Coronary Artery Disease in Diabetes

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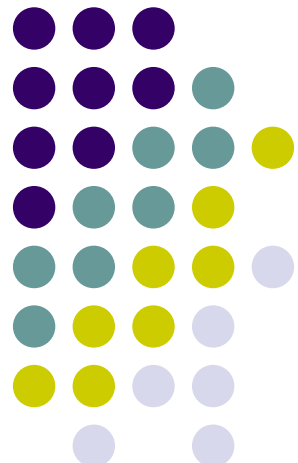
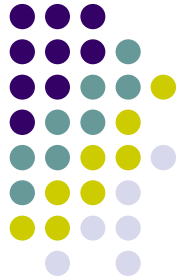
이무용



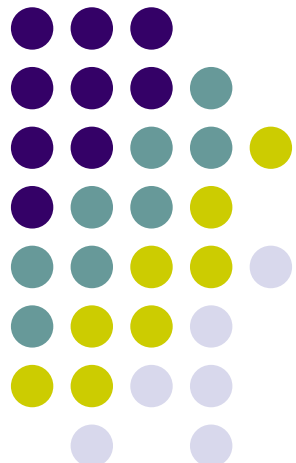
Coronary artery disease in diabetes



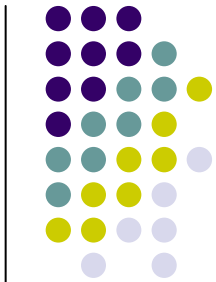
- Cardiovascular disease is the leading cause of death (complications of coronary artery disease)
- Poor hospital and long term mortality in coronary artery disease
- Adverse clinical outcomes following both percutaneous and surgical revascularization

Past

PTCA vs. CABG

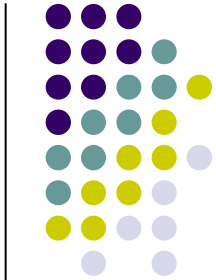


PTCA vs. CABG Trials



- Bypass Angioplasty Revascularization Investigation (BARI)
- Coronary Angioplasty Versus Bypass Revascularization Investigation (CABRI)
- Emory Angioplasty Versus Surgery Trial (EAST)
- Arterial Revascularization Therapy Study (ARTS)

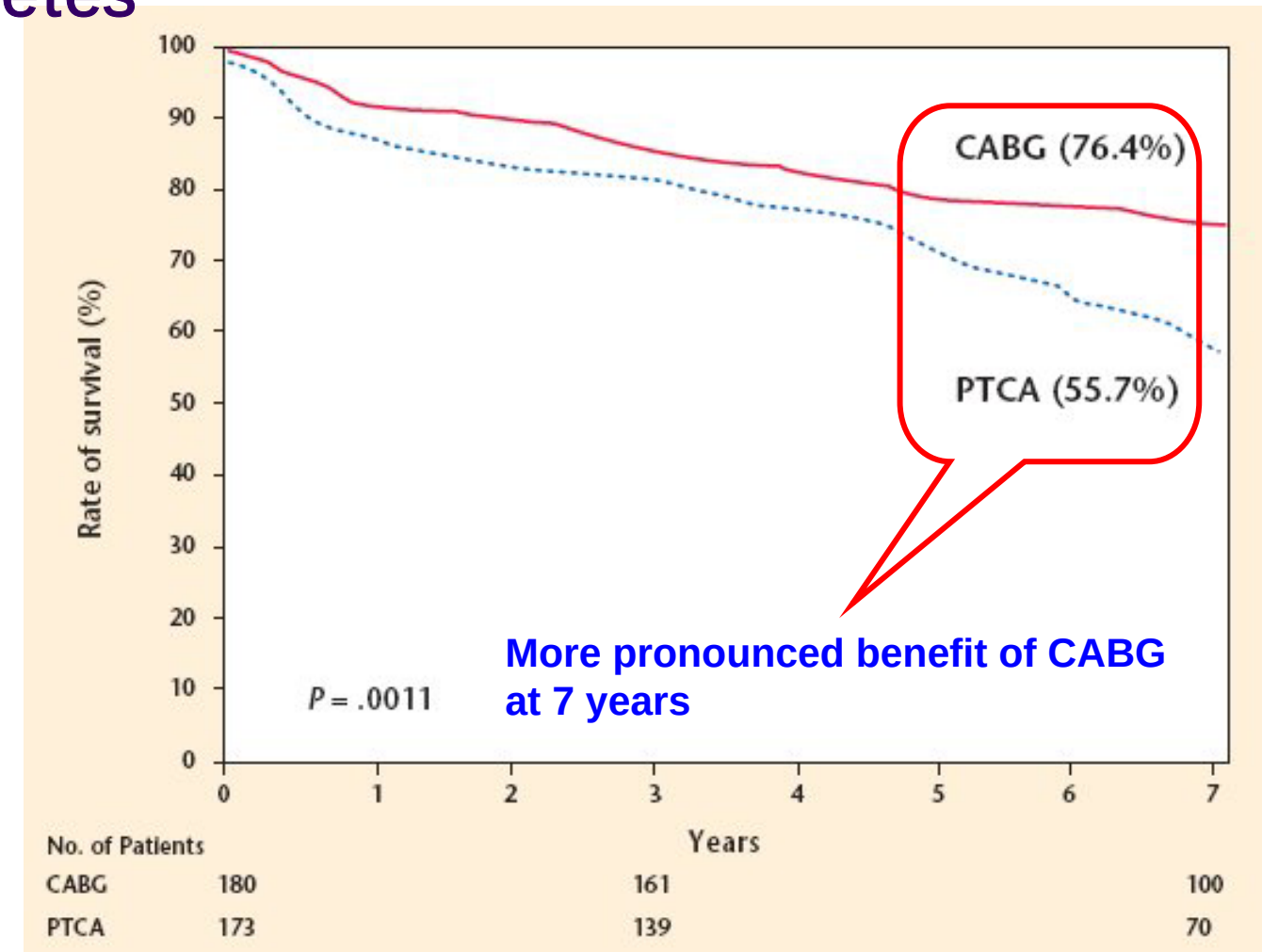
Bypass Angioplasty Revascularization Investigation (BARI) : 5 year mortality and morbidity



	Treated for Diabetes		All Others	
Cause of Death	**PTCA (n=170)**	**CABG (n=173)**	**PTCA (n=734)**	**CABG (n=719)**
Cardiac, n (%)	**35 (20.6)**	**10 (5.8)**	**35 (4.8)**	**34 (4.7)**
Noncardiac, n (%)				
Related to atherosclerosis	6 (3.5)	6 (3.5)	3 (0.4)	6 (0.8)
Medical	13 (7.6)	13 (7.5)	28 (3.8)	26 (3.6)
Suicide/accident/other, n (%)	1 (0.6)	2 (1.2)	0 (0)	3 (0.4)
Unclassifiable, n (%)	4 (2.4)	2 (1.2)	4 (0.5)	5 (0.7)
Total, n (%)	59 (34.7)	33 (19.1)	70 (9.5)	74 (10.3)

Circulation 1997;96:1761-1769

Bypass Angioplasty Revascularization Investigation (BARI) : 7 year outcome in Diabetes



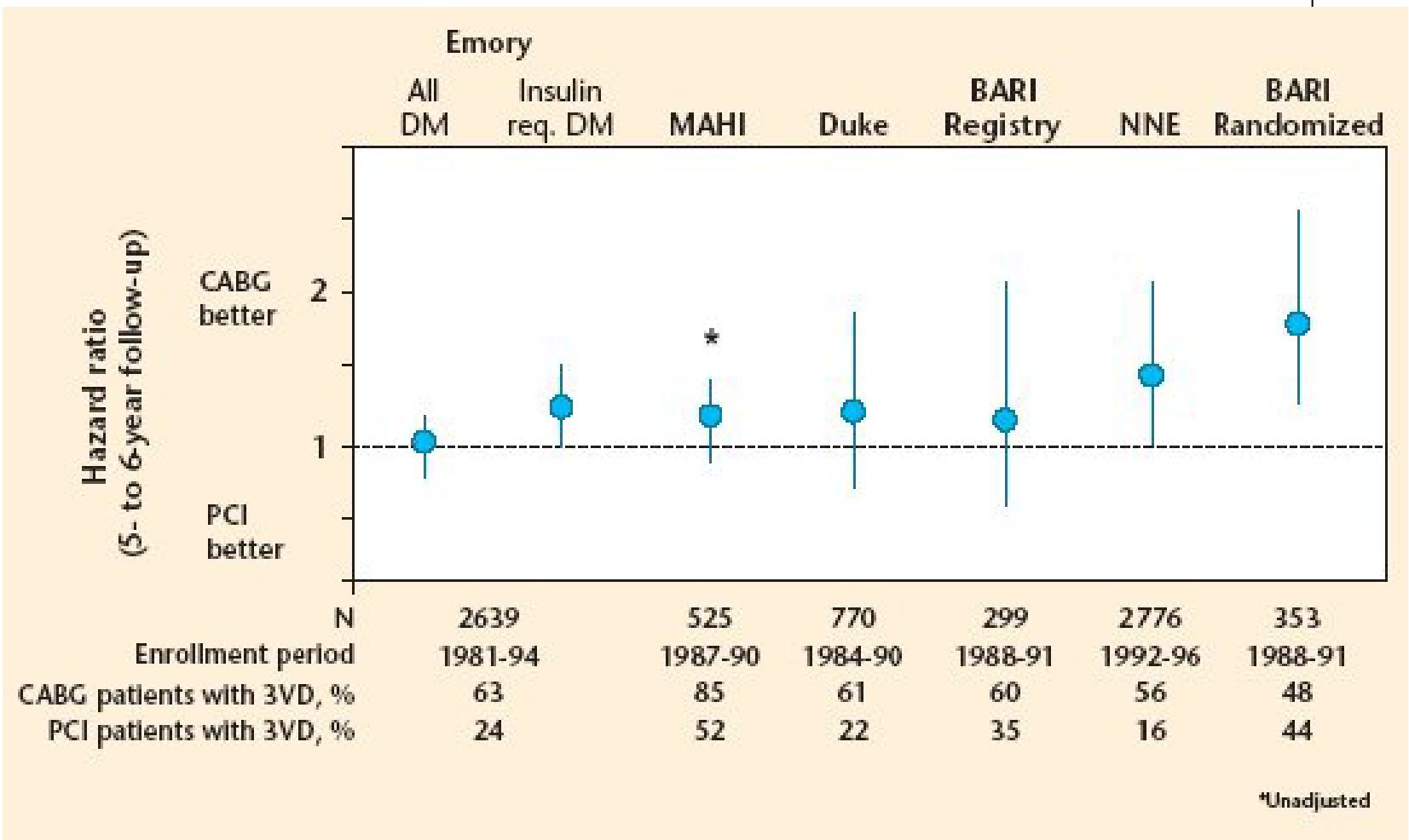
J Am Coll Cardiol 2000;35:1122-1129

Coronary Angioplasty Versus Bypass Revascularization Investigation (CABRI) : 4 year mortality

	Mortality			
	Absolute risk			
	Coronary Angioplasty	Coronary Surgery	RR	95% CI
Entire group	10.9%	7.4%	1.47	0.99 – 2.19
Diabetics	22.6%	12.5%	1.81	0.80 – 4.08
Nondiabetics	9.4%	6.8%	1.39	0.88 – 2.19

Am J Cardiol 2001;87:947-950

Survival following revascularization in diabetics vs. nondiabetics

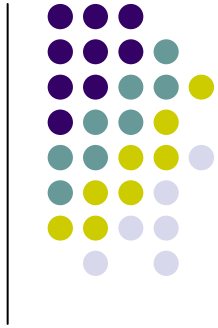


Study	Patient Profile	Groups	Repeat Revascularization, %	Mortality: Patients, %	Mortality: *P* Value	Comments
RITA-1,[28] 1993	1- to 3-Vessel CAD Angina or ischemia	CABG (n = 33)		24.2 at 6.5 y	.09	32% Had single-vessel CAD Stents not used
		PCI (n = 29)		6.9 at 6.5 y		
EAST,[29] 1994	Multivessel CAD Referred for revascularization LVEF >25%	CABG (n = 30)		10.0 at 3 y	NA	Single center Stents not used
		PCI (n = 29)		6.9 at 3 y		
		CABG		24.5 at 8 y	.23	
		PCI		39.9 at 8 y		
CABRI,[30] 1995	Multivessel CAD Angina or ischemia LVEF >35%	CABG (n = 60)		12.5 at 4 y	NA	Stent use rare
		PCI (n = 64)		22.6 at 4 y		
BARI,[31,32] 1996	Multivessel CAD Angina or ischemia	CABG (n = 180)	11.1 at 7 y	19.4 at 5 y	.003	81% IMA use Stents not used
		PCI (n = 173)	69.9 at 7 y	34.5 at 5 y		
		CABG		25.6 at 7 y	.001	
		PCI		44.3 at 7 y		
ARTS,[33,34] 2001	Multivessel CAD Angina or ischemia LVEF >30%	CABG (n = 96)	3.1 at 1 y*	3.1 at 1 y	.294	89% IMA use 3.5% Gp IIb/IIIa inhibitor use
		PCI with stenting (n = 112)	22.3 at 1 y*	6.3 at 1 y		
		CABG	8.4 at 3 y*	4.2 at 3 y	.39	
		PCI	41.1 at 3 y*	7.1 at 3 y		
AWESOME,[35] 2001	Medically refractory unstable angina High CABG risk (prior heart surgery, MI within 7 d, LVEF <35%, age >70 y, or balloon pump use)	CABG (n = 79)	35 at 1 y†	19 at 1 y	.27	54% Stent use 11% Gp IIb/IIIa inhibitor use
		PCI (n = 65)	49 at 1 y†	14 at 1 y		
		CABG	46 at 5 y†	34 at 5 y	.27	
		PCI	51 at 5 y†	26 at 5 y		

Balloon

Stent

Arterial Revascularization Therapy Study (ARTS) : 1-year clinical ourcome

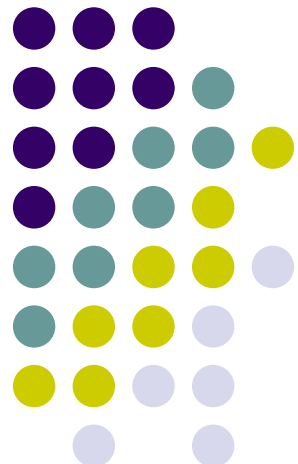


	Diabetes			Nondiabetes		
	Stent	CABG		Stent	CABG	
	(n=112)	(n=96)	p	(n=488)	(n=509)	P
Death, n (%)	7 (6.3)	3 (3.1)	0.294	8 (1.6)	14 (2.8)	0.412
Cerebrovascular events	2 (1.8)	6 (6.3)	0.096	7 (1.4)	6 (1.2)	0.722
MI	7 (6.3)	3 (3.1)	0.294	25 (5.1)	21 (4.1)	0.453
Q-wave	6 (5.4)	2 (2.1)	0.222	22 (4.5)	20 (3.9)	0.649
Repeat revascularization*						
CABG	9 (8.0)	0	<0.001	19 (3.9)	3 (0.6)	<0.001
PTCA	16 (14.3)	3 (3.1)	<0.001	57 (11.7)	15 (2.9)	<0.001
Event-free	71 (63.4)	81(84.4)	<0.001	372 (76.2)	450 (88.4)	<0.001

Circulation. 2001;104:533-538

Present

Era of Drug-Eluting Stent

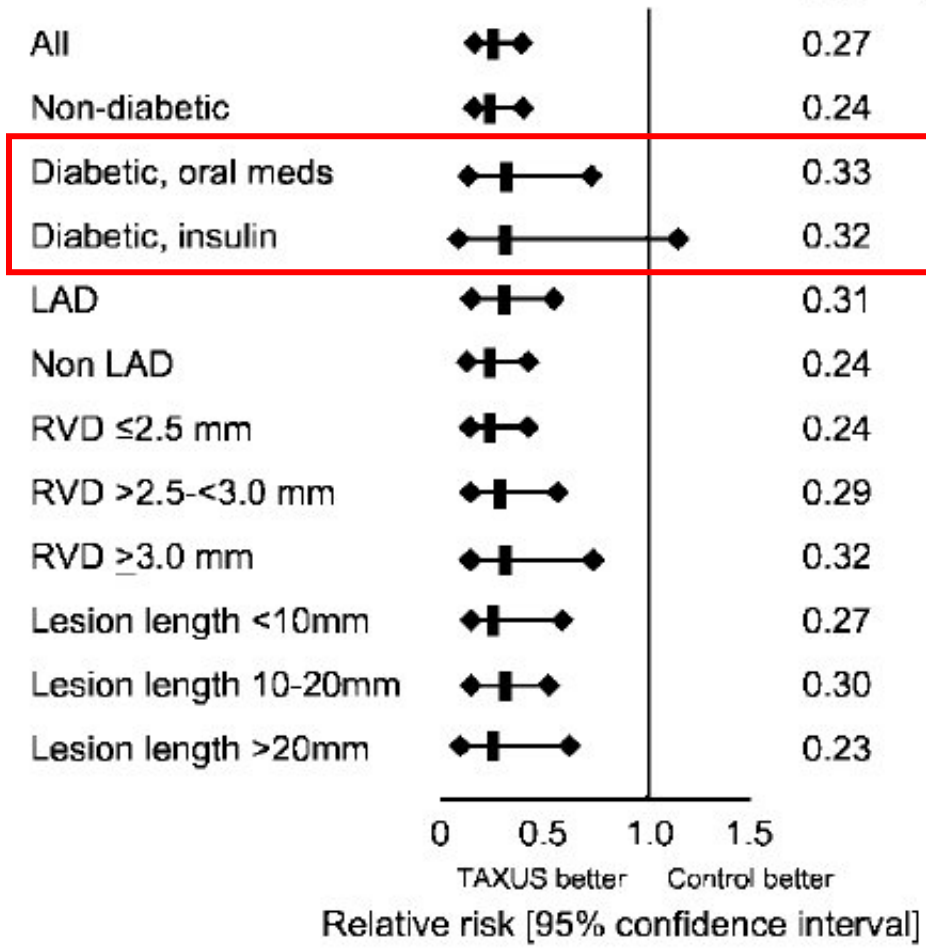


Drug-eluting stent: insulin-requiring vs. non-insulin-requiring in SIRIUS

	Non-Insulin-Requiring			Insulin-Requiring		
	BMS (n=104)	SES (n=93)	p	BMS (n=44)	SES (n=38)	p
Angiographic restenosis	50.7% n=73	12.3% n=65	<0.001	50% n=28	35% n=20	0.38
TLR	23.1%	4.3%	<0.001	20.5%	13.2%	0.56
MACE	26.0%	6.5%	<0.001	22.7%	15.7%	0.58

Circulation 2004;109:2273-2278

Drug-eluting stent: oral medicated vs. insulin medicated in TAXUS-IV



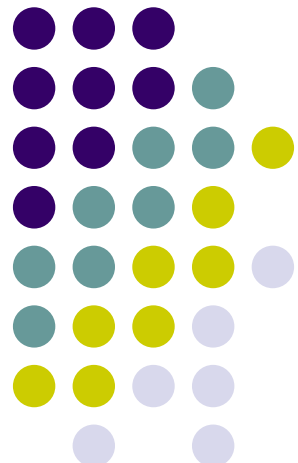
	RR	TAXUS	Control	P value
All	0.27	4.4%	15.1%	<0.0001
Non-diabetic	0.24	3.5%	13.2%	<0.0001
Diabetic, oral meds	0.33	7.9%	21.6%	0.005
Diabetic, insulin	0.32	6.2%	19.4%	0.07
LAD	0.31	5.8%	16.7%	<0.0001
Non LAD	0.24	3.6%	14.0%	<0.0001
RVD ≤2.5 mm	0.24	5.6%	20.6%	<0.0001
RVD >2.5-<3.0 mm	0.29	4.3%	13.3%	0.0003
RVD ≥3.0 mm	0.32	3.5%	11.1%	0.005
Lesion length <10mm	0.27	4.1%	13.4%	0.0005
Lesion length 10-20mm	0.30	4.4%	14.1%	<0.0001
Lesion length >20mm	0.23	5.5%	22.1%	0.001

12 month TLR

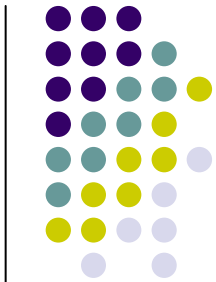
Circulation. 2004;109:1942-1947

New Frontier

Systemic approach to Vascular Biology



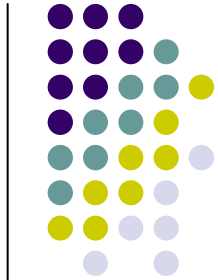
Systemic approach to Vascular Biology



- Peroxisome proliferator activated receptor γ (PPAR-γ)

- Advanced glycation end products (AGE) and Receptor for AGE (RAGE)

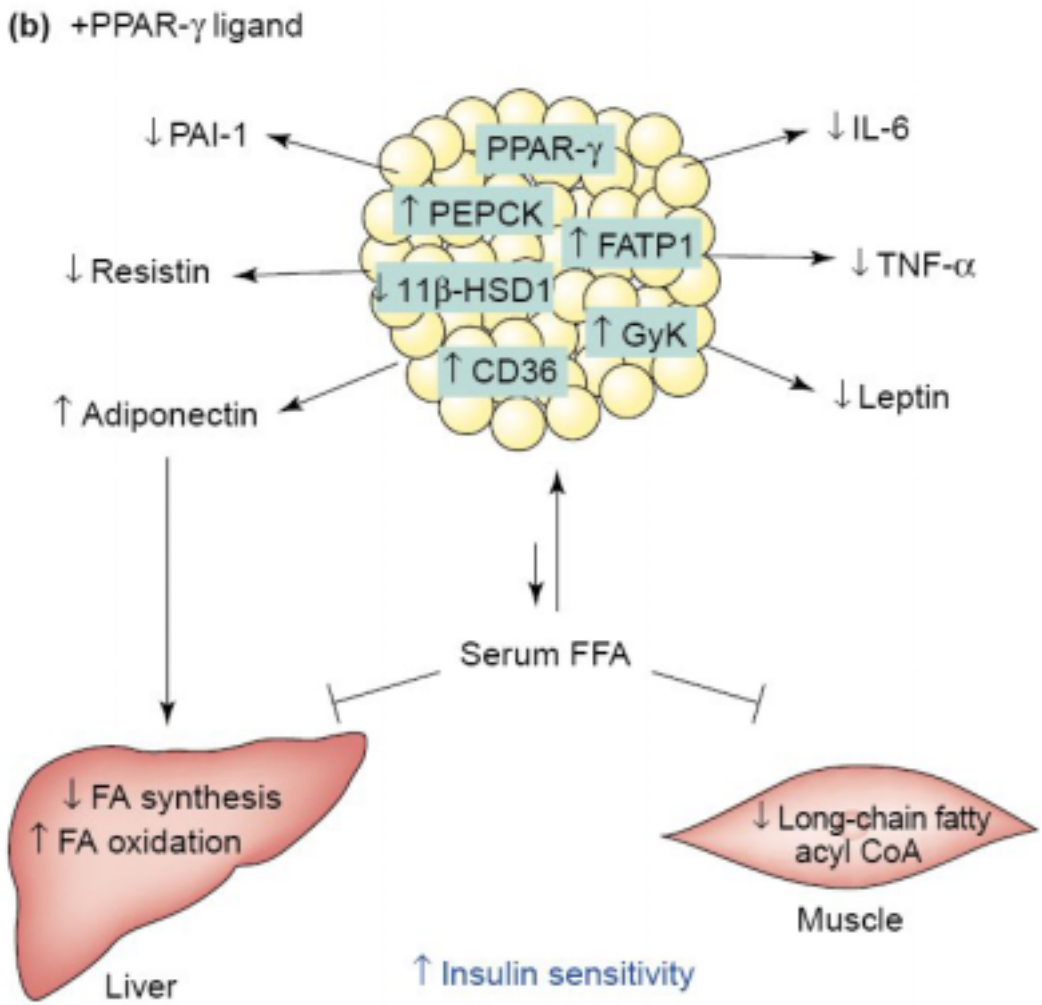
Peroxisome proliferator activated receptor γ (PPAR-γ)



- PPAR-γ ligands
  - Insulin sensitization
  - Promote fatty acid storage in fat depots
  - Regulate the expression of adipocyte-secreted hormones that impact on glucose homeostatsis

- PPAR-γ agonist trials
  - Prevent restenosis after coronary stenting
  - Reduce neointimal tissue proliferation after coronary stenting
  - Inhibitory effect on carotid artery IMT
  - Reduce serum level of cardiovascular disease markers

Peroxisome proliferator activated receptor γ (PPAR-γ) ligand



Trends Pharmacol Sci. 2004;25:331-6

PPAR-γ : prevention of restenosis after coronary stenting in type 2 diabetes

	Control	Rosiglitazone	P
n	45	38	
MLD (mm)	1.91±1.05	2.49±0.88	0.009
Diameter stenosis (%)	40.6±31.9	23.0±23.4	0.004
Lesion length (mm)	16.5±5.2	19.0±6.1	0.03
Late luminal loss (mm)	1.20±0.97	0.65±0.73	0.005
Restenosis (% of stents)	21 (38.2)	9 (17.6)	0.030

Diabetes Care 2004;27;2654-2660

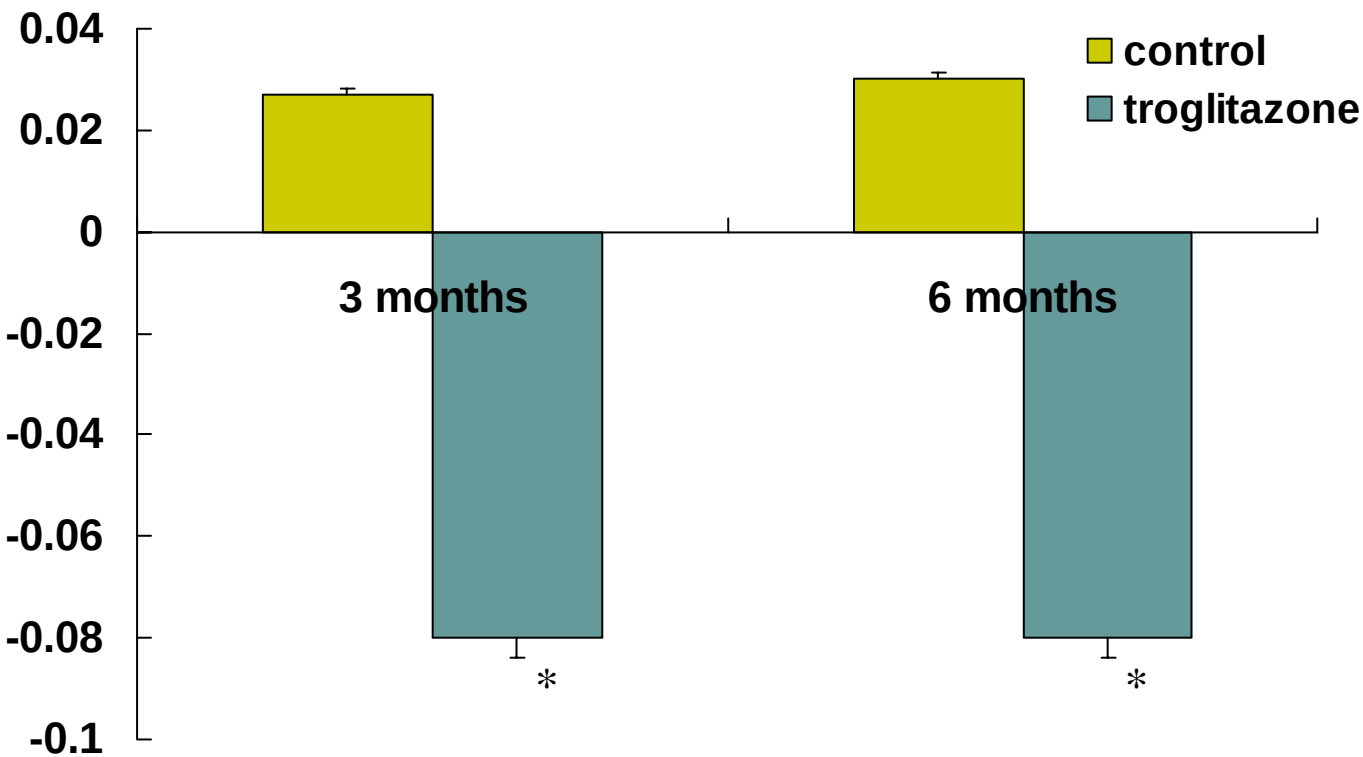
PPAR-γ : reduction of neointimal tissue proliferation after coronary stent implantation in NIDDM

	Troglitazone	Control	P
n	29 stents	33 stents	
Stent area follow up (mm^2)	7.3±1.8	7.3 ±2.3	0.7995
Lumen area follow up (mm^2)	5.3 ±1.7	3.7 ±1.7	0.0002
Intimal area follow up (mm^2)	2.0 ±0.9	3.5 ±1.8	<0.0001
Intimal index follow up (mm^2)	27.1 ±11.5	49.0 ±14.4	<0.0001

Intimal index = averaged IA/averaged SA x 100%

J Am Coll Cardiol 2000;36:1529-1535

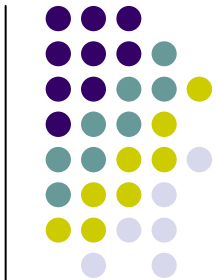
PPAR-γ : Inhibitory effect on carotid artery IMT



Effect of troglitazone (400mg/day, 6 months) on IMT in type 2 diabetes. *p,0.001 vs. control

J Clin Endocrinol Metab. 1998;83:1818-20

Advanced glycation end products (AGE) and Receptor for AGE (RAGE)

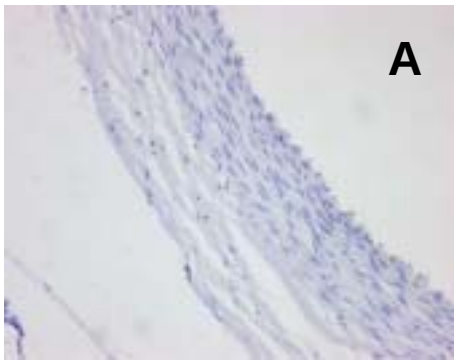


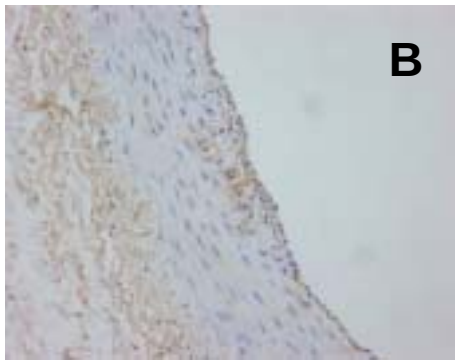
- AGE
  - Action
  - Pharmacological inhibition of AGE
    - Inhibitors of AGE formation : amionoguanidine, OPB-9195
    - AGE-crosslink ‘breakers’ : PTB, ALT-711
    - Antioxidant
- RAGE
  - Action
  - Soluble RAGE (sRAGE)

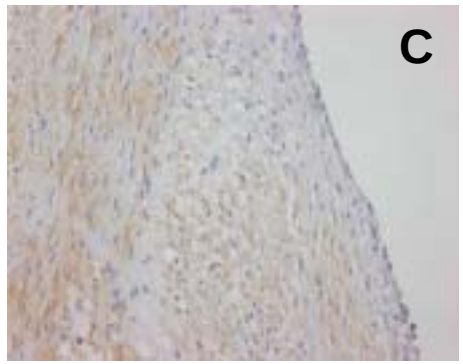
Advanced glycation end products (AGE): Action

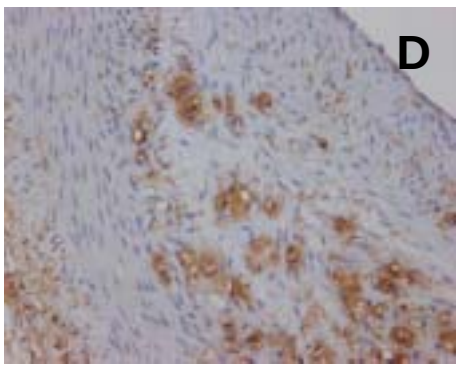
- AGEs in atherosclerosis
  - **Accumulation in the vascular matrix** : narrowing and occlusion
  - **Vascular endothelial dysfunction** : procoagulant state, vasoconstriction, hypertension
  - **Glycoxidation of LDL** : slow degradation of LDL, lipid peroxidation, oxidative stress
  - **Monocyte activation** : vascular cell proliferation, cytokine release, oxidative stress
  - **Trapping of plasma proteins** : initiation of complement activation, oxidation

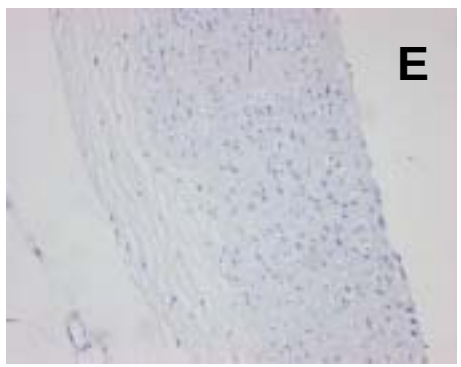
AGE in balloon injured iliac artery of hypercholesterolemic rabbit





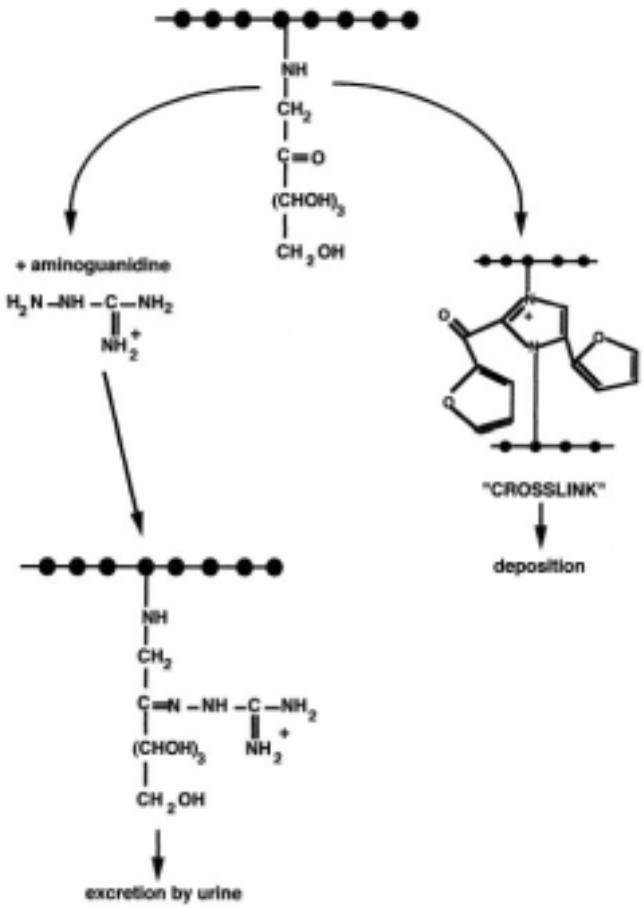






A. Control; B. 7days;
C. 14days; D. 28days;
E. non-injured artery of balloon injured rabbit

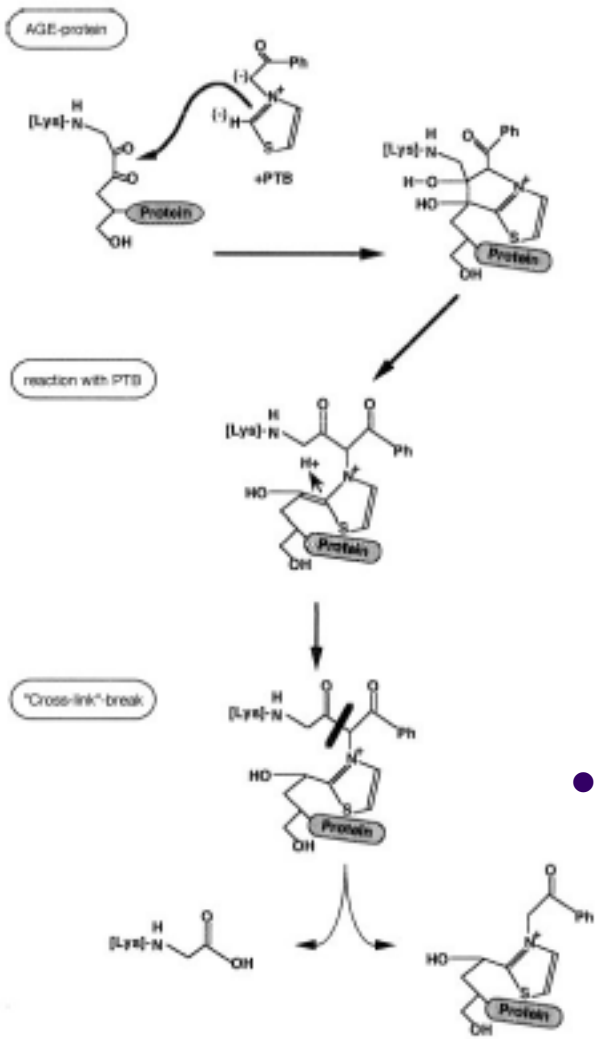
Inhibitors of AGE formation



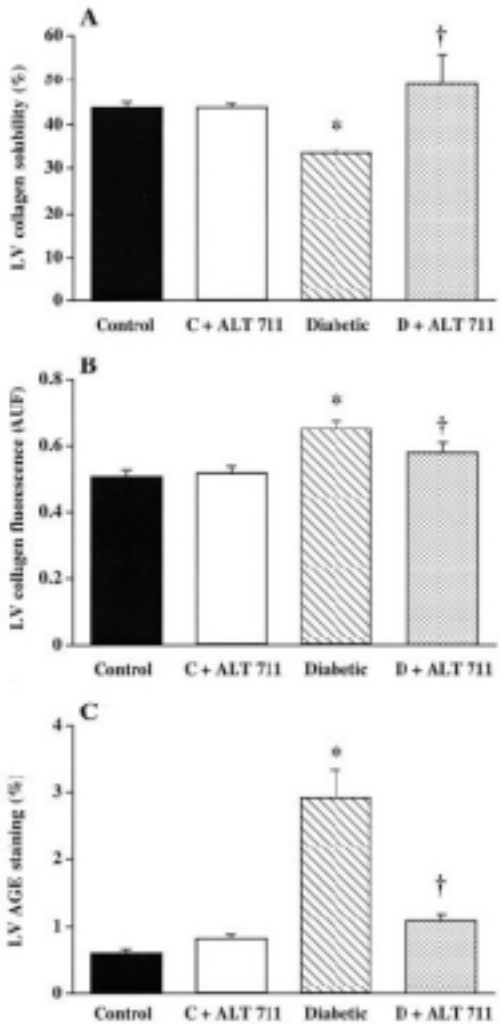
- Prevent AGE formation
- Prevent collagen to collagen cross-linking, decrease collagen stability
- Reduction of AGE accumulation in the renal glomerulus
- Reduce age associate increase in serum and tissue AGEs

- Not effective in patients with a long history of disease (already extensive tissue accumulation)

AGE-crosslink 'breakers': AGE cleaving agents



- Breaks the carbon-carbon bond between two carbonyls of an AGE crosslink : remove irreversibly bound AGEs from connective tissue



- Attenuate diabetes induced myocardial structural changes

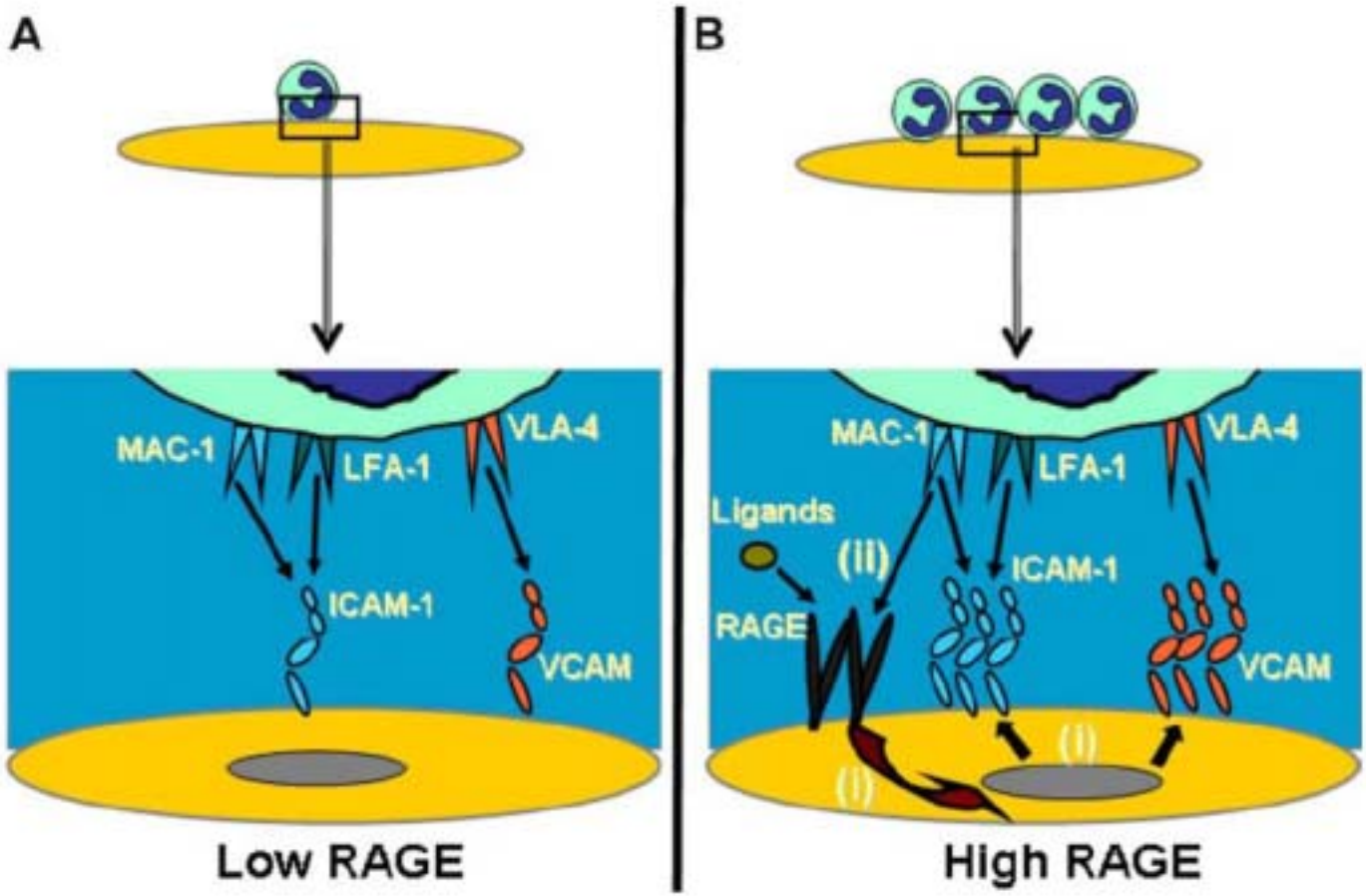
Circ Res. 2003;92:785-792

AGE receptors

- RAGE (receptor for AGE) :
  - AGE scavenger
  - Intracellular signaling receptor
  - Inflammatory response

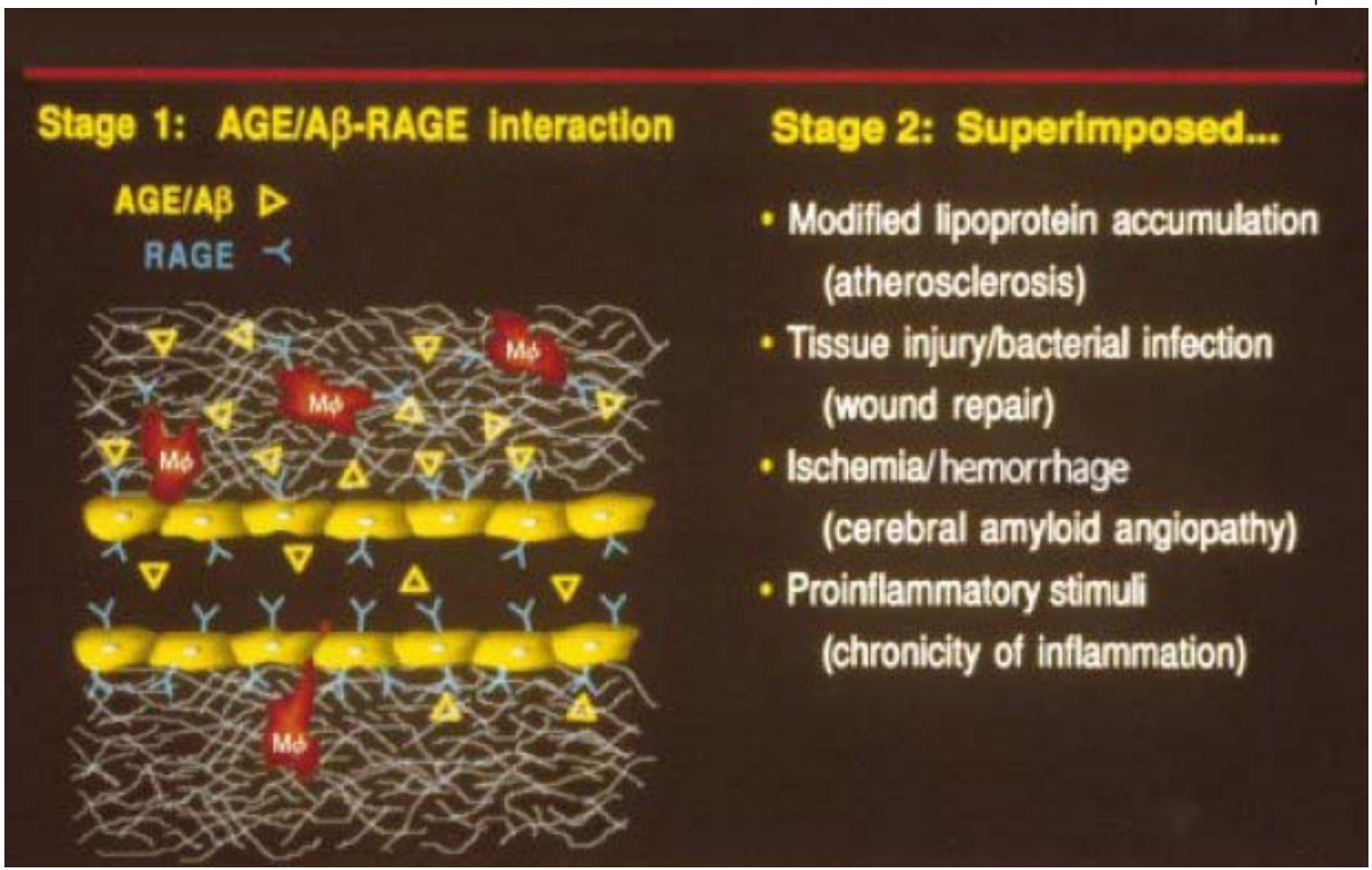
- Macrophage scavenger type II and type II receptor
- Oligosaccaharyl transferase-48 (AGE-R1)
- 80K-H phosphoprotein (AGE-R2)
- Galectin-3 (AGE-R3)

RAGE : central player in the inflammatory response

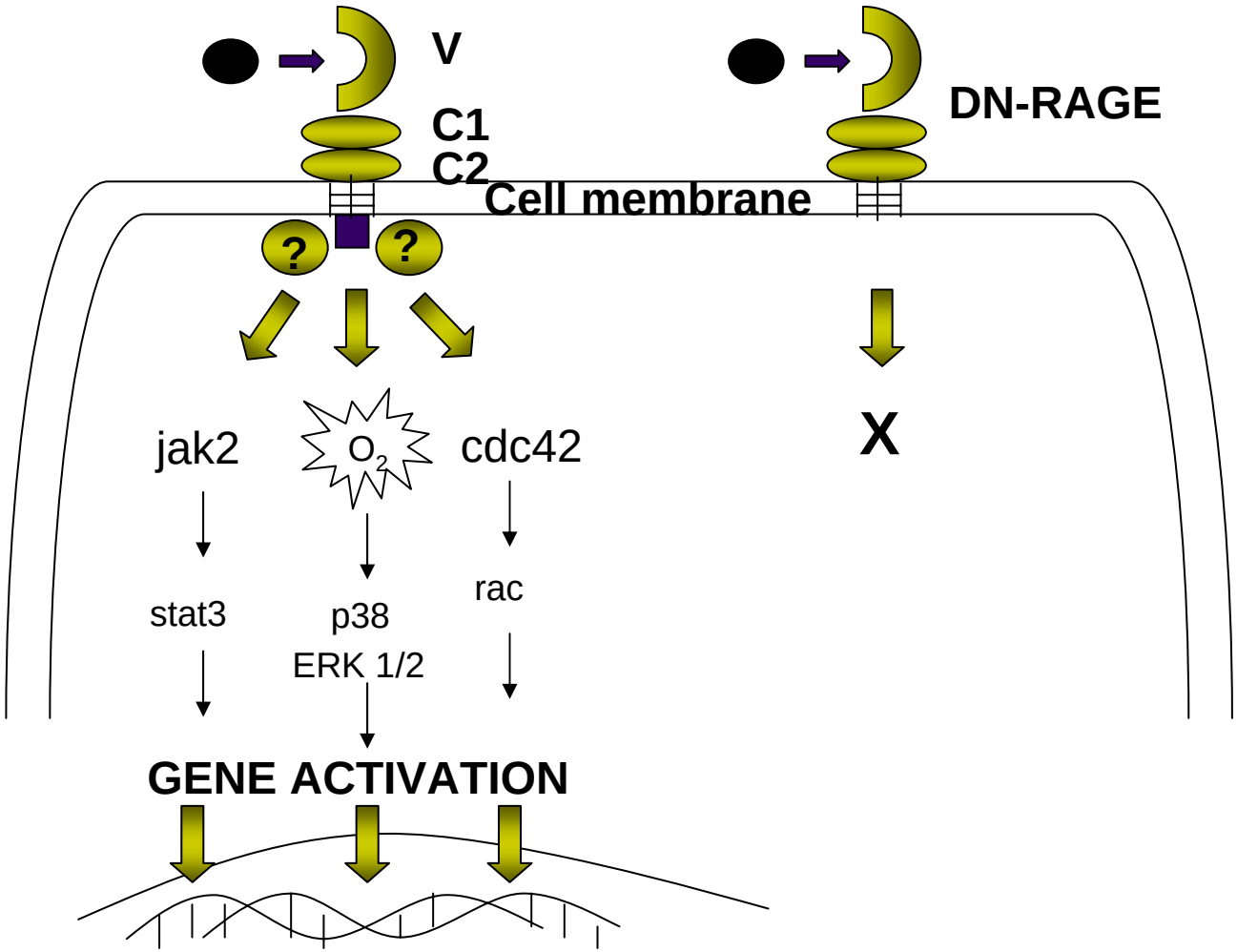


Microbes Infect. 2004;6:1219-25

RAGE : 2 hit model of vascular pertubation

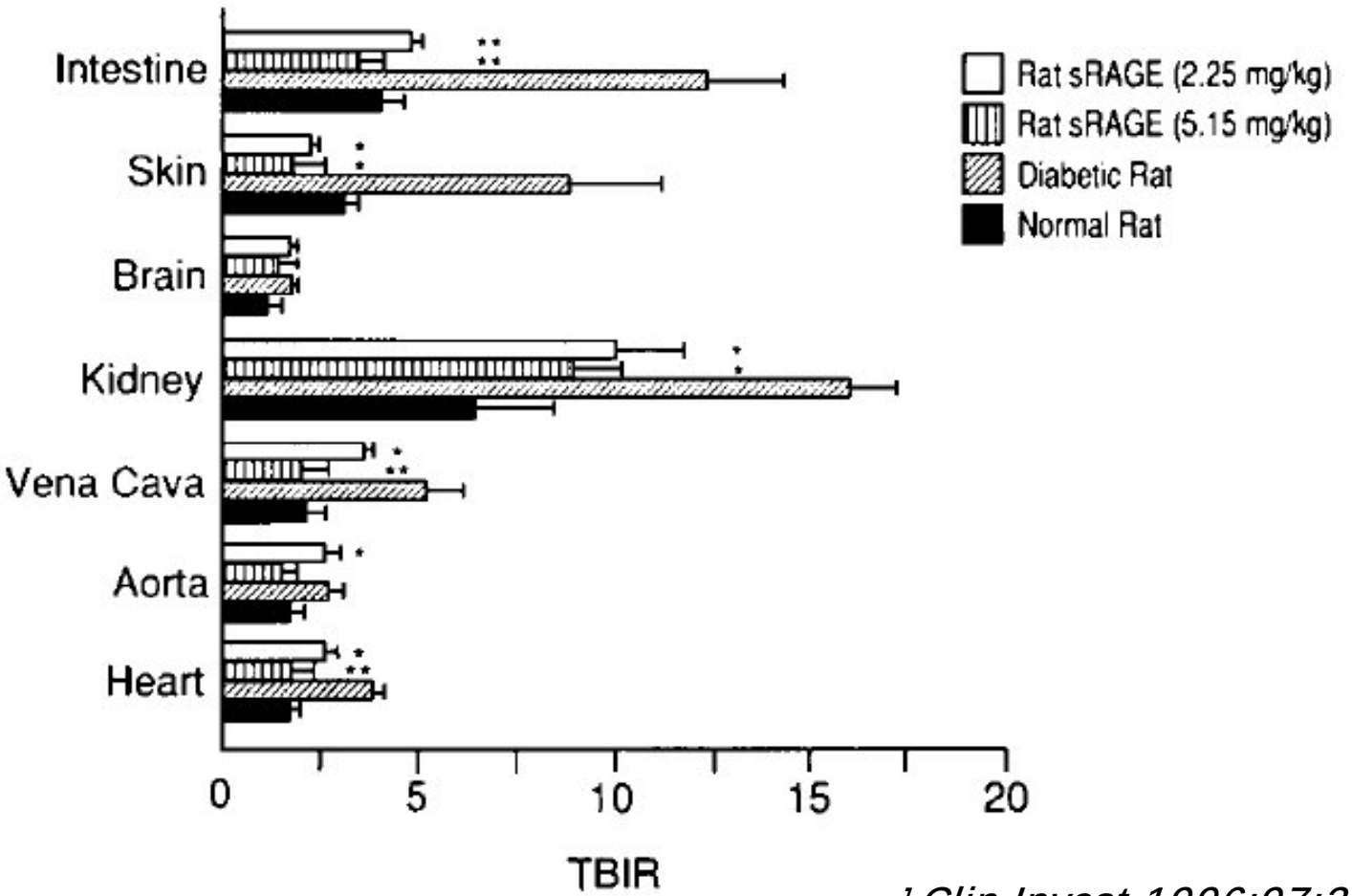


Signaling pathways activated by RAGE/ligand interaction



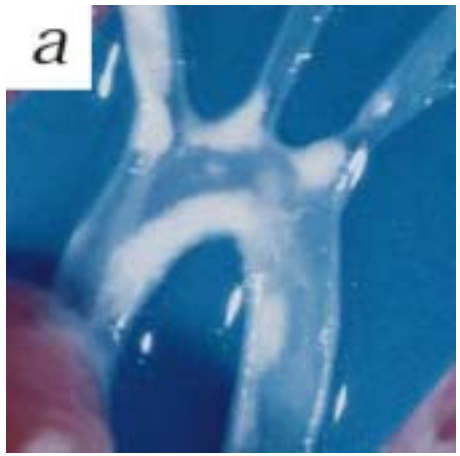
Pharm Res. 2004 ;21:1079-86.

RAGE : Effect of sRAGE infusion on vascular permeability in streptozocin treated rats assessed using the tissue-blood isotope ratio(TBIR) method

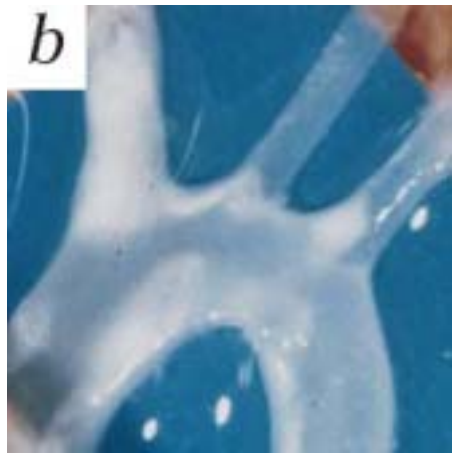


J Clin Invest 1996;97:238-243

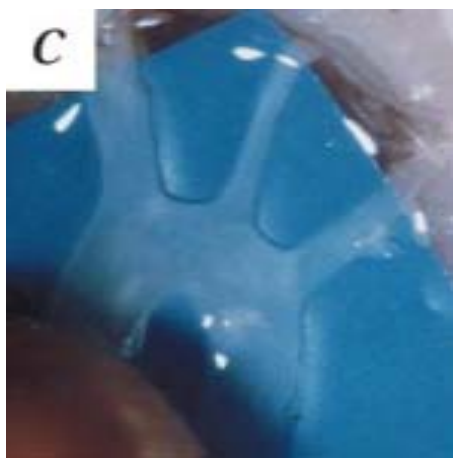
Effect of sRAGE on accelerated atherosclerosis in diabetic apoE mice



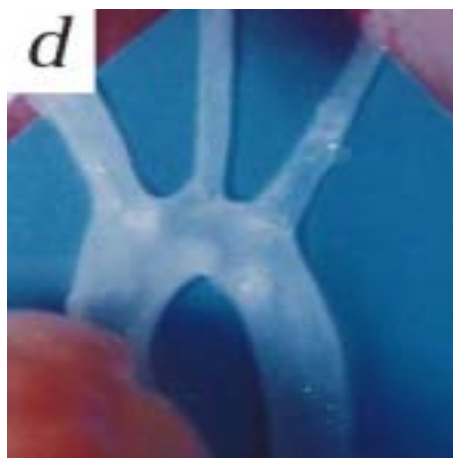
MSA at 80 mg/day



sRAGE at 3 mg/day



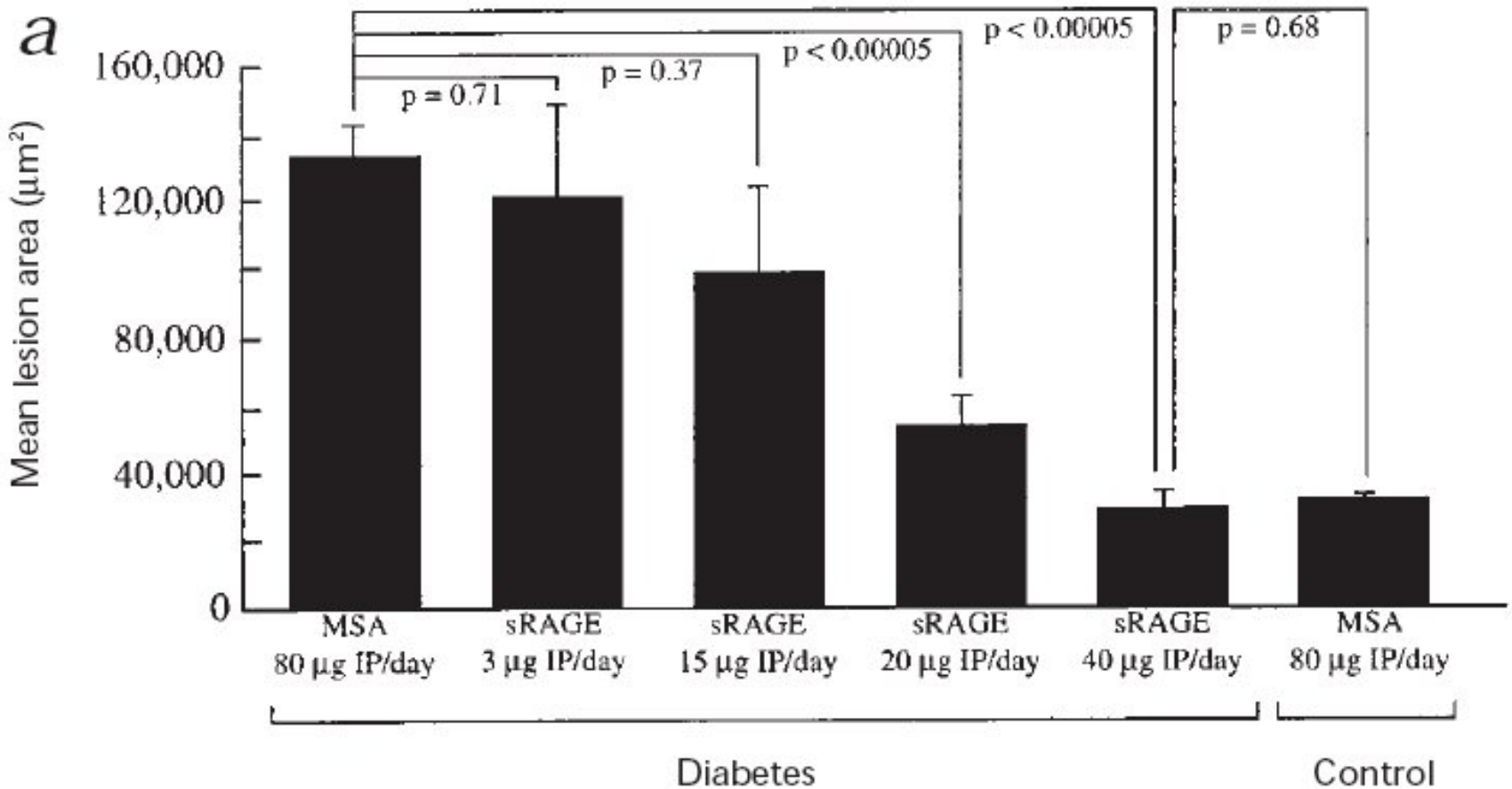
sRAGE 20 mg/day



sRAGE 40 mg/day

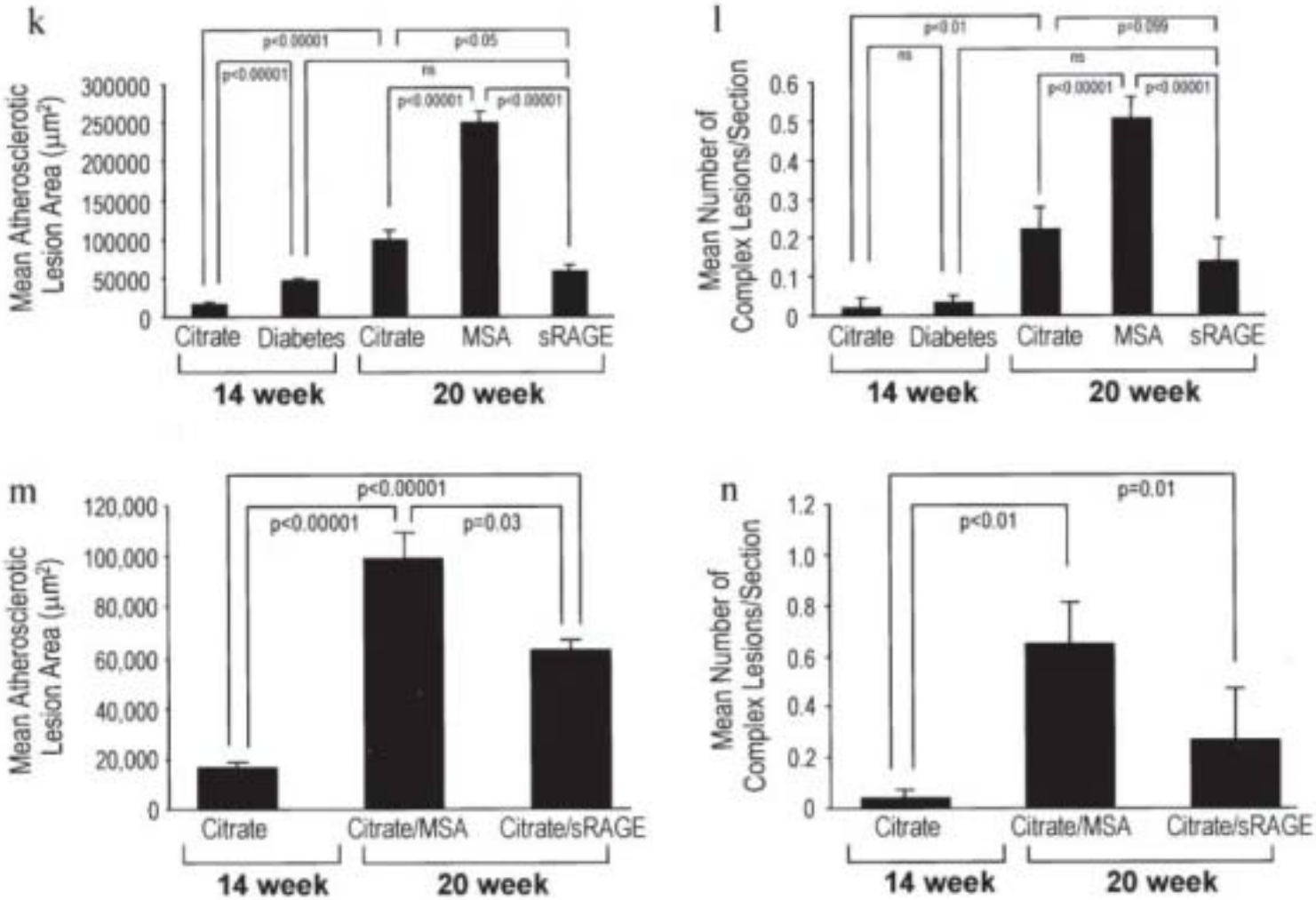
Nat Med. 1998;4:1025-1031

sRAGE suppression accelerated atherosclerosis in diabetic Apo E null mice in a dose-dependent manner



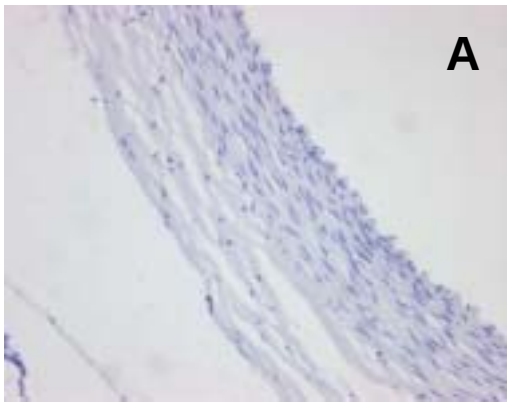
Nat Med. 1998;4:1025-1031

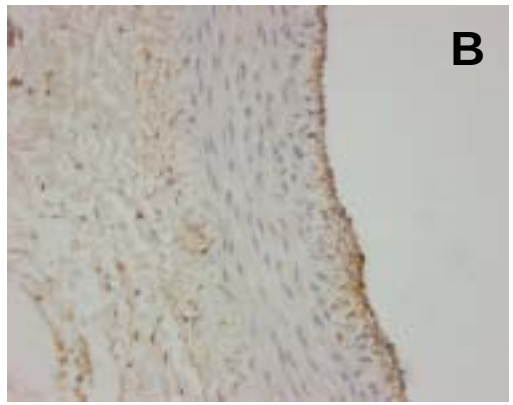
Blockade of RAGE suppress progression of established atherosclerosis in apoE-null mice

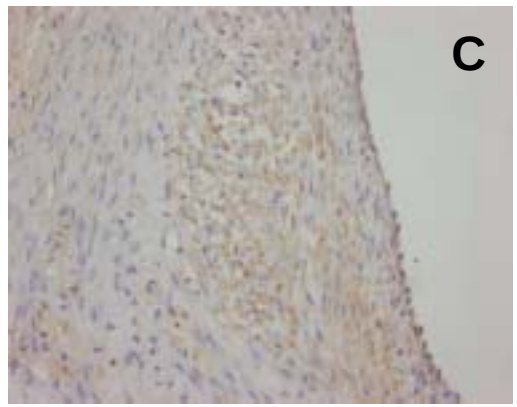


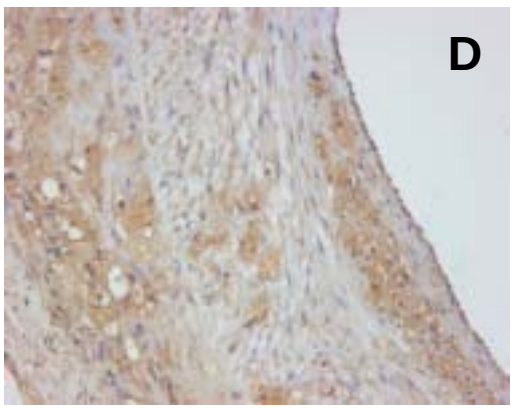
Circulation. 2002;106:2827-2835

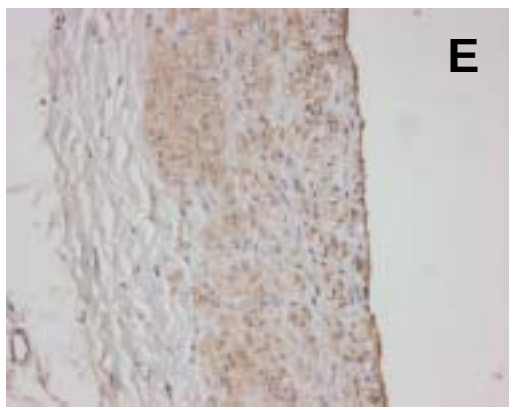
Overexpression of RAGE in balloon injured iliac artery of hypercholesterolemic rabbit





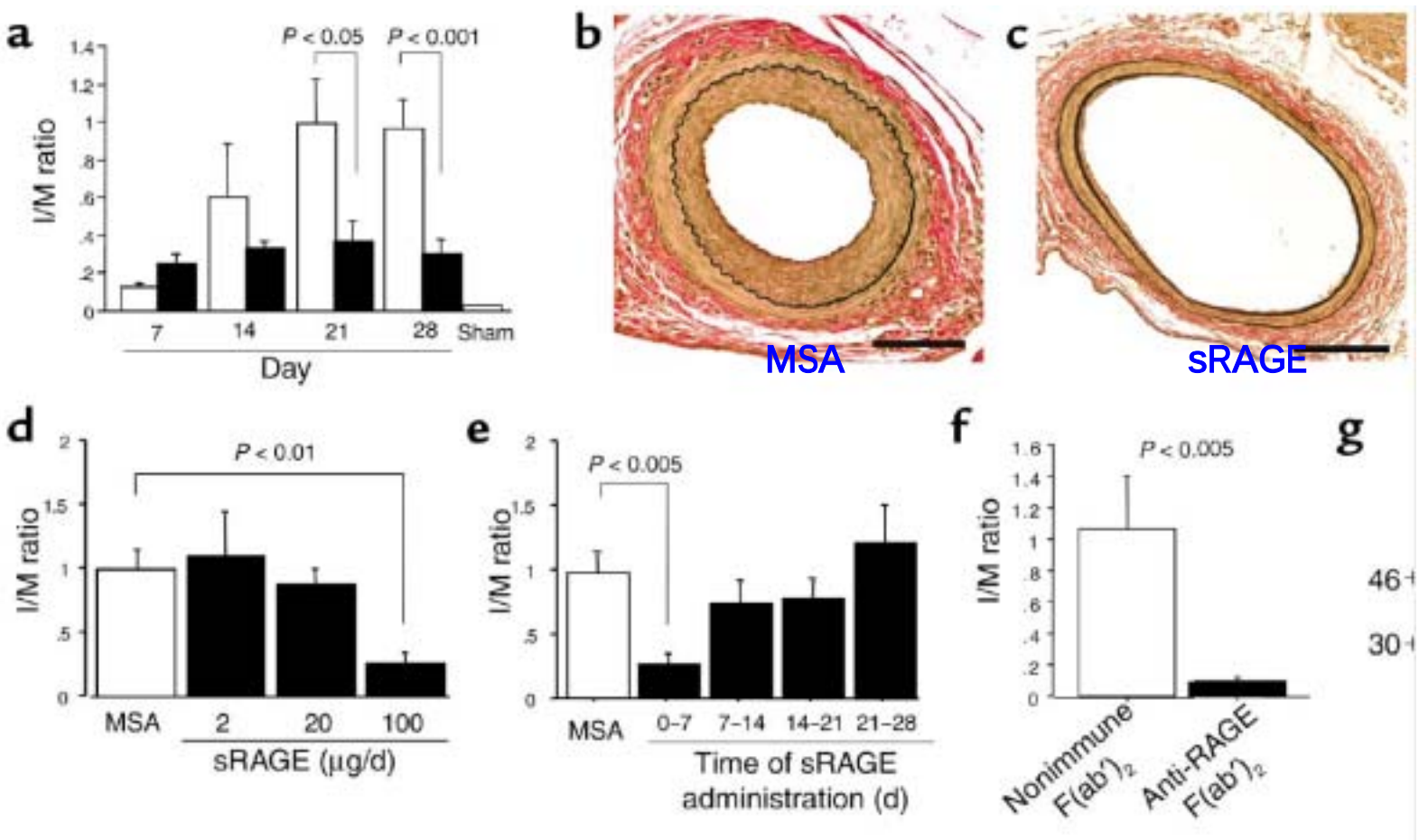






A. Control; B. 7days;
C. 14days; D. 28days;
E. non-injured artery of balloon injured rabbit

RAGE blockade and neointimal expansion after acute arterial injury



J Clin Invest. 2003;111:959-972

Conclusion

- Coronary revascularization
  - CABG or PCI
  - Left main stenosis
  - Multi-vessel disease
  - Long lesion
  - High risk patients
- Systemic therapy