Mechanism & effect of cilostazol on symptomatic PAD

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Medications for intermittent claudication

Symptoms (ischemia)

Cilostazol (IA)*

Not recommended

Pentoxyphylline (IIbA)+
L-arginine, L-carnitine, Ginkgo biloba, Folic acid, B_{12} vitamin (IIbB)
Oral PG (Beraprost) (IIIA)
Vitamin E (IIIA)

Prognosis (death/MI/Stroke)

Aspirin (IA)♣ 75-325mg/day
or Clopidogrel (IB)
Statin (IB) <100 mg per dL, < 70mg per dL (very high risk).
Fibric acid derivative (IIaC) (low HDL-C, normal LDL-C, and high TG)
DM control (IIaC) HbA1C < 7%
HTN <140/90 mmHg, <130/80 mmHg (DM or CRF)
βblocker (IA)
ACEI (IIaB)√ *not asymptomatic*

* 100mg bid per day should be considered in all patients with lifestyle-limiting claudication (in the absence of heart failure)
+ 400mg tid per day (clinical effectiveness is marginal and not well established)
♣ Indicated symptomatic or asymptomatic PAD patients
√ ACE inhibitors may be considered for patients with asymptomatic lower extremity PAD to reduce the risk of adverse cardiovascular events (IIbB)

Contents

1. **Mechanism of cilostazol**
    1. Antiplatelet effect
    2. Vasodilating effect
    3. Inhibit proliferation of human vascular smooth muscle cells & Abolish neointimal formation
    4. Improvement of lipid profiles
    5. Improvement Endothelial cell function
2. **Effect of cilostazol on symptomatic PAD**
    1. Improve Symptom & QOL
    2. Prevent progression of atherosclerosis

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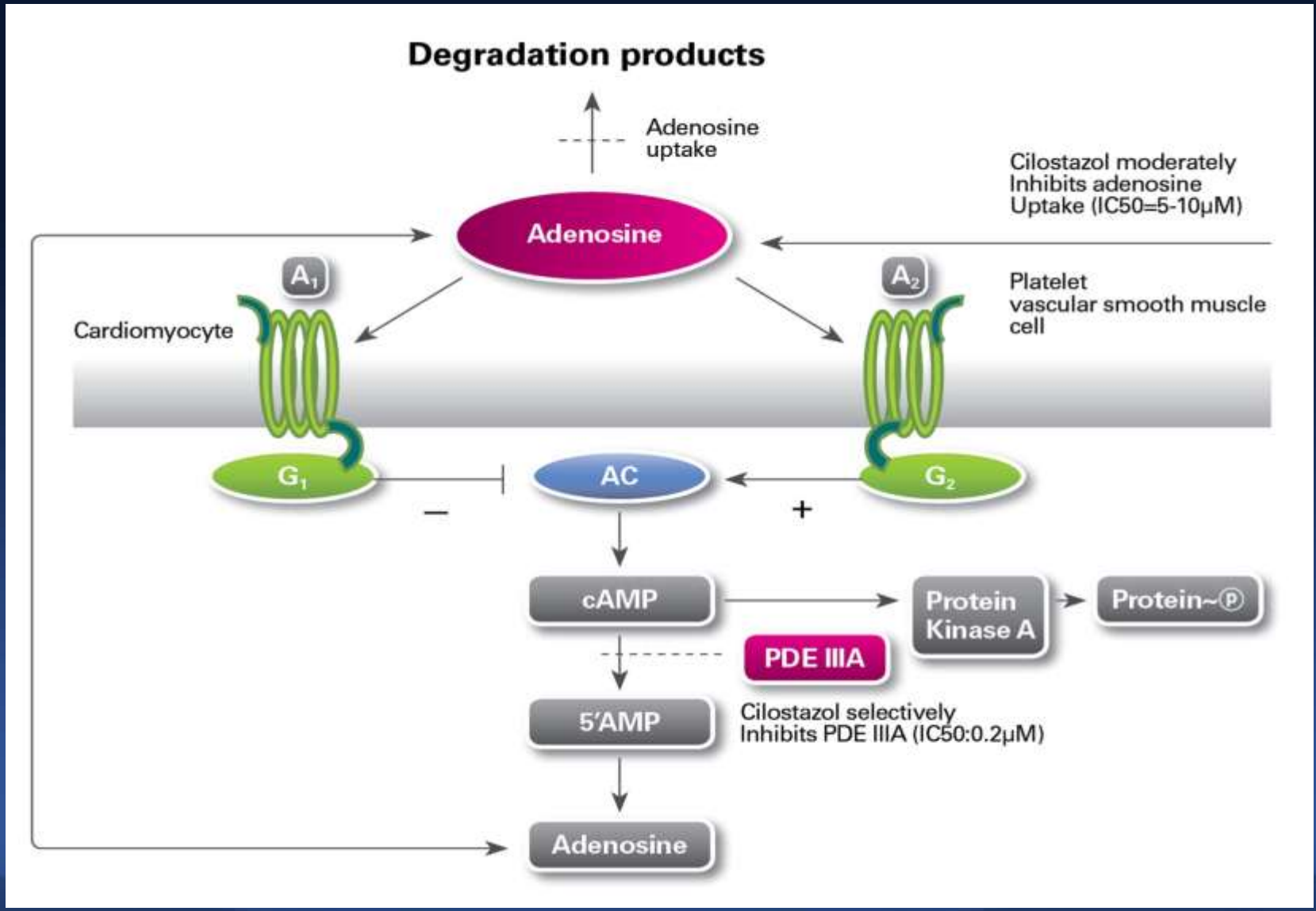
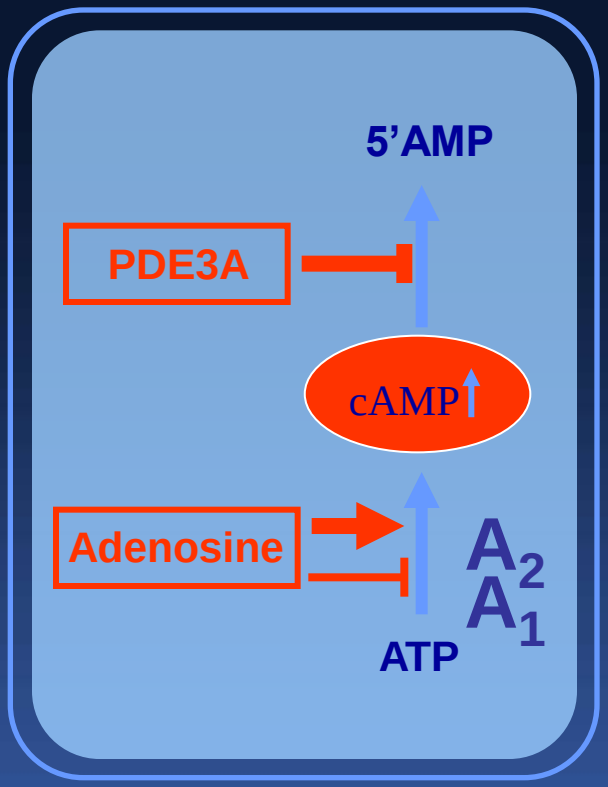
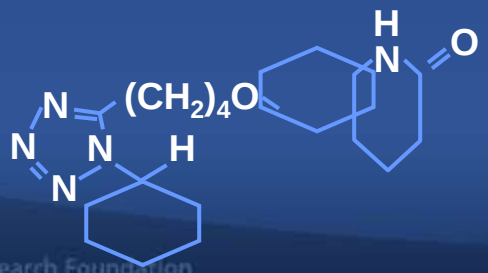
Mechanism overview of Cilostazol

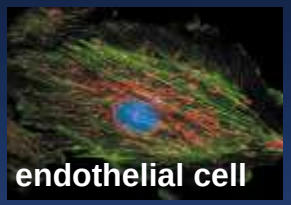


Mechanism overview of Cilostazol

- Cellular targets



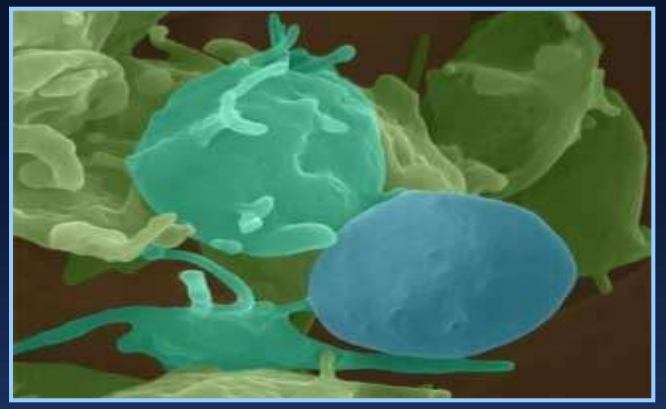


Targets	cAMP actions (selected)
 platelet	Inhibition of aggregation, Inhibit ion of expression of adhesion mo lecules
 endothelial cell	**Inhibition of expression of adhesion molecules Angiogenesis**
 smooth muscle cell	Vasodilatory action Inhibition of proliferation, migration and matrix synthesis, Headache
 cardiocyte	Palpitation Tachycardia

Effects on platelets

Elevation of cAMP via inhibition of PDE3 dependent degradation

Elevation of cAMP via adenosine (A2) induced stimulation of cAMP formation



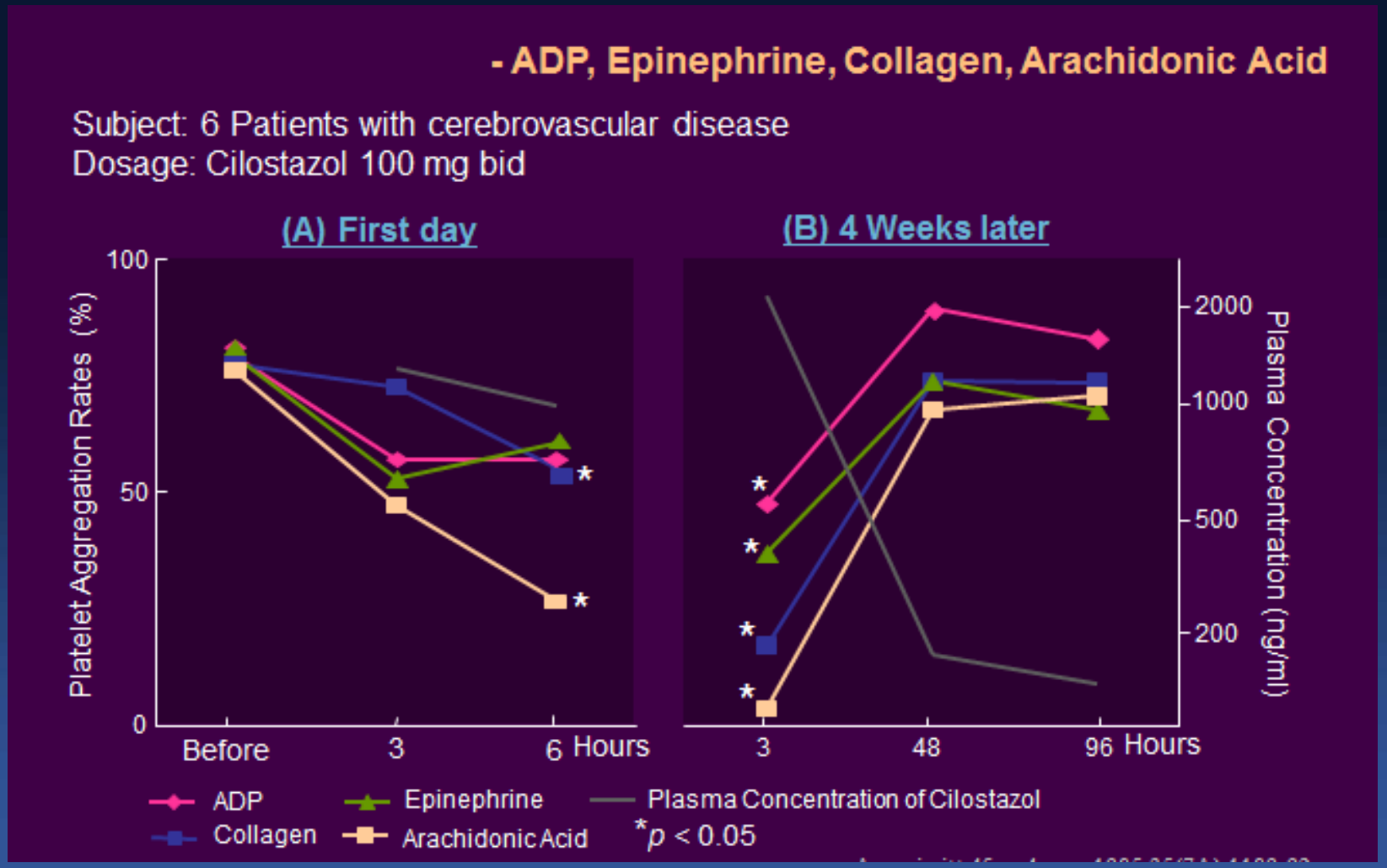
Inhibition of expression of platelet activation markers (P-selectin, platelet derived microparticles)

Inhibition of activation of GP IIb/IIIa receptors

Result:

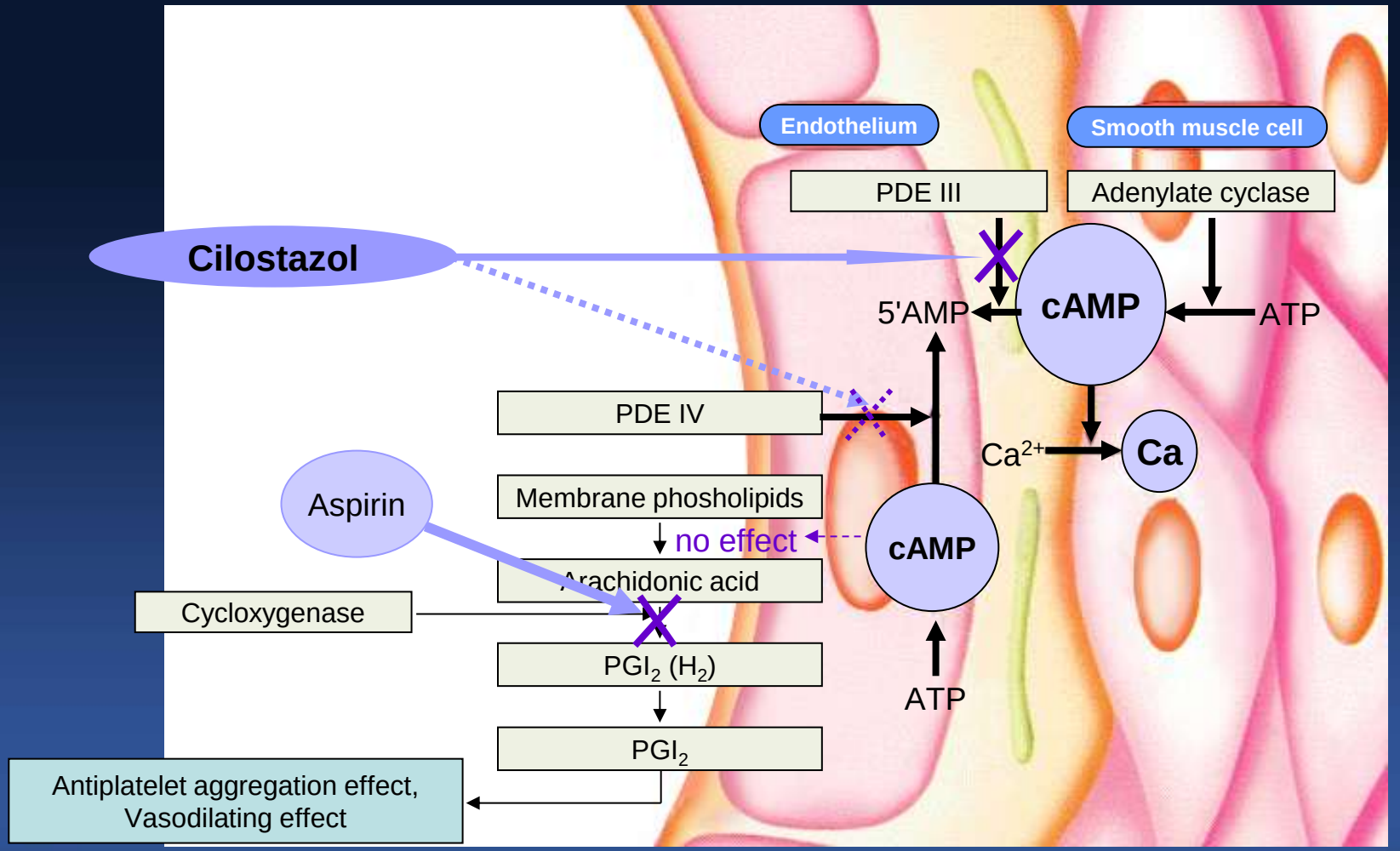
Inhibition of platelet aggregation, adhesion and secretion

Anti-Platelet Aggregation Effect



Arzneimittelforschung. 1985;35(7A):1189-92

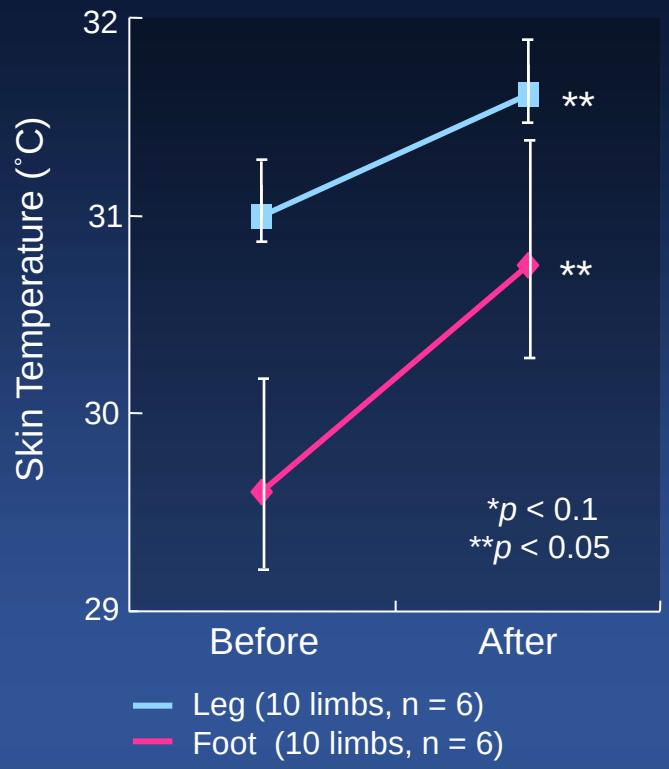
Anti-Platelet Aggregation Effect

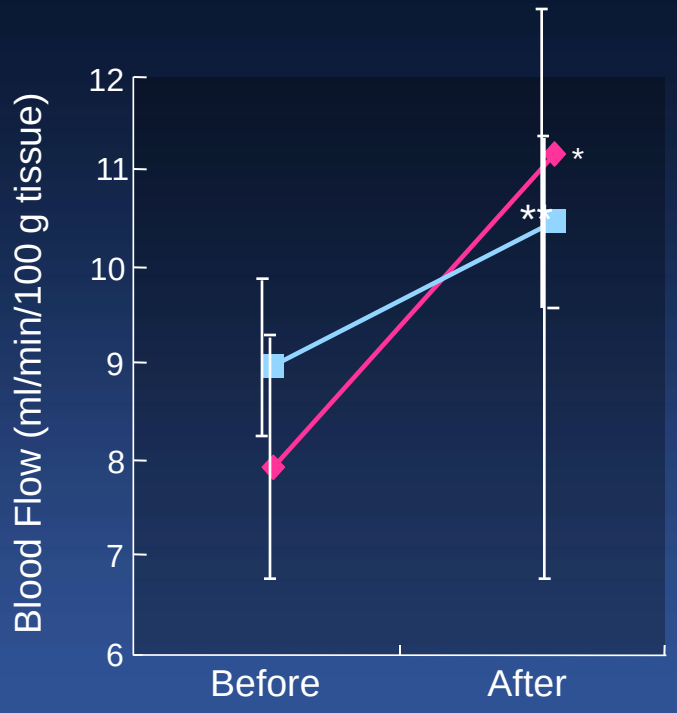


Improvement of Blood Flow

- in peripheral arterial occlusive disease patients

Subject: 6 Peripheral arterial occlusive disease patients (5 TAO, 1 ASO)
Dosage: Cilostazol 200 mg/day for 6 weeks



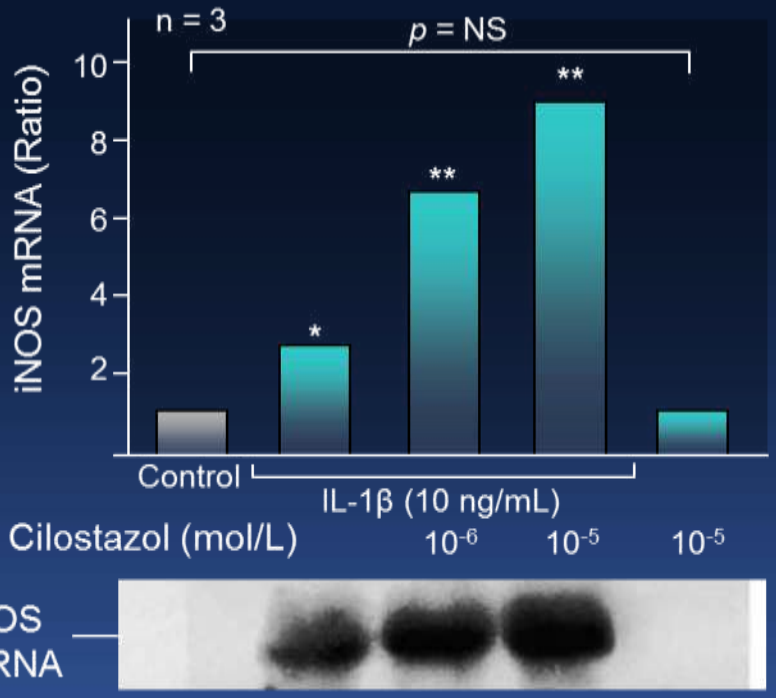


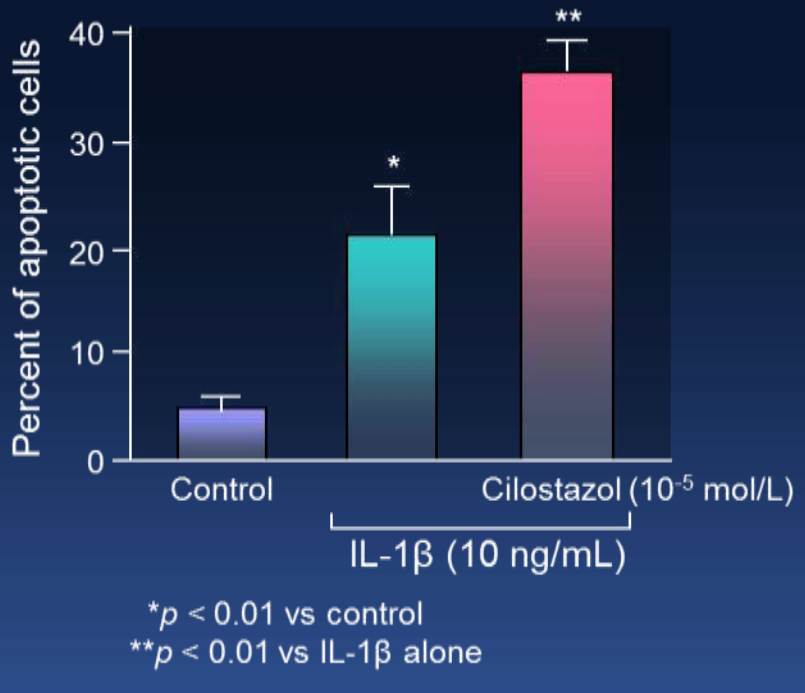
TAO (Thromboangitis Obliterans), ASO (Arteriosclerosis Obliterans)
Arzneimittelforschung. 1985;35(7A);1203-8

in vitro

Pro-apoptotic effect of Cilostazol on VSMC

Rat vascular muscle cell, Cultured for 24 hours



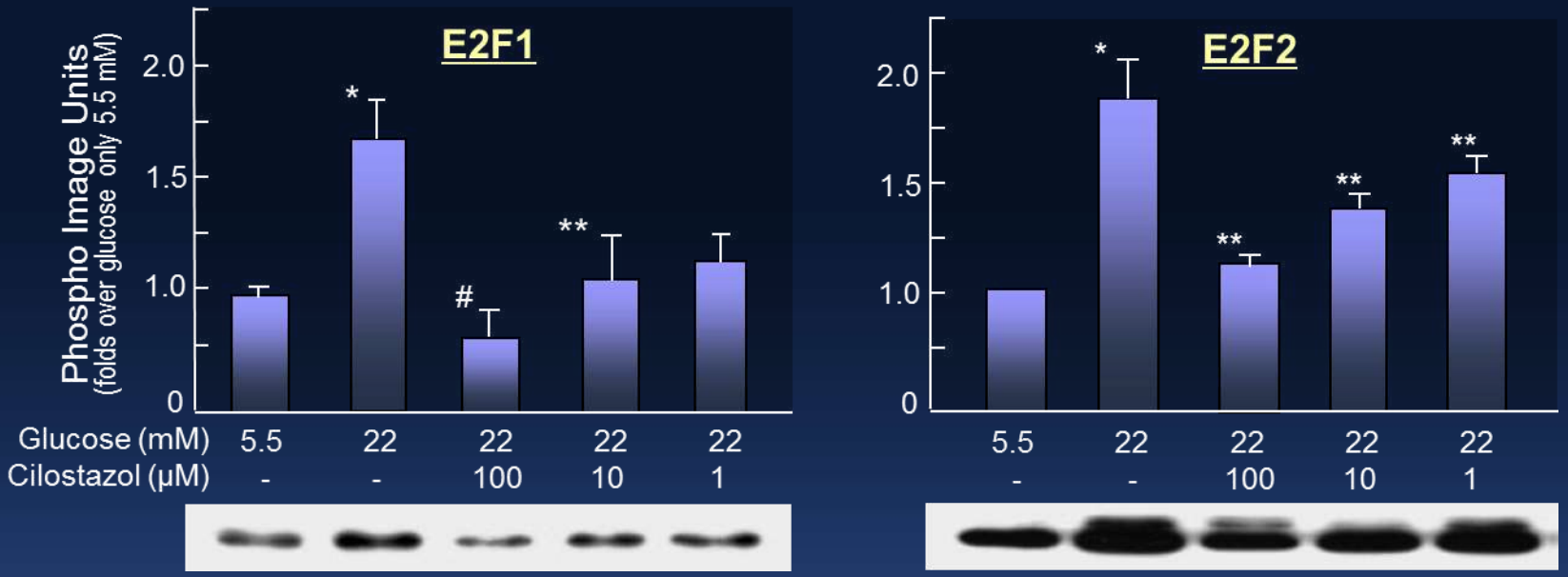


- Cilostazol increases IL-1β induced NO production in the vascular smooth muscle cell.
- Cilostazol increases IL-1β induced apoptosis in the vascular smooth muscle cell.

iNOS: Inducible Nitric Oxide Synthase

Ito C et al. Cellular Signaling. 2002;14:625-632

Effect on E2F Protein Expression

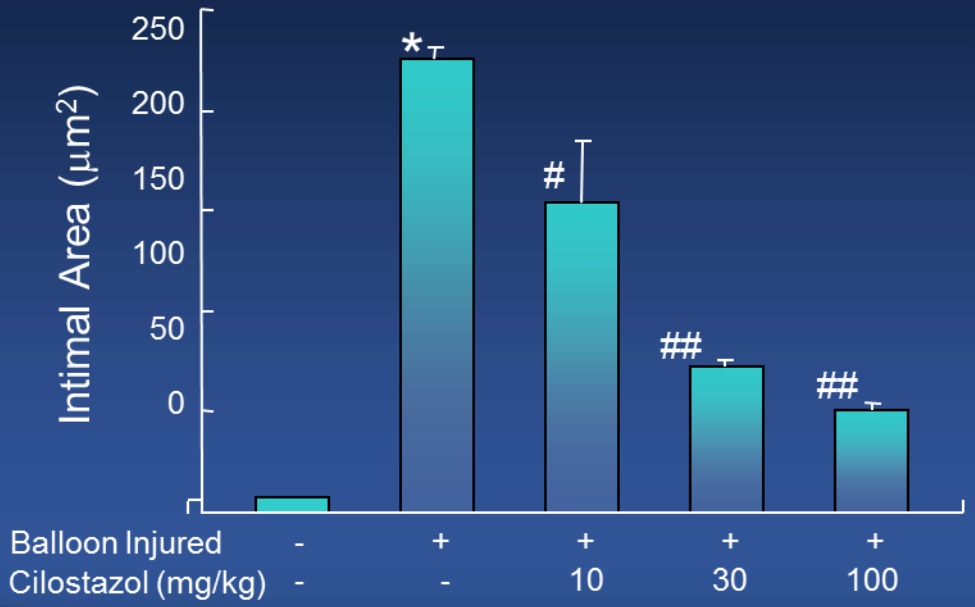


- Cilostazol effectively reduces high-glucose-stimulated E2F activity, as well as proliferation of VSMC.
- Cilostazol helps to prevent the development of restenosis after percutaneous transluminal coronary angioplasty, especially in patients with diabetes.

Lee IK et al. Hypertension. 2005 Apr;45(4):552-6

Effects on Neointimal Formation

- Rat Carotid Artery



A. Control
B. Balloon Injured
C. Cilostazol 10 mg/kg
D. Cilostazol 30 mg/kg
E. Cilostazol 100 mg/kg

Cilostazol inhibited high glucose-induced VSMC proliferation.

*$p < 0.01$ vs control
#$p < 0.05$, ##$p < 0.01$ vs balloon injured.

Lee IK et al. Hypertension. 2005 Apr;45(4):552-6

Improvement of lipid profiles

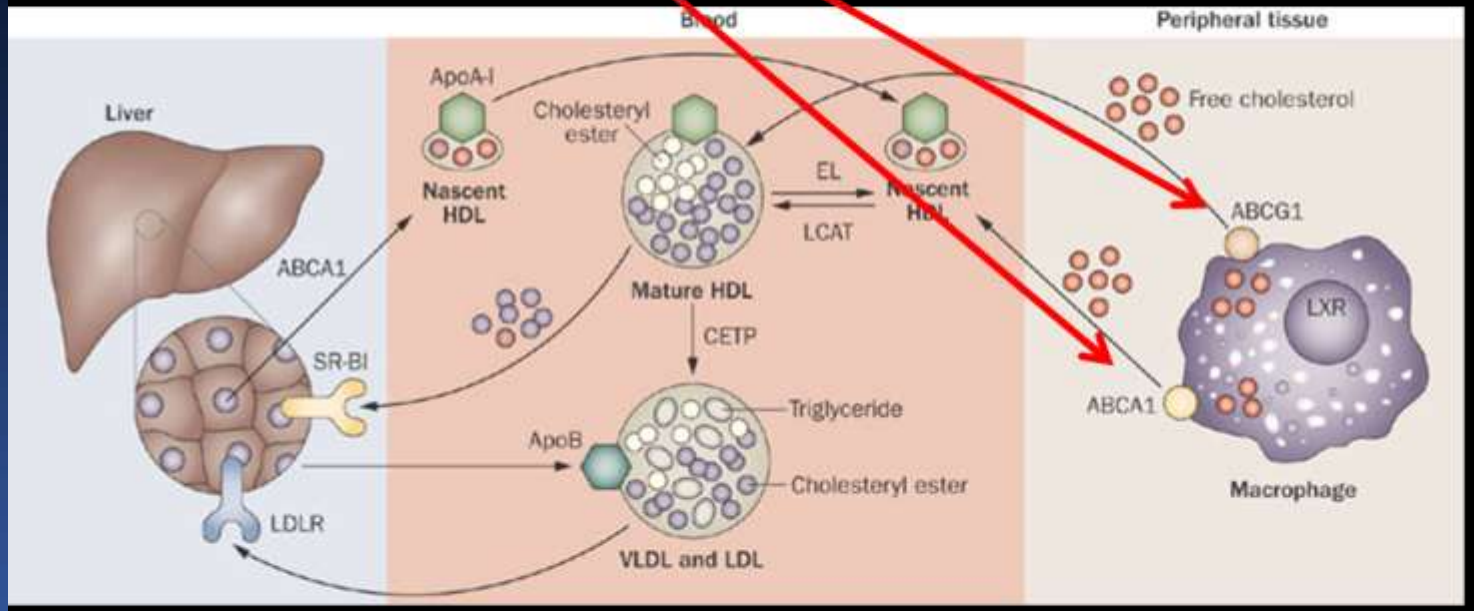
Cilostazol

PDE III

cAMP ↑ → 5'AMP

↓

LPL activity, LPL release ↑



TG ↓

HDL-C ↑

Apo A/ Apo B ↑

RLP ↓

LPL activity ↑

LPL release↑

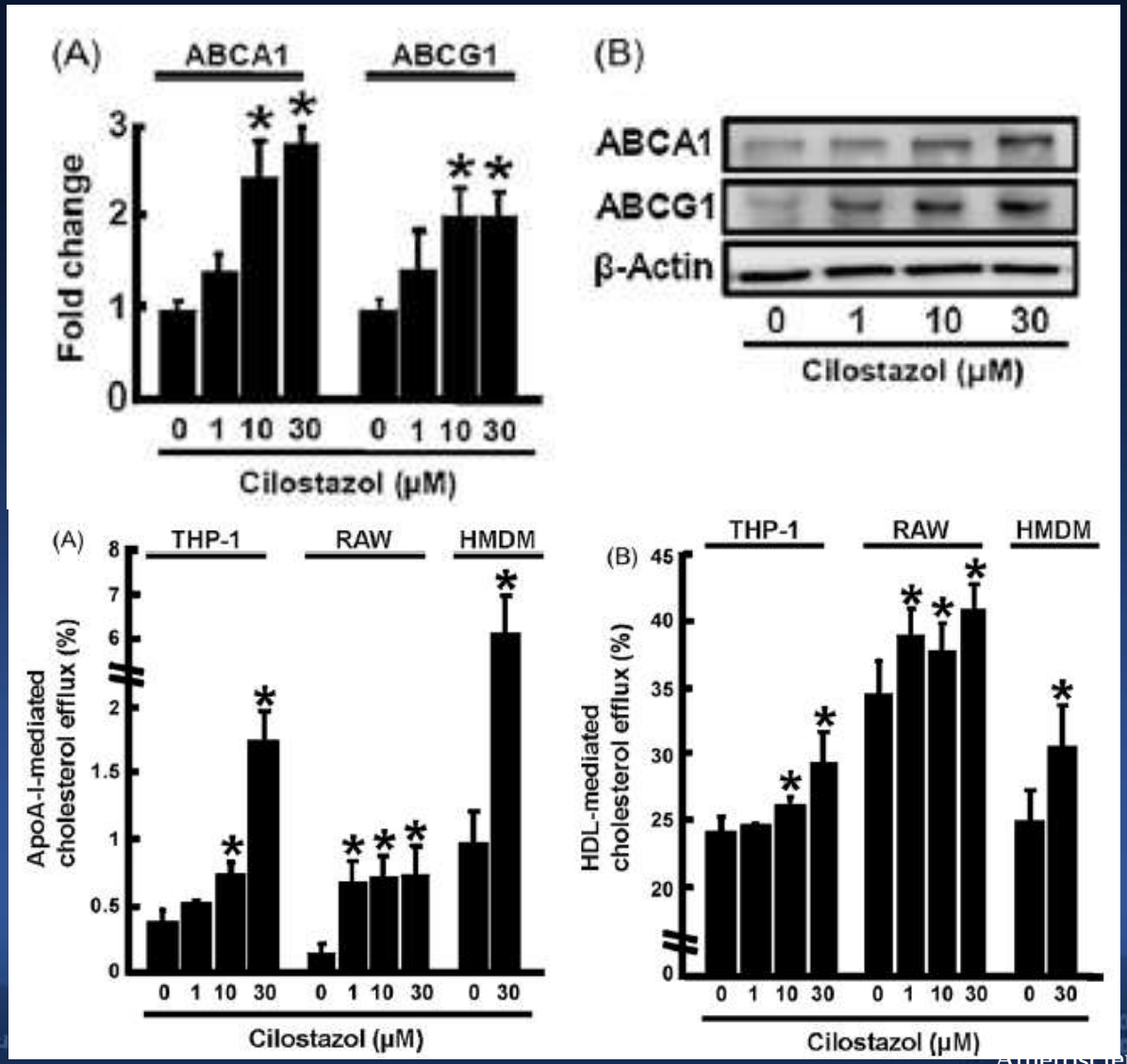
RCT(Reverse cholesterol transport)↑

Cilostazol increases cAMP/PKA activity

Cilostazol stimulates macrophage ABCA1 and ABCG1expression and cholesterol efflux mediated by apoA-I and HDL

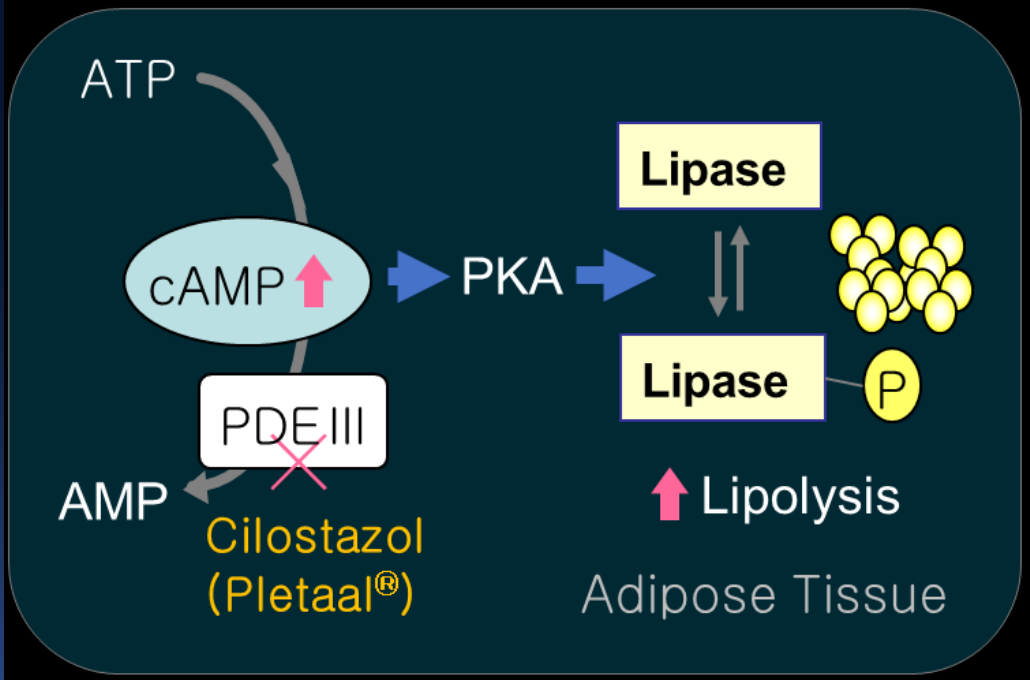
Cilostazol enhances macrophage RCT in vitro and in vivo

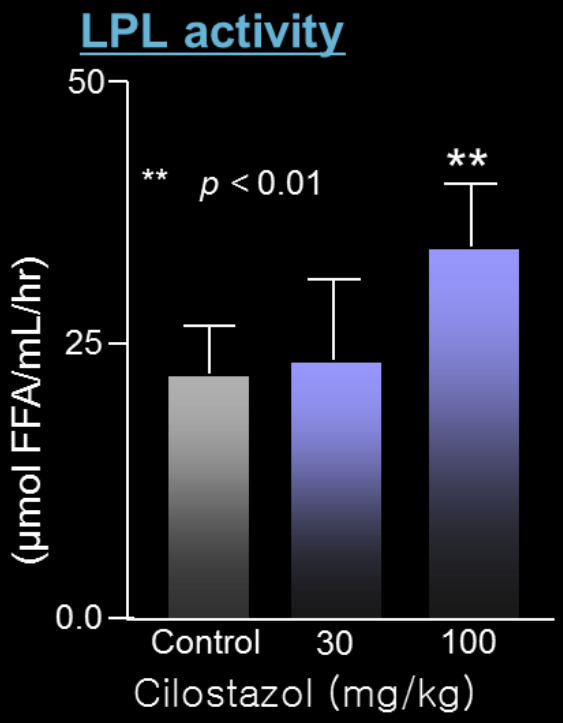
Cilostazol enhances cholesterol efflux from macrophages by increasing ABCA1 and ABCG1 expression ➔ **HDL ↑**



Atherosclerosis 213 (2010) 135–141

Effect on Adipocytes Mechanism of Lipid Metabolism Improvement : TG ↓





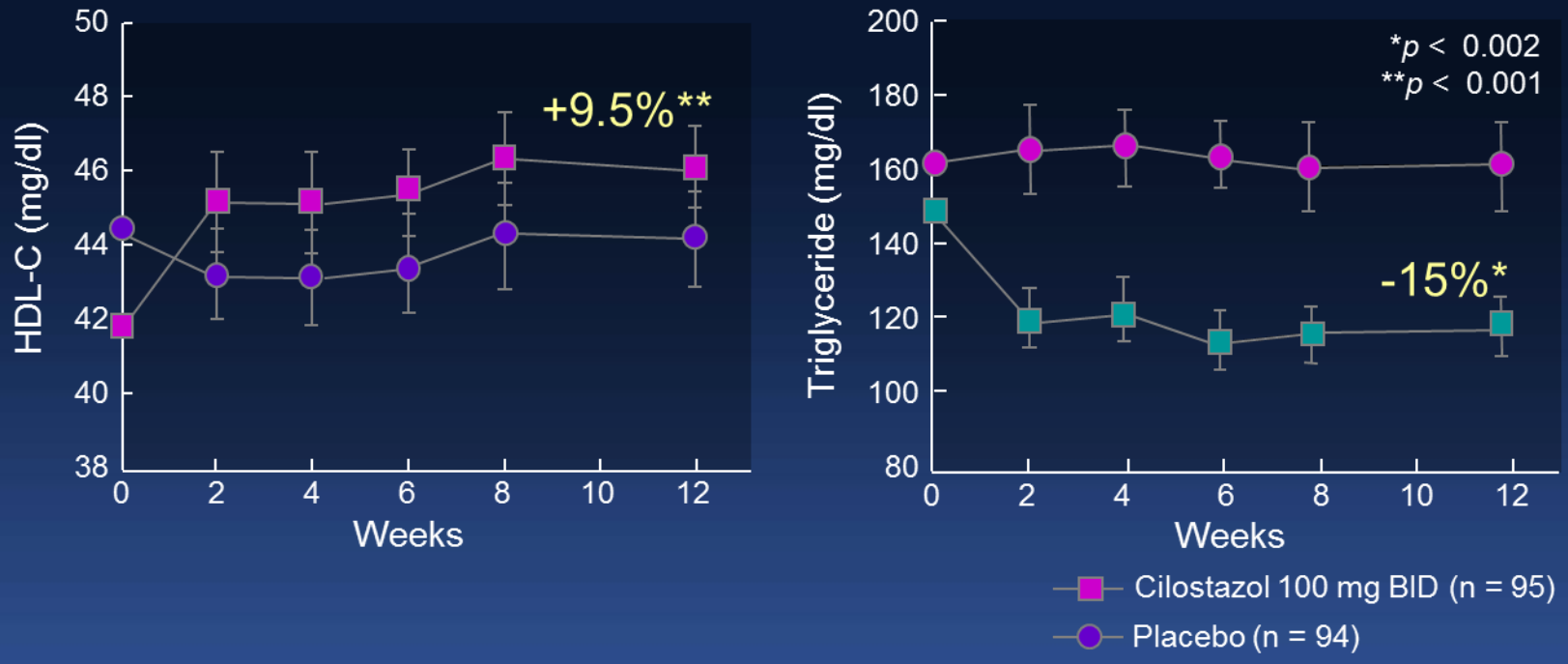
The increase in cAMP/PKA activity results in phosphorylation and increased activity of LPL leading to increased hydrolysis of stored triglyceride.

PKA: Protein Kinase A
LPL: Lipoprotein Lipase

Takeshi Tani et al. Atherosclerosis. 2000;152:299-305
Motoyashiki T, Morita T, Ueki H. Biol Pharm Bull. 1996;19:1412-1416

Clinical Evidence : Effect of Cilostazol on Plasma Lipoproteins in Patients With Intermittent Claudication.

Subjects: 189 patients with intermittent claudication



In addition to improving the symptoms of IC, Cilostazol also favorably modifies plasma lipoproteins in patients with peripheral arterial disease.

Elam MB et. al. Arterioscler Throb Vasc Biol. 1998;18:1942-1947

Clinical Evidence : Meta-Analysis of 8 Phase III Clinical Trial

- Effects on Serum Lipids

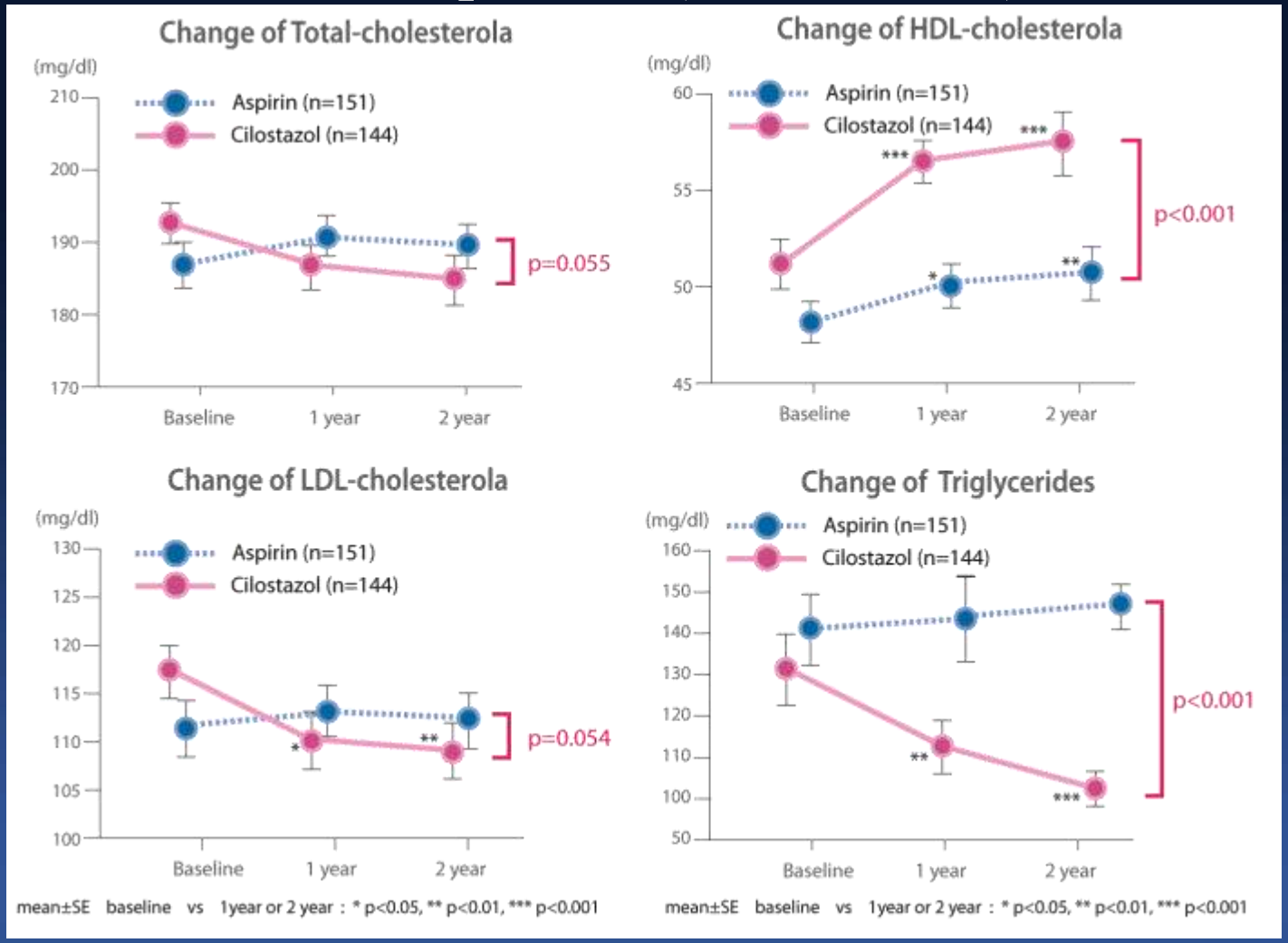
Serum lipid profile through 24 weeks

	Data Point (mean)	Cilostazol 50 mg bid	Cilostazol 100 mg bid	Placebo	Pentoxifylline 400 mg tid
Triglycerides	Baseline (mg/dL)	237	217	229	216
	n	234	736	769	221
	Δ (mg/dL)	-54	**-52***	-22	-21
	Δ (%)	-13	**-16***	0.6	-0.9
HDL cholesterol	Baseline (mg/dL)	48	44	44	41
	n	234	726	769	221
	Δ (mg/dL)	3	**5***	1	2
	Δ (%)	6	**13***	4	8
LDL cholesterol	Baseline (mg/dL)	136	138	140	143
	n	215	673	696	206
	Δ (mg/dL)	-5	-0.3	0.8	3
	Δ (%)	-0.1	2	22	4

*p = 0.001, compared with pentoxifylline or placebo (Analysis of covariance, Willcoxson rank-sum test)
HDL = High-Density Lipoprotein; **LDL** = Low-Density Lipoprotein;

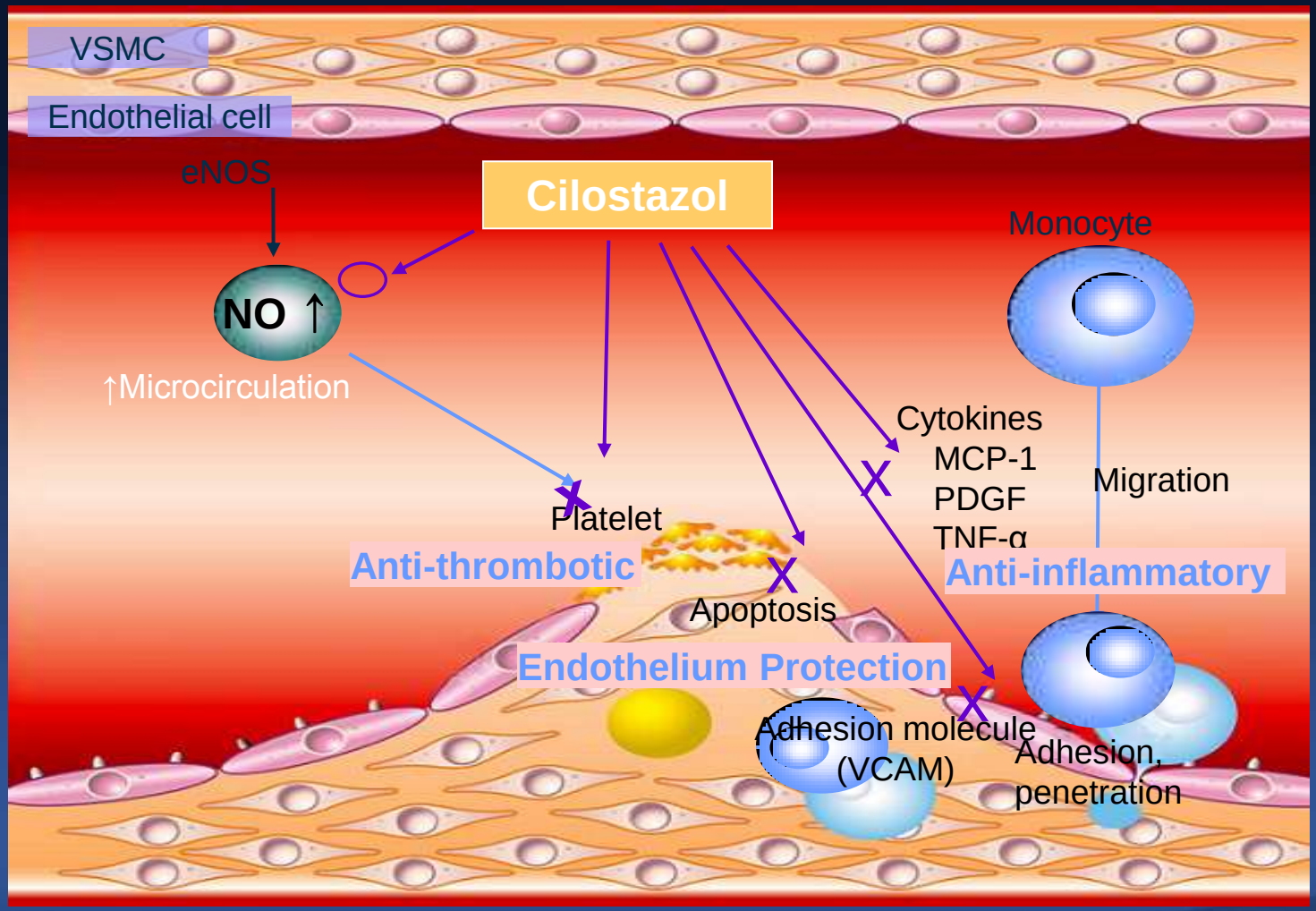
Thompson PD et al. Am J Cardiol. 2002; 90:1314-1319

Clinical Evidence : Effect of Cilostazol on Lipidprofile in type 2 DM with PAD patients (DAPC result)



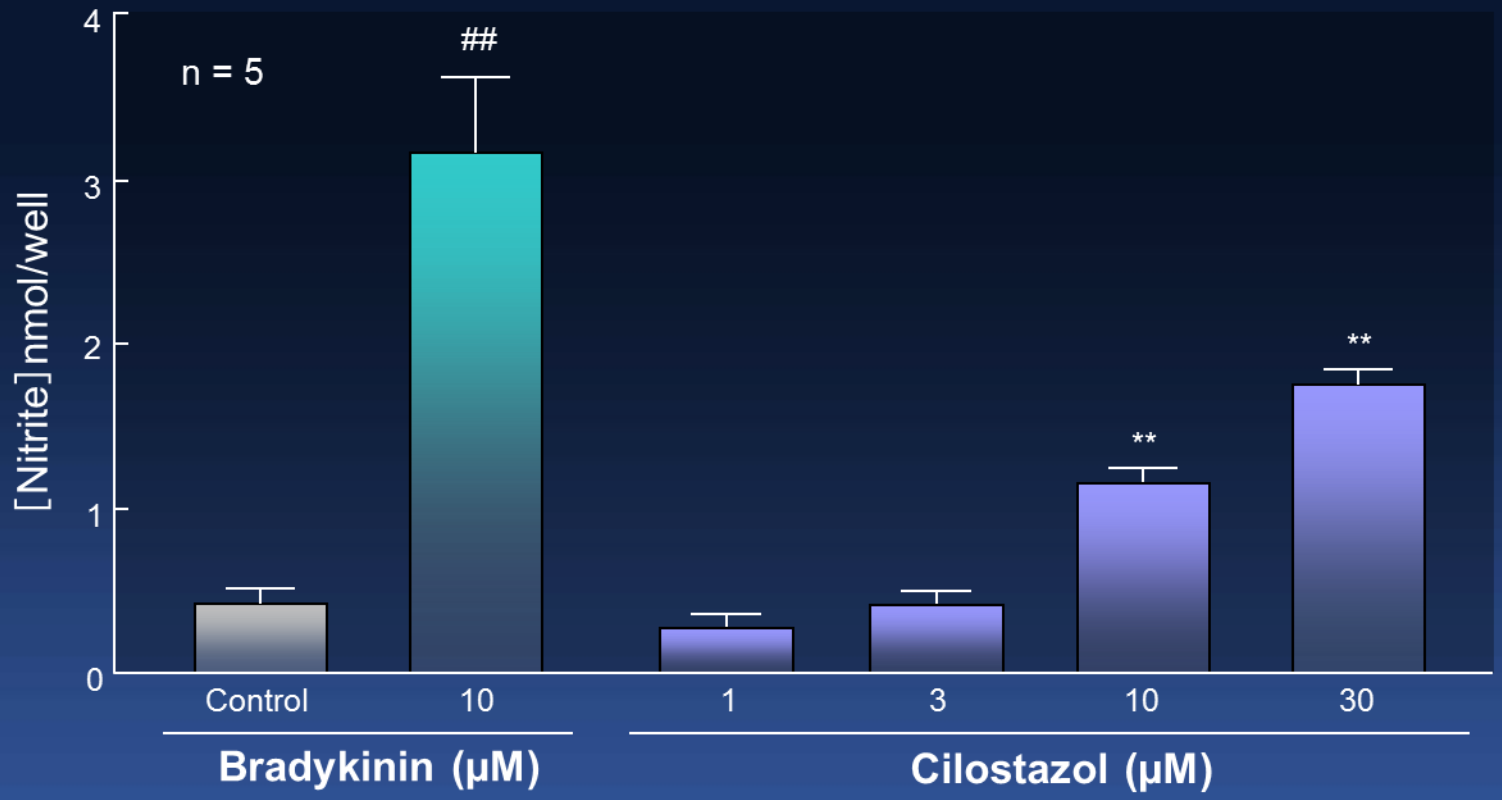
Katakami N. et al. : Circulation. 2010;121:2584-259

Effect of Pletaal® (Cilostazol) on Endothelial Cell



in vitro

Effect on NO Production in Endothelium



Cilostazol increases NO production in the vascular endothelial cell (originated from human femoral artery)

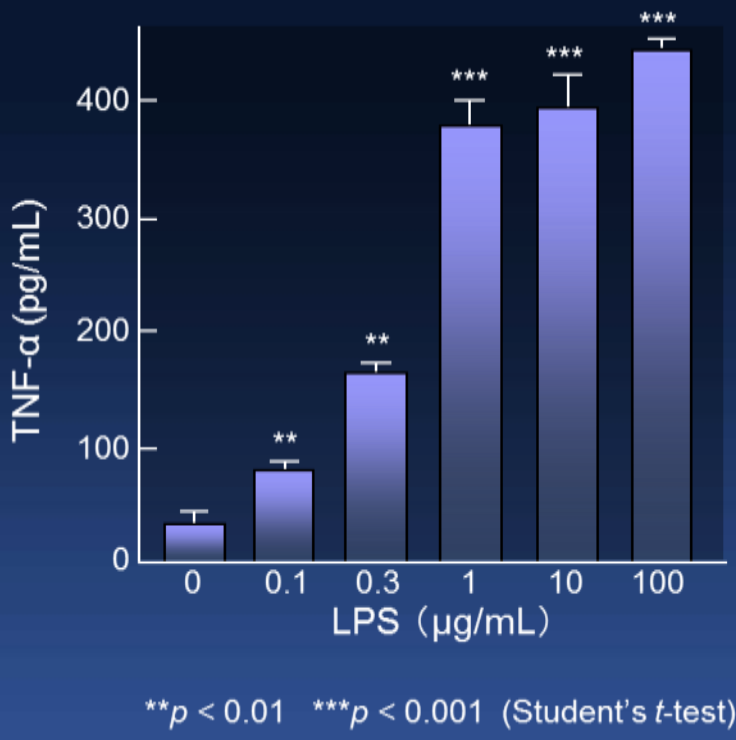
##$p < 0.01$ (two-tailed t -test)
**$p < 0.01$ (two-tailed Dunnett's test)

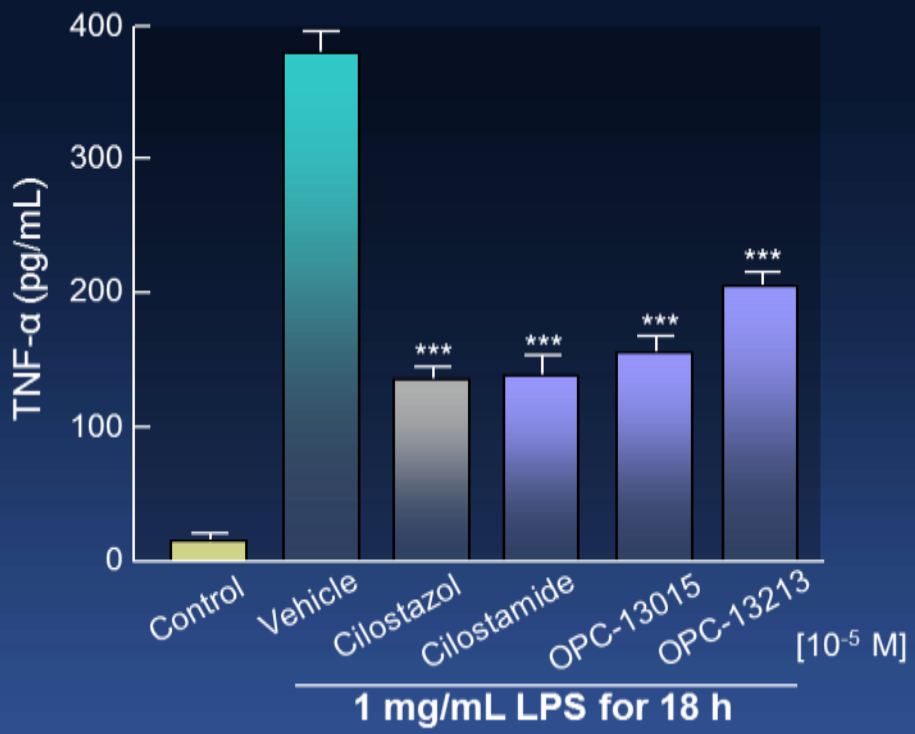
Otsuka Pharmaceutical Data on File

in vitro

Effect of Cilostazol on TNF-α

HUVEC (Human Umbilical Vein Endothelial Cell)





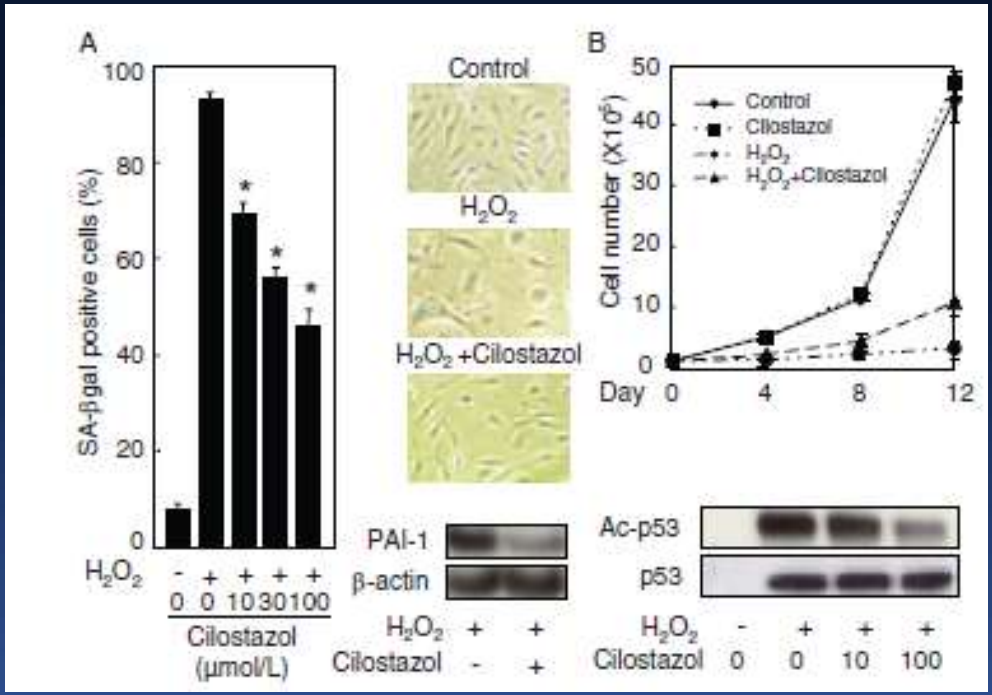
LPS: Lipopolysaccharide

Cilostazol inhibits TNF-α production in the endothelial cell induced by LPS.

Kim KY et al. J Pharmacol Exp Ther. 2002 Feb;300(2):709-15

Inhibits Oxidative Stress via upregulation of Sirt1 in Human Endothelial Cells

√ Cilostazol inhibits oxidative stress–induced premature senescence in human endothelial cells



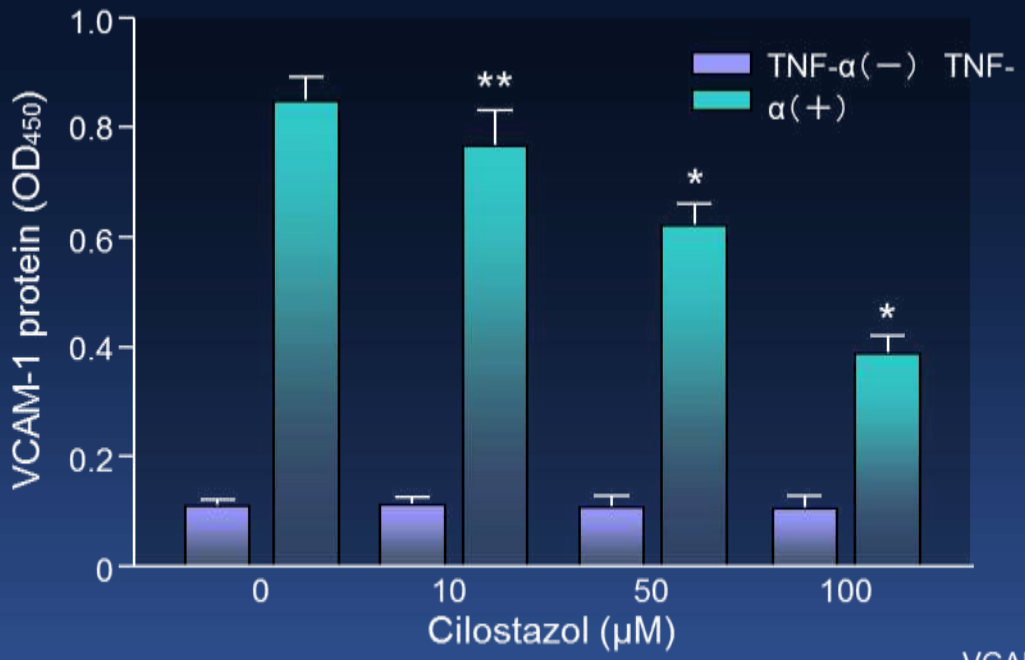
Human umbilical vein endothelial cells (HUVECs) were induced by treatment with hydrogen peroxide (H2O2) as judged by senescence-associated -galactosidase assay (SA-gal), cell morphological appearance, and plasminogen activator inhibitor-1 (PAI-1) expression.

Hidetaka Ota et al. Arteriosler Throm Vasc Biol. 2008,28:1634-1639

in vitro

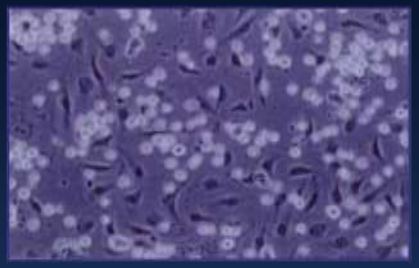
Effect on Expression of Adhesion Molecule

A. Effect on VCAM-1expression

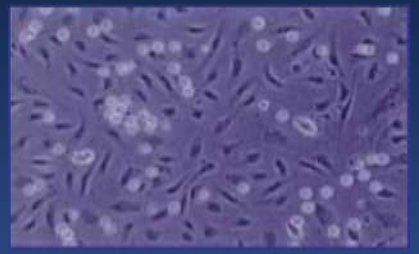


*$p < 0.01$, **$p < 0.05$, (unpaired Student's *t*-test)

B. Effect on U937 cell adhesion to HUVECs



Cilostazol (-)
256±16



Cilostazol (100 μM)
76±20

VCAM-1: Vascular Cell Adhesion Molecule-1
HUVEC: Human Umbilical Vein Endothelial Cell

Cilostazol inhibits onset and proliferation of VCAM on the vascular endothelial cell induced by TNF-α.

Otsuki M et al. Atherosclerosis 2001 Sep;158(1):121-8

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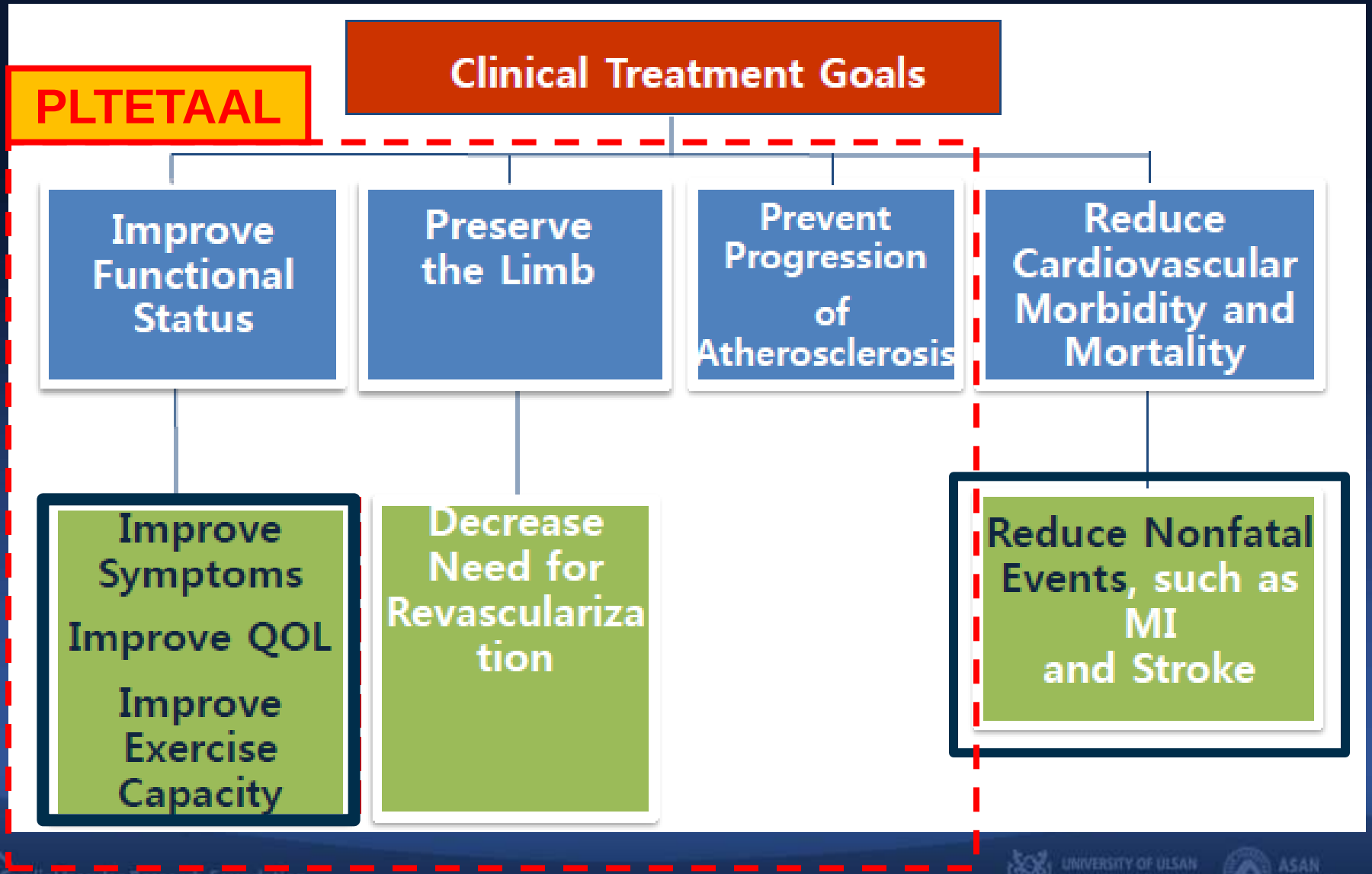
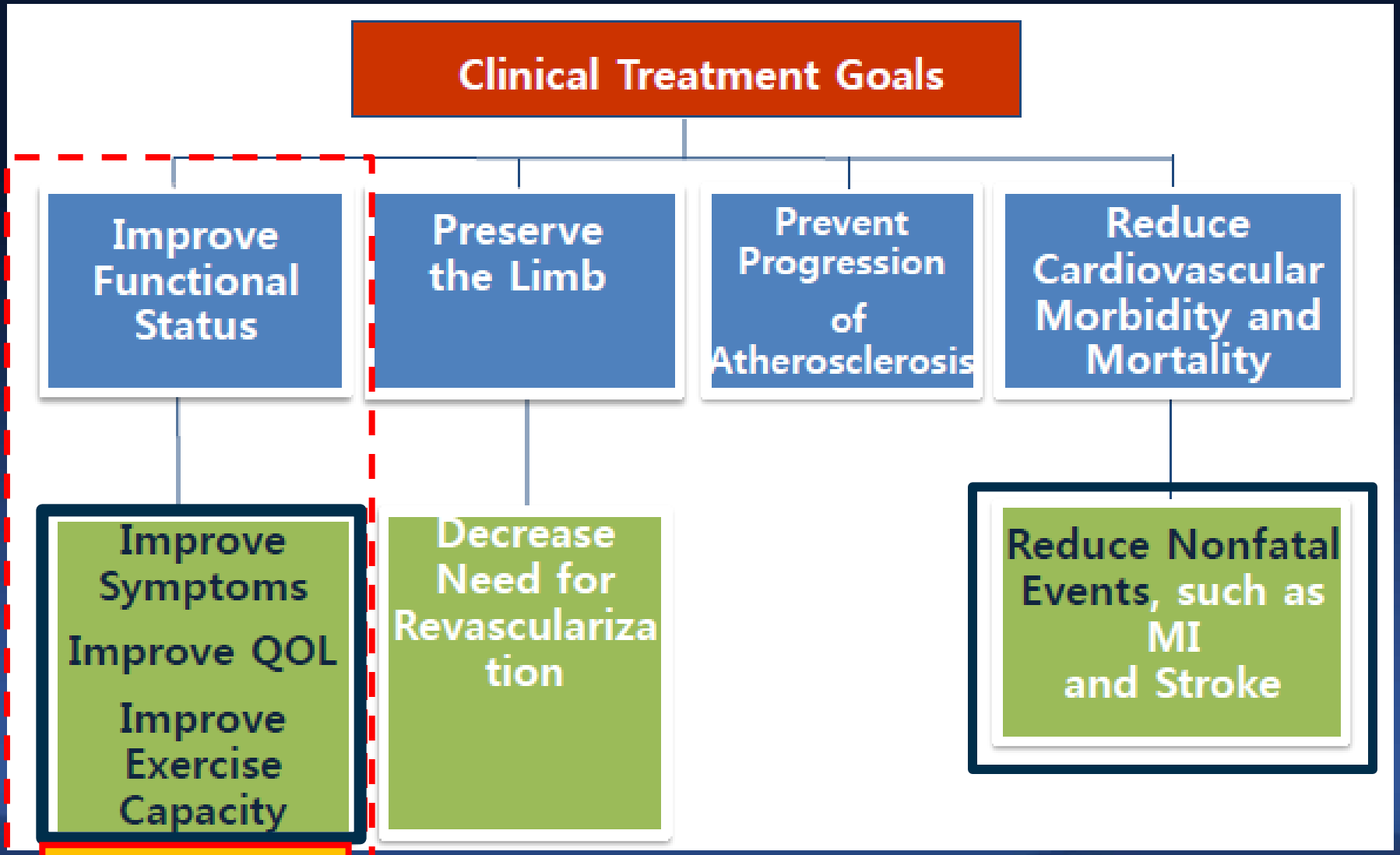
Clinical Treatment Goals of PAD

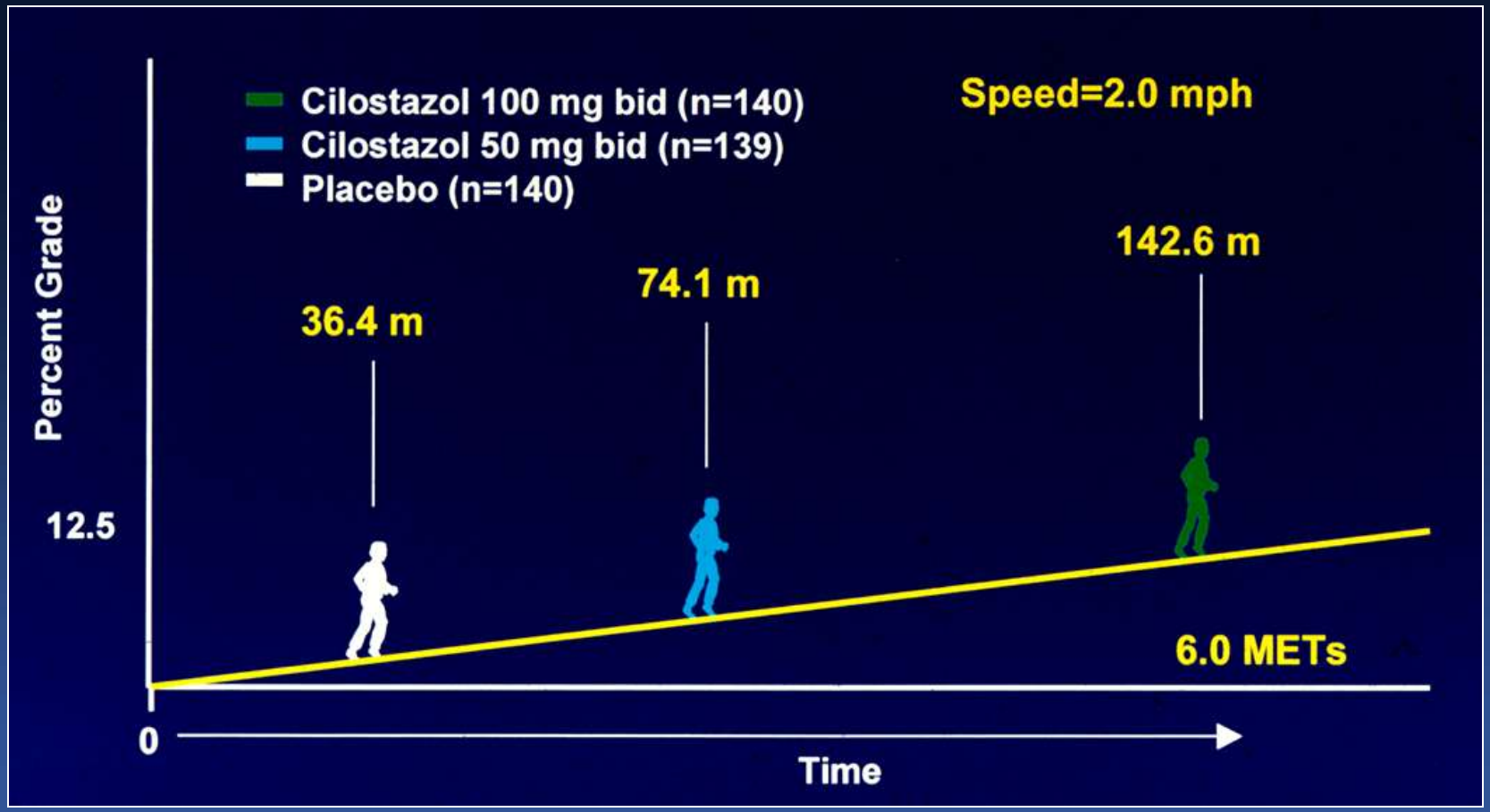


Clinical Treatment Goals of PAD



Dose Response Treadmill Results

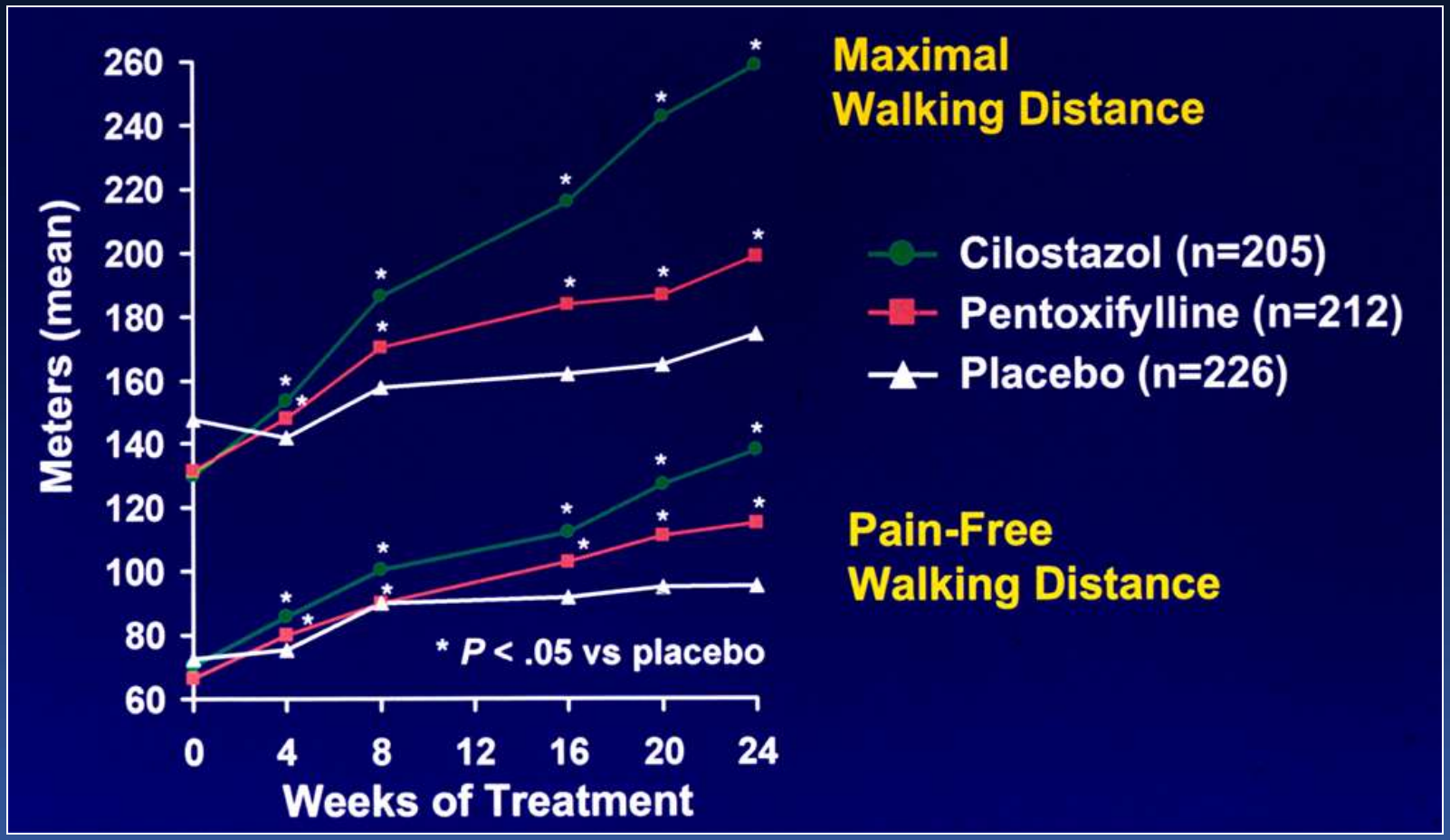
Change in Meters Walked



Cardiovascular and Renal Drugs Advisory Committee
85th Meeting US DHHS, FDA. Bethesda, MD July, 9 1998

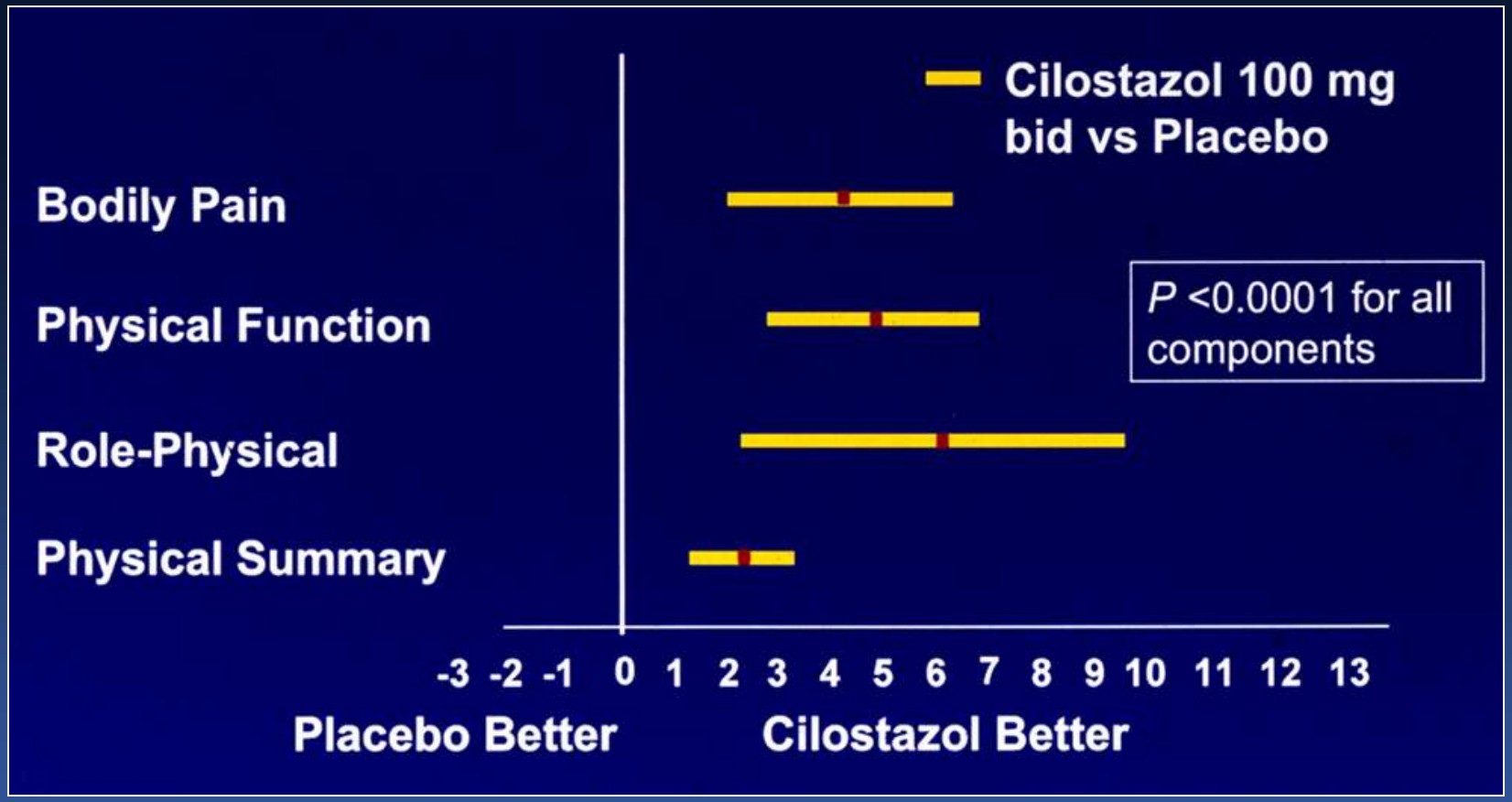
Randomized Trial

Cilostazol, Pentoxifylline and Placebo



Beebe HG, et al
Arch Inten Med 1999;159:2041-50

Estimated Treatment Effect for QOL Data from 6 Pooled U.S. Trials



Cardiovascular and Renal Drugs Advisory Committee
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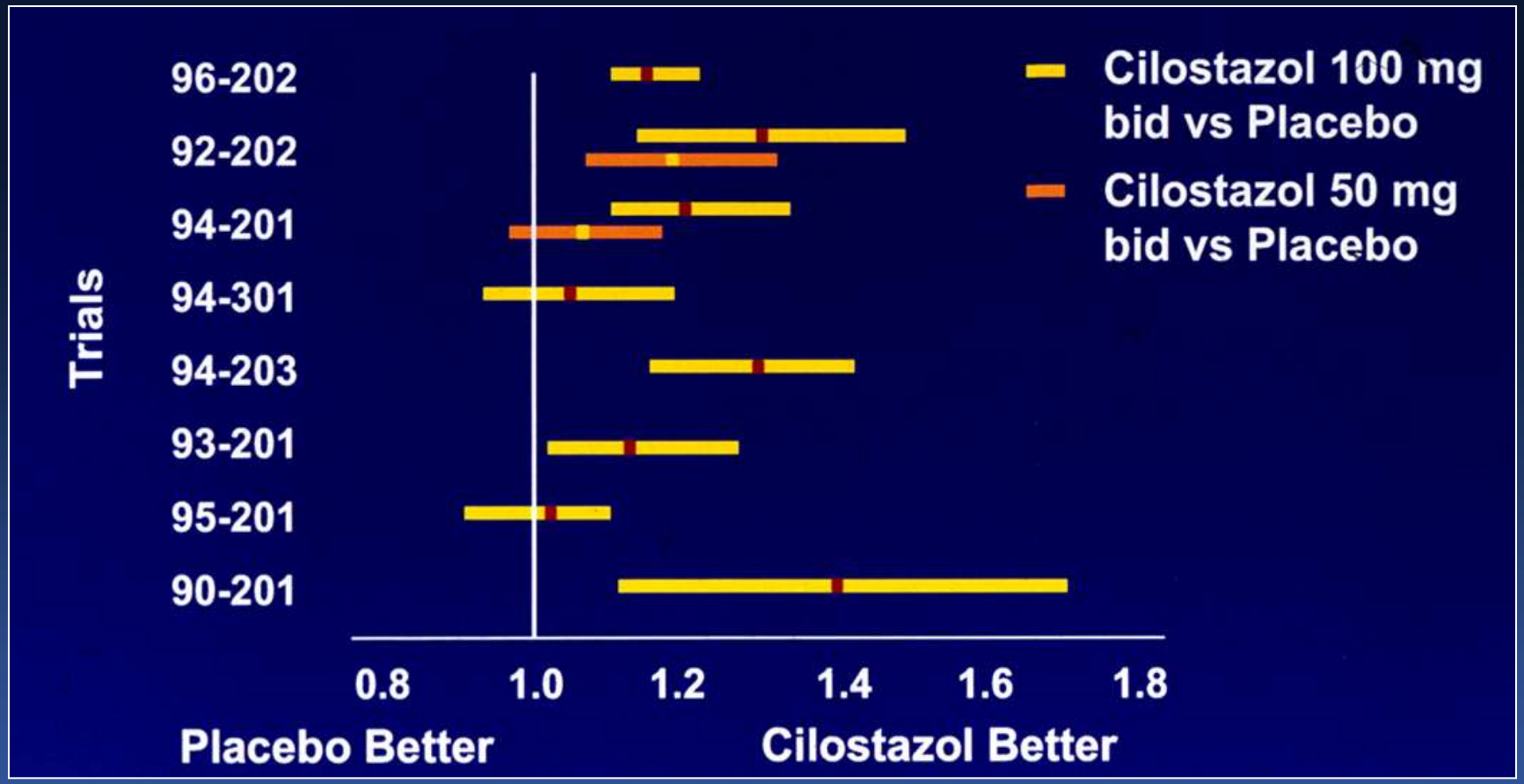
Overview of Cilostazol Efficacy

ACD at End of Treatment for * Controlled Trials



Cardiovascular and Renal Drugs Advisory Committee
85th Meeting US DHHS, FDA. Bethesda, MD July, 9 1998

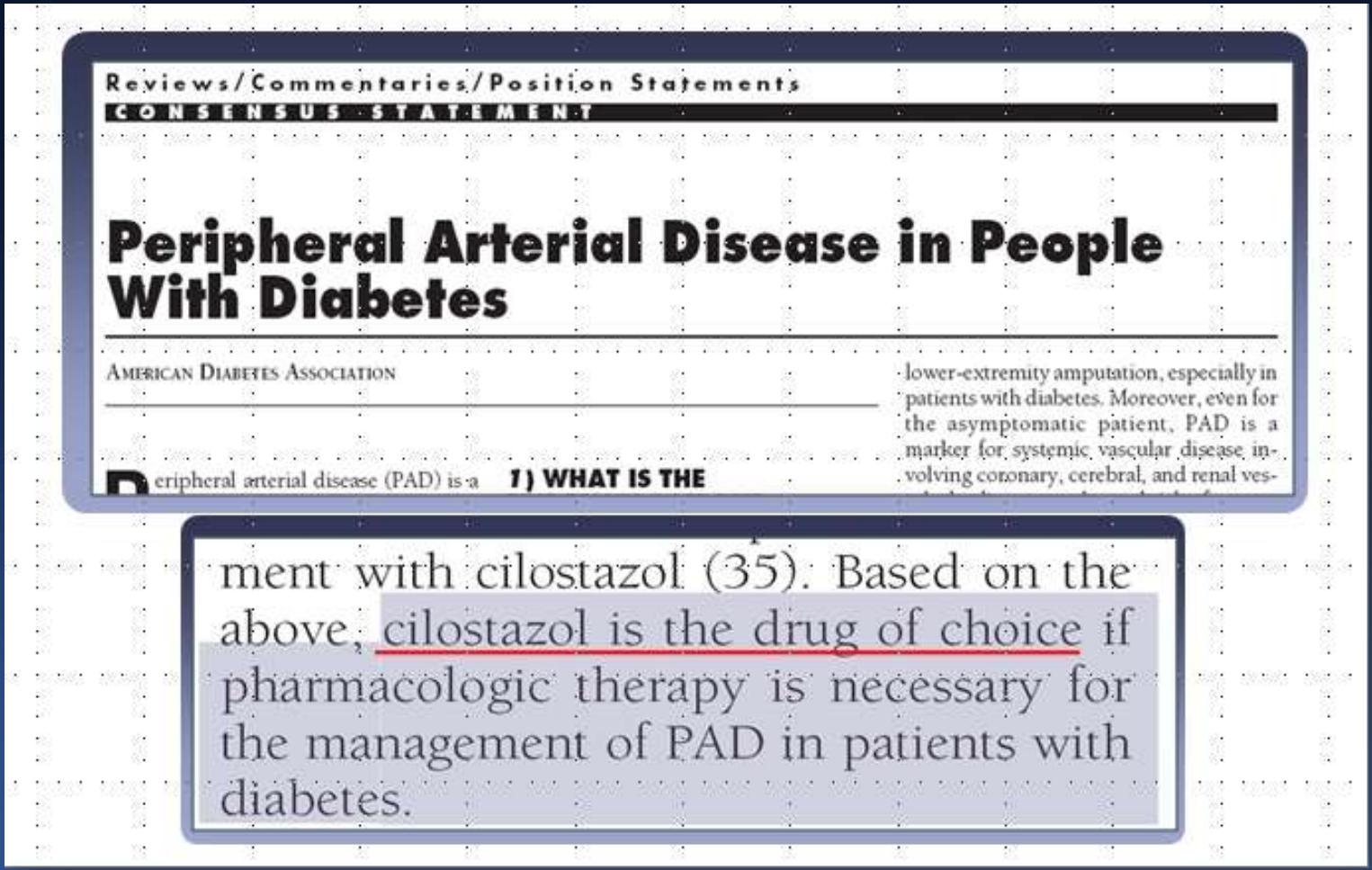
ACC/AHA guideline : Pharmacotherapy of Claudication

Level	Recommendation
Class I A	***Cilostazol(100mg orally 2 times per day)*** *is indicated as an effective therapy to improve symptomas and increase walking distance in patients with lower extremity PAD and intermittent claudication* ***(in the absence of heart failure)*** *A therapeutic trial of* ***cilostazol should be considered*** *in all patients with lifestyle-limiting claudicatioin* ***(in the absecce of heart failure).***
Class II B	***The effectiveness of ginkgo biloba to improve waking distance for patients with intermittent claudication is marginal and not well established.***
Class III A	***Oral vsodilator prostaglandins such as beraprost and iloporst are not effective medications to improve walking distance in patients with intermittent claudication***

Cilostazol

- **Recommendation 16:** Pharmacotherapy for symptoms o f intermittent claudication
  A 3- to 6-month course of **cilostazol should be first-line pharmacotherapy** for the relief of claudication symptoms, as evidence shows both an improvement in treadmill exercise performance and in quality of life.

PAD & Pletaal in Diabetes



Reviews/Commentaries/Position Statements

CONSENSUS STATEMENT

Peripheral Arterial Disease in People With Diabetes

AMERICAN DIABETES ASSOCIATION

Peripheral arterial disease (PAD) is a

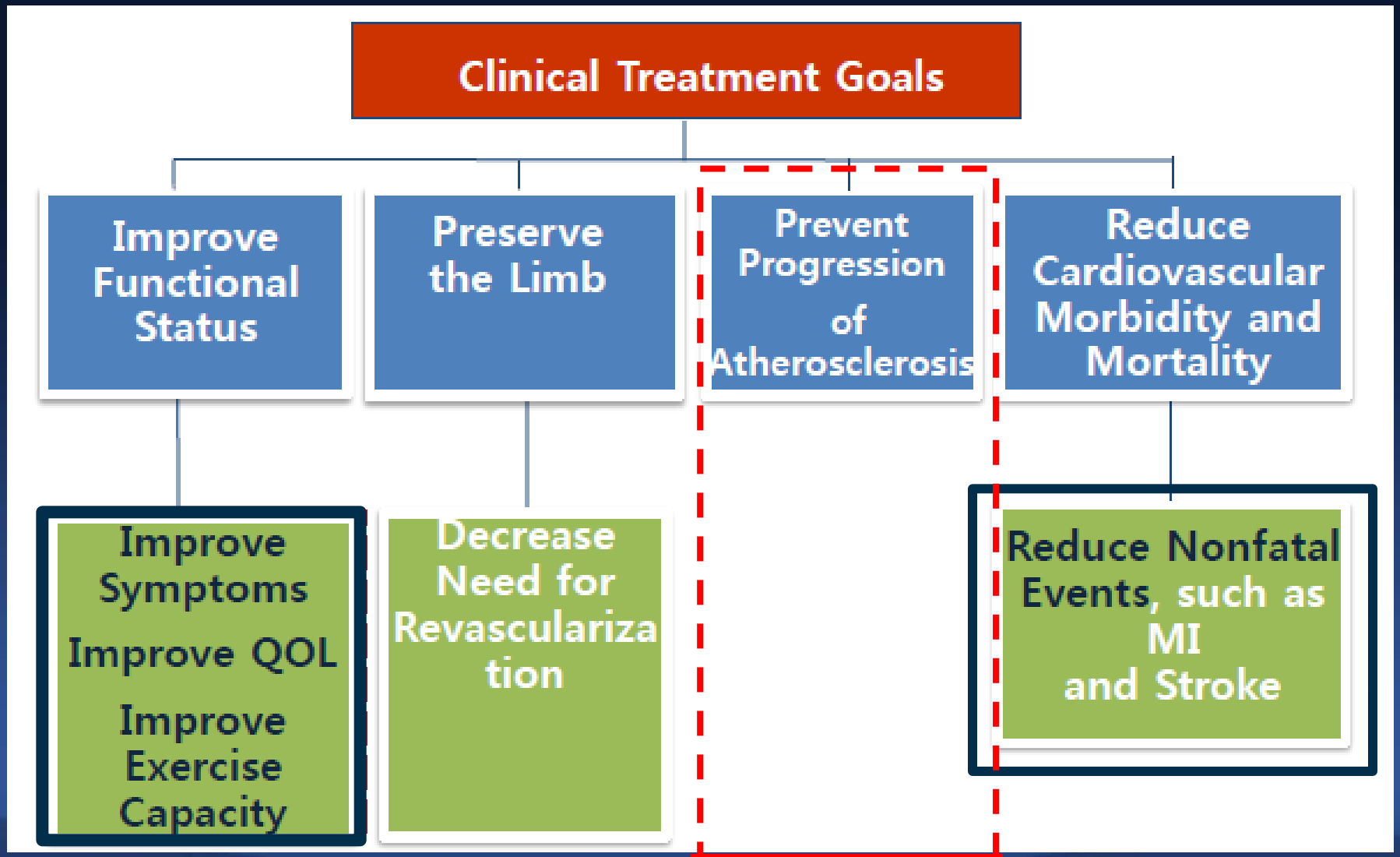
1) WHAT IS THE

lower-extremity amputation, especially in patients with diabetes. Moreover, even for the asymptomatic patient, PAD is a marker for systemic vascular disease involving coronary, cerebral, and renal ves-

ment with cilostazol (35). Based on the above, cilostazol is the drug of choice if pharmacologic therapy is necessary for the management of PAD in patients with diabetes.

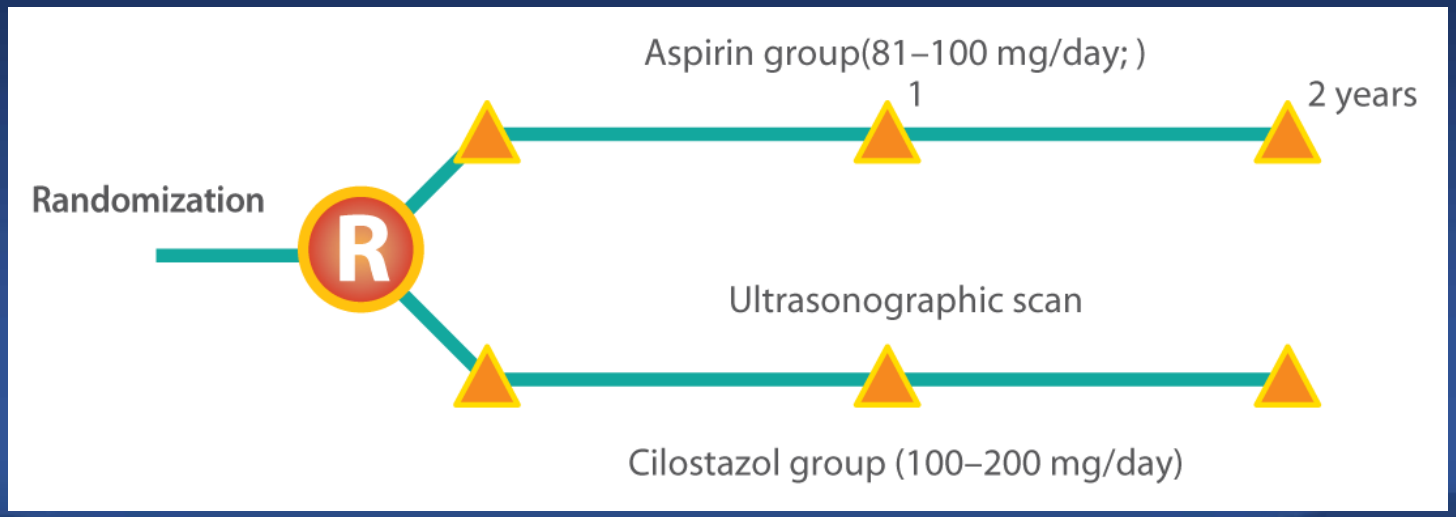
Kaplan-Meler survival curves based on from all causes
Adapted from CriquiMH et al. Nngl med. 1992;326:381-386

Clinical Treatment Goals of PAD



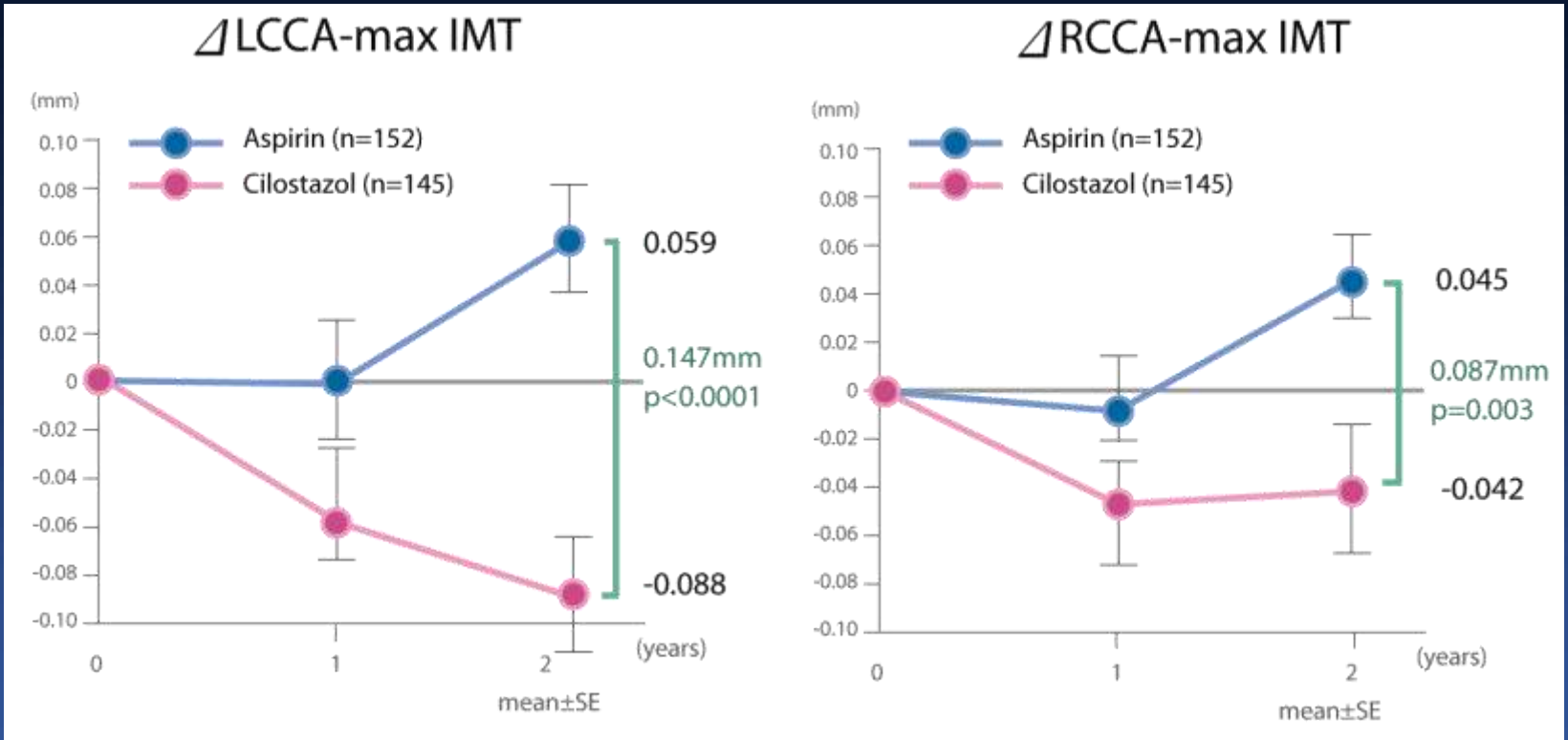
DAPC study(Study of Diabetic Atherosclerosis Prevention by Cilostazol)

- Patients **with type 2 diabetes and arteriosclerosis obliterans** from the Eastern Asian countries were registered online and randomly assigned either to the aspirin group (81–100 mg/day) or the cilostazol group (100–200 mg/day) in this international, 2-year, prospective follow-up interventional study.



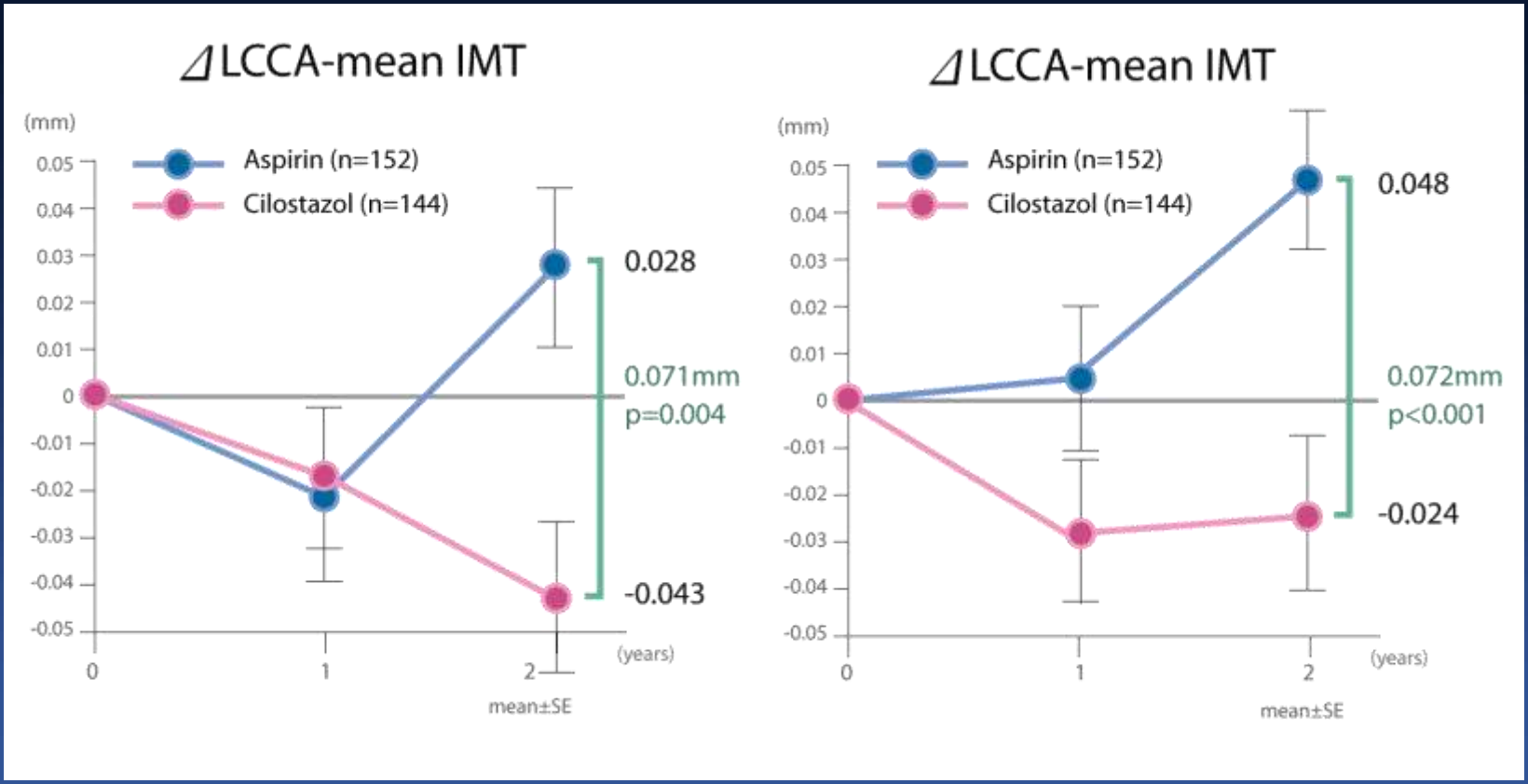
Katakami N. et al. : Circulation. 2010;121:2584-2591

Change in max IMT



Katakami N. et al. : Circulation. 2010;121:2584-2591

Change in mean IMT



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Conclusions

• Cilostazol has cAMP-mediated unique pharmacological effects. It mainly improved clinical outcomes of patients with lower extremity intermittent claudication.

• Cilostazol showed a possibility that it could be used for stroke prevention (antiplatelet effect) and adjunctive therapy (antiproliferative effect) for peripheral intervention

• Because cilostazol improved the pro-atherogenic lipid profile in patients with peripheral arterial disease or type 2 diabetes, which might exert clinically relevant effects on atherogenic dyslipidemia in high-risk patients