 mg/L or ≥2 mg/L**

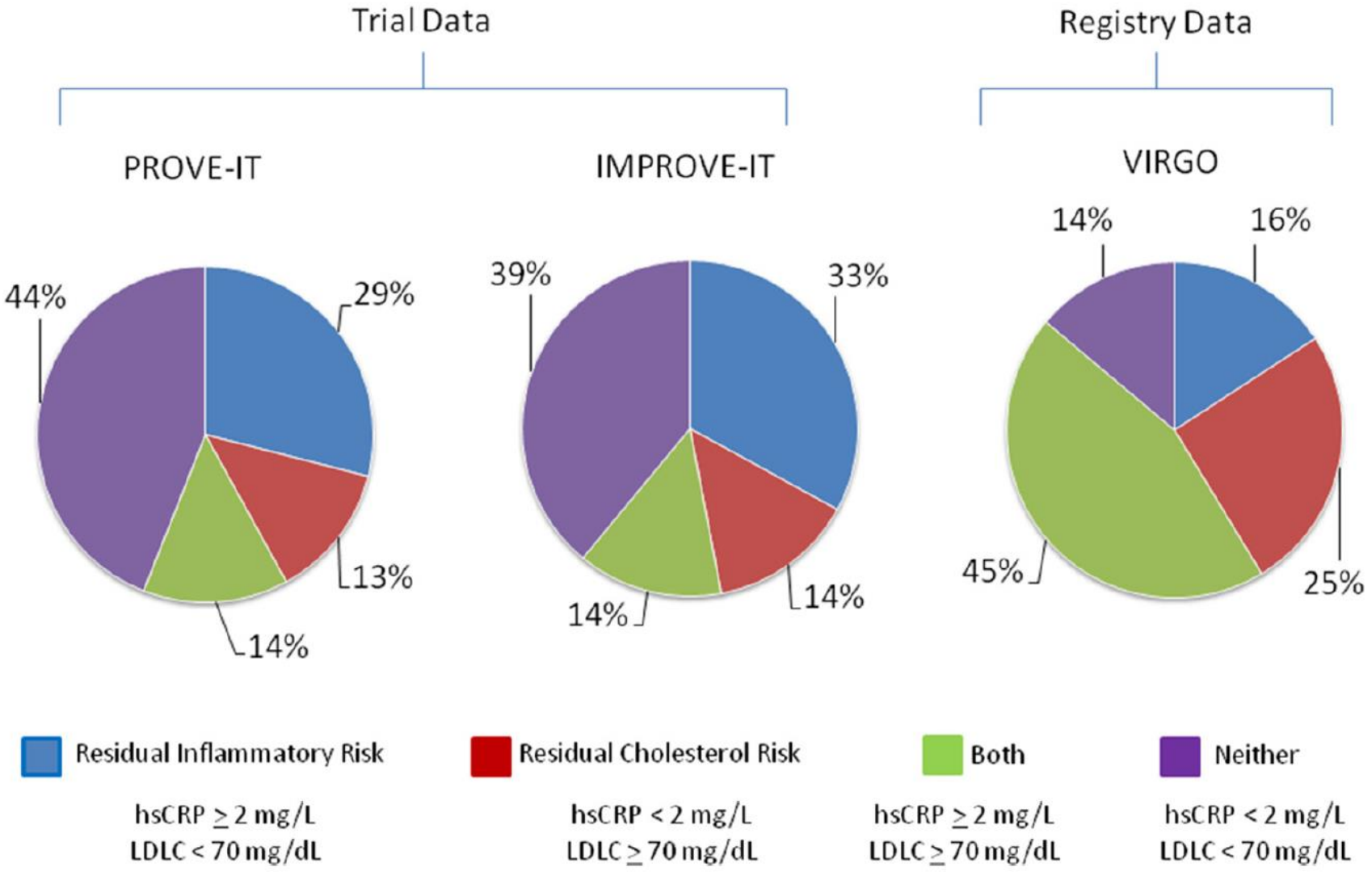


Gallego-Colon E et al. *Atherosclerosis* 2018



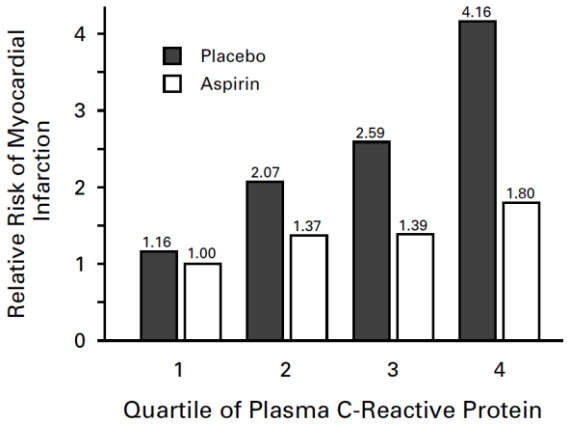
microRNA-33 Regulates Macrophage Autophagy in Atherosclerosis, Volume: 37, Issue: 6, Pages: 1058-1067, DOI: (10.1161/ATVBAHA.116.308916)

How Common Is Residual Cholesterol/Inflammatory Risk?



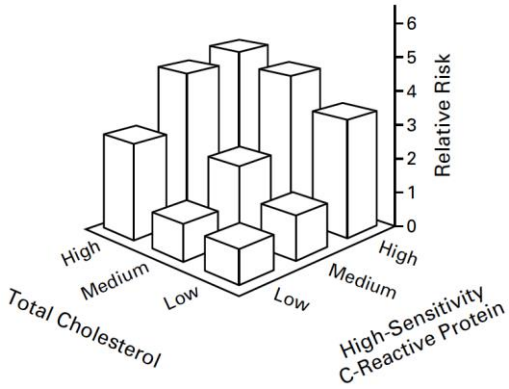
INFLAMMATION, ASPIRIN, AND THE RISK OF CARDIOVASCULAR DISEASE IN APPARENTLY HEALTHY MEN

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.



C-REACTIVE PROTEIN AND OTHER MARKERS OF INFLAMMATION IN THE PREDICTION OF CARDIOVASCULAR DISEASE IN WOMEN

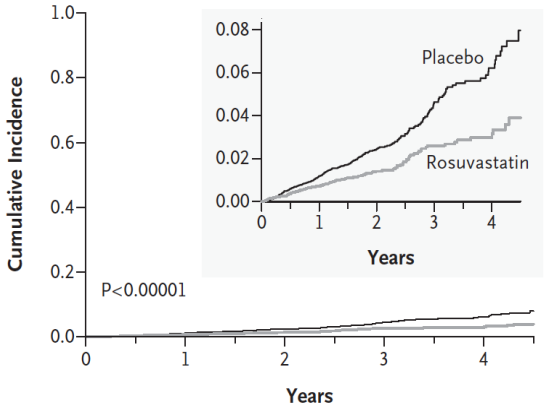
PAUL M. RIDKER, M.D., CHARLES H. HENNEKENS, M.D., JULIE E. BURING, SC.D., AND NADER RIFAI, PH.D.



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.,

A Primary End Point

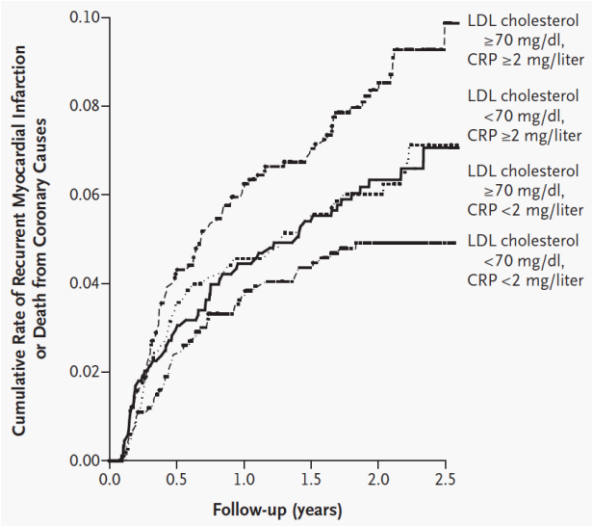


No. at Risk

Rosuvastatin	8901	8631	8412	6540	3893	1958	1353	983	538	157
Placebo	8901	8621	8353	6508	3872	1963	1333	955	531	174

C-Reactive Protein Levels and Outcomes after Statin Therapy

Paul M Ridker, M.D., Christopher P. Cannon, M.D., David Morrow, M.D.,



Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease

S. Jaiswal, P. Natarajan, A.J. Silver, C.J. Gibson, A.G. Bick, E. Shvartz, M. McConkey, N. Gupta, S. Gabriel, D. Ardissino, U. Baber, R. Mehran, V. Fuster, J. Danesh, P. Frossard, D. Saleheen, O. Melander, G.K. Sukhova, D. Neuberg, P. Libby, S. Kathiresan, and B.L. Ebert

A CHIP and Coronary Heart Disease

Subgroup	No. of Participants with Coronary Heart Disease/ No. at Risk	Hazard Ratio (95% CI)	P Value
BioImage			
No mutation (reference)	94/326		
Mutation	19/44	1.8 (1.1–2.9)	0.03
MDC			
No mutation (reference)	299/607		
Mutation	21/33	2.0 (1.2–3.1)	0.003
Fixed-effects meta-analysis		**1.9 (1.4–2.7)**	**<0.001**

B CHIP and Early-Onset Myocardial Infarction

Subgroup	No. of Participants with Myocardial Infarction/ No. at Risk	Odds Ratio (95% CI)	P Value
ATVB			
No mutation (reference)	1716/3293		
Mutation	37/43	5.4 (2.3–13.0)	<0.001
PROMIS			
No mutation (reference)	2488/3844		
Mutation	52/65	3.4 (1.8–6.5)	<0.001
Fixed-effects meta-analysis		**4.0 (2.4–6.7)**	**<0.001**