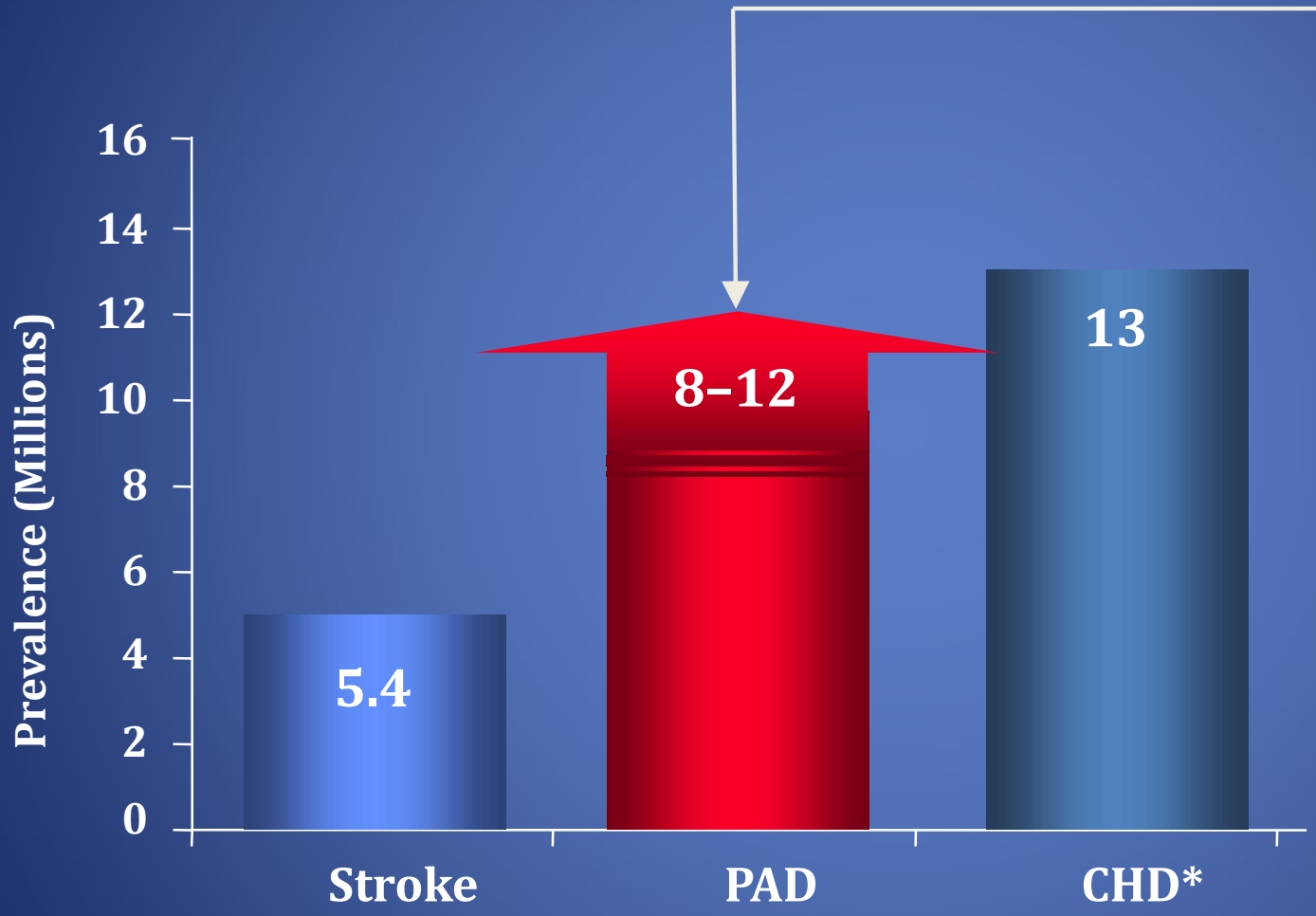
PAD/LEAD

- Riyaz Sumar, MD, FACC, FSCAI
- No disclosures related to the presentation.

Prevalence of PAD in the US



PAD currently affects 8–12 million Americans.

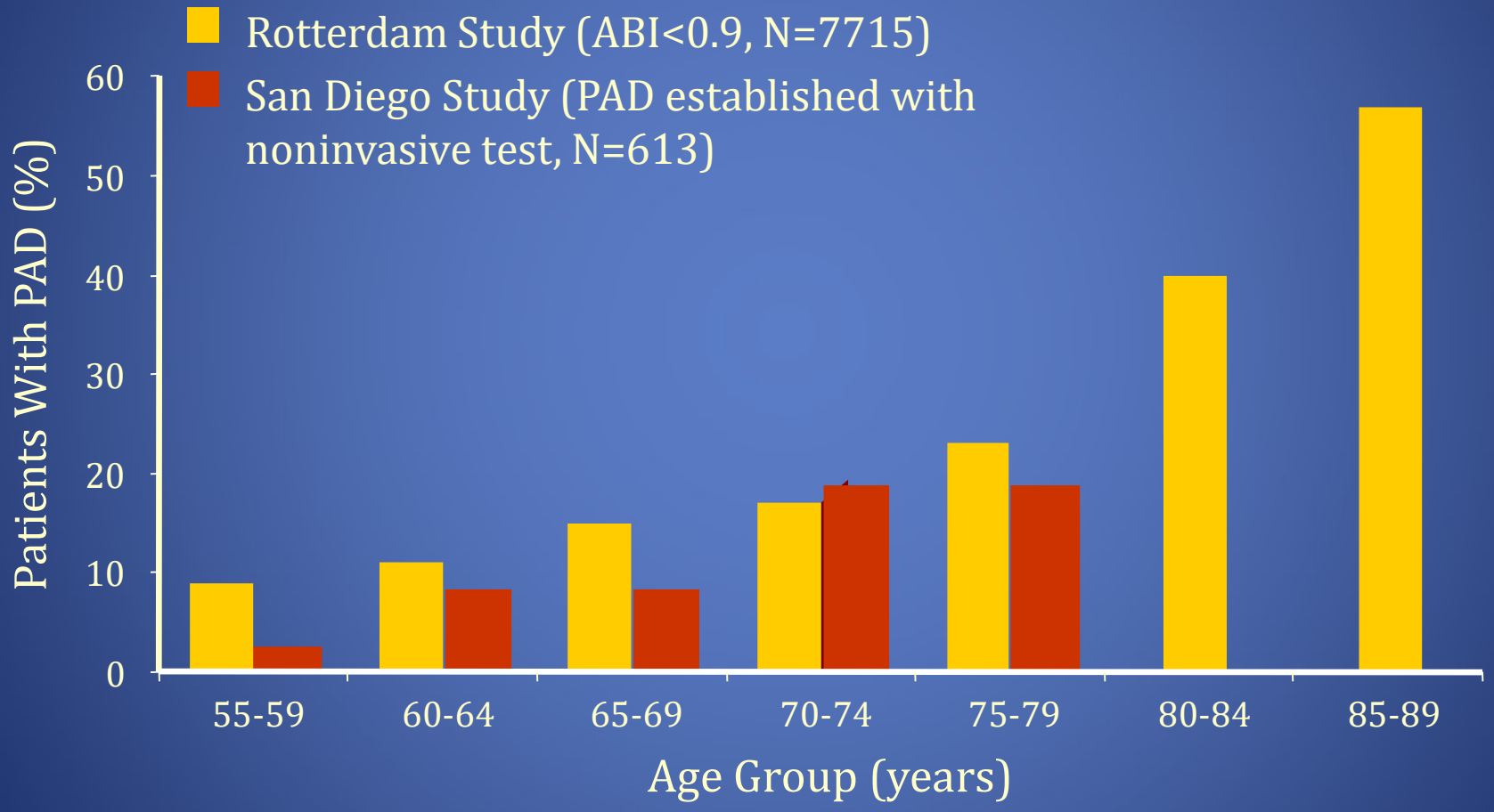
By 2050, the prevalence is expected to reach 19 million.

CHD = coronary heart disease. PAD = peripheral arterial disease.

* Includes myocardial infarction and angina pectoris.

American Heart Association. *Heart Disease and Stroke Statistics—2005 Update*. 2005.

Prevalence of PAD Increases With Age



Adapted from Golomb BA, et al. In: Creager MA, ed. *Management of Peripheral Arterial Disease: Medical, Surgical and Interventional Aspects*; 2000:1-18.
Meijer WT, et al. *Arterioscler Thromb Vasc Biol*. 1998;18:185-192.
Criqui MH, et al. *Circulation*. 1985;71:510-515.

Prevalence of PAD in At-Risk Patients

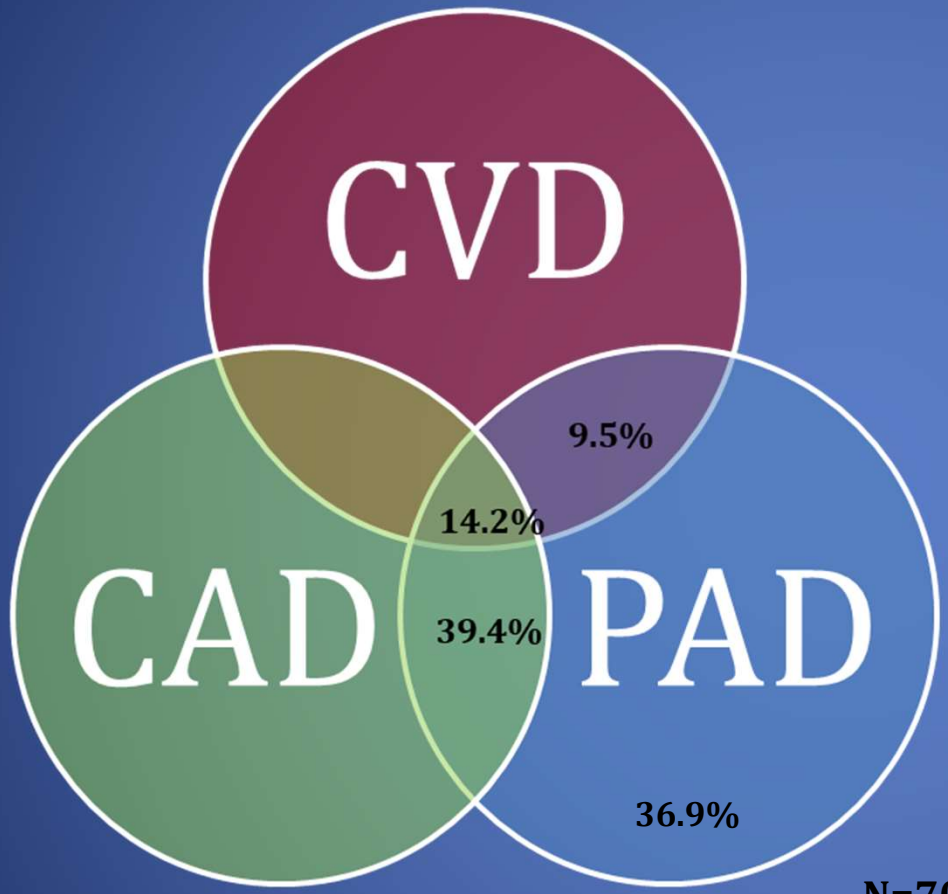
- The PARTNERS* program evaluated 6,979 patients in physicians' offices.
- Patient criteria:
  - ≥70 years, or
  - 50–69 years with a history of smoking and/or diabetes

* PARTNERS=PAD Awareness, Risk, and Treatment: New Resources for Survival. Hirsch AT, et al. *JAMA.* 2001;286:1317-1324.

Prevalence of PAD in community setting

NHANES Age > 40	**4.3 %**
San Diego Mean Age =66	**11.7%**
NHANES Age >70	**14.5%**
Rotterdam Age > 55	**19.1%**
Diehm Age > 65	**19.8%**
PARTNERS Age > 70 or between 50-69 with DM or smoking	**29%**

Epidemiology of Peripheral Vascular Disease



- Similar Risk Factor profile to CAD
- Prevalence up to 30% in patients with DM and Tobacco
- Patients with one manifestation
  often have coexistent disease in other vascular beds.

1. Hirsch AT, et al. *JAMA.* 2001;286:1317-1324.
2. Bhatt DL, et al. REACH Investigation. Presented at: American College of Cardiology Annual Scientific Session; March 8, 2005; Orlando, FL. Abstract 1127-96.

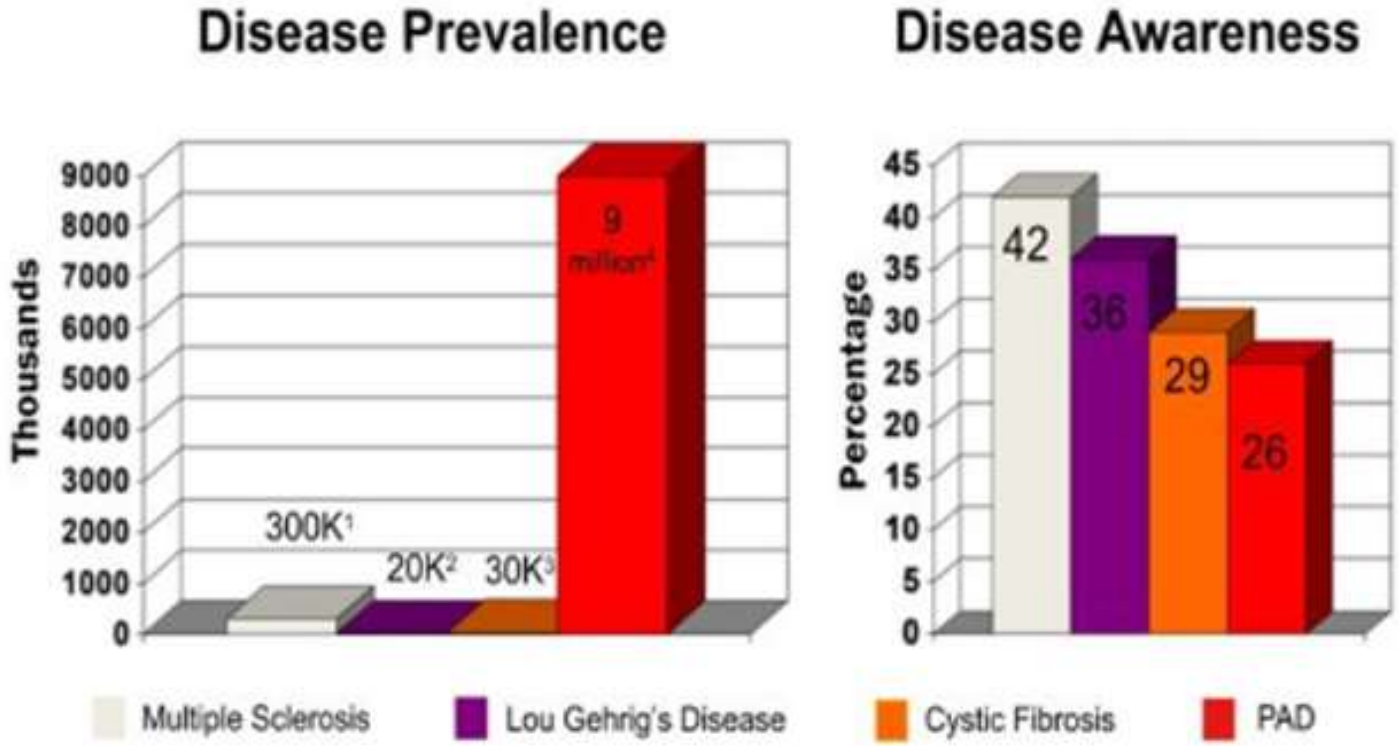
IMS INTEGRATED MEDICAL SERVICES

UNDERDIAGNOSED AND UNDERTREATED

Underdiagnosed

PAD is Common…

But Your Patient Has Never Heard of it!



[1]*Multiple Sclerosis: Hope Through Research, NINDS. NIH Publication No. 96-75. September 1996.*
[2]*Amyotrophic Lateral Sclerosis Fact Sheet. NINDS. NIH Publication No. 00-916. April 2003.*
[3]*Cystic Fibrosis Foundation Fact Sheet, 06/07*
[4]*Am J Prev Med 2007;32:328-33*

Undertreated

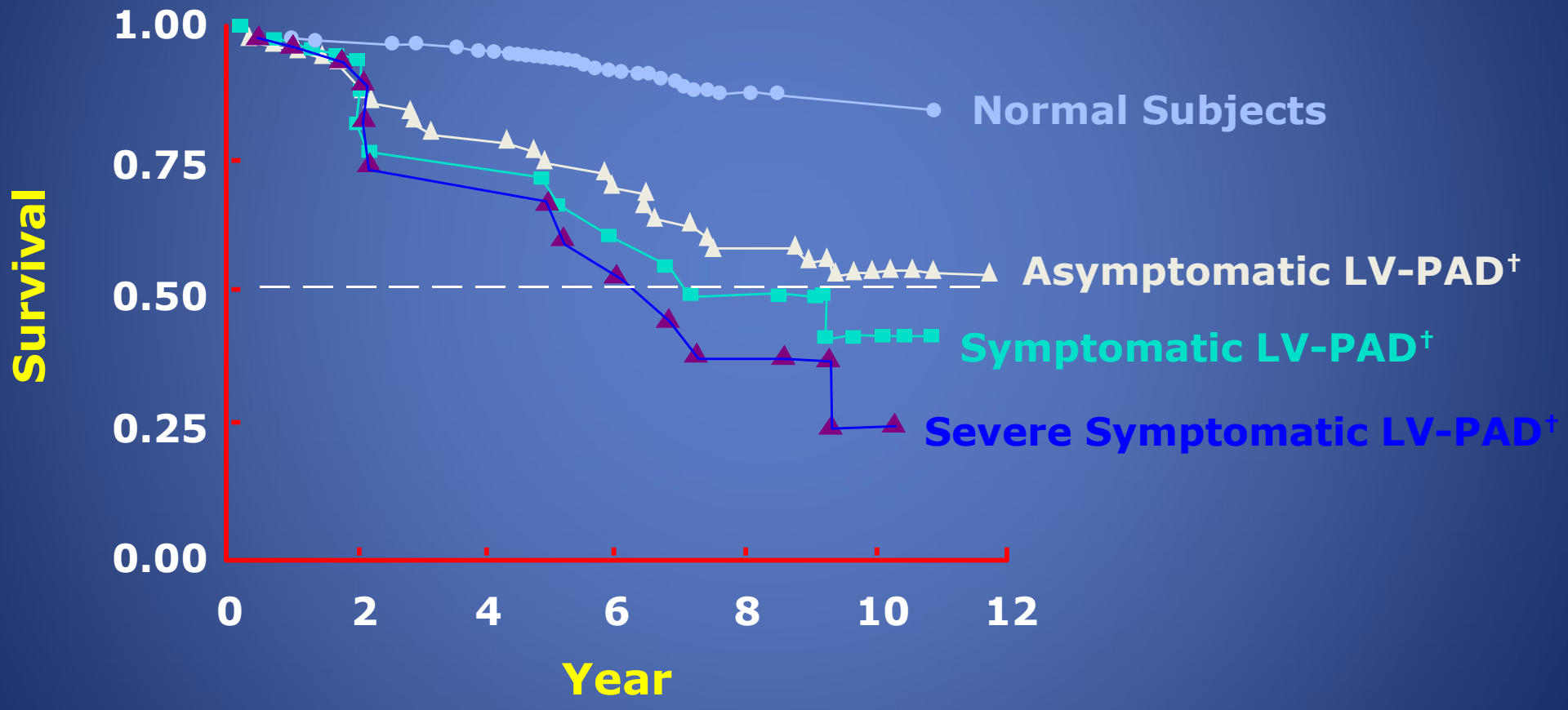
IMS INTEGRATED MEDICAL SERVICES

Atherosclerotic Risk Factors Are Less Intensively Treated in Patients with Peripheral Arterial Disease Than in Patients with Coronary Artery Disease

Mary McGrae McDermott, MD, Shruti Mehta, BA, Helen Ahn, BA, Philip Greenland, MD

It was recognized almost two decades ago that patients with peripheral arterial disease are less intensively treated than patients with coronary artery disease

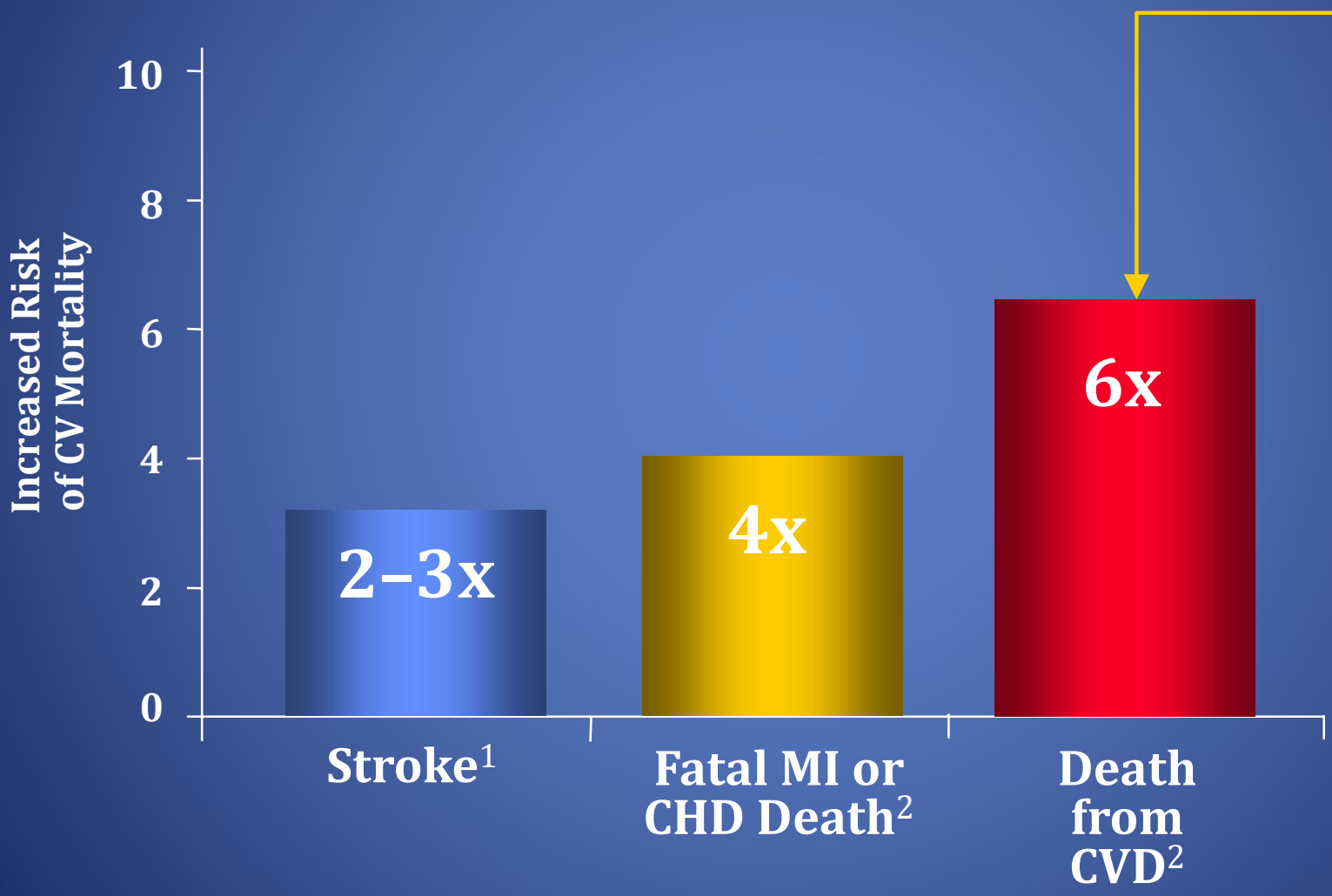
Impact of PAD on Mortality



*Kaplan-Meier survival curves based on mortality from all causes.
†Large-vessel PAD.

Adapted from Criqui MH et al. *N Engl J Med.* 1992;326:381-386.

Cardiovascular Events with PAD

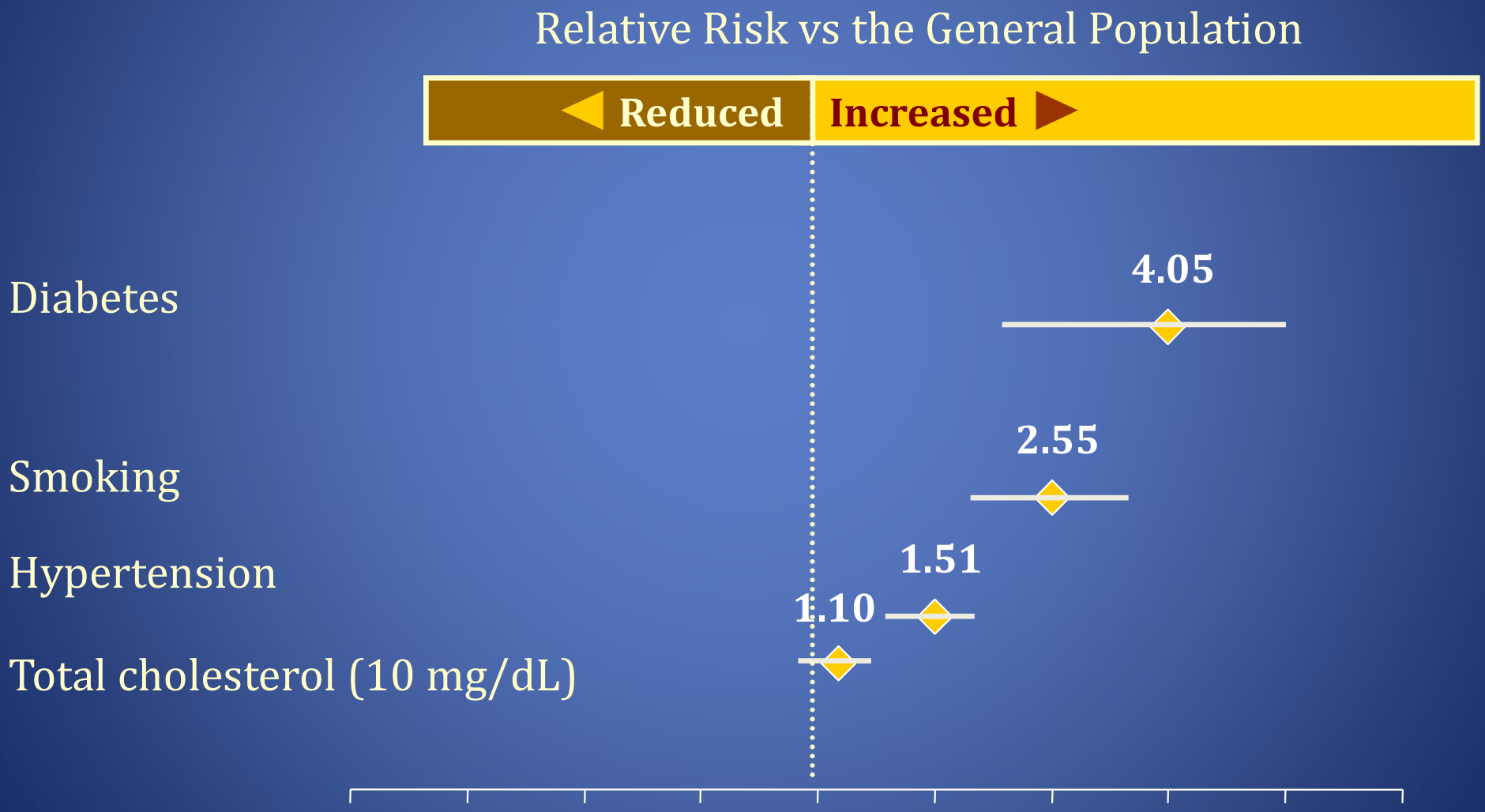


1. Kannel WB. *J Cardiovasc Risk*. 1994;1:333-339.
2. Criqui MH et al. *N Engl J Med*. 1992;326:381-386.

Patients at Increased Risk of PAD

- Age ≥65 y
- Age 50–64 y, with risk factors for atherosclerosis (e.g., diabetes mellitus, history of smoking, hyperlipidemia, hypertension) or family history of PAD
- Age <50 y, with diabetes mellitus and 1 additional risk factor for atherosclerosis
- Individuals with known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis, or AAA)

Independent Risk Factors for PAD*



* PAD diagnosis based on ABI <0.90.

Newman AB, et al. *Circulation.* 1993;88:837-845

History and/or PE Findings Suggestive of PAD

➢ History

•Claudication

•Other non–joint-related exertional lower extremity symptoms (not typical of claudication)

•Impaired walking function

•Ischemic rest pain

➢ Physical Examination

•Abnormal lower extremity pulse examination

•Vascular bruit

•Nonhealing lower extremity wound

•Lower extremity gangrene

•Other suggestive lower extremity physical findings (e.g., elevation pallor/dependent rubor)

Typical vs Atypical Symptoms in Patients With Symptomatic PAD

Typical Symptoms[1]

Intermittent claudication

- Exertional calf pain that
  - causes the patient to stop walking
  - resolves within 10 minutes of rest

Other nonspecific leg symptoms that may be indicative of PAD

Atypical Symptoms[1]

- Exertional leg pain that
  - may involve areas other than the calves
  - may not stop the patient from walking
  - may not resolve within 10 minutes of rest

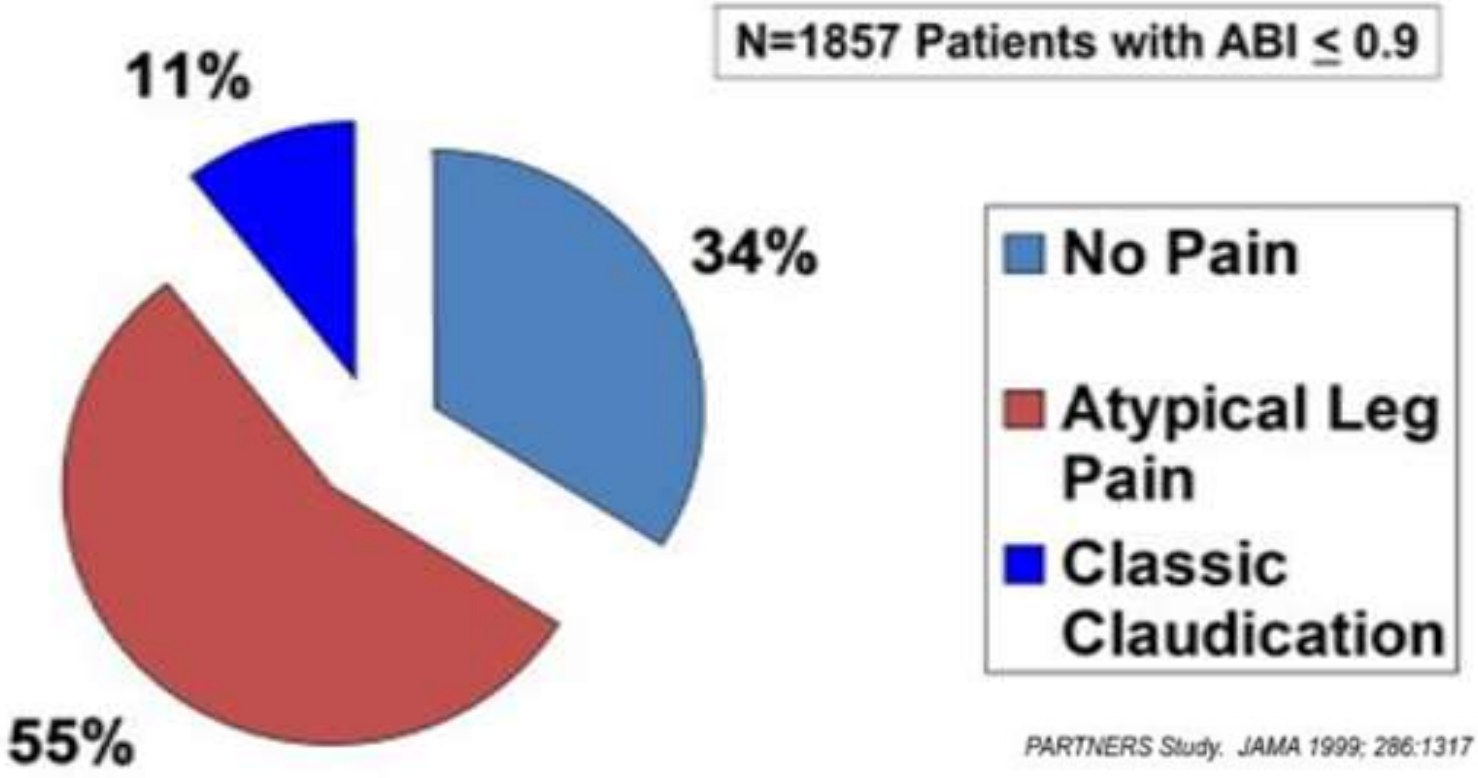
33%[2]

>50%[2]

1. McDermott MM et al. *JAMA*. 2001;286:1599-1606.
2. Hiatt WR. *N Engl J Med.* 2001;344:1608-1621.

Leg Symptoms with PAD

Leg Symptoms Among Patients with PAD in Ambulatory Care Setting



PAD Classification

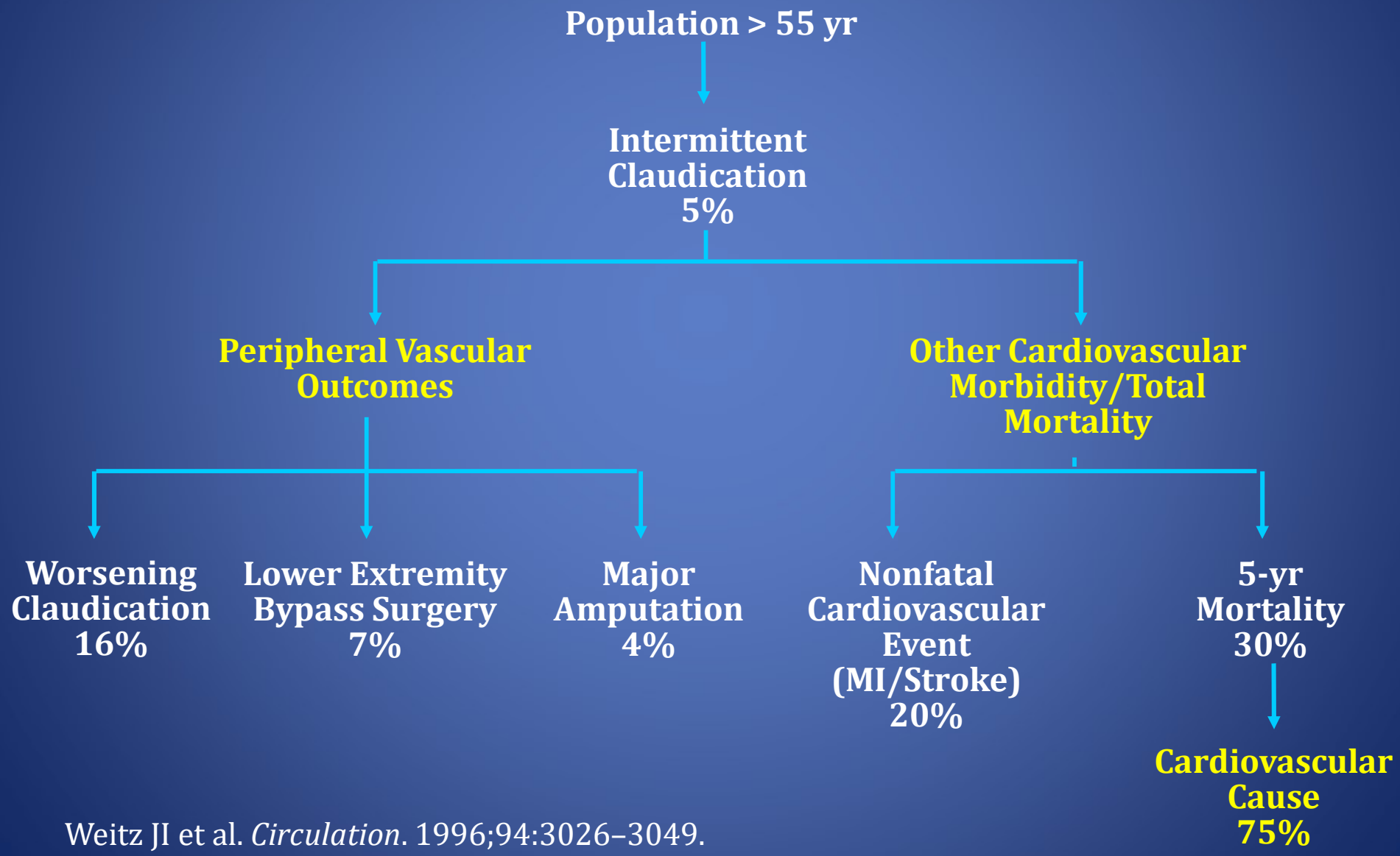
TABLE 1 Clinical Symptom Classification

Fontaine Classification					Rutherford Classification		
Stage	Symptoms	↔	Proposed PARC Universal Data Elements	↔	Grade	Category	Symptoms
I	Asymptomatic		Asymptomatic		0	0	Asymptomatic
II	Intermittent claudication/other exertional limb symptoms		Mild claudication/limb symptoms (no limitation in walking)	↔	0	1	Mild claudication
IIa		↔	Moderate claudication/ limb symptoms (able to walk without stopping >2 blocks or 200 m or 4 min)		1	2	Moderate claudication
IIb			Severe claudication/limb symptoms (only able to walk without stopping <2 blocks or 200 m or 4 min)	↔	1	3	Severe claudication
III	Ischemic rest pain	↔	Ischemic rest pain (pain in the distal limb at rest felt to be due to limited arterial perfusion)	↔	II	4	Ischemic rest pain
IV	Ulceration or gangrene	↔	Ischemic ulcers on distal leg	↔	III	5	Ischemic ulceration
			Ischemic gangrene	↔	III	6	Ischemic gangrene

↔ = comparable terms.

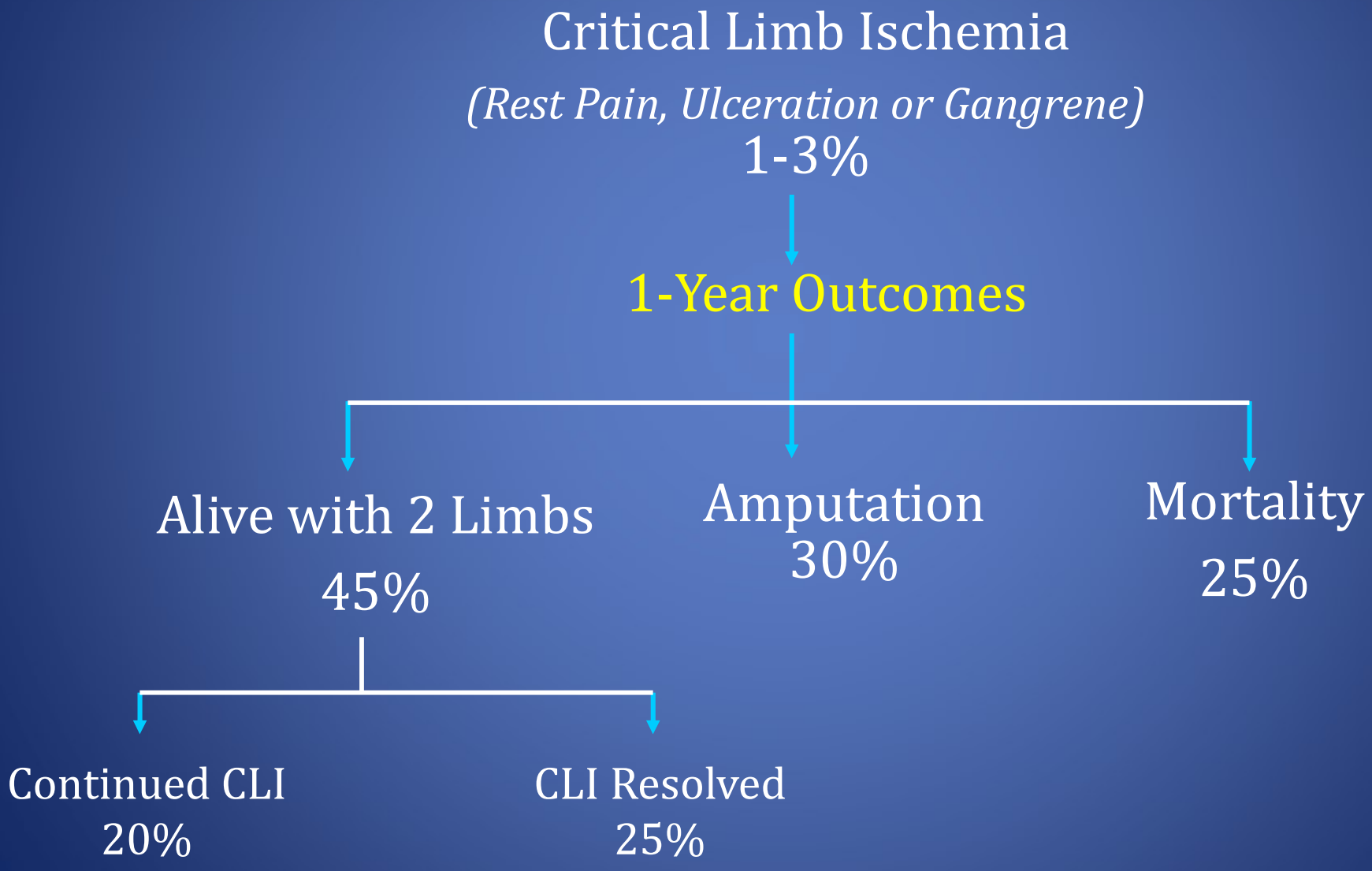
Patel MR et al. JACC 2015

Natural History
Intermittent Claudication



Weitz JI et al. *Circulation*. 1996;94:3026–3049.

Natural History of Critical Limb Ischemia



Hirsh et al. *JACC*. 2006;47:1239-1312.

Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments or Diagnostic Testing in Patient Care*

(Updated August 2015)

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — **Benefit = Risk**
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — **Risk > Benefit**

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R — **(Randomized)**
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR — **(Nonrandomized)**
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD — **(Limited Data)**
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO — **(Expert Opinion)**

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

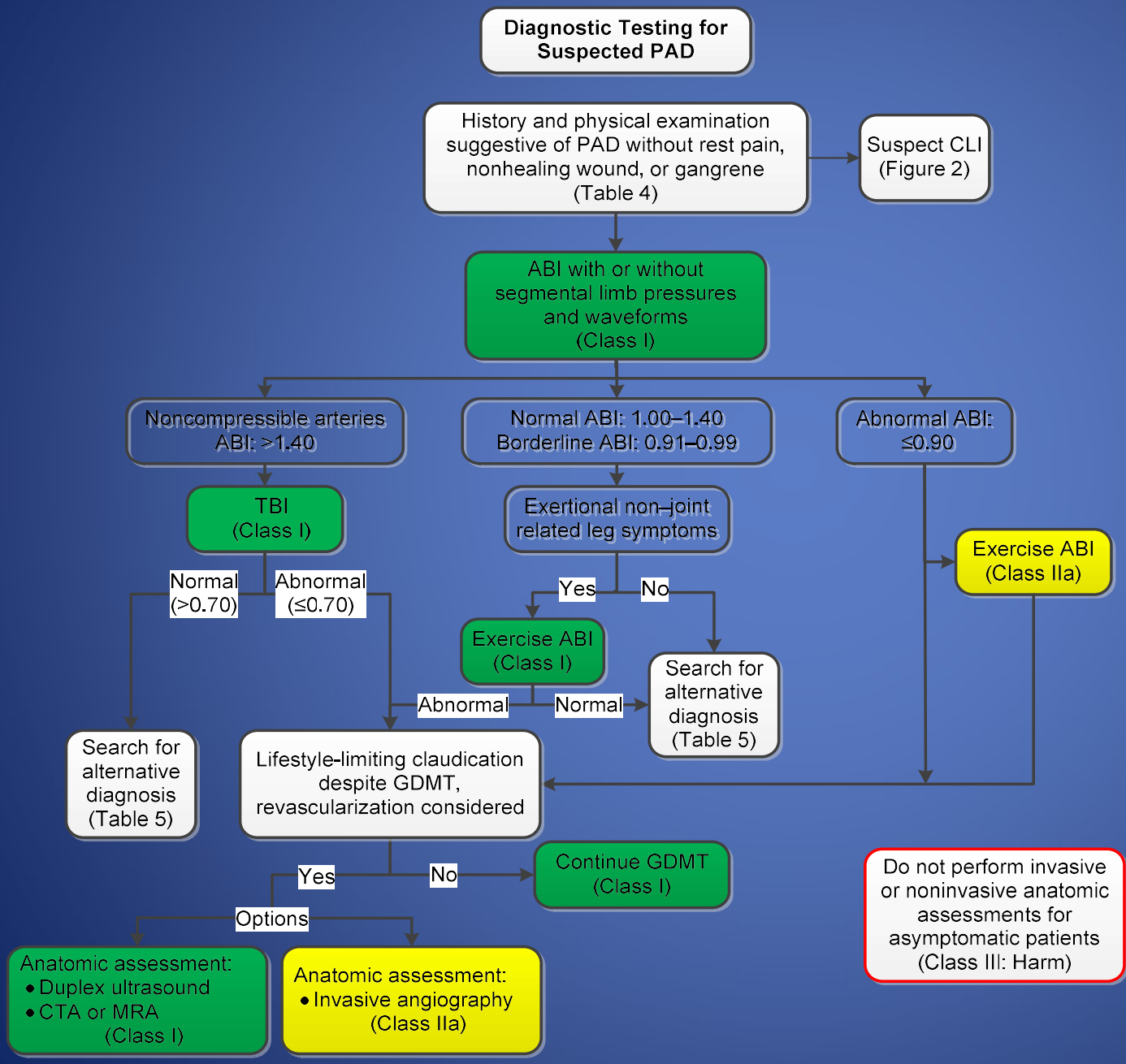
‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Diagnostic Testing

- Ankle-brachial index
- Segmental limb pressures
- Pulse volume recordings
- Doppler velocity waveform analysis
- Functional testing
  - Treadmill exercise testing
- Duplex scanning
- Advanced imaging techniques

Diagnostic Testing for Suspected PAD

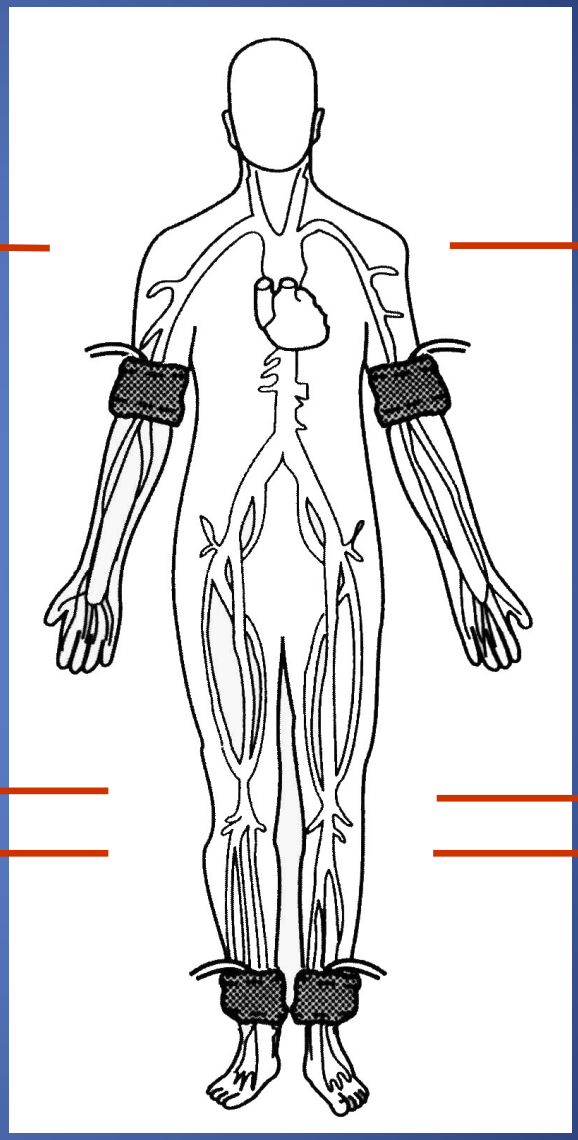


Colors correspond to Class of Recommendation in Table 1.

ABI indicates ankle-brachial index; CLI, critical limb ischemia; CTA, computed tomography angiography; GDMT, guideline-directed management and therapy; MRA, magnetic resonance angiography; PAD, peripheral artery disease; and TBI, toe-brachial index.

How to Perform and Calculate the ABI

≥1.0	— Normal
0.81-0.90	— Mild Obstruction
0.41-0.80	— Moderate Obstruction
≤0.40	— Severe Obstruction



Right ABI

Higher Right Ankle Pressure / Higher Arm Pressure = mm Hg / mm Hg

Left ABI

Higher Left Ankle Pressure / Higher Arm Pressure = mm Hg / mm Hg

Resting ABI for Diagnosing PAD

COR	LOE	Recommendations
I	B-NR	In patients with history or physical examination findings suggestive of PAD the resting ABI, with or without segmental pressures and waveforms, is recommended to establish the diagnosis.
I	C-LD	Resting ABI results should be reported as abnormal (ABI ≤0.90), borderline (ABI 0.91–0.99), normal (1.00–1.40), or noncompressible (ABI >1.40).
IIa	B-NR	In patients at increased risk of PAD but without history or physical examination findings suggestive of PAD , measurement of the resting ABI is reasonable.
III: No Benefit	B-NR	In patients not at increased risk of PAD and without history or physical examination findings suggestive of PAD , the ABI is not recommended.

Imaging for Anatomic Assessment

COR	LOE	Recommendations
I	B-NR	Duplex ultrasound, CTA, or MRA of the lower extremities is useful to diagnose anatomic location and severity of stenosis for patients with symptomatic PAD in whom revascularization is considered.
I	C-EO	Invasive angiography is useful for patients with CLI in whom revascularization is considered.
IIa	C-EO	Invasive angiography is reasonable for patients with lifestyle-limiting claudication with an inadequate response to GDMT for whom revascularization is considered.
III: Harm	B-R	Invasive and noninvasive angiography (i.e., CTA, MRA) should not be performed for the anatomic assessment of patients with asymptomatic PAD.

Physiological Testing

COR	LOE	Recommendations
I	B-NR	TBI should be measured to diagnose patients with suspected PAD when the ABI is greater than 1.40.
I	B-NR	Patients with exertional non–joint-related leg symptoms and normal or borderline resting ABI (>0.90 and ≤1.40) should undergo exercise treadmill ABI testing to evaluate for PAD.
IIa	B-NR	In patients with PAD and an abnormal resting ABI (≤0.90), exercise treadmill ABI testing can be useful to objectively assess functional status.

Screening for Atherosclerotic Disease in Other Vascular Beds for the Patient With PAD

Abdominal Aortic Aneurysm

COR	LOE	Recommendation
IIa	B-NR	A screening duplex ultrasound for AAA is reasonable in patients with symptomatic PAD.

Screening for Asymptomatic Atherosclerosis in Other Arterial Beds (Coronary, Carotid, and Renal Arteries)

- Prevalence of atherosclerosis in the coronary, carotid, and renal arteries higher in patients with PAD than in those without PAD.
- However, intensive atherosclerosis risk factor modification in patients with PAD justified regardless of the presence of disease in other arterial beds.
- Only justification for screening for disease in other arterial beds is if revascularization results in a reduced risk of MI, stroke, or death, and this has never been shown.
- Thus, no evidence to demonstrate that screening all patients with PAD for asymptomatic atherosclerosis in other arterial beds improves clinical outcome.
- Intensive treatment of risk factors through GDMT is the principle method for preventing adverse cardiovascular ischemic events from asymptomatic disease in other arterial beds.

Smoking Cessation

COR	LOE	Recommendations
I	A	Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit.
I	A	Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (i.e., varenicline, buproprion, and/or nicotine replacement therapy) and/or referral to a smoking cessation program.
I	B-NR	Patients with PAD should avoid exposure to environmental tobacco smoke at work, at home, and in public places.

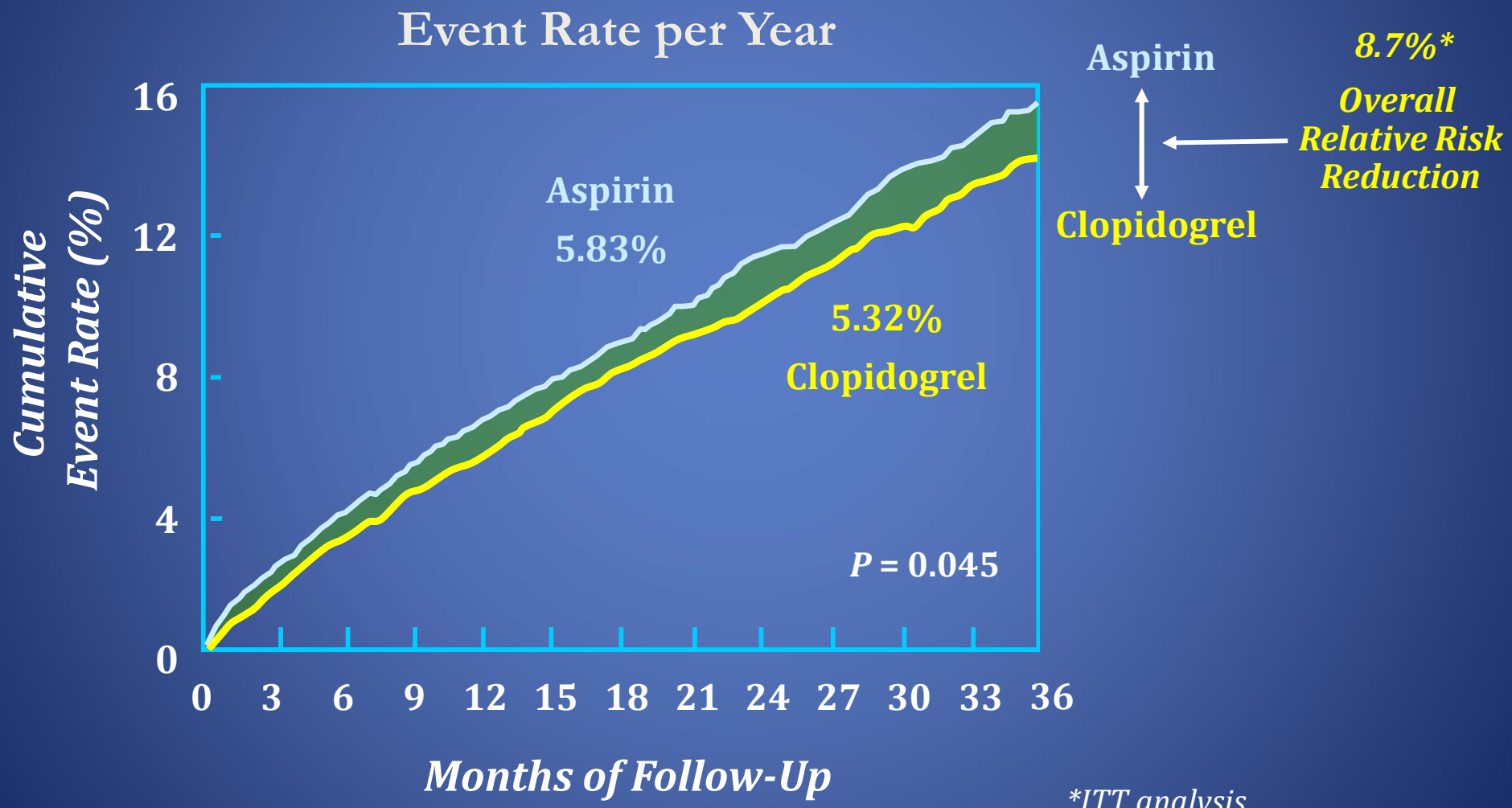
Antiplatelet Agents

COR	LOE	Recommendations
I	A	Antiplatelet therapy with aspirin alone (range 75–325 mg per day) or clopidogrel alone (75 mg per day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD.
IIa	C-EO	In asymptomatic patients with PAD (ABI ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death.
IIb	B-R	In asymptomatic patients with borderline ABI (0.91–0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain.

Antiplatelet Agents (cont'd)

COR	LOE	Recommendations
IIb	B-R	The effectiveness of dual-antiplatelet therapy (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established.
IIb	C-LD	Dual-antiplatelet therapy (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization.
IIb	B-R	The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain.

Clopidogrel vs. Aspirin in Prevention of Ischemic Events



*ITT analysis.

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

Oral Anticoagulation

COR	LOE	Recommendations
IIb	B-R	
III: Harm	A	should not be used

Rivaroxaban 2.5 mg BID plus aspirin is:

-Significantly superior to aspirin alone in reducing MACE or MALE or major amputation (31% RRR)

-Increased major bleeding, but no significant increase in fatal or critical organ bleeding

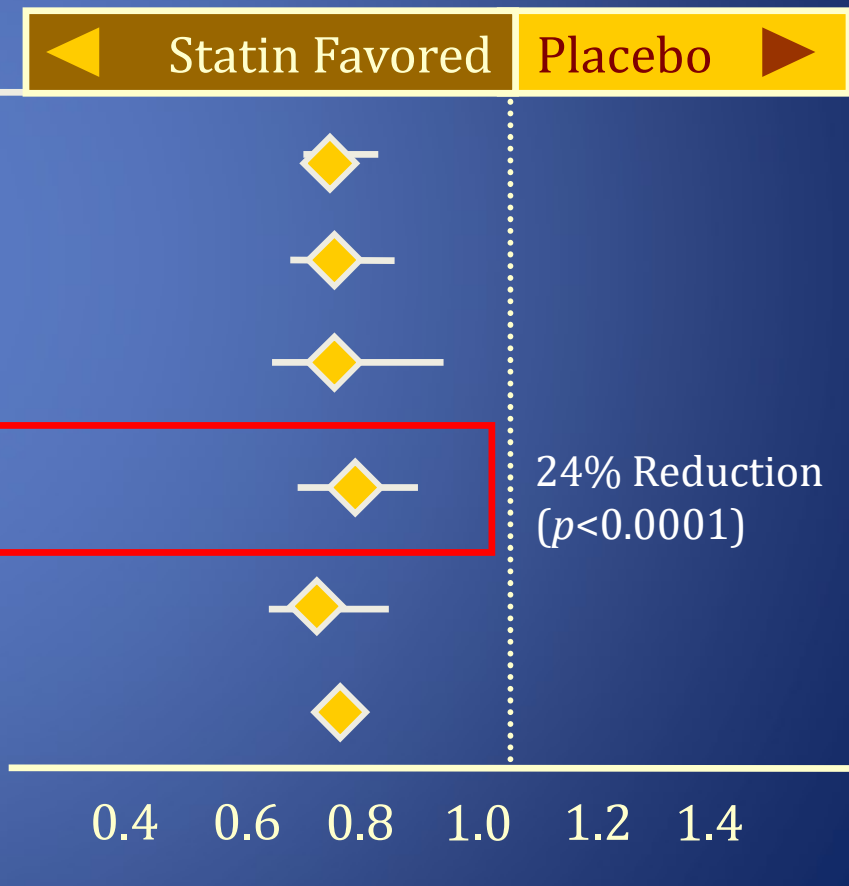
Anand, et al.
Lancet 2018; 391: 219–29

Statin Agents

COR	LOE	Recommendations
I	A	Treatment with a statin medication is indicated for all patients with PAD.

Heart Protection Study: Vascular Event by Prior Disease

Existing Disease	Incidence of Events: Statin (n=10,269)	Incidence of Events: Control (n=10,267)
Previous MI	23.5	29.4
Other CHD	18.9	24.2
No prior CHD or CVD	18.7	23.6
Peripheral arterial disease	24.7	30.5
Diabetes	13.8	18.6
All patients	19.8	25.2



MI - myocardial infarction; CHD - coronary heart disease; CVD - cerebrovascular disease; PAD - peripheral arterial disease; CI - confidence interval; SE - standard error

Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7-22.

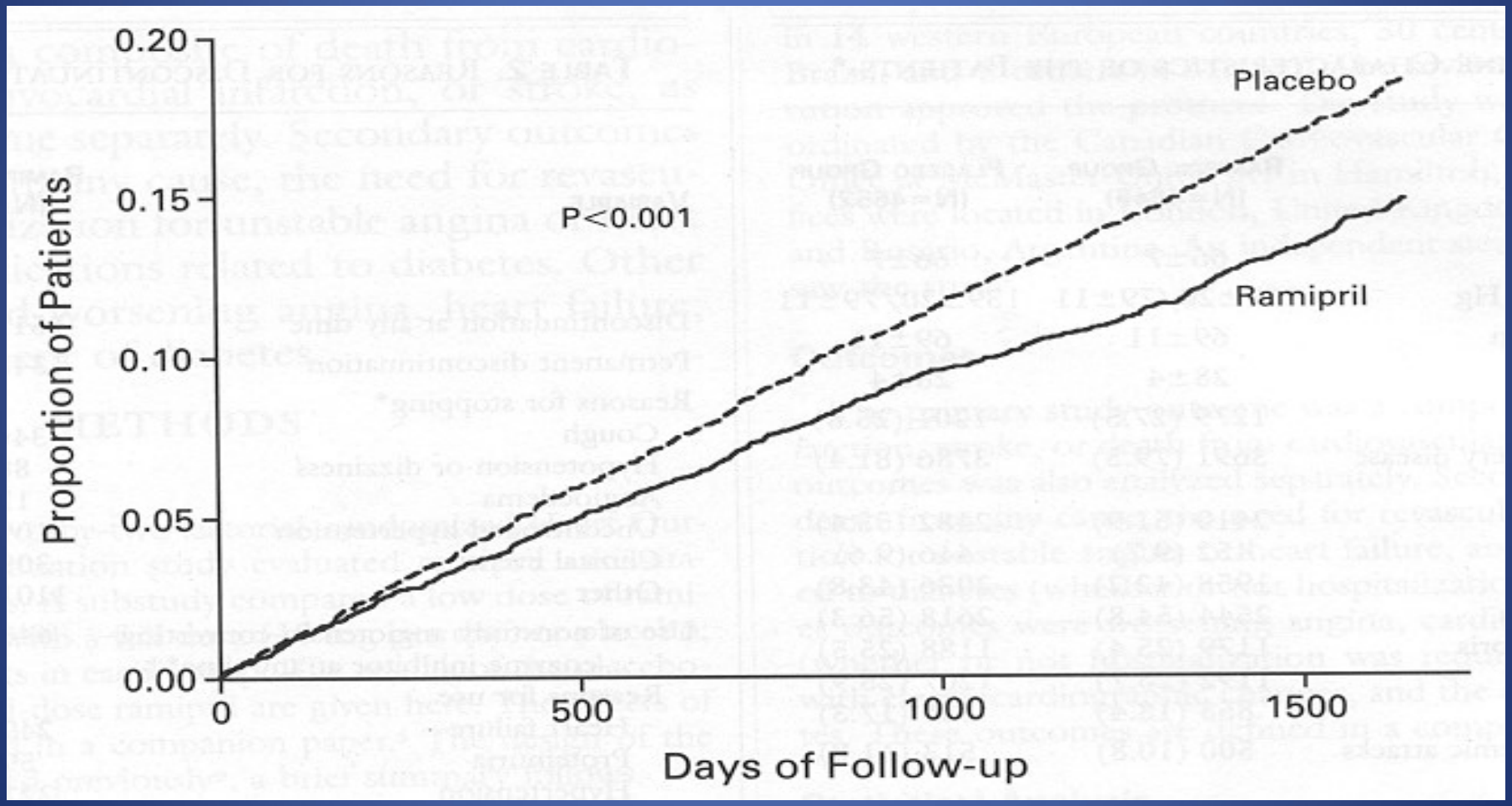
Glycemic Control

COR	LOE	Recommendations
I	C-EO	Management of diabetes mellitus in the patient with PAD should be coordinated between members of the healthcare team.
IIa	B-NR	Glycemic control can be beneficial for patients with CLI to reduce limb-related outcomes.

Antihypertensive Agents

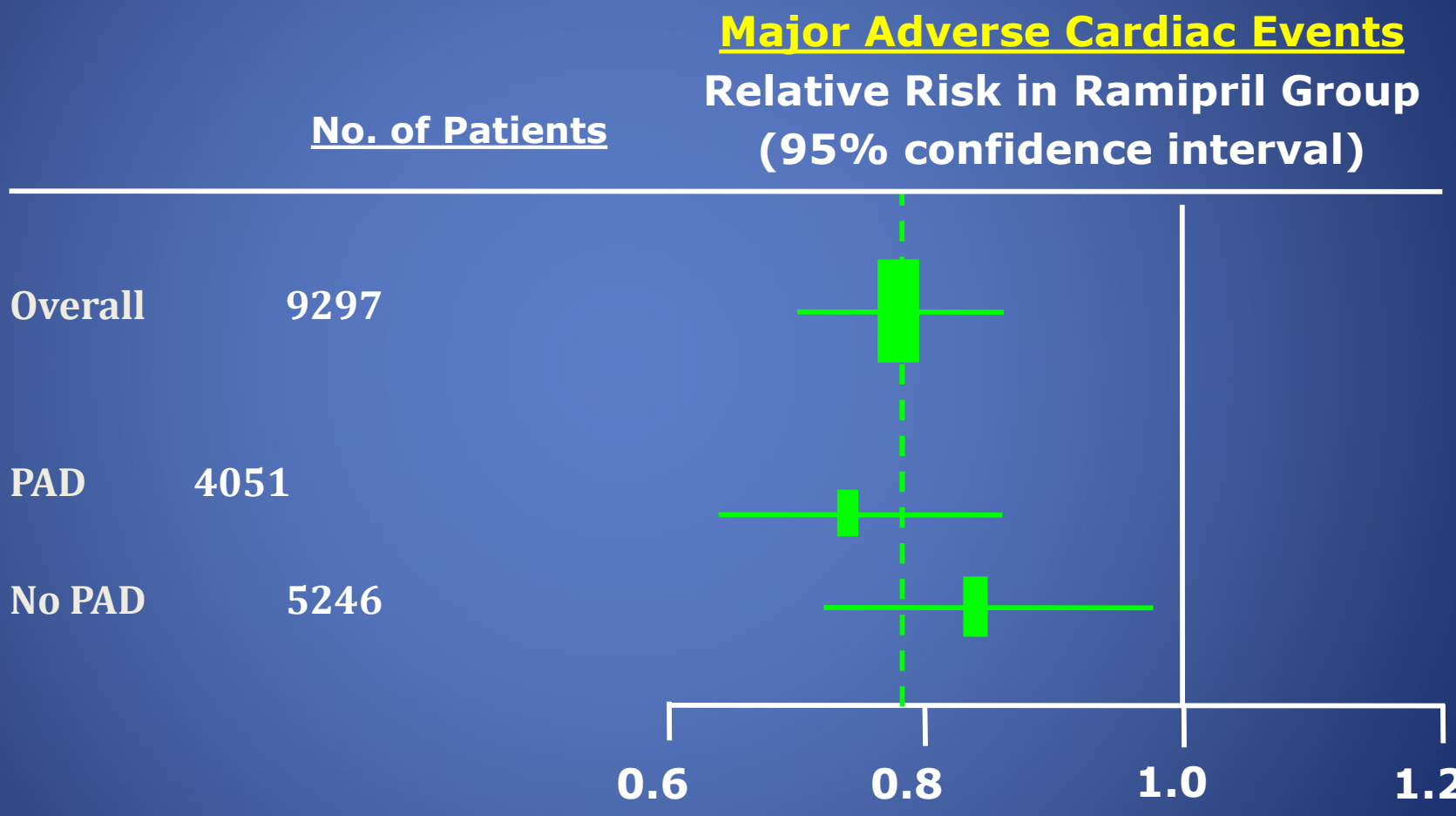
COR	LOE	Recommendations
I	A	Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death.
IIa	A	The use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD.

ACE Inhibition and Cardiovascular Events in High-Risk Patients



The Heart Outcome Prevention Evaluation Study.
***NEJM* 2000;342:145-53.**

Effect of ACE Inhibition on Cardiovascular Events in PAD



The Heart Outcome Prevention Evaluation Study. *NEJM* 2000;342:145-53.

Influenza Vaccination

COR	LOE	Recommendation
I	C-EO	Patients with PAD should have an annual influenza vaccination.

Homocysteine Lowering

COR	LOE	Recommendation
III: No Benefit	B-R	B-complex vitamin supplementation to lower homocysteine levels for prevention of cardiovascular events in patients with PAD is not recommended.

Structured Exercise Therapy

COR	LOE	Recommendations
I	A	In patients with claudication, a supervised exercise program is recommended to improve functional status and QoL and to reduce leg symptoms.
I	B-R	A supervised exercise program should be discussed as a treatment option for claudication before possible revascularization.
IIa	A	In patients with PAD, a structured community- or home-based exercise program with behavioral change techniques, can be beneficial to improve walking ability and functional status.
IIa	A	In patients with claudication, alternative strategies of exercise therapy, including upper-body ergometry, cycling, and pain-free or low-intensity walking that avoids moderate-to-maximum claudication while walking, can be beneficial to improve walking ability and functional status.

Cilostazol, Pentoxifylline and Chelation Therapy

COR	LOE	Recommendations
Cilostazol		
I	A	Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with claudication.
Pentoxifylline		
III: No Benefit	B-R	Pentoxifylline is not effective for treatment of claudication.
Chelation Therapy		
III: No Benefit	B-R	Chelation therapy (e.g., ethylenediaminetetraacetic acid) is not beneficial for treatment of claudication.

General Principle for Revascularization

- Claudicants should be revascularized only after a trial of exercise and pharmacotherapy.
  - An exception may be isolated iliac artery stenosis
- Inflow and outflow should always be assessed prior to revascularization. Inflow lesions should be revascularized first followed by outflow lesions if bothersome symptoms persist.
- Revascularization for critical limb ischemia with associated tissue loss should aim to provide straight line flow to the foot.

Revascularization for Claudication

COR	LOE	Recommendation
IIa	A	Revascularization is a reasonable treatment option for the patient with lifestyle-limiting claudication with an inadequate response to GDMT.

Endovascular Revascularization for Claudication

COR	LOE	Recommendations
I	A	Endovascular procedures are effective as a revascularization option for patients with lifestyle-limiting claudication and hemodynamically significant aortoiliac occlusive disease.
IIa	B-R	Endovascular procedures are reasonable as a revascularization option for patients with lifestyle-limiting claudication and hemodynamically significant femoropopliteal disease.
IIb	C-LD	The usefulness of endovascular procedures as a revascularization option for patients with claudication due to isolated infrapopliteal artery disease is unknown.
III: Harm	B-NR	Endovascular procedures should not be performed in patients with PAD solely to prevent progression to CLI.

Minimizing Tissue Loss in Patients With PAD

COR	LOE	Recommendations
I	C-LD	Patients with PAD and diabetes mellitus should be counseled about self–foot examination and healthy foot behaviors.
I	C-LD	In patients with PAD, prompt diagnosis and treatment of foot infection are recommended to avoid amputation.
IIa	C-LD	In patients with PAD and signs of foot infection, prompt referral to an interdisciplinary care team can be beneficial.
IIa	C-EO	It is reasonable to counsel patients with PAD without diabetes mellitus about self-foot examination and healthy foot behaviors.
IIa	C-EO	Biannual foot examination by a clinician is reasonable for patients with PAD and diabetes mellitus.

Management of CLI

Revascularization for CLI

COR	LOE	Recommendation
I	B-NR	In patients with CLI, revascularization should be performed when possible to minimize tissue loss.
I	C-EO	An evaluation for revascularization options should be performed by an interdisciplinary care team before amputation in the patient with CLI.

Longitudinal Follow-Up

COR	LOE	Recommendations
I	C-EO	Patients with PAD should be followed up with periodic clinical evaluation, including assessment of cardiovascular risk factors, limb symptoms, and functional status.
I	C-EO	Patients with PAD who have undergone lower extremity revascularization (surgical and/or endovascular) should be followed up with periodic clinical evaluation and ABI measurement.
IIa	B-R	Duplex ultrasound can be beneficial for routine surveillance of infrainguinal, autogenous vein bypass grafts in patients with PAD.
IIa	C-LD	Duplex ultrasound is reasonable for routine surveillance after endovascular procedures in patients with PAD.
IIb	B-R	The effectiveness of duplex ultrasound for routine surveillance of infrainguinal prosthetic bypass grafts in patients with PAD is uncertain.

Summary of PAD and Its Management

- PAD is common and has a significant impact upon cardiovascular outcomes
- Treatment of PAD, even asymptomatic, should focus on risk factor modification/risk reduction
- Treatment of intermittent claudication should include exercise therapy, drug therapy and selective use of revascularization
- Treatment for critical limb ischemia warrants aggressive efforts at revascularization, including surgery, to reduce the risk of amputation

Questions

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