Preventive Effects of Rosiglitazone on Restenosis after Coronary Stenting in Patients with Type 2 Diabetes

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Background

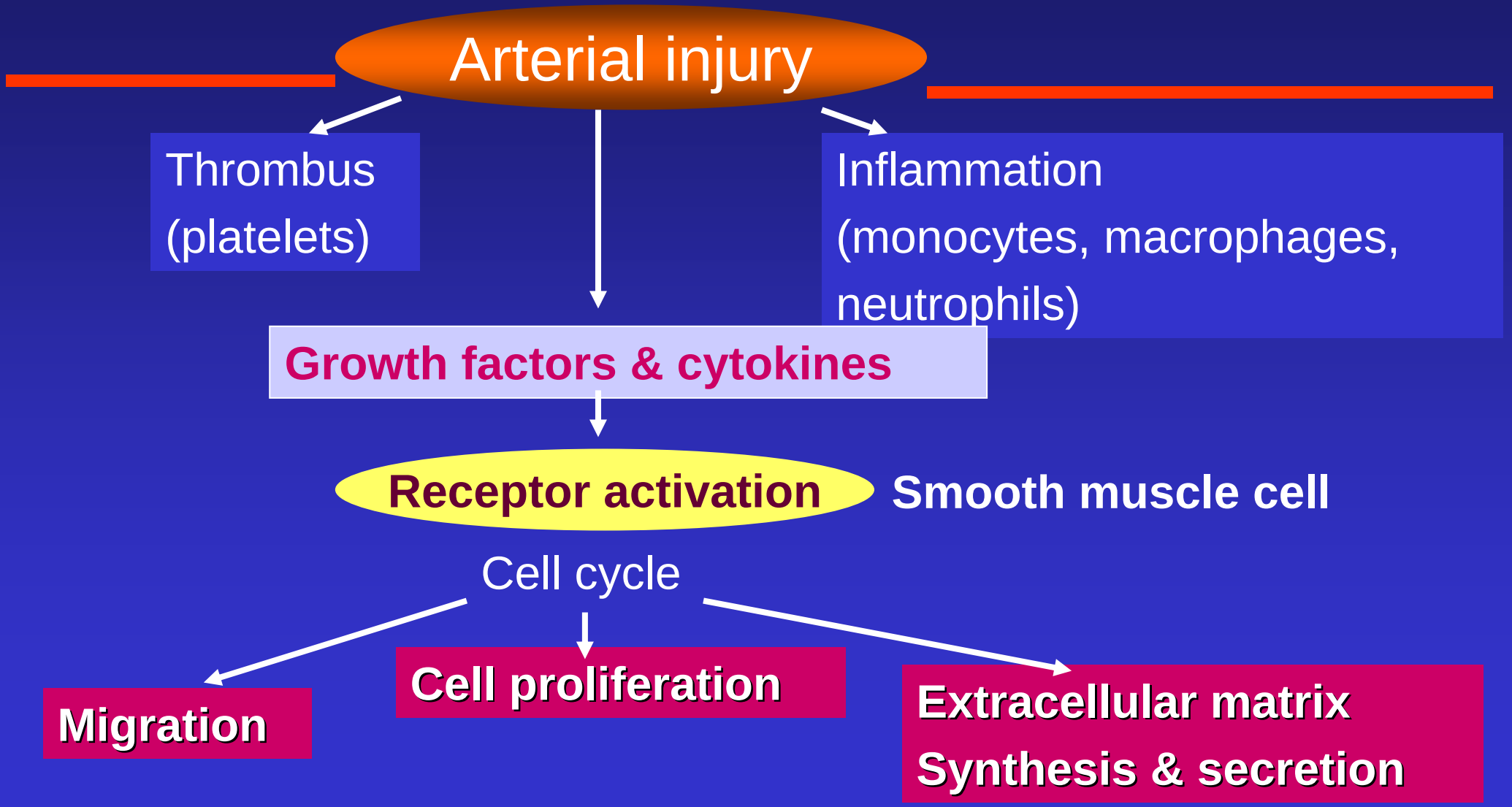
1. Cardiovascular disease is one of the important leading cause of deaths in Type 2 diabetic patients.

2. As a result of dramatic increase in implantation numbers, in-stent restenosis has been significant clinical and socio-economic problems.

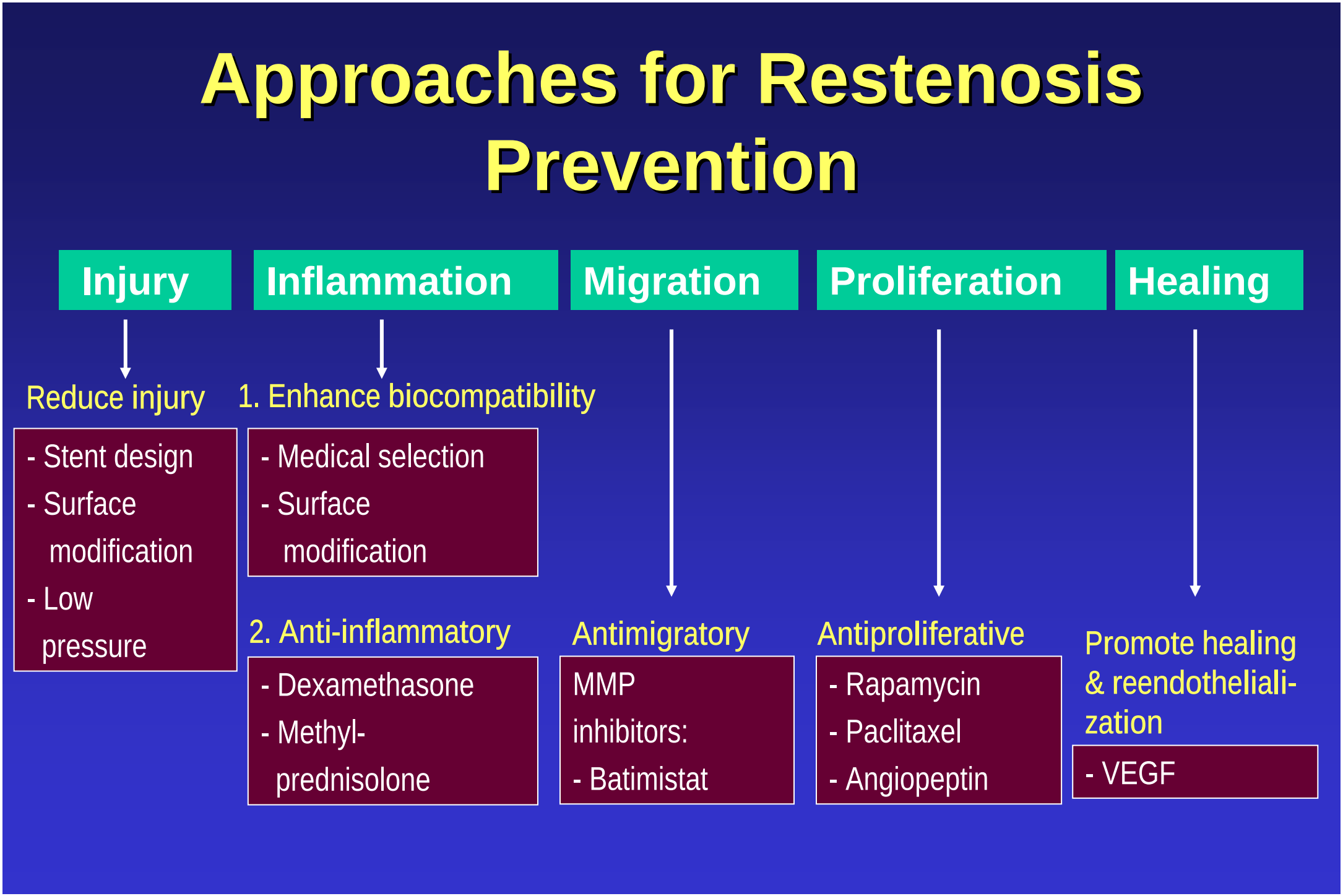
3. The in-stent restenosis rate after coronary stenting has reached up to 45-50 % in type 2 DM patients comparing to 15-25% in non-diabetic patients.

4. The most effective treatment modality for in-stent restenosis has not yet identified.

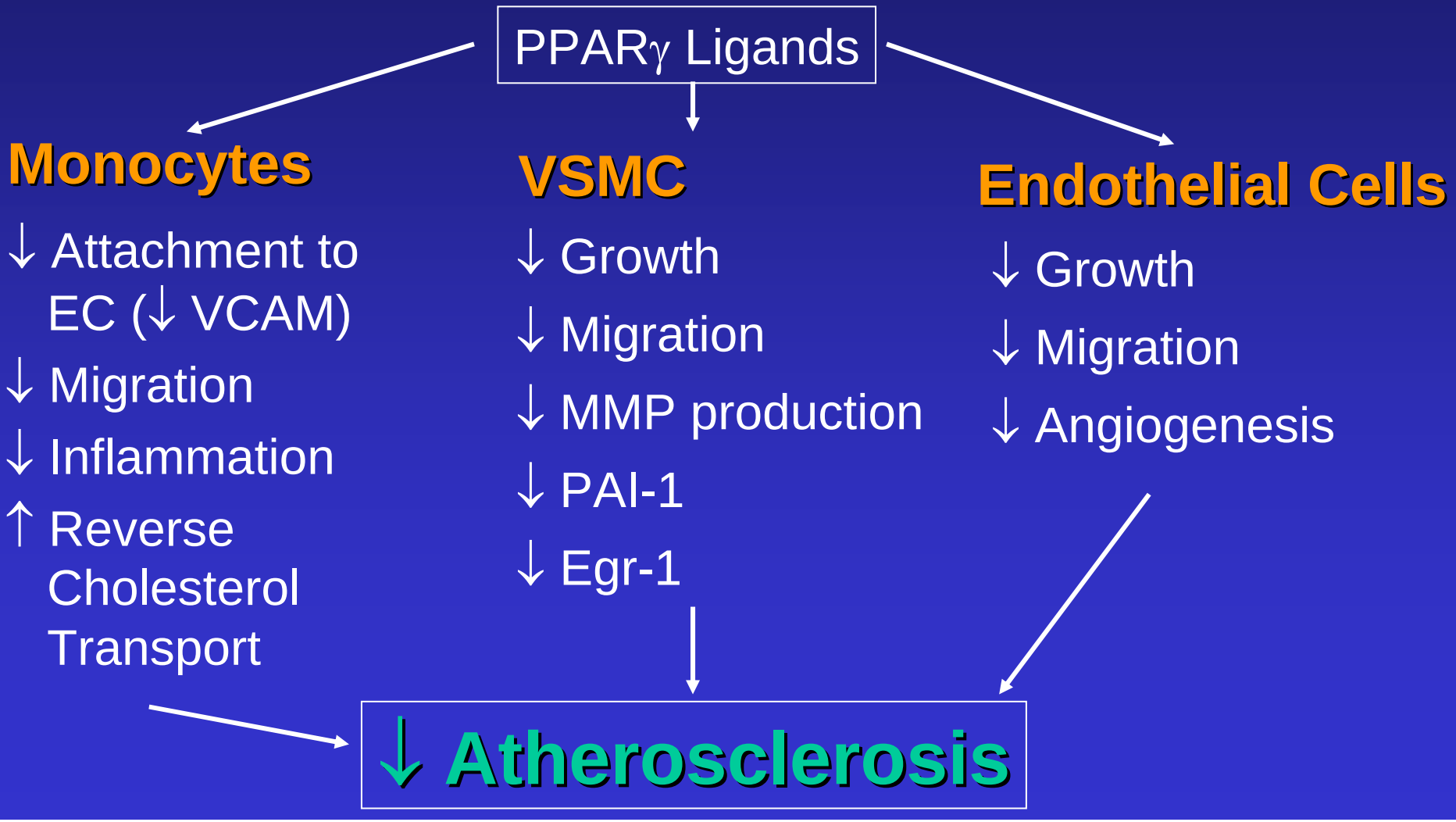
Pathogenesis of Restenosis



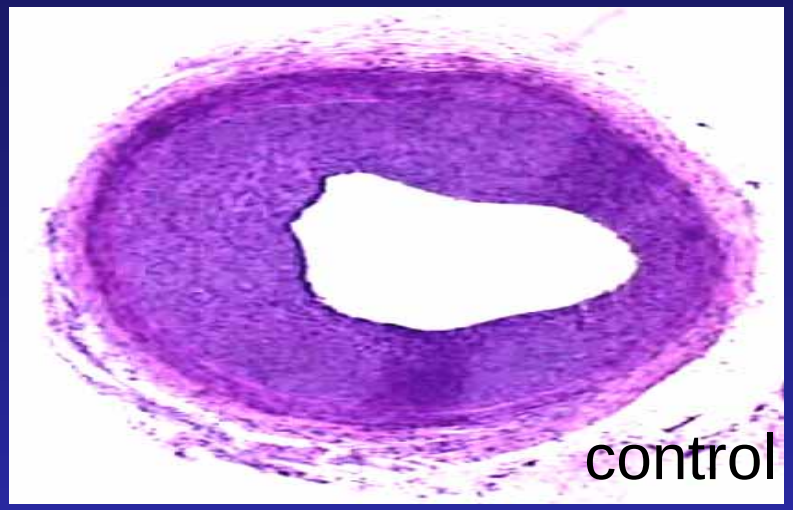
Approaches for Restenosis Prevention

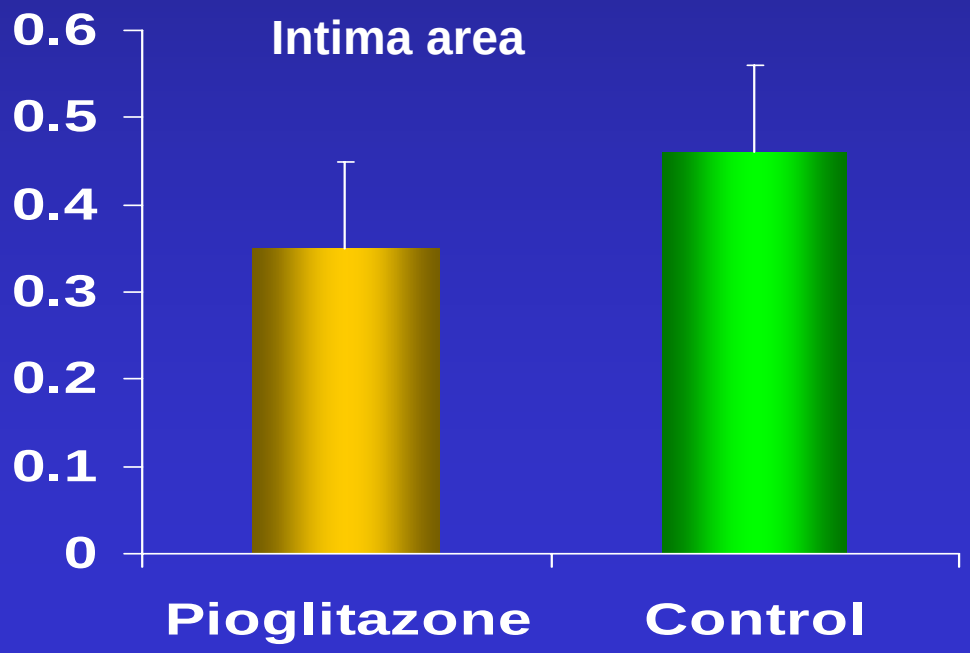


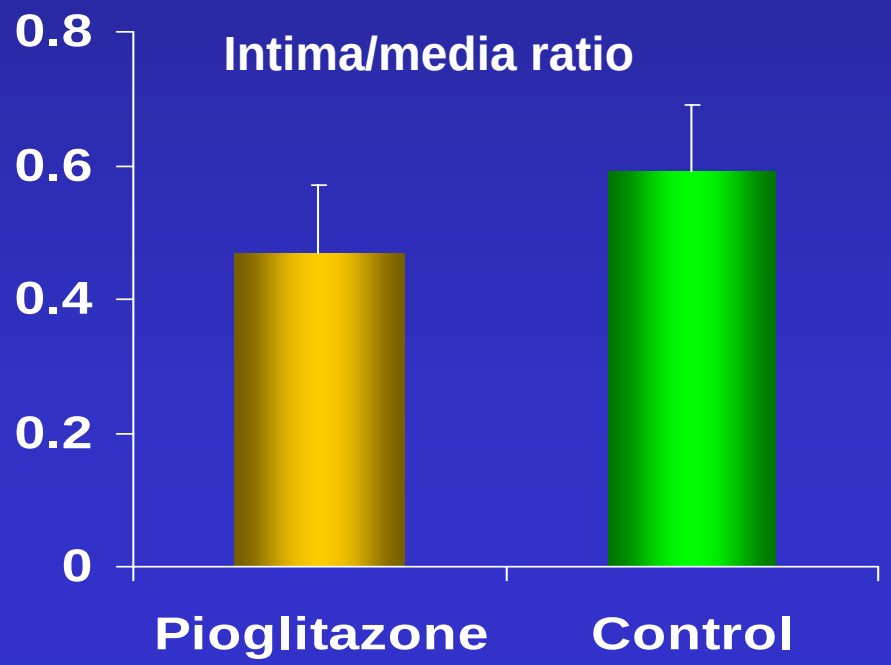
Atherogenic Effects of PPARγ Ligands in the Vasculature



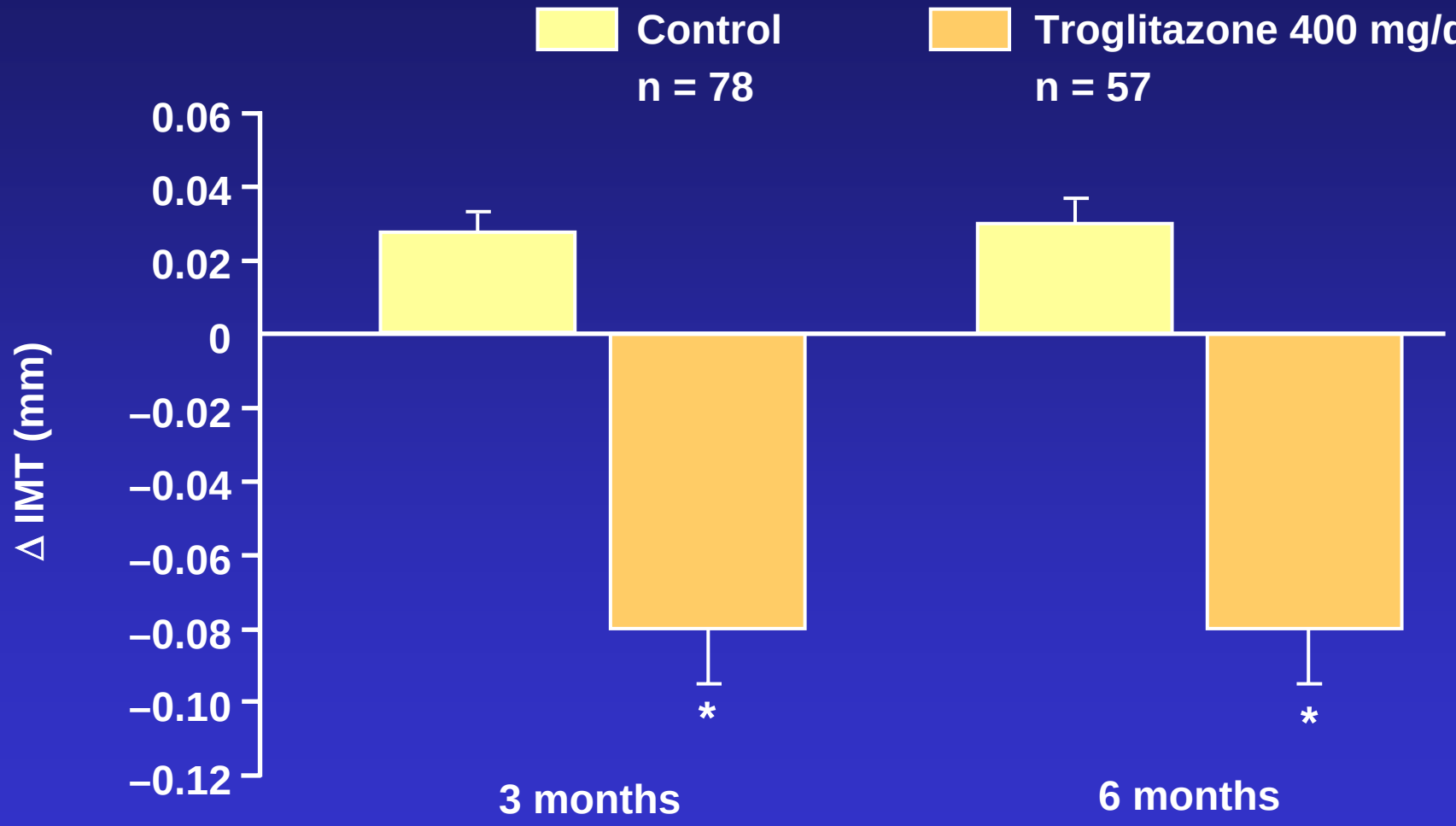
Male OLETF rat, Balloon injury at 16 weeks and pioglitazone for 3weeks







TZDs: effects on carotid arterial intimal and medial co mplex thickness (IMT) in type 2 diabetes



Error bars = SE

Japanese subjects with type 2 diabetes
*P < 0.001 vs. control

Minamikawa J, *et al. J Clin Endocrinol Metab* 1998; 83:1818–1820.

Study Purpose

- To investigate the preventive effect of PPAR-γ agonist, rosiglitazone on restenosis after coronary stenting in type II DM patients.

- Primary endpoint :

  => 6 month follow-up angiographic binary restenosis rate

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Subjects (I)

- Inclusion criteria :
  - Type II DM patients undergoing coronary stenting at YUMC (Nov. 2001 ~ Dec. 2002)

- Exclusion criteria :
  - LVEF < 40% or evidence of CHF
  - GOT/GPT > 2 x upper limit of normal range
  - Cr > 2.0 mg/DL
  - Previous CABG
  - Primary PTCA

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Subjects (II)

- Rosi group : n = 47

  => angiographic follow-up : n = 38

- Control group : n = 48

  => angiographic follow-up : n = 45

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Study design and Method

- Prospective, Randomized study
- Anthropometry, Serologic lab : initial and 6 month
- Rosiglotazone : at least 8mg before angiography, and daily 4mg for 6months.
- Control Blood Sugar : continue individual conventional therapy (sulfonylurea, biguanide, insulin)

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Baseline Characteristics

	Control	Rosiglitazone	P
No. (male/female)	45 (34/11)	38 (24/14)	NS
Age (years)	59.9±9.3	60.9±9.3	NS
DM duration (years)	7.2±3.8	7.5±4.9	NS
BMI (kg/cm^2)	24.8±3.35	24.9±2.96	NS
Fasting glucose (mg/dL)	150.3±28.4	160.3±34.4	NS
HbA1c (%)	7.72±1.13	7.79±1.30	NS
Fasting insulin (μU/mL)	4.97±2.51	5.60±2.70	NS
Total cholesterol (mg/dL)	191.1±48.9	190.5±37.6	NS
HDL-cholesterol (mg/dL)	41.1±10.9	38.9±11.0	NS
Triglyceride (mg/dL)	159.5±55.1	167.7±60.8	NS
Free fatty acid (μmol/L)	580.3±101.7	669.2±127.4	NS
hsCRP (mg/L)	2.01±1.33	2.92±1.98	NS

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Medications

	Control	Rosiglitazone	P
Treatments: No. (%)			NS
HMG-CoA reductase inhibitor	37 (88.1)	31 (81.6)	
ACE inhibitors	30 (71.4)	28 (73.7)	
Antiplatelet agents	38 (90.5)	34 (89.5)	
Sulfonylureas	26 (61.9)	25 (65.8)	
Biguanides	22 (52.3)	21 (55.3)	
α-glucosidase inhibitor	15 (35.7)	10 (26.3)	

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Baseline Angiographic Characteristics

	Control	Rosiglitazone	P
Stented coronary vessels	56	50	NS
LAD	29	29	
LCX	13	8	
RCA	14	12	
Left main		1	
Reference diameter (mm)	3.15±0.49	3.16±0.49	NS
Minimum lumen diameter (mm)	0.65±0.41	0.83±0.57	NS
Diameter stenosis (%)	79.4±12.8	74.4±15.8	NS
Lesion length (mm)	16.48±5.16	19.02±6.09	<0.05

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Post-stenting Angiographic Data

	Control	Rosiglitazone	P
Stent diameter (mm)	3.24±0.42	3.29±0.41	NS
Stent length (mm)	18.40±4.75	20.28±5.73	NS
Post-stenting			
MLD (mm)	3.10±0.43	3.13±0.48	NS
Diameter stenosis (%)	2.49±4.26	2.25±4.44	NS
Acute gain (mm)	2.45±0.57	2.30±0.53	NS

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Follow-up Biochemical Characteristics

	Control		Rosiglitazone	
	Baseline	FU	Baseline	FU
Fasting glucose (mmol/l)	8.34±1.58	6.87±1.52	8.90±1.91	7.35±1.89
HbA1c (%)	7.72±1.13	7.23±0.93	7.79±1.30	7.17±0.98
Fasting insulin (pmol/l)	35.7±18.0	34.2±18.9	40.2±19.4	34.5±19.7
HDL-cholesterol (mmol/l)	1.06±0.28	1.14±0.27	1.01±0.28	1.12±0.21
Triglyceride (mmol/l)	1.80±0.62	1.43±0.69	1.89±0.69	1.34±0.44
Free fatty acid (μmol/L)	580.3±101.7	548±95.6	669.2±127.4	492.0±101.4
hsCRP (mg/L)	2.01±1.33	1.79±1.22	2.92±1.98	0.62±0.44

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Follow-Up Angiographic Data

	Control	Rosiglitazone	P
MLD (mm)	1.91±1.05	2.49±0.88	0.009
Diameter Stenosis (%)	40.60±31.90	23.00±23.40	0.004
Lumen loss (mm)	1.20±0.97	0.65±0.73	0.005
Loss index	0.49±0.42	0.29±0.31	0.014
Restenosis rate (%)	38.2	17.6	0.03

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Clinical Follow-Up Data

at 6 months

	Rosi	Control	p
Death	0	0	
MI	1*	0	
Target lesion revascularization	3	7	
MACE	3	7	0.25

** MI due to subacute thromosis*

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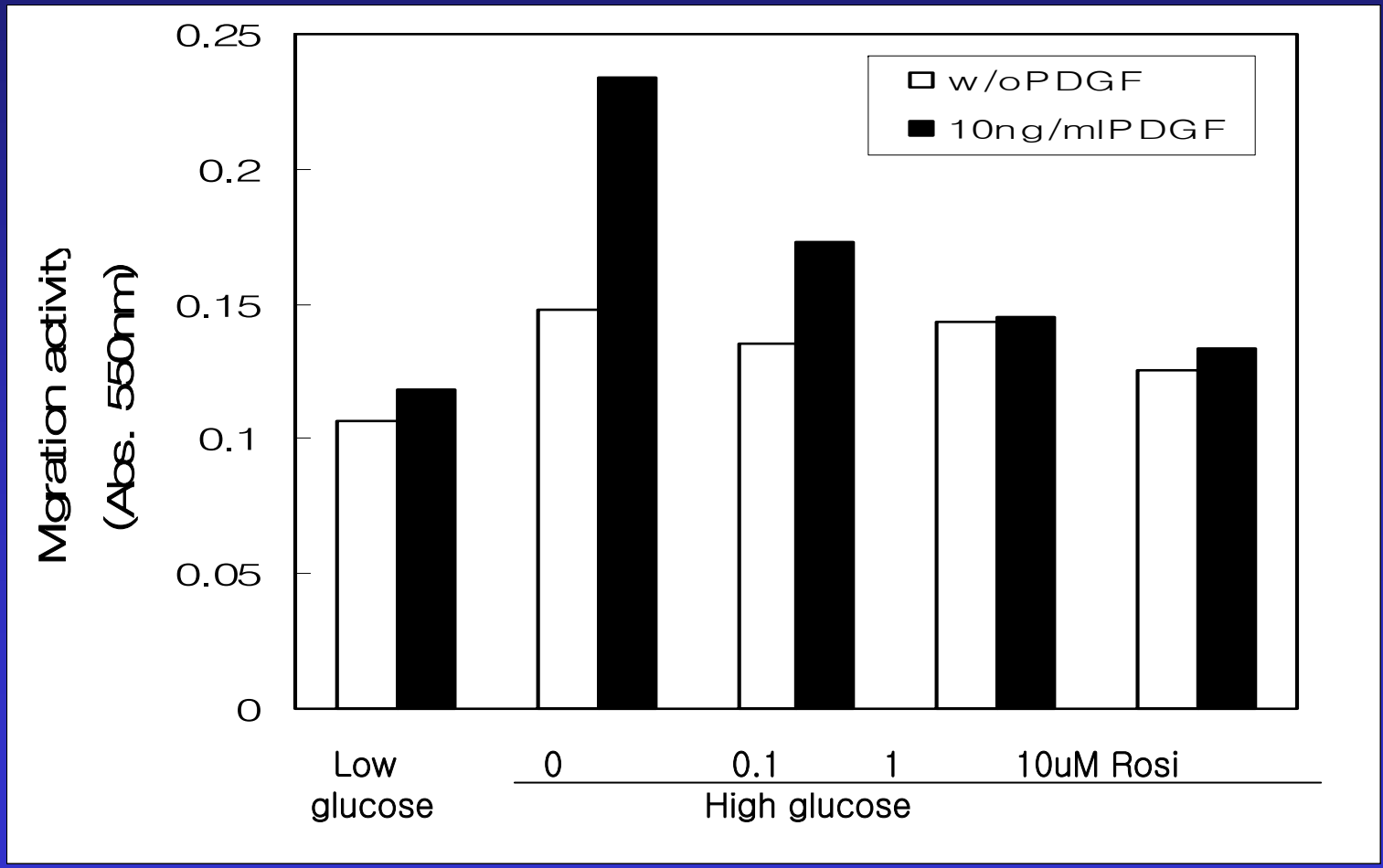
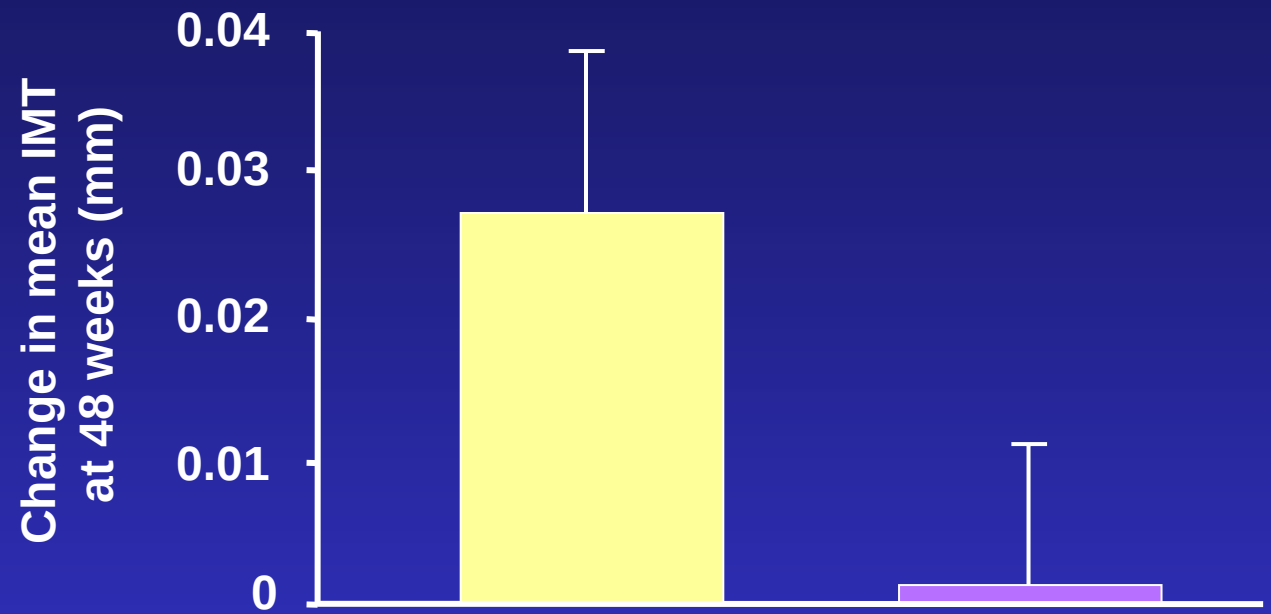
The Effects of Rosiglitazone on VSMC migration



Rosiglitazone: effect on carotid IMT progression



	PBO	RSG
Baseline	0.815	0.823
n =	41	39
Progression rate (mm/48 weeks) =	0.031	– 0.012*

IMT = intima-media thickness
Patients with clinically stable coronary artery disease without diabetes
RSG dose 4 mg/day for initial 8 weeks; 8 mg/day for remaining 40 weeks
**P* = 0.03 vs. PBO

Error bars = SE

Sidhu JS, *et al. Arterioscler Thromb Vasc Biol* 2004; 24:930–934.

Conclusion

- In this study, rosiglitazone has dramatically reduced restenosis rate of CAOD pateints with coronary stenting in Type 2 diabetes.

- In type 2 diabetes patients with CAOD, using PPAR-γ agonist, not only for glucose lowering and insulin sensitizing effect, but also for anti-inflammatory effect, has to be strongly considered.