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Peripheral Artery Disease: Comprehensive Management of Patients with Intermittent Claudication

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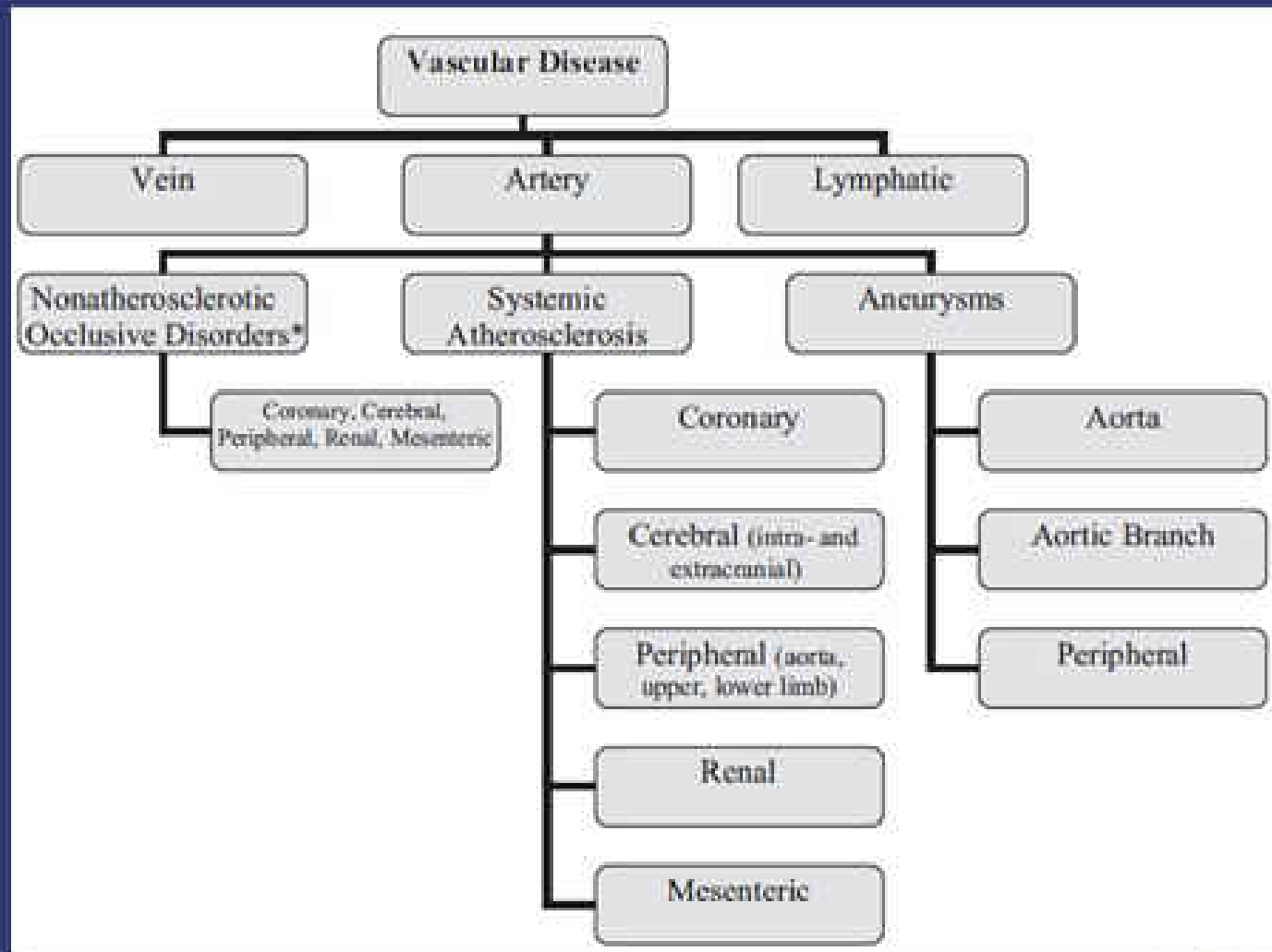
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VASCULAR CENTER

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Conflicts of Interest

- **Consultant**
 - Abbott Vascular
 - Arsenal Medical
 - Atheromed
 - Bacchus Vascular
 - Baxter, Incorporated
 - Becker Venture Services Group
 - Harvard Clinical Research Institute
 - Hypermed, Incorporated
 - LC Sciences, Incorporated
 - Micelle, Incorporated
 - Nexeon Medical Systems
 - Takeda Pharmaceuticals
- **Equity**
 - Access Closure, Inc
 - Icon Interventional, Inc
 - Sadra Medical
 - Square One, Inc
 - Vascular Therapies, Inc
- **Research Support**
 - Abbott Vascular
 - Genzyme
 - Philips Medical Systems
- **Board Member**
 - VIVA Physicians (Not For Profit 501(c) 3 Organization)
 - www.vivapvd.com

First of All, What's the Right Name?



What's The New Name?

Recommended	Previous Terms	Pathophysiology	Anatomy	Duration and Severity
Vascular diseases		Diseases of arteries, veins, and lymphatics; includes atherosclerosis and nonatherosclerotic diseases	All vessels without anatomic designation	Acute to chronic; asymptomatic to severe
Peripheral artery disease	Peripheral vascular disease, peripheral arterial disease, peripheral arterial occlusive disease, arteriosclerosis obliterans	Atherosclerosis, thrombosis, noncardiac emboli, inflammatory, etc	Stenosis or occlusion of upper- or lower-extremity arteries	Acute to chronic; may be asymptomatic; symptoms and signs range from asymptomatic with functional limitations to intermittent claudication, rest pain, ulcers, and gangrene

Classification of PAD

Fontaine

Rutherford

Stage	Clinical	Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild Claudication	0	1	Mild Claudication
IIb	Mod-Severe Claudication	I	2	Moderate Claudication
		I	3	Severe Claudication
III	Ischemic Rest Pain	II	4	Rest Pain
		III	5	Minor Tissue Loss
IV	Ulceration/Gangrene	IV	6	Major Tissue Loss

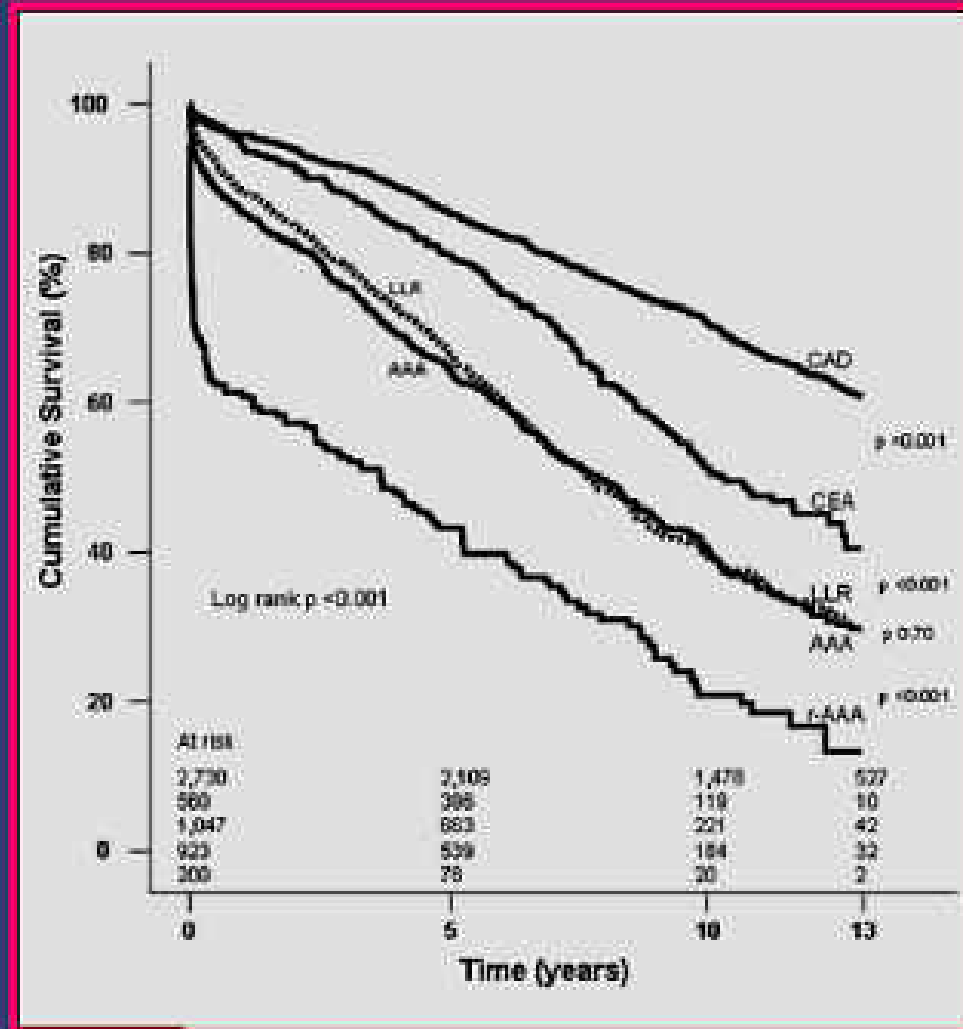
Peripheral Artery Disease

- Aortoiliac Disease
- Common Femoral Artery Disease
- Profunda Femoris Artery Disease
- Superficial Femoral Artery Disease
- Popliteal Artery Disease
- Infrapopliteal Artery Disease

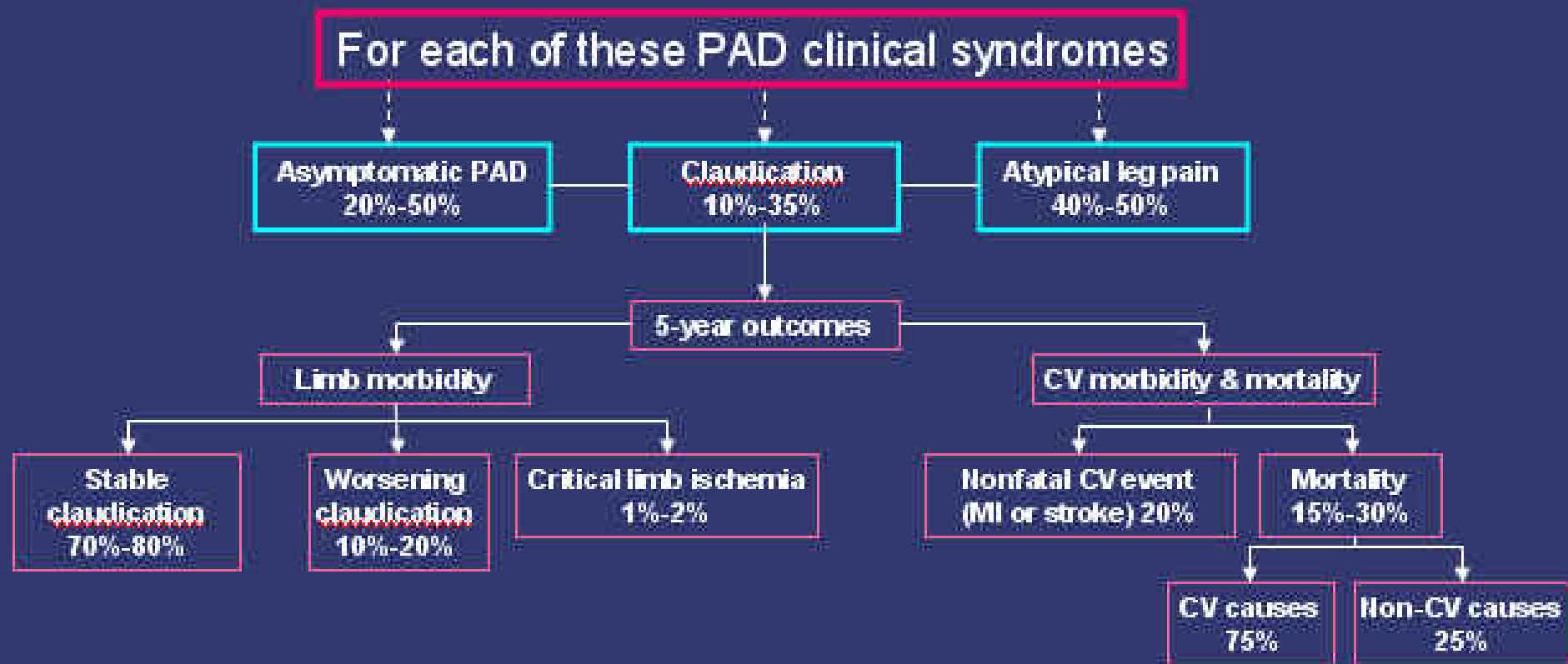
Basic Tenets

- The most important issue with intermittent claudication is NOT improvement in walking distance

Risk of Mortality: PAD vs CAD

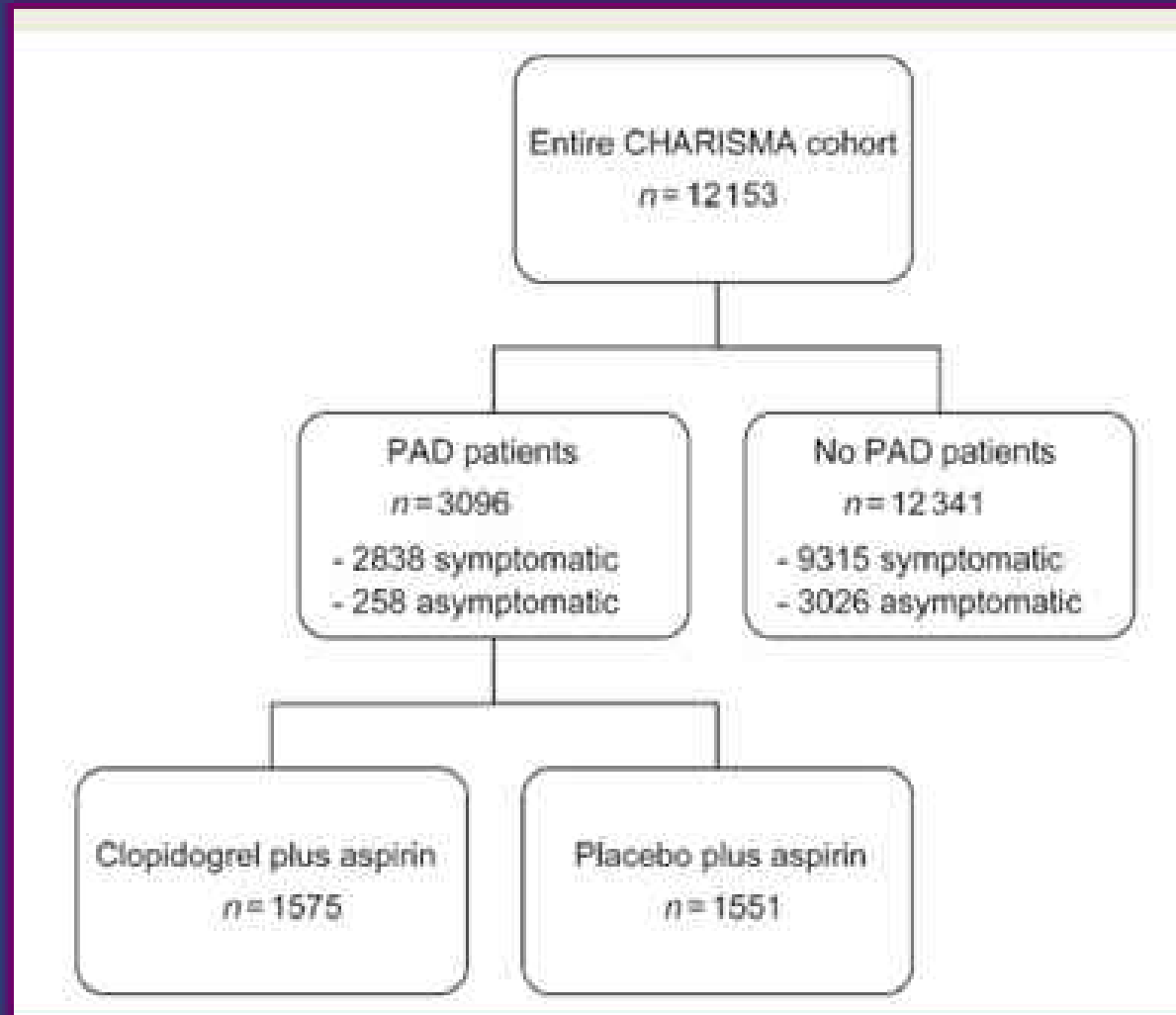


Natural History of Atherosclerotic Lower Extremity PAD



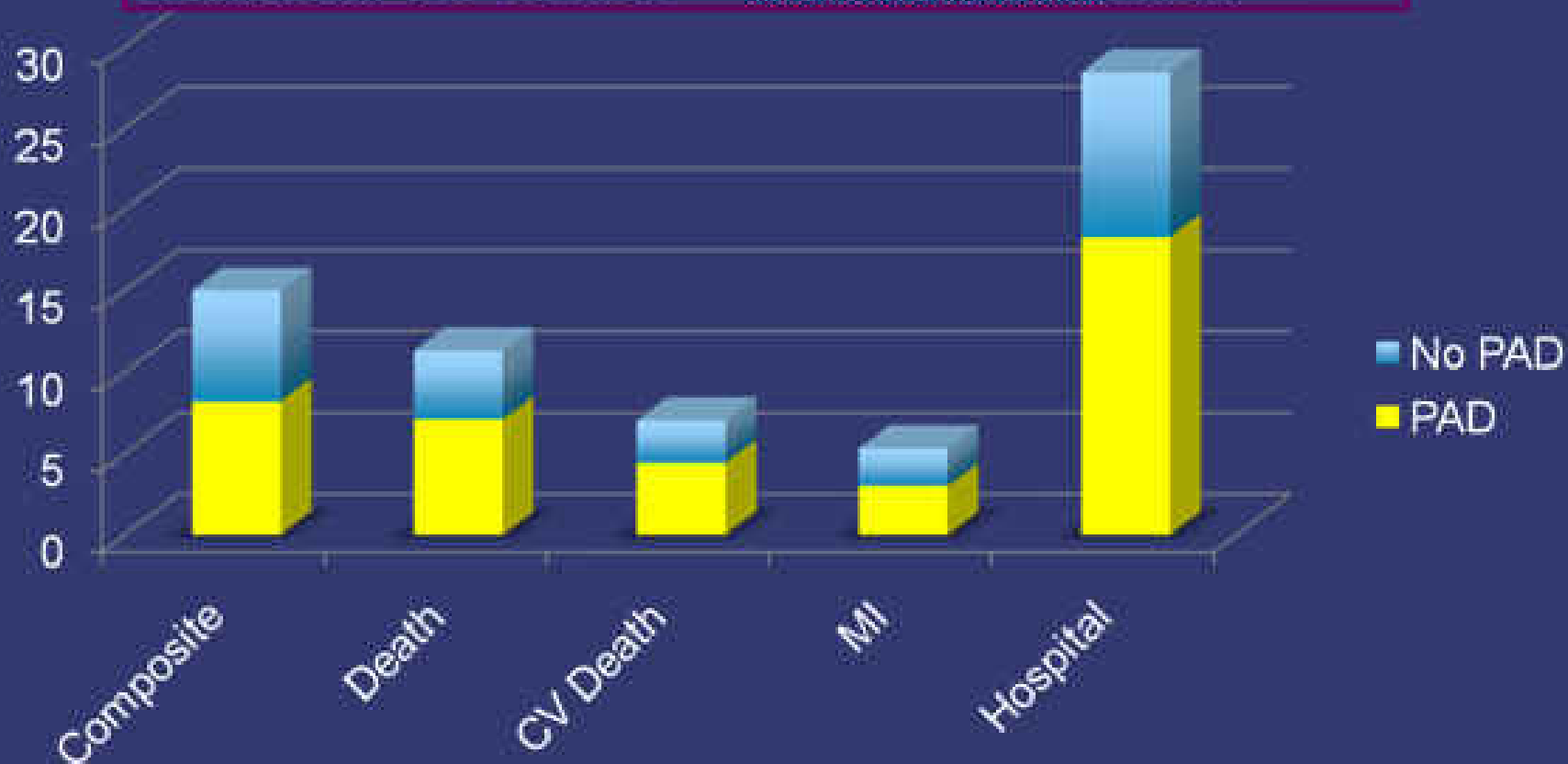
Hirsch AT, et al. ACC/AHA Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aorta): A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Peripheral Arterial Disease [Lower Extremity, Renal, Mesenteric, and Abdominal Aorta]). *Circulation*. 2006;113:e463-654.

Impact of PAD: CHARISMA



Impact of PAD: CHARISMA

3096 Patients with PAD (92% Symptomatic)
Randomized to ASA + Clopidogrel vs ASA



PAD Dramatically Limits Functional Ability

- **Maximal walking speed**
 - Normal = 3-4 mph
 - PAD = 1-2 mph
- **Maximal walking distance**
 - Normal = unlimited
 - PAD, 31% difficulty walking in home
 - PAD, 66% difficulty walking 1/2 block
- **Peak VO_2**
 - PAD reduced 50% (NYHA class III CHF)

Basic Tenets of PAD Therapy

- Modify cardiovascular risk factors to coronary heart levels
- Identify concomitant coronary, cerebrovascular, renal artery disease
- Maximize medical therapy to improve quality of life
- Then.....consider intervention based on clinical presentation and anatomic findings

Comprehensive Medical Therapy for PAD

- Supervised Exercise Training (A)
- Tobacco Cessation (B)
- Control of Hypertension (A)
- Control of Hyperlipidemia (B)
- Glycemic Control (B)
- Antiplatelet Therapy (A)
 - ASA (A)
 - Clopidogrel (B)
- Cilostazol 100 mg po BID (A)

World Health



Efficacy of Supervised Exercise: The “Gardner 21-Study Meta-Analysis”

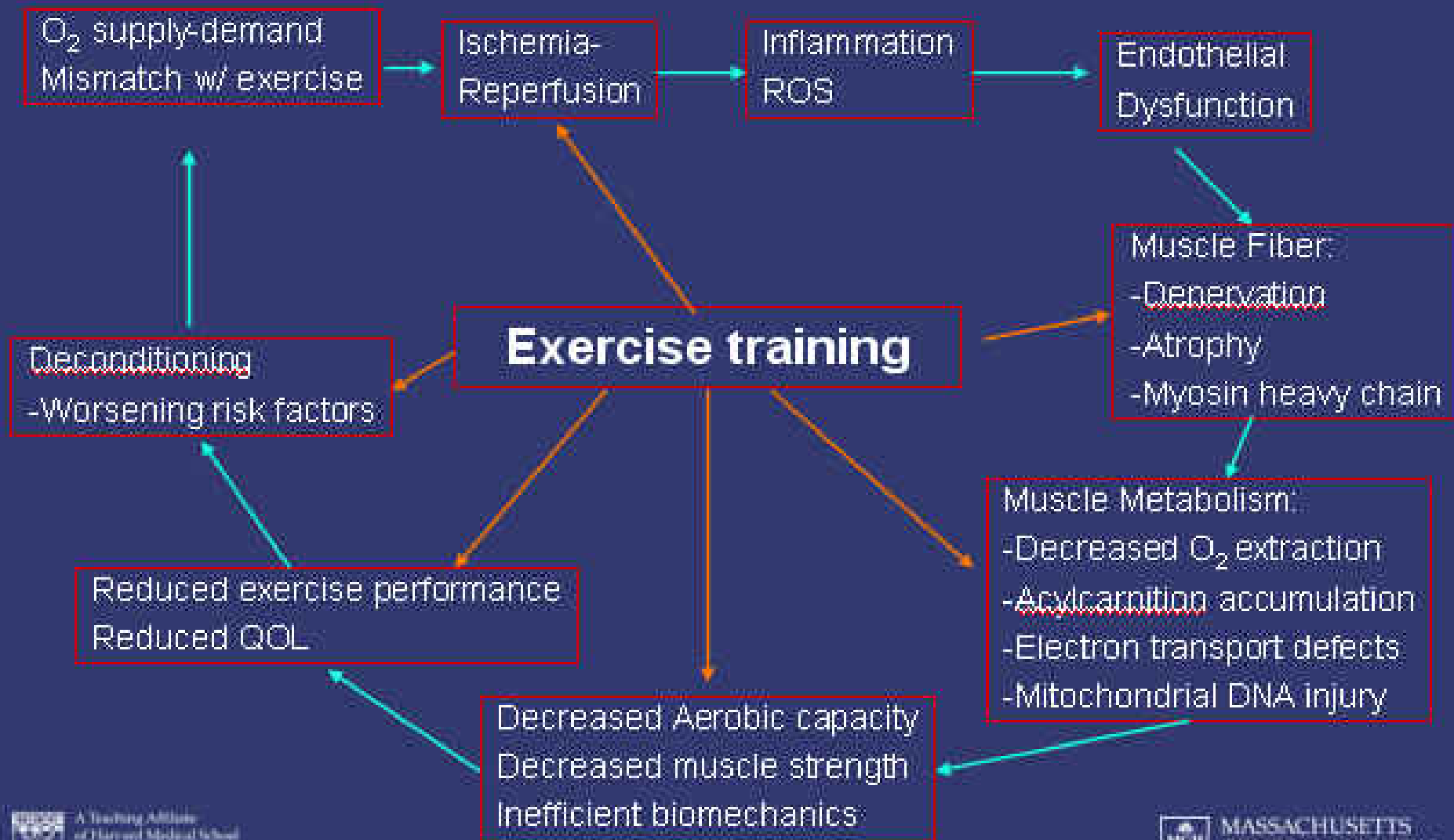
	Exercise	Control	Change
Pain-Free Walking Distance	180% *	40%	2 blocks
Maximal Walking Distance	130% *	30%	3 blocks

Predictors of improvement:

- Exercise to a moderate level of claudication pain
- Walking exercise (vs. other modalities)
- > 3 (or 6) months exercise training
- Supervised exercise

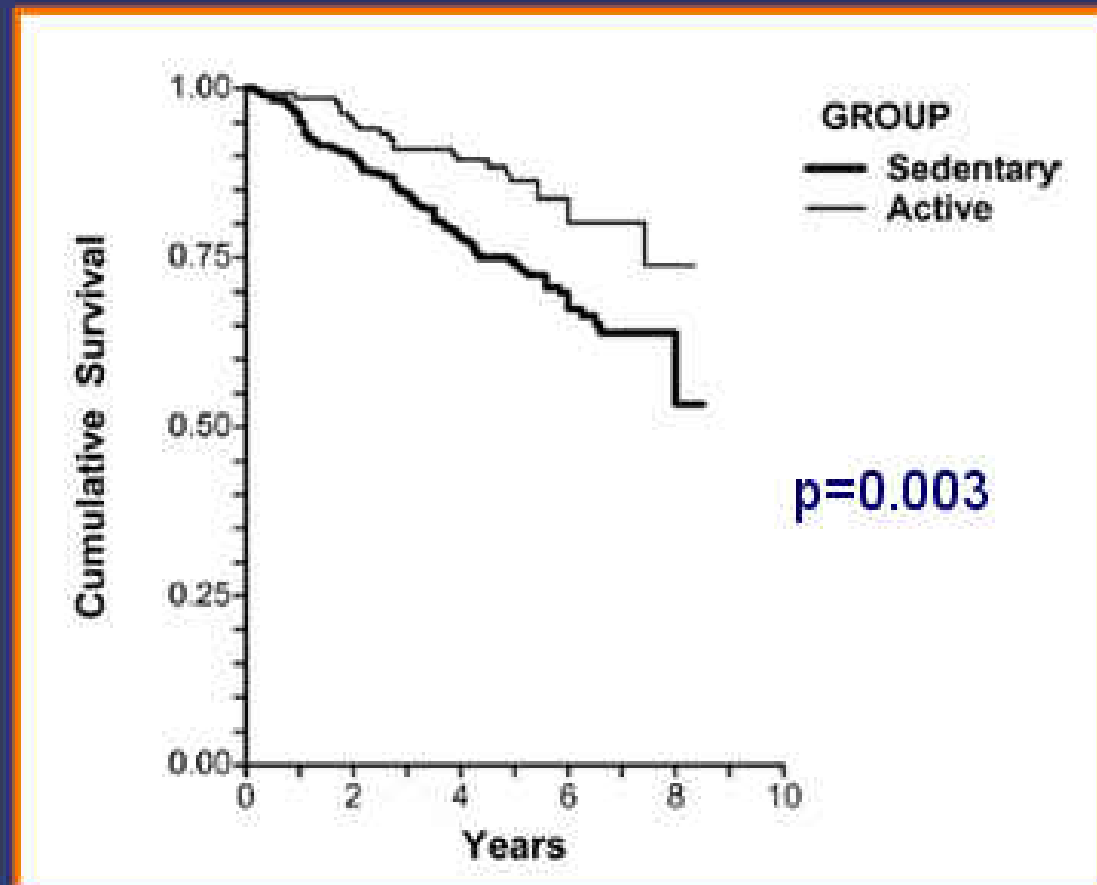
Gardner AW. *JAMA*. 1995;274:975-80.

How Might Exercise Training Reduce CV Events?

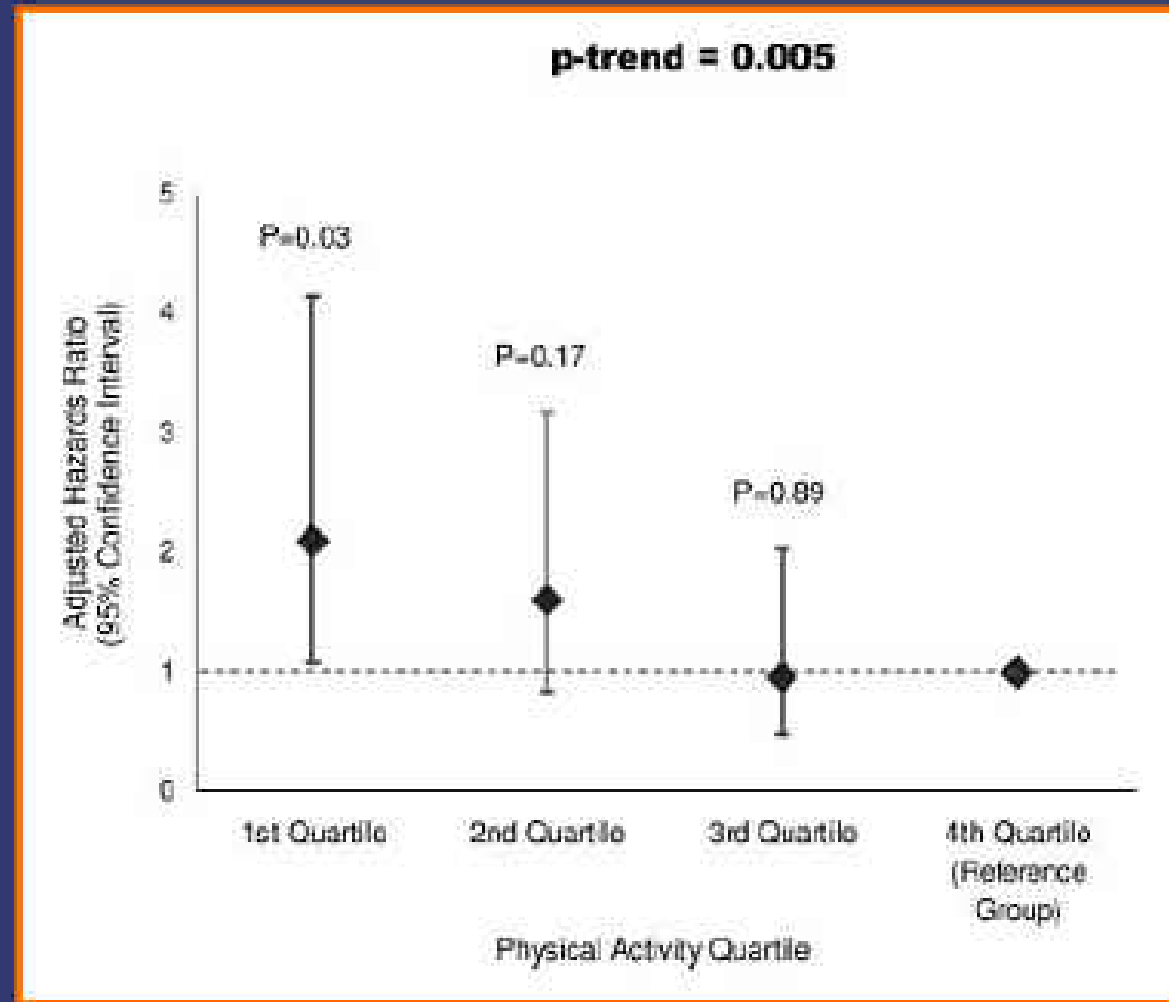


Physical Activity and All-Cause Mortality in PAD

434 PAD Patients Followed for ~ 5 Years



Cardiovascular Events/Mortality in 460 PAD Patients Based on Baseline Activity



Will Your Patients Do This?



A Teaching Affiliate
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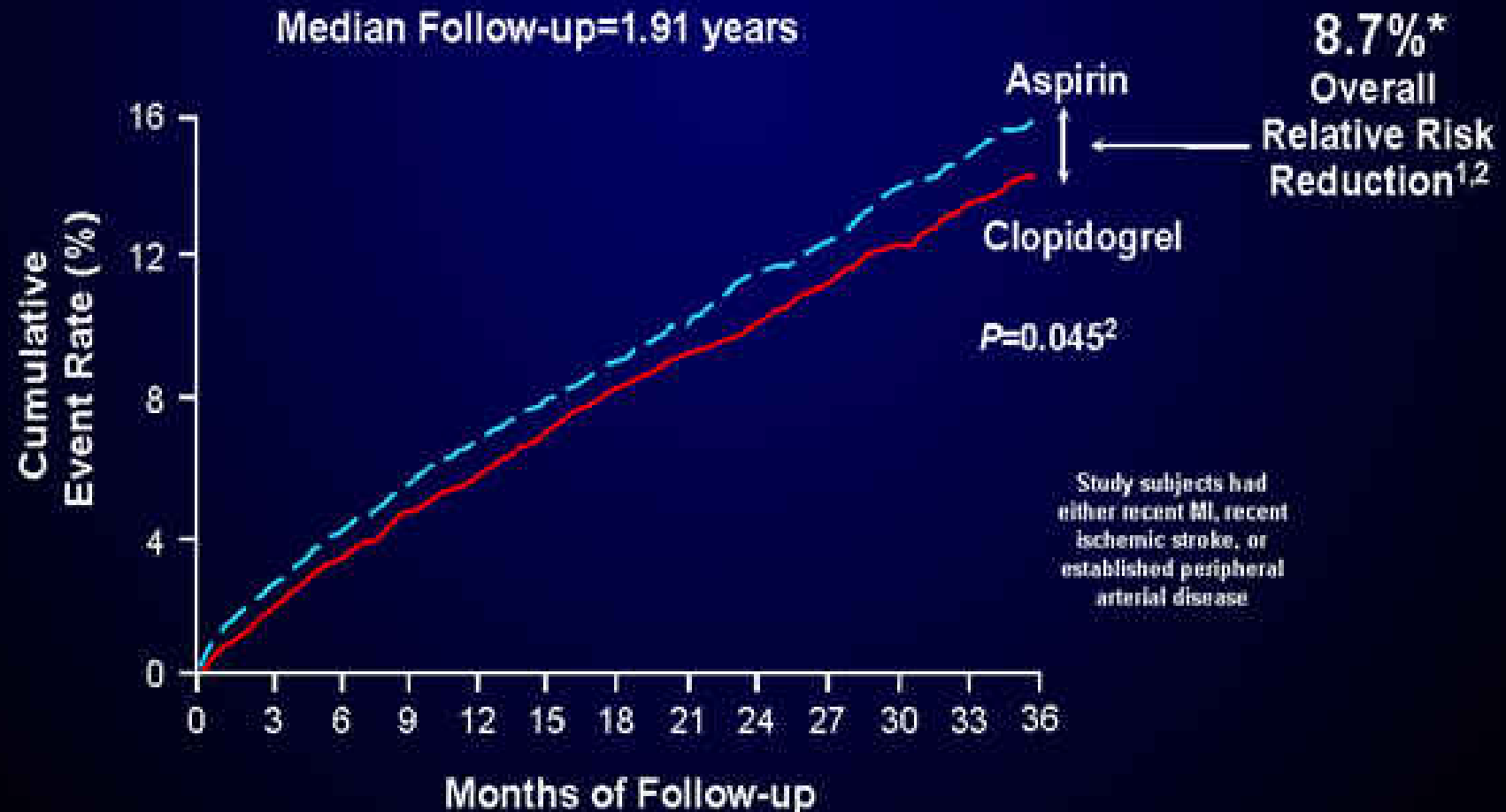
Or, More Likely, This?



Efficacy of Clopidogrel vs Aspirin in MI, Ischemic Stroke, or Vascular Death (N=19,185)



Median Follow-up=1.91 years



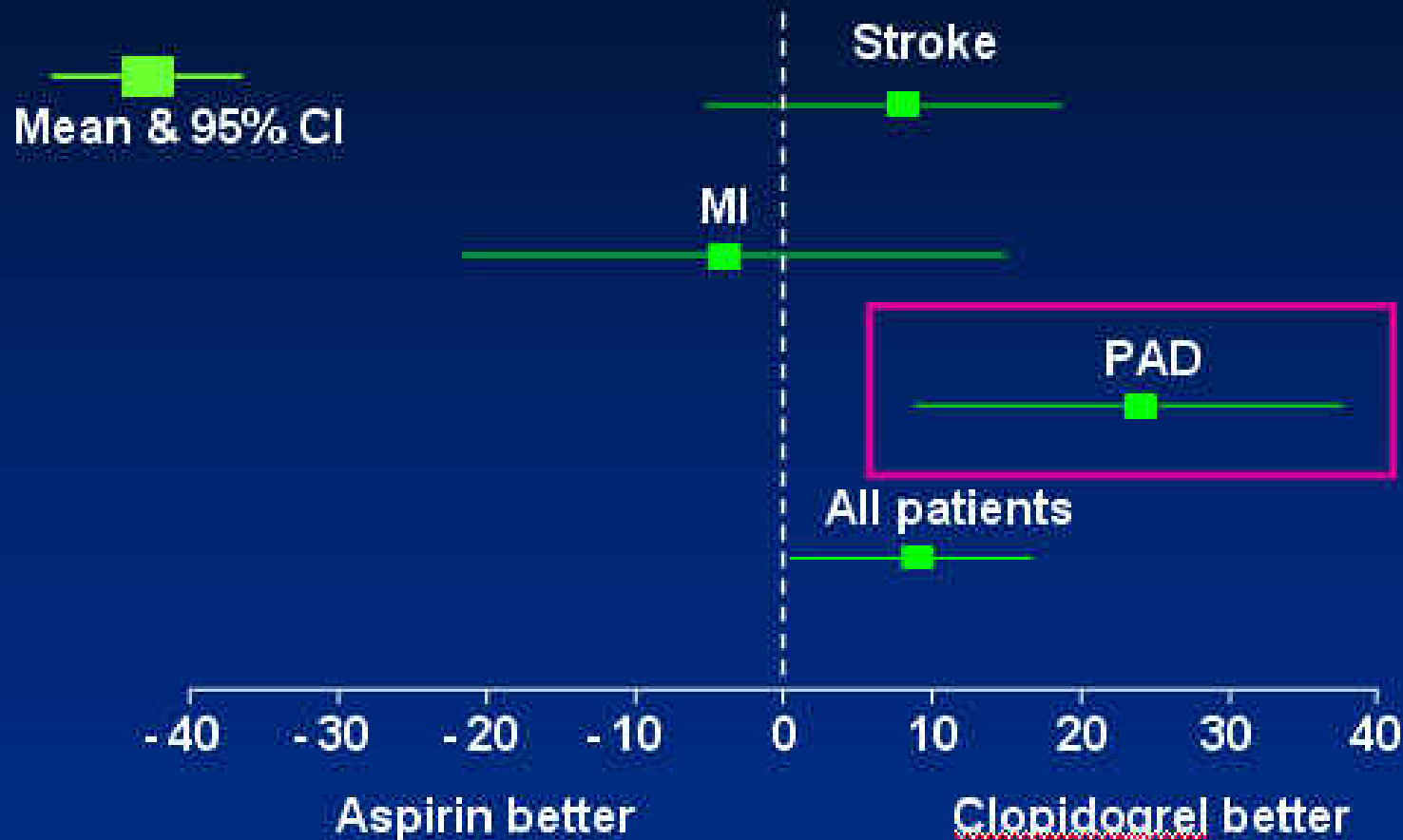
* ITT analysis.

1. CAPRIE Steering Committee. *Lancet*. 1996;348:1329-1339.

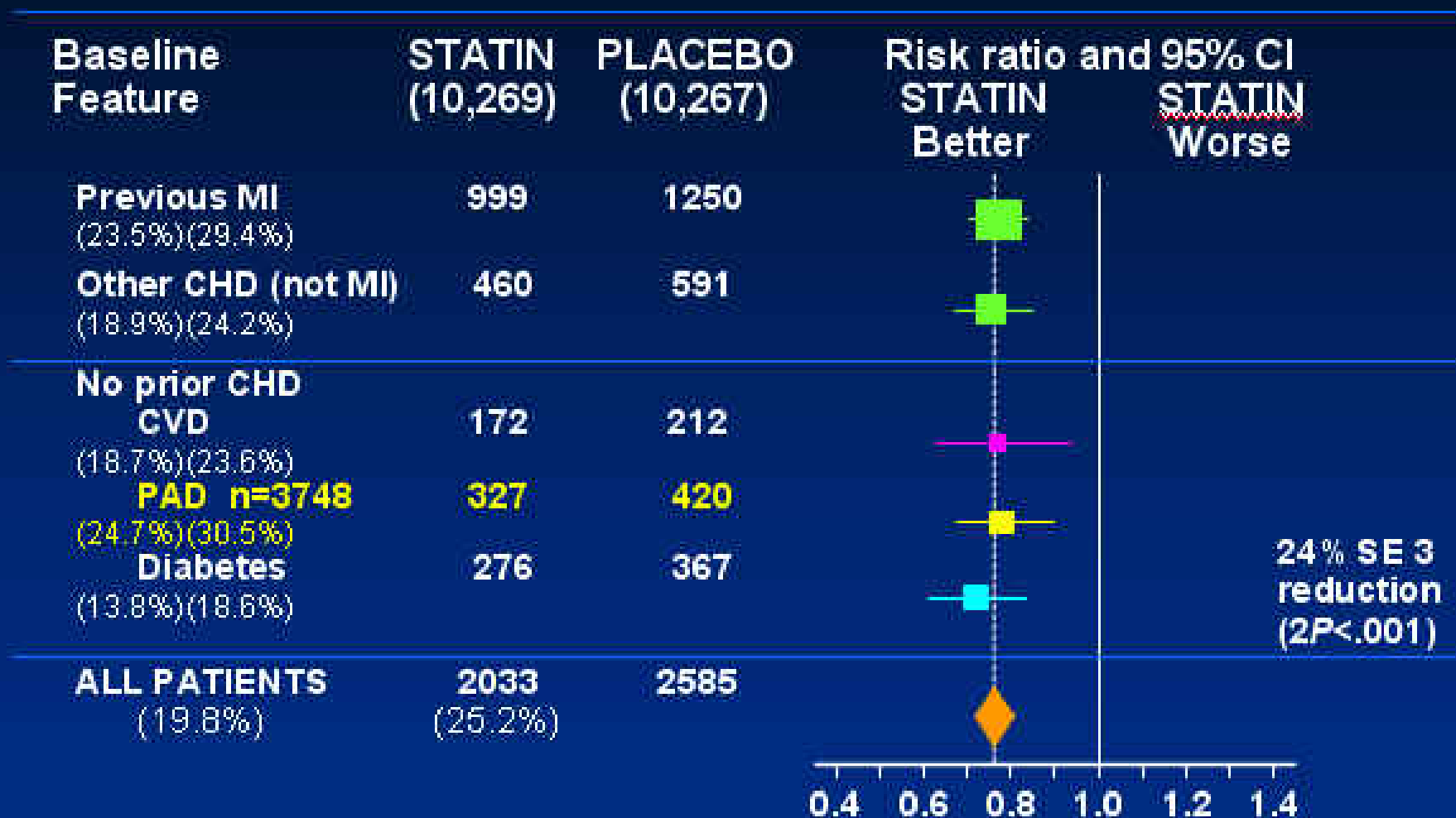
2. PLAVIX Prescribing Information, sanofi-aventis U.S. LLC.

CAPRIE Study

Outcome by Subgroup



Heart Protection Study: Vascular Event by Prior Disease

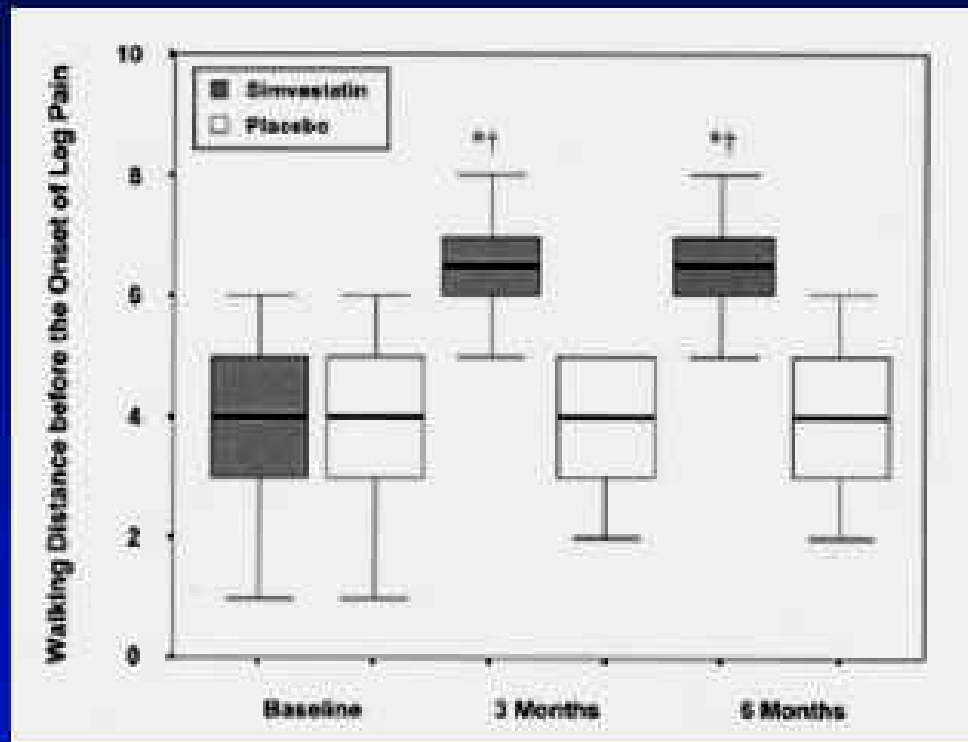


Reprinted with permission from Heart Protection Study Collaborative Group.
Lancet. 2002;360:7-22.

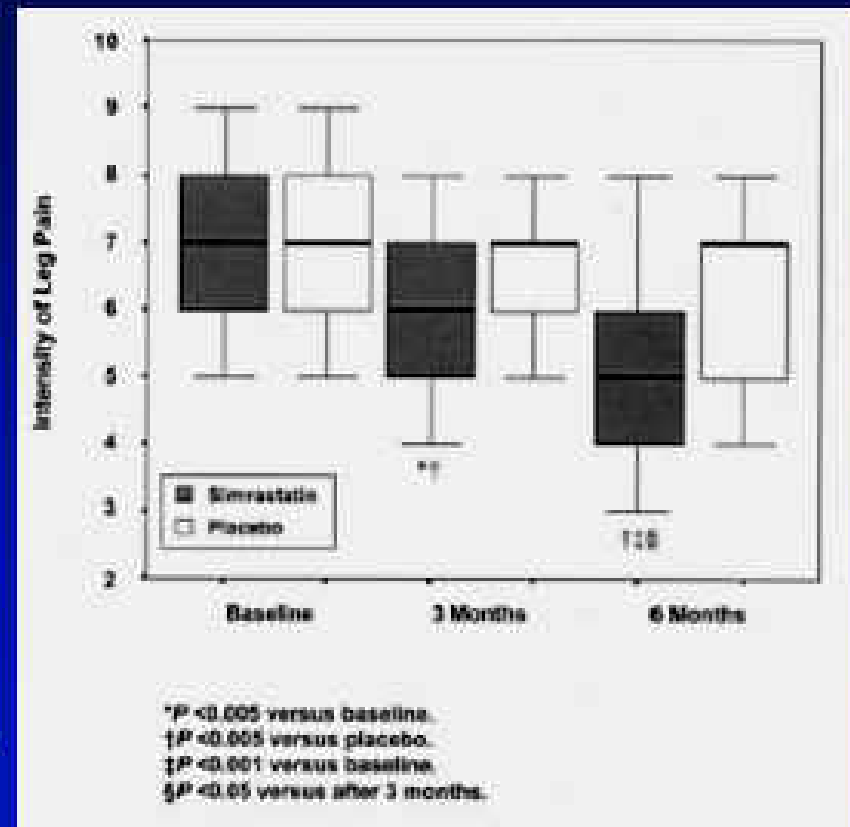
Simvastatin and Intermittent Claudication

- | 86 patients with moderate IC based on PAD
 - n 43 received Simvastatin 40 mg/d
 - n 43 received matching placebo
- | Patients followed for 6 months with exercise tests and symptom questionnaires

Simvastatin and Intermittent Claudication

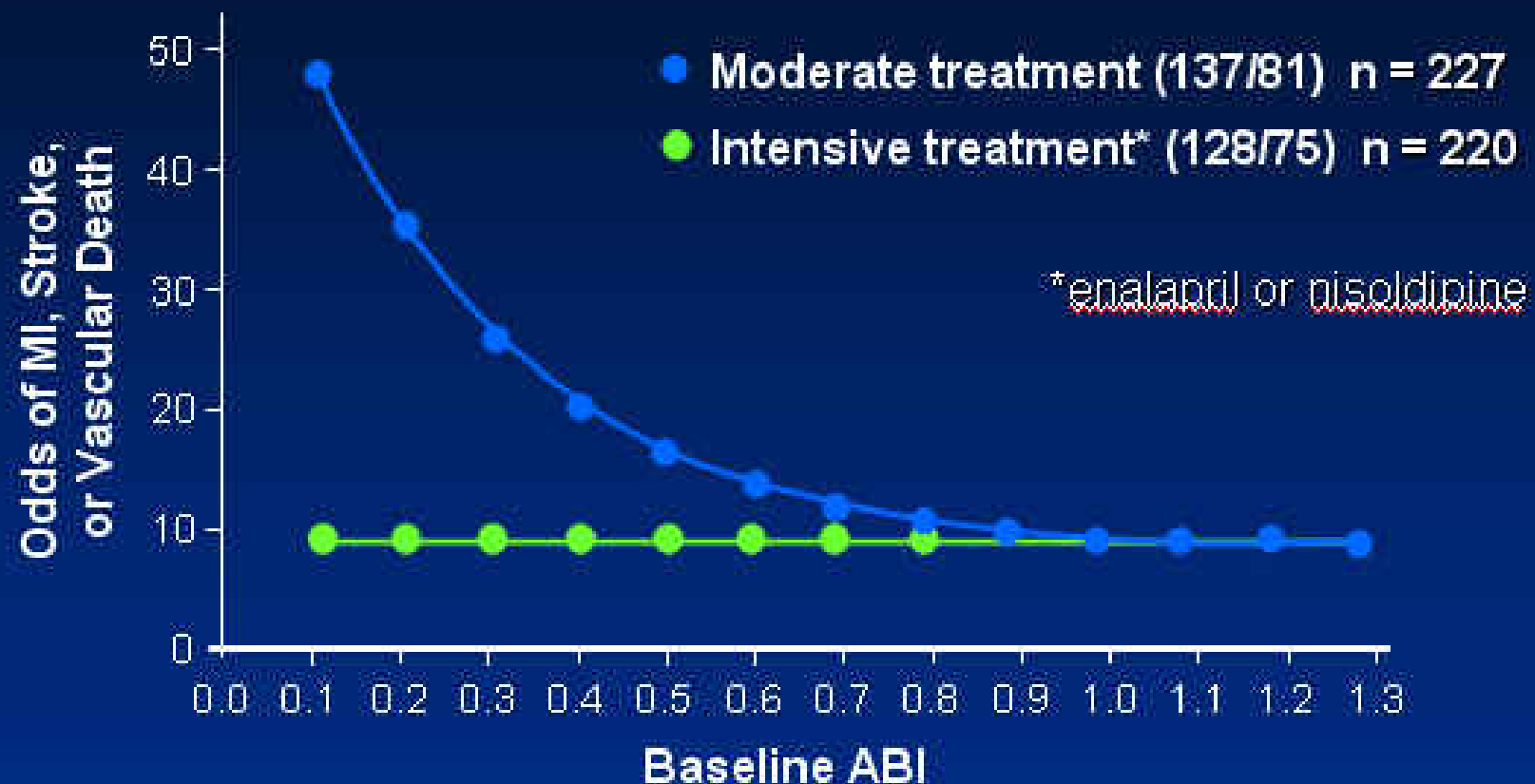


ICD



Intensity of Leg Pain

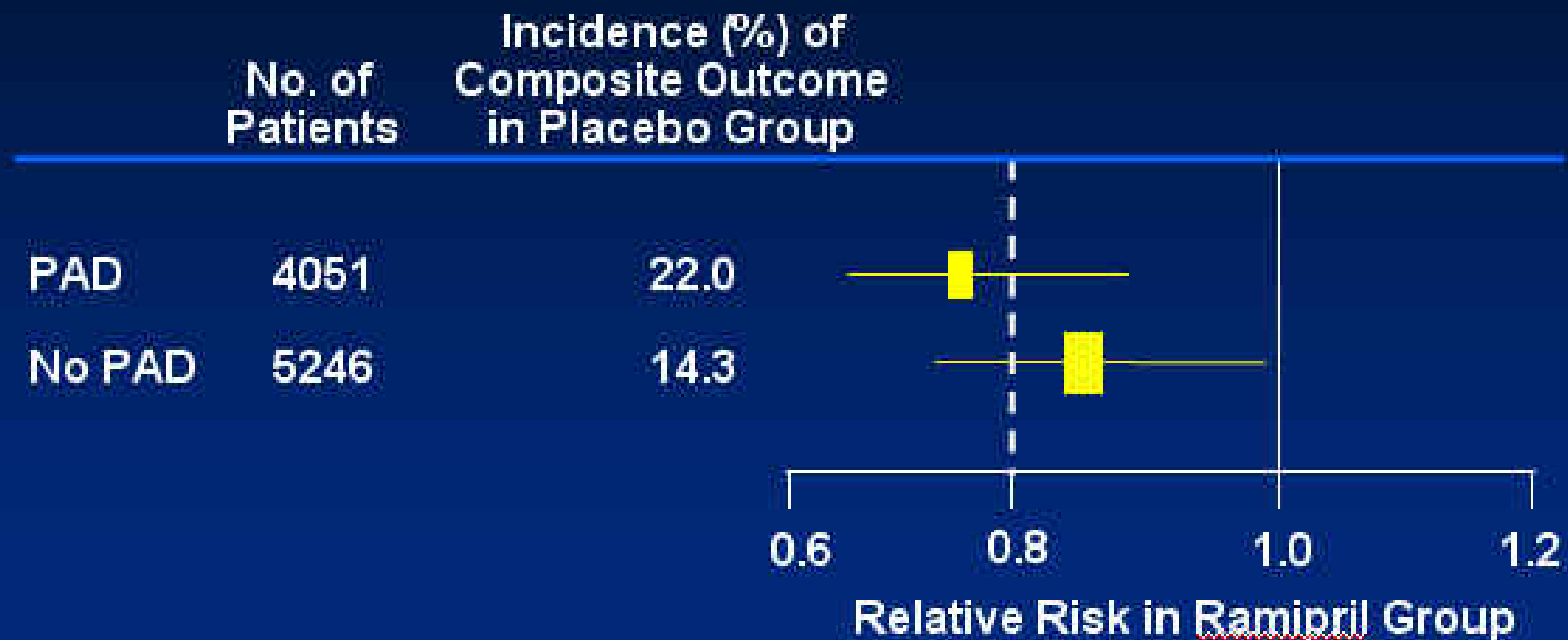
Intensive BP Therapy in PAD: The ABCD Trial



ABCD = Appropriate Blood Pressure Control in Diabetes Study

Reprinted with permission from Mehler PS, et al. *Circulation*. 2003;107:753-756.

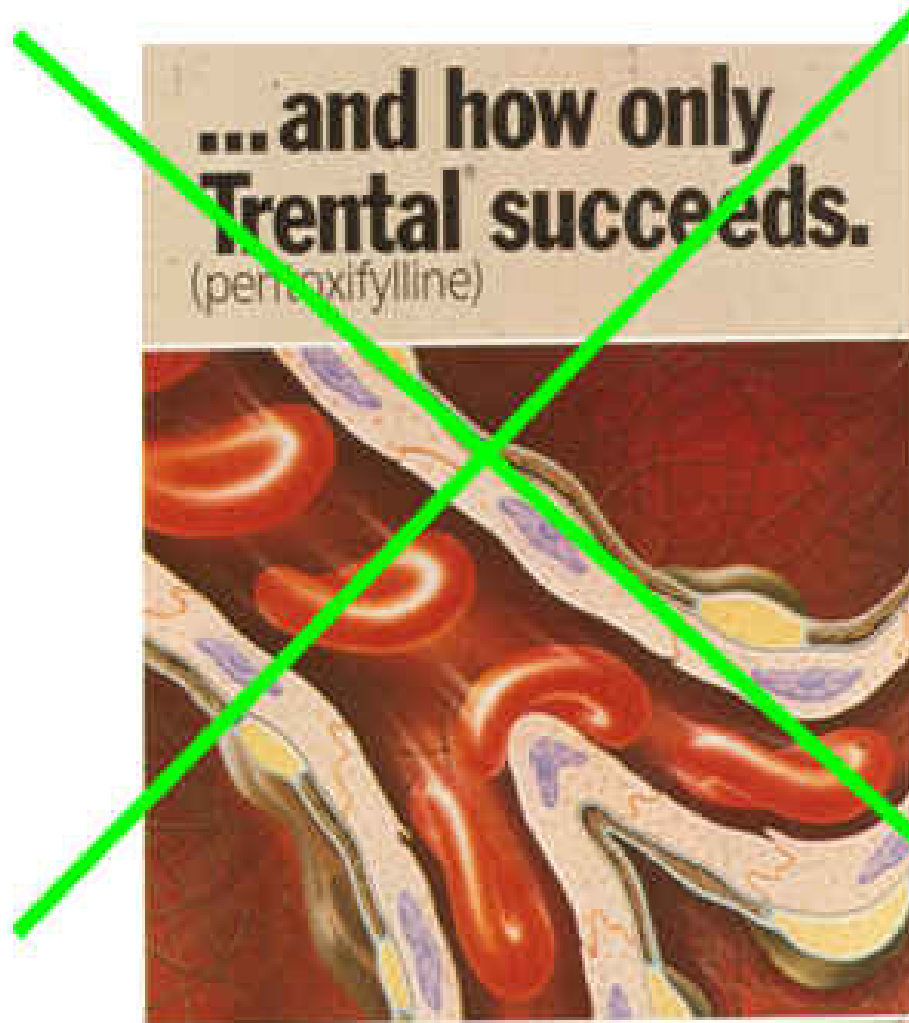
The HOPE Study: PAD Subgroup Analysis



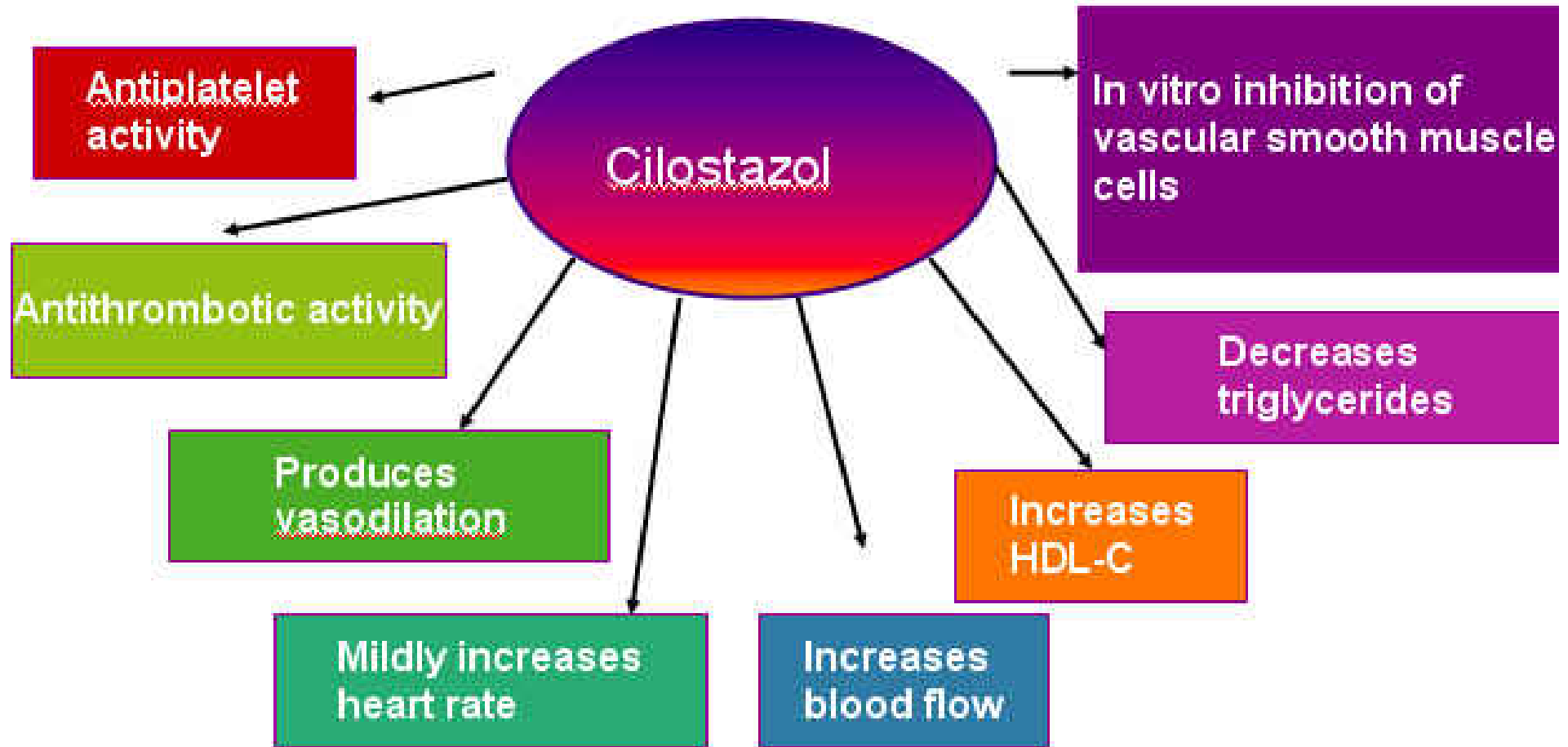
HOPE = Heart Outcomes Prevention Evaluation Study

HOPE Study Investigators. *N Engl J Med*. 2000;342:145-153.

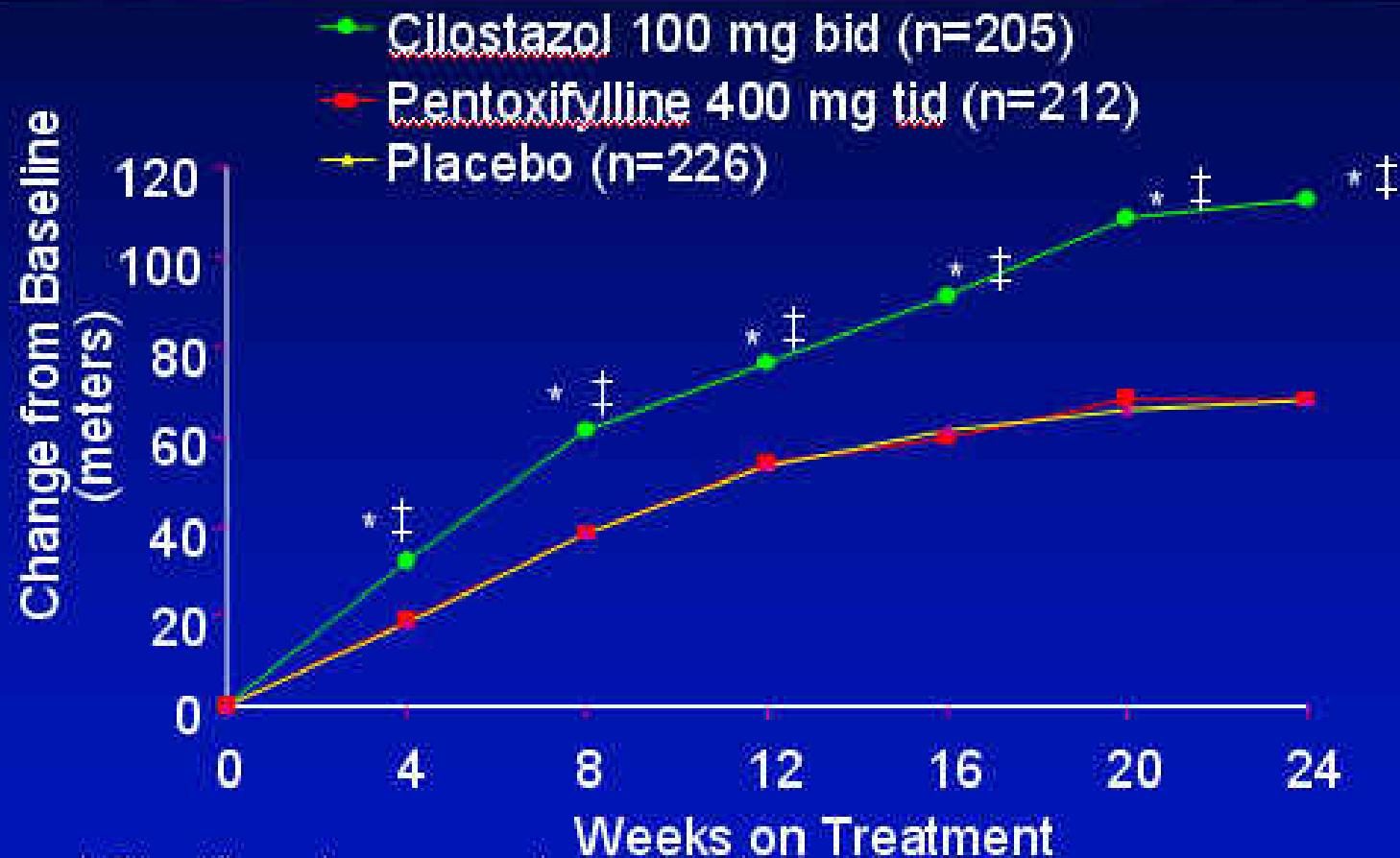
Pentoxifylline



Pharmacologic Effects of Cilostazol



Comparison of Cilostazol vs Pentoxifylline vs Placebo



* Significantly greater than placebo, $p \leq 0.05$

‡ Significantly greater than pentoxifylline, $p \leq 0.05$

Often, Simple Advice on Foot Care is All That is Required



Presented at the American College of Cardiology
Annual Scientific Sessions, Orlando, Florida, USA
March 30, 2009



**A Randomized, Double-blind, Placebo-controlled, Parallel-
group, Study of Ad2/Hypoxia Inducible Factor (HIF)-1 α /VP16
in Patients with Intermittent Claudication**

Mark A. Creager, Jeffrey W. Olin, Jill Belch, Gregory Moneta, Timothy D. Henry,
Sanjay Rajagopalan, Brian H. Annex, Nicolas Chronos, William R. Hiatt,
on behalf of the WALK Investigators

Objectives



- n To assess the efficacy of HIF-1 α /VP16 compared to placebo in the treatment of severe intermittent claudication
- n To assess thesafety and tolerability of HIF-1 α /VP16 compared to placebo in patients with intermittent claudication



Experimental Protocol

- n Patients were randomly assigned to receive a single treatment with 1 of 3 doses of Ad2/HIF-1 α /VP16, or placebo, in a ratio of 1:1:1:1, in a double blind manner.

Dosing Group	Dose per Limb	Injections per Limb
Ad2/HIF 1 α /VP16 2x10 ⁹ vp	1x10 ⁹ vp	20
Ad2/HIF 1 α /VP16 2x10 ¹⁰ vp	1x10 ¹⁰ vp	20
Ad2/HIF 1 α /VP16 2x10 ¹¹ vp	1x10 ¹¹ vp	20
Placebo	NA	20

- n Each injection consisted of a fixed volume of 100 μ L for a total volume of 2.0 mL per limb.

Treatment Administration

Standardized Grid for Injections



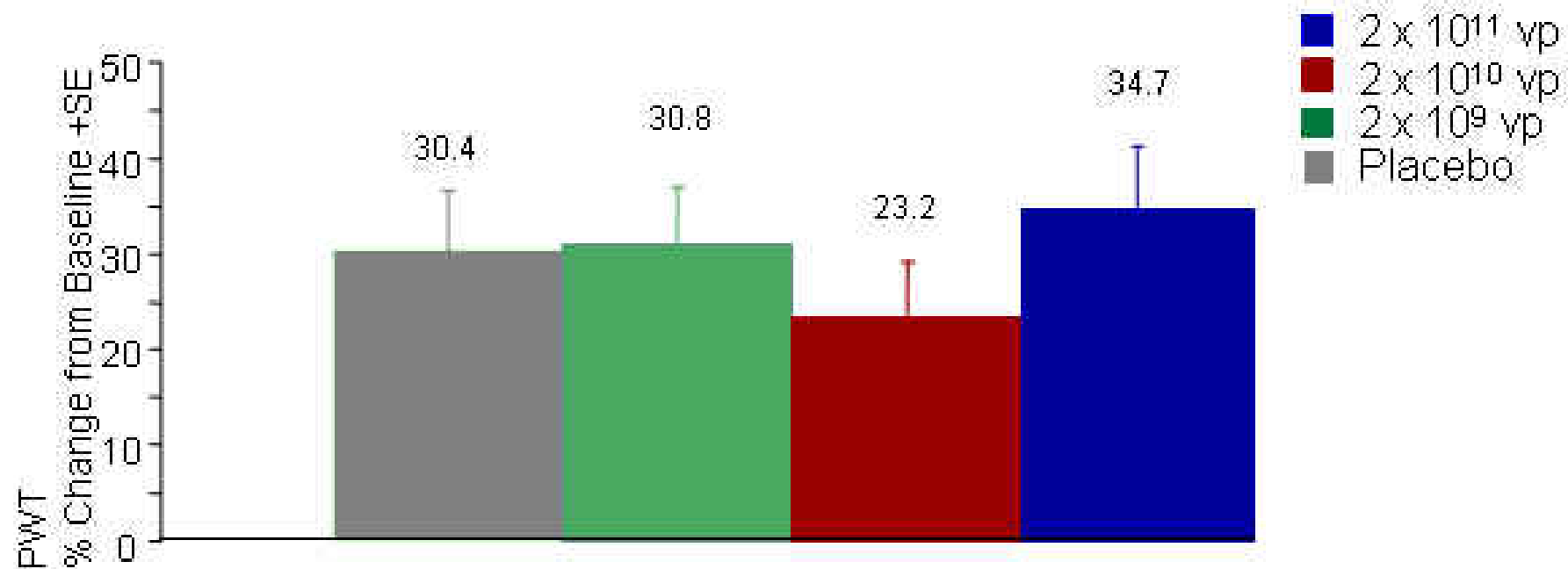
Efficacy Endpoints



- n Primary Endpoint:
 - | Percent change from baseline in **Peak Walking Time** at 6 months

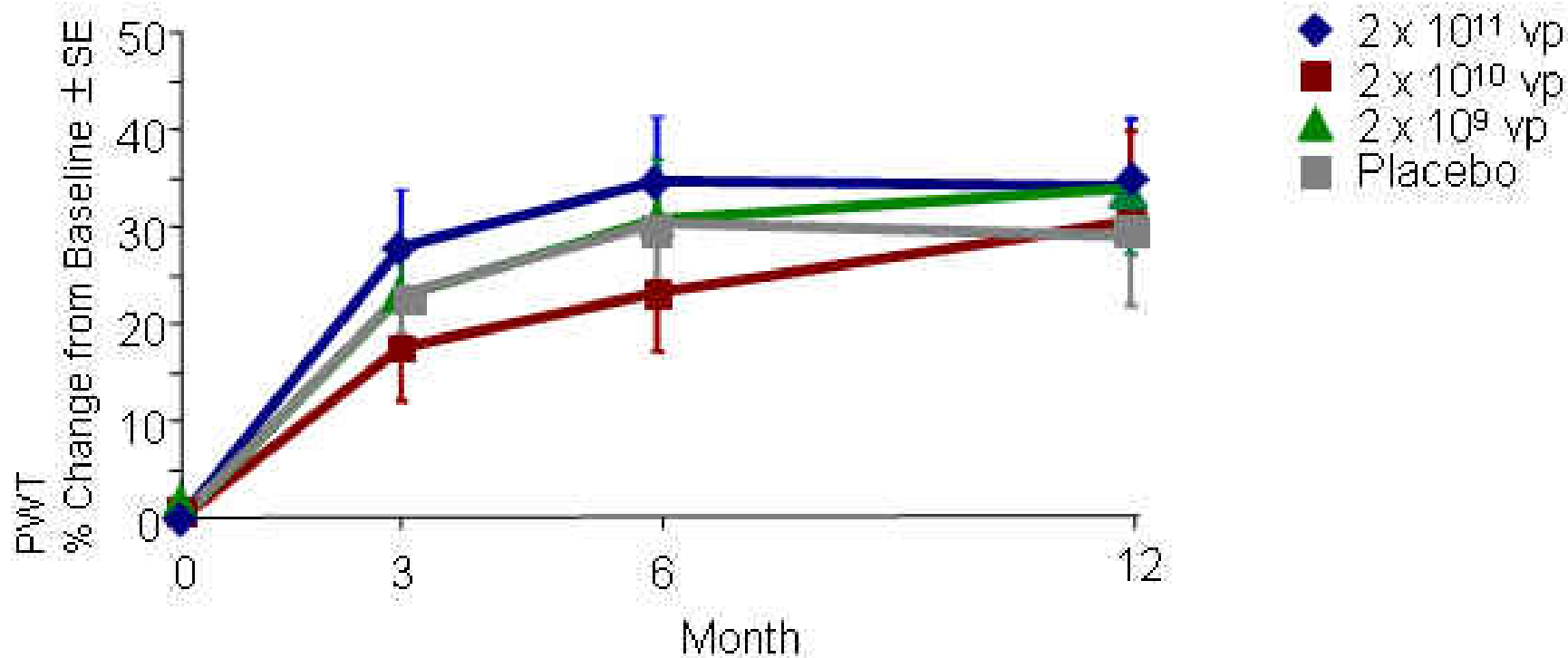
- n Secondary Endpoints:
 - | Percent change from baseline in **Peak Walking Time** at 3 and 12 months
 - | Percent change from baseline in **Claudication Onset Time** at 3, 6, and 12 months

Primary Efficacy Endpoint: Peak Walking Time at 6 months



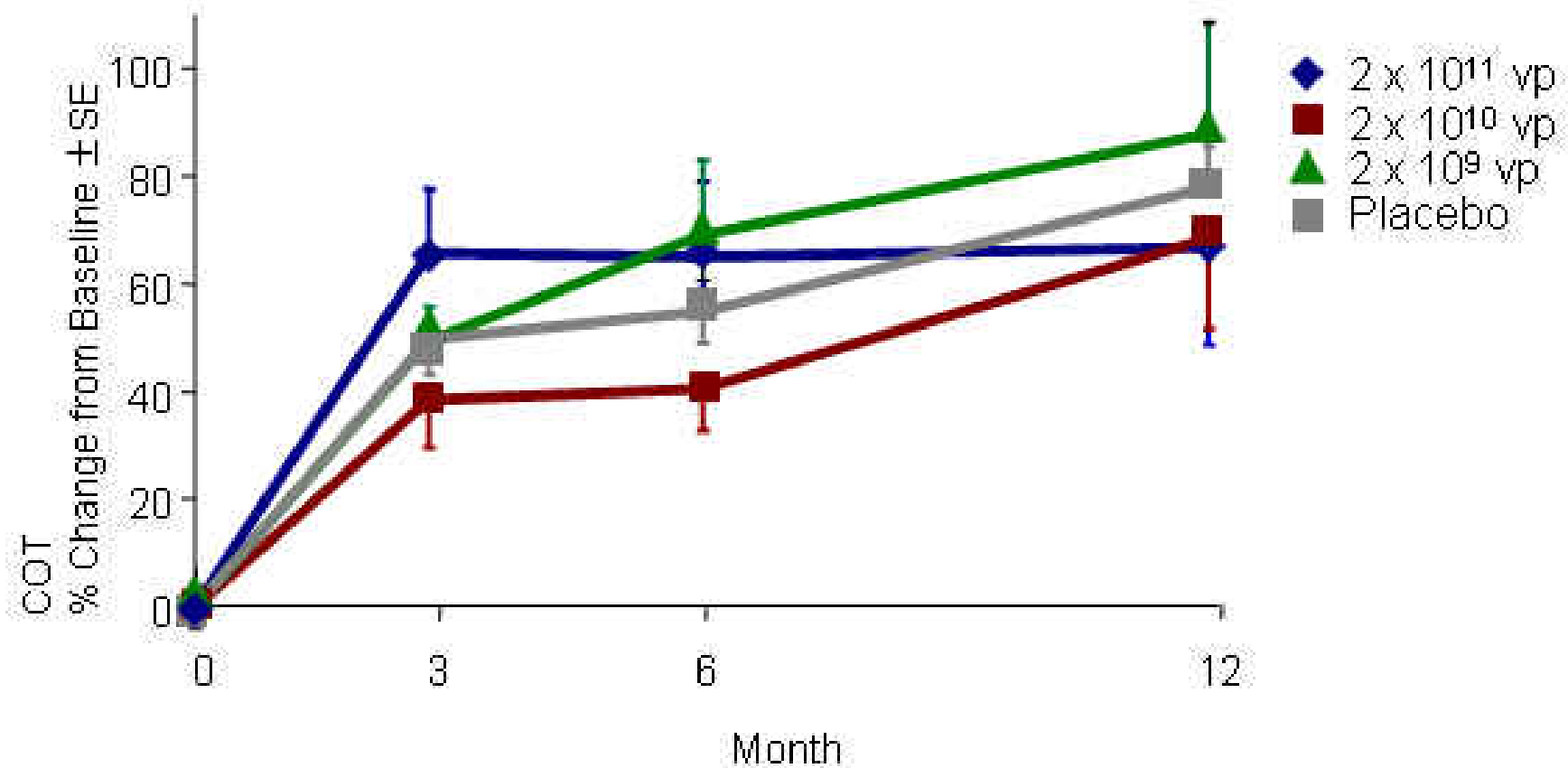
All p-values NS

Secondary Endpoint: Peak Walking Time at 3 & 12 months



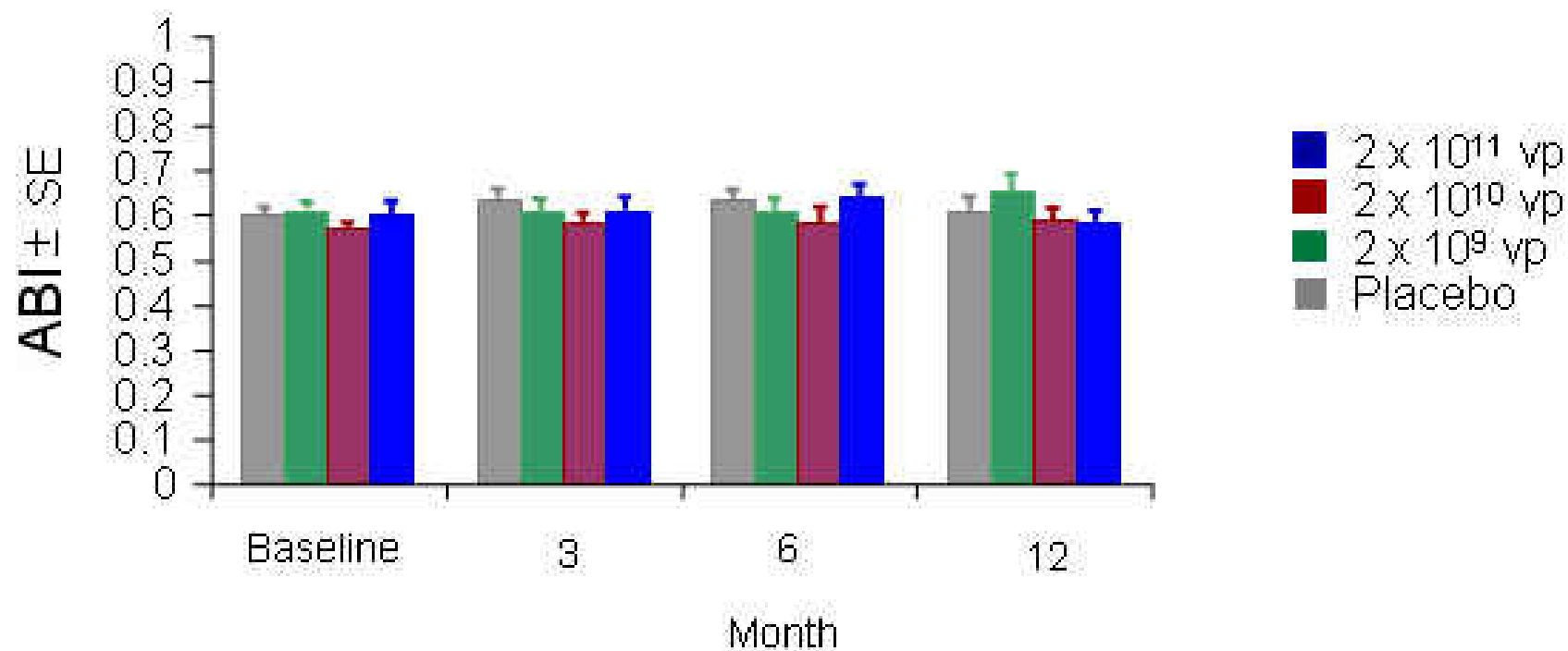
All p-values NS

Secondary Endpoint: Claudication Onset Time



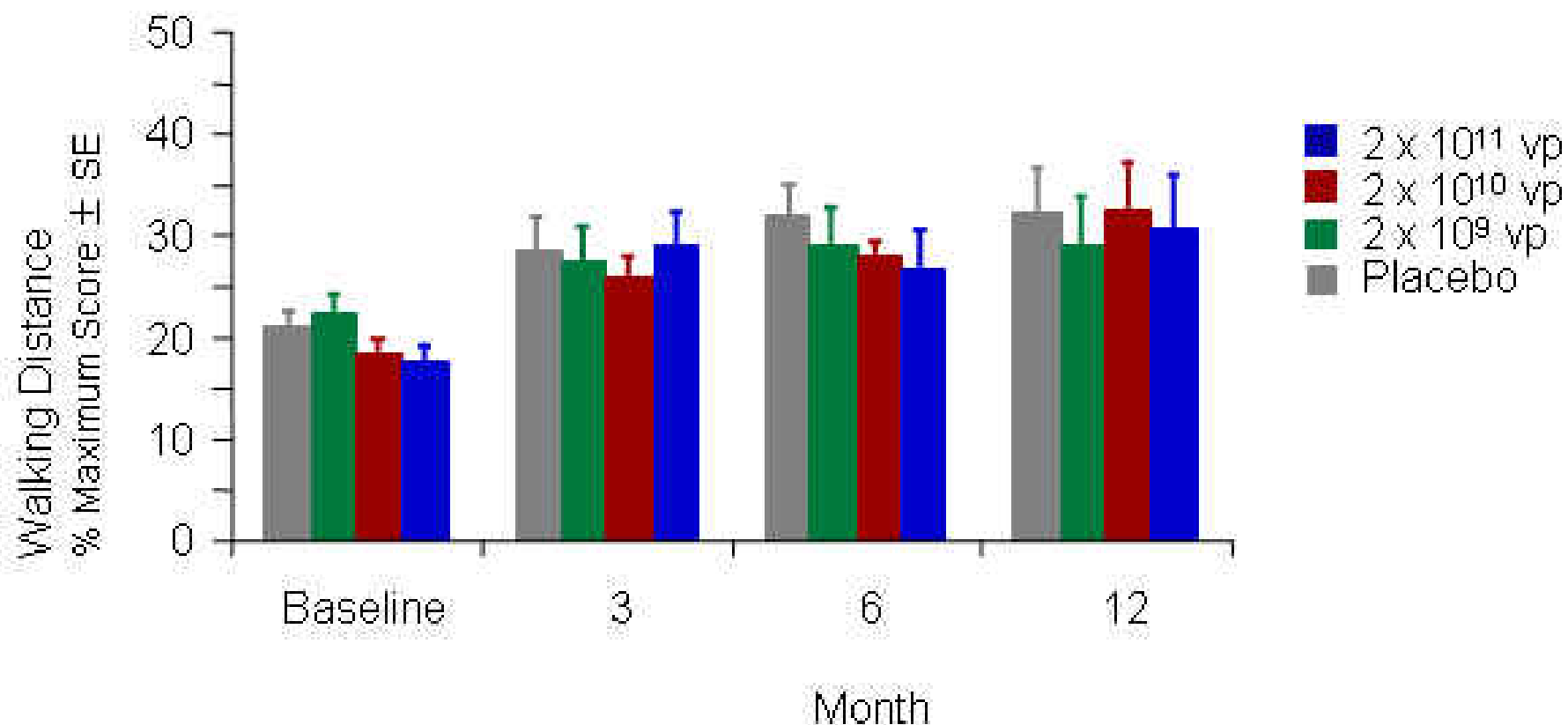
All p-values NS

Ankle Brachial Index: Index Leg



All p-values NS

Walking Impairment Questionnaire: Walking Distance



All p-values NS

Endovascular Rx: Technical Principles

Principles

Straight line flow
Prox revasc=
↑Tech success
Distal revasc=
↑Tech difficulty
↑Restenosis

Restenosis rates

Iliac
10%-20%

Inflow
Outflow

Superficial femoral/
popliteal artery
20%-60%

Tibioperoneal
30%-75%

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OCTOBER 20-23, 2009
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