2010 춘계순환기학회

Inflammation in Atherosclerosis
From Experimental to Clinical Study

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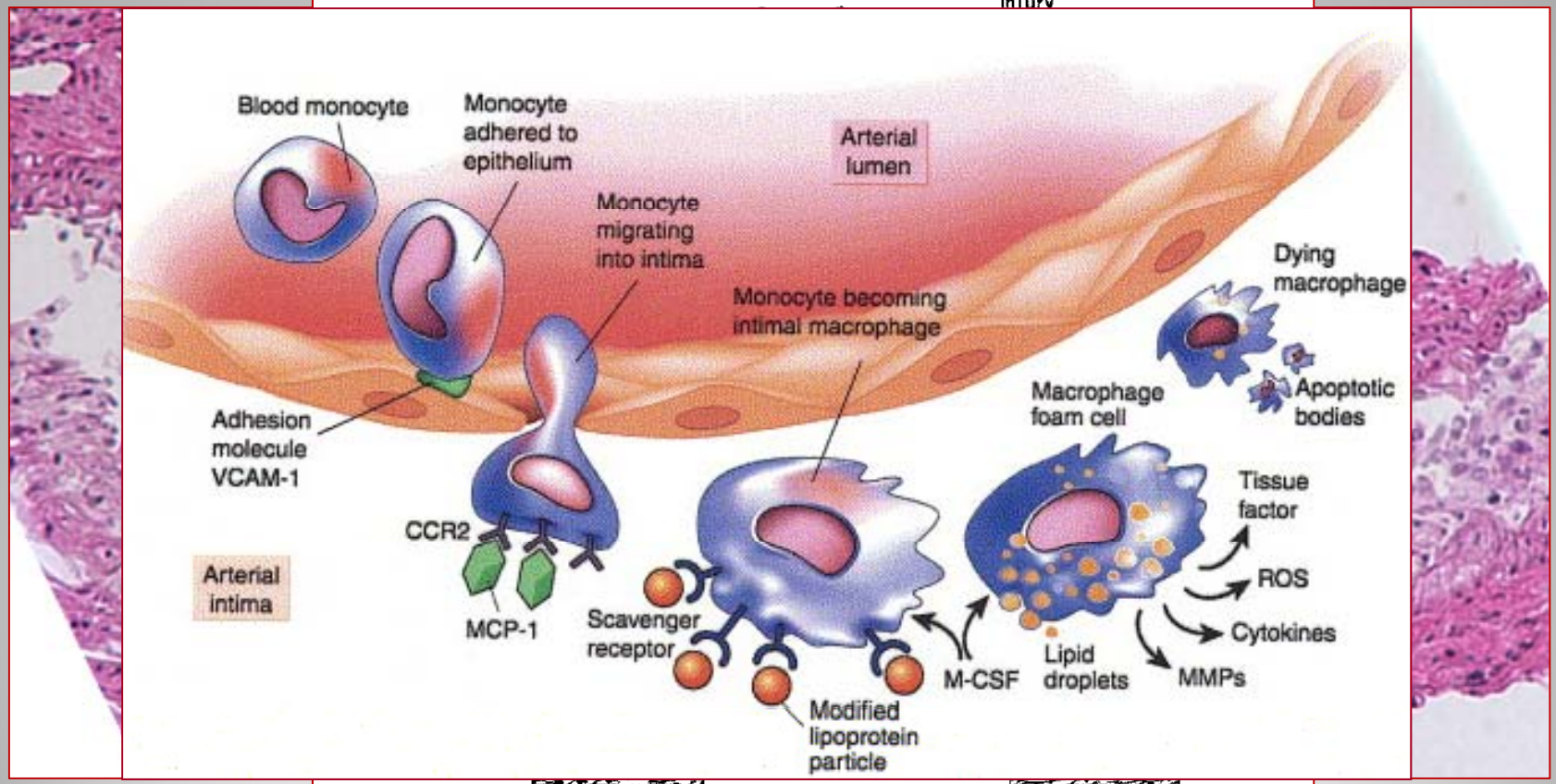
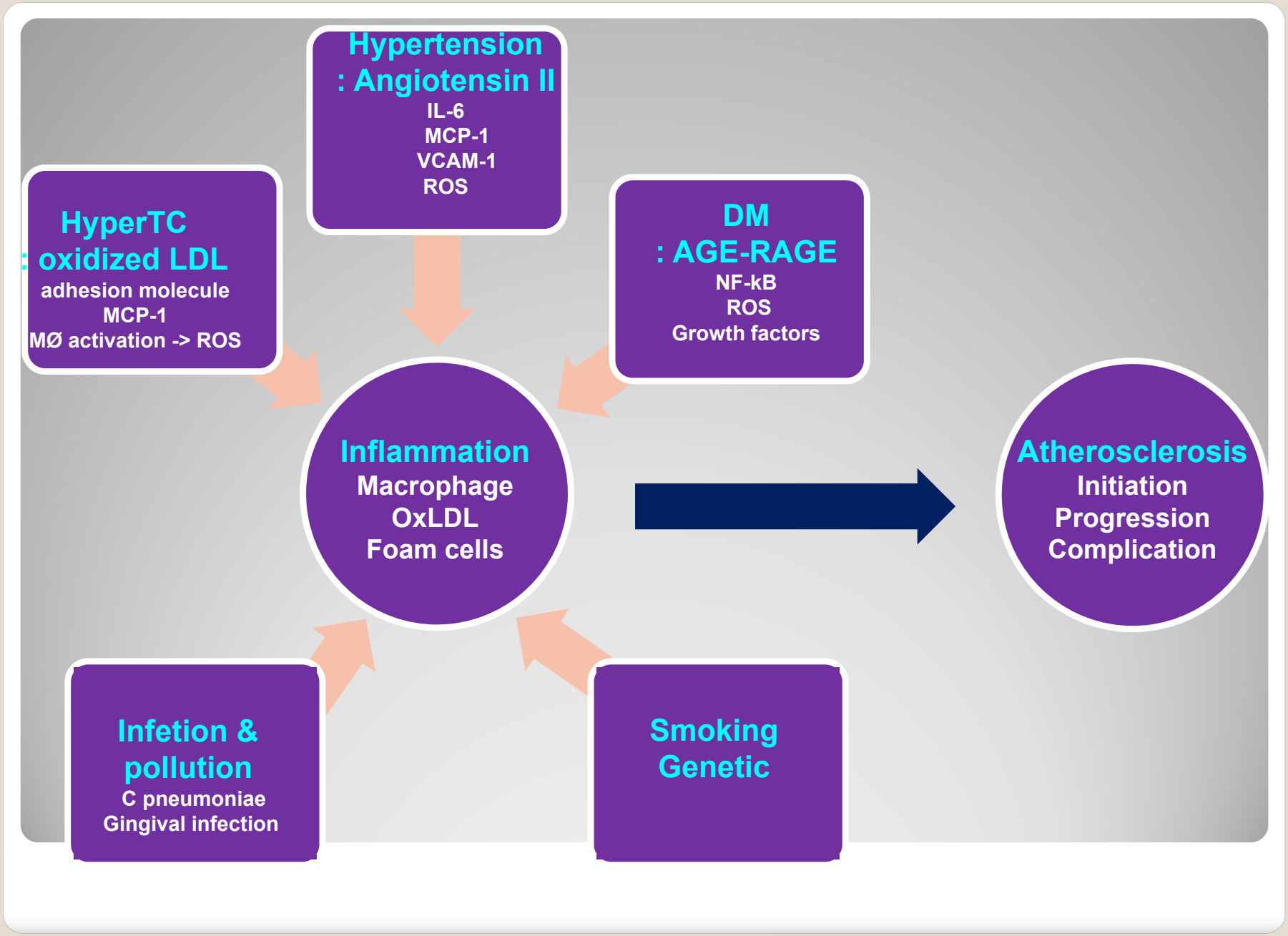
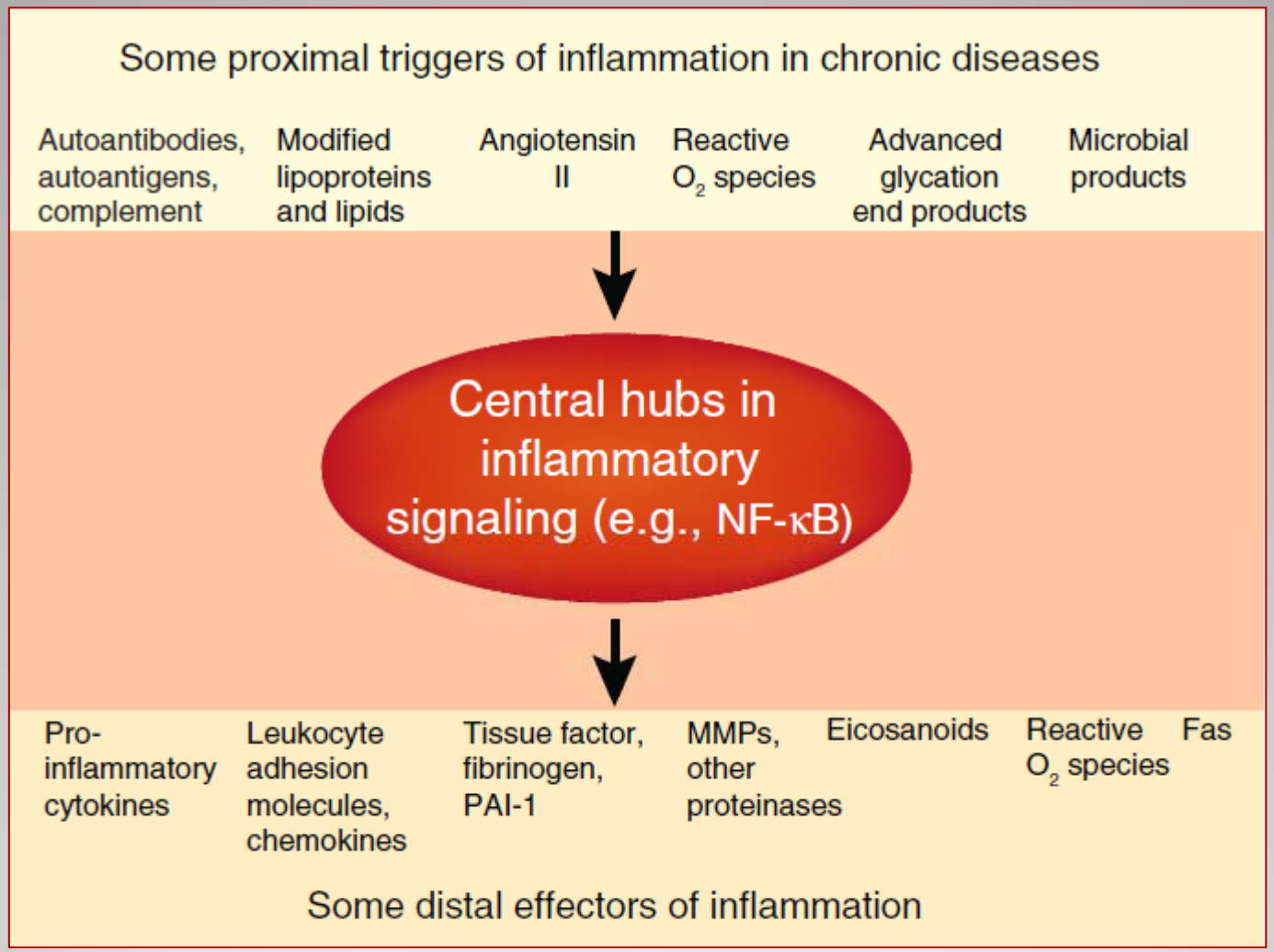
서울성모병원
순환기내과

장 기 육

Atherosclerosis & Theory evolution



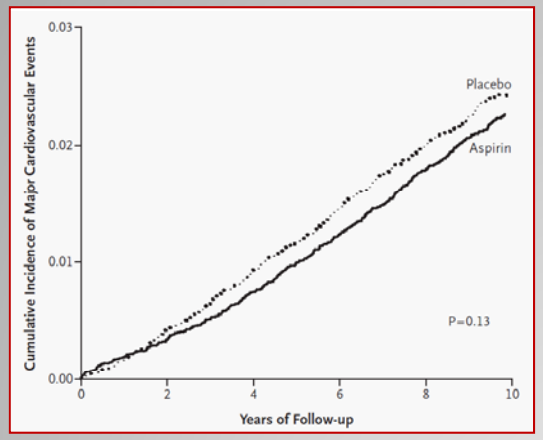

Hypertension
: Angiotensin II
IL-6
MCP-1
VCAM-1
ROS
HyperTC
: oxidized LDL
adhesion molecule
MCP-1
MØ activation -> ROS
DM
: AGE-RAGE
NF-kB
ROS
Growth factors
Inflammation
Macrophage
OxLDL
Foam cells
Atherosclerosis
Initiation
Progression
Complication
Infetion &
pollution
C pneumoniae
Gingival infection
Smoking
Genetic


Some proximal triggers of inflammation in chronic diseases
Autoantibodies, autoantigens, complement
Modified lipoproteins and lipids
Angiotensin II
Reactive O_2 species
Advanced glycation end products
Microbial products
Central hubs in inflammatory signaling (e.g., NF-κB)
Pro-inflammatory cytokines
Leukocyte adhesion molecules, chemokines
Tissue factor, fibrinogen, PAI-1
MMPs, other proteinases
Eicosanoids
Reactive O_2 species
Fas
Some distal effectors of inflammation

Clinical Translation of Inflammation from Basic Research to Clinical Practice

- Primary prevention에서 아스피린의 몰락과 스타틴의 부상
- hsCRP의 cardiovascular risk marker로서 급부상 : JUPITER
- ^{18}F FDG-PET/CT의 vascular area로의 진입
- Telmisartan : a dual-mode ARB as a RAS inhibitor
  & partial PPARγ agonist
- Long-acting niacin의 재발견

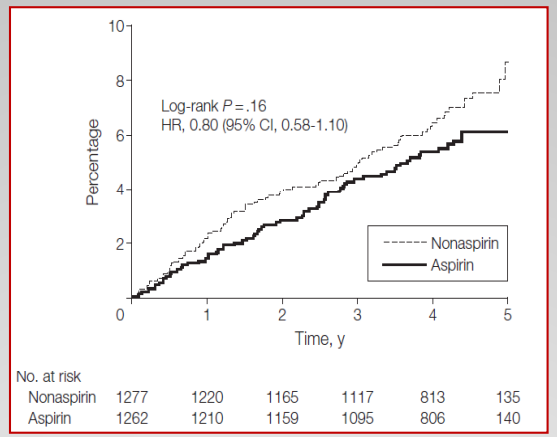
Primary Prevention Study : Aspirin



WHS (Women's Health Study)

Inclusion : healthy women > 45 years old

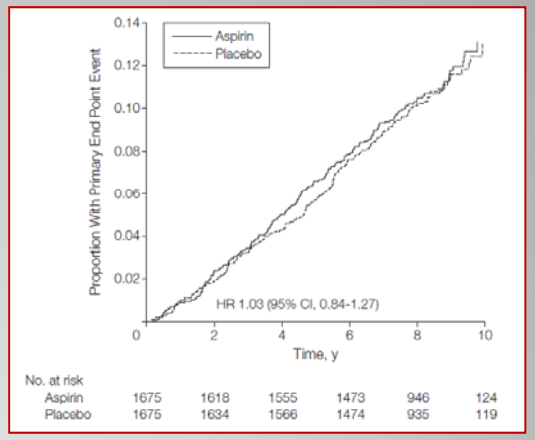
N Engl J Med 2005;1352:1293-1304



JPAD (Japanese primary prevention of atherosclerosis with asprin for diabetes)

Inclusion : type 2 diabetes without Hx of atherosclerotic disease

JAMA 2008;300:2134-2141

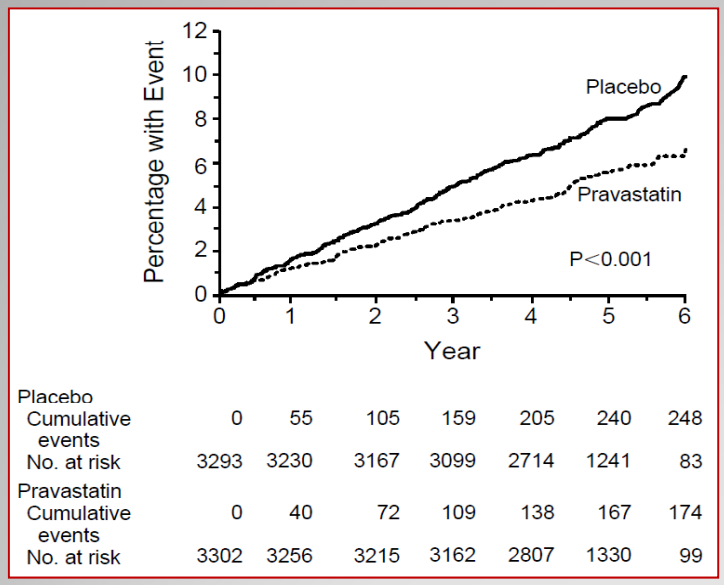


AAA (Aspirin for asymptomatic atherosclerosis)

Inclusion : persons >50 years old with a low ABI

JAMA 2010;303:841-848

Primary Prevention Study : Statin

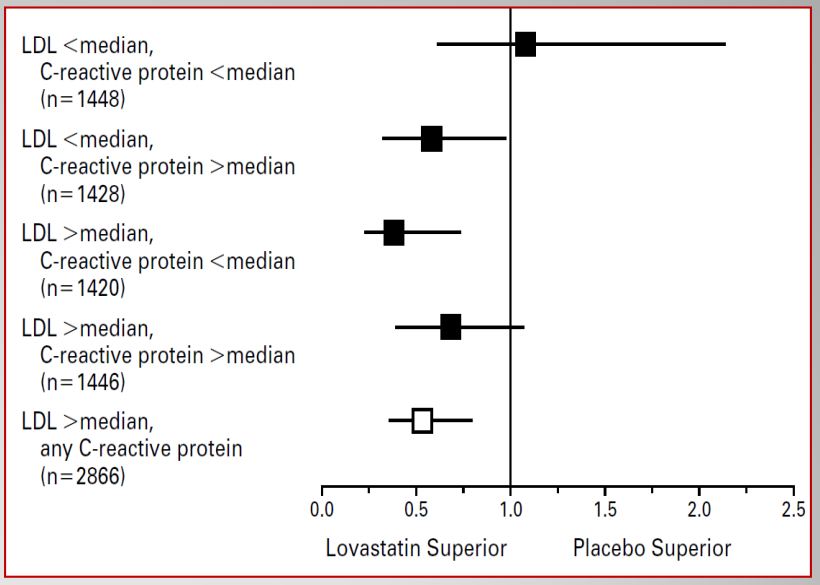


Placebo							
Cumulative events	0	55	105	159	205	240	248
No. at risk	3293	3230	3167	3099	2714	1241	83
Pravastatin							
Cumulative events	0	40	72	109	138	167	174
No. at risk	3302	3256	3215	3162	2807	1330	99

WOSCOPS (West of Scotland Coronary Prevention Study)

Inclusion : healthy men > 45 years of age With hyperTC but no MI

N Engl J Med 2005;1352:1293-1304

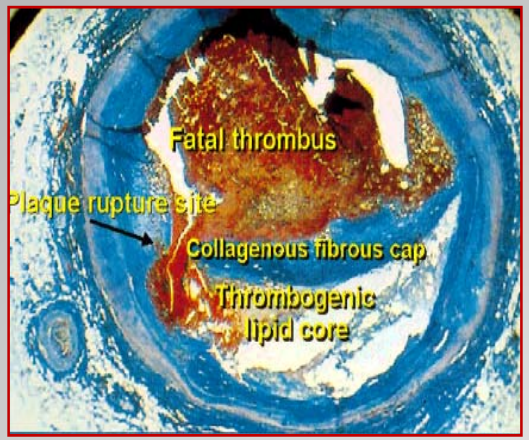


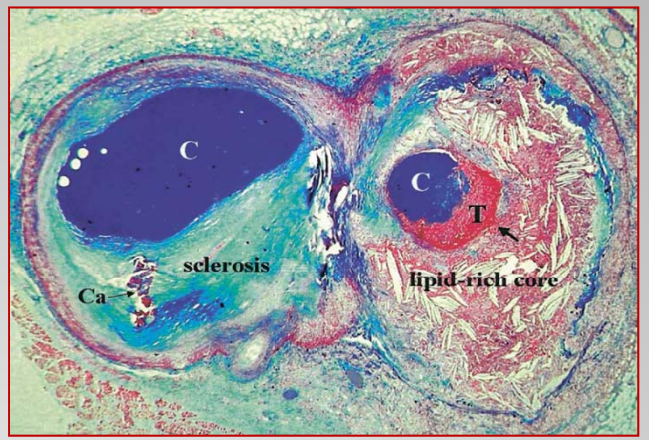
AFCAPS/TexCAPS (Airforce/Texas Coronary Atherosclerosis Prevention Study)

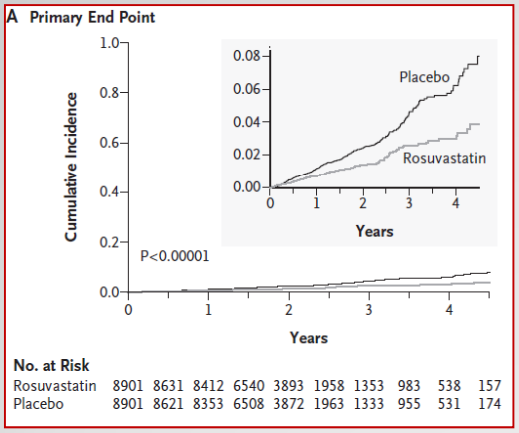
Inclusion : healthy persons > 45 years old with average level of lipid profile

N Engl J Med 2001;344:1959-1965

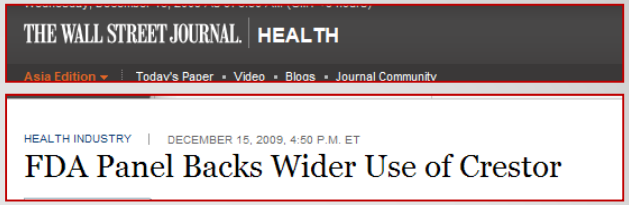
Who has vulnerable atherosclerotic plaques?





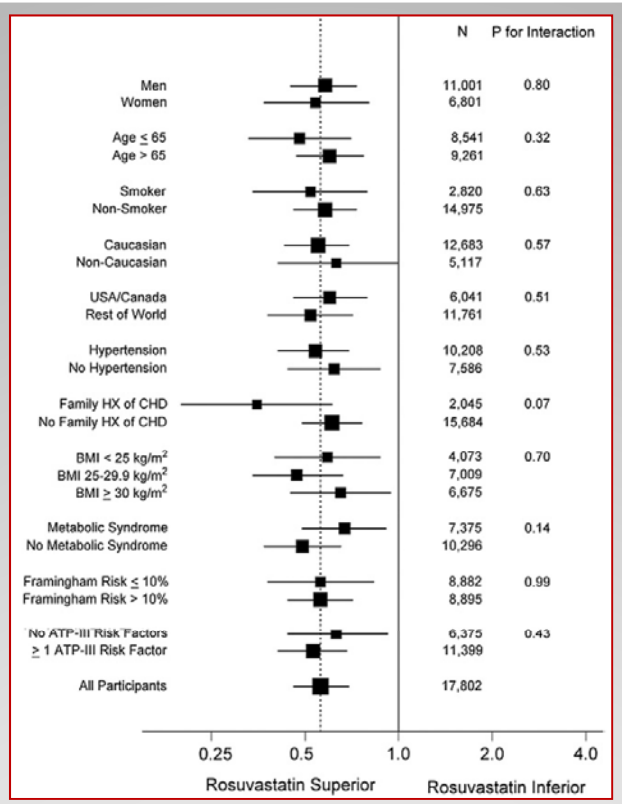


JUPITER trial, NEJM 2008

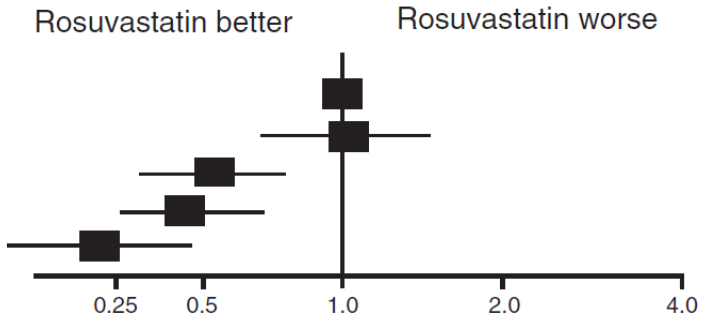


FDA approves statin for 1ary prevention

- ≥ 50 in men, ≥ 60 in women with LDL < 130 mg/dL
- **hsCRP ≥ 2 mg/L**



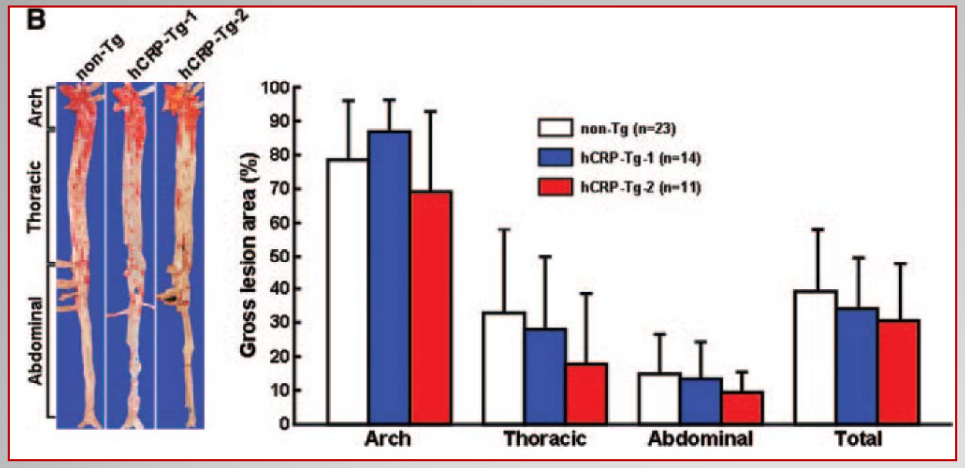
	N	Rate
Placebo	7832	1.11
LDL≥70mg/dL,hsCRP≥2 mg/L	1384	1.11
LDL<70mg/dL,hsCRP≥2 mg/L	2921	0.62
LDL≥70mg/dL,hsCRP<2 mg/L	726	0.54
LDL<70mg/dL,hsCRP<2 mg/L	2685	0.38

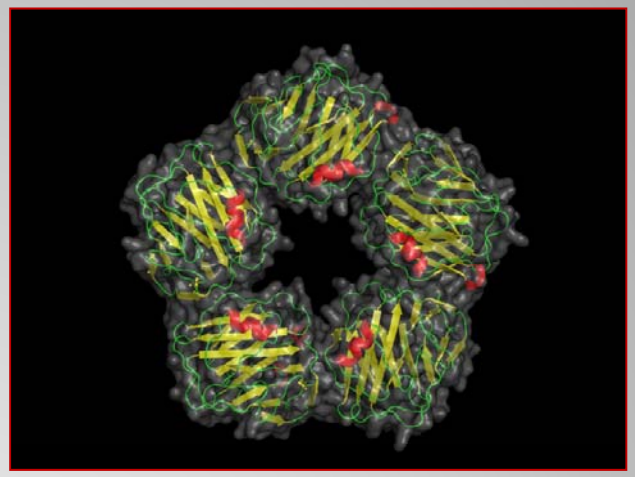


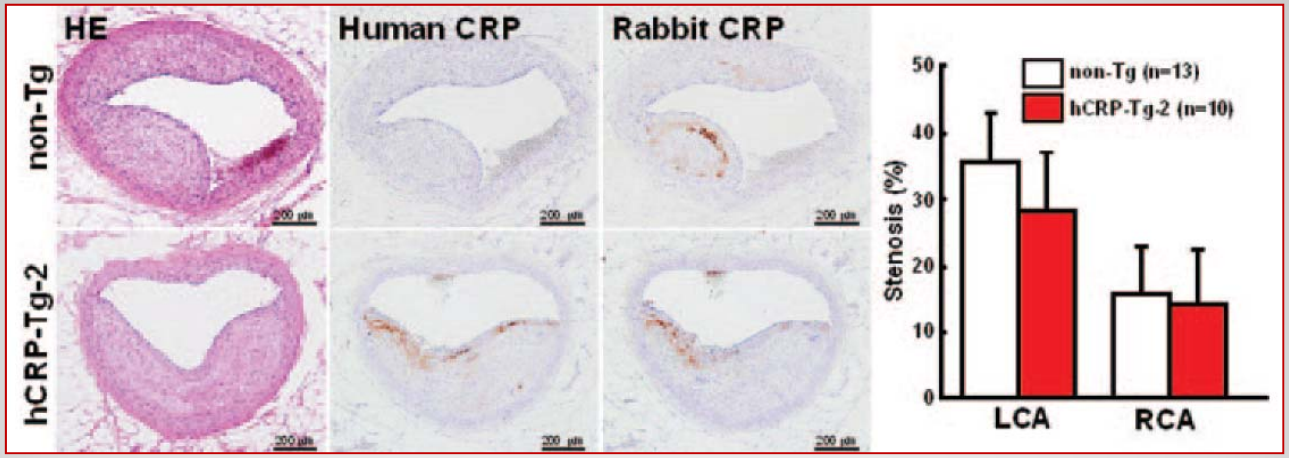
hsCRP : therapeutic target vs predictive marker

- **Does CRP promote atherosclerosis in humans?**
- **Do we have to develop CRP-lowering therapies?**
- **Do we have to treat patients with high-level of CRP?**
- **Just a reflective marker of local vascular inflammation**

Human CRP does not promote atherosclerosis in transgenic rabbits

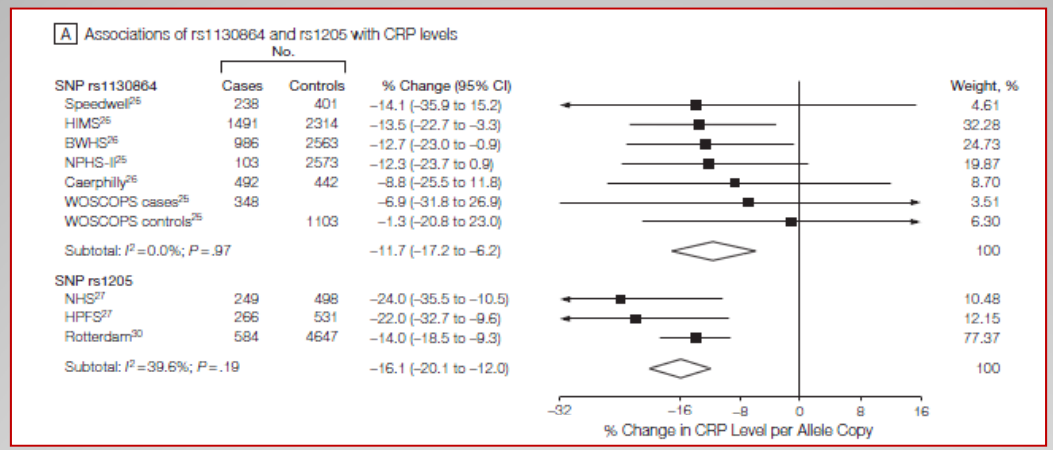


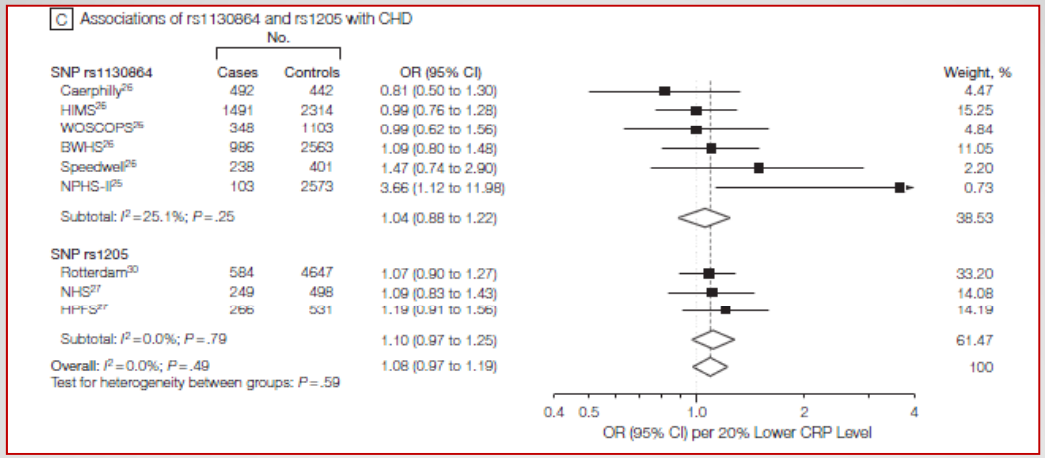




Koike T et al, Circulation 2009;120:2088-2094

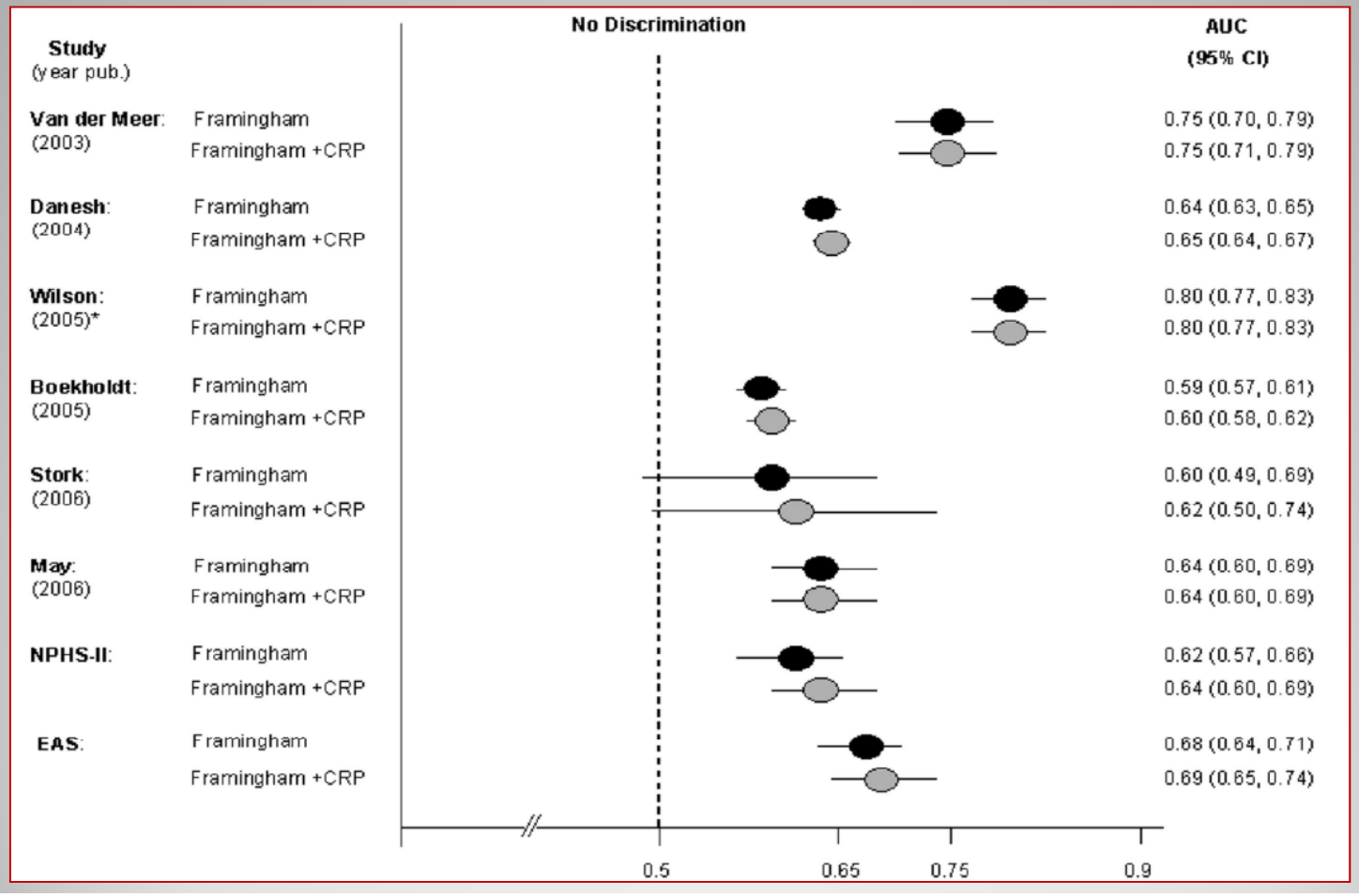
The lack of concordance between the effect on CHD risk of CRP genotypes and CRP levels argues against a causal association of CRP with CHD



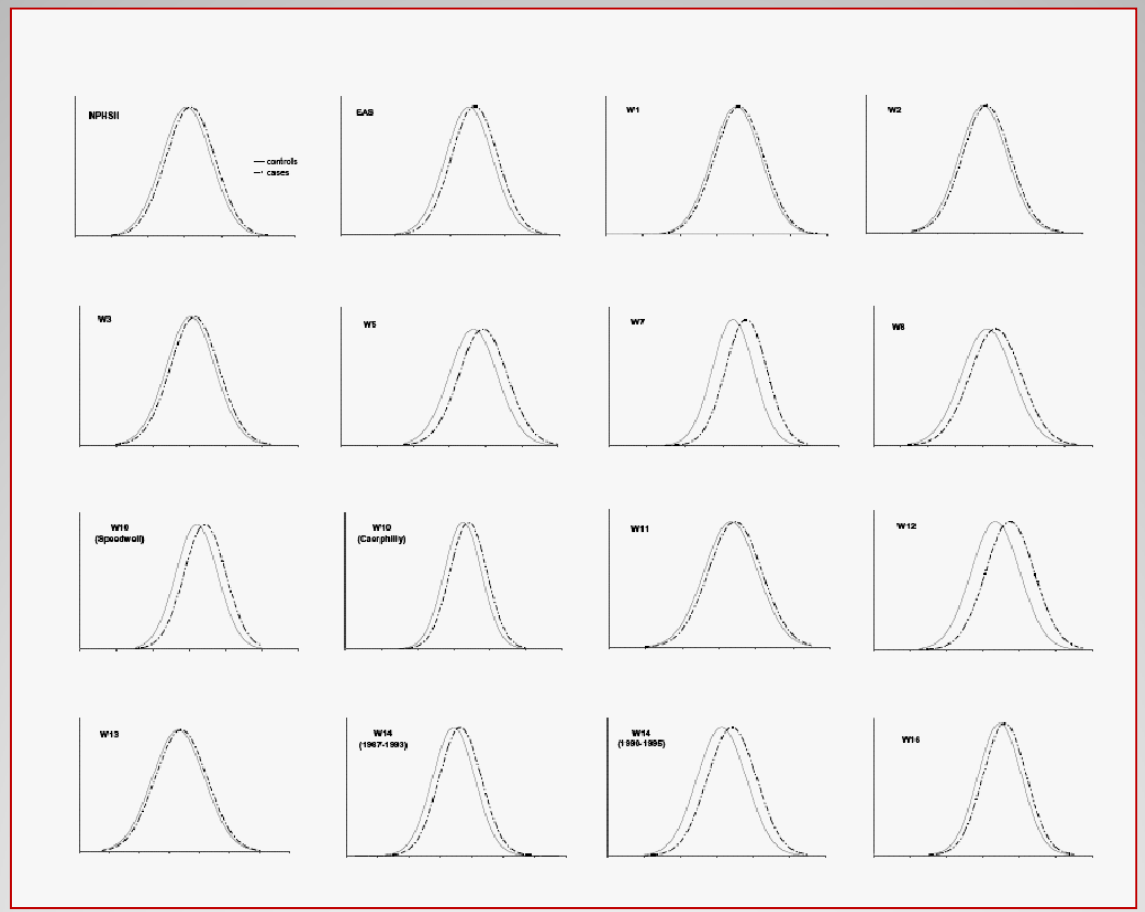


Elliott P et al, JAMA 2009;302:37-48

The addition of CRP to Framingham risk equation models has limited discrimination ability



Frequency distributions of log-CRP values among incident cases (dashed line) and controls (solid line)

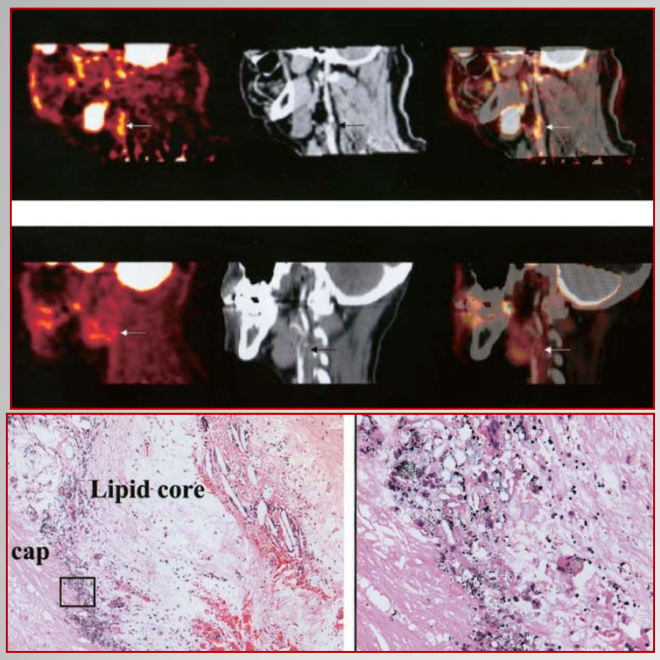


Reynolds Risk Score

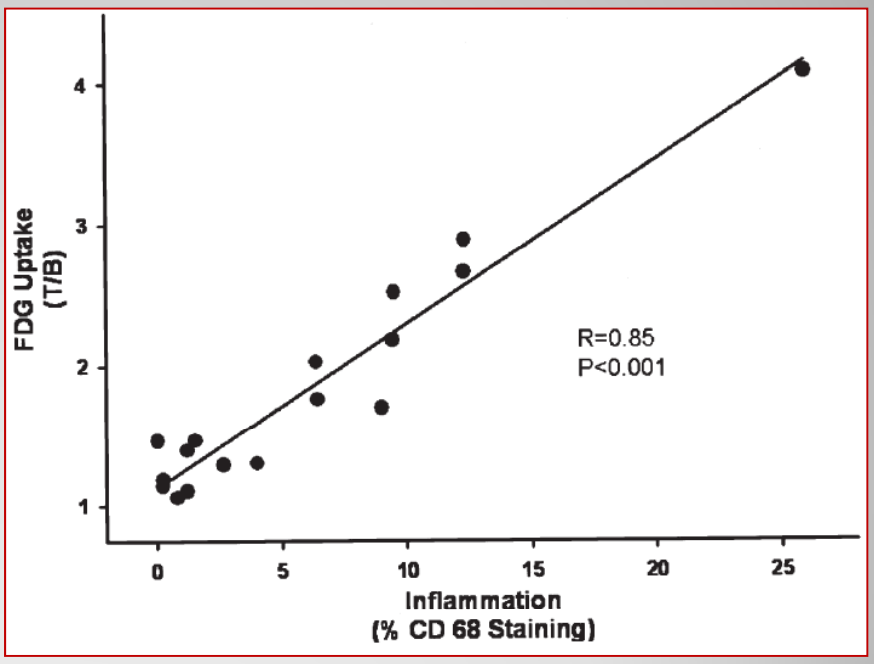
- Age
- Systolic blood pressure
- Total cholesterol
- HDL-cholesterol
- Smoker
- hsCRP
- Parental history of MI before age 60 y

^{18}F-FDG PET/CT

The only potential tool to image, track, quantify vascular inflammation & the response to anti-atherosclerosis therapy in humans

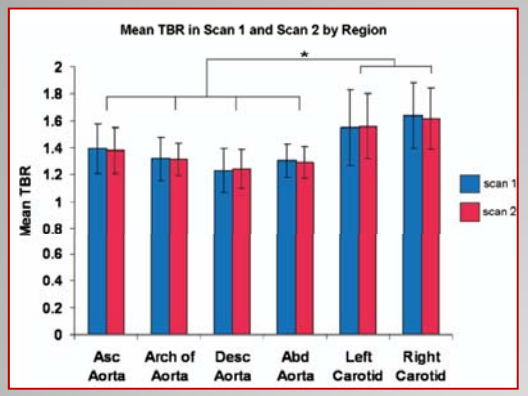


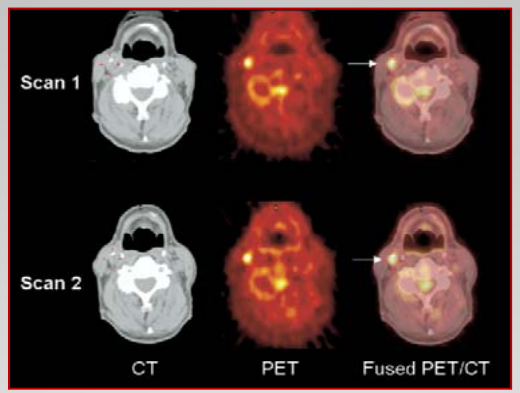
Circulation 2002;105:2708-11

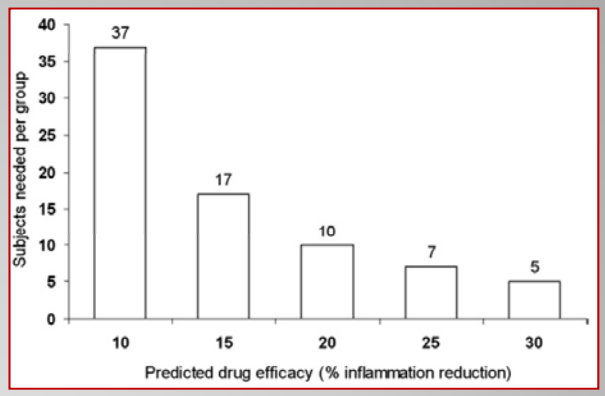


J Am Coll Cardiol 2006;48:1818-24

Current Limitation & Future Role of ^{18}F-FDG PET/CT in Atherosclerosis







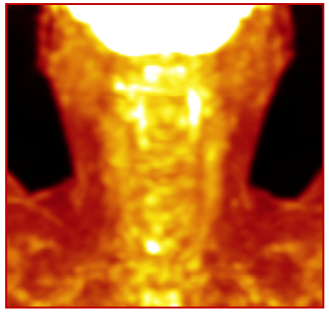
J Am Coll Cardiol 2007;50:892-6

- Low variability in plaque FDG uptake changes (carotid plaque)
  - Useful as an imaging biomarker for monitoring pharmacological intervention
  - Less number of sample size required when evaluating drug effects

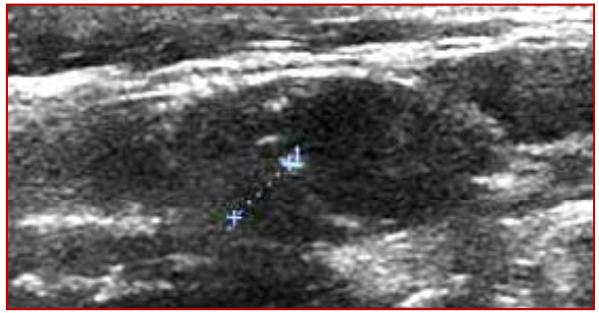
Current Limitation of ^{18}F-FDG PET/CT in Atherosclerosis

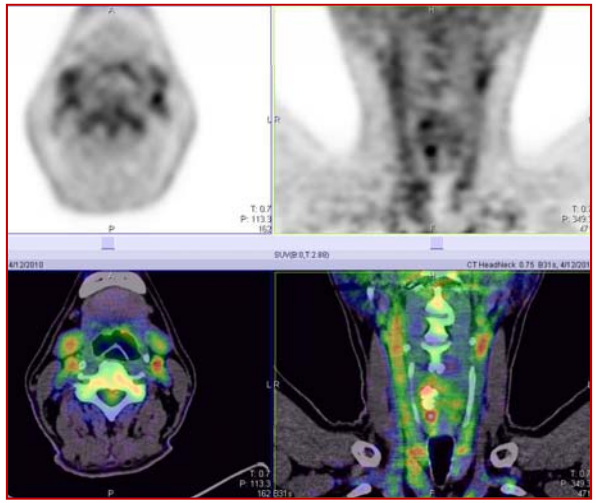
- Lack of natural uptake stability over a longer period
- Lack a reliable quantification method of vascular FDG uptake
- Lack of a large prospective study of vascular ^{18}F-FDG PET/CT in patients without cancer

Discrepancy between structure & inflammation imaging

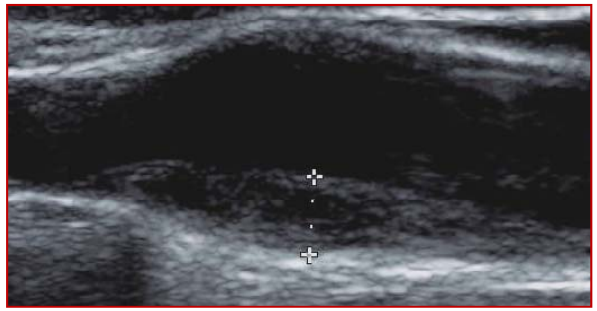


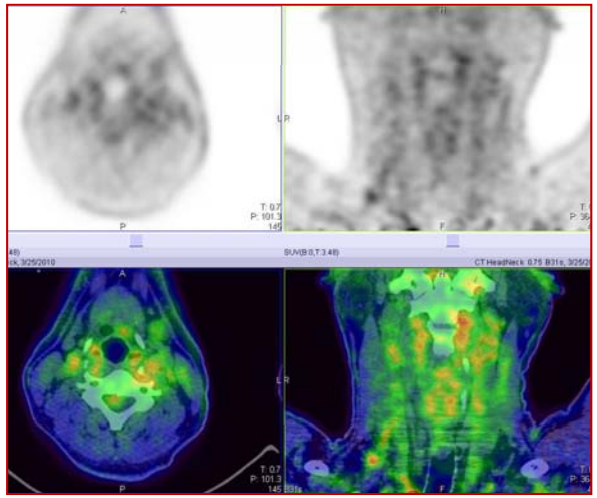
Highly inflamed plaque



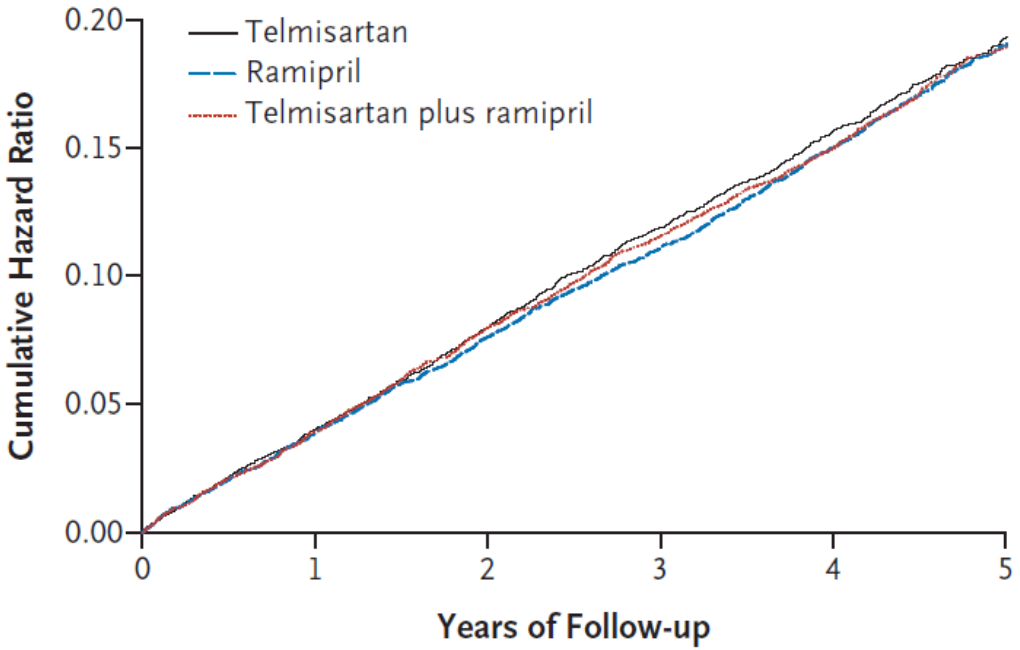


Less inflamed plaque



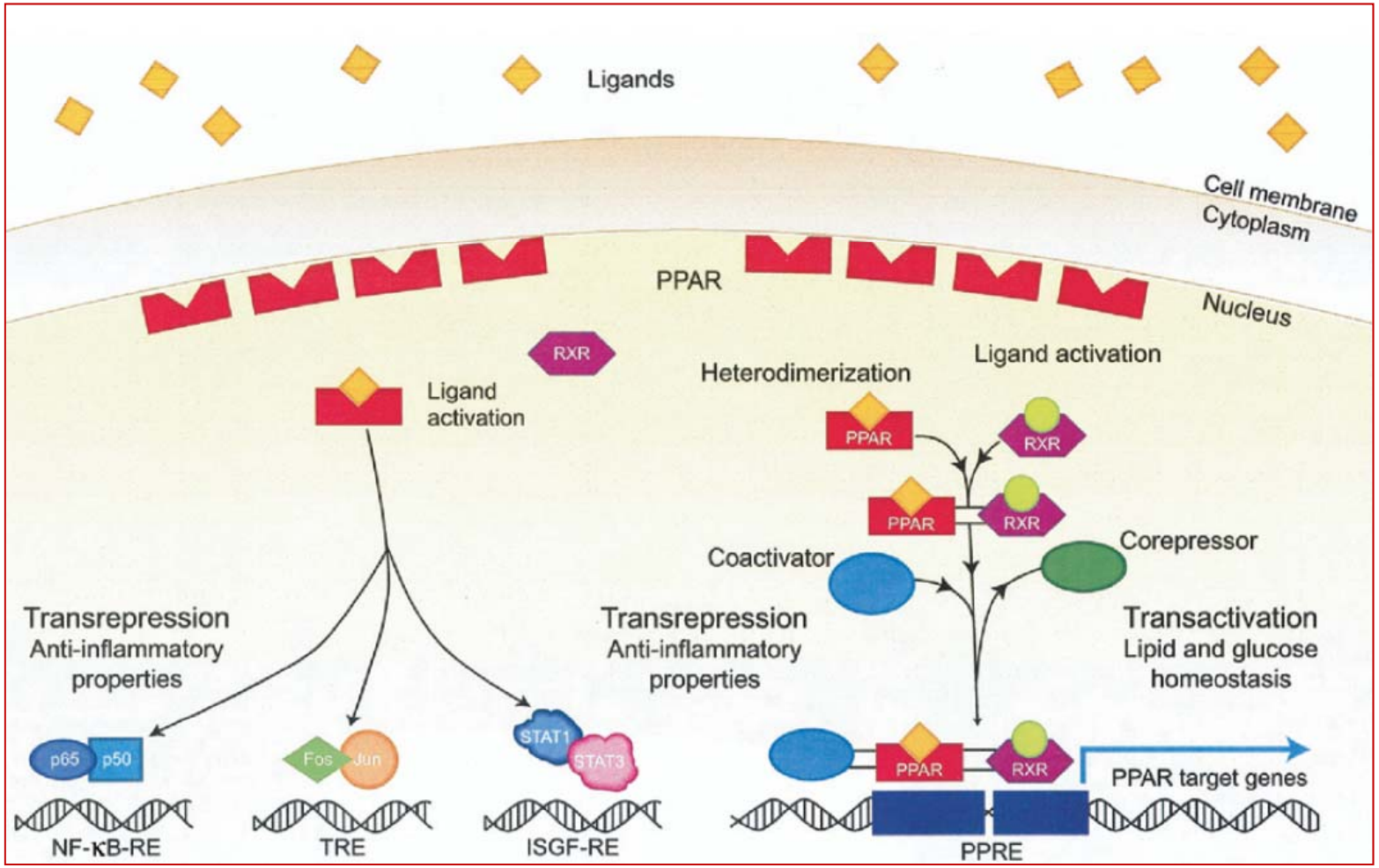


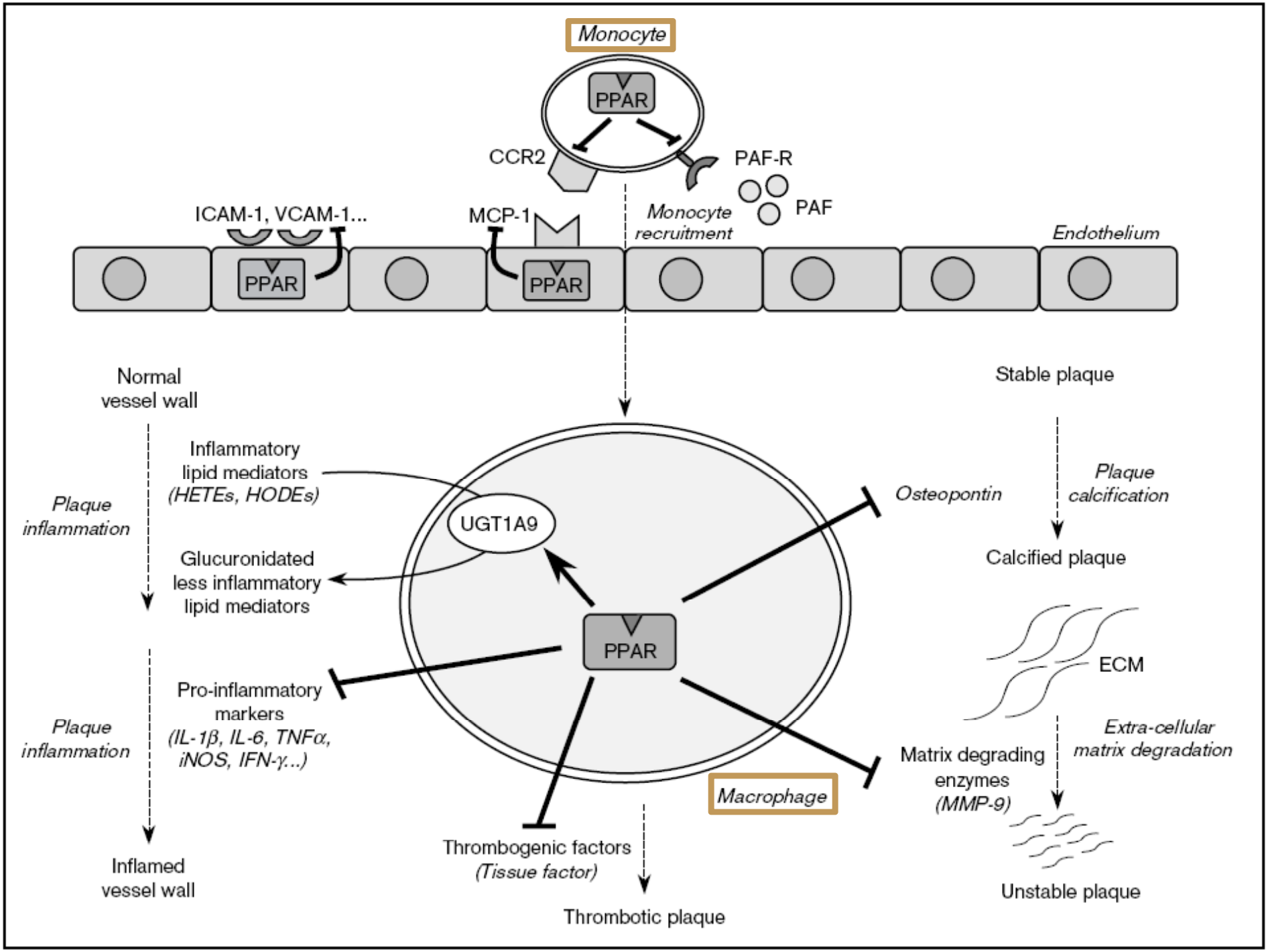
ONTARGET trial : Telmisartan



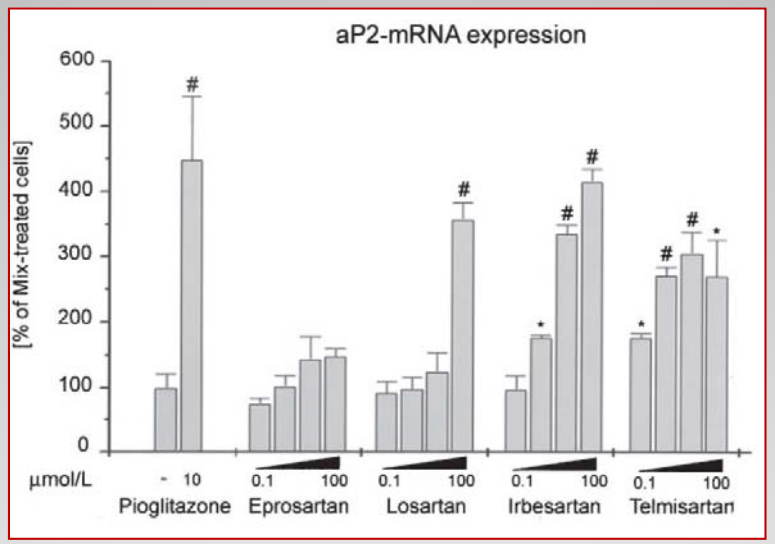
No. at Risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

PPAR-γ & vascular inflammation




Monocyte
PPAR
CCR2
PAF-R
PAF
ICAM-1, VCAM-1...
MCP-1
Monocyte recruitment
Endothelium
PPAR
PPAR
Normal vessel wall
Stable plaque
Inflammatory lipid mediators (HETEs, HODEs)
Plaque inflammation
UGT1A9
Osteopontin
Plaque calcification
Glucuronidated less inflammatory lipid mediators
Calcified plaque
PPAR
ECM
Pro-inflammatory markers (IL-1β, IL-6, TNFα, iNOS, IFN-γ...)
Plaque inflammation
Extra-cellular matrix degradation
Matrix degrading enzymes (MMP-9)
Macrophage
Thrombogenic factors (Tissue factor)
Inflamed vessel wall
Thrombotic plaque
Unstable plaque

Dual mode of action : RAS inhibitor & partial PPARγ agonist

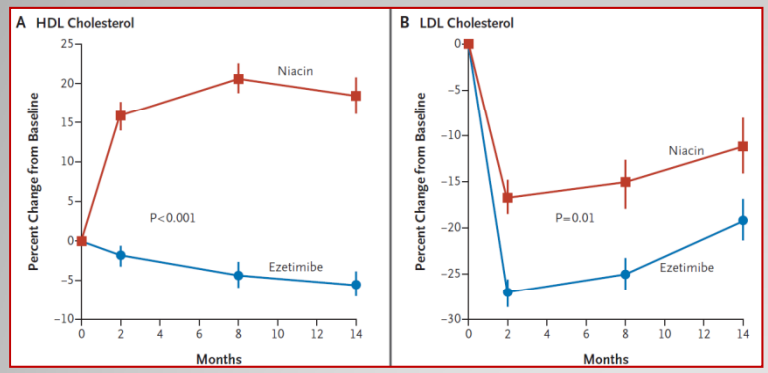


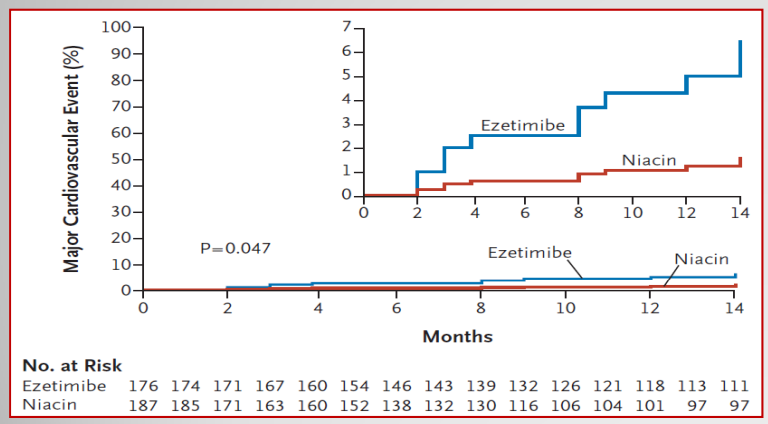
- PPAR-γ activation at clinical dose of TERT
- No fluid retention : PPAR-γ activation of collecting duct
  - partial activation of PPAR-γ
  - attenuation of salt & water retention via RAS inhibtion

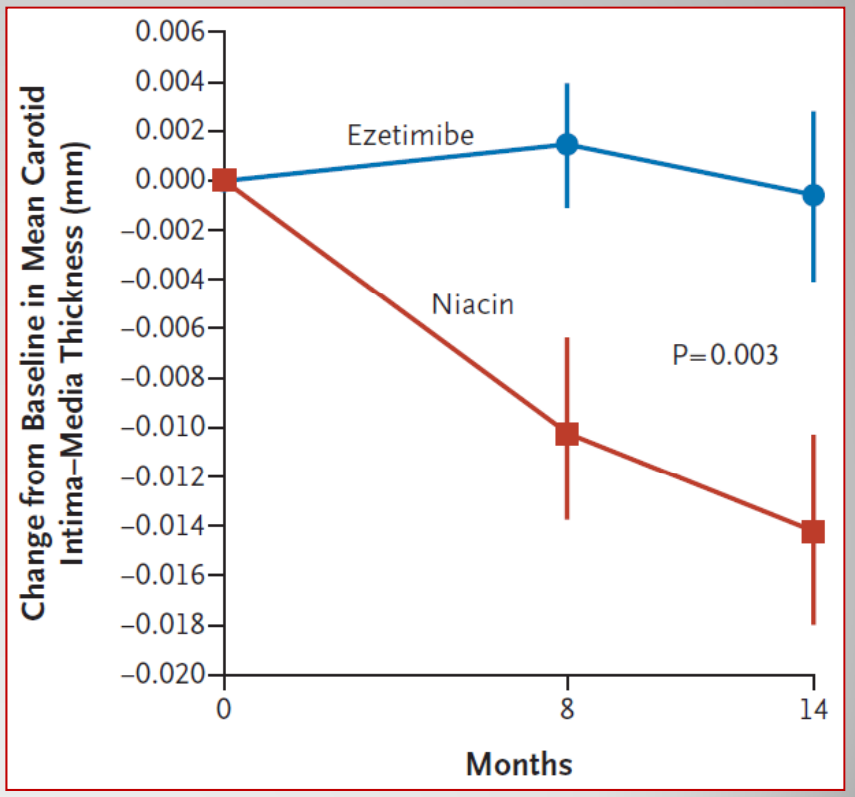
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 26, 2009 VOL. 361 NO. 22

Extended-Release Niacin or Ezetimibe and Carotid Intima–Media Thickness



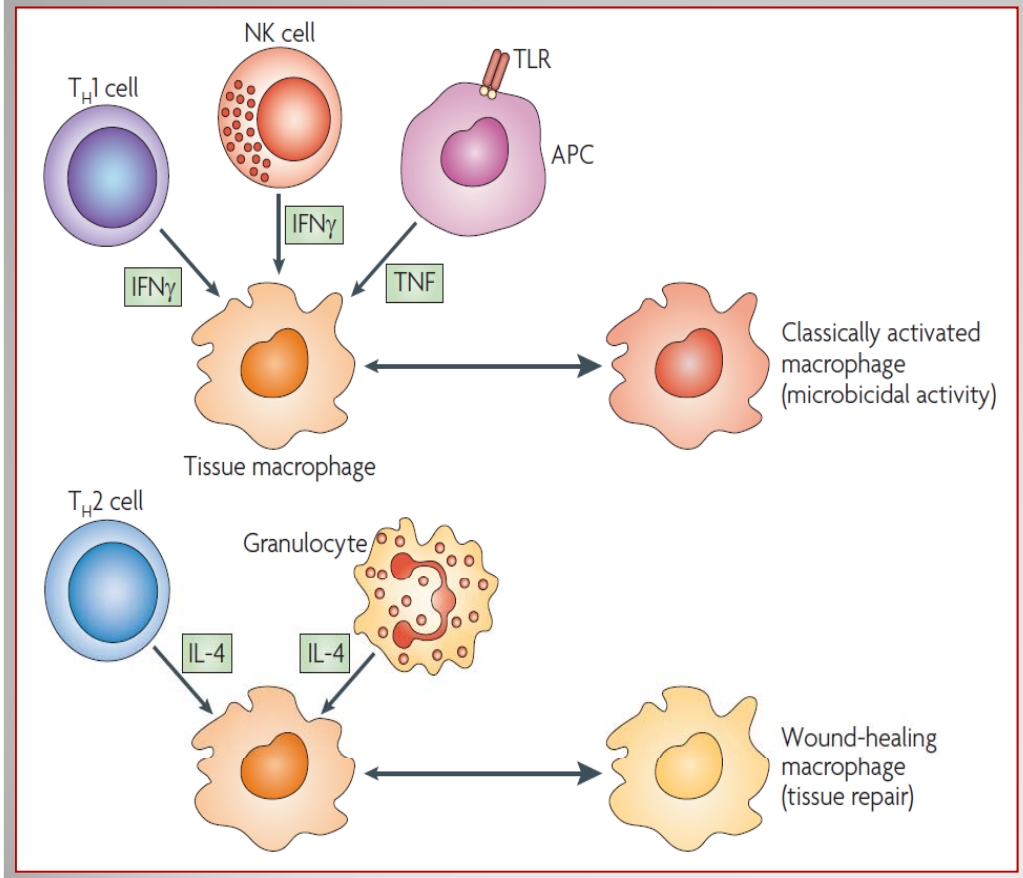


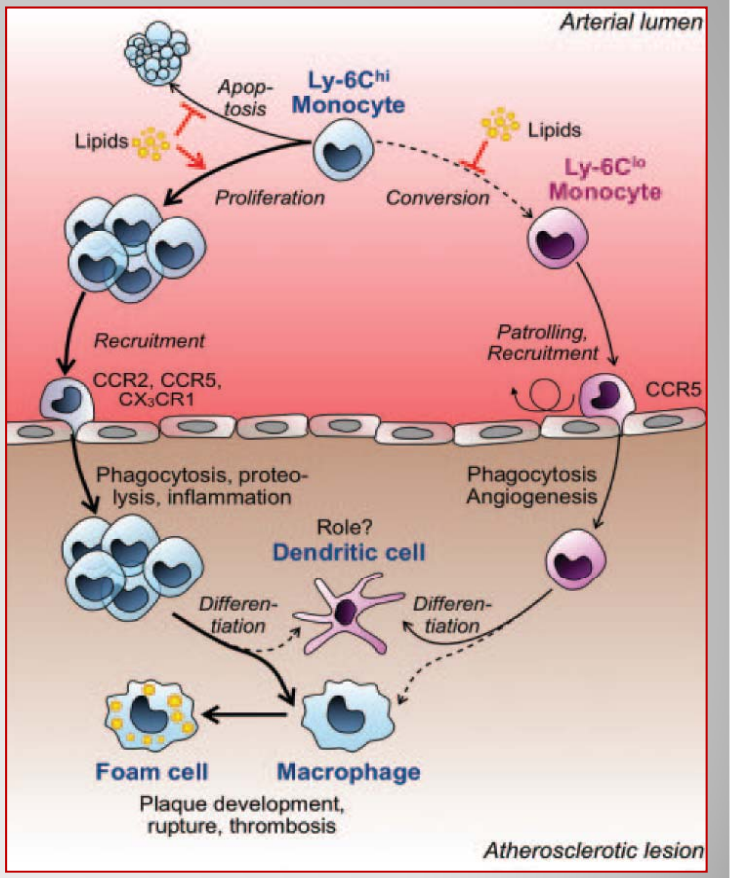


정리

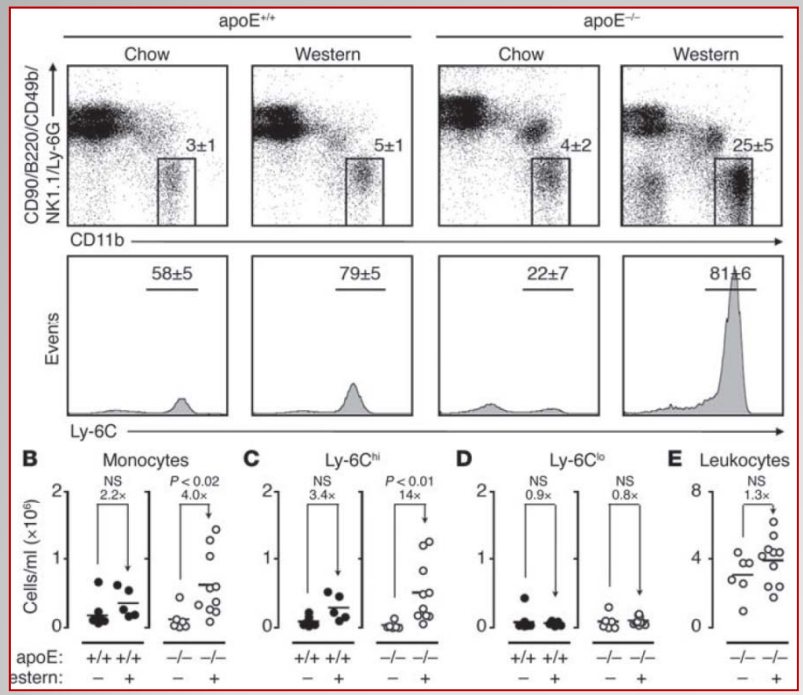
- Primary prevention에서 아스피린의 몰락과 스타틴의 부상
- hsCRP의 cardiovascular risk marker로서 급부상 : JUPITER
- 18F FDG-PET/CT의 vascular area로의 진입
- Telmisartan : a dual-mode ARB as a RAS inhibitor
  & partial PPARγ agonist
- Long-acting niacin의 재발견

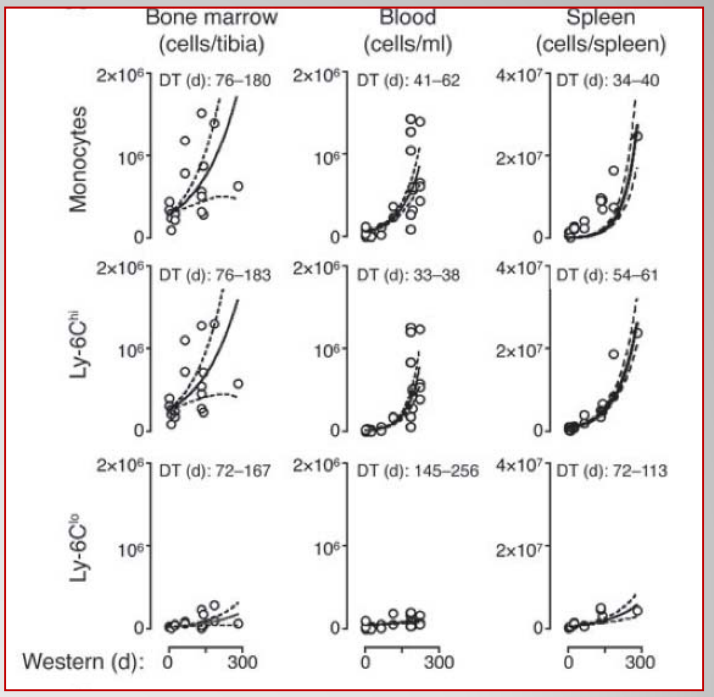
Monocyte/Macrophage Heterogeneity: M1 vs M2





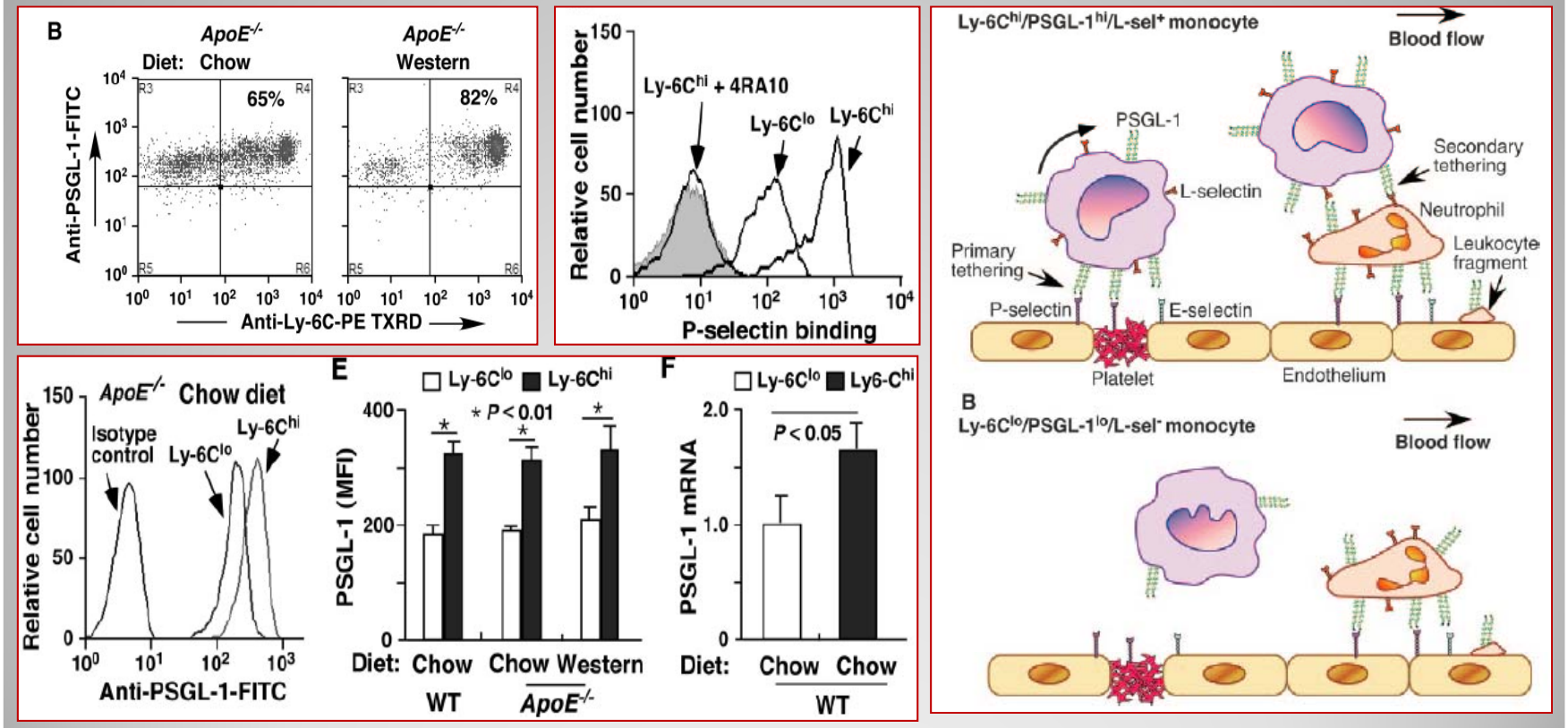
Ly-6C^{hi} (M1) monocytes dominate hypercholesterolemia-associated monocytosis and give rise to macrophages in atheromata





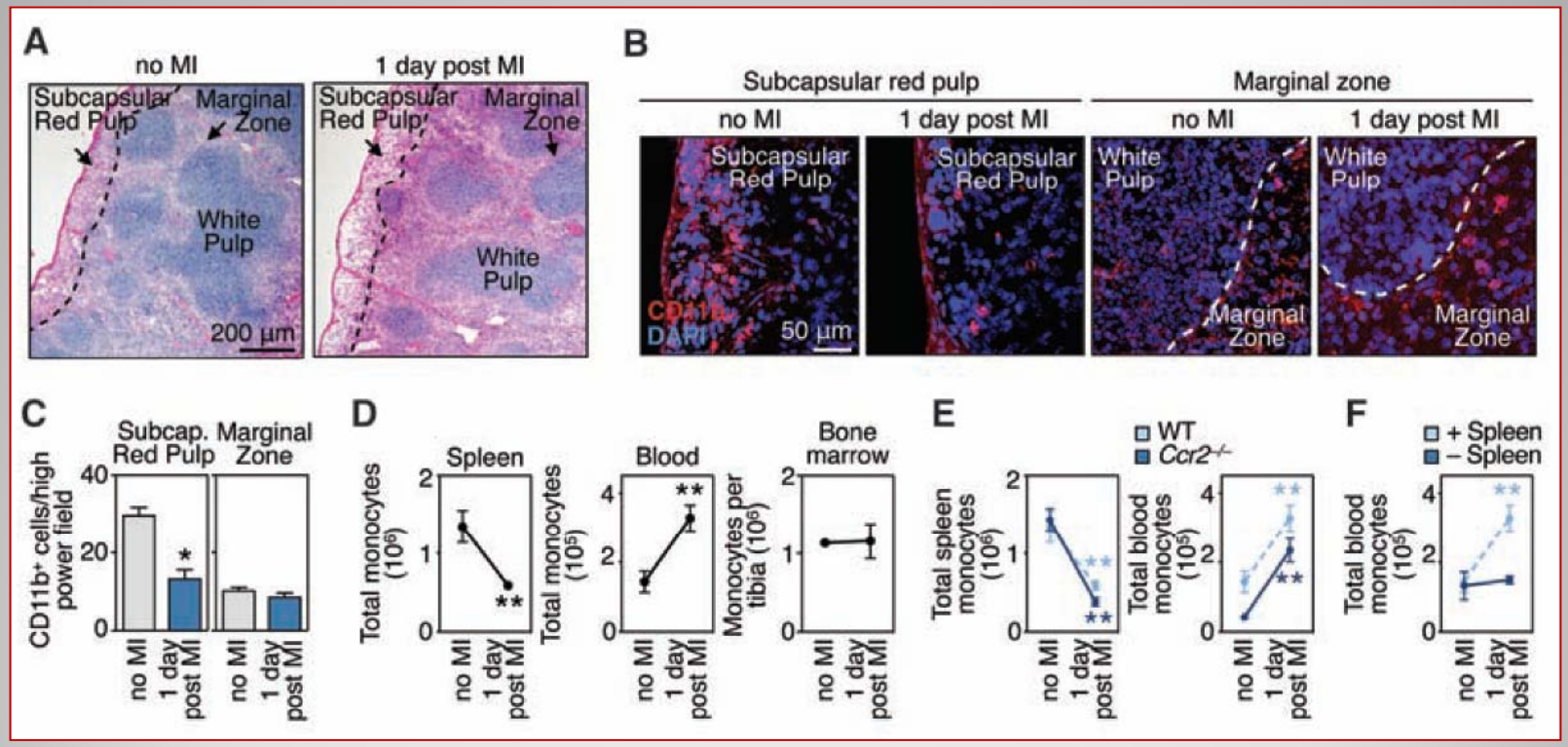
Swirski FK, et al. J Clin Invest 2007;117:195-205

P-selectin glycoprotein ligand-1 is highly expressed on Ly-6C^{hi} (M1) monocytes and a major determinant for Ly-6C^{hi} monocyte recruitment to sites of atherosclerosis in mice



An G, et al. Circulation 2008;117:3227-37.

Spleen is a reservoir of monocytes and rapidly deploy monocytes to inflammatory sites



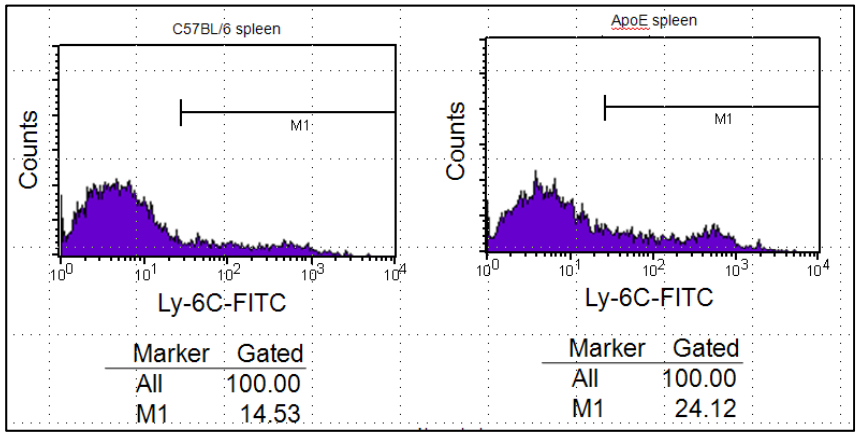
Swirski FK, et al. Science 2009;325:612-616

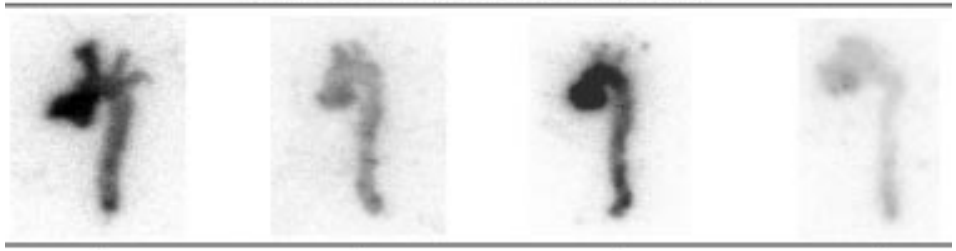
정리

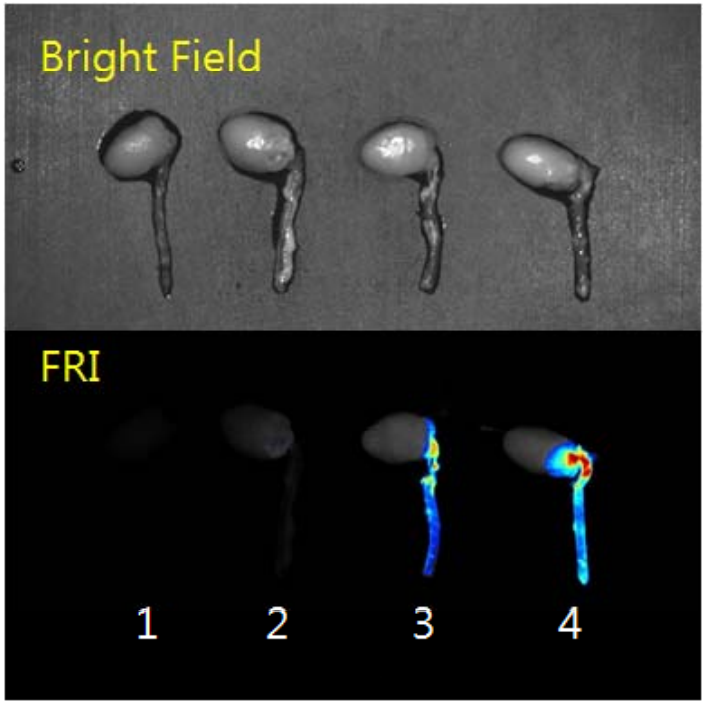
- Hypercholesterolemia increase the reservoir of Ly-6C^{hi} (M1) monocytes which produce proinflammatory cytokines and higher levels of PSGL-1 in spleen -> peripheral blood, accumulate in atherosclerotic plaques and rapidly become lesional macrophages

- What is a role of M2 monocytes in the pathogenesis of atherosclerosis?

Cell tracking experiment in atherosclerosis







Conclusion

- The recent clinical application of advances in the biology of atherosclerosis to clinical practices has provided hsCRP as a new risk marker, 18F FDG-PET/CT as a vascular inflammation monitoring tool, and telmisartan & niacin as an another class of anti-atherosclerosis therpy.

- Monocyte heterogeneity in atherosclerosis will be a novel area of atherosclerosis research to give insights into more clear understanding of vascular inflammation

감사합니다.