Latest treatment approaches for patients with PAD Management of the condition with exercise

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Goals

- Identify patients with PAD using history, physical exam and appropriate noninvasive testing
- Treat PAD patients with :
  - risk factor modification including antiplatelet therapies, to decrease the risk of MI and stroke
  - Therapies to improve limb status

PAD

- Asymptomatic
- Claudication
- Rest Pain
- Tissue Loss- Gangrene or ulceration

Vascular Disease in the US

	Annual Incidence (Millions)	Prevalence (Millions)
Stroke	0.73[1]	4.6[2]
TIA	0.50[3]	4.9[4]
ACS	1.93[5]*	12.6[2†]
PAD	---	8–12[6]

TIA = transient ischemic attack. ACS = acute coronary syndrome. PAD = peripheral arterial disease.
*Includes coronary insufficiency, nocturnal and variant angina, atrial/papillary and undetermined MI;
†includes history of MI or stable/unstable angina pectoris or both.

1. Broderick J et al. *Stroke*. 1998;29:415-421.
2. American Heart Association. 2002 Heart and Stroke Statistical Update.
3. Brown et al. Amer. Stroke Assoc. 25th Int. Stroke Conference. 2000.
4. NSA Press Release. April 25, 2000.
5. National Hospital Discharge Survey 1999. National Center for Health Statistics/Centers for Disease Control and Prevention. Series 13, No.151. September 2001.
6. Hirsch AT et al. *JAMA*. 2001;286:11:1317-1324.

PAD-Related Risk Factors

Risk Factor	Relative Risk	95% CI
Diabetes[1]	4.05*	2.8-5.9
Smoking[1]	2.55*	1.76-3.68
Hyperlipidemia[1] (10 mg/dL increase in total cholesterol)	1.10*	1.06-1.14
Hypertension[1]	1.51*	1.15-1.99
Hyperhomocysteinemia[2]	1.44†	1.10-1.87

* PAD diagnosis based on ABI <0.90.

† PAD diagnosis based on history of peripheral arterial reconstruction or limb amputation, or an ABI <0.50.

1. Newman AB et al. *Circulation*. 1993;88:837-845.
2. Hoogeveen EK et al. *Arterioscler Thromb Vasc Biol*. 1998;18:133-138.

Identifying Patients at Risk for PAD

- Consider PAD in:
  - Any patients with exertional leg pain
  - Patients >50 years old with risk factors
  - All patients >70 years old

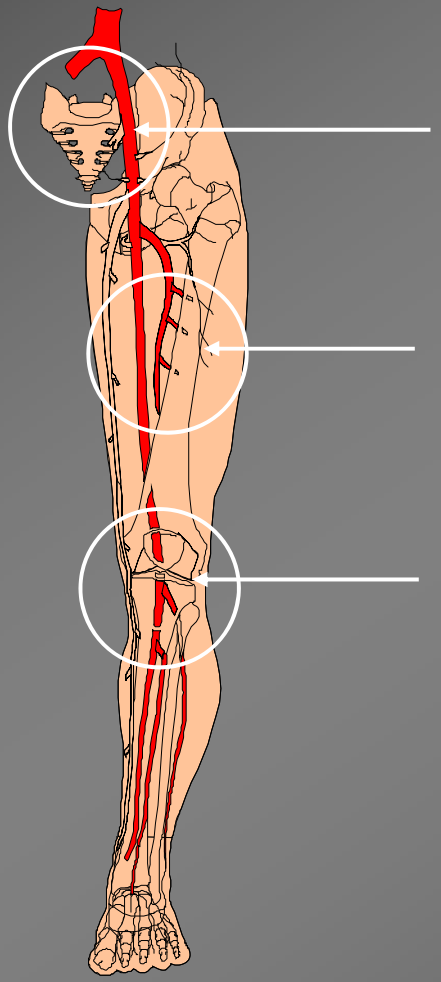
Diagnosis and Assessment of Disease Severity

- Vascular history
- Physical examination
- Ankle-brachial index (ABI) measurement
- Noninvasive vascular laboratory tests

Functional Description of Intermittent Claudication

- Symptoms
  - Exertional aching pain, cramping, tightness, fatigue
  - Occur in muscle groups, not joints (buttocks, hips, legs, calves)
  - Are reproducible from one day to the next on similar terrain
  - Resolve completely with 2-5 minutes of rest

Common Sites of Claudication



Obstruction in	Ischemia in
Aorta or iliac artery	Buttock, hip, thigh
Femoral artery or branches	Thigh, calf
Popliteal artery or distal	Calf, ankle, foot

Relationship Between Comorbidities and Atypical Leg Symptoms

Disease	Atypical/ Carry On (n=41)	Atypical/Stop (n=90)
Neuropathy score, mean	4.3	3.1
Diabetes, %	24.4	26.7
Disk disease,%	29.3	31.1
Spinal stenosis, %	9.7	13.6
Depression, %	5.1	18.8

McDermott MM et al. *JAMA*. 2001;286:1599-1606.

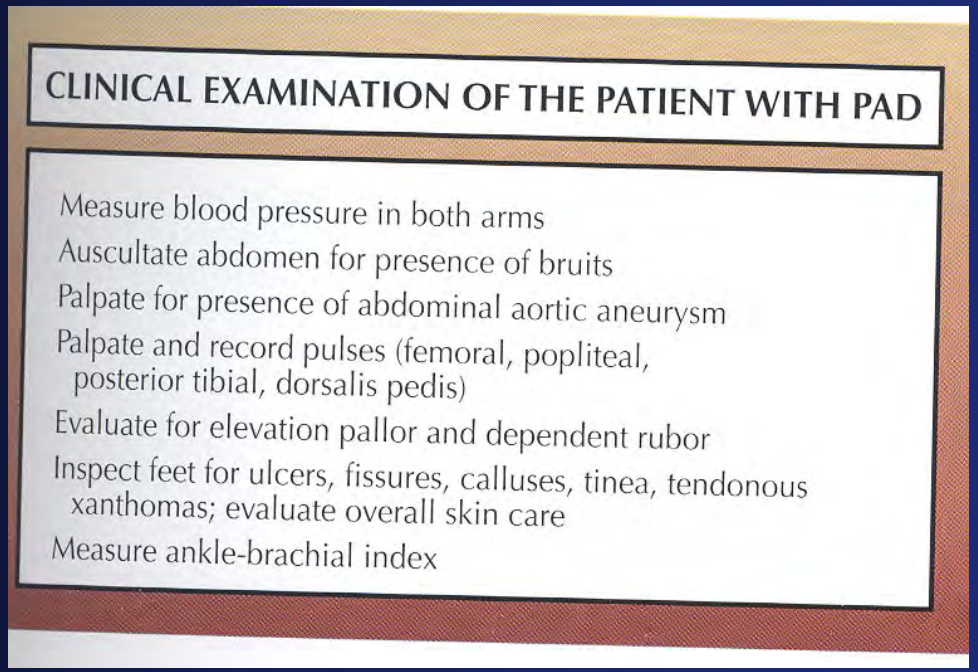
Does the Patient Have Intermittent Claudication?

	Claudication	Pseudoclaudication
Characteristic of discomfort	Cramping, tightness, aching, fatigue	Same, tingling, burning, numbness
Location of discomfort	Buttock, hip, thigh, calf, foot	Same
Exercise-induced	Yes	Variable
Distance	Consistent	Variable
Occurs with standing	No	Yes
Action for relief	Stand	Sit, change position
Time to relief	Less than 5 minutes	Up to 30 minutes

Important Questions for Patients

- Do you develop any cramping or fatigue in the muscles of either leg that occurs when you walk?
- Do symptoms only start when you walk?
- Do symptoms resolve once you stop walking?
- Do the symptoms occur in one or both legs?
- Do you have any nonhealing foot wounds?

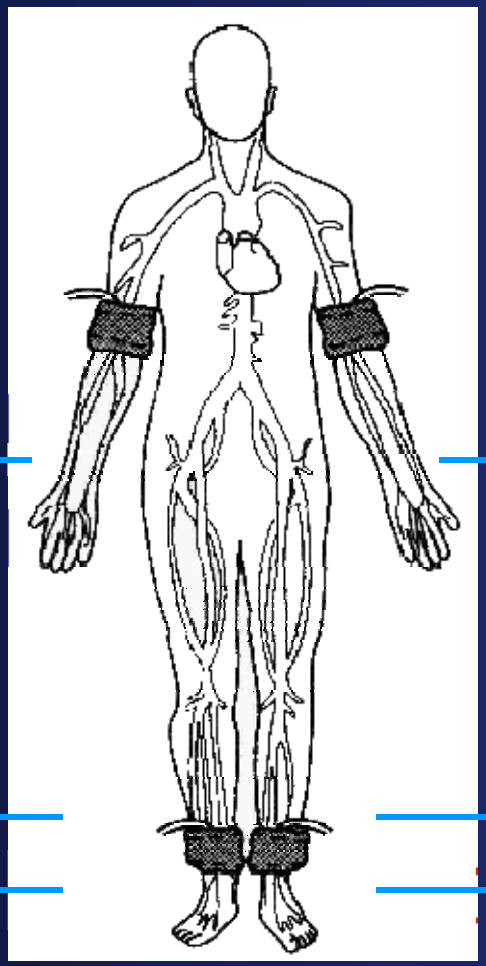
Physical Exam



CLINICAL EXAMINATION OF THE PATIENT WITH PAD

- Measure blood pressure in both arms
- Auscultate abdomen for presence of bruits
- Palpate for presence of abdominal aortic aneurysm
- Palpate and record pulses (femoral, popliteal, posterior tibial, dorsalis pedis)
- Evaluate for elevation pallor and dependent rubor
- Inspect feet for ulcers, fissures, calluses, tinea, tendonous xanthomas; evaluate overall skin care
- Measure ankle-brachial index

Office Measurement of the Ankle–Brachial Index (ABI)



Adapted from the PARTNERS Program.

Understanding the ABI

$$\text{ABI} = \frac{\text{Ankle systolic pressure}}{\text{Brachial artery systolic pressure}}$$

- **Both ankle and brachial systolic pressures should be taken using a hand-held Doppler instrument**
- **For both arm and leg, use higher of 2 pressures**
- **The ABI is 95% sensitive and 99% specific for PAD**

TASC Working Group. *J Vasc Surg*. 2000;31(1 suppl):S1-S296.

The Ankle-Brachial Index (ABI)

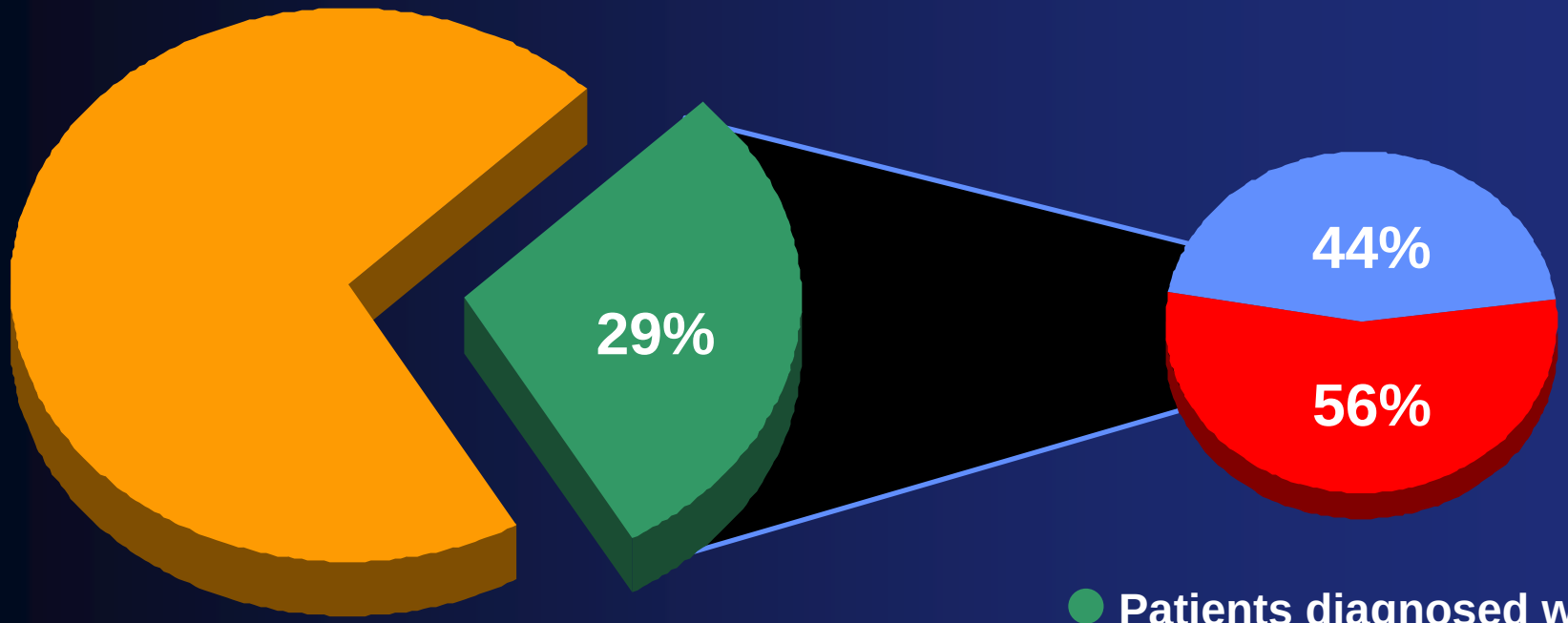
- **ABI measurement is the optimal method to detect PAD**
  - **Inexpensive, accurate, and office-based**
  - **Provides an international standard, validated by angiographic detection, for defining PAD prevalence**
  - **Predicts limb survival, propensity for wound healing, and short- and long-term patient survival[1,2]**
- **When is an ABI measurement indicated?**
  - **Presence or suspicion of claudication; pain at rest; or nonhealing foot ulcer**
  - **Age >70 years or >50 years with risk factors (diabetes, smoking)**

1. McKenna et al. *Atherosclerosis*. 1991;87:119-128.
2. Newman et al. *JAMA*. 1993;270:487-489.

PARTNERS

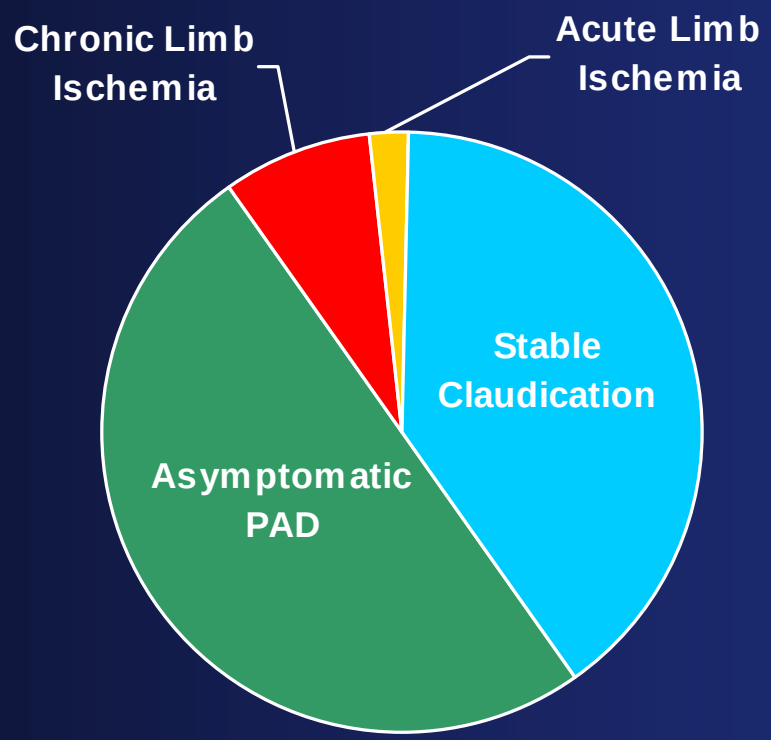
Diagnosis of PAD in High-Risk Patients

29% of patients were diagnosed with PAD using ankle-brachial index



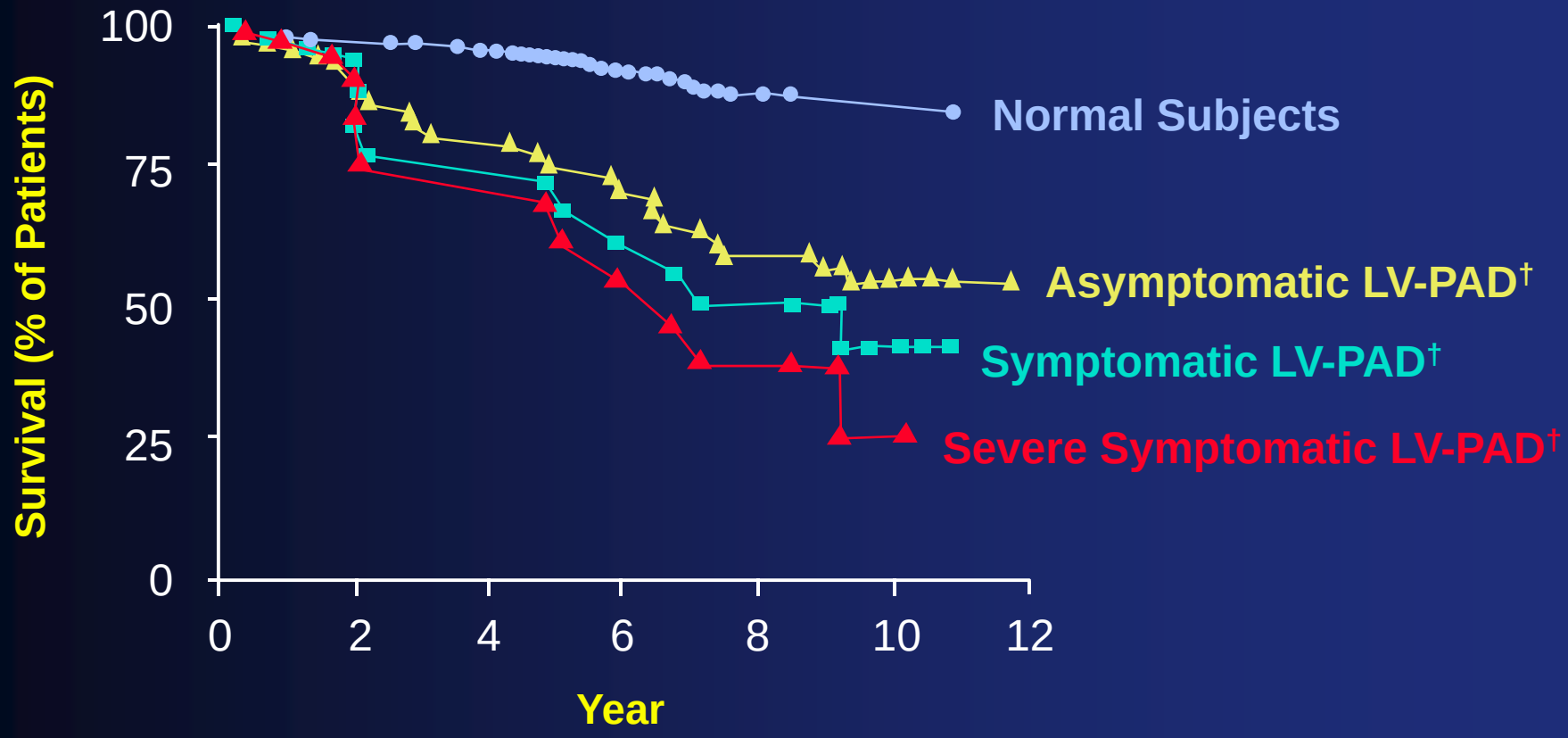
Hirsch AT et al. *JAMA*. 2001;286:1317-1324.

Clinical Presentation of PAD Patients



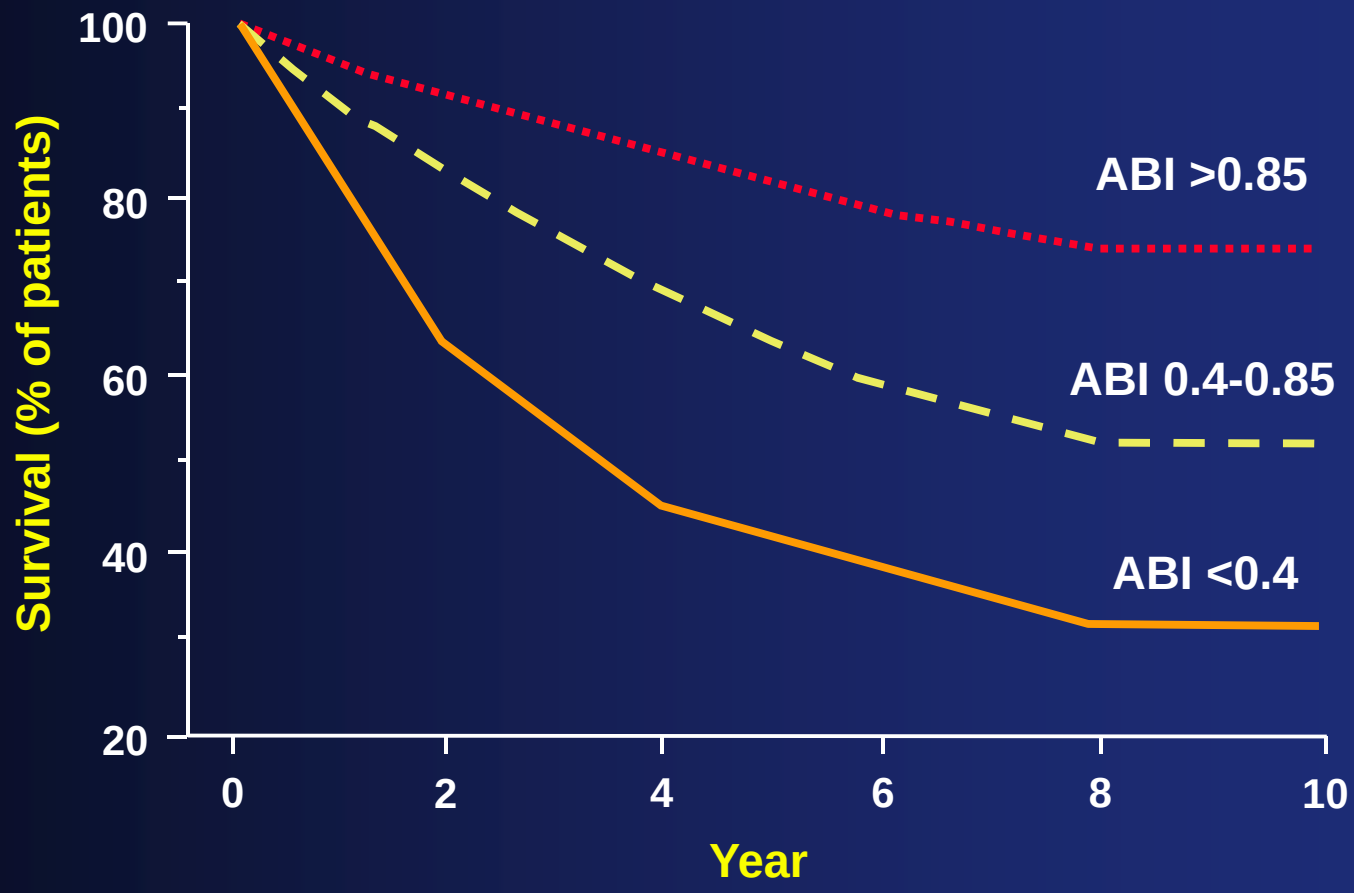
Adapted from Hirsch AT. *Fam Pract Recertification*. 2000;15(suppl):6-12.

Peripheral Arterial Disease (PAD) Mortality*



*Kaplan-Meier survival curves based on mortality from all causes.
†Large-vessel PAD.
Criqui MH et al. *N Engl J Med*. 1992;326:381-386.

Decline in Survival Associated With Severity of PAD



ABI = ankle-brachial index, PAD = peripheral arterial disease.

McKenna M et al. *Atherosclerosis*. 1991;87:119-128.

Correlation of ABI with Leg Function and Physical Activity

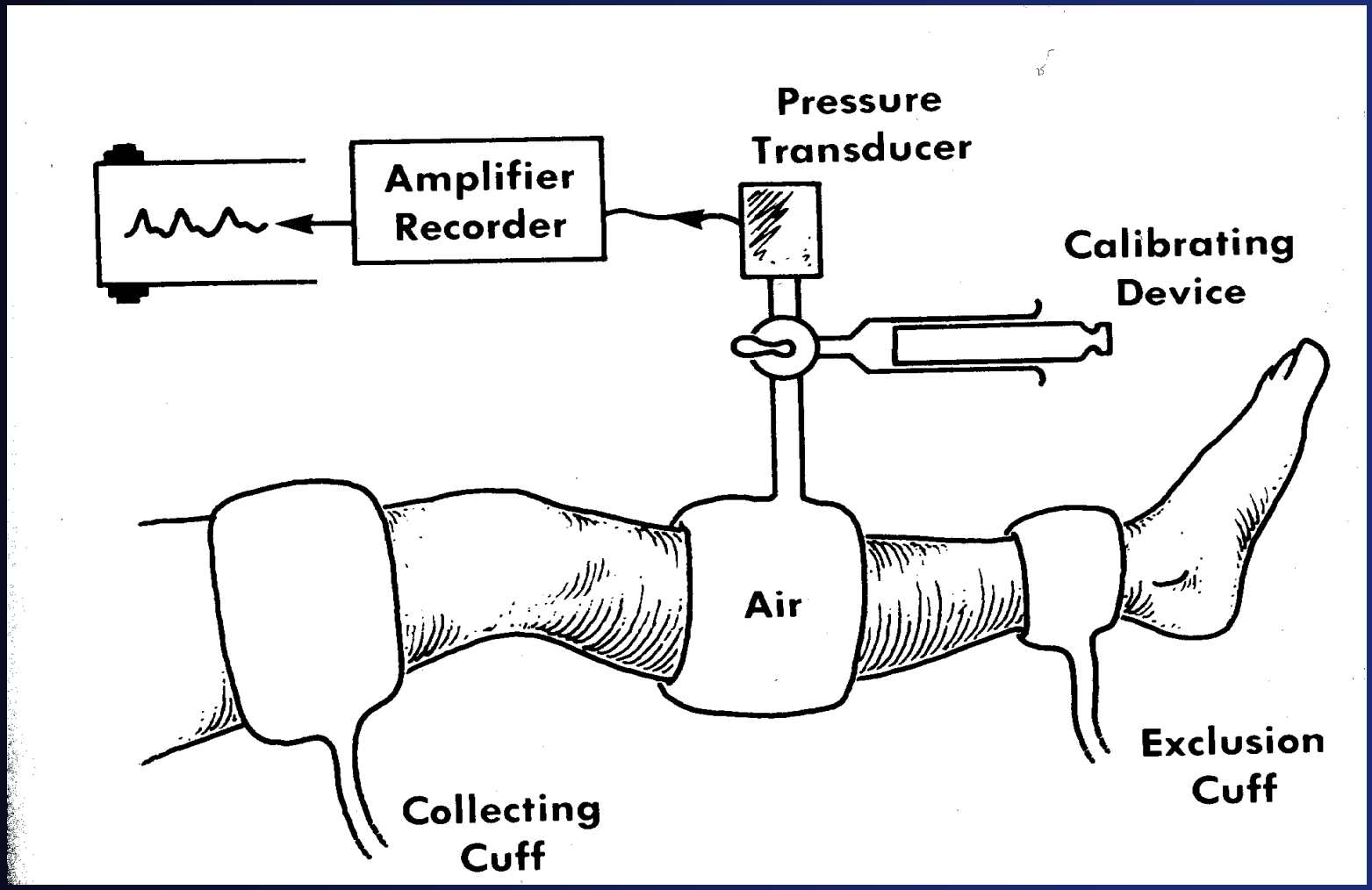
- As compared with higher ABI scores, lower ABI scores were consistently associated with:
  - shorter distance walked in 6 minutes
  - lower accelerometer-measured activity over 7 days
  - poorer standing balance
  - slower walking velocity at usual and fast pace
  - lower summary performance scores
- More than 60% of participants with ABI <0.40 had to stop during the 6-minute walk, while fewer than 5% with ABI ≥ 1.0 stopped

McDermott MM, et al. *Ann Intern Med.* 2002;136:873-883.

Other Noninvasive Diagnostic Tests

- Segmental blood pressure recording
- Segmental pulse volume recording
- Exercise stress testing
- Reactive hyperemia
- CW Doppler and duplex ultrasound

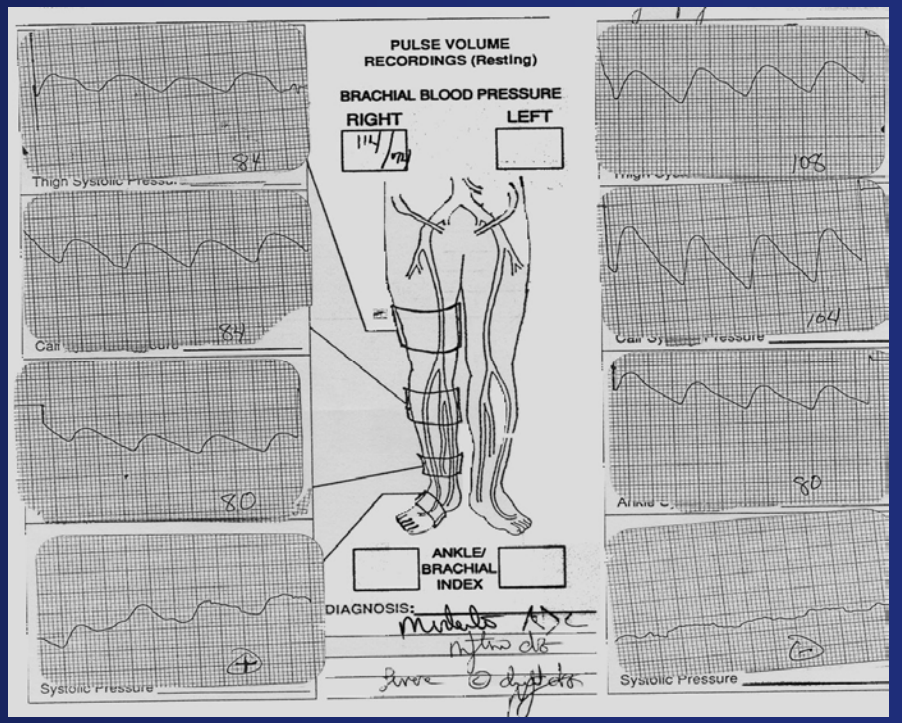
Rose SC. *J Vasc Interv Radiol.* 2000;11:1257-1275.



Pulse Volume recorder

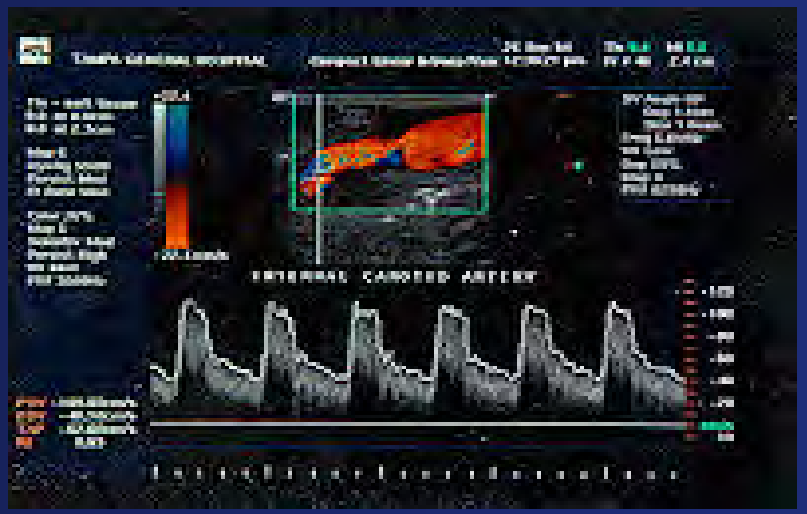
Pulse volume recordings

- Require specific equipment and training
- Provide information on level and severity of disease
- Can be used in exercise testing as well



Duplex Ultrasonography

- Duplex Studies
- Provide too much information
- Time consuming
- Expensive



Noninvasive Tests Summary

NONINVASIVE VASCULAR TESTING FOR PAD

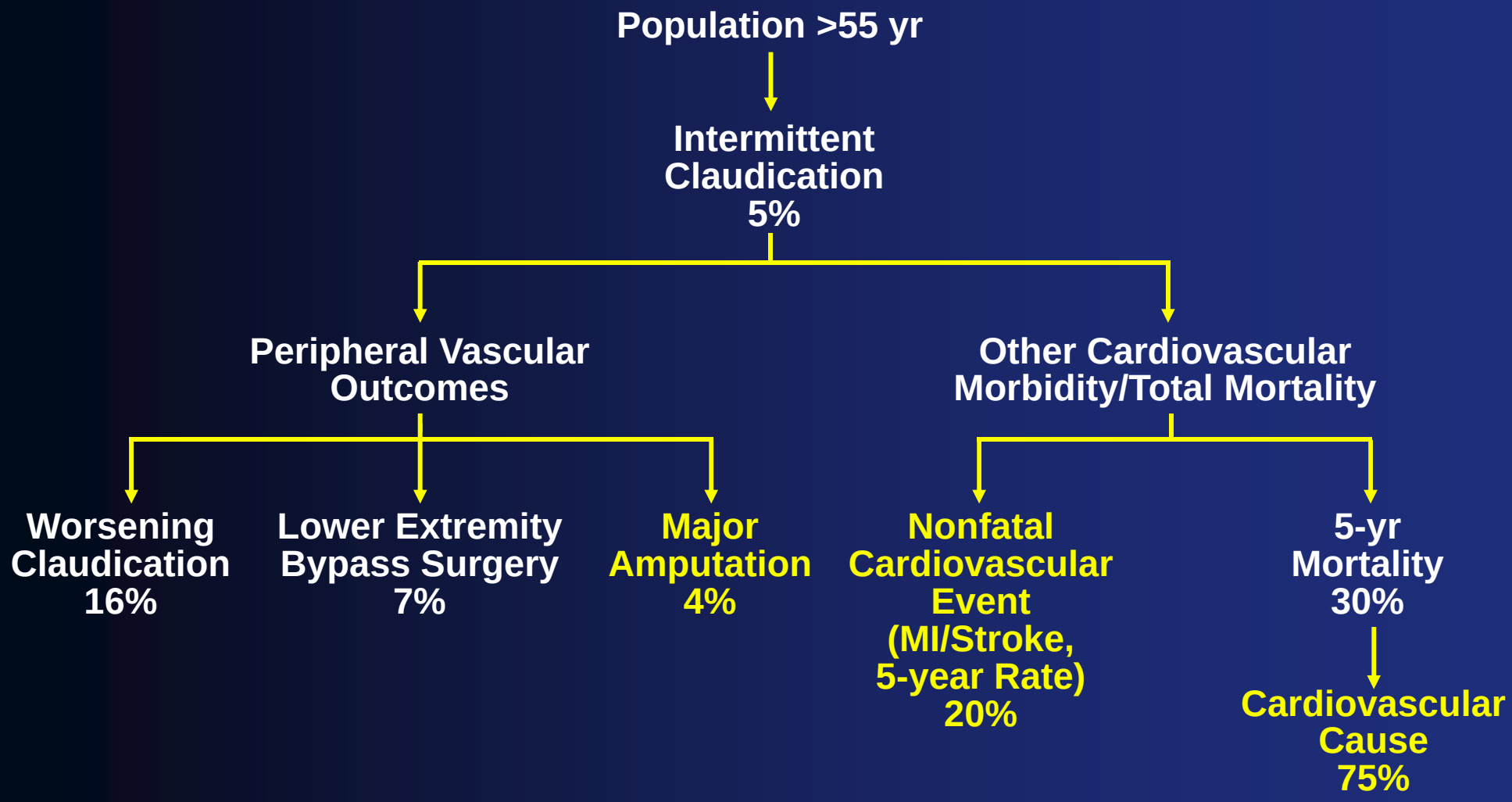
TEST	DISEASE LOCALIZATION	QUANTITATION OF DISEASE SEVERITY	RELATIVE COST
ABI	–	++	+
Segmental pressure analysis	++	++	+
Pulse volume recordings	+	+	+
Transcutaneous oximetry	+	+++	++
Doppler waveform analysis	+++	++	++
Arterial duplex	+++	++	+++
Exercise Doppler	–	+++	+++

Arteriography

- Provides an anatomic but not a physiologic assessment
- Perform only when considering a revascularization intervention (eg, surgery, PTA, stents)
- Always assess inflow and outflow (ie, aortogram with runoffs)

Peripheral Arterial Disease: Disease Management

Progression of Intermittent Claudication



Adapted from Weitz JI et al. *Circulation*. 1996;94:3026-3049.

PAD Management: Treatment Goals

- **Reduce risk of MI and stroke**
- **Relieve symptoms of claudication by**
  - **Supervised exercise (regular, structured, cardiac rehabilitation model)**
  - **Pharmacotherapy**
  - **Revascularization (endovascular or surgical)**

PAD Management: Prevention of Ischemic Events

Risk factor modification

- Smoking cessation
  - Goal: complete cessation
- Lipid management
  - Initiate therapy at LDL $\geq$ 70 mg/dL
- Blood pressure control
  - Goal <120/70 mm Hg[1]
  - 130/80 if diabetic
- Blood sugar control (diabetic patients)
  - Goal: HbA_{1c} <6.5%[2]

Physical Activity

30 min / day

Weight

BMI 18-25

A-Fib

NSR or INR 2-3

Antiplatelet therapies

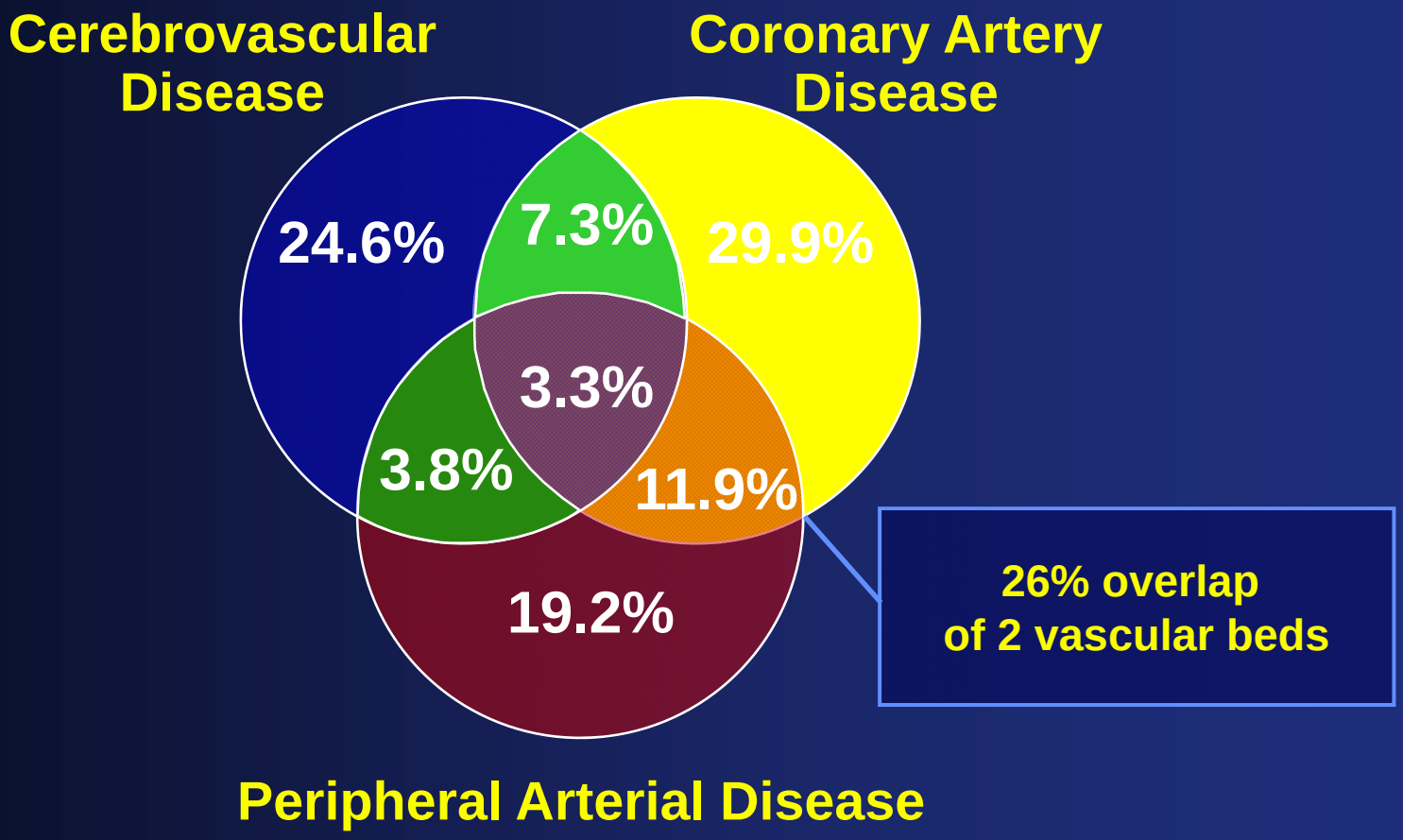
☞ **Goal: reduction in risk of MI, stroke, and vascular death**

[1] JNC VI. NIH Pub. No. 90-4080. Nov 1997:19.

[2] American Diabetes Association. *Diabetes Care*. 1997;20:1183-1197.

CAPRIE Study

Distribution of Symptomatic Atherosclerosis in CAPRIE



Data on file, Sanofi-Synthelabo Inc.

CAPRIE Study

Clopidogrel versus **A**spirin
in **P**atients at **R**isk of **I**schemic **E**vents

Rationale

- **Patients who have atherosclerotic disease (recent MI, recent ischemic stroke, or established PAD) are at risk for subsequent ischemic events and will benefit from antiplatelet therapy**
- **Atherosclerosis is a generalized vascular disease**
- **Antiplatelet agents have been proven to be effective in diverse manifestations of atherosclerotic disease**

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

Methodology

Study Design	Prospective, randomized, blinded
Number of Patients	19,185 patients with atherosclerotic vascular disease
Patient Types Included	Recent ischemic stroke (≤ 6 mo) Recent MI (≤ 35 d) Established peripheral arterial disease
Study Drugs	Clopidogrel bisulfate: 75 mg qd Aspirin: 325 mg qd
Treatment Duration	Up to 3 yrs (mean 1.6 yr)
Investigational Centers	304 in 16 countries, including the US

PLAVIX Prescribing Information.

CAPRIE Study

Inclusion Criteria

Recent Ischemic Stroke

- Presumed ischemic origin
- Onset ≥1 wk and ≤ 6 mo before randomization
- Persistent neurologic signs ≥1 wk from onset
- CT or MRI ruling out intracranial hemorrhage, nonrelevant intracranial disease

Recent Myocardial Infarction

- Onset ≤35 days before randomization

Two of:

- Ischemic pain ≥20 min
- CK, CK-MB, LDH, or AST 2x normal
- New ≥40 msec Q waves in ≥2 adjacent leads or new dominant R wave in V_1

Established Peripheral Arterial Disease

- Current intermittent claudication

AND

Ankle-brachial index ≤0.85; 2 readings on separate days

OR

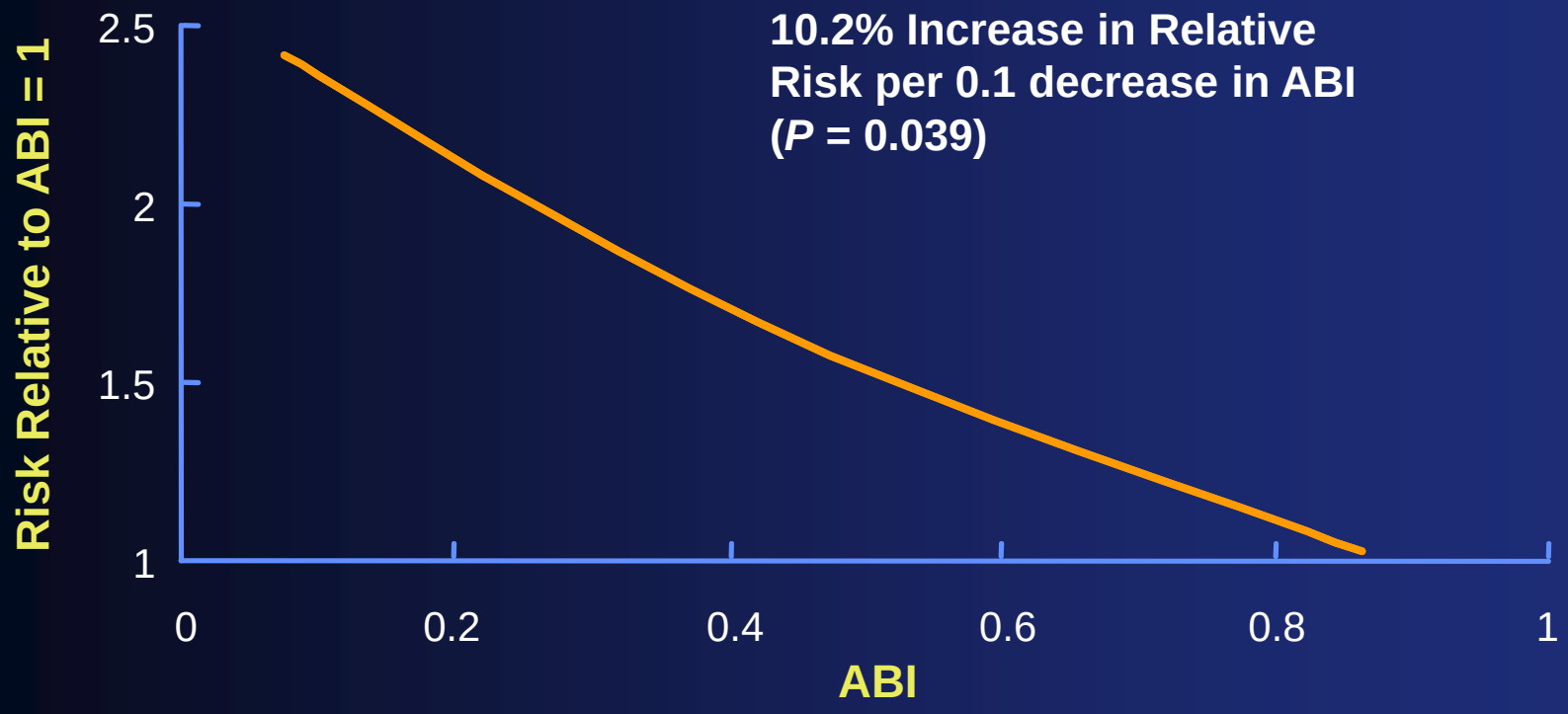
- Previous intervention (amputation, reconstructive surgery, or angioplasty)

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

CAPRIE

ABI: Predictor of Ischemic Events

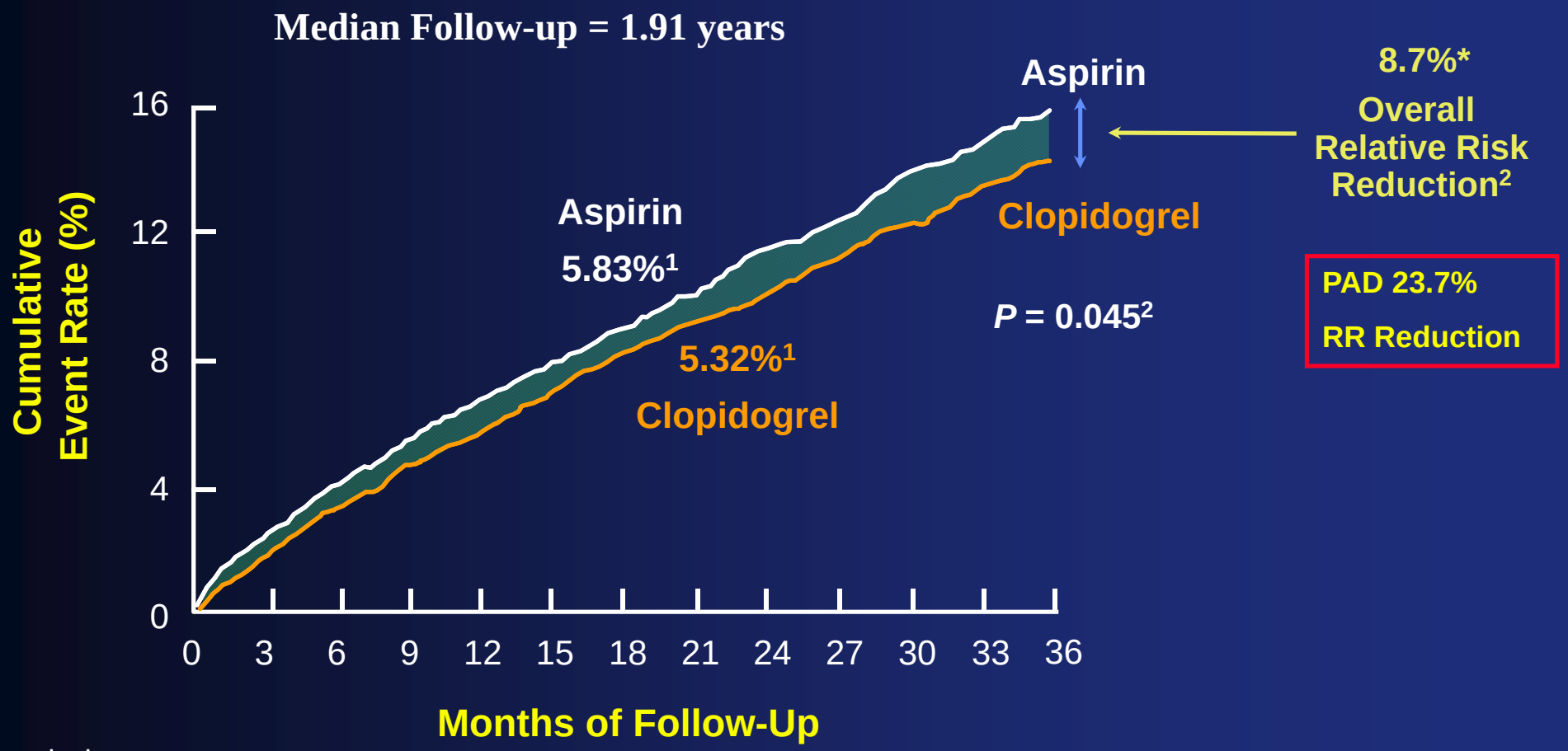
Inverse Relationship Between ABI and Risk of Cardiovascular Events



Dormandy JA. *Cerebrovasc Dis.* 1999;9(Suppl 1):1–128. [abstract 4]

CAPRIE Study

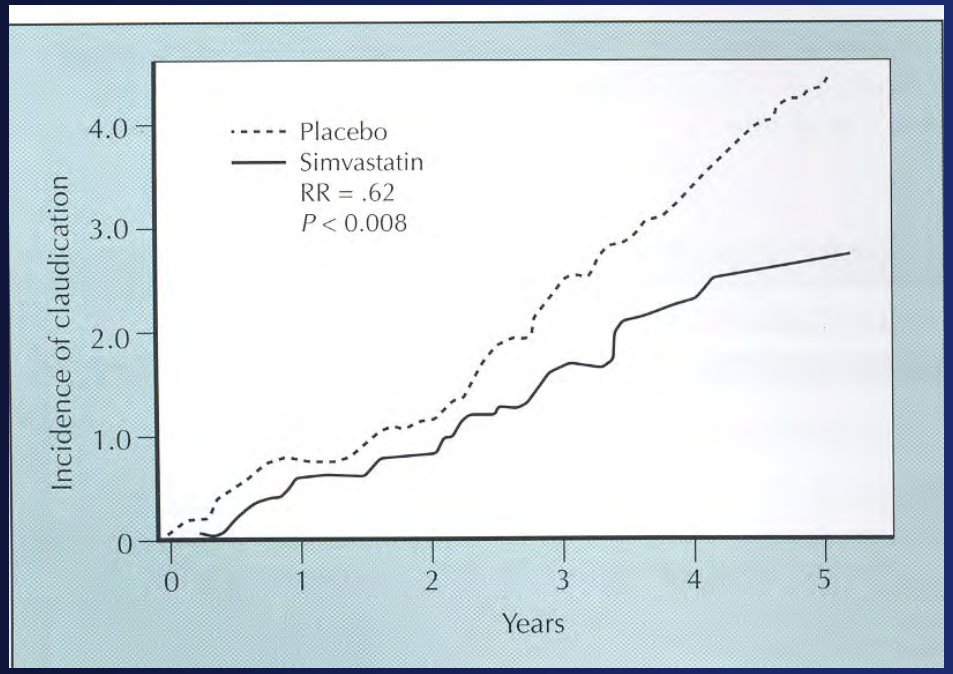
Efficacy of Clopidogrel vs Aspirin in MI, Ischemic Stroke, or Vascular Death (N = 19,185)



*ITT analysis.

1. CAPRIE Steering Committee. *Lancet*. 1996;348:1329-1339.
2. PLAVIX Prescribing Information.

Lipid Treatment



PAD Management: Antiplatelet Therapies

- **Lifetime antiplatelet therapy recommended for patients at risk for ischemic events [1,2]**
- **Clopidogrel is the only oral antiplatelet therapy indicated for reducing the risk of MI, stroke, and vascular death in patients with established PAD[3]**

[1] Antiplatelet Trialists' Collaboration. *BMJ*. 1994;308:81-106.

[2] Clagett GP, Krupski WC. *Chest*. 1995;108(suppl 4):431S-443S.

[3] Plavix® (clopidogrel bisulfate) Prescribing Information. March 2001.

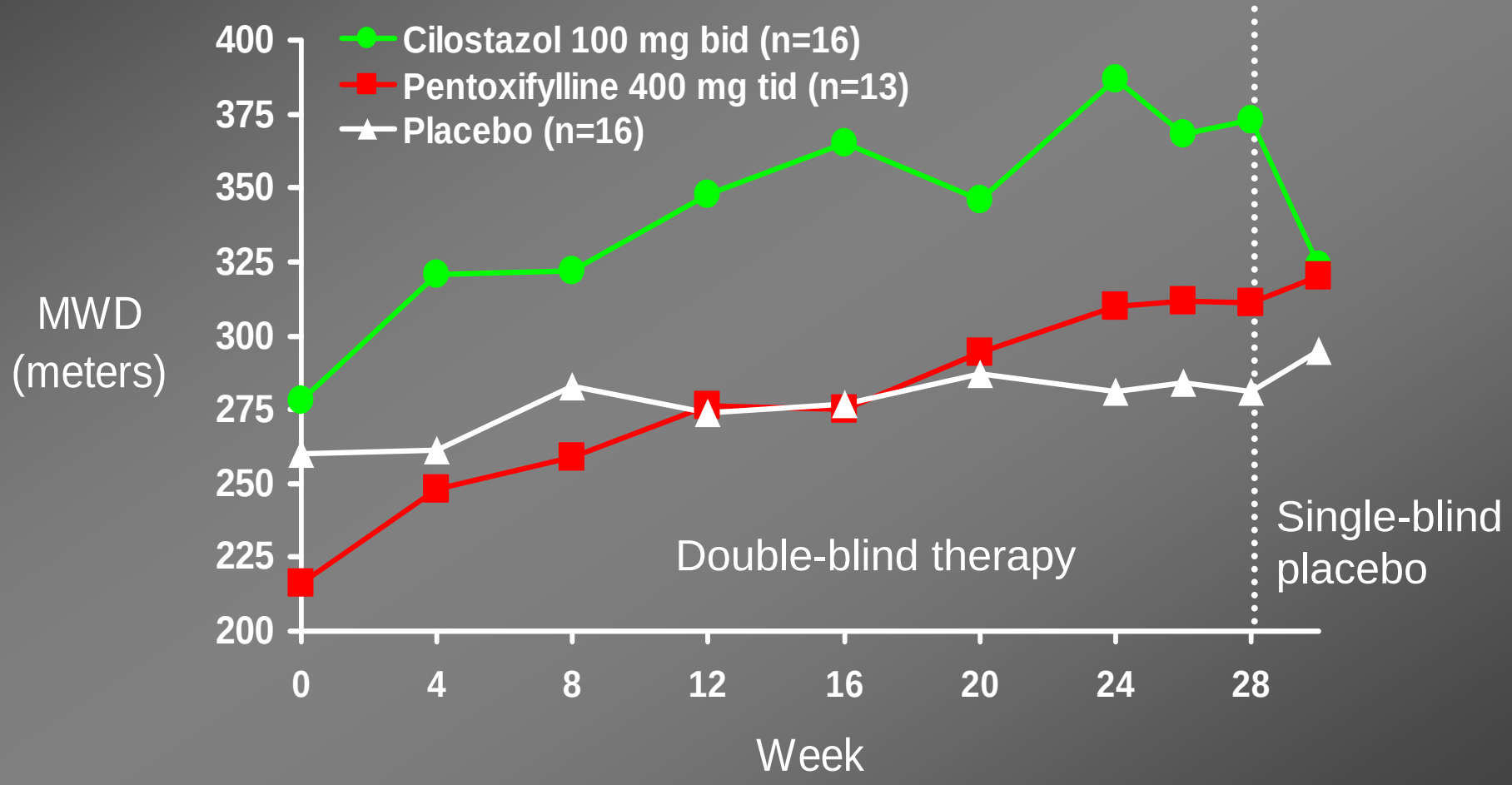
Symptomatic Therapies

Therapy	Mechanism
Pentoxifylline (Trental®)*	• ↓ Blood viscosity
Cilostazol (Pletal®)†	• ↓ Platelet aggregation • Trigger vasodilation • Improve lipid profile

*Trental is a registered trademark of Aventis Pharmaceuticals Inc.
†Pletal is a registered trademark of Otsuka America Pharmaceutical, Inc.

Fernandez BB Jr. *Am J Med Sci.* 2002;323:244-251.

Maximal Walking Distance Before and After Drug Withdrawal

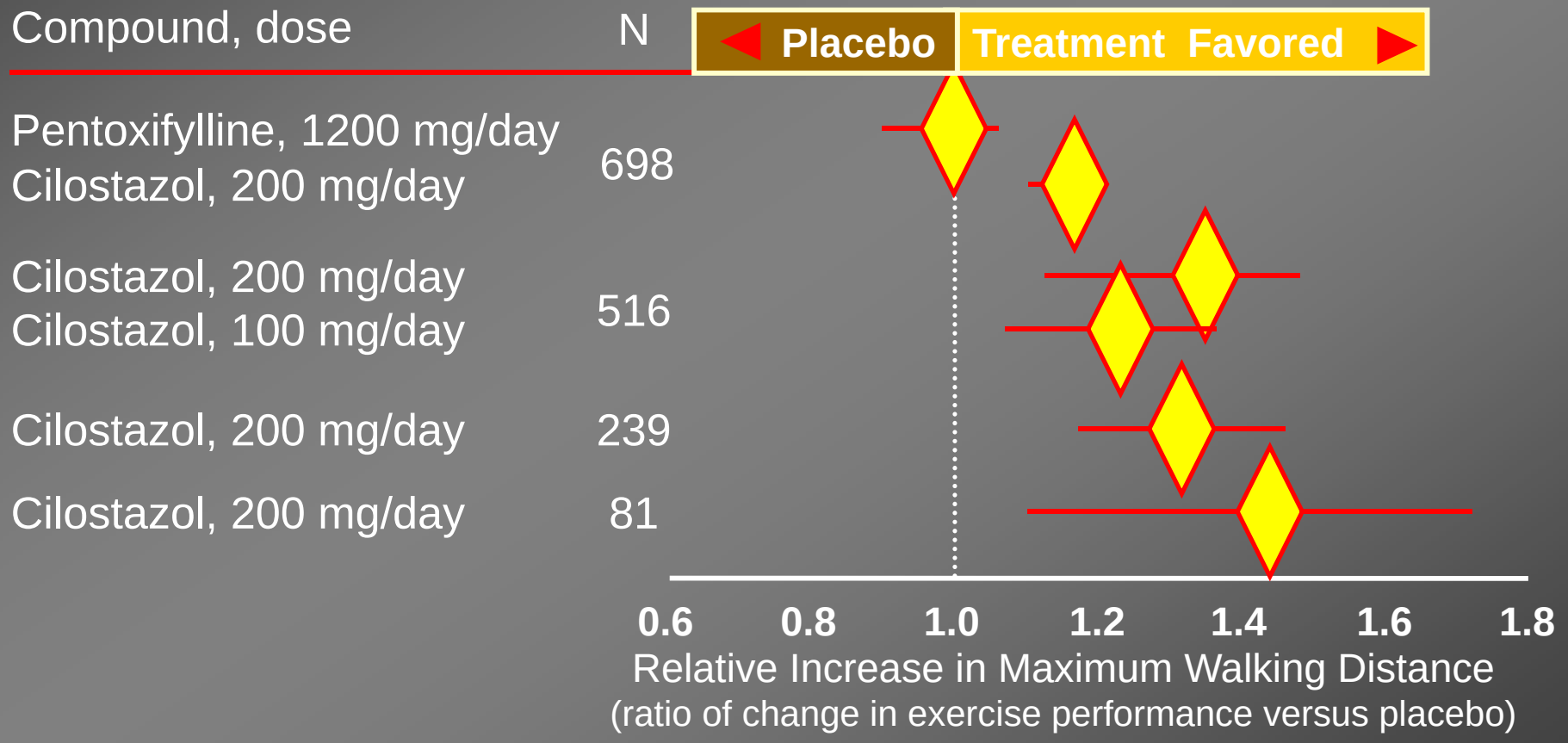


Dawson et al. *Am J Surg.* 1999;178:141-6.

Treatment of PAD

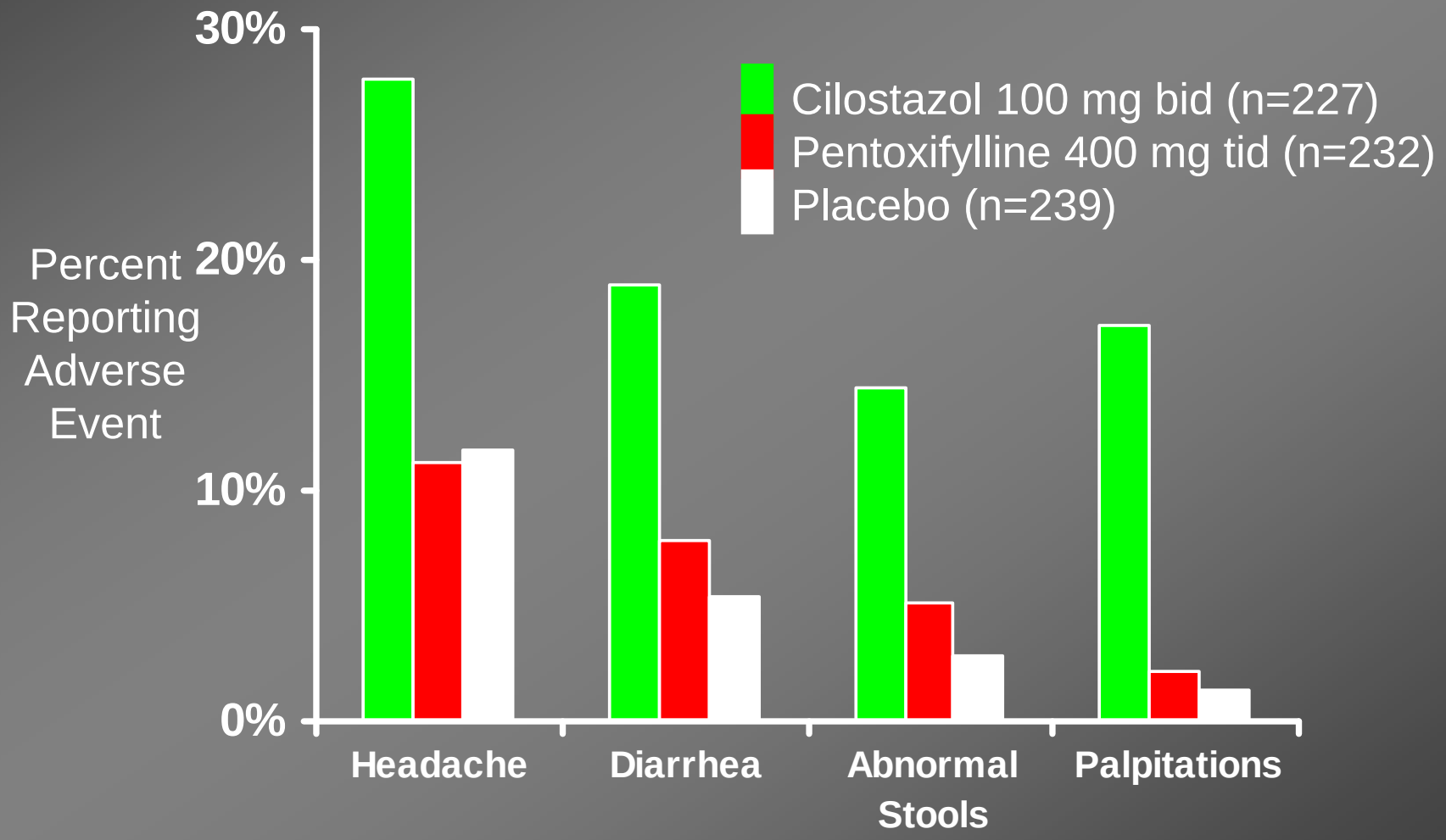
Effect of Drug Therapy on Walking Distance

Meta-analysis of 4 randomized, placebo-controlled trials



Hiatt WR. *N Engl J Med.* 2001; 344;1608-1621.

Most Common Adverse Event



Dawson et al. *Am J Med.* 2000.

Exercise for PAD?

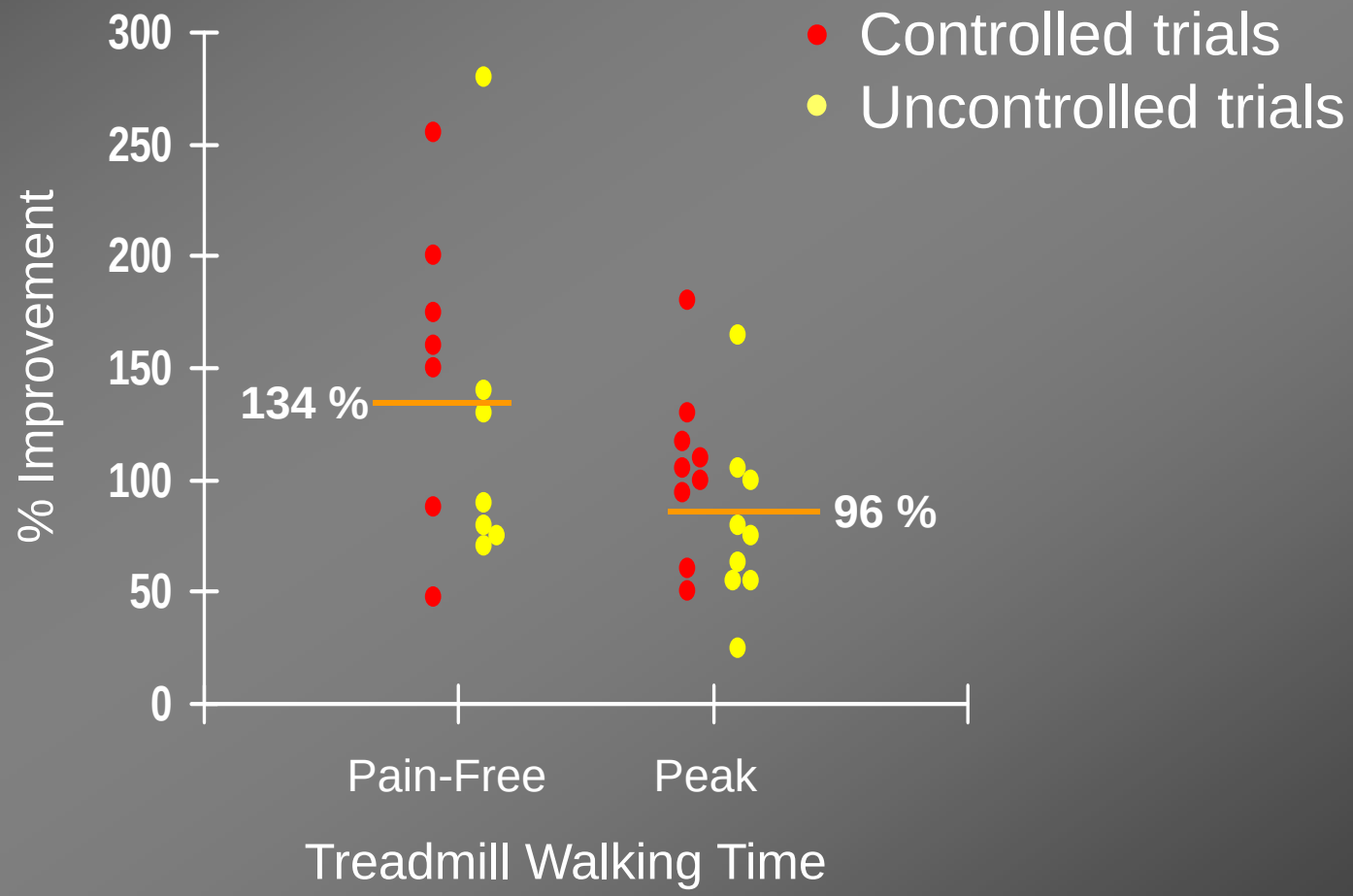
- Your legs hurt when you walk so go out and walk?

Requirements of Exercise Programs

A successful program includes
5 sessions per week (3 supervised + 2 unsupervised)

Regensteiner JG. *Angiology.* 1997;48:291-300.

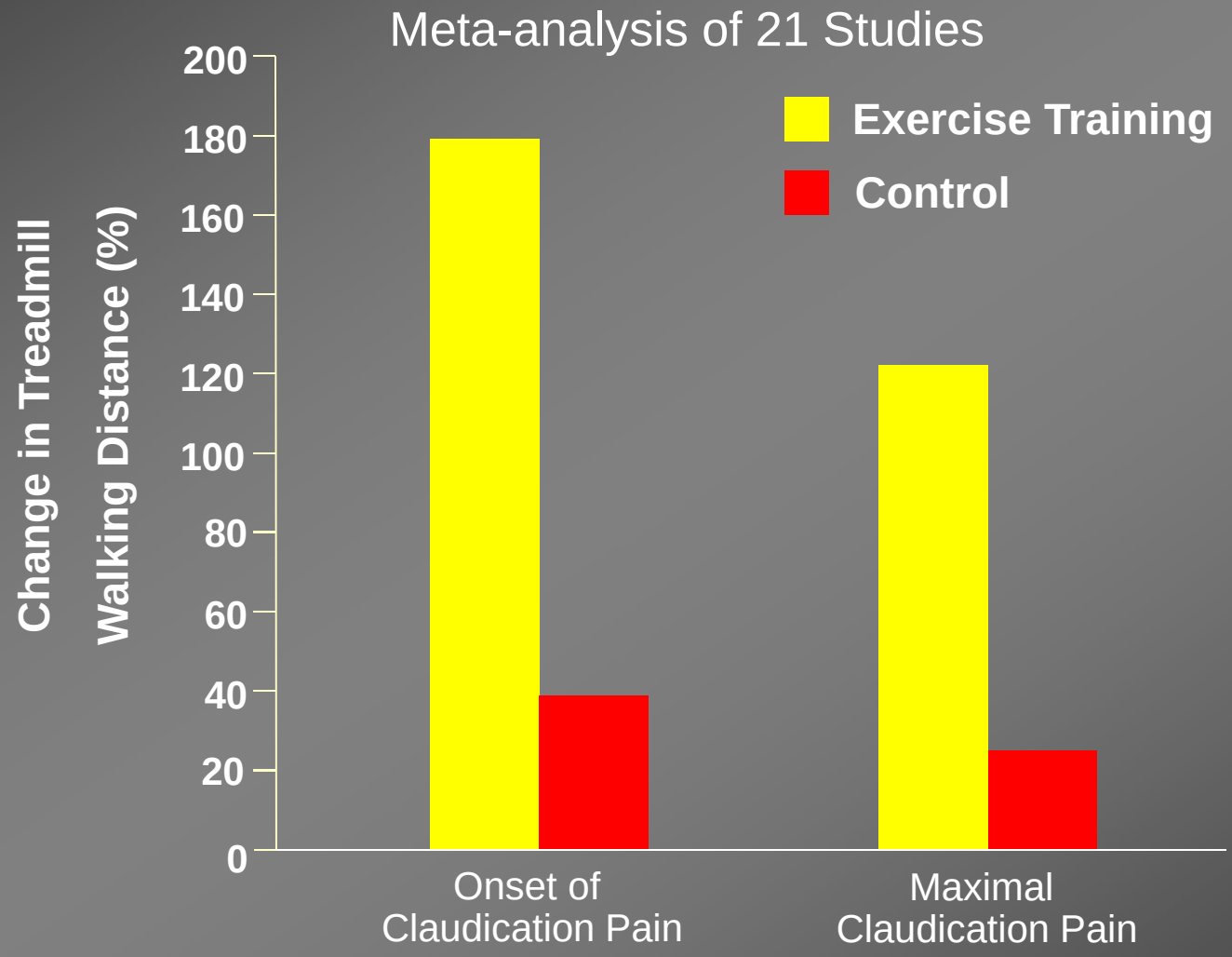
Effect of Exercise Training on Walking Ability in PAD



Gardner AW. *JAMA*. 1995;274:975-980.

Treatment of PAD

Effect of Exercise Training



Gardner AW. *JAMA*. 1995;274:975-980.

Treatment of PAD

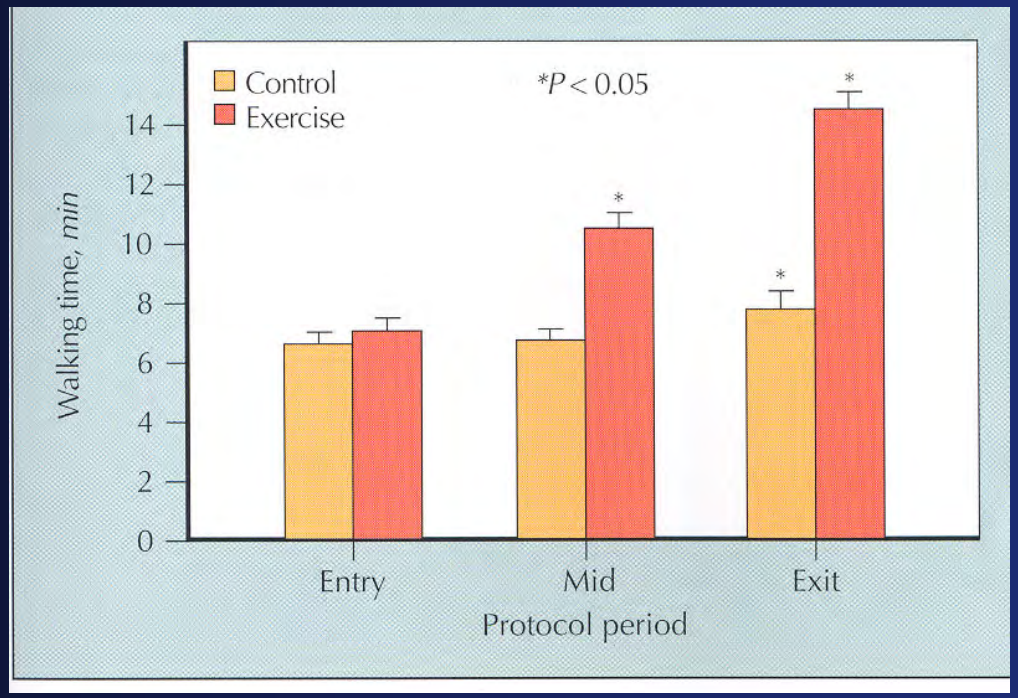
Effect of Exercise Components on Walking Distance

Exercise Duration	< 30 min/session	144 ± 419
	≥ 30 min/session	653 ± 364 *
Exercise Frequency	< 3 session/wk	249 ± 350
	≥ 3 sessions/wk	541 ± 263 *
Length of Program	< 26 weeks	275 ± 228
	≥ 26 weeks	519 ± 409 *
Training End Point	Onset of Pain	196 ± 78
	Near-Maximal Pain	607 ± 427 *
Mode of Exercise	Walking	512 ± 483 *
	Combination	287 ± 127

* $P < 0.05$

Gardner. *JAMA* 1995;274:975-980.

Exercise Program



ACC/AHA 2005 Guidelines

Treatment of Claudication

Exercise

- I/A Supervised exercise training should be the initial treatment
  - 30-45 minute sessions
  - 3 or more times per week
  - At least 12 weeks
- IIb/B Value of unsupervised exercise programs is not well established

Drug therapy

- I/A Cilostazol 100 mg twice daily
  - Can improve symptoms & increase walking distance
  - Indicated for lifestyle-limiting claudication
  - Contraindicated in patients with heart failure
- Pentoxifylline 400 mg three daily
  - IIb/A Consider as an alternative to cilostazol
  - IIb/C Effectiveness of pentoxifylline is marginal and not well established

Intermittent Claudication Exercise Programs

- **Pros**
  - Effective at improving exercise performance, walking distance, and physical functioning
  - Safe, with no recorded morbidity or mortality
  - Potential to improve other atherosclerosis risk factors
  - Cost-effective
- **Cons**
  - Require motivated and compliant patient
  - Limited availability of supervised programs

Follow-up and Counseling

- Set reasonable expectations for patient
  - Exercise program
  - Other lifestyle changes
- Refer patient for supervised walking program, if available

Follow-up Care for Patients in PAD Rehabilitation

- Reevaluate patient 90 days after initiation of therapeutic program
  - Assess symptomatic status of limb
  - Reassess atherosclerotic risk factor intervention and antiplatelet therapy
  - Review compliance with home exercise therapy
  - Consider pharmacologic therapy for nonresponders
- Continue monitoring every 90 days until patient improves
  - Thereafter, monitor every 6 months

Indications for Revascularization for Intermittent Claudication

- Lifestyle-limiting symptoms
- Continued disability despite appropriate nonsurgical management
- Technically feasible revascularization options exist
- Expectation of favorable risk/benefit ratio

Surgical and Endovascular Treatment Options

- **Surgical**
  - **endarterectomy**
  - **bypass**
- **Endovascular**
  - **percutaneous transluminal angioplasty**
  - **percutaneous transluminal angioplasty with stent placement**

Creager M. *Management of Peripheral Arterial Disease. Medical, Surgical and Interventional Aspects.* 2000.

Revascularization for Aorto-Iliac Arterial Disease

Aortofemoral Bypass

- Primary patency at 5 years of 81-85%[1]
- Perioperative mortality 5-8%[1]
- Reserved for severe diffuse disease cases[2]
- Indicated for Rutherford class ≥ 3[2]

1. Raptis S. et al. Eur. J. Vasc. Endovasc. Sur. 1995; 9: 97-102
2. Rosenfield K and Isner JM. Chap 97 in Textbook of Cardiovascular Medicine 1998

Percutaneous Intervention

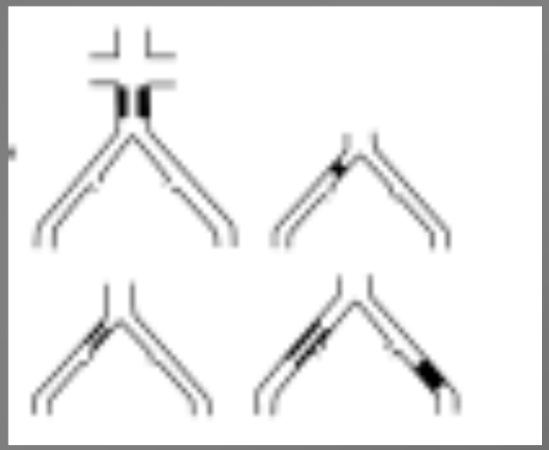
- Patency at 5 years of 65-80%[1]
- Perioperative mortality 0.1%[1]
- Treatment of choice[3]
- Indicated for Rutherford class ≥ 2[2]

1. Becker GJ et al. Radiology 1989;170:921-940
2. Belli A-M et al. Clin Radiol 1990;41:380-3
3. Rosenfield K and Isner JM. Chap97 in Textbook of Cardiovascular Medicine 1998

Lesion-guided approach for treatment of aorto-iliac disease

A
Endovascular is procedure of choice

B
Endovascular is preferred therapy



C
Surgery is preferred for good-risk

D
Surgery is procedure of choice

TASC II 2007: Europ J Vasc Endovasc Surg 2007:33(S1):S52

Treatment of PAD

Revascularization for Femoro-Popliteal Disease

Femoro-Popliteal Bypass Surgery

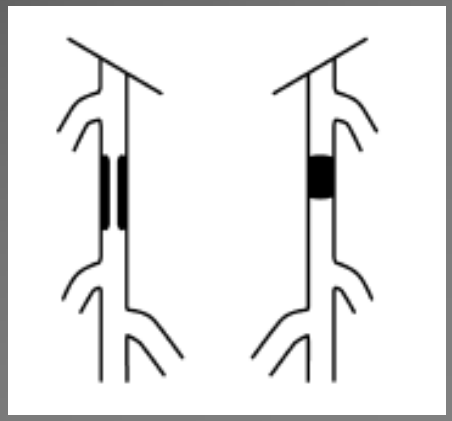
- Primary patency at 5 years of 60-80%
- Autologous veins preferred to synthetic grafts
- Perioperative mortality 0-3%
- Indicated for Rutherford class ≥ 3

Femoro-Popliteal Angioplasty

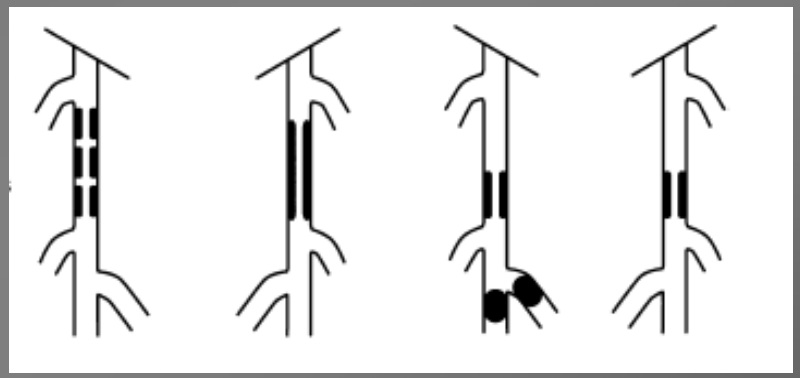
- Patency at 2-5 years ranges between 40-70%
- Technical problems due several anatomic issues:
  - Occlusions vs stenosis
  - Diffuse disease
  - Adductor canal
  - Disease in run off vessels
- Perioperative mortality is very low
- Indicated for Rutherford class ≥ 2

Lesion-guided approach for treatment of femoro-popliteal disease

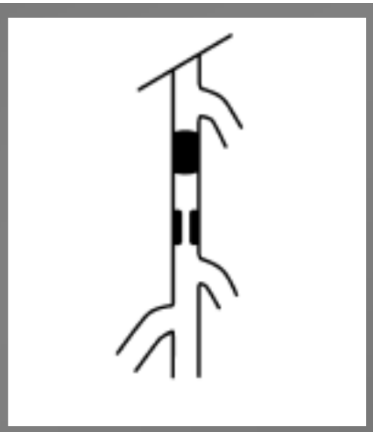
A
Endovascular is procedure of choice



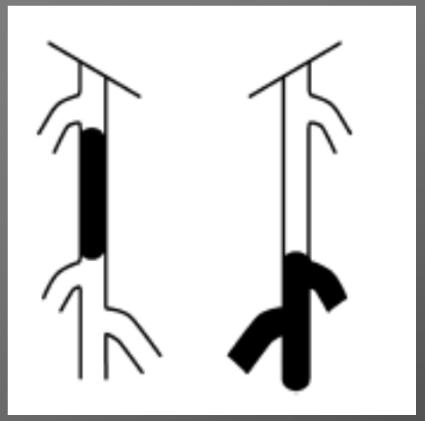
B
Endovascular is preferred therapy



C
Surgery is preferred for good-risk



D
Surgery is procedure of choice



TASC II 2007: Europ J Vasc Endovasc Surg 2007:33(S1):S58

ACC/AHA 2005 Guidelines

Treatment of Claudication

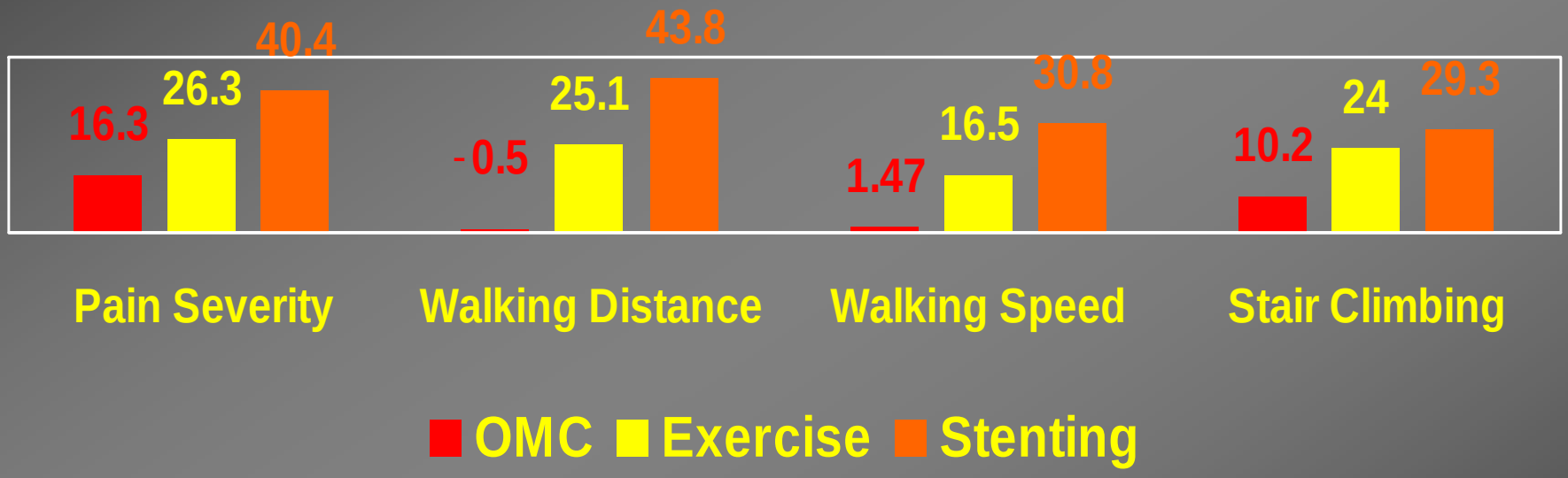
Endovascular therapies

- I/A — Only indicated for patients with
  - Vocational or lifestyle-limiting disability;
  - Reasonable likelihood of symptomatic improvement;
  - Prior failure of exercise or pharmacological therapy; and,
  - Favorable risk-benefit ratio
- III/C — Not indicated as a prophylactic treatment
- I/B — Preferred method for revascularization of TASC type A iliac and femoropopliteal arterial lesions

Surgery

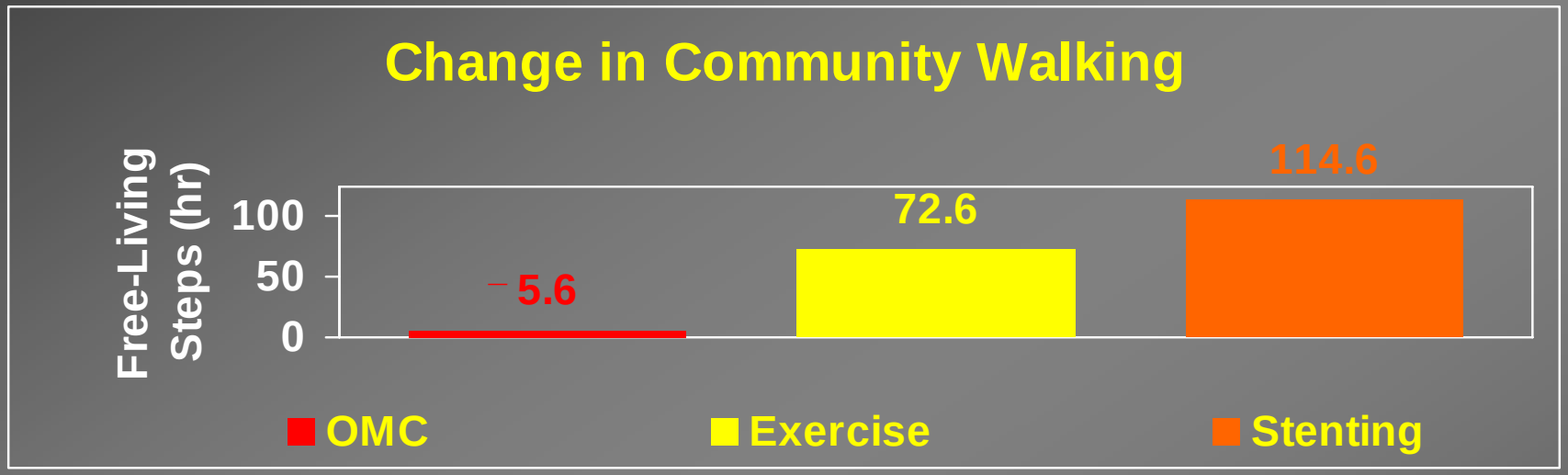
- I/B — Indicated for patients
  - With significant functional disability from symptoms
  - Who are unresponsive to exercise or pharmacotherapy
  - Who have a reasonable likelihood of symptomatic improvement
- III/C — Surgical intervention is not indicated to prevent progression to limb-threatening ischemia

Exercise vs Stenting for Claudication



CLEVER: Circulation. 2012;125:130-139

Exercise vs Stenting for Claudication



Pair-wise comparisons		
	Difference (steps)	*P* value
Exercise vs. OMC	78	0.06
Stent vs OMC	120	0.10
Exercise vs Stenting	42	0.47

CLEVER: Circulation. 2012;125:130-139

Albany Vascular Institute Experience

Infrainguinal Bypass for Claudication

1987-1997

-4468 lower extremity bypass operations performed

- 409 (9%) indication=claudication

Case

- 41 year old white male
- CC: Right calf cramping at 1 block
- Sx: worsening over last 2 months

Case Study

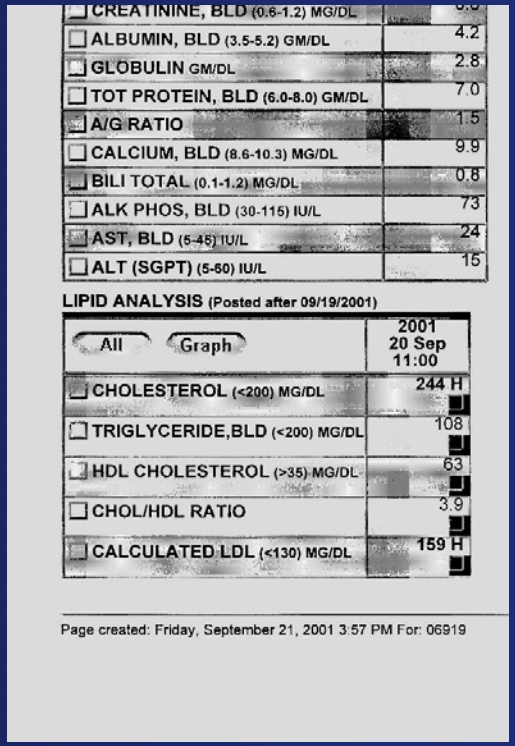
- PMH: S/P PTCA at age 38 for angina
- Family History: Father expired from MI at age 51, Brother nonfatal MI age 45
- Smoke: 2 ppd
- Social History: UPS delivery
- Medications: none

Case Study

- Physical exam
  - BP 114/74 HR 75 5 feet 10in 165 lbs.
  - Lungs clear, Cor RRR no murmurs
  - Abdomen: negative
  - Carotids without bruits
  - Absent distal pulses decreased right femoral pulse

Case Study

- Hct 46%
- LFTS normal
- PT/PTT normal



CREATININE, BLD (0.6-1.2) MG/DL	
ALBUMIN, BLD (3.5-5.2) GM/DL	4.2
GLOBULIN GM/DL	2.8
TOT PROTEIN, BLD (6.0-8.0) GM/DL	7.0
A/G RATIO	1.5
CALCIUM, BLD (8.6-10.3) MG/DL	9.9
BILI TOTAL (0.1-1.2) MG/DL	0.8
ALK PHOS, BLD (30-115) IU/L	73
AST, BLD (5-45) IU/L	24
ALT (SGPT) (5-60) IU/L	15

LIPID ANALYSIS (Posted after 09/19/2001)

All Graph	2001 20 Sep 11:00
CHOLESTEROL (<200) MG/DL	244 H
TRIGLYCERIDE,BLD (<200) MG/DL	108
HDL CHOLESTEROL (>35) MG/DL	63
CHOL/HDL RATIO	3.9
CALCULATED LDL (<130) MG/DL	159 H

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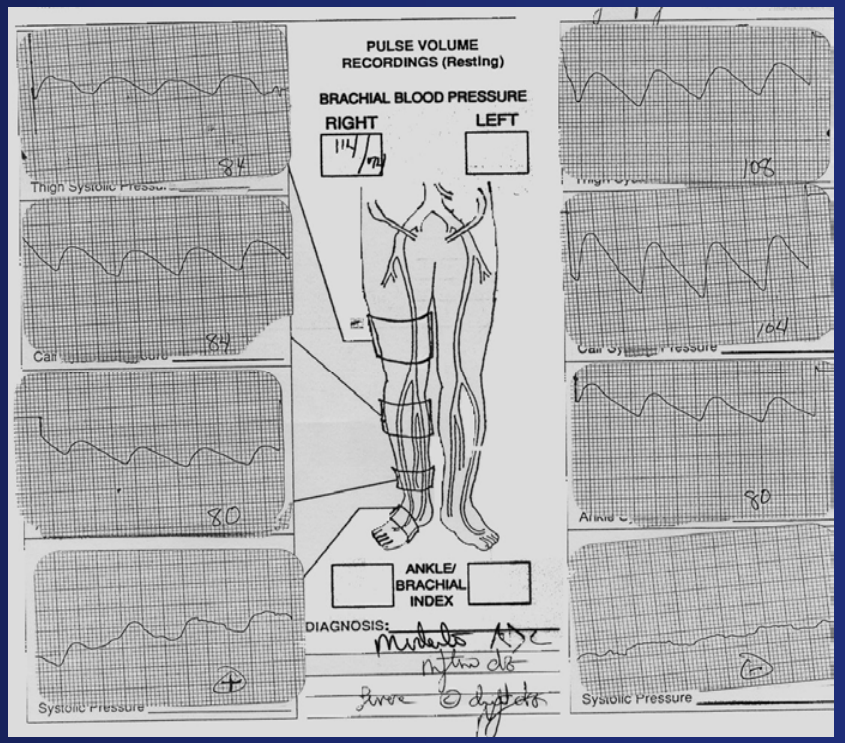
Case Study

- Abnormal ABI Bilateral
- PVRS dampened at thigh bilateral



Case Study

- Whats the next step?
  - Lipid management
  - Plavix
  - Smoking cessation
  - Cilostazol
  - exercise

Case Study

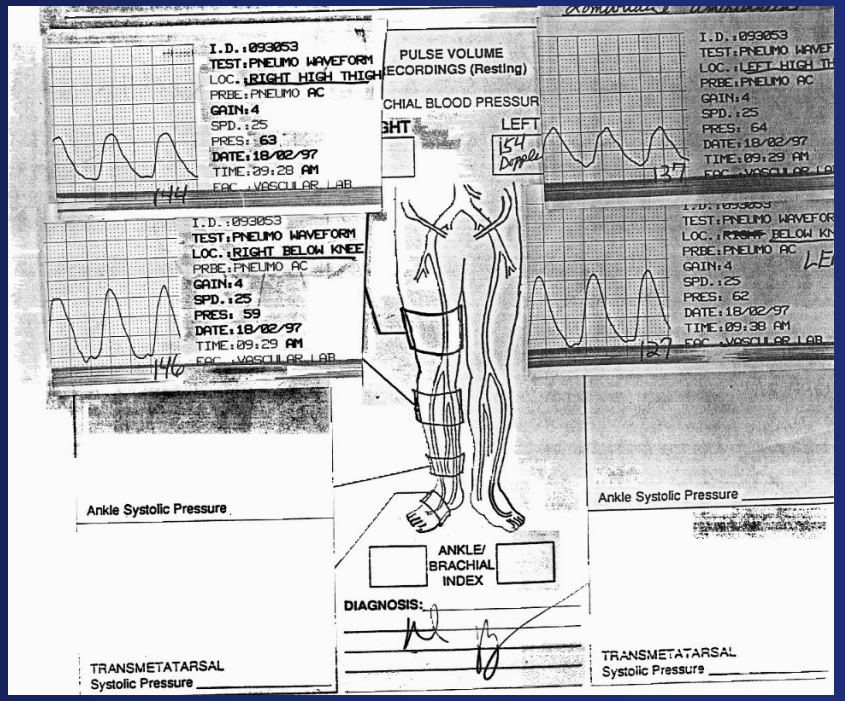
- 3 month follow-up
- Walking distance decreased no longer can work
- Lipids at goal
- On Clopidogrel

Case Study

- Underwent aortoiliac endarterectomy

Case Study

- Postoperative PVR'S
- Continues in follow-up



Clinical Treatment Goals for Patients With PAD