1ère Année de Médecine

Cas de liaison

Athérosclérose #6

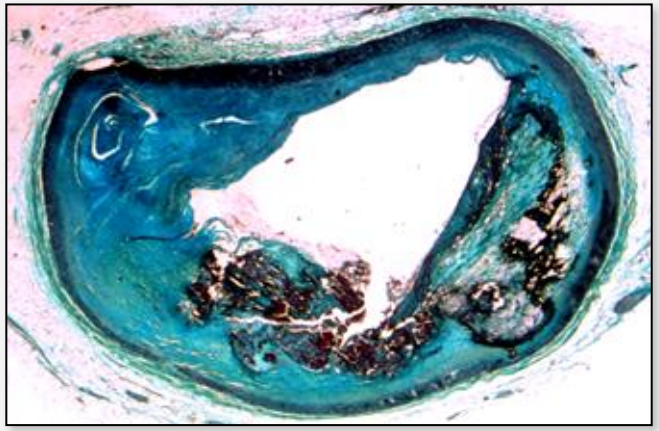
Prof. François Mach, MD,
Service de Cardiologie
Département de Médecine
Hôpital Universitaire de Genève
Francois.Mach@hcuge.ch

www.cardiology-geneva.ch

Genève, le 29 janvier 2026

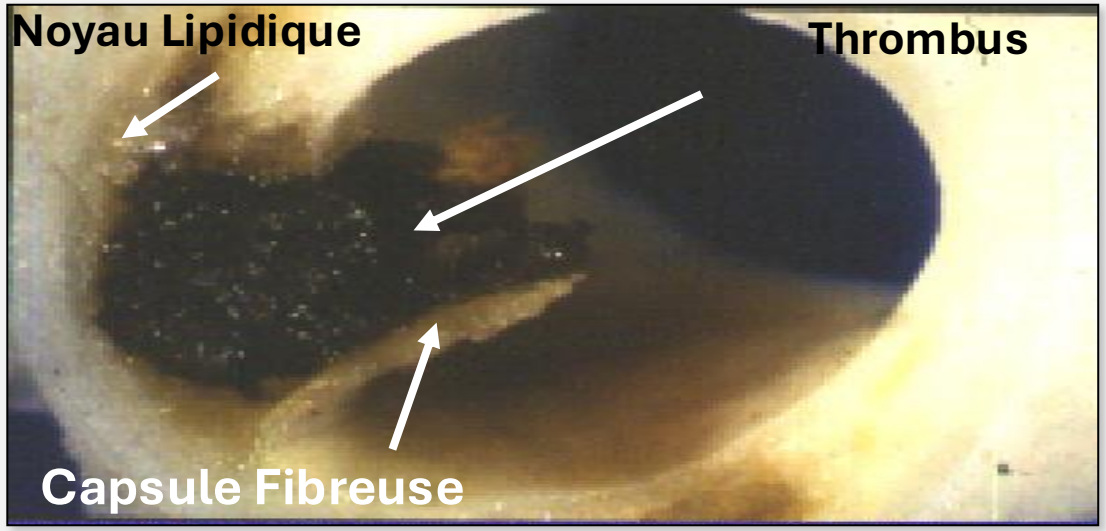
Principales manifestations cliniques

Rupture

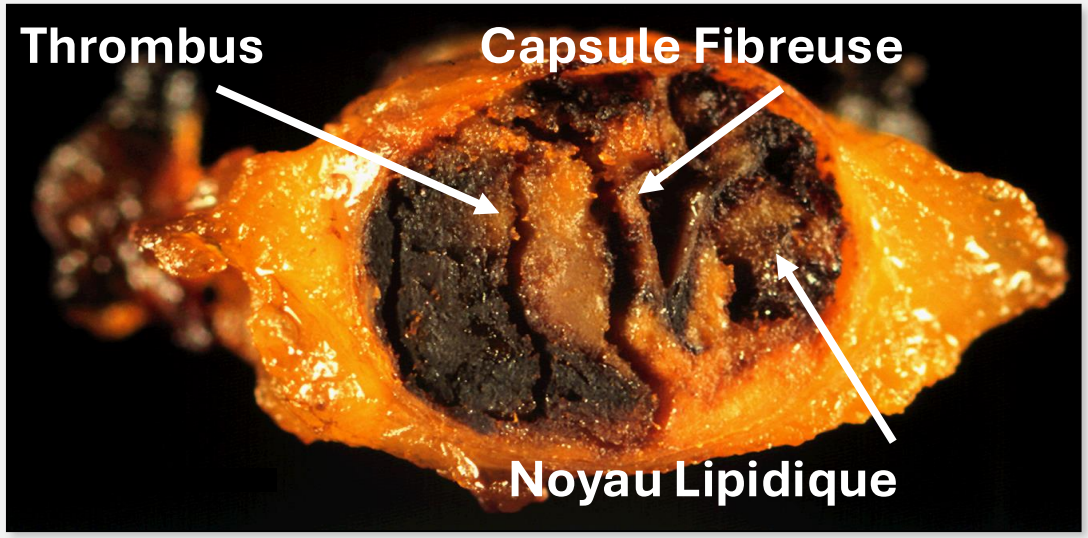


Plaque

Attaque Cérébrale

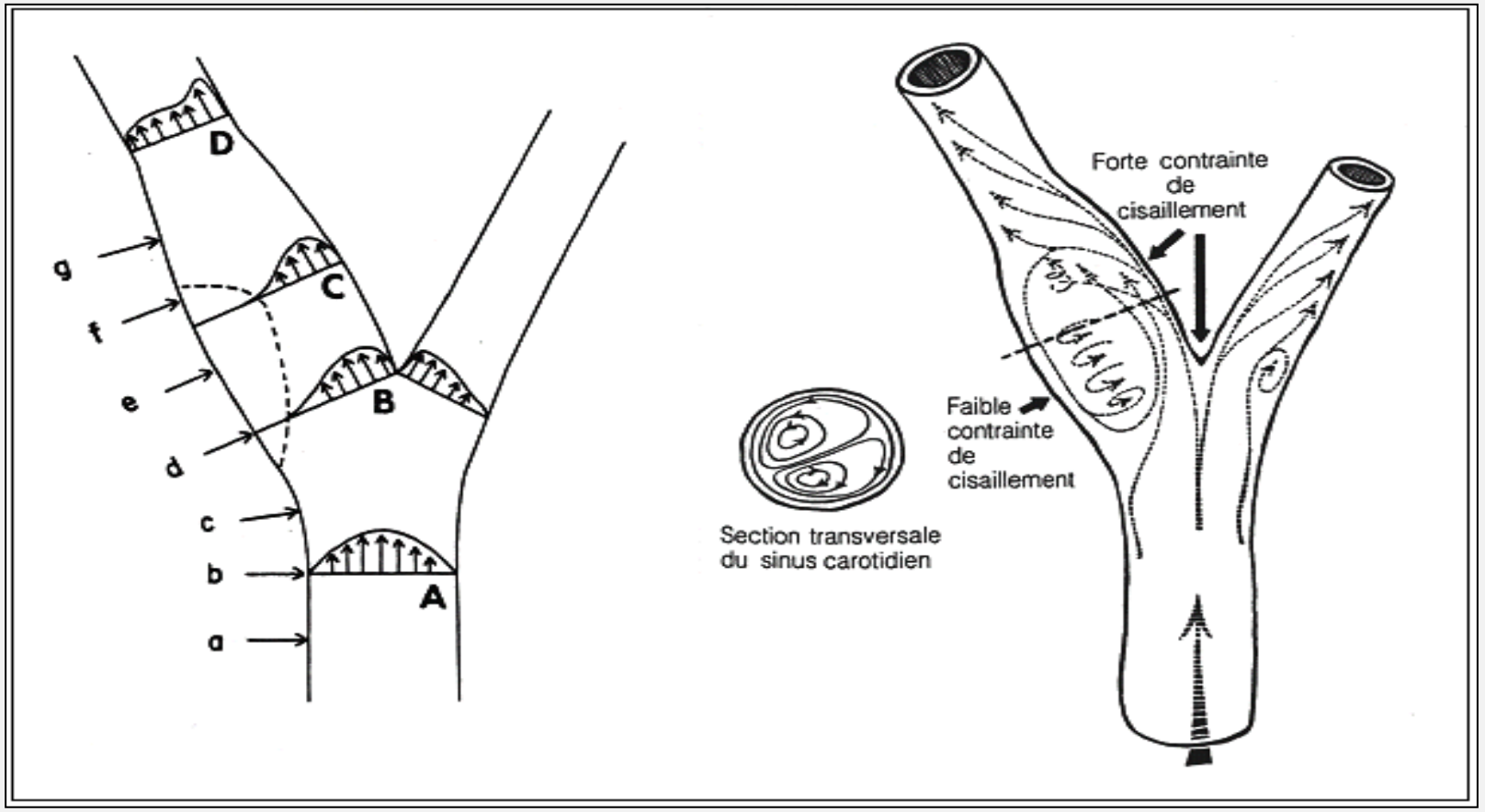


Infarctus Aigu du Myocarde



Caractéristiques des plaques d'athérosclérose

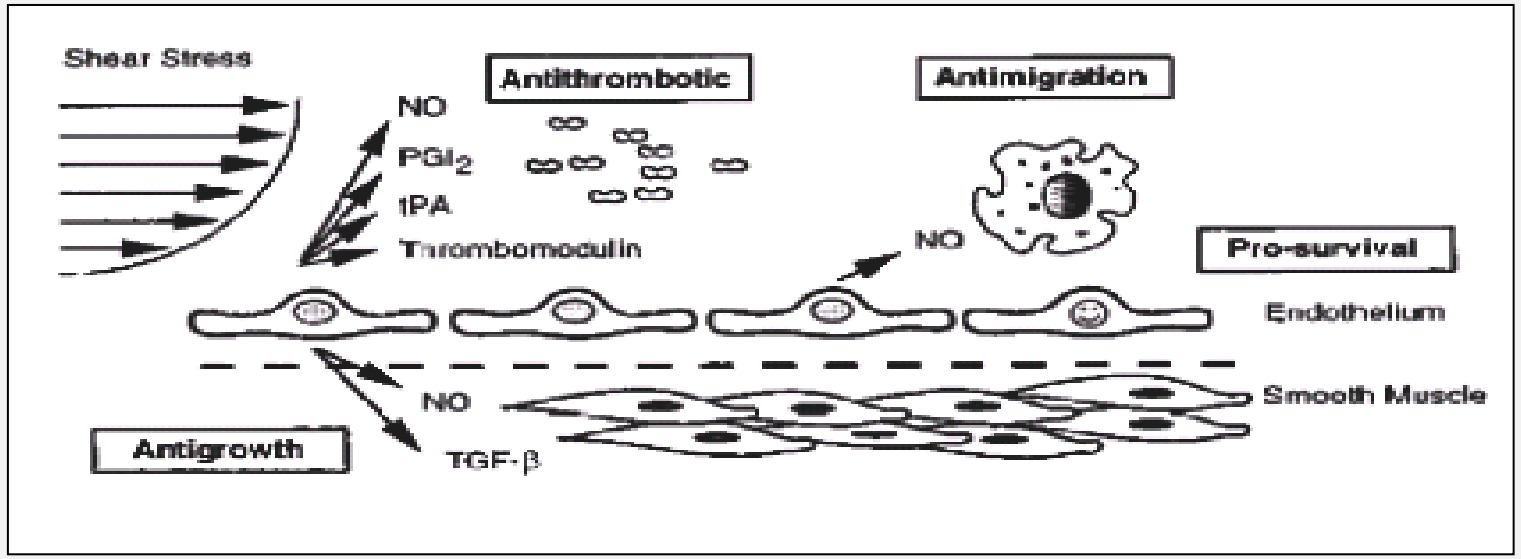
Athérosclérose & forces hémodynamiques



Steady laminar blood flow

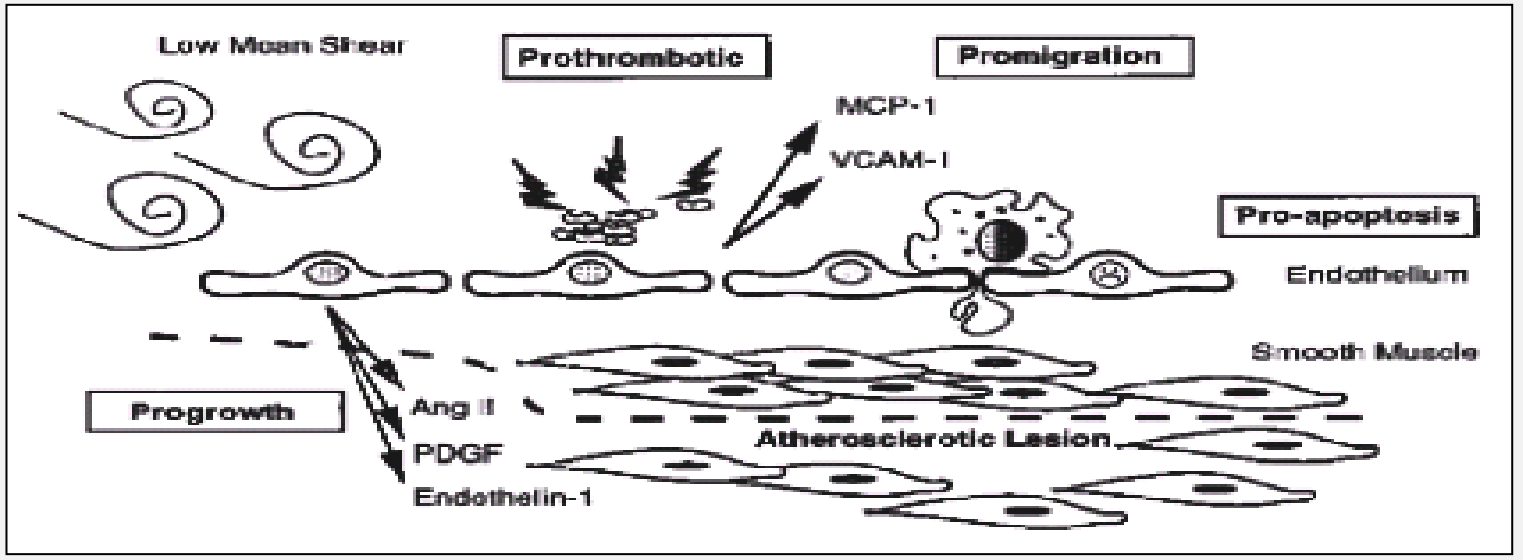
Turbulent, reversal blood flow

Caractéristiques des plaques d'athérosclérose

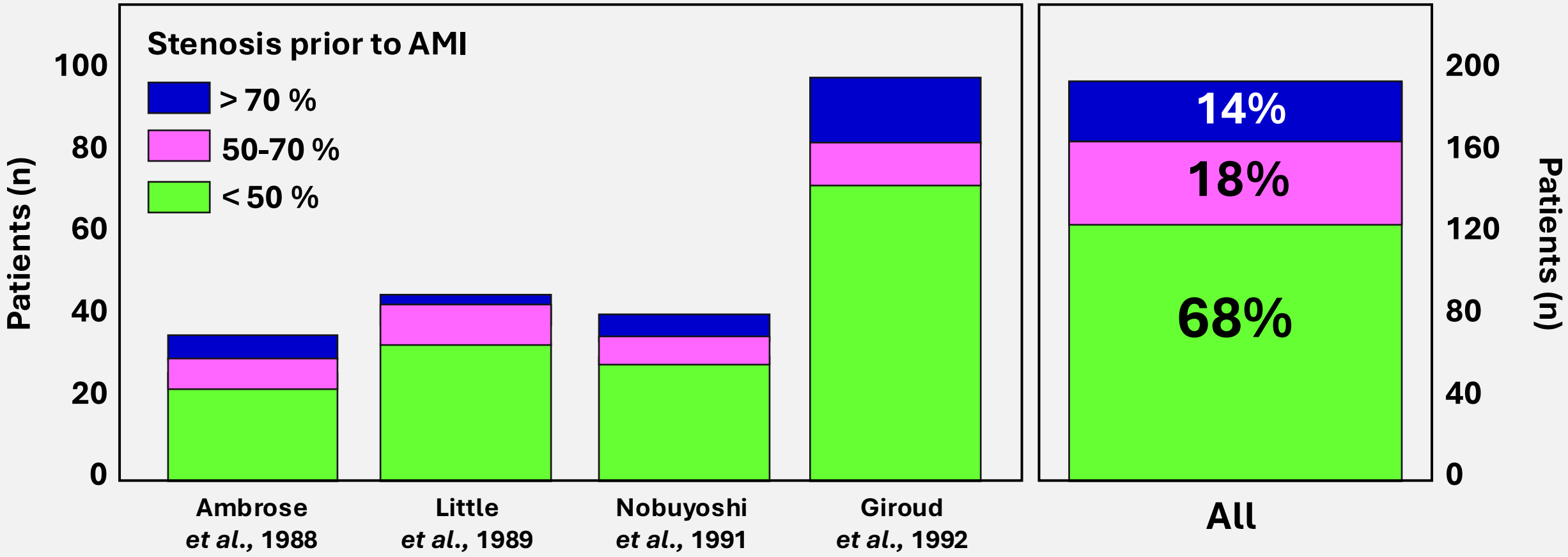


Steady laminar blood flow

Turbulent, reversal blood flow

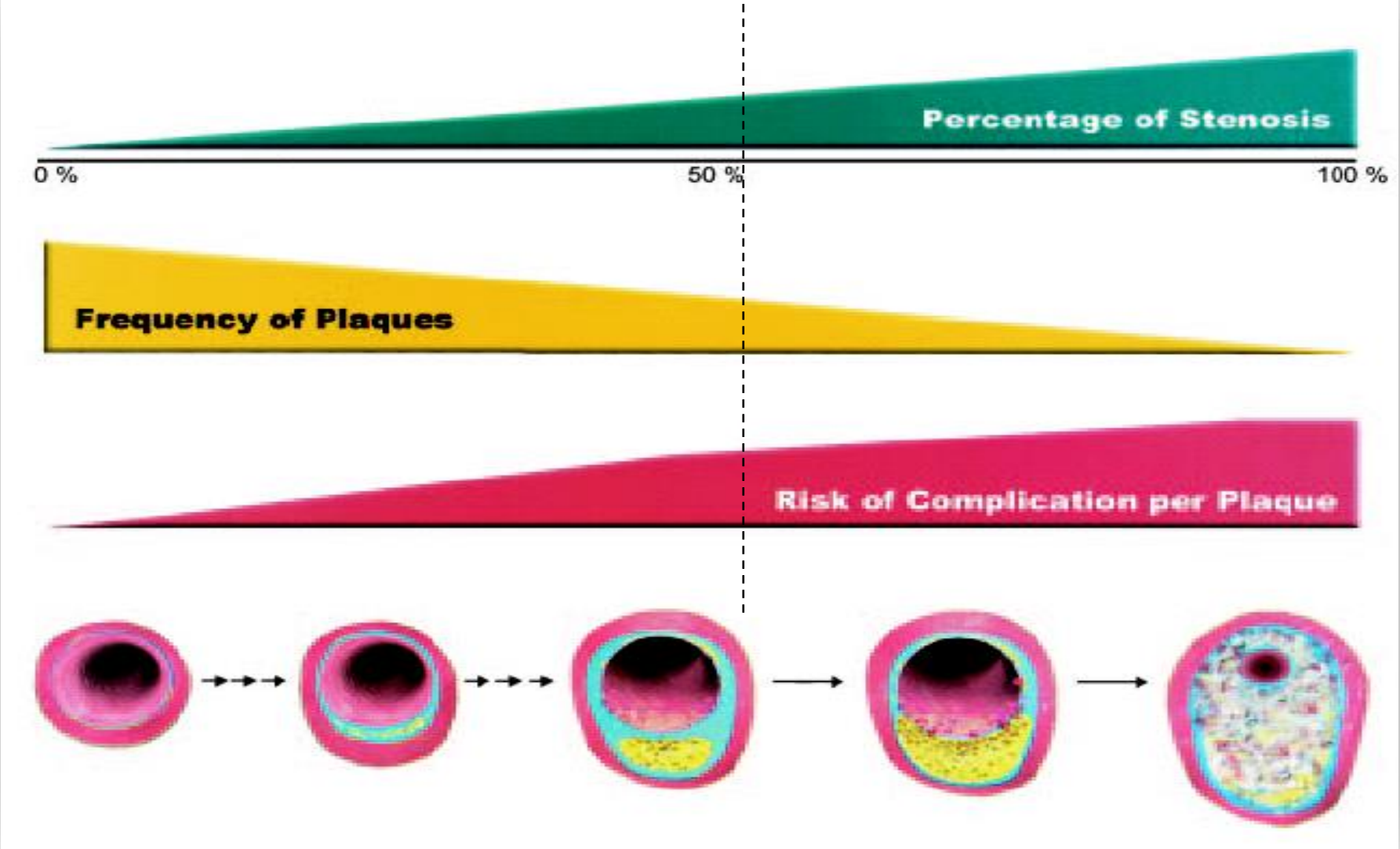


L'évolution vers l'infarctus aigu du myocarde ne dépend pas du degré de sténose coronarienne

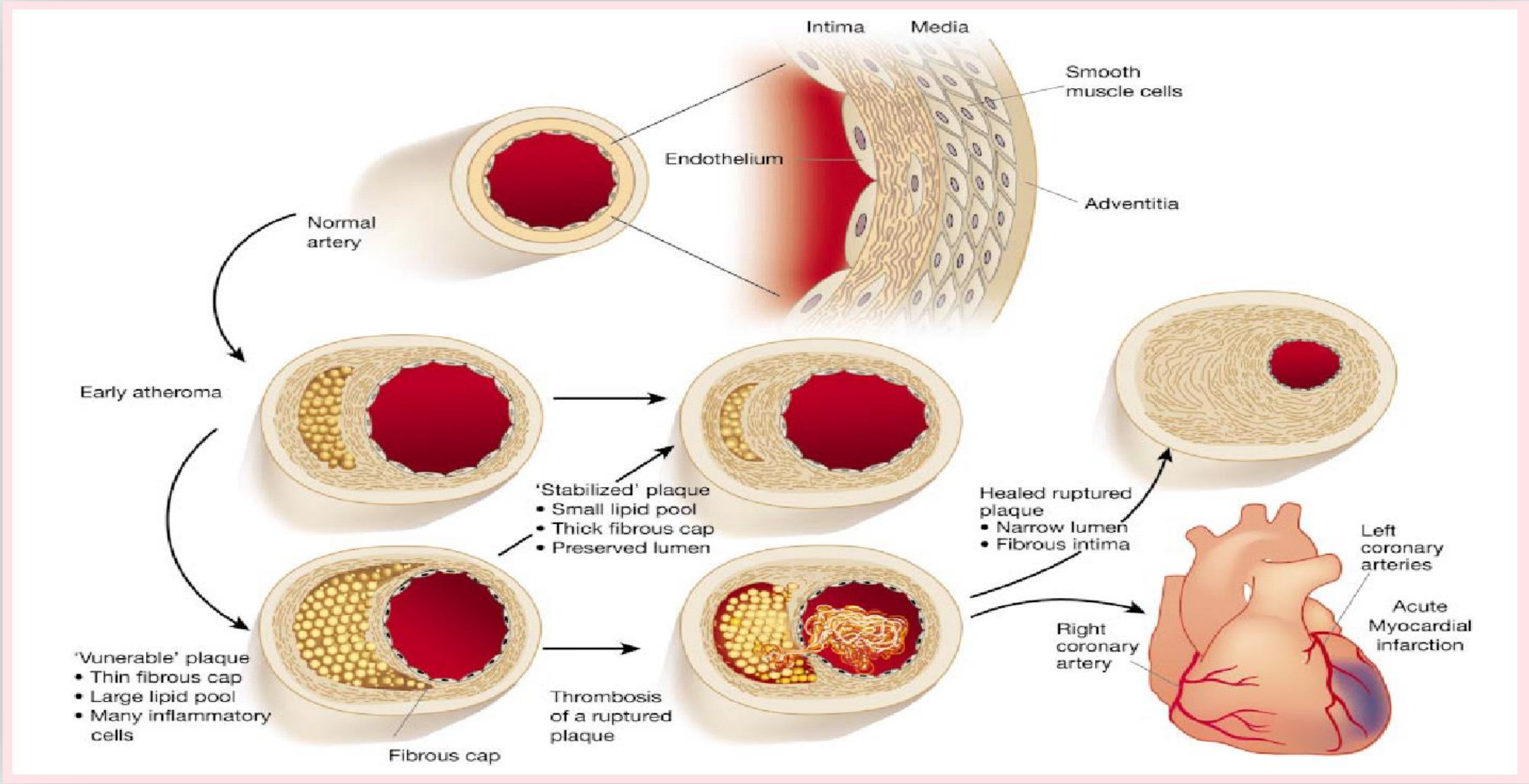


Circulation 1995;92:657

L’évolution vers l’infarctus aigu du myocarde ne dépend pas du degré de sténose coronarienne

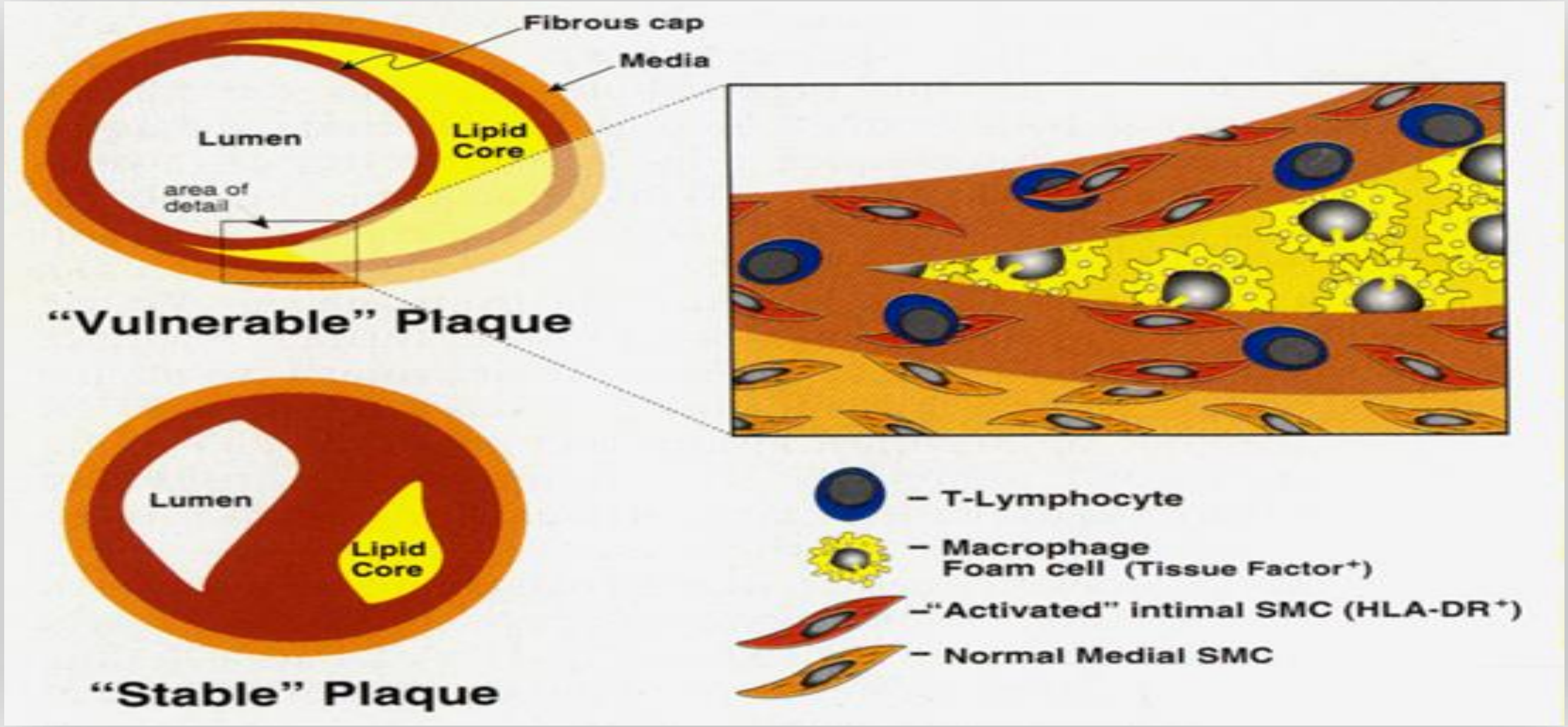


Plaque d'athérosclérose



Nature 2002;420:868

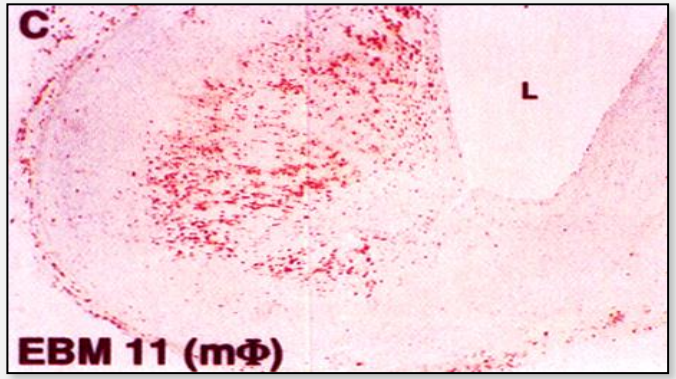
Caractéristiques des plaques d'athérosclérose



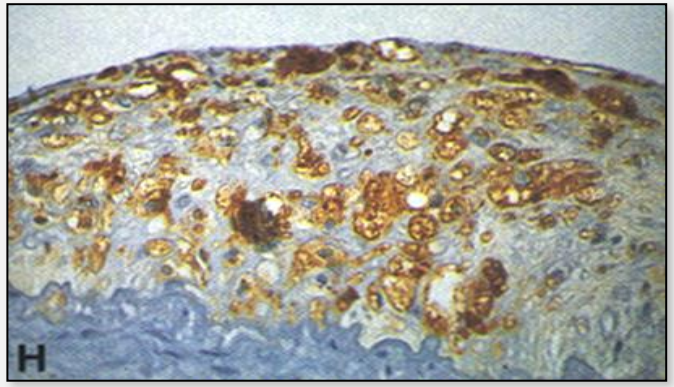
Circulation 1995;91:2844

Caractéristiques des plaques d'athérosclérose

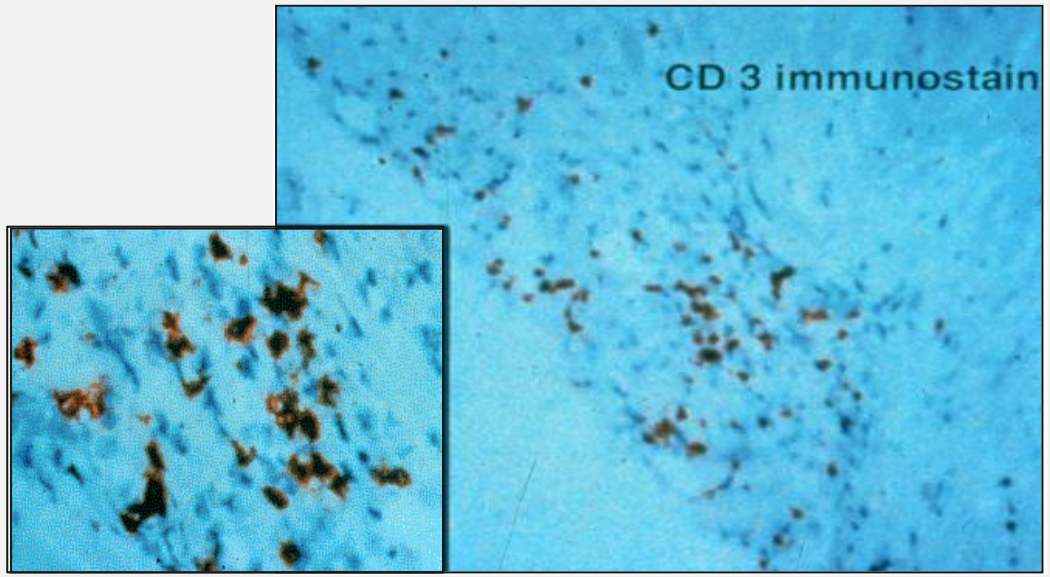
Présence de Macrophages et Lymphocytes dans l'athérome



Circulation 1996;94:2756



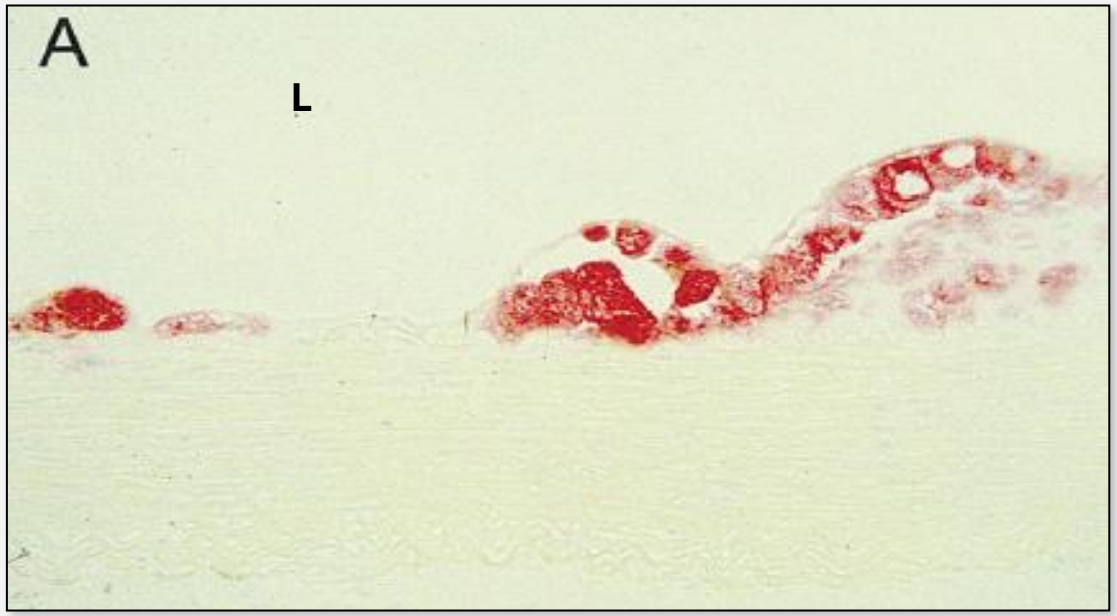
Circulation 1996;94:2890



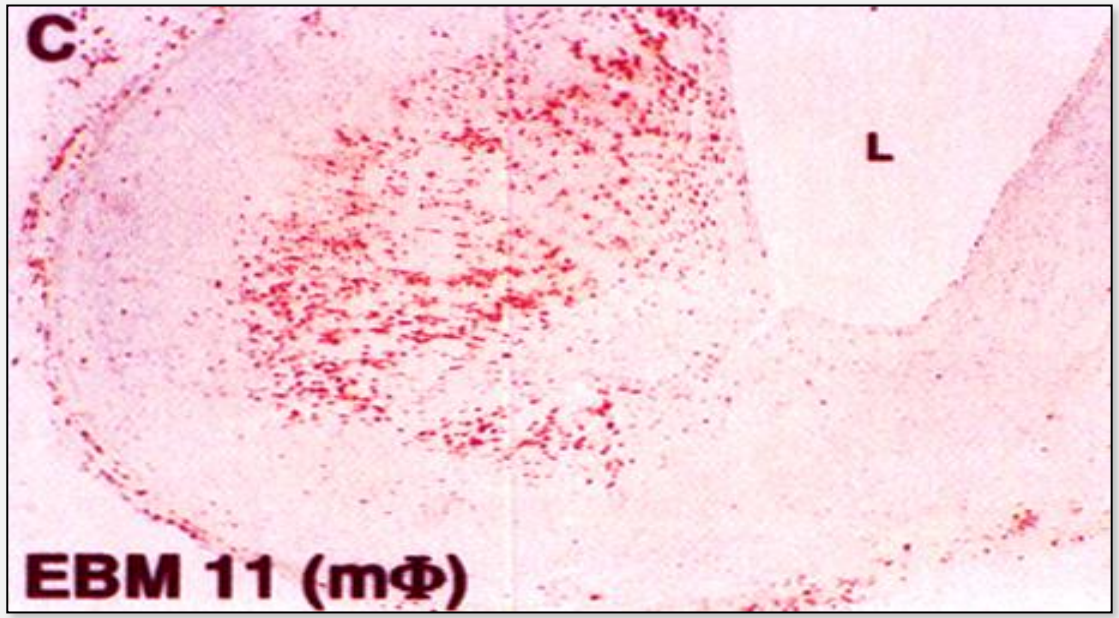
Atherosclerosis 1994;14:1210

Caractéristiques des plaques d'athérosclérose

Présence de Macrophages dans l'athérome

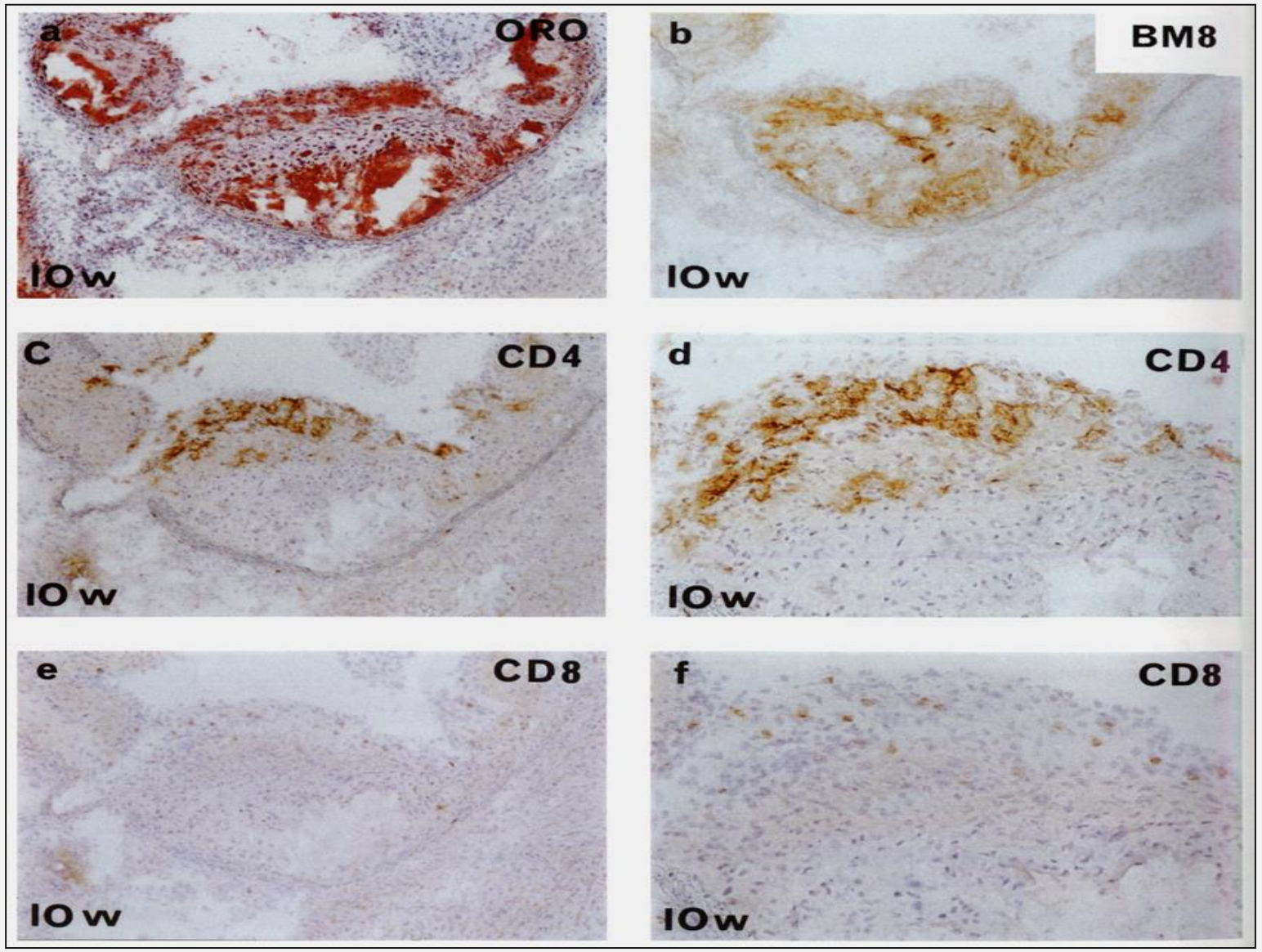


Cell 2001;104:503



Circulation 1996;94:2756

Caractéristiques des plaques d'athérosclérose

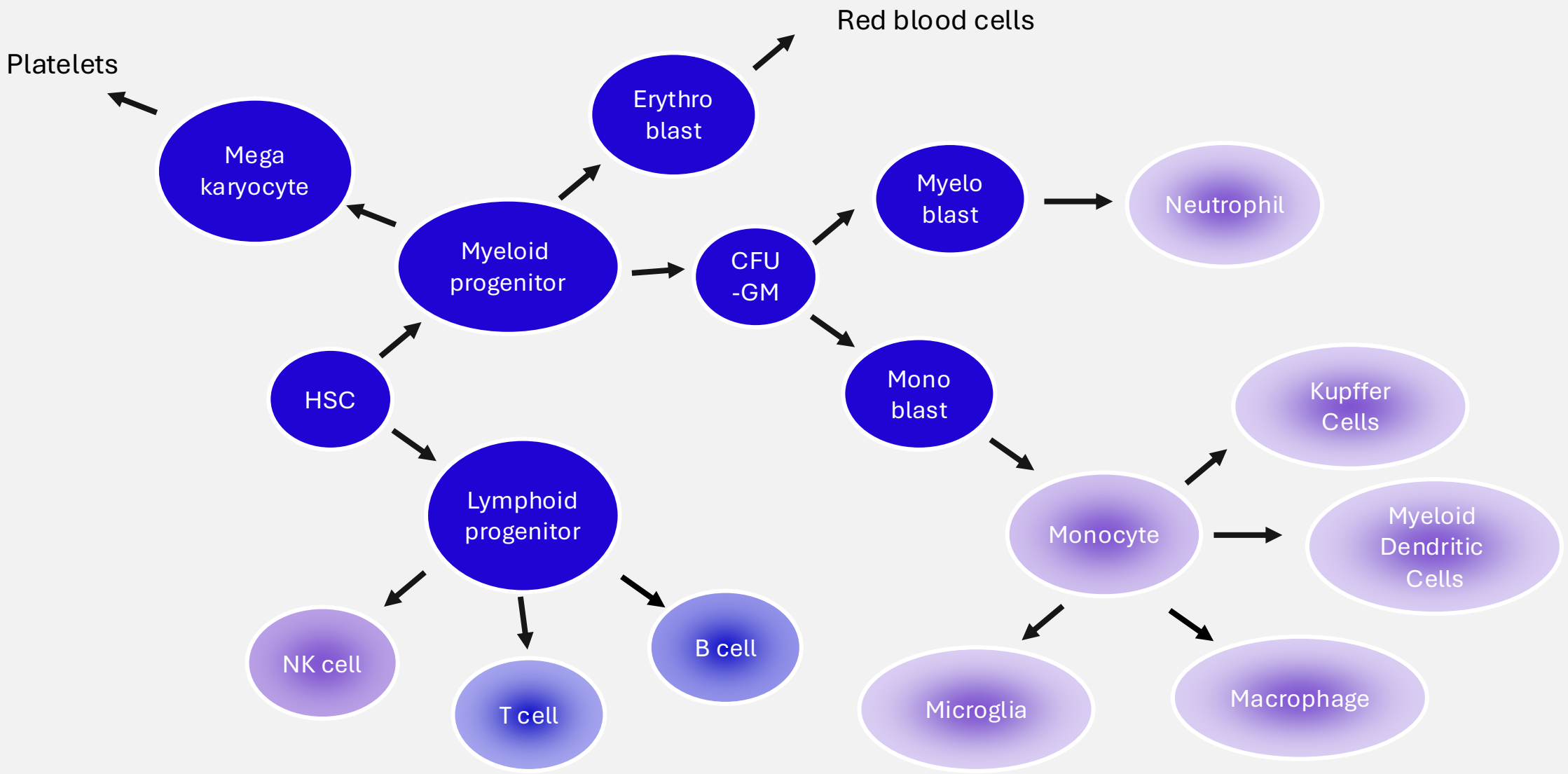


Lymphocytes T

Lésions d'athérosclérose
Valves aortiques de souris
ApoE -/- après 10 semaines
de régime riche en cholestérol

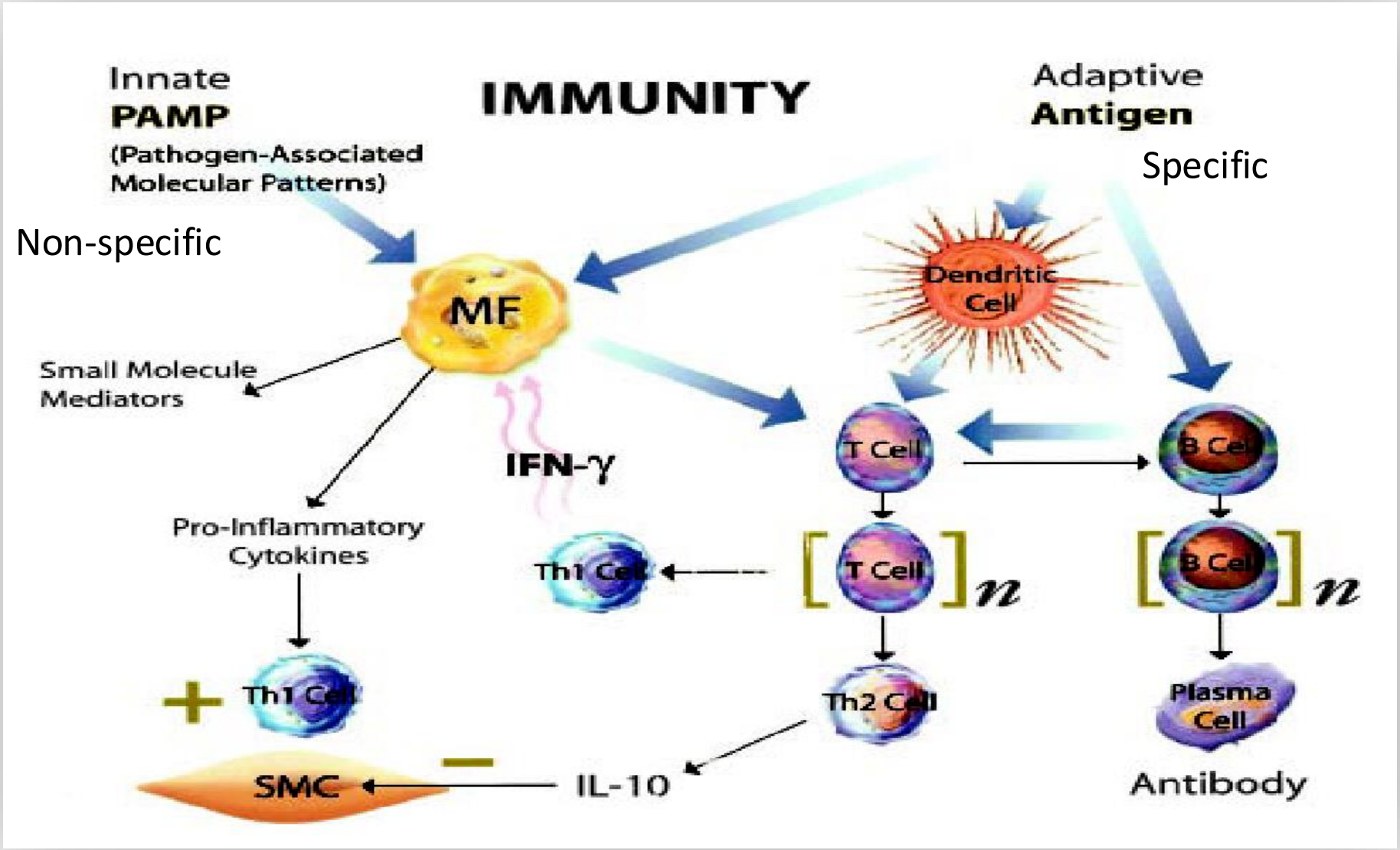
Am J Pathol 1996;149:359

Différentiation des cellules sanguines



HSC = Haematopoietic Stem Cell

Immunité et athérosclérose



Circ Res 2002;91:281

Implication des B cells dans l'athérogenèse

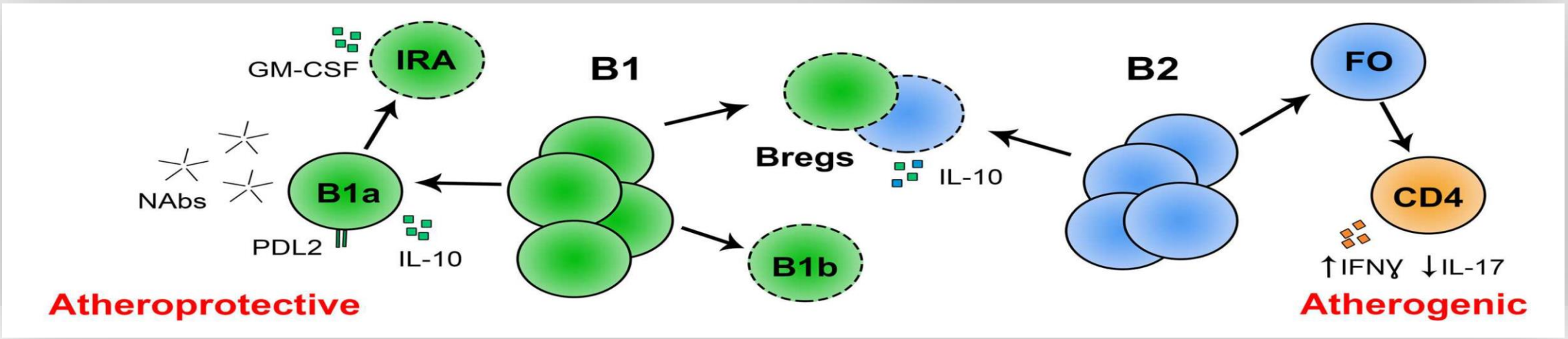
frontiers in IMMUNOLOGY

B cell subsets in atherosclerosis

*Heather M. Perry [1,2], Timothy P. Bender [3,4] and Coleen A. McNamara [2,5] **

Table 1 | B cell subset markers.

Subset	Surface markers*
Follicular	$CD19^{+}$ $B220^{+}$ IgM^{dull} IgD^{hi} $CD21^{mid}$ $CD23^{+}$
Marginal zone	$CD19^{+}$ $B220^{+}$ IgM^{hi} IgD^{dull} $CD1d^{hi}$ $CD21^{hi}$ $CD23^{-}$
B-1a	$CD19^{+}$ $B220^{low/mid}$ IgM^{hi} IgD^{dull} $CD43^{+}$ $CD11b^{+}$ $CD5^{+}$
B-1b	$CD19^{+}$ $B220^{low/mid}$ IgM^{hi} IgD^{dull} $CD43^{+}$ $CD11b^{+}$ $CD5^{-}$



Frontiers in Immunol 2012;3:1

Athérosclérose & inflammation

Atherosclerosis — An Inflammatory Disease

Russell Ross, Ph.D.

Table 1. Characteristics of Atherosclerosis and Other Chronic Inflammatory Diseases.*

Disease	Monocytes and Macrophages	Lymphocytes	Granulocytes	Connective-Tissue Cells	Extracellular Matrix	Pathogenetic Mechanisms	Studies
Atherosclerosis	+	+	−	Smooth-muscle cells	Collagen types I, III, and IV, elastin, fibronectin, proteoglycan	Endothelial-cell injury and dysfunction; fibrous cap; new matrix formation and degradation; necrotic core	Ross,[9] Libby and Hansson,[109] Ross and Fuster[110]
Cirrhosis	+	+	−	Fibroblasts, Ito cells	Collagen types I and III	Parenchymal-cell injury; new matrix and scarring replacing necrotic parenchyma	Maher,[111] Anthony et al.[112]
Rheumatoid arthritis	+	+	+/−	Synovial fibroblasts	Collagen types I and III, fibronectin, proteoglycan	Synovial-cell injury; erosion of cartilage; new matrix scarring (pannus)	Sewell and Trentham,[113] Harris [114]
Glomerulosclerosis	+	+	−	Mesangial cells	Collagen types I and IV, fibronectin	Epithelial- and endothelial-cell injury and dysfunction; decrease in glomerular filtration; new matrix formation	Johnson,[115] Magil and Cohen[116]
Pulmonary fibrosis	+	+	+/−	Smooth-muscle cells, fibroblasts	Collagen types III and IV, fibronectin	Inflammatory exudate in alveoli and bronchi, organized by extensive matrix deposition and scarring	Kuhn et al.,[117] Lukacs and Ward,[118] Brody et al.[119]
Chronic pancreatitis	+	+	−	Fibroblasts	Collagen, fibronectin, proteoglycan	Epithelial (ductal) injury; periductal inflammation; interstitial fat necrosis; new matrix formation	lSarles et al.,[120] 2 DiMagno et al.[121]

*Plus signs denote the presence of a cell type, and minus signs its absence.

N Engl J Med 1999;340:115

Pathophysiologie de l'athérosclérose

ATHEROSCLEROSIS — AN INFLAMMATORY DISEASE

RUSSELL ROSS, PH.D.

N Engl J Med 1999;340:115

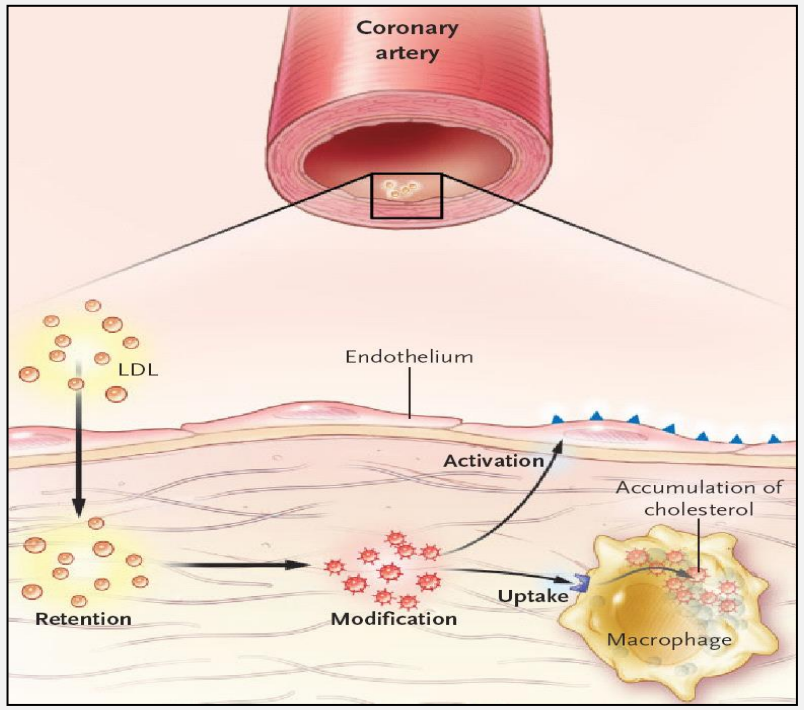
insight review articles

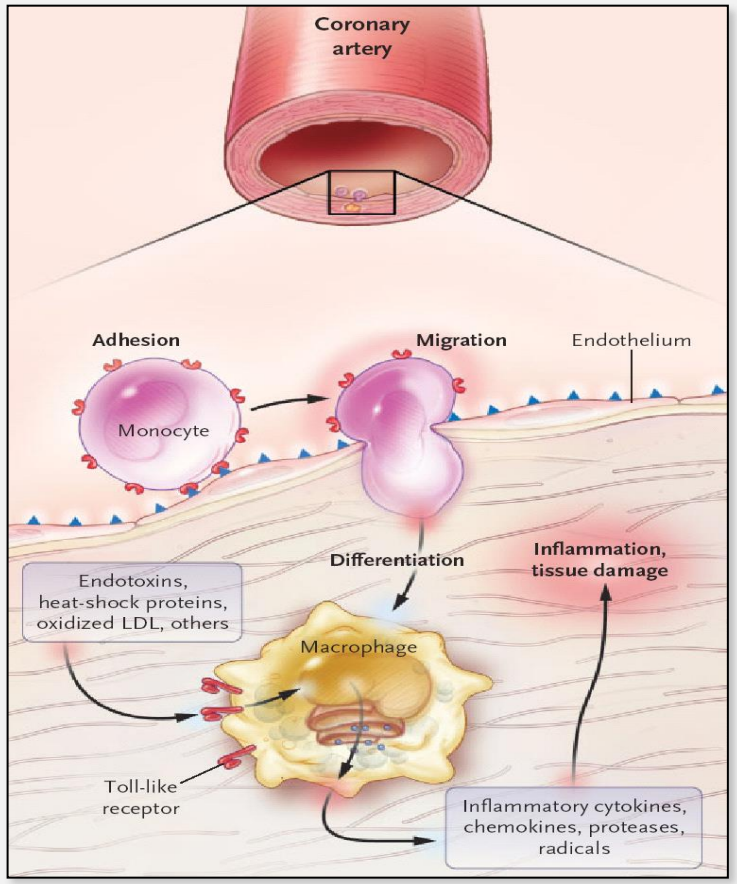
Inflammation in atherosclerosis

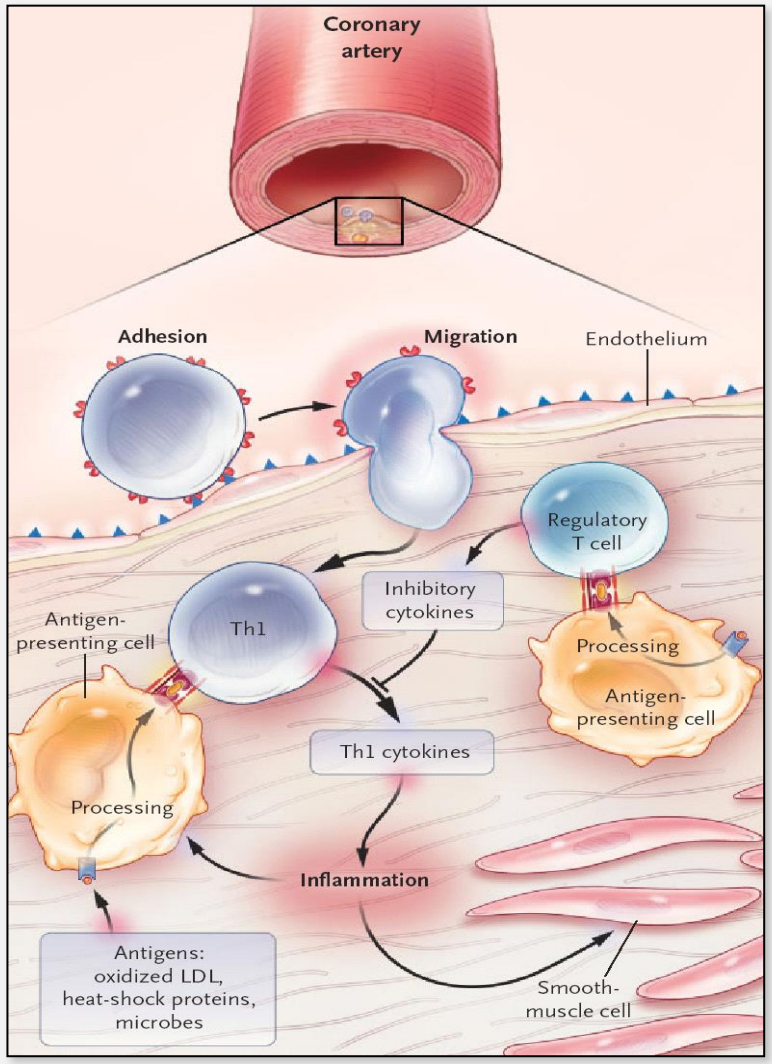
Peter Libby

Nature 2002;420:868

Pathophysiologie de l'athérosclérose

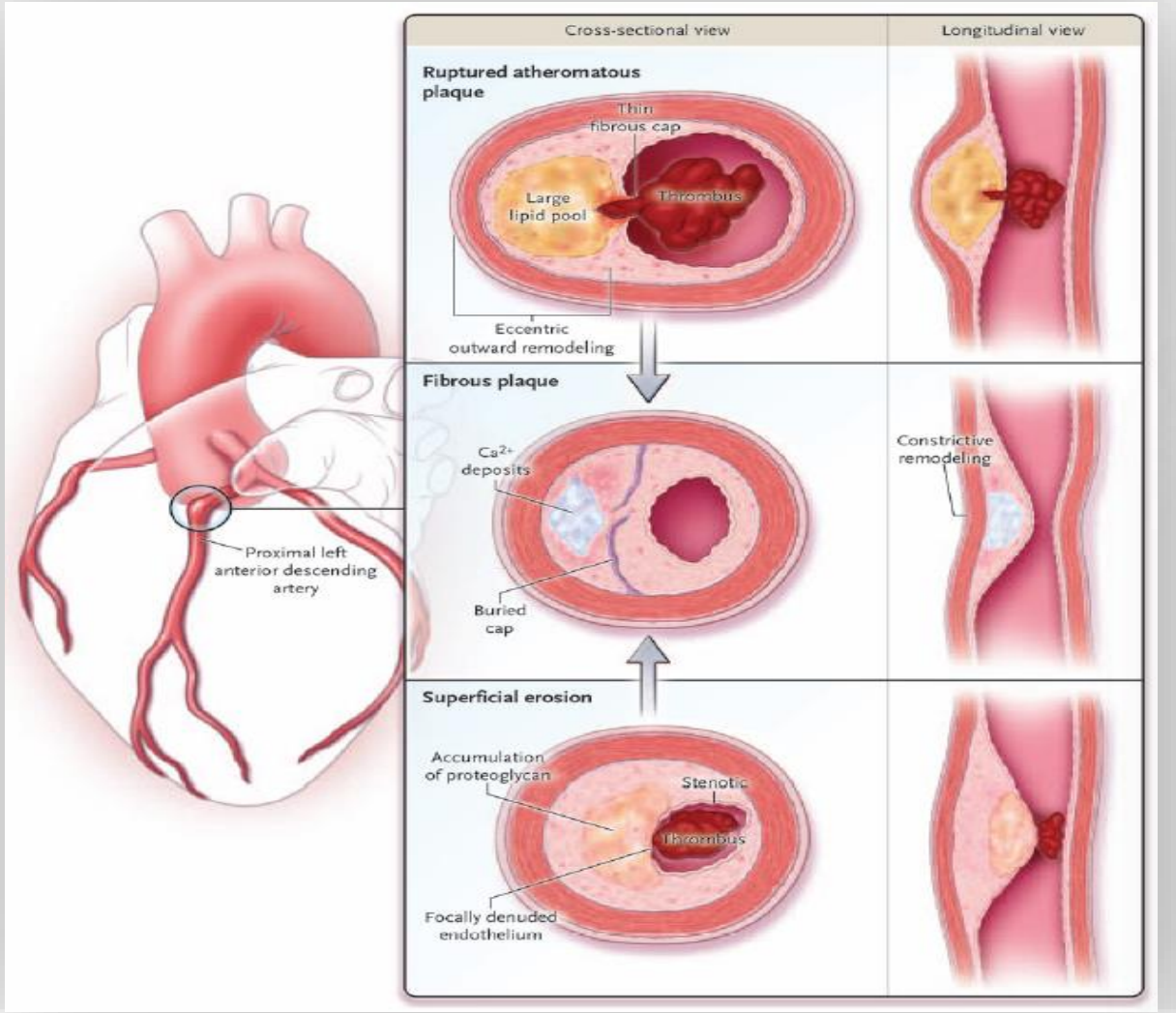






N Engl J Med 2005;352:1685

Pathophysiologie de l'athérosclérose

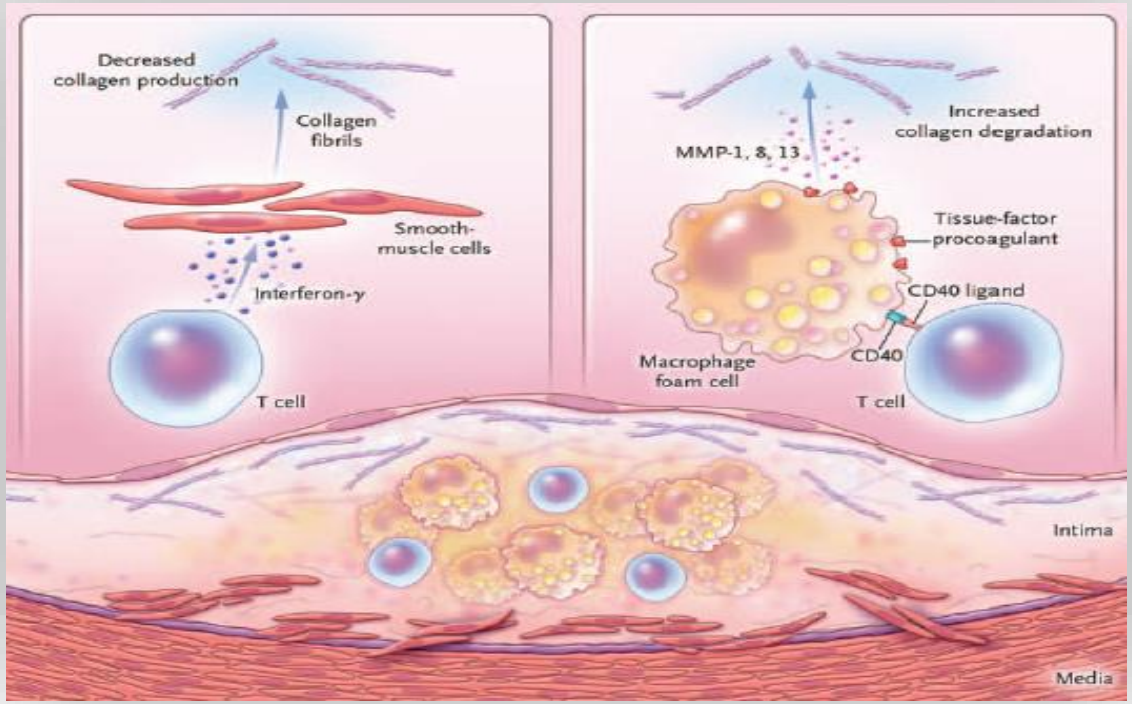


REVIEW ARTICLE

MECHANISMS OF DISEASE

Mechanisms of Acute Coronary Syndromes and Their Implications for Therapy

Peter Libby, M.D.



New Engl J Med 2013;368:2001

Inflammation

Mechanisms of Disease

FRANKLIN H. EPSTEIN, M.D., *Editor*

ACUTE-PHASE PROTEINS AND OTHER SYSTEMIC RESPONSES TO INFLAMMATION

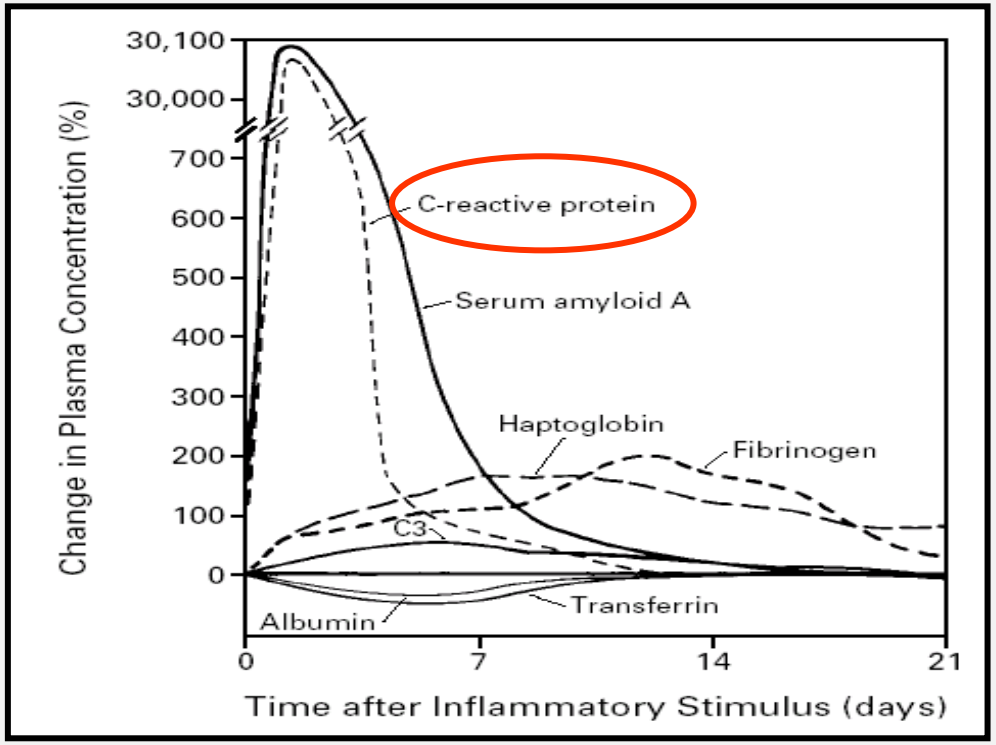
CEM GABAY, M.D., AND IRVING KUSHNER, M.D.

TABLE 1. HUMAN ACUTE-PHASE PROTEINS.

Proteins whose plasma concentrations increase
Complement system
C3
C4
C9
Factor B
C1 inhibitor
C4b-binding protein
Mannose-binding lectin
Coagulation and fibrinolytic system
Fibrinogen
Plasminogen
Tissue plasminogen activator
Urokinase
Protein S
Vitronectin
Plasminogen-activator inhibitor 1
Antiproteases
α_1-Protease inhibitor
α_1-Antichymotrypsin
Pancreatic secretory trypsin inhibitor
Inter-α-trypsin inhibitors
Transport proteins
Ceruloplasmin
Haptoglobin
Hemopexin
Participants in inflammatory responses
Secreted phospholipase A_2
Lipopolysaccharide-binding protein
Interleukin-1–receptor antagonist
Granulocyte colony-stimulating factor
Others
C-reactive protein
Serum amyloid A
α_1-Acid glycoprotein
Fibronectin
Ferritin
Angiotensinogen

TABLE 2. OTHER ACUTE-PHASE PHENOMENA.

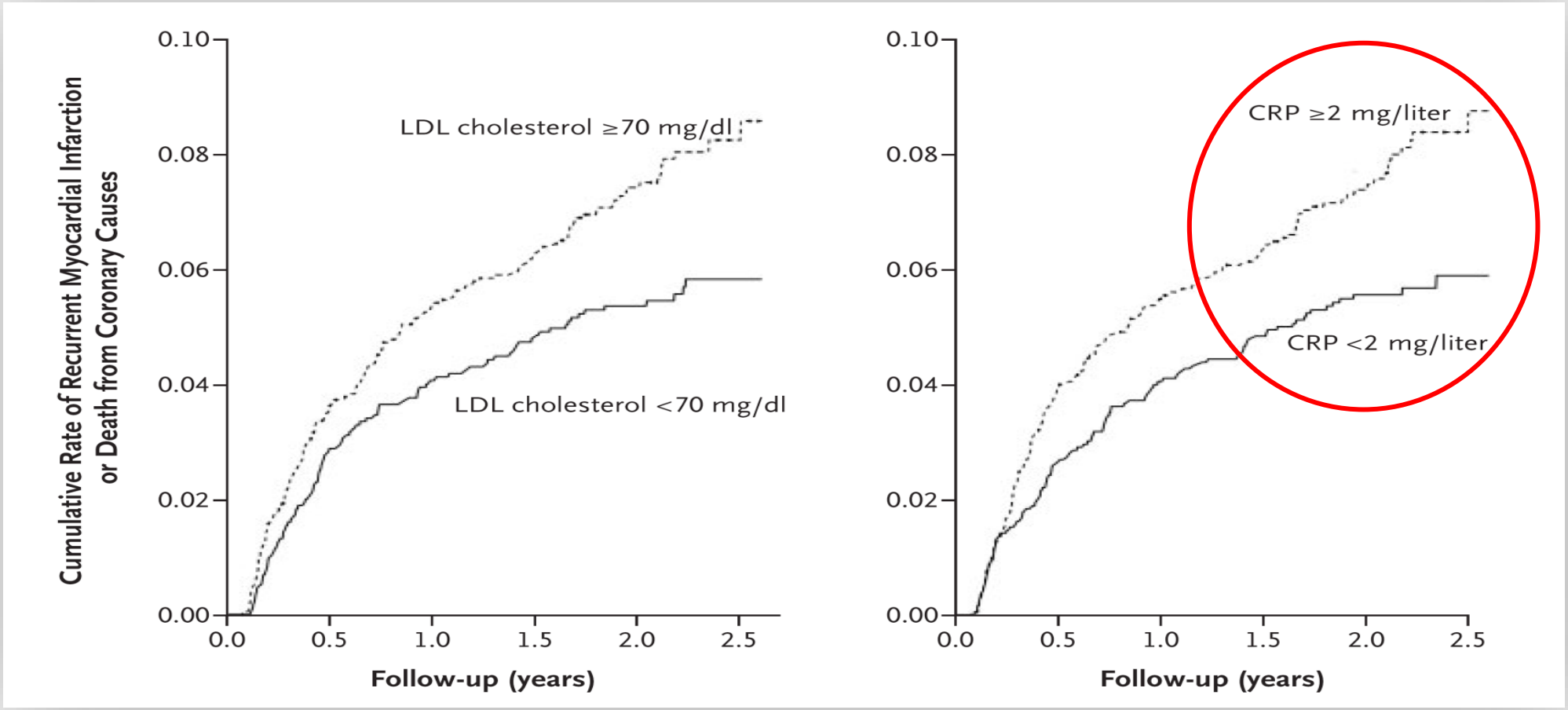
Neuroendocrine changes
Fever, somnolence, and anorexia
Increased secretion of corticotropin-releasing hormone, corticotropin, and cortisol
Increased secretion of arginine vasopressin
Decreased production of insulin-like growth factor I
Increased adrenal secretion of catecholamines
Hematopoietic changes
Anemia of chronic disease
Leukocytosis
Thrombocytosis
Metabolic changes
Loss of muscle and negative nitrogen balance
Decreased gluconeogenesis
Osteoporosis
Increased hepatic lipogenesis
Increased lipolysis in adipose tissue
Decreased lipoprotein lipase activity in muscle and adipose tissue
Cachexia
Hepatic changes
Increased metallothionein, inducible nitric oxide synthase, heme oxygenase, manganese superoxide dismutase, and tissue inhibitor of metalloproteinase-1
Decreased phosphoenolpyruvate carboxykinase activity
Changes in nonprotein plasma constituents
Hypozincemia, hypoferremia, and hypercupremia
Increased plasma retinol and glutathione concentrations



N Engl J Med 1999;340:448

CRP & risque cardio-vasculaire

CRP = Marqueur du risque CV [infarctus et mortalité coronarienne]



N Engl J Med 2005;352:20

Athérosclérose & Inflammation

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.

Methods We measured plasma C-reactive protein, a marker for systemic inflammation, in 543 apparently healthy men participating in the Physicians' Health Study in whom myocardial infarction, stroke, or venous thrombosis subsequently developed, and in 543 study participants who did not report vascular disease during a follow-up period exceeding eight years. Subjects were randomly assigned to receive aspirin or placebo at the beginning of the trial.

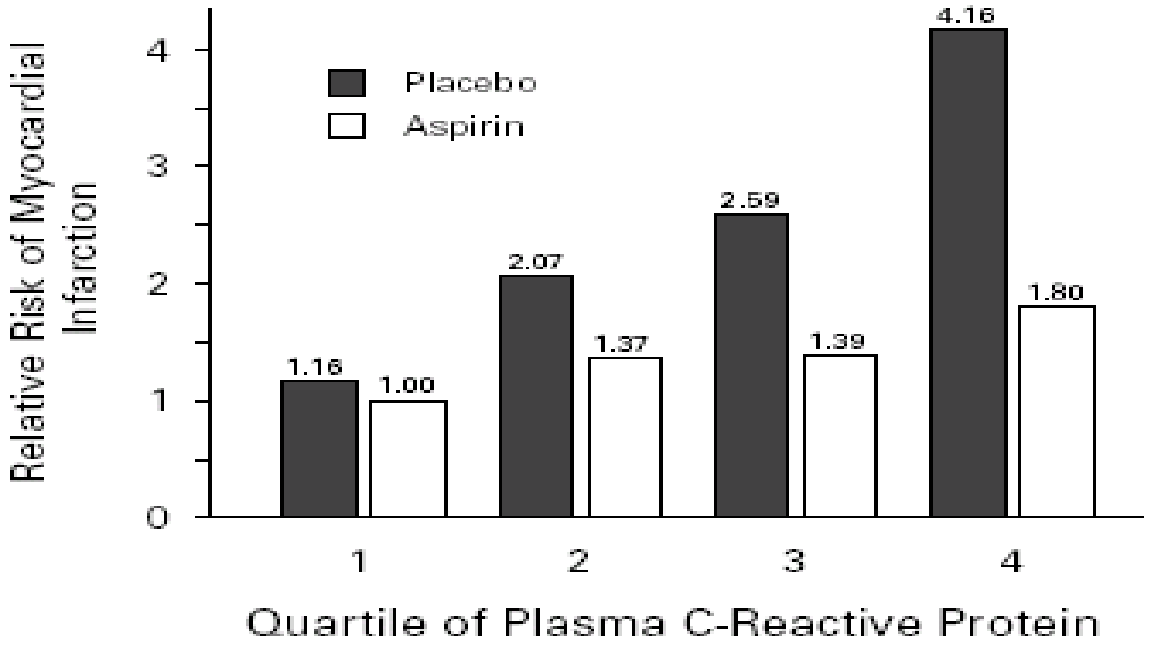
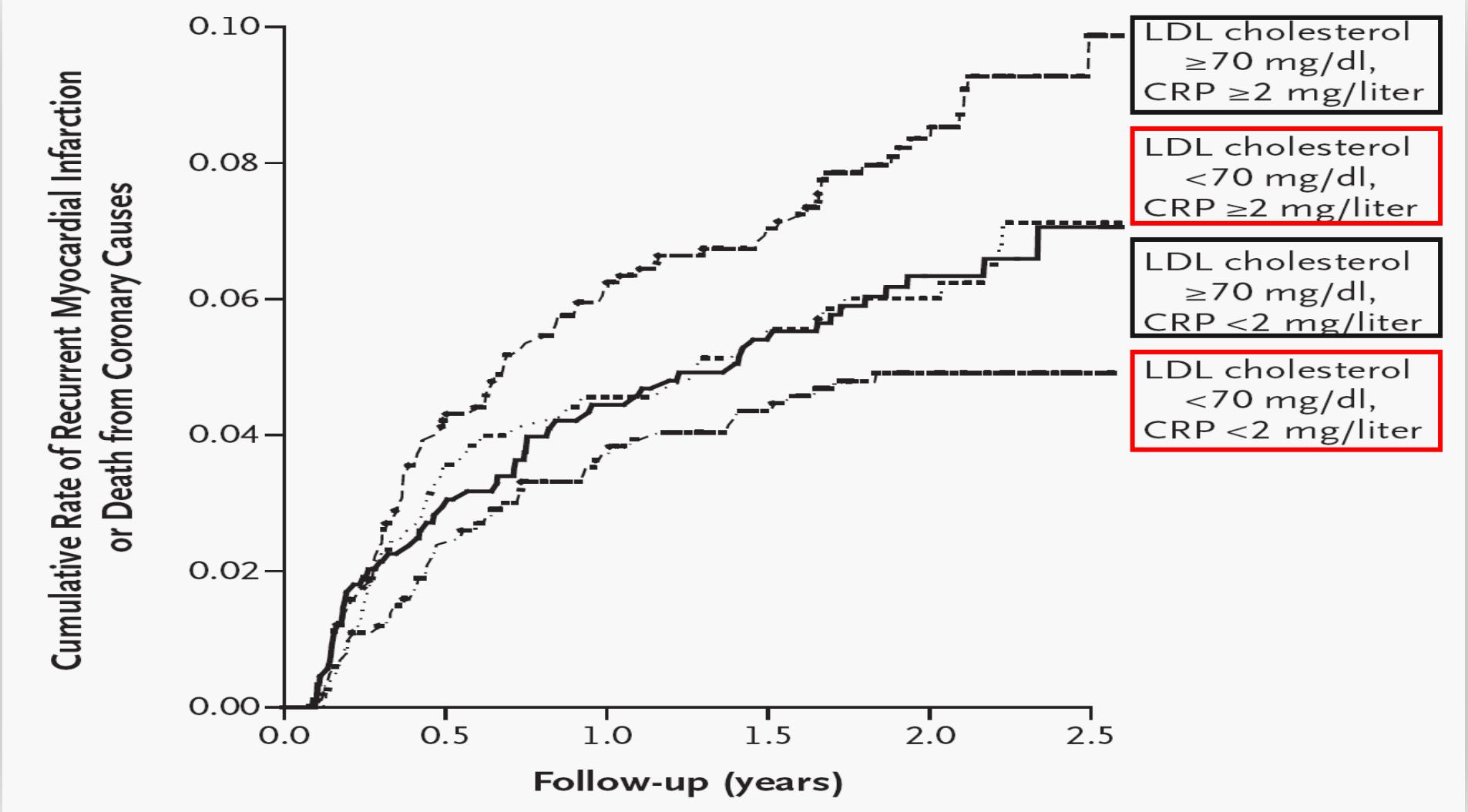


Figure 2. Relative Risk of a First Myocardial Infarction Associated with Base-Line Plasma Concentrations of C-Reactive Protein, Stratified According to Randomized Assignment to Aspirin or Placebo Therapy.

N Engl J Med 1997;336:1813

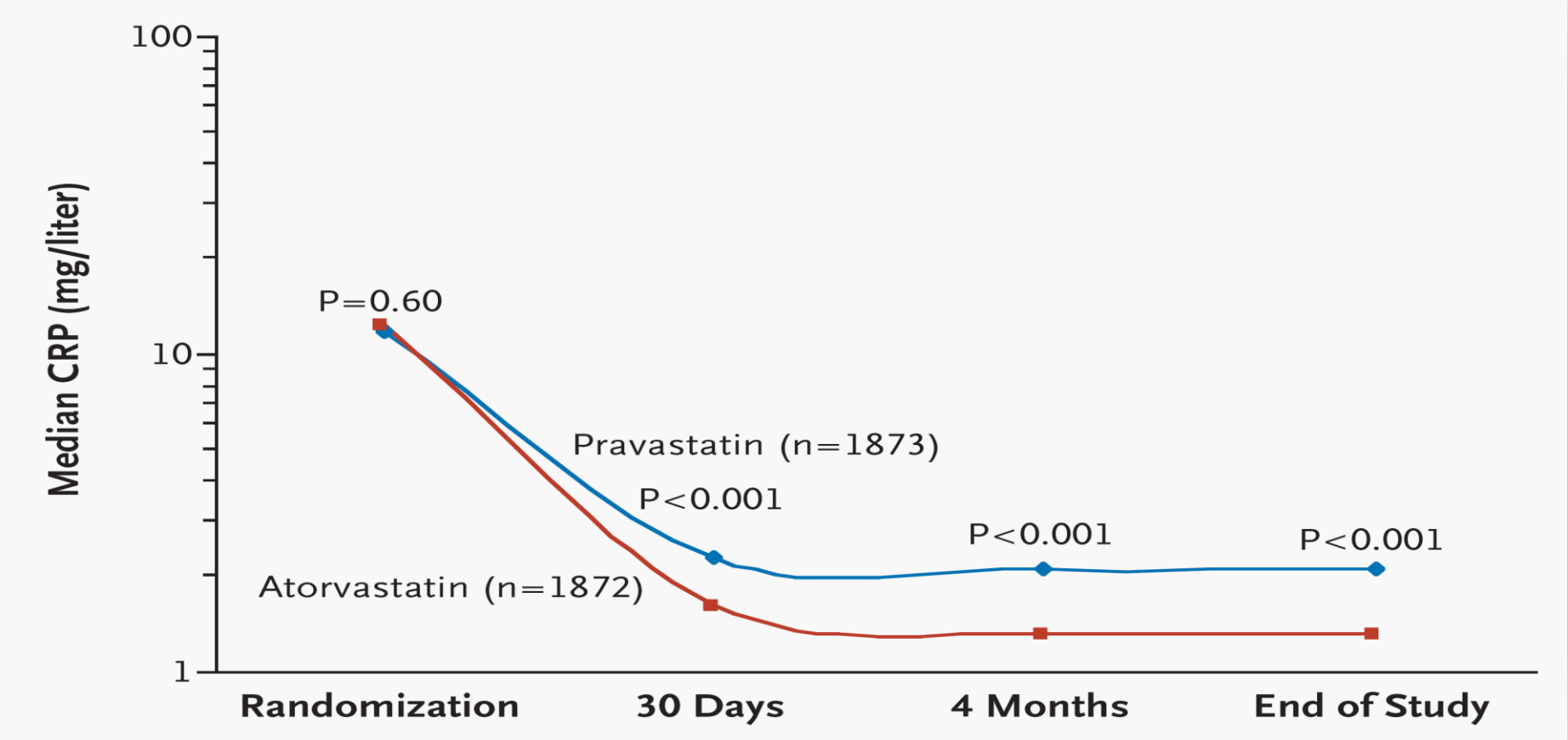
Athérosclérose & Inflammation



N Engl J Med 2005;352:20

Statines & Inflammation

Clinical studies demonstreated that statin treatment reduces CRP levels *in vivo* in human



N Engl J Med 2005;352:29

Statines & Inflammation

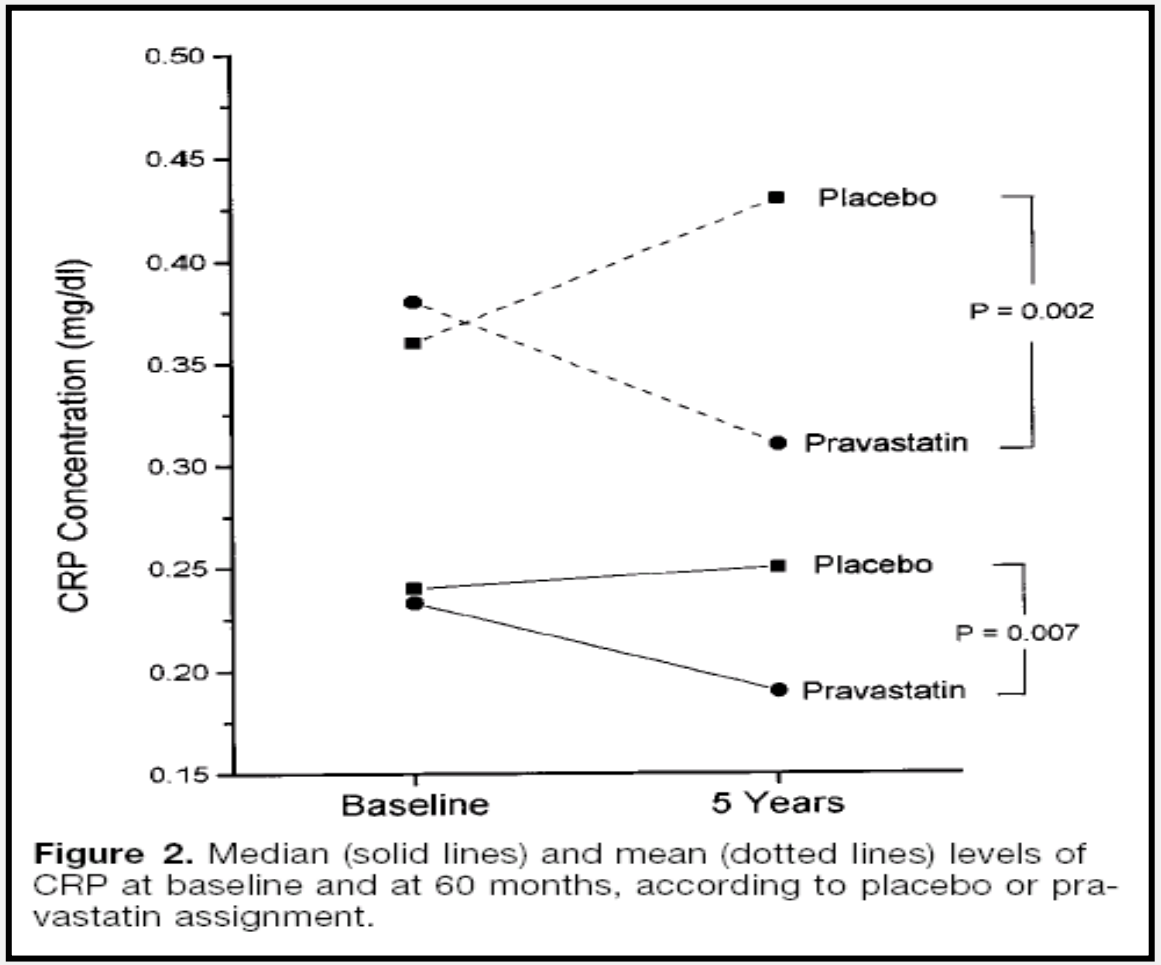
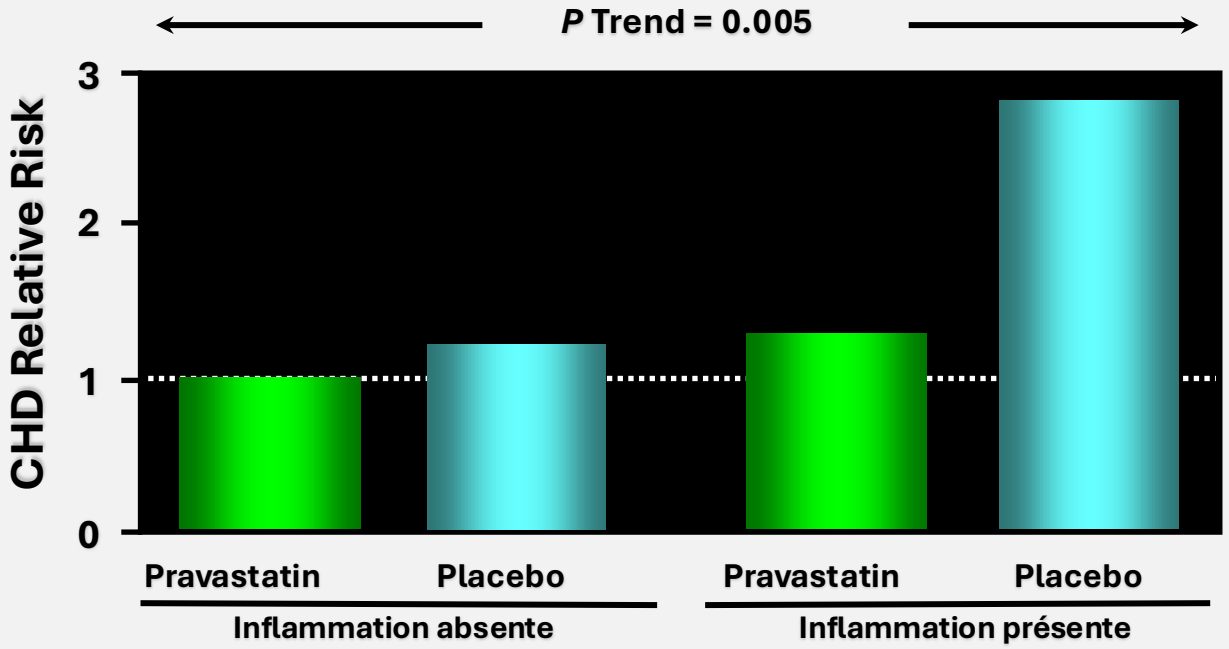


Figure 2. Median (solid lines) and mean (dotted lines) levels of CRP at baseline and at 60 months, according to placebo or pravastatin assignment.

CARE *Circulation* 1999;100:230



Circulation 1998;98:839

Athérosclérose & Inflammation

JUPITER
Primary Objectives

Ridker et al NEJM 2008

Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

To investigate whether rosuvastatin 20 mg compared to placebo would decrease the rate of first major cardiovascular events among apparently healthy men and women with LDL < 130 mg/dL (3.36 mmol/L) who are nonetheless at increased vascular risk on the basis of an enhanced inflammatory response, as determined by hsCRP ≥ 2 mg/L.

To enroll large numbers of women and individuals of Black or Hispanic ethnicity, groups for whom little data on primary prevention with statin therapy exists.

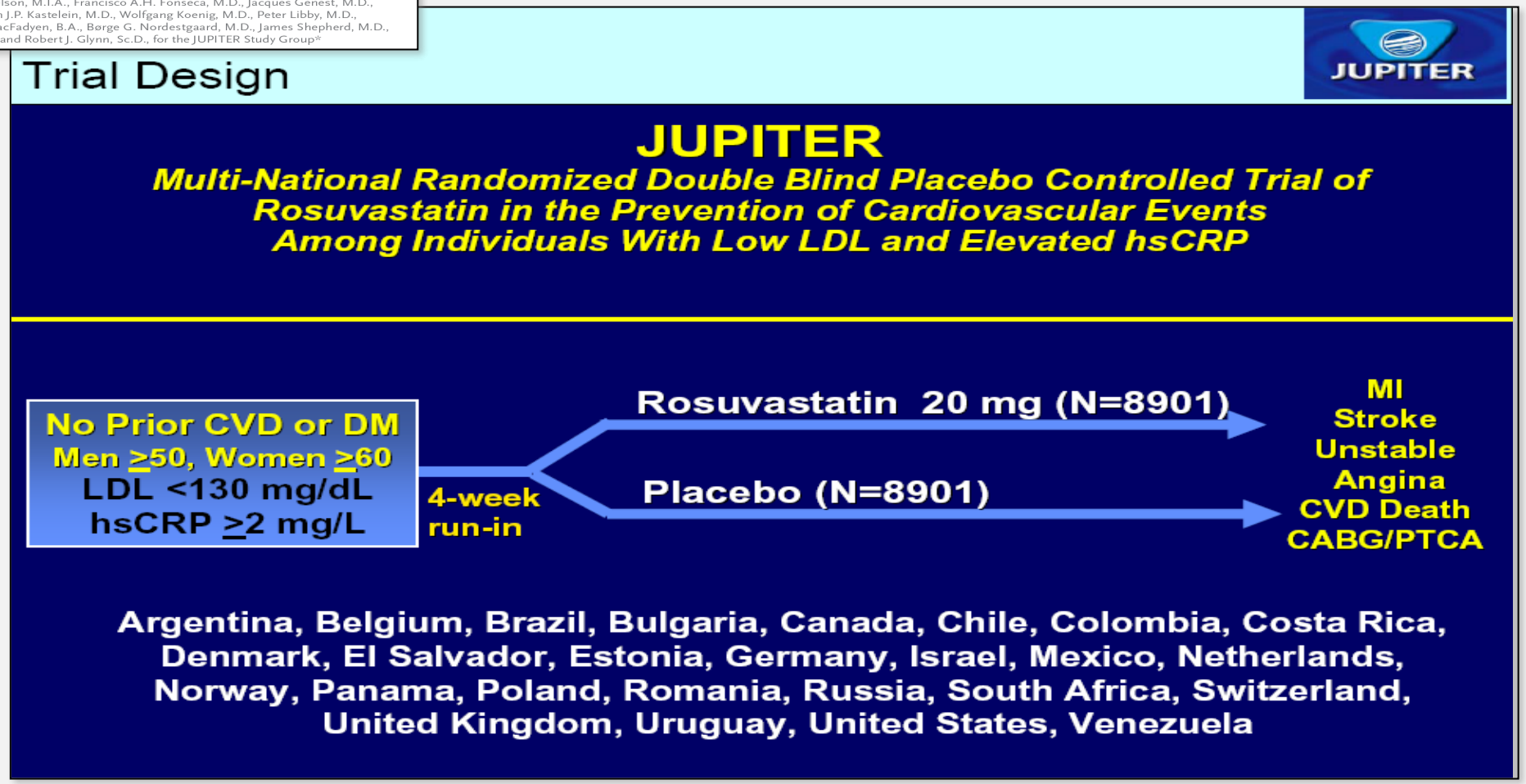
Athérosclérose & Inflammation

The NEW ENGLAND JOURNAL of MEDICINE

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

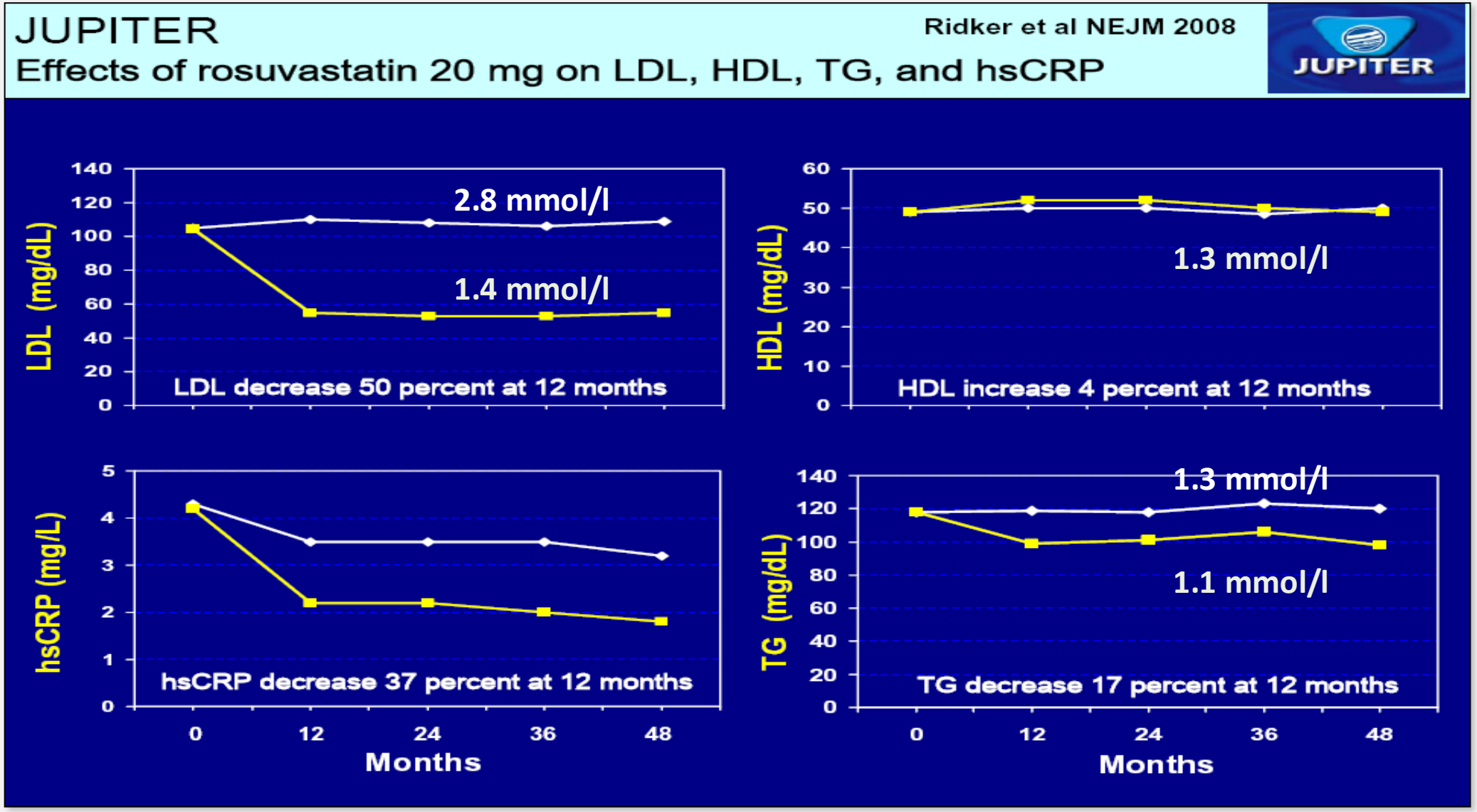
Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

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*



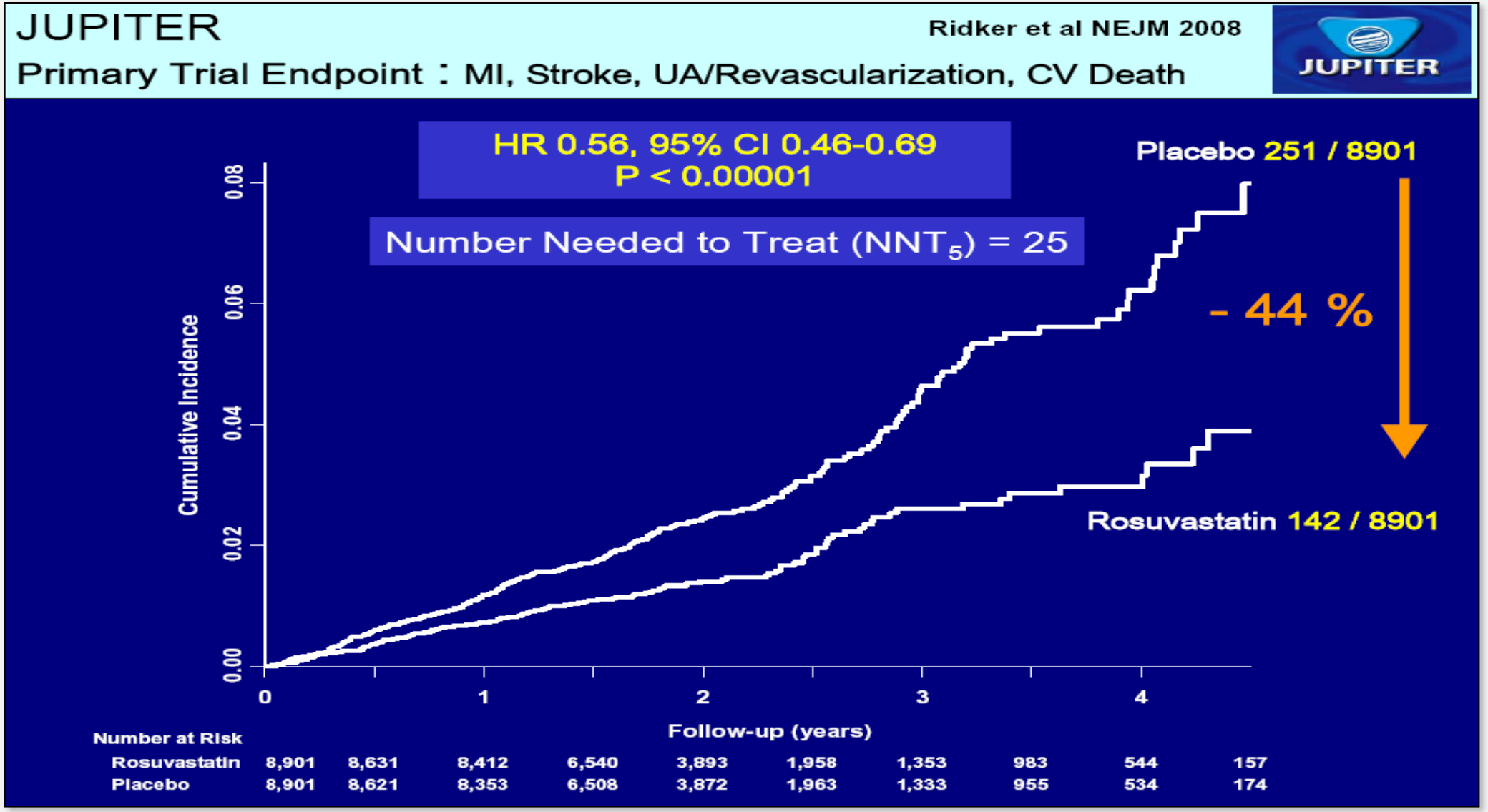
N Eng J Med 2008;359:2195

Athérosclérose & Inflammation



N Eng J Med 2008;359:2195

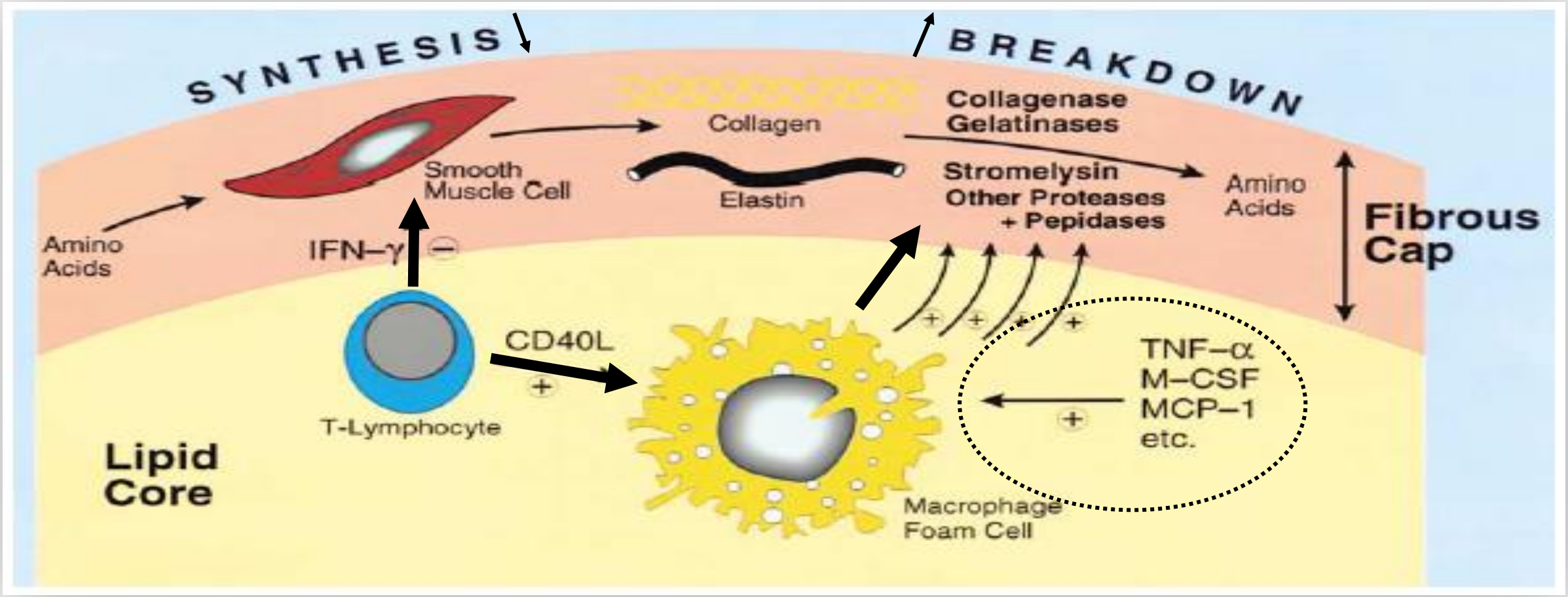
Athérosclérose & Inflammation



N Eng J Med 2008;359:2195

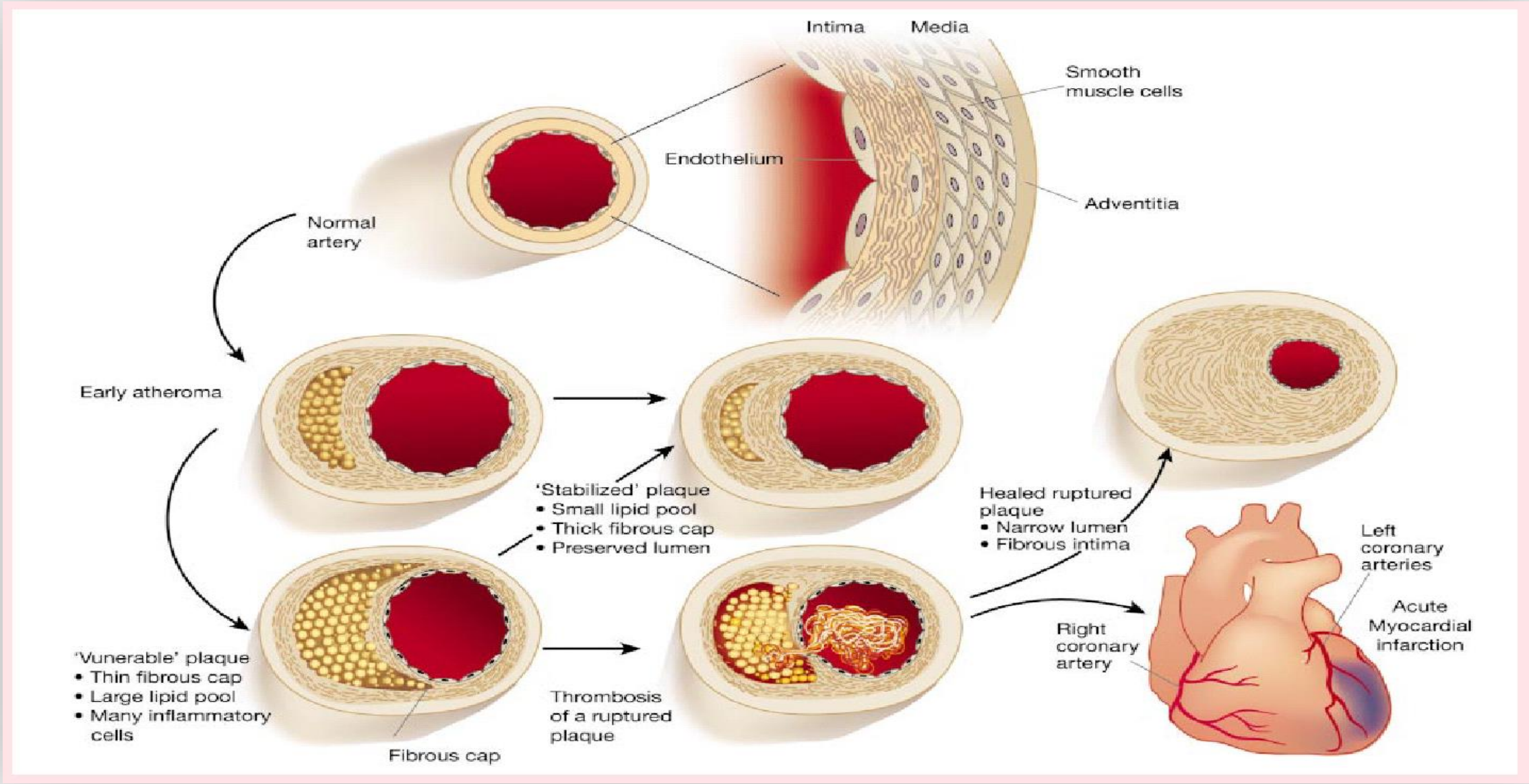
Caractéristiques des Plaques d'Athérosclérose

Plaque Stable ⟹ **Plaque Vulnérable**



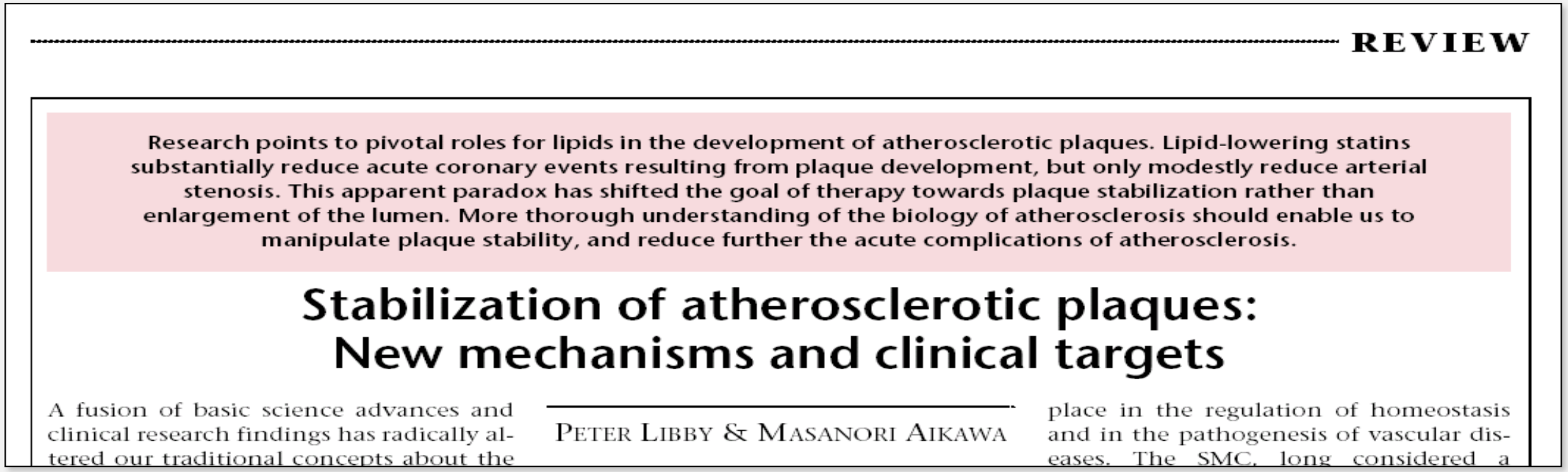
Circulation 1995;91:2844

Plaque d'athérosclérose



Nature 2002;420:868

Stabilisation de l'Athérosclérose



REVIEW

Research points to pivotal roles for lipids in the development of atherosclerotic plaques. Lipid-lowering statins substantially reduce acute coronary events resulting from plaque development, but only modestly reduce arterial stenosis. This apparent paradox has shifted the goal of therapy towards plaque stabilization rather than enlargement of the lumen. More thorough understanding of the biology of atherosclerosis should enable us to manipulate plaque stability, and reduce further the acute complications of atherosclerosis.

Stabilization of atherosclerotic plaques: New mechanisms and clinical targets

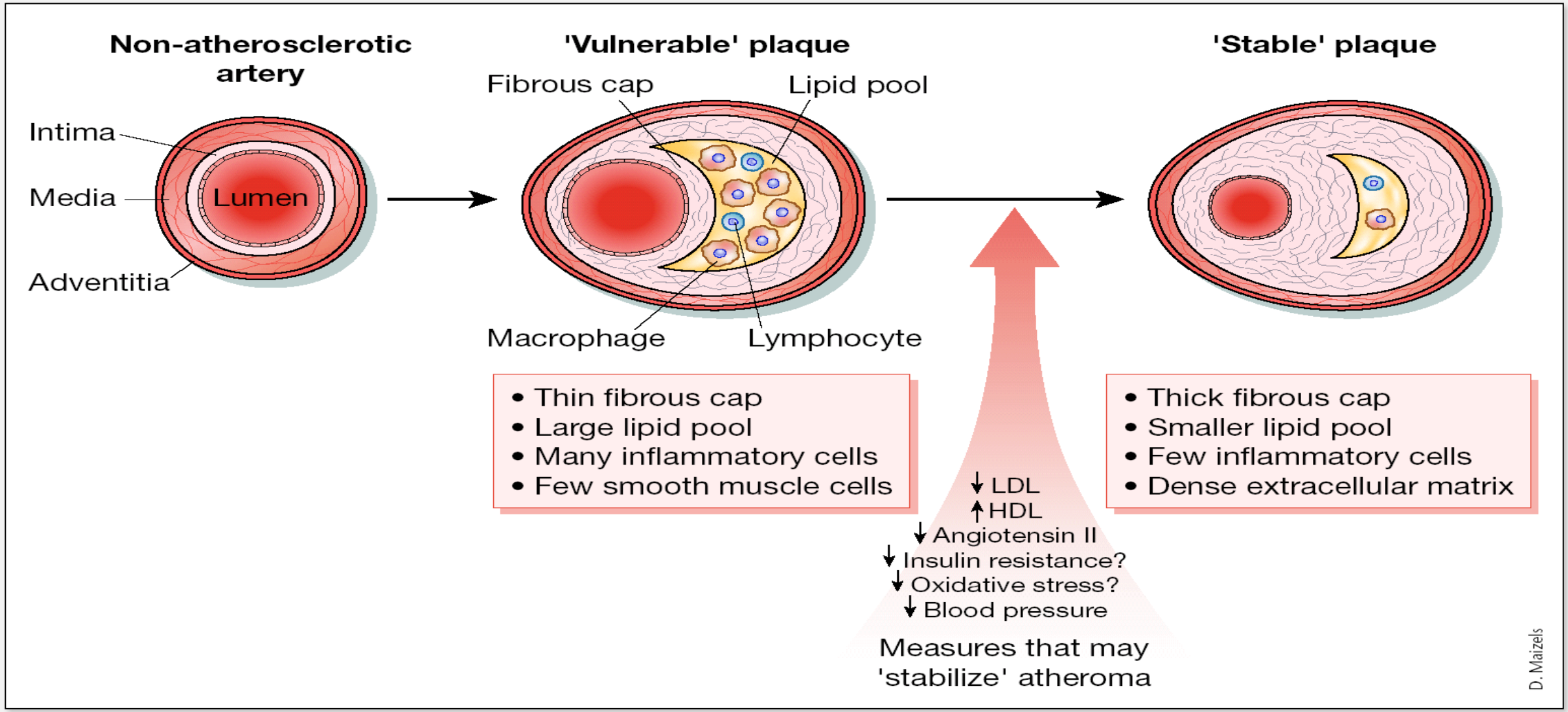
PETER LIBBY & MASANORI AIKAWA

A fusion of basic science advances and clinical research findings has radically altered our traditional concepts about the

place in the regulation of homeostasis and in the pathogenesis of vascular diseases. The SMC, long considered a

Nature Med 2002;8:1257

Stabilisation de l'Athérosclérose



Nature Med 2002;8:1257

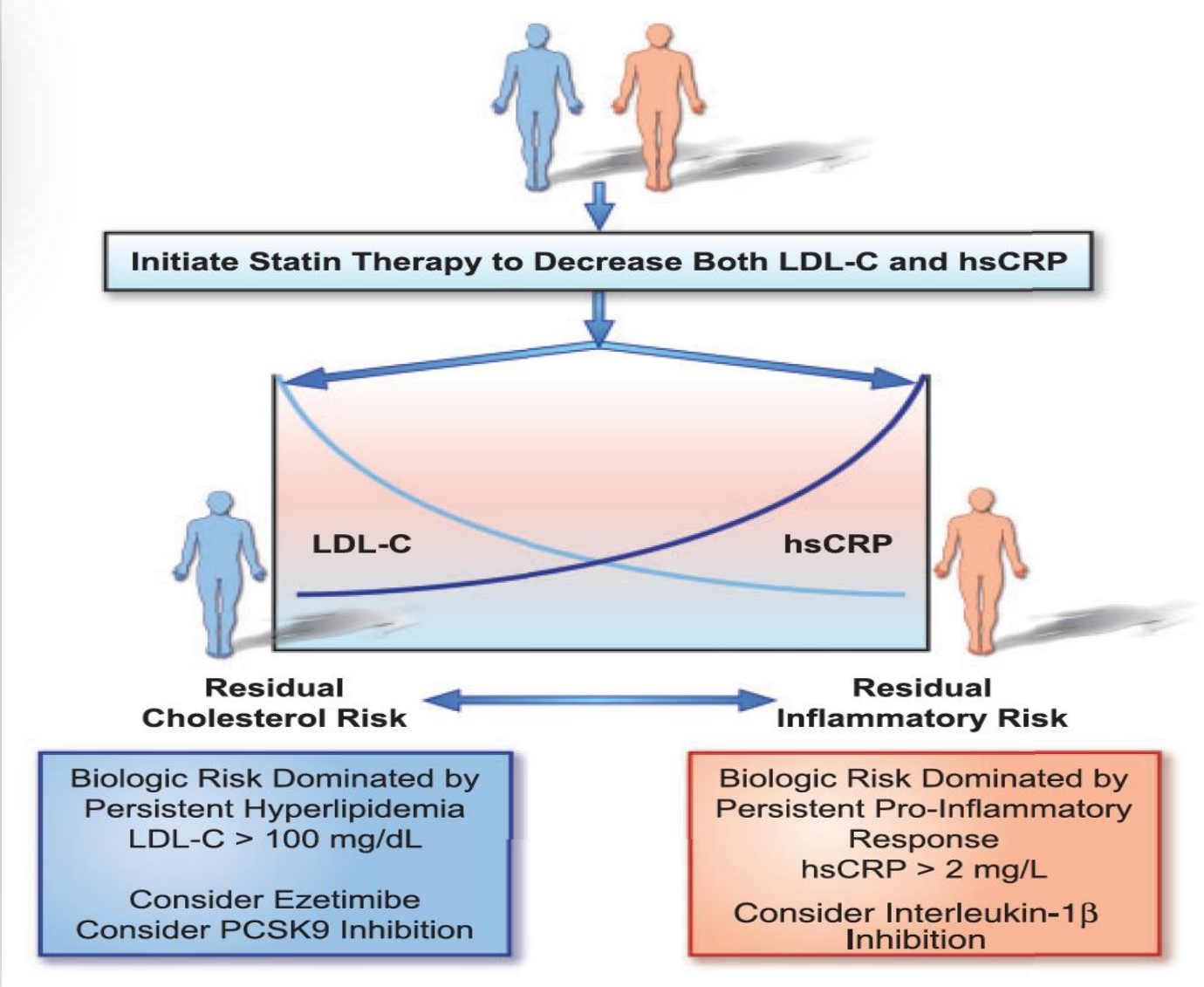
Traitement anti-inflammatoire de l'athérosclérose

ESC European Society of Cardiology
European Heart Journal (2018) 0, 1–3
doi:10.1093/eurheartj/ehy723

VIEWPOINT

Has the time finally come to measure hsCRP universally in primary and secondary cardiovascular prevention?

Paul M Ridker[1]*, Wolfgang Koenig[2], John J. Kastelein[3], François Mach[4], and Thomas F. Lüscher[5]



Traitement anti-inflammatoire de l'athérosclérose

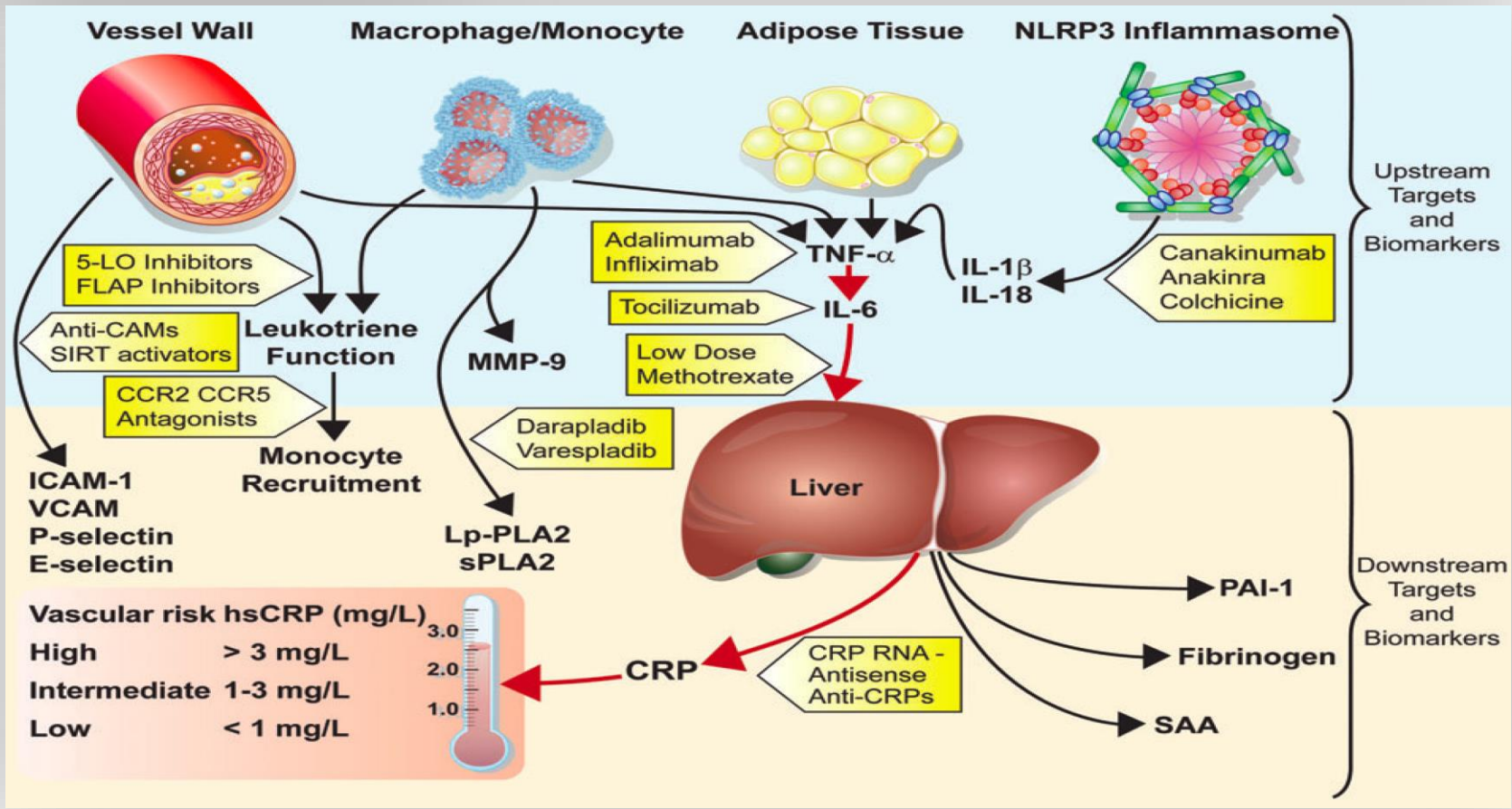
European Heart Journal (2014) **35**, 540–543
doi:10.1093/eurheartj/eht398

EDITORIAL

Targeting inflammatory pathways for the treatment of cardiovascular disease

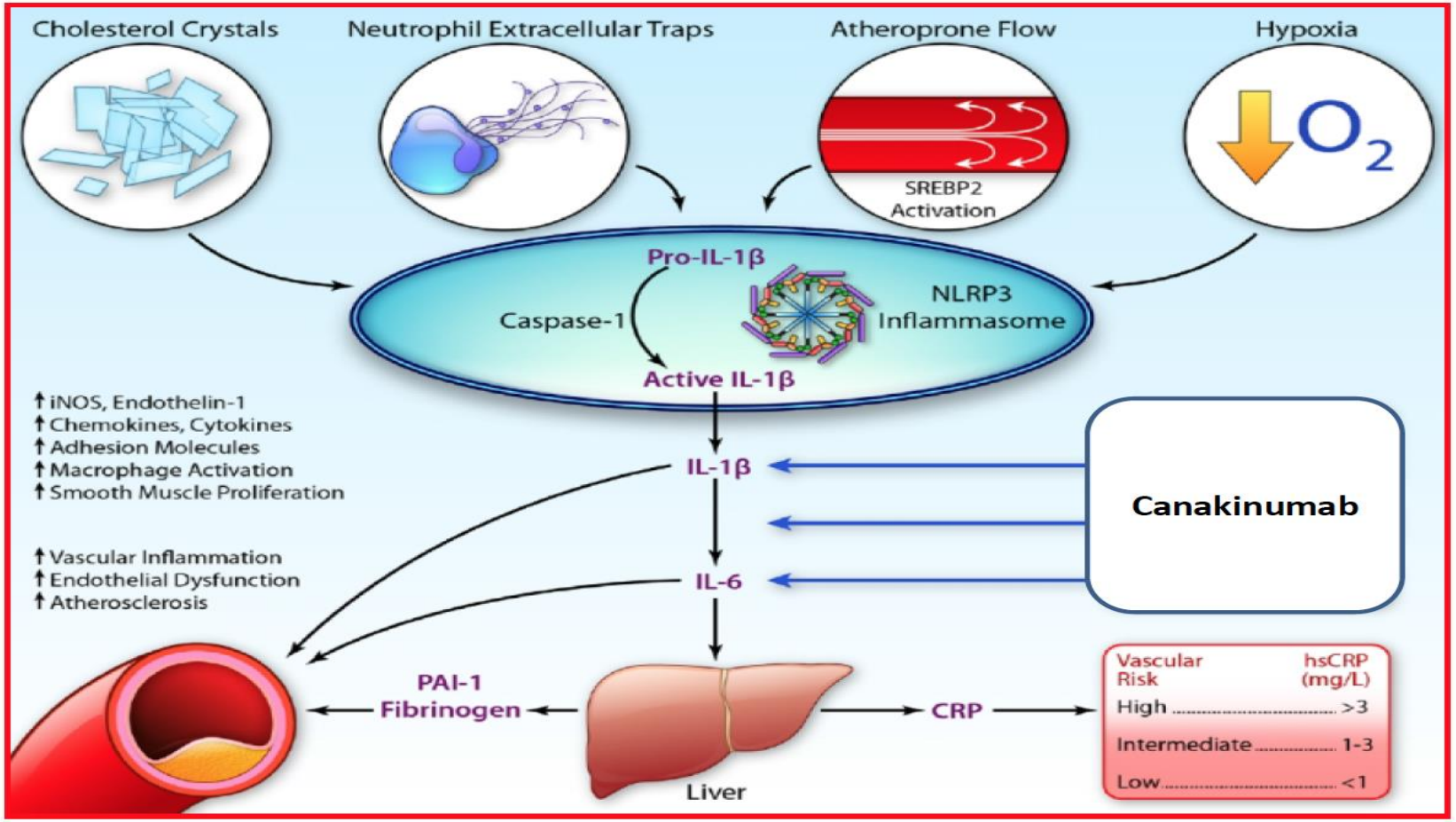
Paul M Ridker*

Eur Heart J 2014;35:540



Traitement anti-inflammatoire de l'athérosclérose

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



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

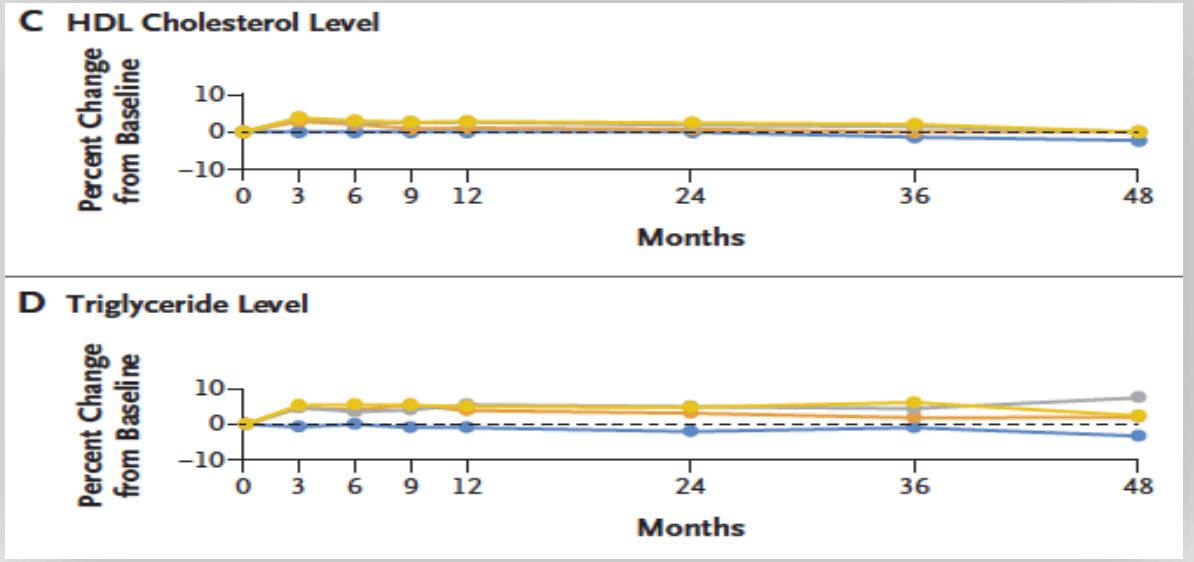
Ridker ESC 2017

Traitement anti-inflammatoire de l'athérosclérose

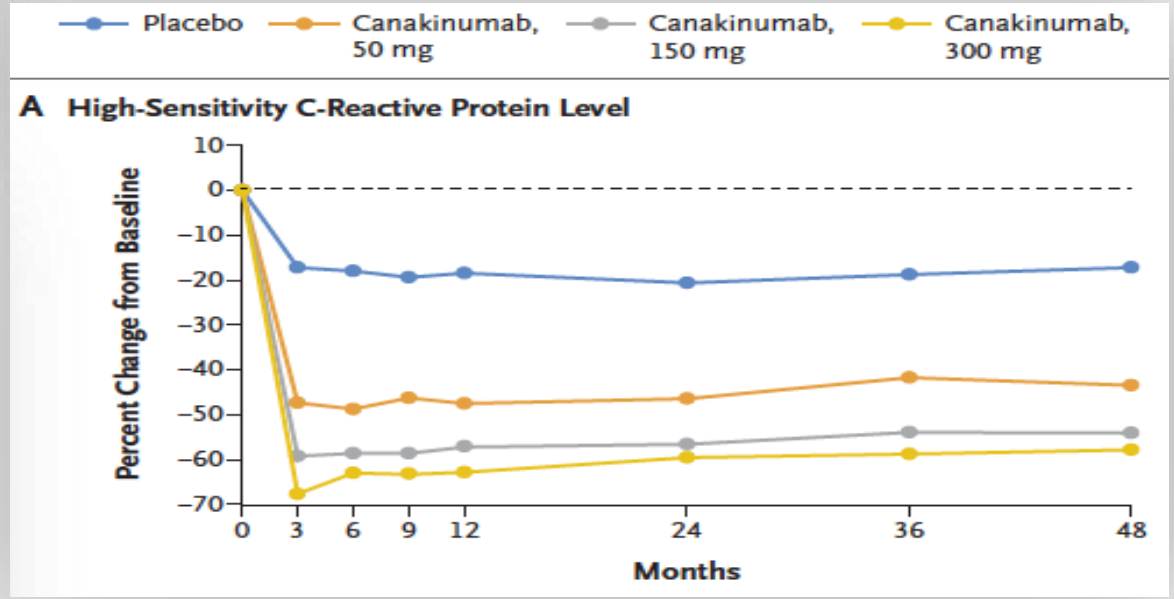
ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

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*

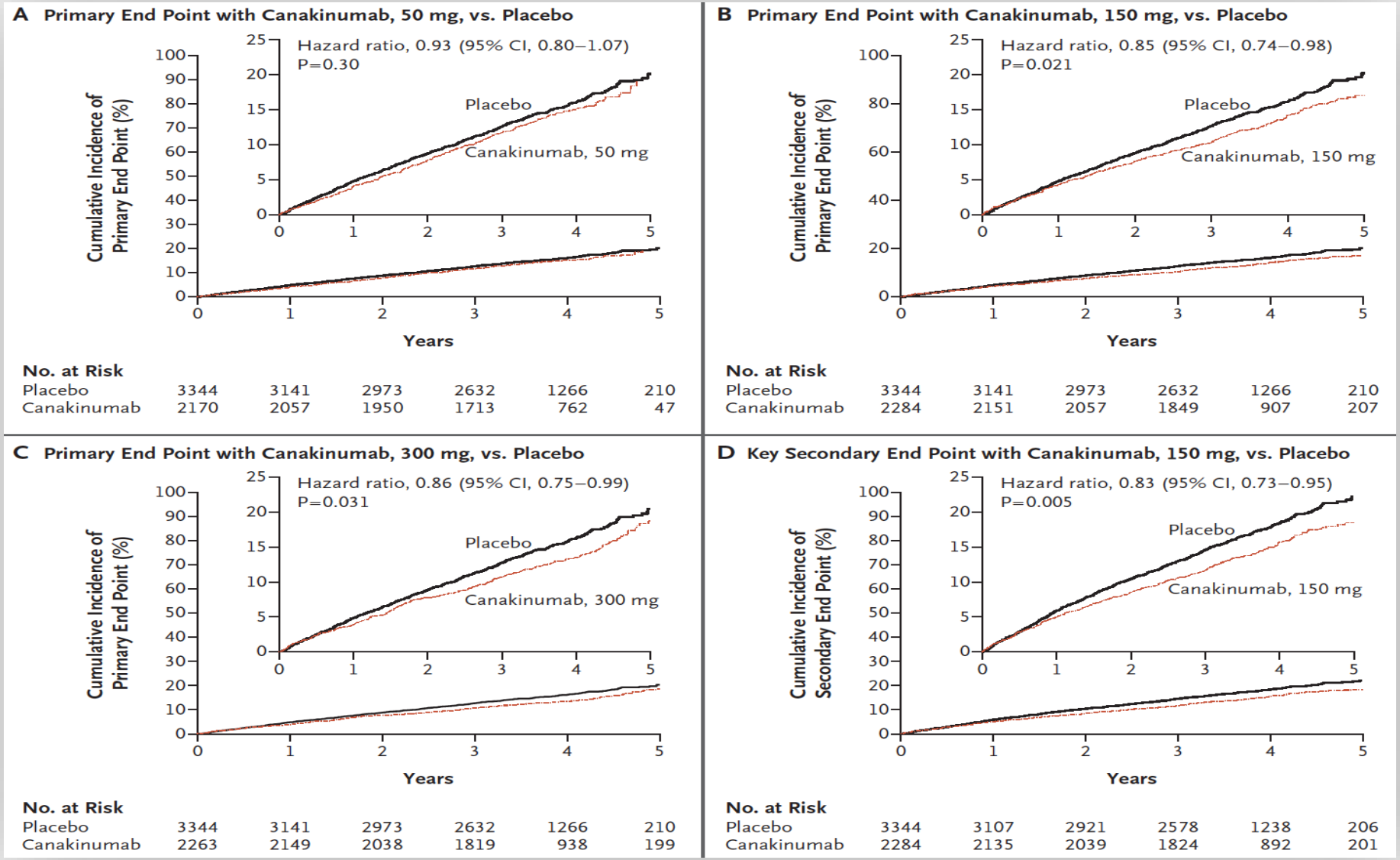


Canakinumab = mAb anti-IL-1β



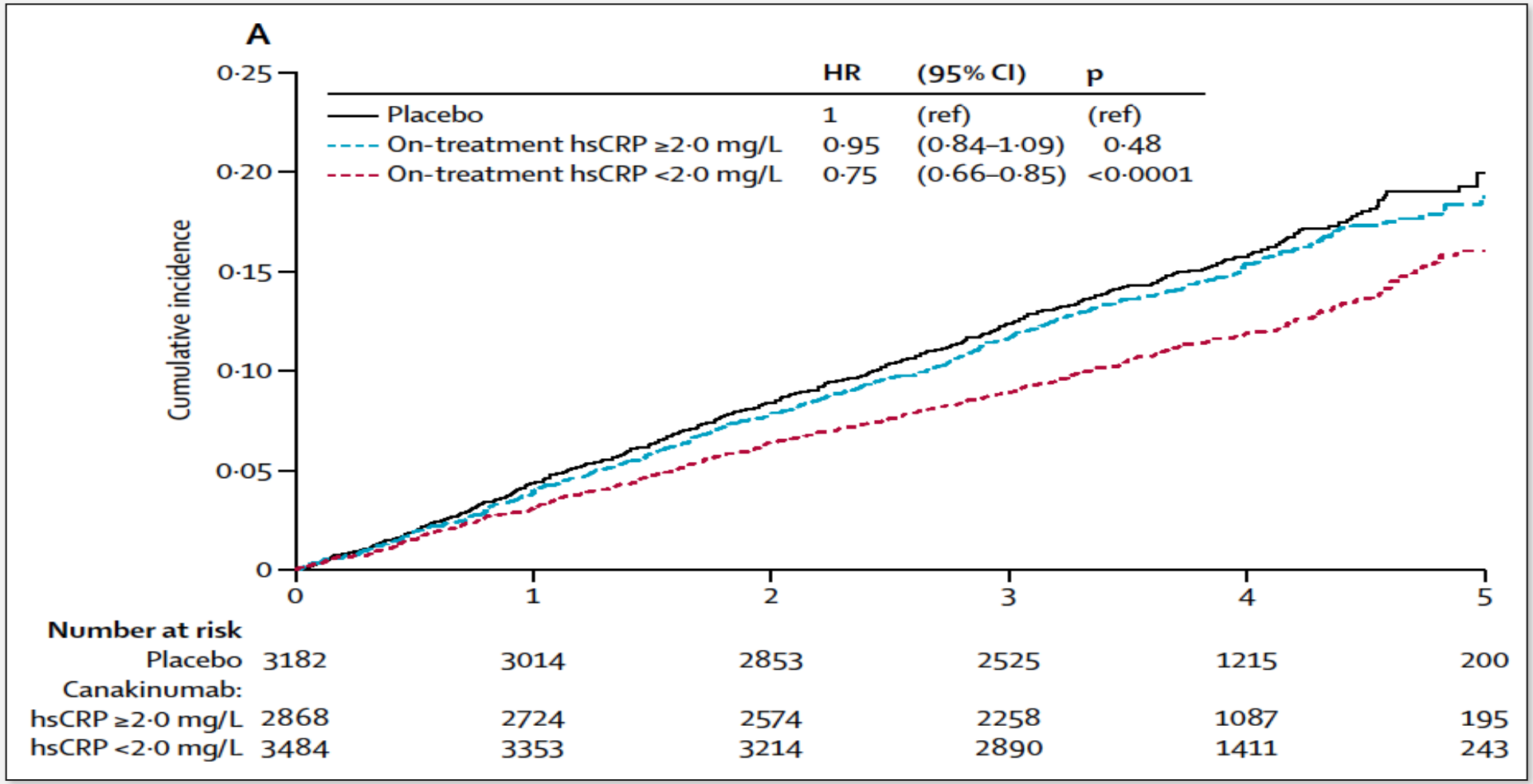
N Engl J Med 2017;377:1119

Traitement anti-inflammatoire de l'athérosclérose



N Engl J Med 2017;377:1119

Traitement anti-inflammatoire de l'athérosclérose



Lancet 2018;391:319

Traitement anti-inflammatoire de l'athérosclérose

Table 3. Incidence Rates and Numbers of Serious Adverse Events and Selected Safety Laboratory Data During Treatment, Stratified According to Trial Group.*

Adverse Event or Laboratory Variable	Placebo Group (N=3344)	Canakinumab				P Value	
		50-mg Group (N=2170)	150-mg Group (N=2284)	300-mg Group (N=2263)	All Doses (N=6717)	For Trend across Doses vs. Placebo	For Combined Dose Groups vs. Placebo
Event — incidence rate per 100 person-yr (no. of patients with event)							
Any serious adverse event	11.96 (1202)	11.41 (741)	11.71 (812)	12.33 (836)	11.82 (2389)	0.43	0.79
Any serious adverse event of infection	2.86 (342)	3.03 (230)	3.13 (258)	3.25 (265)	3.14 (753)	0.12	0.14
Cellulitis	0.24 (30)	0.24 (19)	0.37 (32)	0.41 (35)	0.34 (86)	0.02	0.09
Pneumonia	0.90 (112)	0.94 (74)	0.94 (80)	0.99 (84)	0.95 (238)	0.56	0.62
Urinary tract infection	0.22 (27)	0.18 (14)	0.24 (21)	0.20 (17)	0.21 (52)	0.84	0.87
Opportunistic infection†	0.18 (23)	0.16 (13)	0.15 (13)	0.20 (17)	0.17 (43)	0.97	0.78
Pseudomembranous colitis	0.03 (4)	0.13 (10)	0.05 (4)	0.12 (10)	0.10 (24)	0.13	0.03
Fatal infection or sepsis	0.18 (23)	0.31 (25)	0.28 (24)	0.34 (29)	0.31 (78)	0.09	0.02
Any cancer‡	1.88 (231)	1.85 (144)	1.69 (143)	1.72 (144)	1.75 (431)	0.31	0.38
Fatal cancer‡	0.64 (81)	0.55 (44)	0.50 (44)	0.31 (27)	0.45 (115)	<0.001	0.02
Other adverse event							
Injection-site reaction†	0.23 (29)	0.27 (21)	0.28 (24)	0.30 (26)	0.28 (71)	0.49	0.36
Arthritis	3.32 (385)	2.15 (164)	2.17 (180)	2.47 (201)	2.26 (545)	0.002	<0.001
Osteoarthritis	1.67 (202)	1.21 (94)	1.12 (95)	1.30 (109)	1.21 (298)	0.04	<0.001
Gout	0.80 (99)	0.43 (34)	0.35 (30)	0.37 (32)	0.38 (96)	<0.001	<0.001
Drug-induced liver injury†	0.18 (23)	0.15 (12)	0.13 (11)	0.05 (4)	0.11 (27)	0.004	0.05
Leukopenia	0.24 (30)	0.30 (24)	0.37 (32)	0.52 (44)	0.40 (100)	0.002	0.01
Neutropenia	0.06 (7)	0.05 (4)	0.07 (6)	0.18 (15)	0.10 (25)	0.01	0.17
Any hemorrhage	4.01 (462)	3.33 (249)	4.15 (327)	3.82 (301)	3.78 (877)	0.94	0.31
Thrombocytopenia	0.43 (53)	0.56 (44)	0.54 (46)	0.71 (60)	0.60 (150)	0.02	0.03
Hepatic variable — percent of patients with condition (no.)							
Alanine aminotransferase >3× normal value	1.4 (46)	1.9 (42)	1.9 (44)	2.0 (45)	2.0 (131)	0.19	0.06
Aspartate aminotransferase >3× normal value	1.1 (36)	1.5 (32)	1.5 (35)	1.5 (34)	1.5 (101)	0.30	0.11
Alkaline phosphatase >3× normal value	0.4 (15)	0.5 (11)	0.4 (10)	0.5 (12)	0.5 (33)	0.67	0.82
Bilirubin >2× normal value	0.8 (26)	1.0 (21)	0.7 (15)	0.7 (15)	0.8 (51)	0.34	0.83

N Engl J Med 2017;377:1119

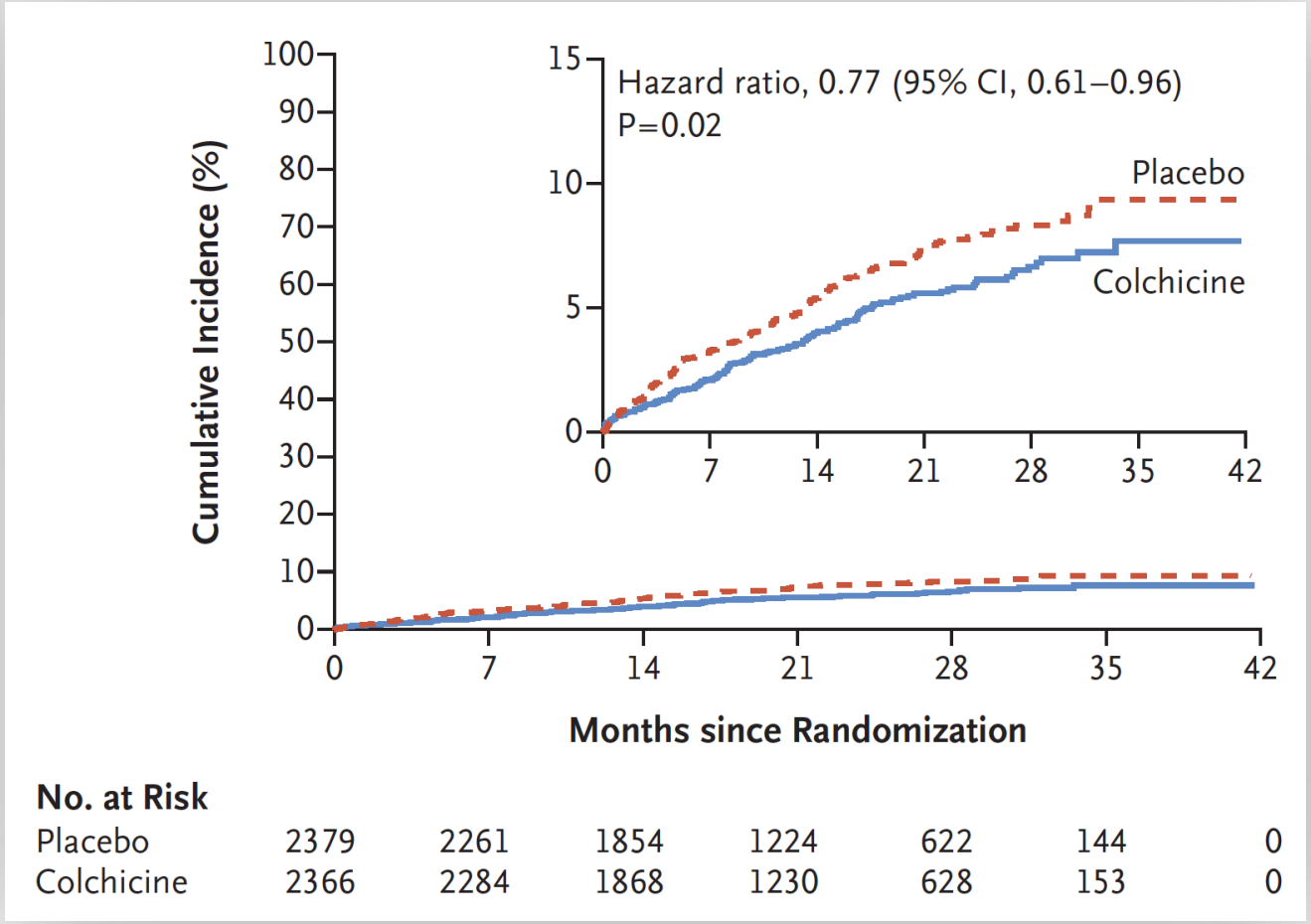
Traitement anti-inflammatoire de l'athérosclérose

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 26, 2019 VOL. 381 NO. 26

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

Jean-Claude Tardif, M.D., Simon Kouz, M.D., David D. Waters, M.D., Olivier F. Bertrand, M.D., Ph.D., Rafael Diaz, M.D., Aldo P. Maggioni, M.D., Fausto J. Pinto, M.D., Ph.D., Reda Ibrahim, M.D., Habib Gamra, M.D., Ghassan S. Kiwan, M.D., Colin Berry, M.D., Ph.D., José López-Sendón, M.D., Petr Ostadal, M.D., Ph.D., Wolfgang Koenig, M.D., Denis Angoulvant, M.D., Jean C. Grégoire, M.D., Marc-André Lavoie, M.D., Marie-Pierre Dubé, Ph.D., David Rhainds, Ph.D., Mylène Provencher, Ph.D., Lucie Blondeau, M.Sc., Andreas Orfanos, M.B., B.Ch., Philippe L. L'Allier, M.D., Marie-Claude Guertin, Ph.D., and François Roubille, M.D., Ph.D.



New Engl J Med December 2019;381:2497

Traitement anti-inflammatoire de l'athérosclérose

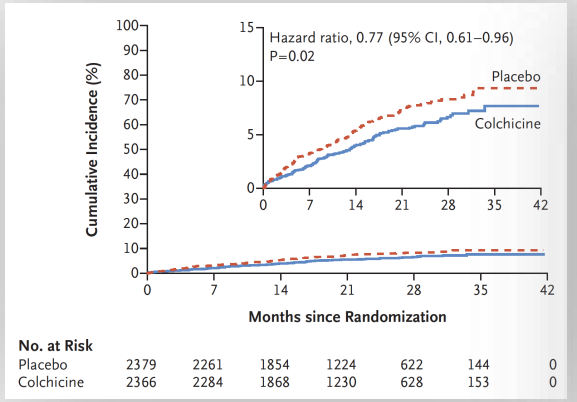


Table 2. Major Clinical End Points (Intention-to-Treat Population).*

End Point	Colchicine (N=2366)	Placebo (N=2379)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary composite end point	131 (5.5)	170 (7.1)	0.77 (0.61–0.96)	0.02†
Components of primary end point				
Death from cardiovascular causes	20 (0.8)	24 (1.0)	0.84 (0.46–1.52)	
Resuscitated cardiac arrest	5 (0.2)	6 (0.3)	0.83 (0.25–2.73)	
Myocardial infarction	89 (3.8)	98 (4.1)	0.91 (0.68–1.21)	
Stroke	5 (0.2)	19 (0.8)	0.26 (0.10–0.70)	
Urgent hospitalization for angina leading to revascularization	25 (1.1)	50 (2.1)	0.50 (0.31–0.81)	
Secondary composite end point‡	111 (4.7)	130 (5.5)	0.85 (0.66–1.10)	
Death	43 (1.8)	44 (1.8)	0.98 (0.64–1.49)	
Deep venous thrombosis or pulmonary embolus	10 (0.4)	7 (0.3)	1.43 (0.54–3.75)	
Atrial fibrillation	36 (1.5)	40 (1.7)	0.93 (0.59–1.46)	

New Engl J Med December 2019;381:2497

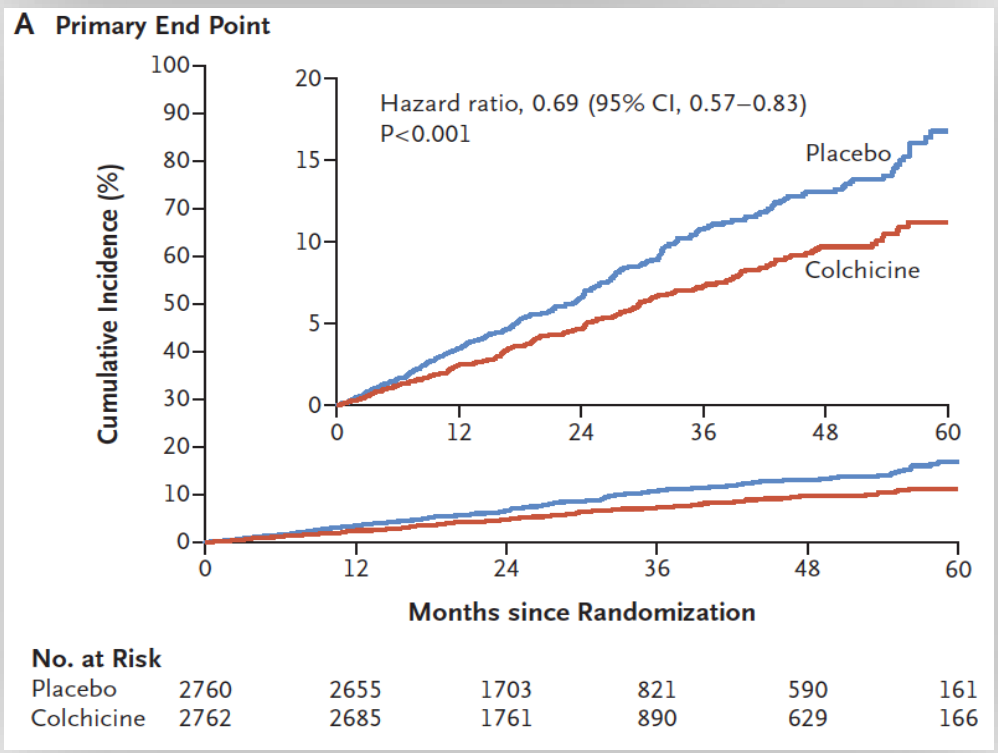
Traitement anti-inflammatoire de l'athérosclérose

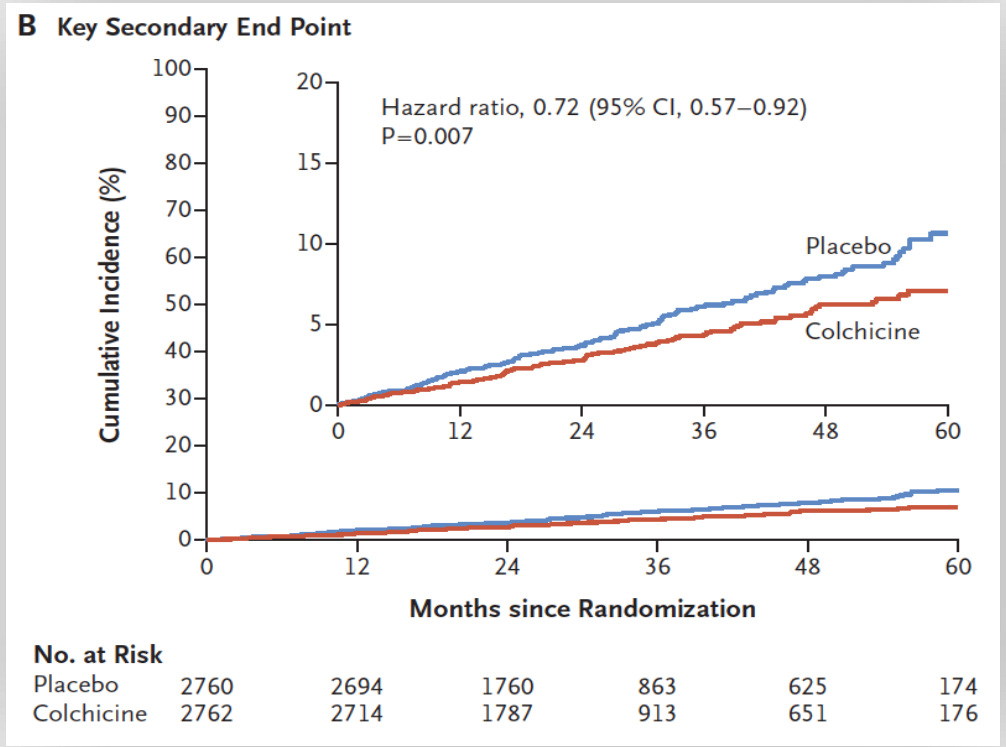
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Colchicine in Patients with Chronic Coronary Disease

S.M. Nidorf, A.T.L. Fiolet, A. Mosterd, J.W. Eikelboom, A. Schut, T.S.J. Opstal, S.H.K. The, X.-F. Xu, M.A. Ireland, T. Lenderink, D. Latchem, P. Hoogslag, A. Jerzewski, P. Nierop, A. Whelan, R. Hendriks, H. Swart, J. Schaap, A.F.M. Kuijper, M.W.J. van Hessen, P. Saklani, I. Tan, A.G. Thompson, A. Morton, C. Judkins, W.A. Bax, M. Dirksen, M. Alings, G.J. Hankey, C.A. Budgeon, J.G.P. Tijssen, J.H. Cornel, and P.L. Thompson, for the LoDoCo2 Trial Investigators*





New Engl J Med Novenber 5 2020;383:1838

Traitement anti-inflammatoire de l'athérosclérose

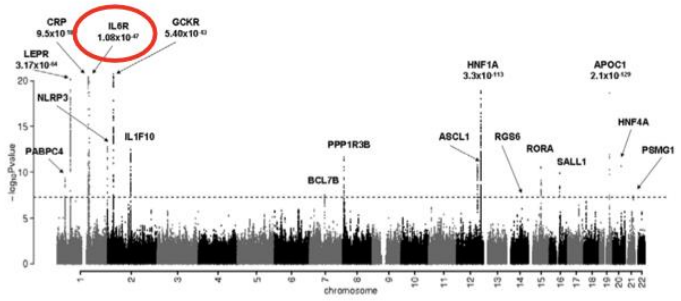
Table 2. Adverse Events in the Intention-to-Treat Population.*

Event	Colchicine (N=2762)		Placebo (N=2760)		Hazard Ratio or Cumulative Incidence Ratio (95% CI)
	no. of patients/ total no. (%)	*no. of events/100 person-yrs*	*no. of patients/ total no. (%)*	*no. of events/100 person-yrs*	
Noncardiovascular death	53/2762 (1.9)	0.7	35/2760 (1.3)	0.5	1.51 (0.99–2.31)
Diagnosis of cancer	120/2762 (4.3)	1.6	122/2760 (4.4)	1.6	0.98 (0.76–1.26)
Hospitalization for infection	137/2762 (5.0)	1.8	144/2760 (5.2)	1.9	0.95 (0.75–1.20)
Hospitalization for pneumonia	46/2762 (1.7)	0.6	55/2760 (2.0)	0.7	0.84 (0.56–1.24)
Hospitalization for gastrointestinal reason	53/2762 (1.9)	0.7	50/2760 (1.8)	0.7	1.06 (0.72–1.56)
Gout	38/2762 (1.4)	—	95/2760 (3.4)	—	0.40 (0.28–0.58)
Neutropenia	4/2762 (0.1)	—	3/2760 (0.1)	—	NR
Myotoxic effects†	3/2762 (0.1)	—	3/2760 (0.1)	—	NR
Myalgia‡	384/1811 (21.2)	—	334/1807 (18.5)	—	1.15 (1.01–1.31)
Dysesthesia: numbness or tingling‡	143/1811 (7.9)	—	150/1807 (8.3)	—	0.95 (0.76–1.18)

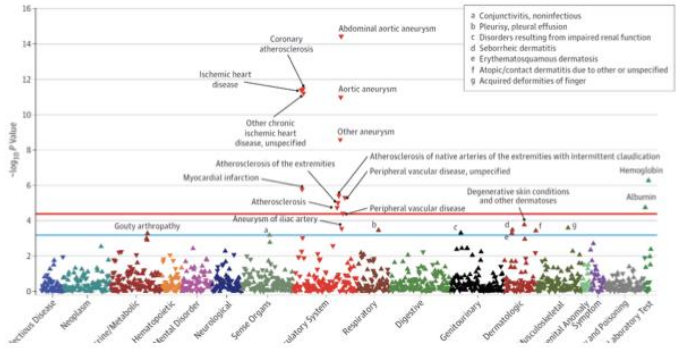
New Engl J Med Novenber 5 2020;383:1838

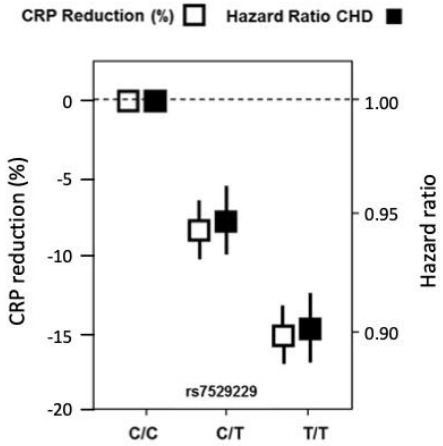
IL-6 as a target to reduce inflammation and cardiovascular disease

GWAS, PheWAS and mendelian randomisation studies all support a potential causal role for IL-6 signalling in atherosclerotic disease



Dehgman A et al. *Circulation* 2011;123:731–738





Ridker PM. *Circ Res* 2016;118(1):145–156

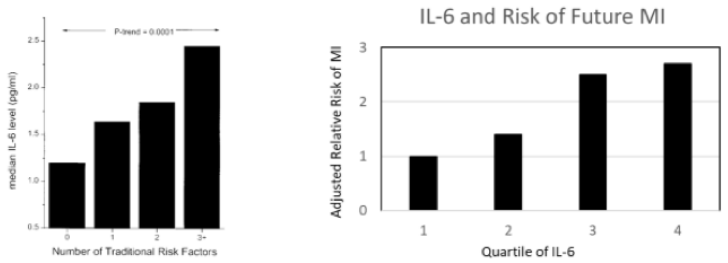
Swerdlow DI et al. *Lancet* 2012;379;1214–1224

IL-6 as a target to reduce inflammation and cardiovascular disease

IL-6 levels are a powerful predictor of future CV events

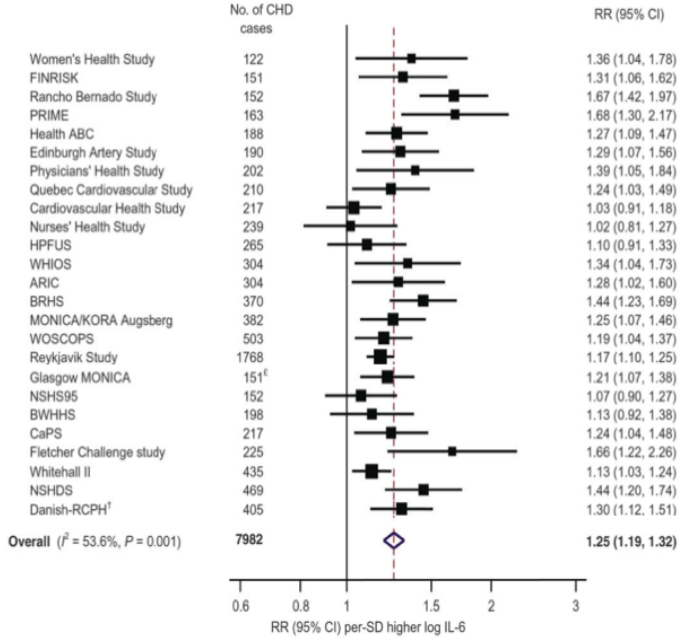
Plasma Concentration of Interleukin-6 and the Risk of Future Myocardial Infarction Among Apparently Healthy Men

Paul M. Ridker, MD; Nader Rifai, MD; Meir J. Stampfer, MD; Charles H. Hennekens, MD



Conclusions—In apparently healthy men, elevated levels of IL-6 are associated with increased risk of future MI. These data thus support a role for cytokine-mediated inflammation in the early stages of atherogenesis. **(*Circulation*. 2000;101:1767-1772.)**

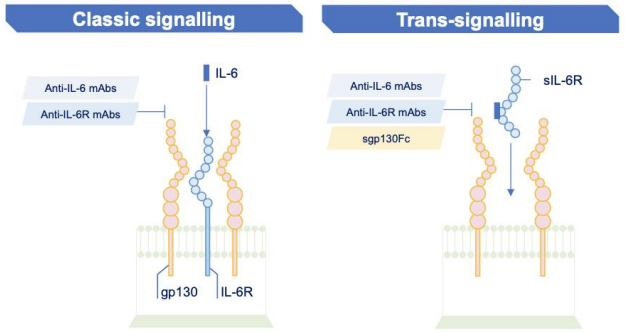
Ridker PM et al. *Circulation* 2000;101:1767–1772



Kaptoge S et al, *Eur Heart J* 2014;35:578–589

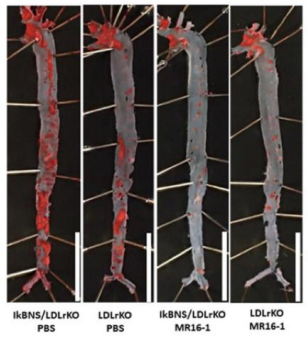
IL-6 as a target to reduce inflammation and cardiovascular disease

Murine models of IL-6 inhibition support a potential causal role for IL-6 signalling in atherosclerotic disease



Modalities for IL-6 signalling and IL-6 therapeutics

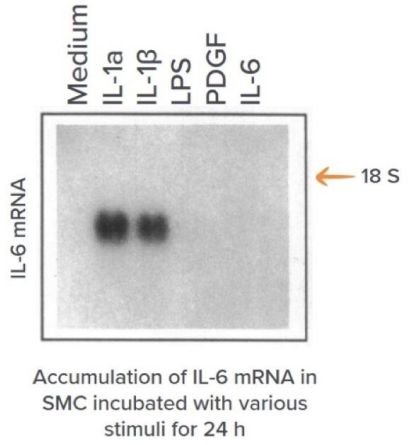
Garbers C et al. *Nat Rev Drug Disc* 2018;45



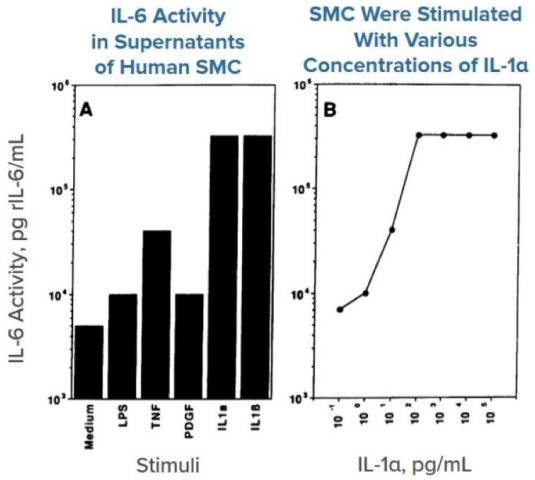
MR16-1: murine anti-IL-6 receptor antibody

Akita K et al. *Front Cardiovasc Med* 2017;4:84

IL-1 induces IL-6, a further amplification of cytokine signalling in SMCs



Accumulation of IL-6 mRNA in SMC incubated with various stimuli for 24 h



Loppnow H, Libby P. *J Clin Invest* 1990;85:731–738

IL, interleukin; LPS, lipopolysaccharide; mRNA, messenger ribonucleic acid; PDGF, platelet-derived growth factor; SMC, smooth muscle cell; TNF, tumour necrosis factor

IL-6 as a target to reduce inflammation and cardiovascular disease

Ziltivekimab is being investigated for cardiovascular risk reduction but currently not approved in this indication.

Ziltivekimab Cardiovascular Outcomes Study (ZEUS)

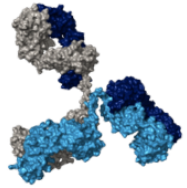
6200 patients
- **ASCVD**
- **CKD stage 3–4**
- **hsCRP ≥2 mg/L**

IL-6 inhibition with ziltivekimab 15 mg SC monthly + usual care

Matching placebo injection SC monthly + usual care

Major adverse CV events

Renal disease progression



Ziltivekimab: **Narrow spectrum fully human monoclonal antibody targeting the IL-6 ligand that is being developed specifically for atherosclerosis**

RESCUE Trial: ziltivekimab 15 mg SC monthly markedly lowered hsCRP, fibrinogen, sPLA2 and Lp(a) without adverse lipid effects

Ridker PM, Rane M. *Circ Res* 2021;128:1728–1746
Ridker PM et al. *Lancet* 2021;397(10289):2060–2069
Novo Nordisk. NCT05021835. Available at: https://clinicaltrials.gov/ct2/show/NCT05021835 (accessed August 2023)

ASCVD, atherosclerosis cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; hsCRP, high-sensitivity C-reactive protein; Lp(a), lipoprotein(a); SC, subcutaneous; sPLA2, secreted phospholipases A2

Atherosclerosis & inflammation

ATHEROSCLEROSIS –
INFLAMMATORY DIS

RUSSELL ROSS, PH.D.

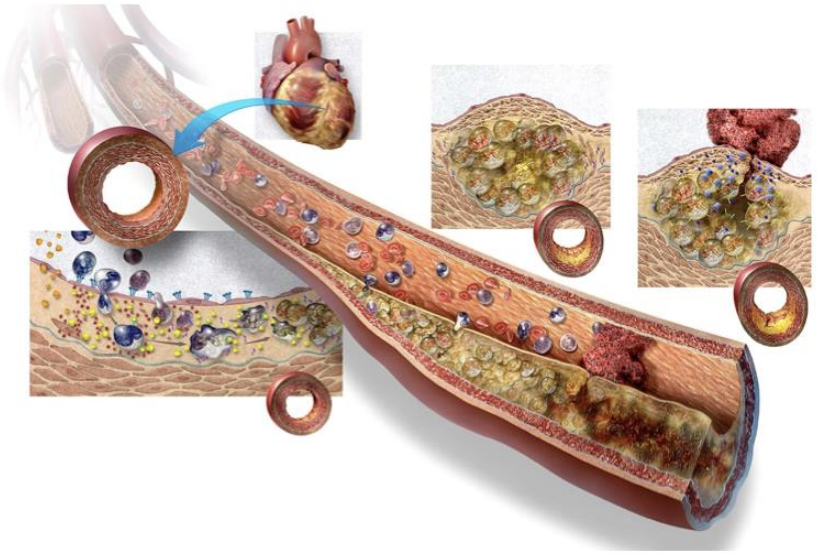
TABLE 1. CHARACTERISTICS

DISEASE	MONOCYTES AND MACROPHAGES	LYMPHOCYTES	GRAN LOCYT
Atherosclerosis	+	+	–
Cirrhosis	+	+	–
Rheumatoid arthritis	+	+	+/-
Glomerulosclerosis	+	+	–
Pulmonary fibrosis	+	+	+/-
Chronic pancreatitis	+	+	–

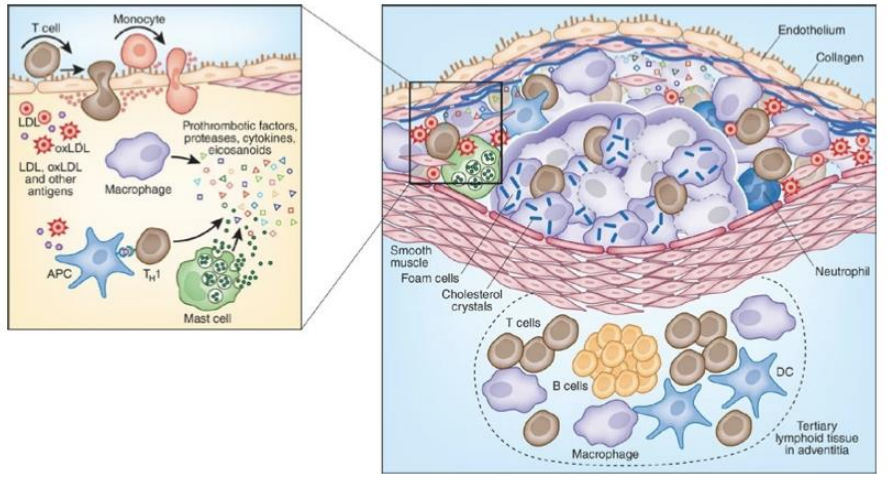
*Plus signs denote the presence of a cell type, a

N Engl J Med 1999;340:115

Atherosclerosis – inflammation in the vessel wall

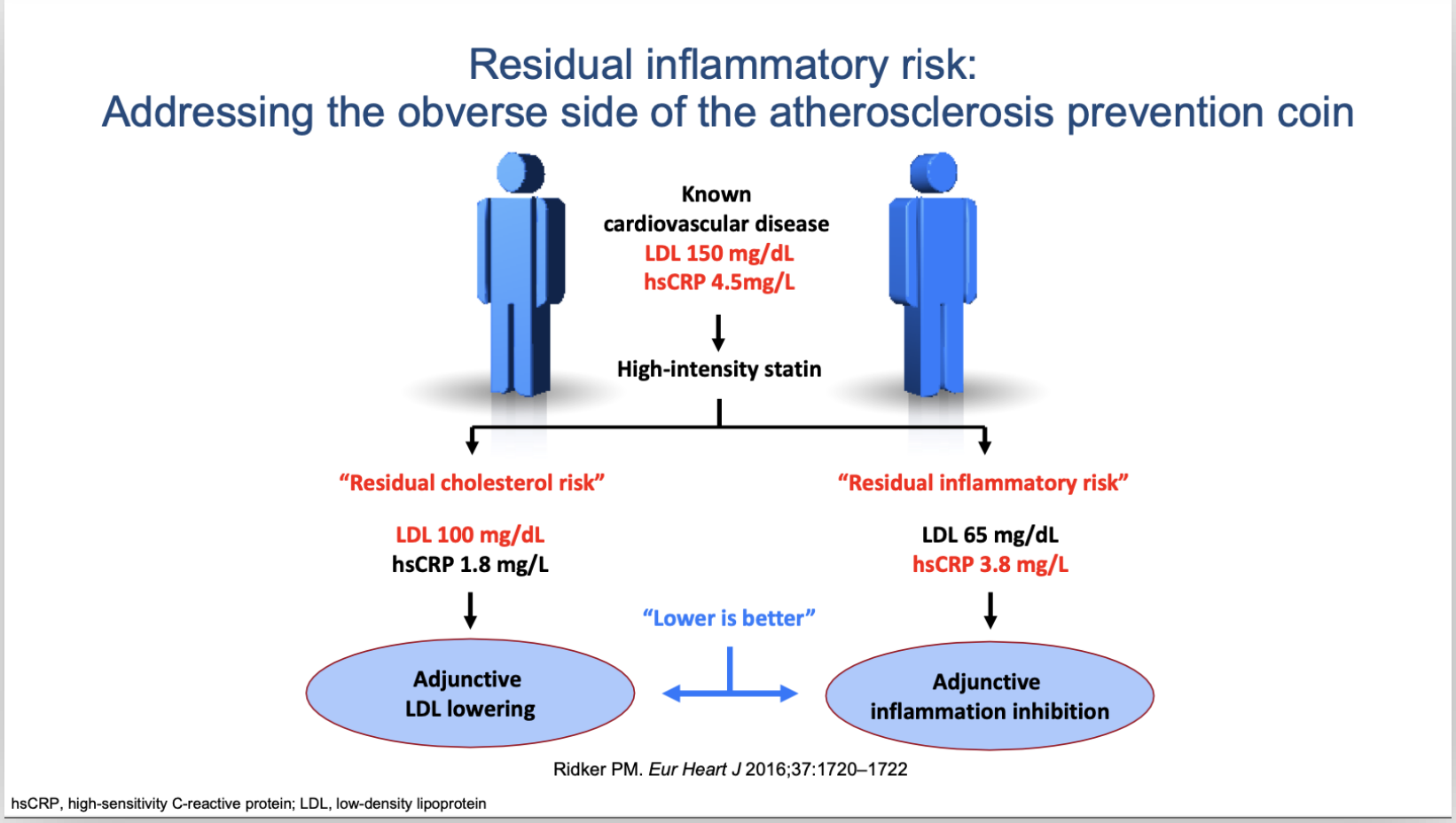


Libby P; *Scientific American* 2002;286(5):47–55



Hansson GK and Hermansson A. *Nature Immunology* 2011;12:204–212

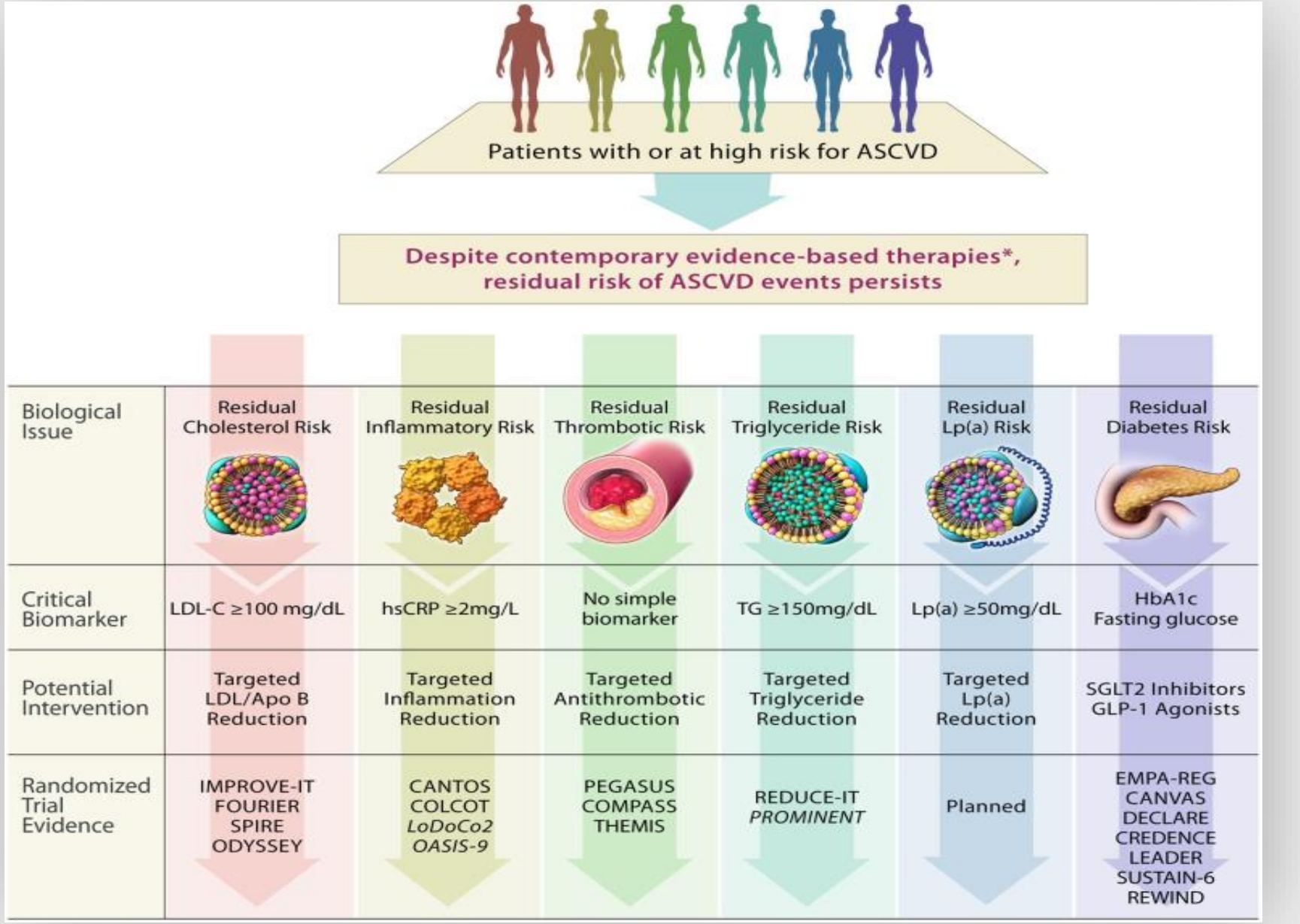
Residual risk, LDL-cholesterol and inflammation



Ridker PM. *Eur Heart J* 2016;37:1720–1722

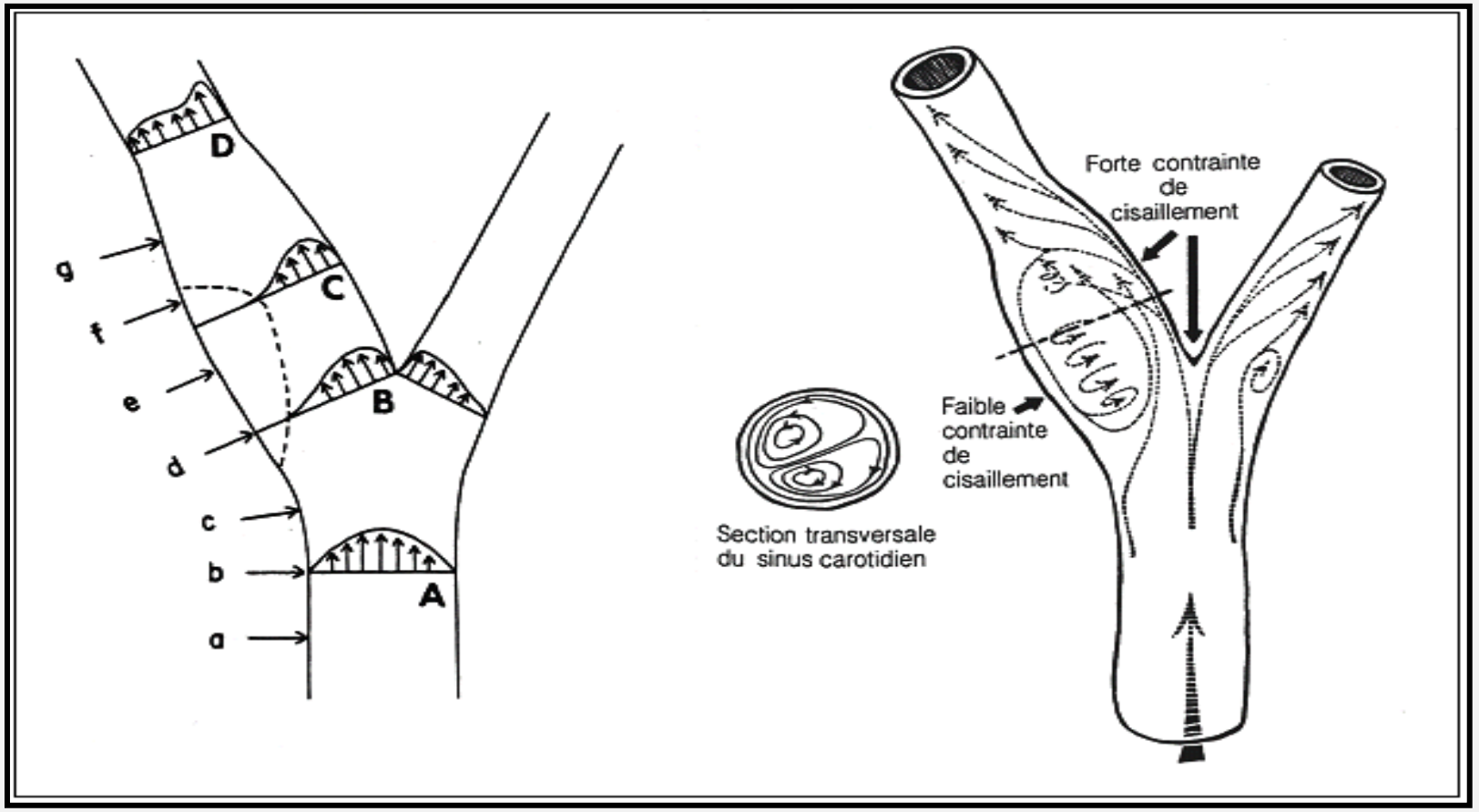
hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein

Residual Risk



Eur Heart J 2021;42:113

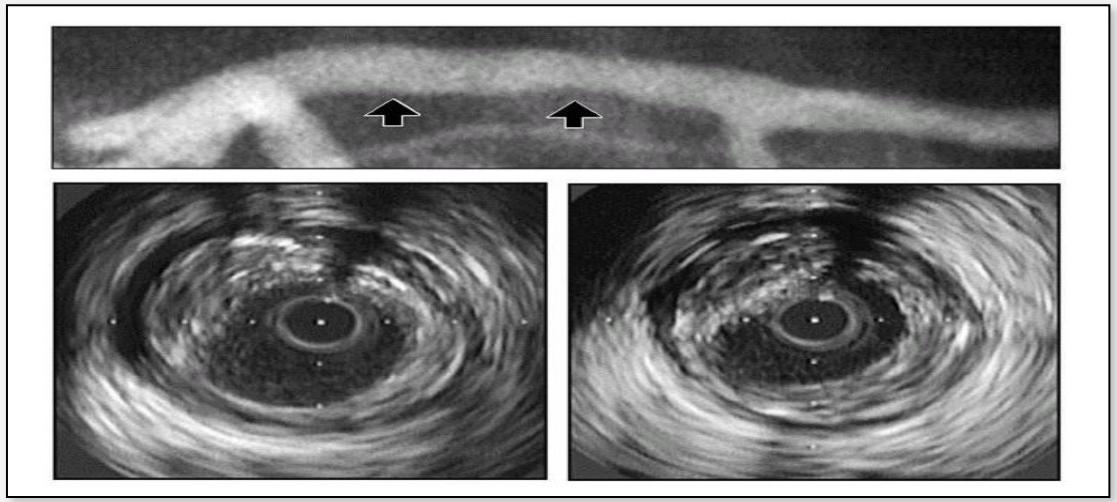
Athérosclérose & forces hémodynamiques

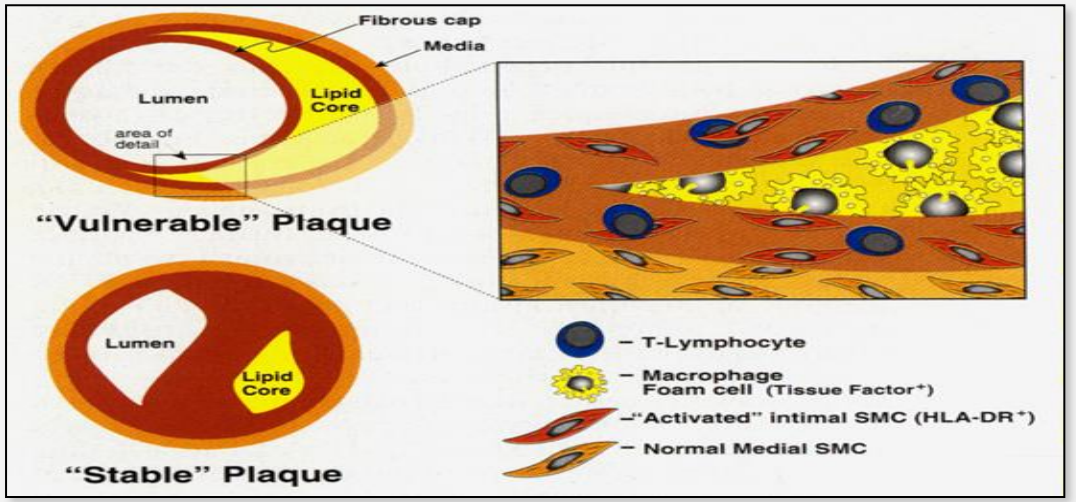


Steady laminar blood flow

Turbulent, reversal blood flow

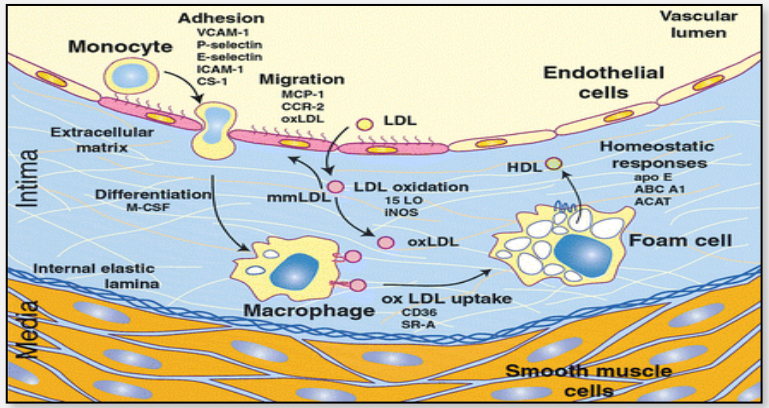
Conclusions/Messages

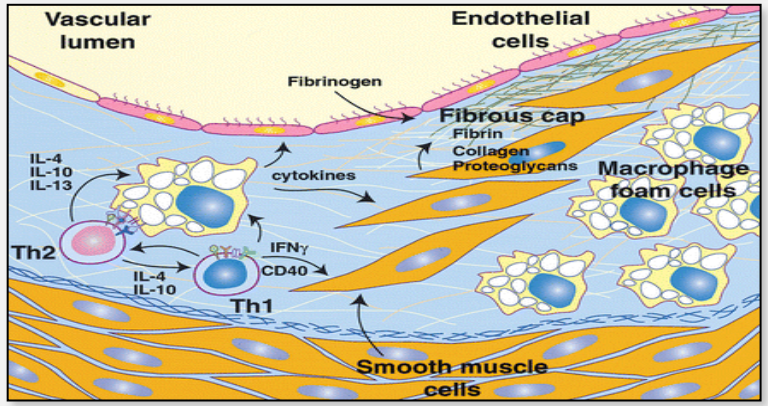


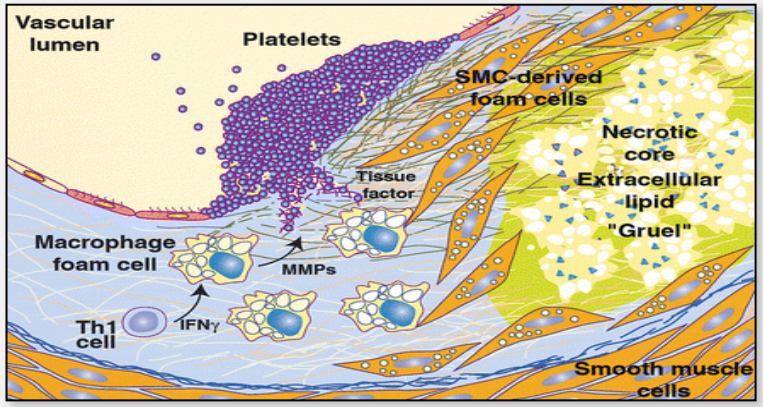


Qualité (cellulaire) des lésions bien plus que leur taille (sténose) détermine la possibilité de rupture, et donc de provoquer des symptômes cliniques.

Conclusions/Messages



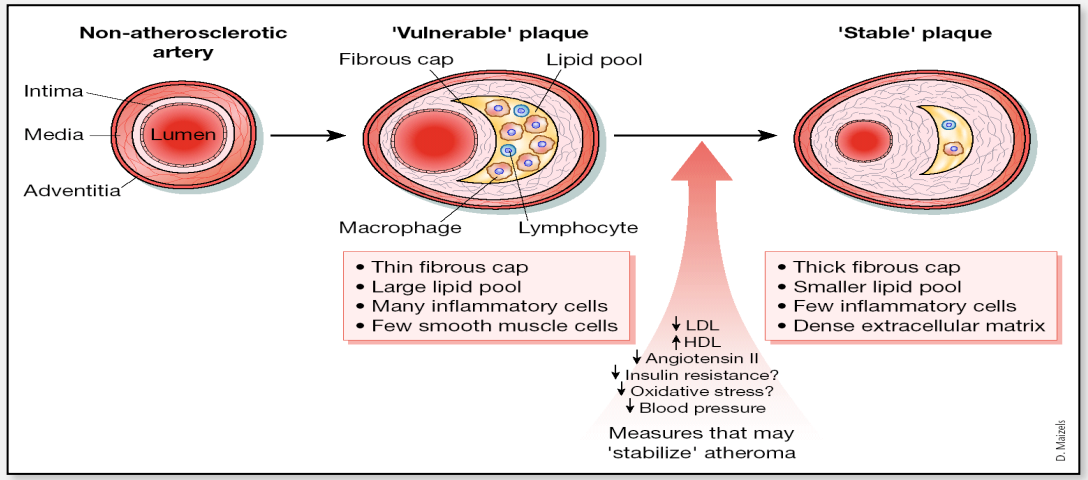




L'inflammation (via cellules & molécules) joue un rôle crucial durant toutes les étapes de l'athérosclérose.

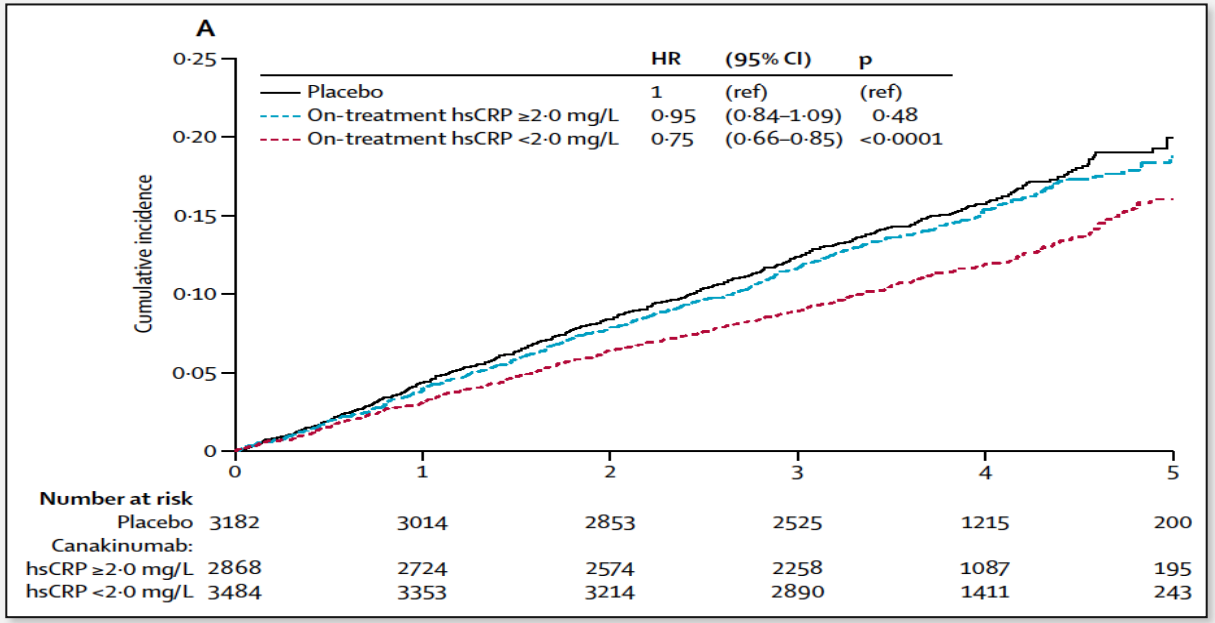
La présence de lymphocytes T et de cellules présentatrices d'antigènes (macrophages) dans l'athérome suggère une réponse immune locale à différents antigènes (oxidized-LDL).

Conclusions/Messages



La stabilisation des lésions d'athérosclérose (via l'amélioration des facteurs de risque, médicaments) diminue les risque d'événements cardiovasculaires (infarctus et accident cérébral).

Conclusions/Messages



Un traitement anti-inflammatoire, sans effet sur les lipides pourrait permettre de diminuer encore, le risque de futurs événements CV.