

# Management of Patients with Peripheral Artery Disease

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# Disclosure Information

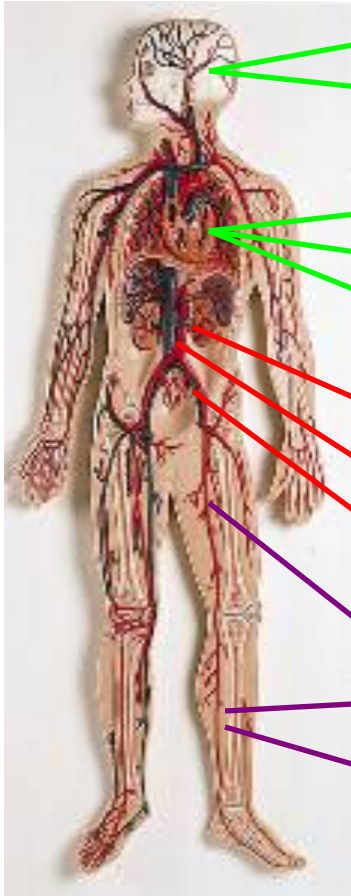
- Consultant
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  - Cardiovascular Systems Inc.
  - Cordis

***Off label use of products will be discussed in this presentation as indicated.***

# Four Main Points

- Atherosclerosis is a “pan-vascular” process
- PAD is underappreciated, but confers profound cardiovascular morbidity
- Early recognition, treatment, and risk reduction are critical
- Endovascular strategies rival longstanding surgical paradigm for revascularization

# Atherosclerosis is a “pan-vascular” process



TIA

Ischemic stroke

STEMI

NSTEMI

Unstable angina/ACS

Renovascular hypertension

Mesenteric ischemia

Erectile dysfunction

Claudication

Critical limb ischemia, rest pain, gangrene,  
amputation

# Prevalence of PAD

Age	Abnormal ABI	Projected US Prevalence
40-59	3%	2.1 million
60-69	8%	1.6 million
>70	19%	4.7 million
	Total	8.4 million

# International Prevalance of PAD: 2013 Meta-analysis of 34 studies

202 Million with  
PAD worldwide

23.5% increase  
between 2000-  
2010

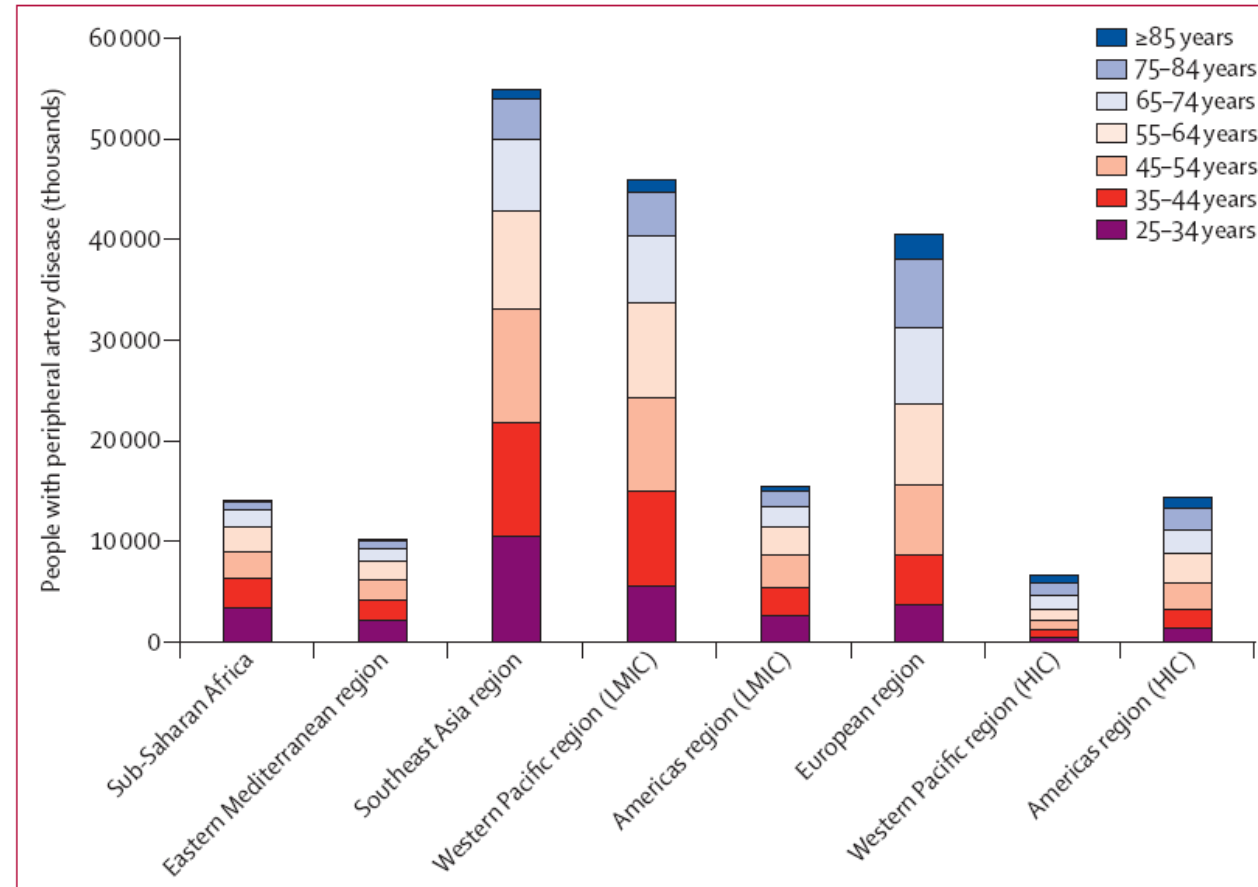
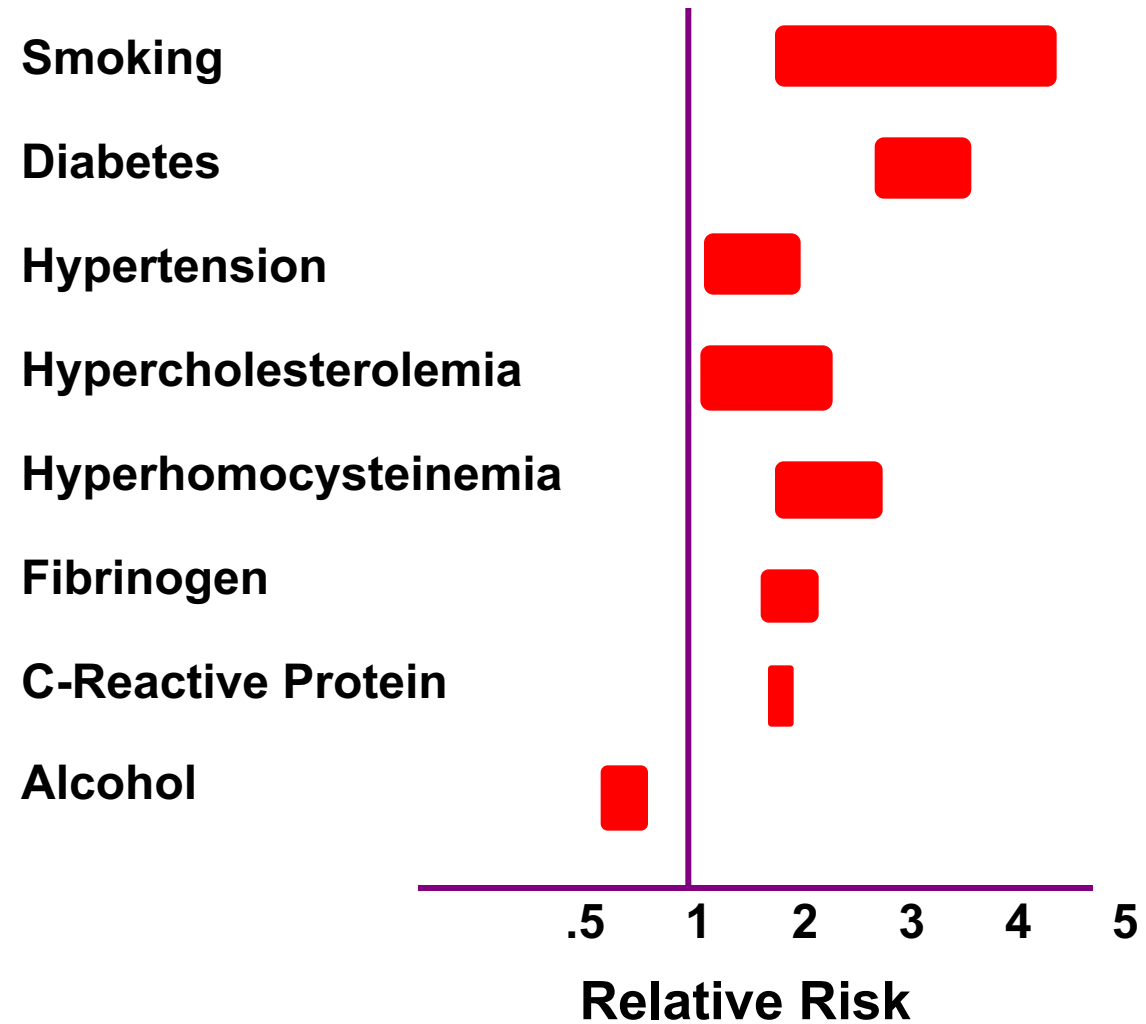


Figure 3: Estimate of the number of cases, and contributing age groups, in eight WHO regions in the year 2010  
LMIC=low-income and middle-income countries. HIC=high-income countries.

Fowkes, FGR. Lancet. 2013:  
S0140-6736(13)61249-0

# Risk of Peripheral Artery Disease



# Symptoms and Signs of PAD

- Intermittent Claudication
  - Pain, ache, fatigue in leg with exercise
  - resolves with rest
- Rest pain
  - Pain or paresthesias in foot or toes
  - worsened by leg elevation
  - improved by dependency
- Decreased or absent pulses
- Bruits
- Muscle atrophy
- Pallor of feet with elevation
- Dependent rubor
- Signs of chronic ischemia
  - Hair loss,
  - Thickened nails,
  - Smooth & shiny skin
  - Coolness
  - Pallor or cyanosis



- History
- Physical exam
- Non-invasive assessments
- Invasive angiography and evaluations

Claudication is mistaken for signs and symptoms of:

- Degenerative disc disease
- Spinal stenosis (“pseudoclaudication”)
- Other orthopedic pain (hip OA)
- Diabetic neuropathy
- Deconditioning / muscular strain

# Non-invasive Vascular Diagnostic Tests

- Segmental Pressure Measurement
- Pulse Volume Recording
- Treadmill Exercise Testing Physiologic
- Color-Assisted Duplex Ultrasonography Anatomic
- Magnetic Resonance Angiography
- CT Angiography

# The Ankle-Brachial Index

- Simple, painless, accurate, highly reproducible
- Clinical utility
  - Diagnosis of PAD
  - Prognosis: predictor of MACCE

**TABLE 4** History and/or Physical Examination 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)

**Recommendations for Resting ABI for Diagnosing PAD**

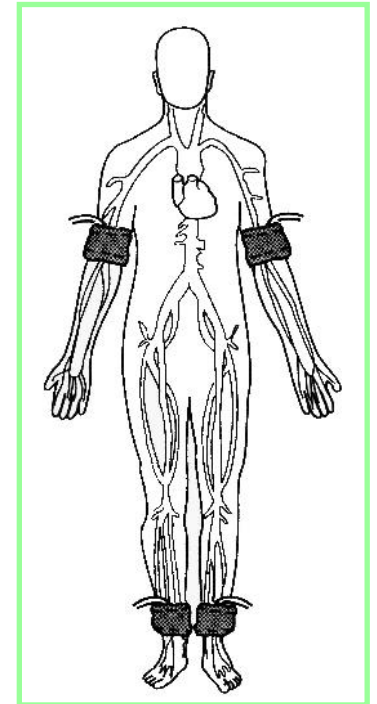
COR	LOE	RECOMMENDATIONS
I	B-NR	In patients with history or physical examination findings suggestive of PAD (Table 4), the resting ABI, with or without segmental pressures and waveforms, is recommended to establish the diagnosis (60-65).
I	C-LD	Resting ABI results should be reported as abnormal (ABI ≤0.90), borderline (ABI 0.91-0.99), normal (1.00-1.40), or noncompressible (ABI >1.40) (46,63-66).
IIa	B-NR	In patients at increased risk of PAD (Table 3) but without history or physical examination findings suggestive of PAD (Table 4), measurement of the resting ABI is reasonable (41,42,67-89).
III: No Benefit	B-NR	In patients not at increased risk of PAD (Table 3) and without history or physical examination findings suggestive of PAD (Table 4), the ABI is not recommended (87,90).

# The Ankle-Brachial Index

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

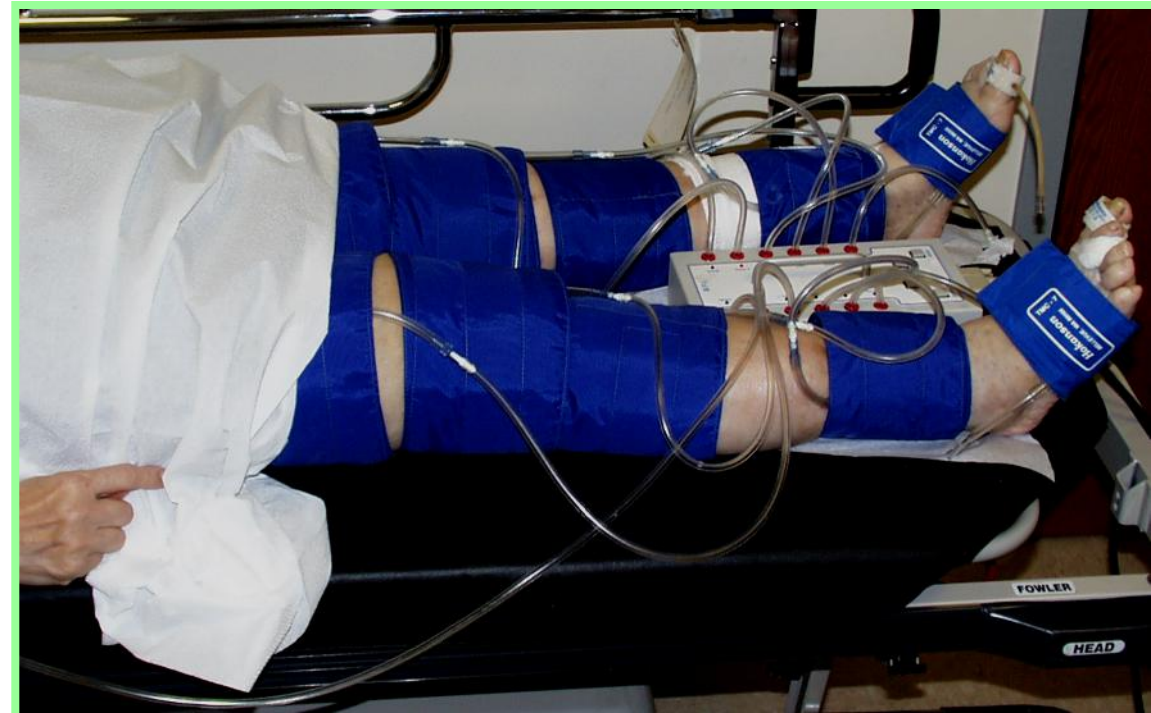
- **Ankle and brachial systolic pressures taken using a hand-held Doppler instrument**
- **The ABI is 95% sensitive, 99% specific for PAD**

<b>Normal</b>	<b>ABI</b>	<b>0.90-1.30</b>
<b>PAD</b>	<b>ABI</b>	<b>&lt;0.90</b>
<b>Rest pain/ulceration</b>	<b>ABI</b>	<b>&lt;0.40</b>
<b>Non-compressible</b>	<b>ABI</b>	<b>&gt;1.30</b>



# Segmental Limb Pressures: “PVR”

- **Identify location and severity of PAD**
- **Differentiate claudication from pseudoclaudication**
- BP cuffs on thigh, calf, ankle, transmetatarsal, digit
- Continuous wave doppler at DP or PT
- Obtain bilateral arm pressures
- Obtain segmental pressures (in order):
  1. Foot, ankle pressure
  2. Calf pressure
  3. Low thigh pressure
  4. High thigh pressure
- ***Determines level of obstruction***



# Graded Exercise Treadmill Test: “Functional Yardstick”

- Important component of comprehensive vascular testing
- Requires programmable treadmill
- Standard protocol
  - 2.0 MPH, 12% grade
  - Maximum 5 minutes
- Gardner/Hiatt Protocols
  - Constant Speed
  - Variable Grade as exercise continues

# Indications for Treadmill Test

- Any patient with atypical exertional limb symptoms
  - Determine IC vs pseudoclaudication
- Assess functional status vis-a-vis PAD
- Demonstrate impact of revascularization
- May uncover occult angina pectoris/CAD

## Treadmill Stress Test



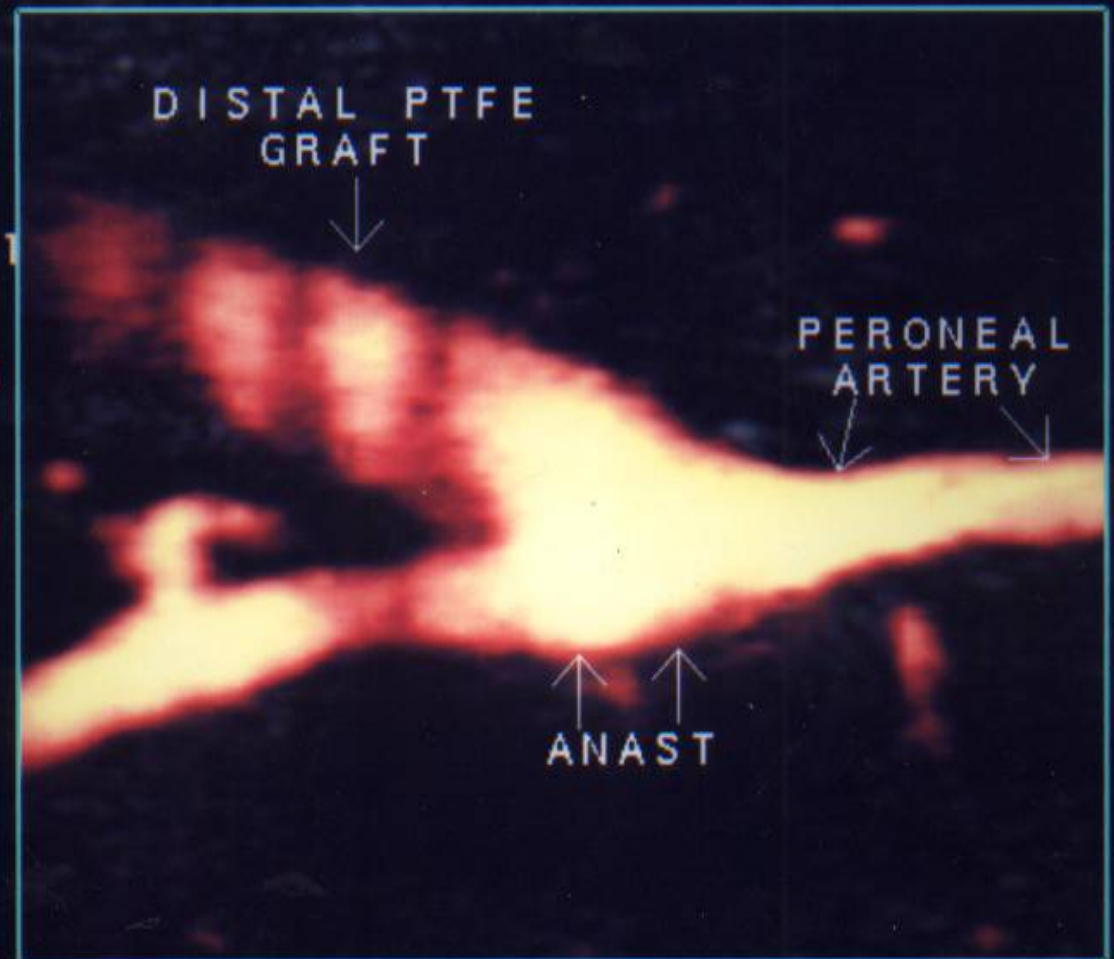
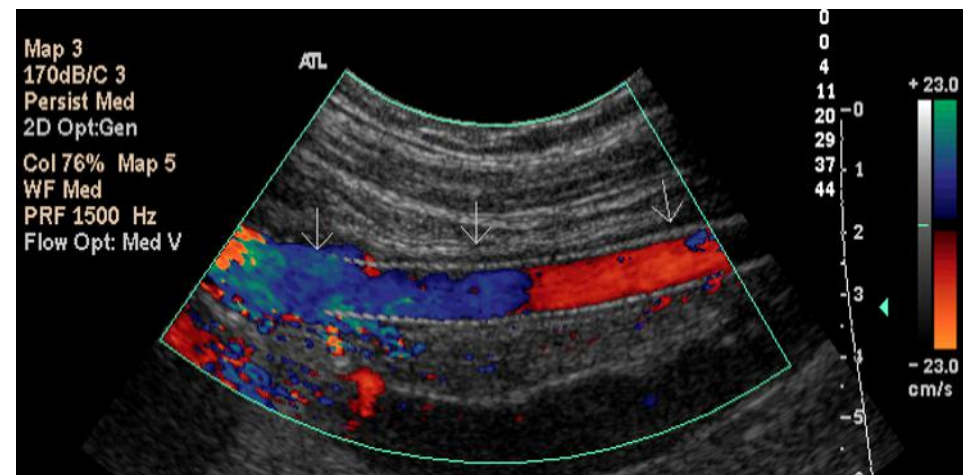
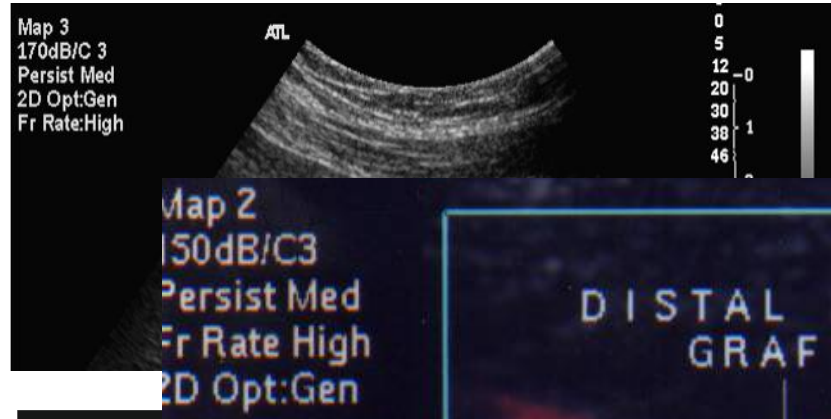
# Arterial Duplex Ultrasound Testing:

- Reproducible, reliable, accurate
- Painless, risk-free, *relatively* inexpensive
- Predicts ideal access for intervention
- Direct visualization and characterization of arterial stenosis, occlusion, injury
- Excellent method to assess adequacy of revascularization over time



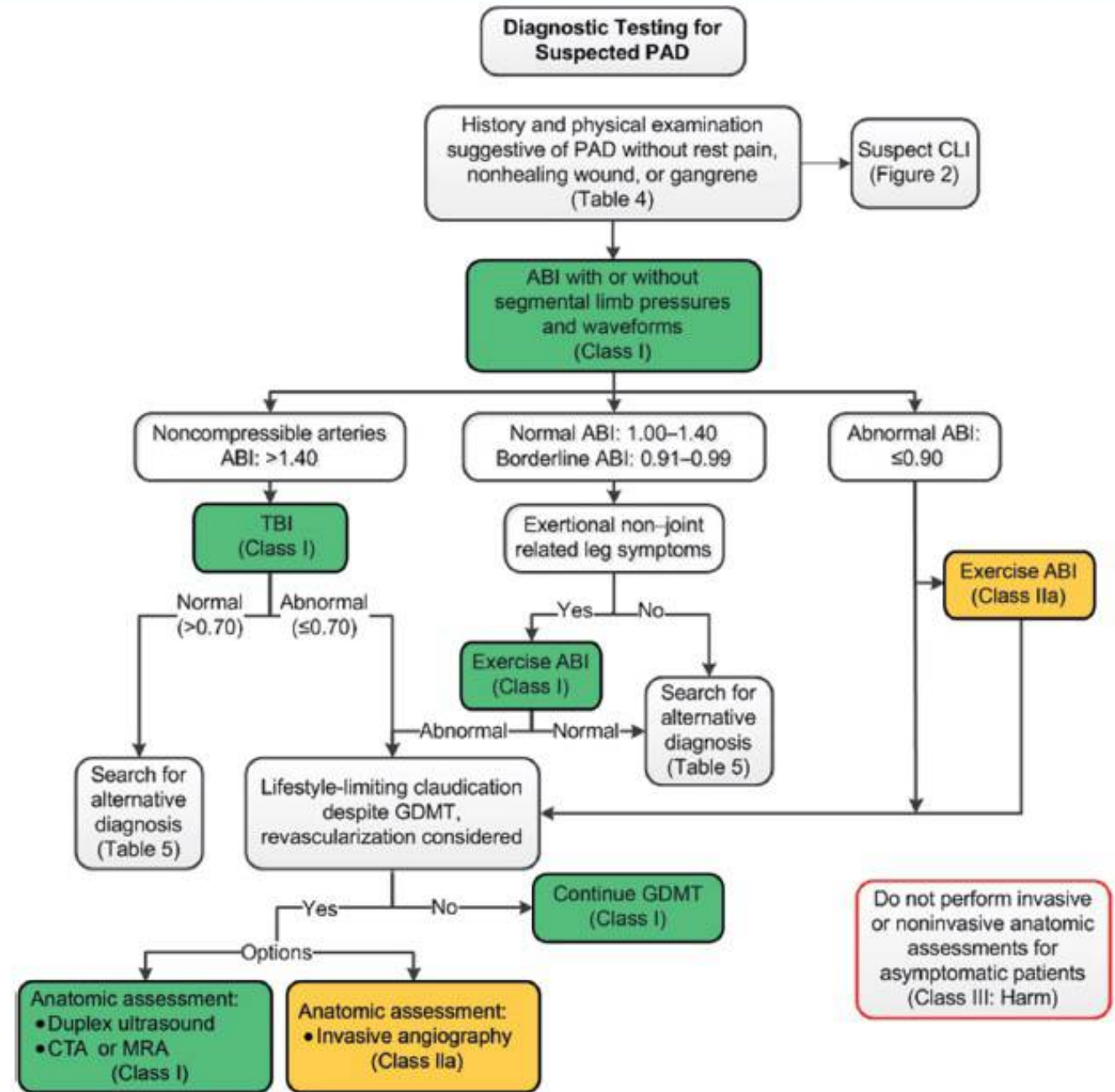


# Post-revascularization Imaging: Iliac stent, and PTFE bypass

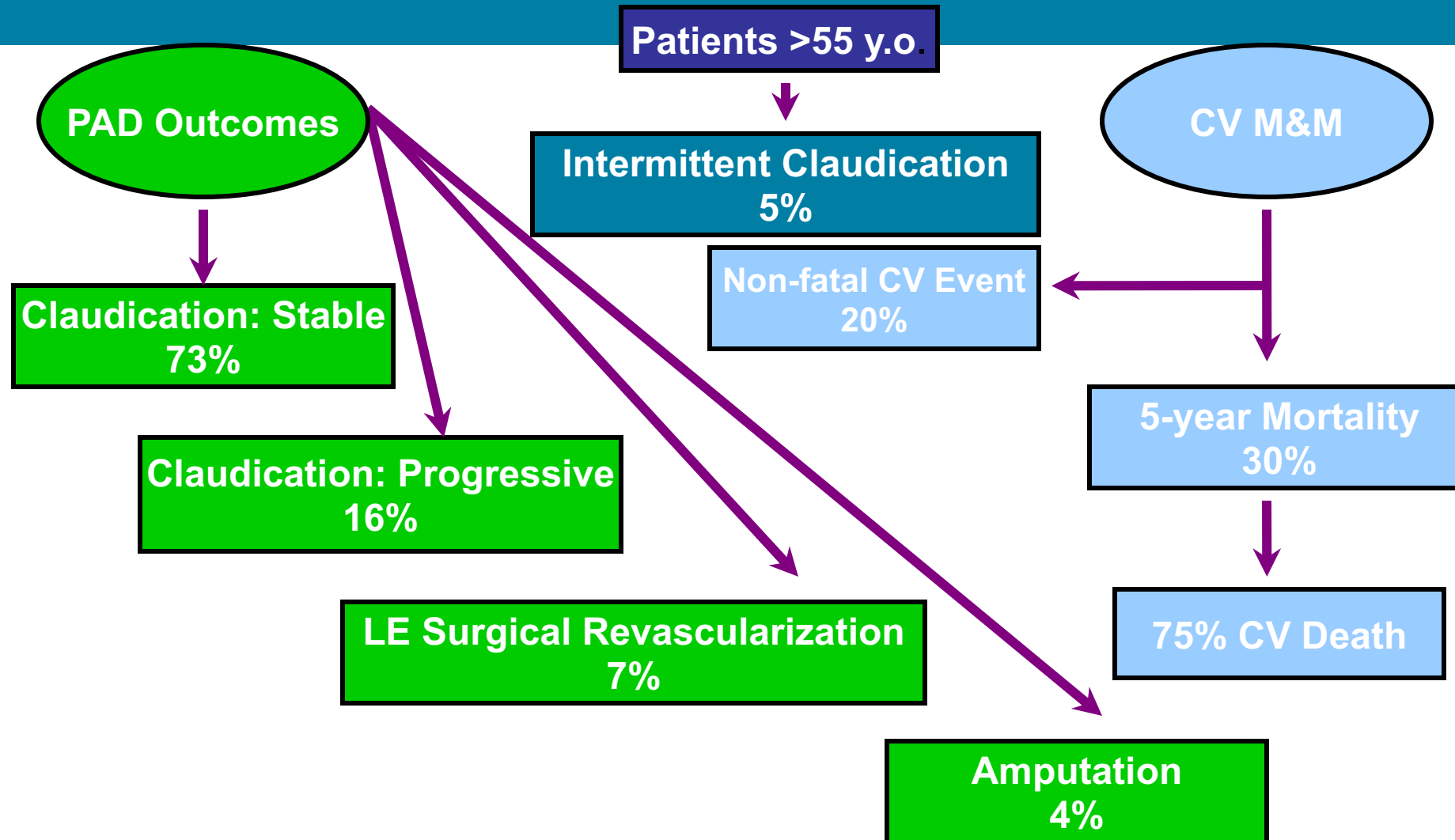


# Diagnostic algorithm for PAD

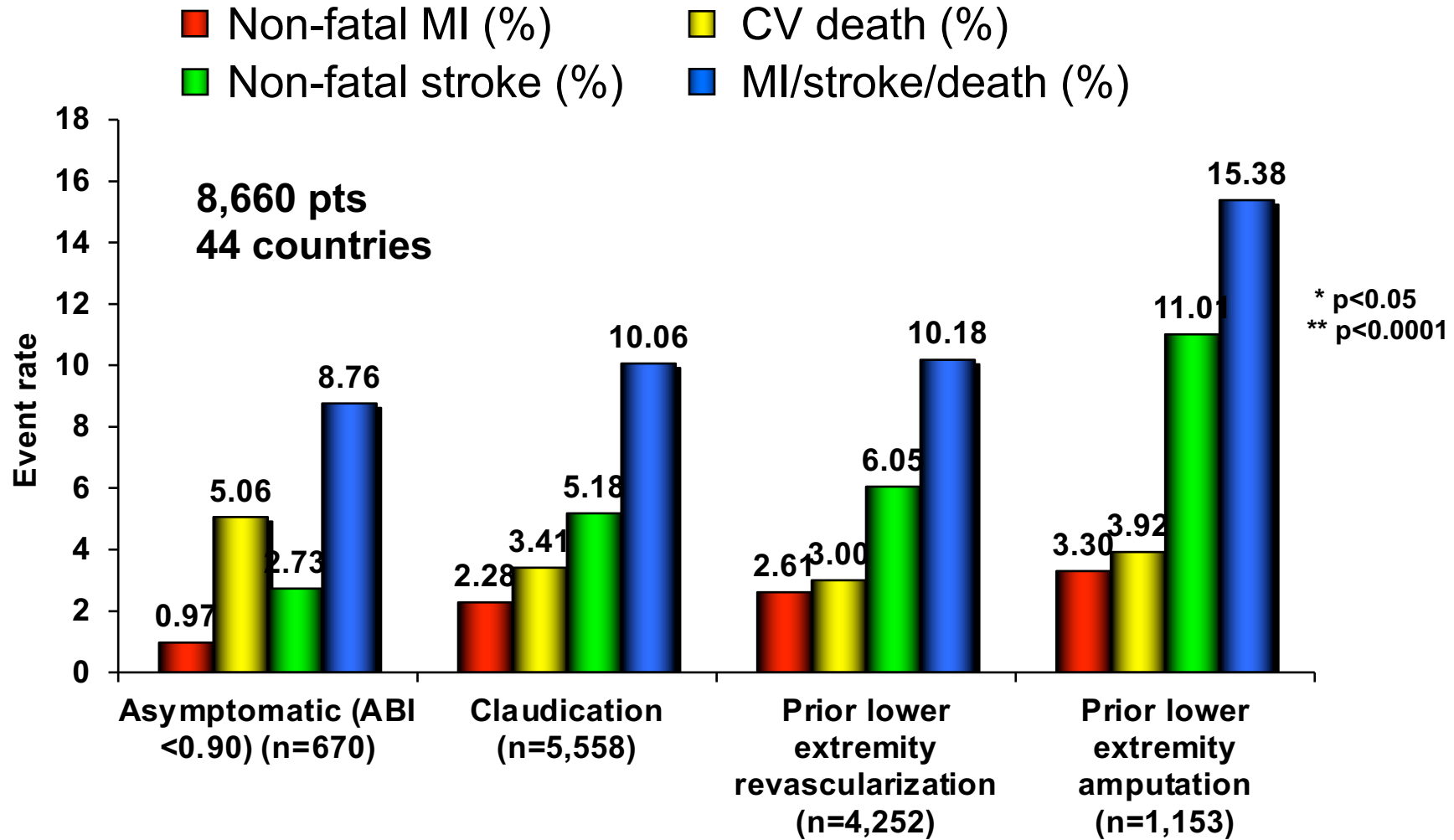
FIGURE 1 Diagnostic Testing for Suspected PAD



# Lower extremity claudication: The Tip of the Iceberg



# Two-year CV Event Rates in PAD Patients



Abstract presentation, ESC, September 5, 2007

1. Bhatt DL et al, on behalf of the REACH Registry Investigators. *JAMA* 2006;295(2):180-189.
2. Ohman EM et al, on behalf of the REACH Registry Investigators. *Am Heart J* 2006;151(4):786.e1-10.

# Mortality of PAD

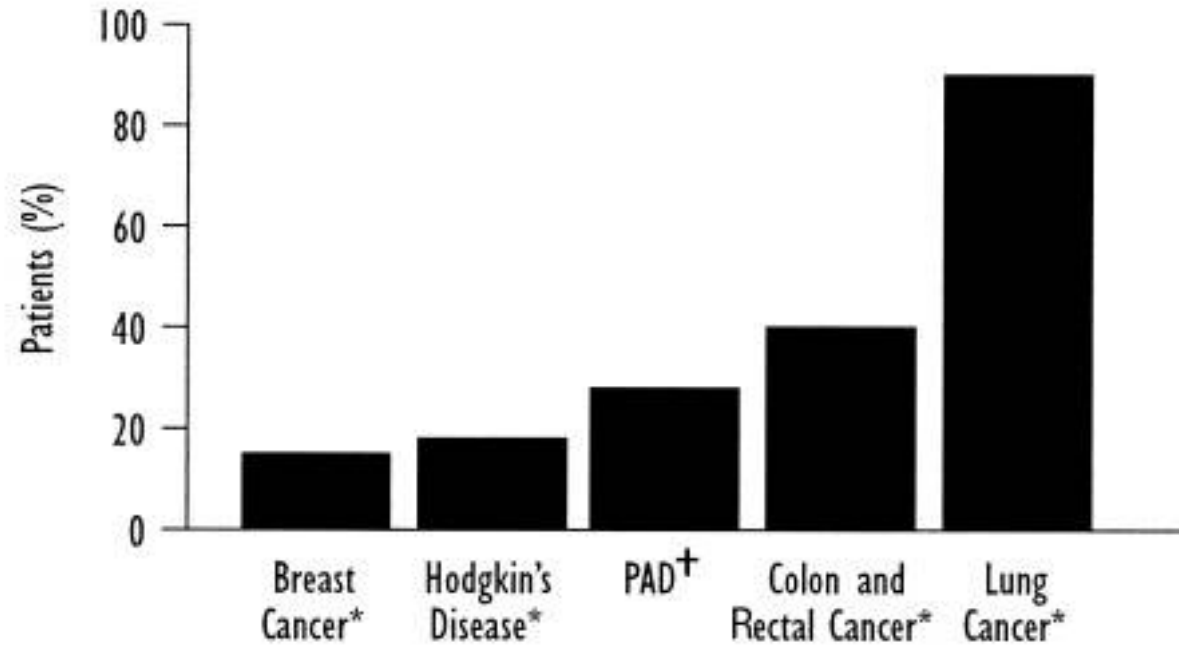
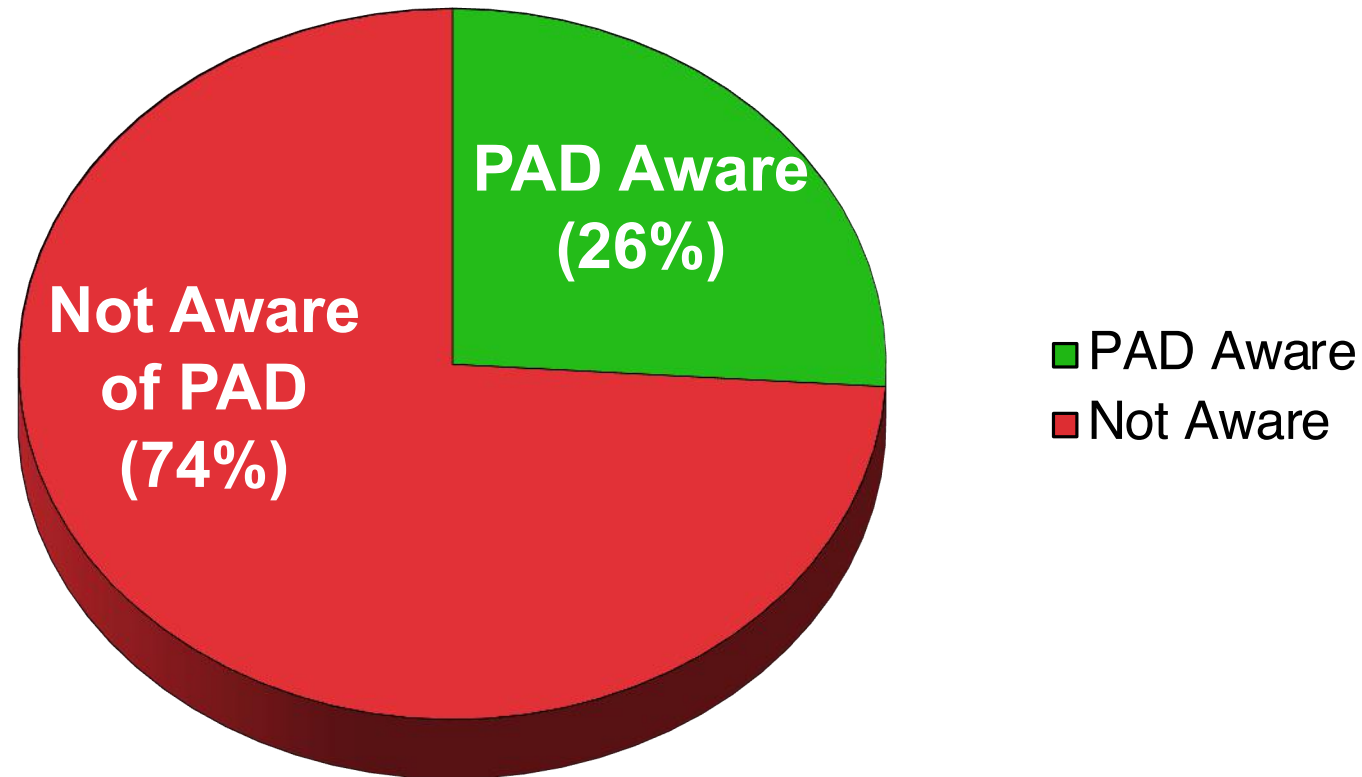


FIGURE 2. Five-year mortality rates for peripheral arterial disease (PAD) and common types of cancer. (\*Data from the American Cancer Society.<sup>20</sup> †Data from *Vascular Surgery*.<sup>21</sup>)

# Three Out of Four Adults Surveyed are Not Familiar with PAD

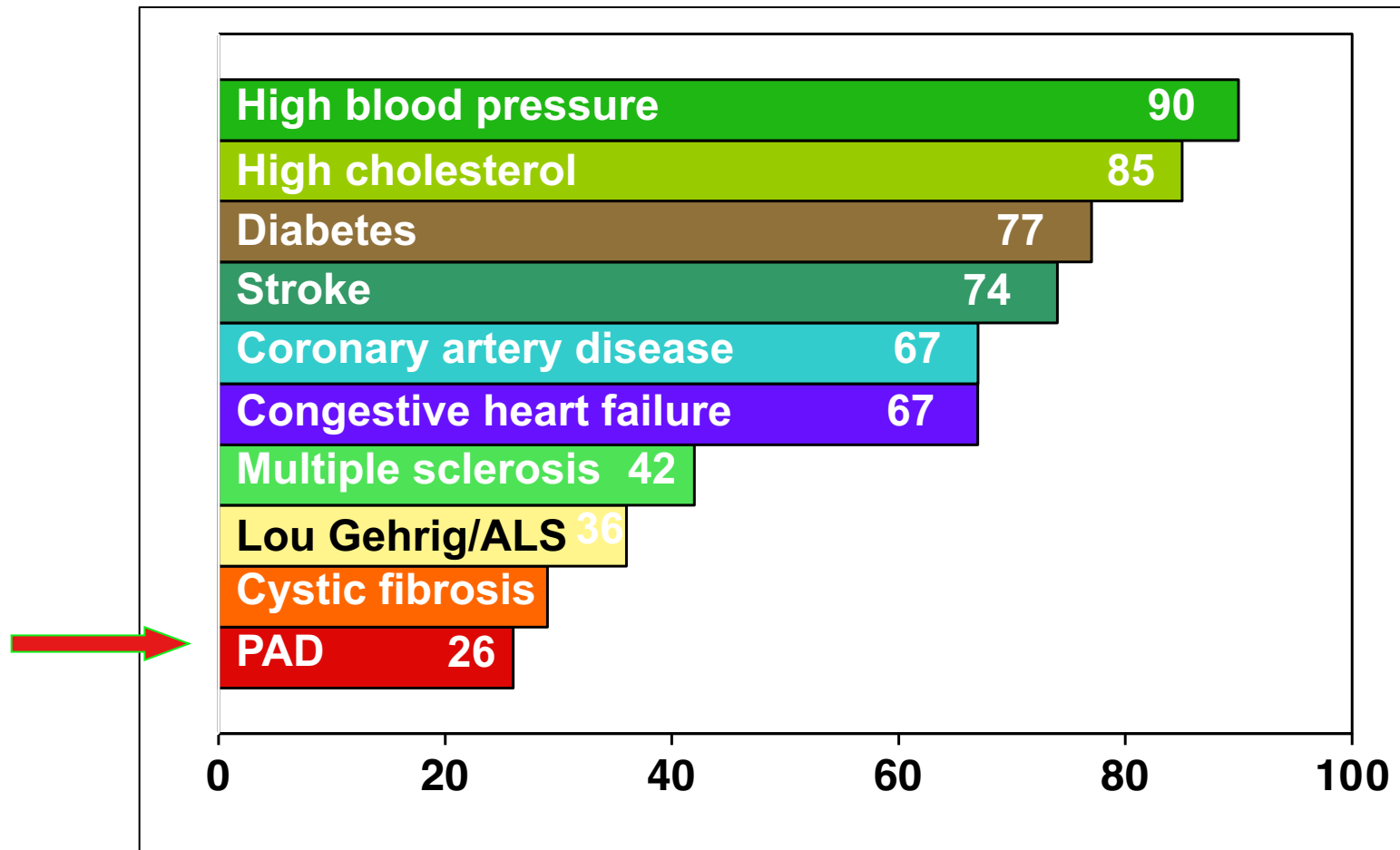
How familiar are you with PAD:  
very familiar, somewhat familiar, not too familiar or not at all familiar?



“PAD Aware” defined by “somewhat” or “very familiar” responses

# PAD Awareness is Markedly Lower than Other CV and Non-CV Diseases

How familiar are you with the following conditions:  
very familiar, somewhat familiar, not too familiar or not at all familiar?



# Treatment of Patients with PAD

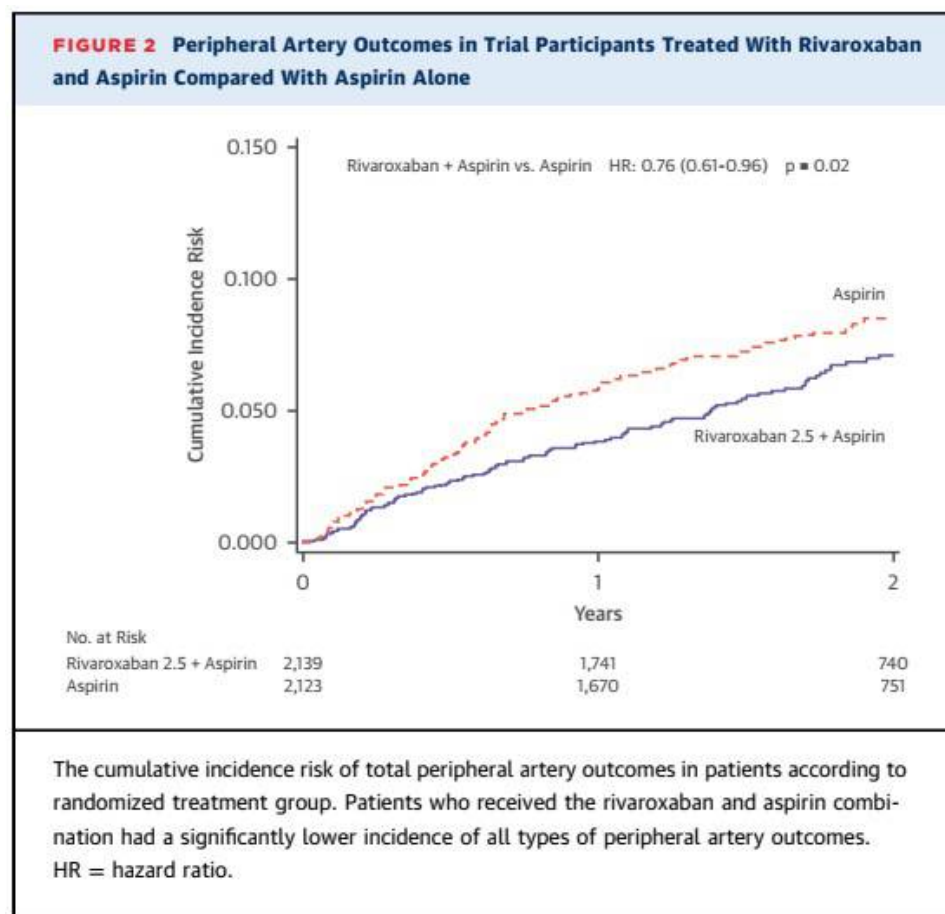
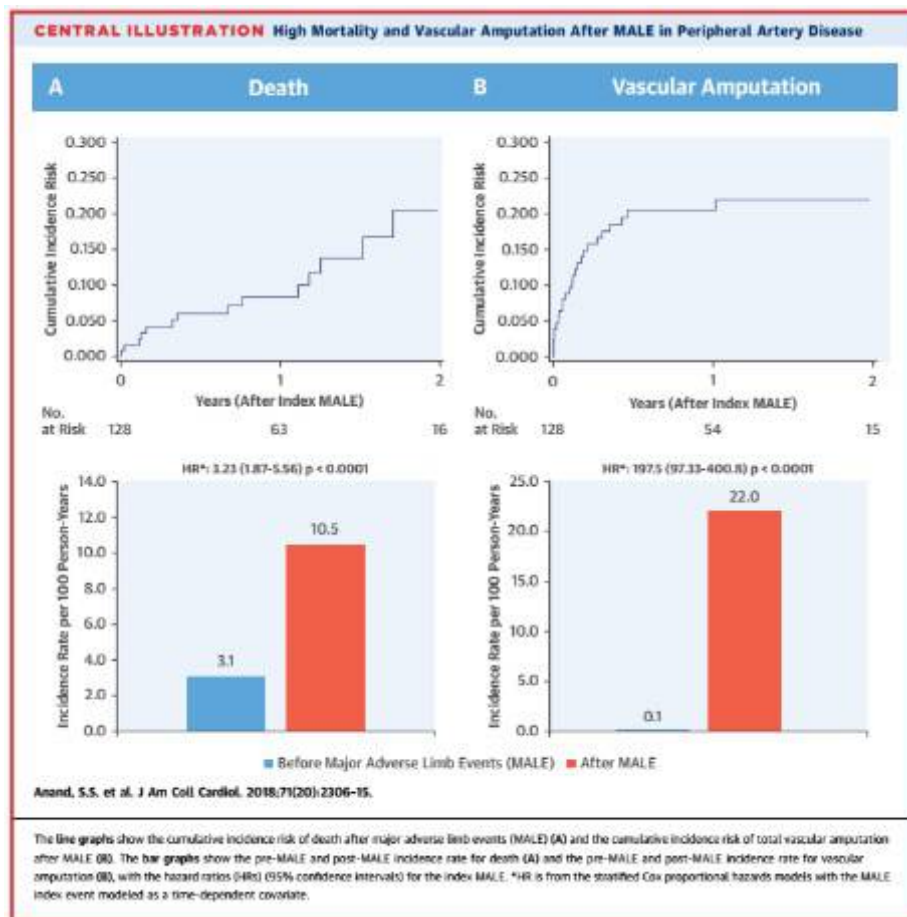
- Hygienic and supportive measures to prevent skin breakdown and infection
- Exercise conditioning
- Pharmacotherapy for claudication
- Revascularization
- Most importantly: modification of risk factors



# Reducing Cardiovascular Morbidity and Mortality in Patients with PAD

- Smoking cessation
- Cholesterol reduction (high-intensity statin)
- Treatment of diabetes (tailored)
- Antihypertensive therapy (BP < 130/80)
- Antiplatelet therapy
- **Class I indication: GDMT**

# Low-dose rivaroxaban in PAD: COMPASS trial



# VOYAGER-PAD: Low Dose Rivaroxaban and an Antiplatelet Agent in PAD-Post Procedure

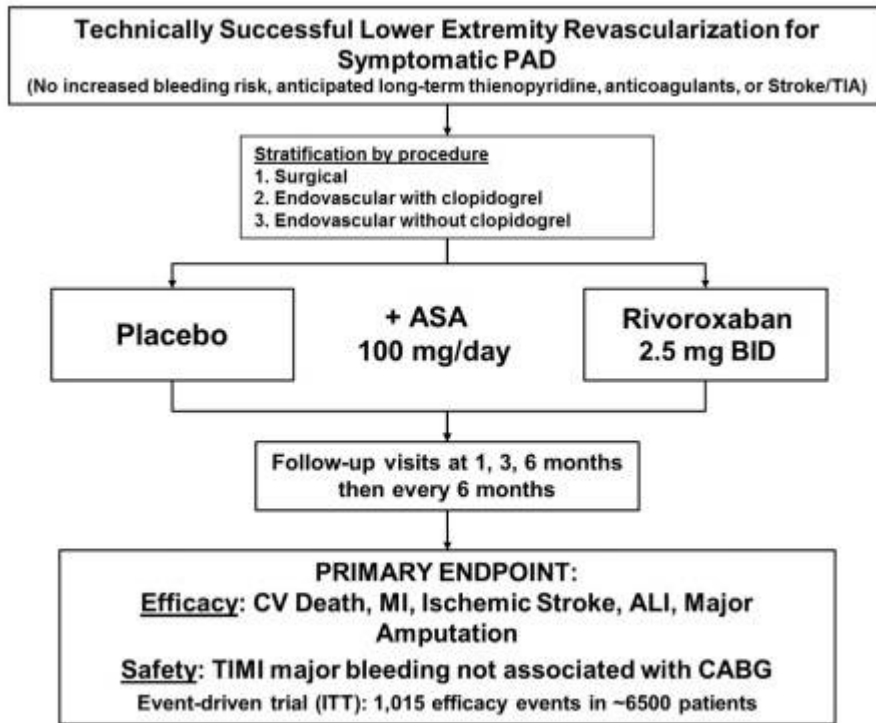
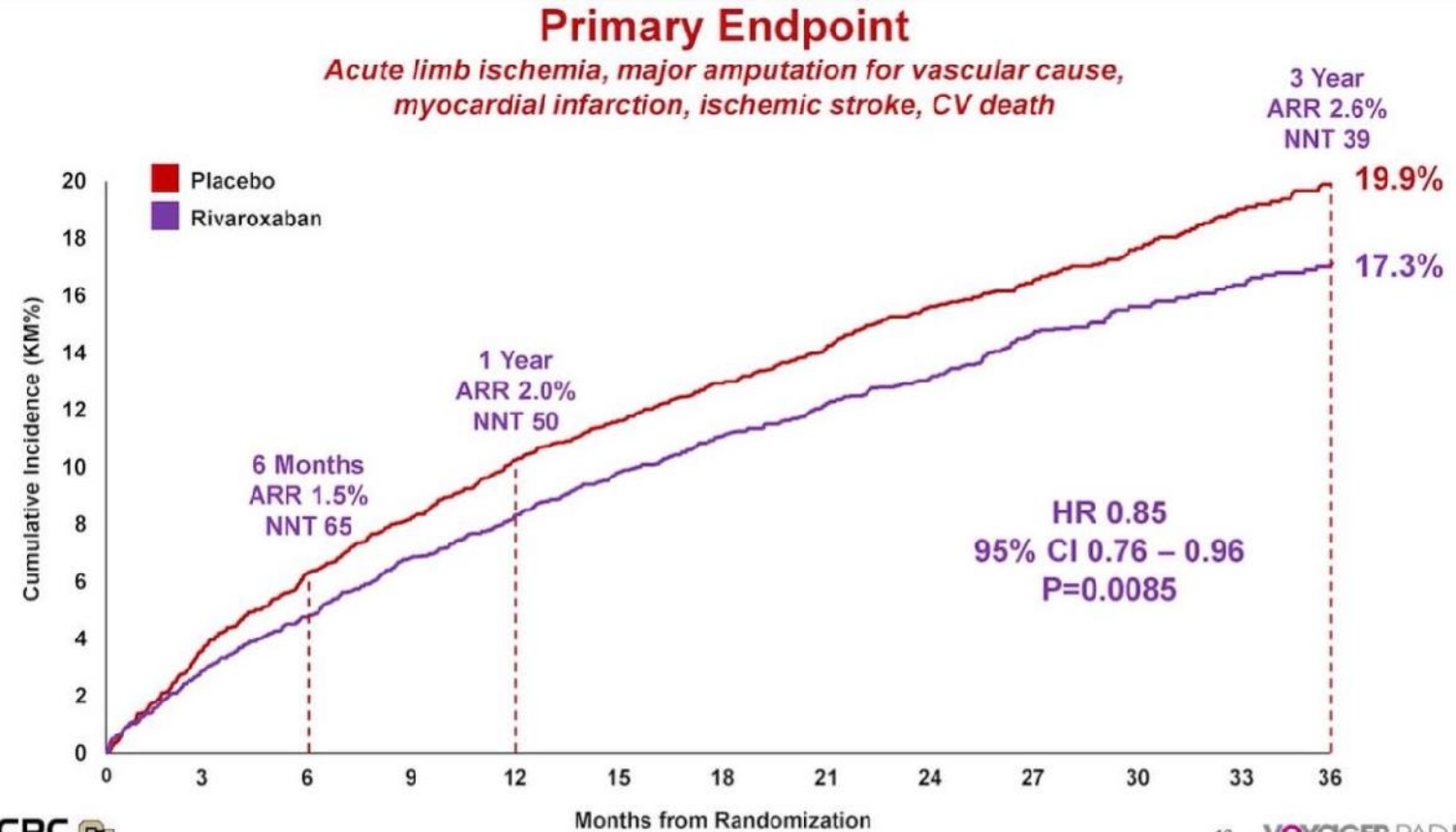


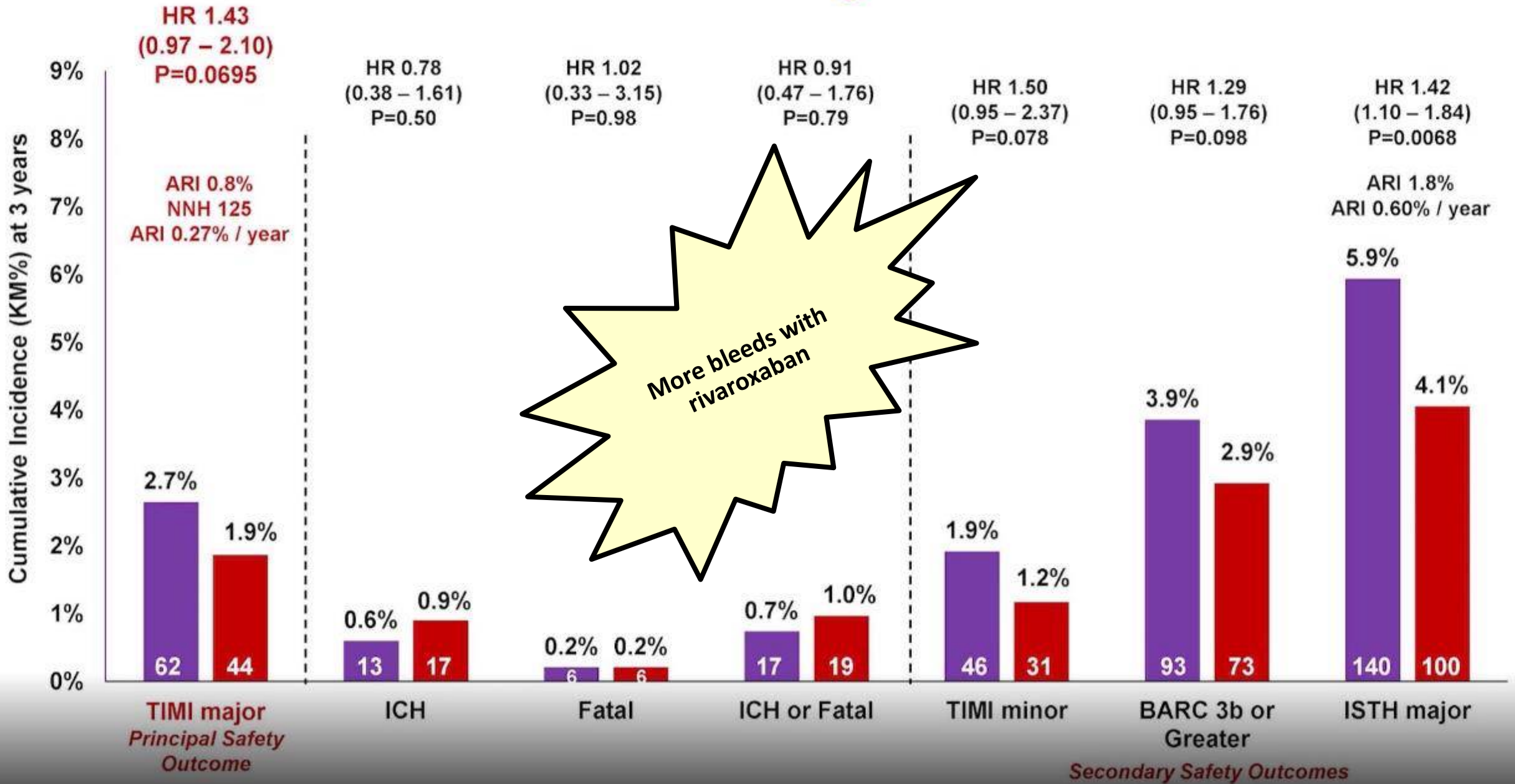
Figure 1. VOYAGER PAD study design.



ARR – absolute risk reduction. NNT number needed to treat

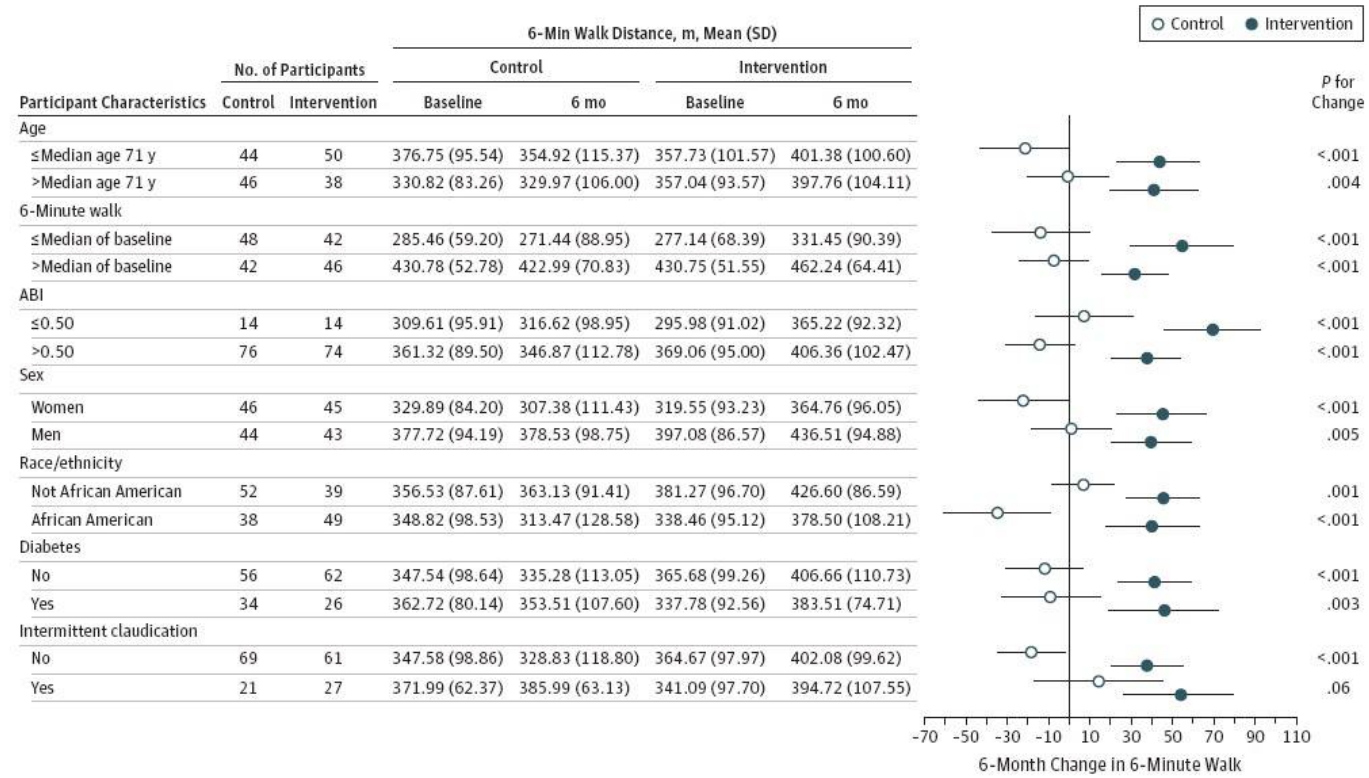
# Safety

Placebo  
Rivaroxaban



# Efficacy of Home Walking Programs

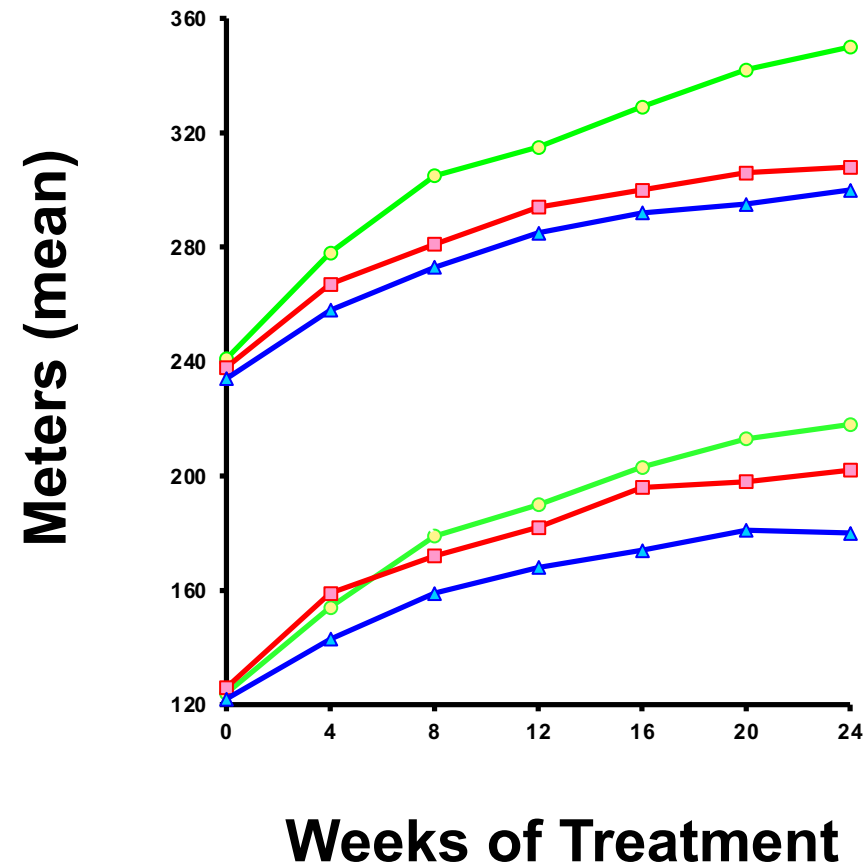
Figure 2. Association Between Home-Based Walking Exercise Intervention and Change in 6-Minute Walk at 6-Month Follow-up Within Subsets of GOALS Participants.



Change in 6-minute walk is shown for specific subsets of participants within the Group-Oriented Arterial Leg Study (GOALS) according to whether they were randomized to the intervention vs control group. P values represent the change

in 6-minute walk between the intervention vs control group for each study characteristic. Error bars indicate 95% CIs.

# Effect of Cilostazol vs. Pentoxifylline on Walking Distance in Patients with Claudication



## Maximal Walking Distance

- Cilostazol (n=205)
- Pentoxifylline (n=212)
- ▲ Placebo (n=226)

## Pain-Free Walking Distance

\* Significantly greater than placebo,  $P \leq 0.05$   
‡ Significantly greater than pentoxifylline,  $P \leq 0.05$

- Cilostazol (Class I)
  - Phosphodiesterase inhibitor
  - Inhibits platelet aggregation
  - Peripheral vasodilatation
  - Contraindicated in CHF
- *Pentoxifylline (Class III: no benefit)*
  - *Increases RBC deformability*
  - *Reduces fibrinogen*
  - *Inhibits platelet adhesion*
  - *Reduces blood viscosity*

# Indications for Revascularization

- Critical limb ischemia
  - Rest pain (“the five Ps”)
  - Ulcers, gangrene, necrosis
- Disabling claudication
- Quality of life

# ERASE trial: Supervised Exercise Therapy +/- Endovascular Treatment of AI/FP disease

Table 2. Functional Performance Measures

Functional Performance Measures	Mean (99% CI)		Between-Group Difference	P Value <sup>a</sup>
	Supervised Exercise (n = 106)	Endovascular Revascularization Plus Supervised Exercise (n = 106)		
<b>Maximum walking distance, m</b>				
At baseline	285 (244 to 326)	264 (228 to 300)		
1 mo	438 (282 to 595) <sup>b</sup>	1004 (835 to 1174) <sup>b</sup>	566 (358 to 774)	<.001
6 mo	851 (683 to 1018) <sup>b</sup>	1260 (1076 to 1444) <sup>b</sup>	409 (183 to 636)	<.001
12 mo	955 (786 to 1124) <sup>b</sup>	1237 (1058 to 1418) <sup>b</sup>	282 (60 to 505)	.001
<b>Pain-free walking distance, m</b>				
At baseline	135 (113 to 157)	117 (96 to 138)		
1 mo	181 (23 to 339) <sup>b</sup>	724 (561 to 886) <sup>b</sup>	543 (340 to 744)	<.001
6 mo	542 (378 to 707) <sup>b</sup>	1071 (900 to 1243) <sup>b</sup>	529 (315 to 743)	<.001
12 mo	712 (549 to 876) <sup>b</sup>	1120 (948 to 1293) <sup>b</sup>	408 (195 to 622)	<.001
<b>Ankle brachial index at rest<sup>c</sup></b>				
At baseline	0.68 (0.64 to 0.72)	0.71 (0.67 to 0.76)		
1 mo	-0.02 (-0.07 to 0.02) <sup>b</sup>	0.19 (0.15 to 0.23) <sup>b</sup>	0.21 (0.15 to 0.27)	<.001
6 mo	0.04 (-0.01 to 0.09) <sup>b</sup>	0.16 (0.11 to 0.20) <sup>b</sup>	0.12 (0.05 to 0.17)	<.001
12 mo	0.03 (-0.02 to 0.08) <sup>b</sup>	0.16 (0.11 to 0.21) <sup>b</sup>	0.13 (0.06 to 0.19)	<.001
<b>Ankle brachial index after exercise<sup>c</sup></b>				
At baseline	0.40 (0.34 to 0.46)	0.43 (0.38 to 0.48)		
1 mo	0.03 (-0.02 to 0.09) <sup>b</sup>	0.36 (0.30 to 0.42) <sup>b</sup>	0.33 (0.25 to 0.40)	<.001
6 mo	0.12 (0.06 to 0.18) <sup>b</sup>	0.33 (0.27 to 0.39) <sup>b</sup>	0.21 (0.13 to 0.29)	<.001
12 mo	0.11 (0.05 to 0.18) <sup>b</sup>	0.33 (0.27 to 0.40) <sup>b</sup>	0.22 (0.13 to 0.31)	<.001

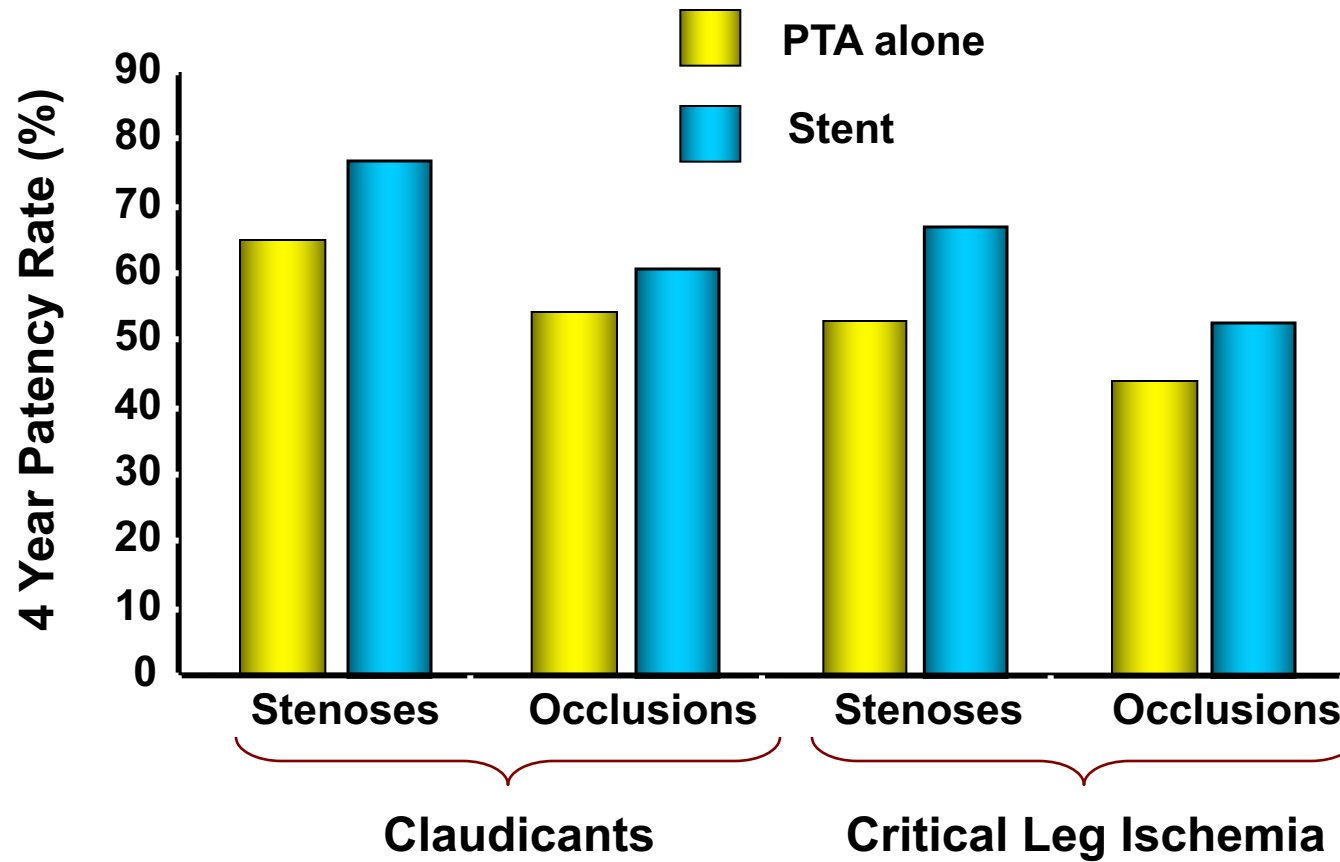
N=212

SET: 2-3x/wk x 3 months

Fakhry F, et al. JAMA. 2015; 314(18): 1936-1944.



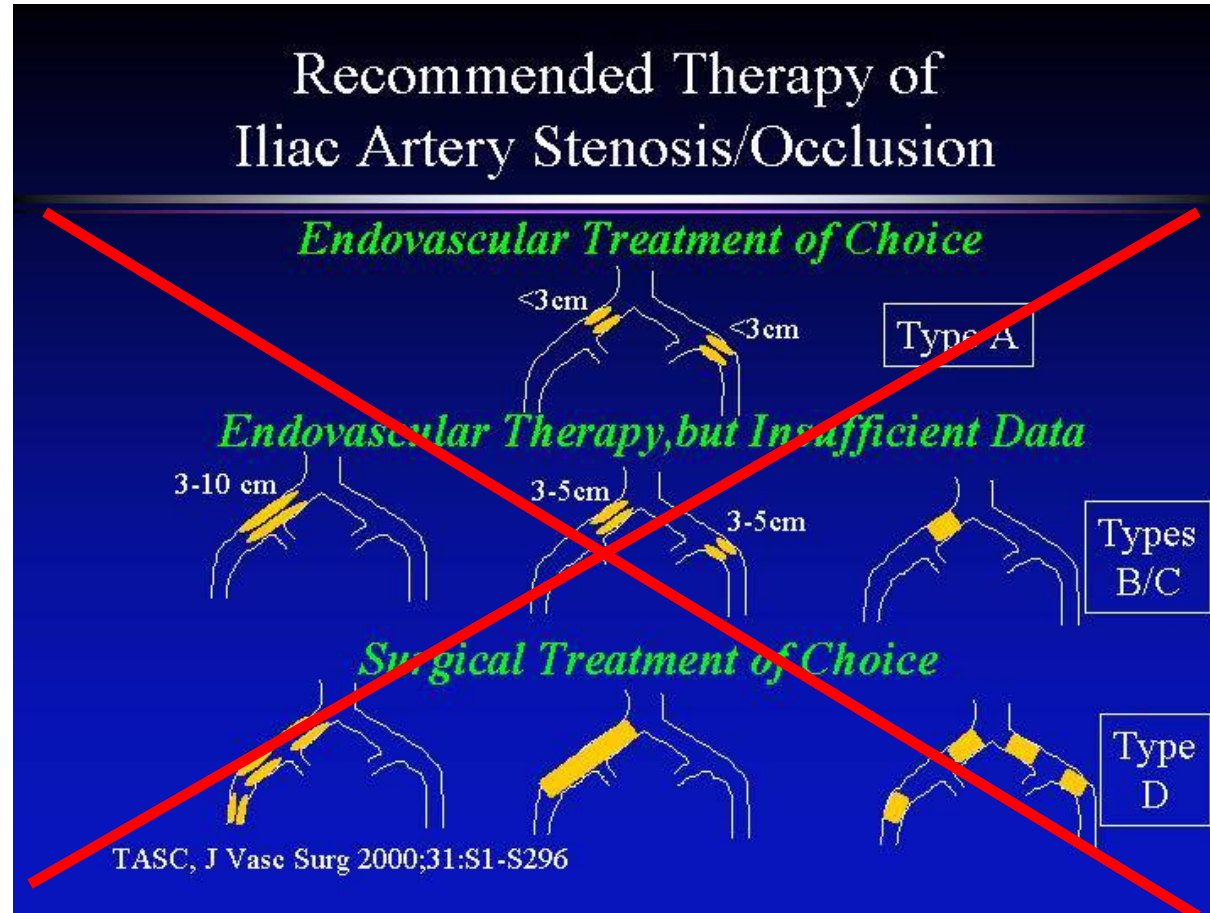
# Patency Rates of Iliac Artery PTA vs. Stents



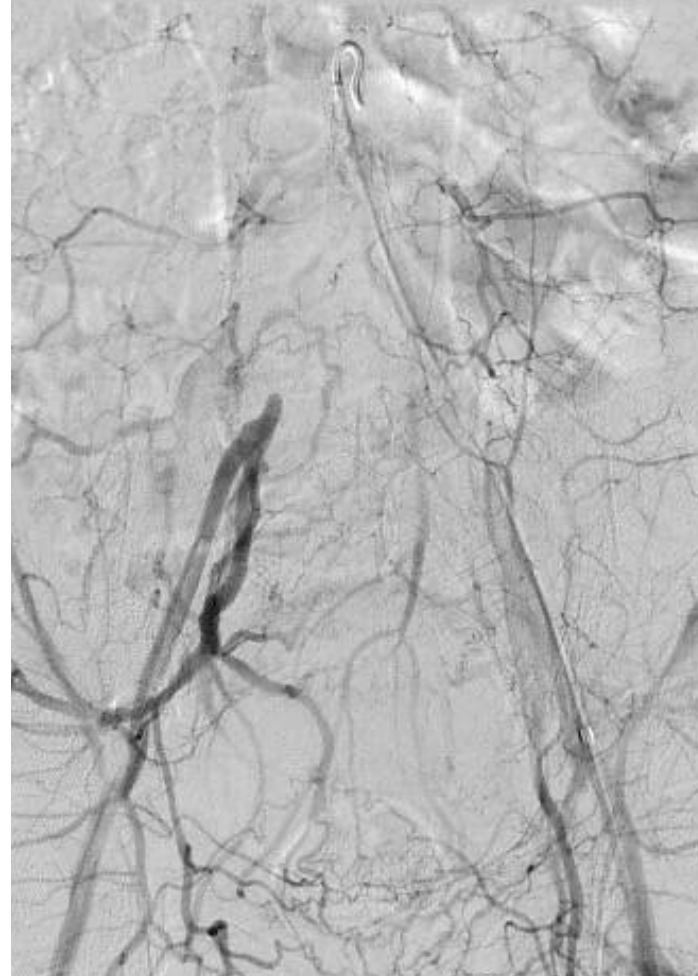
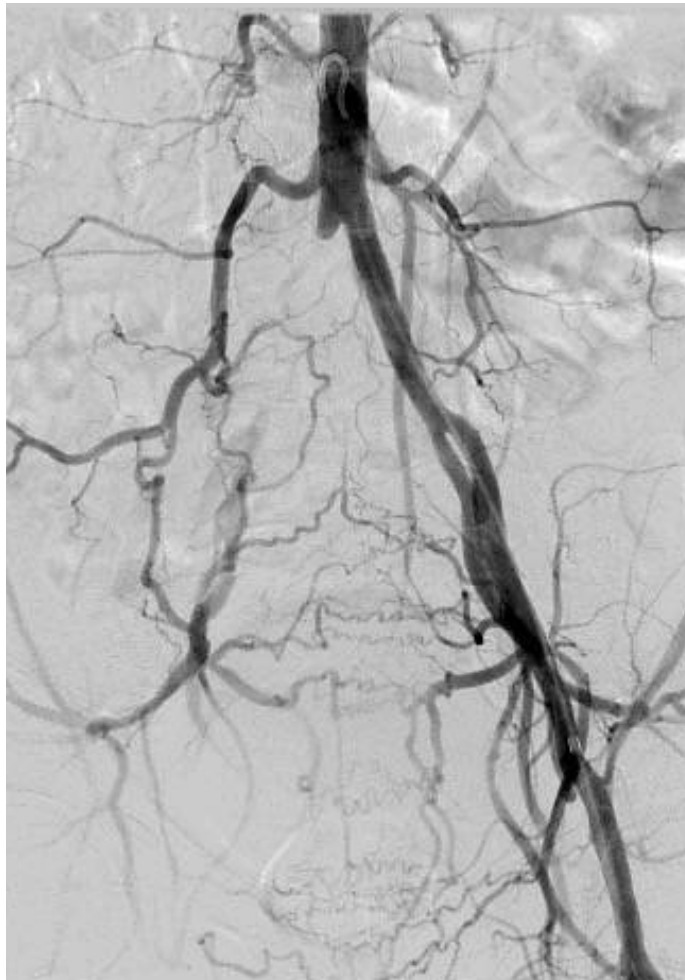
## Aortobifemoral bypass

- Durable
  - 5 year primary patency 80.4%
  - 10 year primary patency 72.1%
- Risk
  - Operative Mortality 3.3%
  - Systemic Morbidity 8.3%
- Significant Recovery (weeks)

# Should new techniques and technologies lower our threshold to intervention?



# A 65 year old man with claudication...



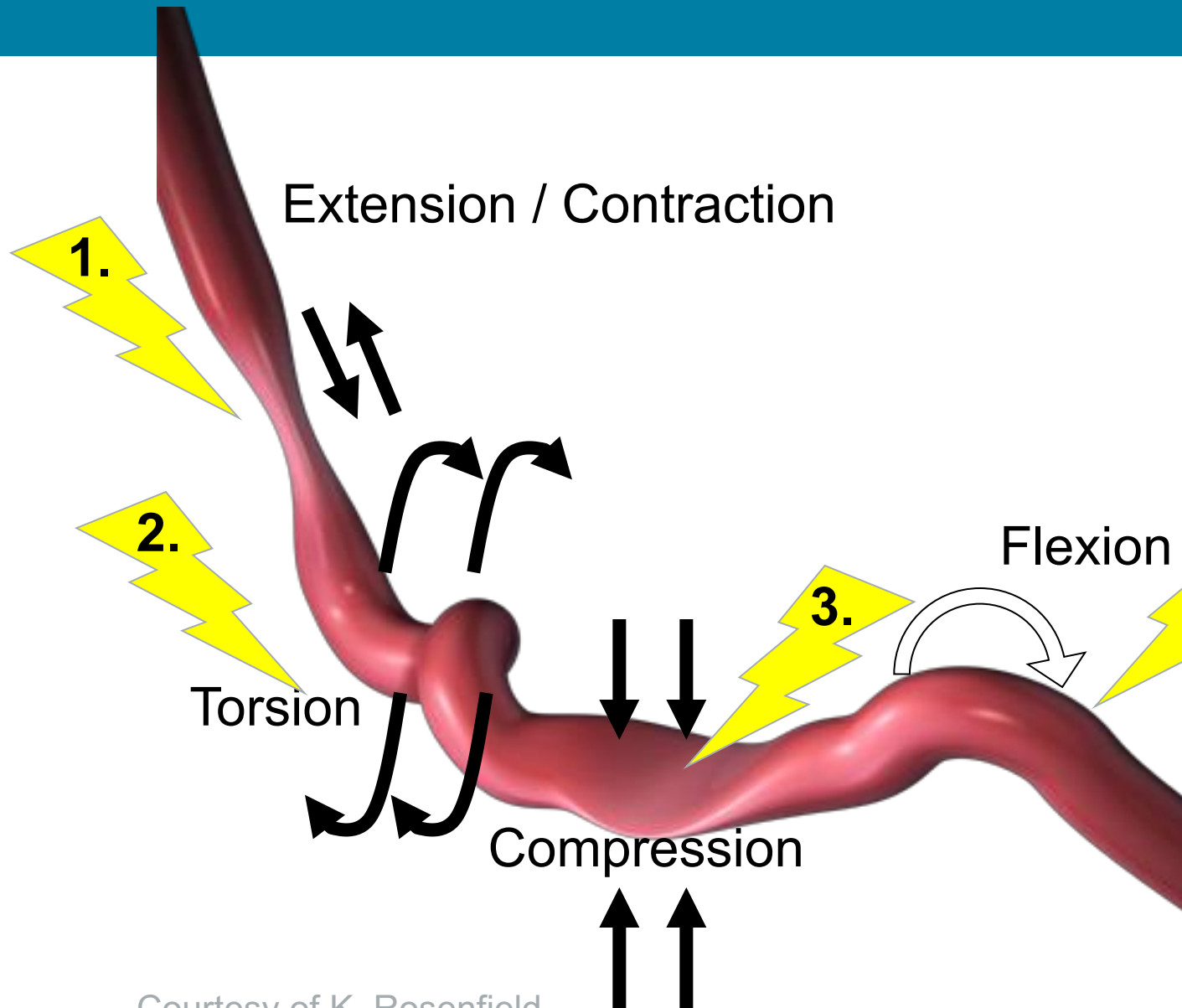
# Endovascular Therapy for Aortoiliac Disease: *Advantages*

- Less Invasive
- Safer/Fewer Adverse Events
- Similar Efficacy Compared to Surgery
- Shorter Length of Hospital Stay
- Faster return to work
- Potentially more cost-effective

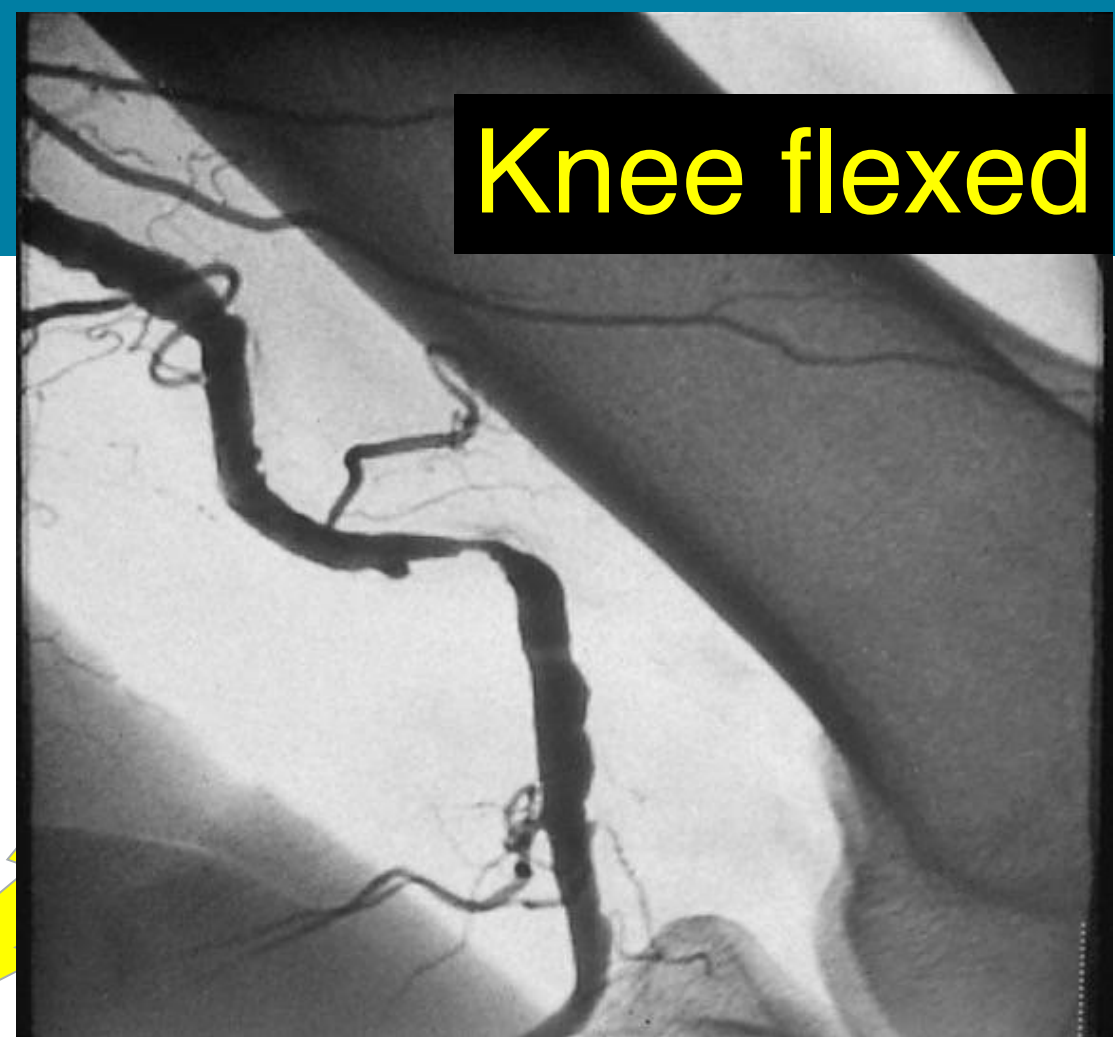
# Superficial Femoral and Popliteal Arteries

- The achilles heel of the vascular specialist
- Historically, difficult to maintain patency following revascularization
  - Surgical
  - Endovascular

# Mechanical Forces



Courtesy of K. Rosenfield



Courtesy of G. Ansel

# Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial

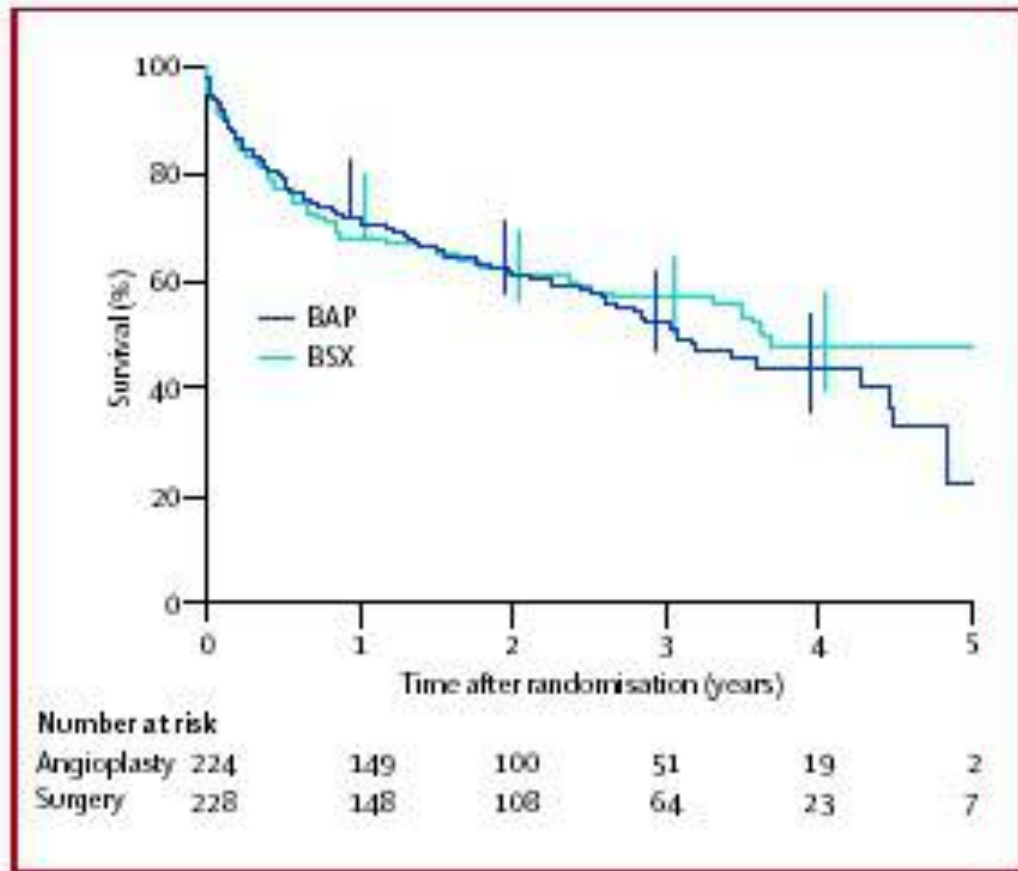


Figure 2: Amputation-free survival after bypass surgery and balloon angioplasty

Bars show 95% CIs for survival up to 1, 2, 3, and 4 years of follow-up, which were calculated from the cumulative hazards.

	During same hospital stay as first intervention		Following discharge from hospital after first intervention	
	Angioplasty (n=237)	Surgery (n=197)	Angioplasty (n=230)	Surgery (n=186)
Mortality	7	11 (n.s.)	0	0
Morbidity				
Angina	4	4	1	2
Myocardial infarction	6	13	2	2
Stroke	1	3	2	0
Haematoma (numbers needing surgical drainage)	16 (2)	19 (9)	1 (0)	5 (0)
Wound infection	18	45	25	29
Chest infection	4	10	3	2
Urine infection	8	7	2	6
False aneurysm (numbers needing surgical repair)	0 (0)	2 (1)	0 (0)	0 (0)
Venous thromboembolism	1	0	2	0
Other	2	2	8	9
Further interventions				
Angioplasty	3	1	1	0
Surgery	21	2	13	0
Amputation of trial leg				
Above/below knee	4/5	3/3	0/1	0/0
Partial foot or toe	11	11	2	2
Graft re-exploration	0	5	0	0
Embolectomy	1	2	1	0
Thrombectomy	0	3	0	1
Wound debridement	3	6	1	1
Other (non-vascular)	0	0	0	1

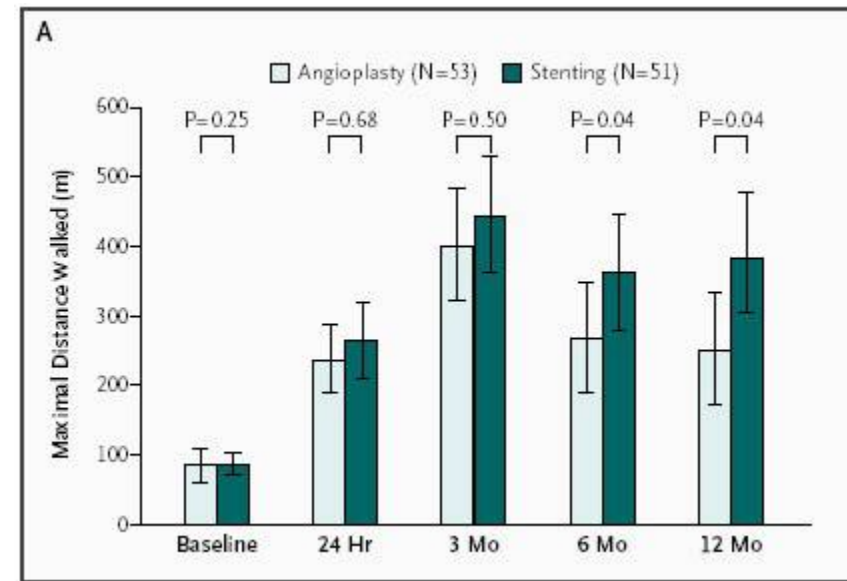
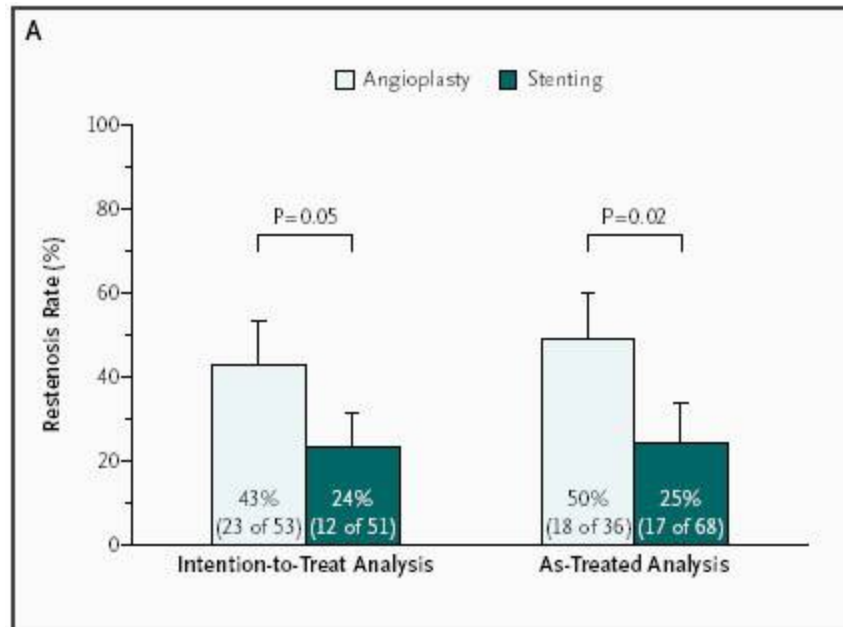
Data are number of individuals. Patients could have had more than one morbidity or re-intervention event both before and after discharge, but within 30 days.

Table 2: Mortality, morbidity, and re-interventions within 30 days after first intervention



## Balloon Angioplasty versus Implantation of Nitinol Stents in the Superficial Femoral Artery

Martin Schillinger, M.D., Schila Sabeti, M.D., Christian Loewe, M.D., Petra Dick, M.D., Jasmin Amighi, M.D.,  
Wolfgang Mlekusch, M.D., Oliver Schlager, M.D., Manfred Cejna, M.D., Johannes Lammer, M.D., and Erich Minar, M.D.



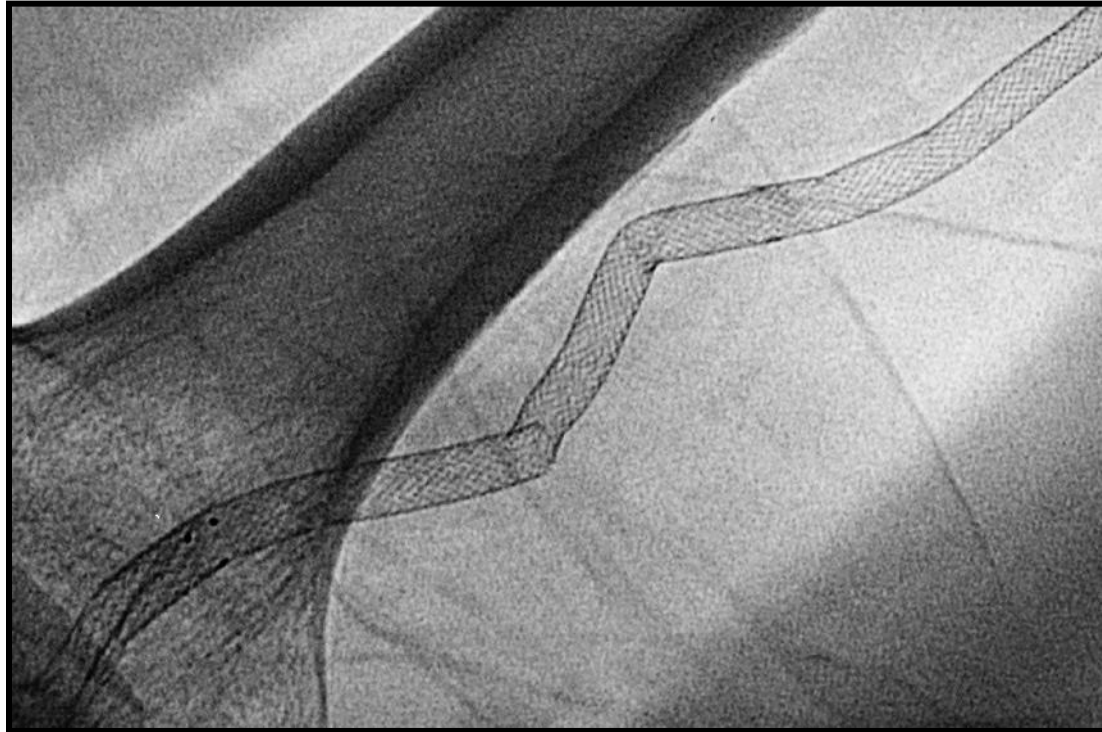
# SFA Compressive Forces:

## Nitinol Stent Fractures...word of caution...and new tech

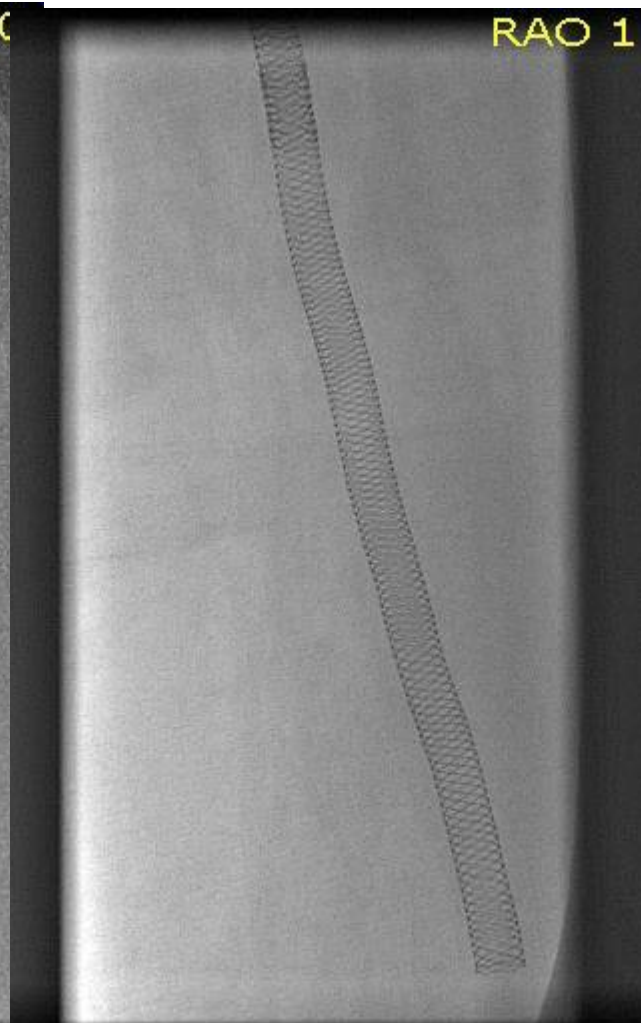
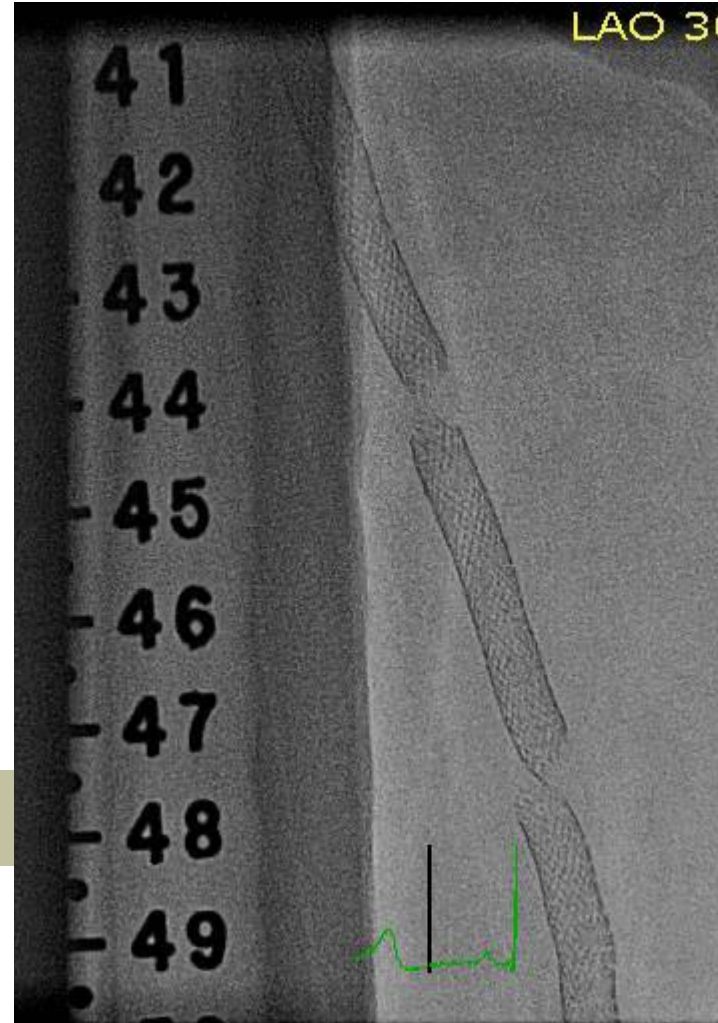


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**Cross-table lateral knee flexed**



# Critical Limb Ischemia: Infrapopliteal PTA

## Tibioperoneal (Outflow Lesion) Angioplasty Can Be Used as Primary Treatment in 235 Patients With Critical Limb Ischemia Five-Year Follow-Up

Gerald Dorros, MD; Michael R. Jaff, DO; Ari M. Dorros, MD;  
Lynne M. Mathiak, RN; Thomas He, PhD

**Background**—In a prospective, nonrandomized, consecutive series of tibioperoneal vessel angioplasty (TPVA), critical limb ischemia (CLI) patients' data were analyzed with regard to immediate and follow-up success.

**Methods and Results**—TPVA was successful in 270 of 284 critically ischemic limbs (95%), with 167 limbs (59%) requiring dilatation of 333 ipsilateral inflow obstructions to access and successfully dilate 486 of 529 (92%) tibioperoneal lesions. A clinical success (relief of rest pain or improvement of lower-extremity blood flow) was attained in 270 limbs at risk (95%). Clinical 5-year follow-up of 215 of 221 successful CLI patients (97%) with 266 successfully revascularized limbs revealed that bypass surgery occurred in 8% and significant amputations in 9% of limbs; 91% of the limbs were salvaged. The cohort's probability of survival was 56%: 58% for Fontaine class III and 33% for class IV patients. Class III compared with class IV patients had significantly ( $P < 0.05$ ) fewer surgical bypasses (3% versus 16%) and amputations: above-knee, 1% versus 4%; below-knee, 3% versus 12%; and transmetatarsal, <1% versus 21%.

**Conclusions**—TPVA, often in combination with inflow lesions, is an effective primary treatment for critical limb ischemia. The poor cumulative survival reflects the existence of severe comorbidities, which could potentially be affected by aggressive and effective cardiovascular diagnostic and therapeutic strategies. (*Circulation*. 2001;104:2057-2062.)

**Key Words:** angioplasty ■ peripheral vascular disease ■ surgery ■ vasculature



- 284 limbs (235 pts) 1986-96
- Diabetes - 51%
- PTA Success -95%
  - Inflow also treated in 57%
- 5 year follow-up (215 pts) mean 34 mos
  - Surgery- 8%
  - Amputation - 9%
  - LIMB SALVAGE - 91%
  - Survival - 56%

***“Establishes definitive role of percutaneous Rx as initial therapy in revasc for CLI”***



- Prospective, randomized, multicenter, open label superiority trial
- **2,100** patients at **120** clinical sites in USA and Canada
- Funded by National Heart Lung and Blood Institute at level of \$24,990,000
- Compare:
  - Treatment efficacy
  - Functional outcomes
  - Cost
- Patients with CLI and infrainguinal PAD
- Best **open surgical** vs. best **endovascular** revascularization
- **Primary endpoint: Major Adverse Limb Event (MALE)-free survival**

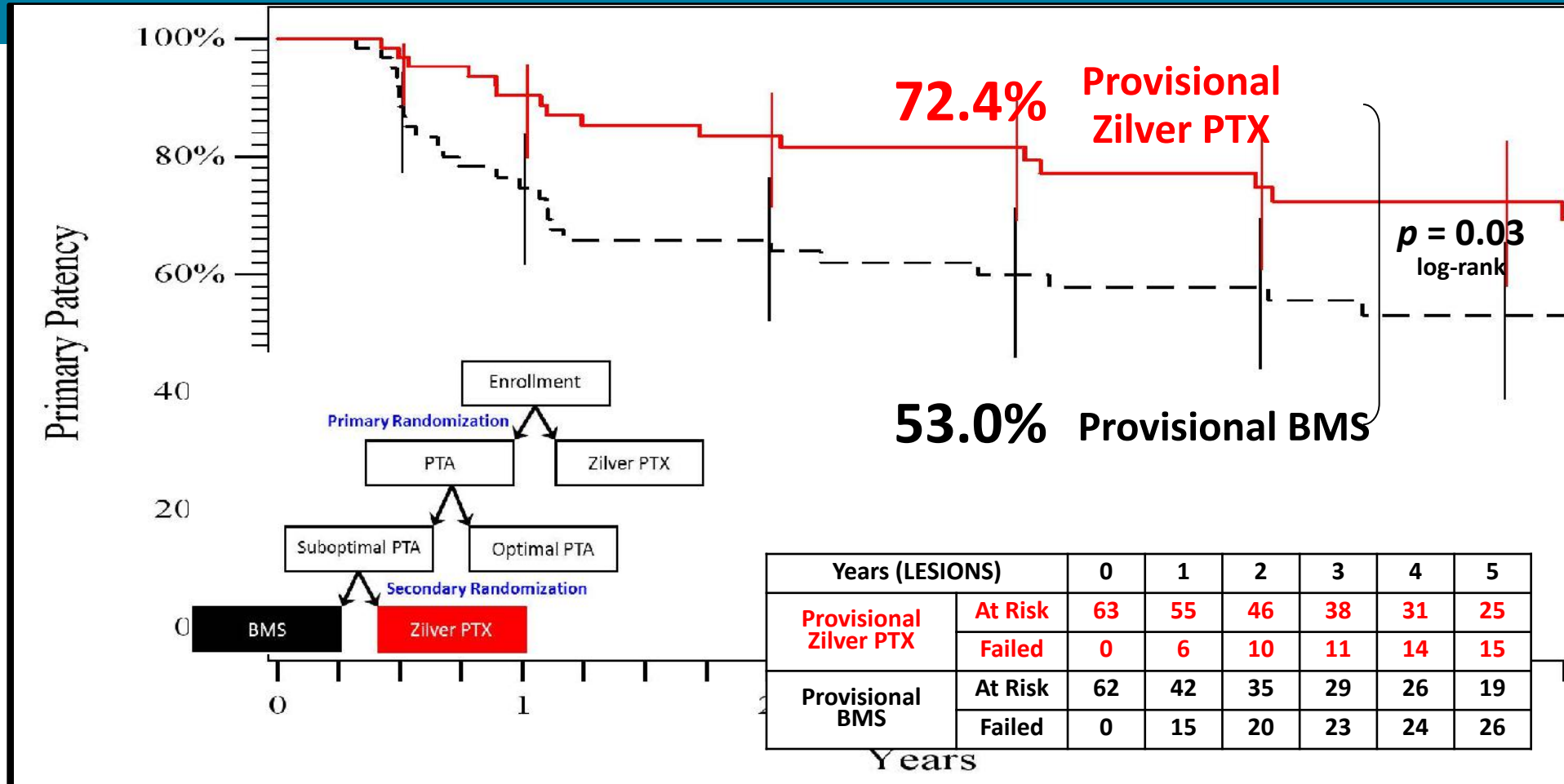
- PTA
- Atherectomy
  - Rotational
  - Directional (“Hawk”)
  - Laser
- Intravascular lithotripsy
- Thrombolytic Therapy
- Cryoplasty
- Stents below the knee
- **DES**
- **DCB**

No current data supporting improved long-term patency with one technique over another...

Until newer DES/DCB developed

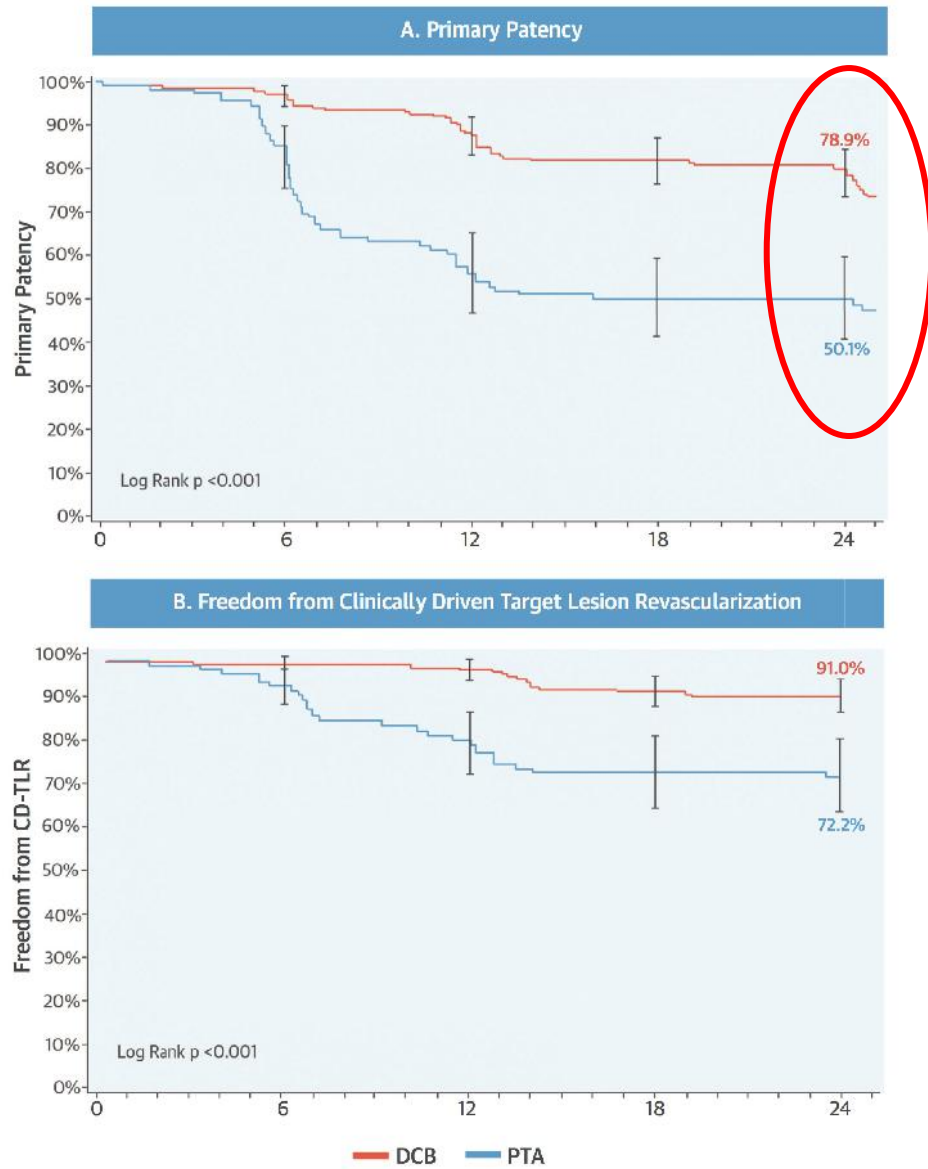
# 5-year Primary Patency (PSVR < 2.0)

## Provisional Zilver PTX vs. BMS



**At 5 years, Zilver PTX demonstrates a 41% reduction in restenosis compared to BMS**

# IN.PACT SFA: 2-year outcomes



- Reduce restenosis
- No chronic implant
- Better treatment of “no-stent” zones
- Treatment option for in-stent restenosis
- Reduce need for anti-platelet therapy (DAPT)
- Simplicity? Cost reduction?
- BUT: FDA Warning (possible toxicity)



# 2016 AHA/ACC LEPAD Guidelines: Revascularization driven by symptoms

- *“Lifestyle-limiting claudication is defined by the patient rather than by any test”*
- AODL, vocational, recreational activities
- Revasc is one component of customized care plan:
  - GDMT
  - Structured exercise therapy
  - Care to minimize tissue loss

## Recommendation for 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 (13,25,26,190,191).

# Guideline statements: Endovascular

## Recommendations for 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 <u>aortoiliac</u> occlusive disease (13,25,26,190,194,196,201).
IIa	B-R	Endovascular procedures are reasonable as a revascularization option for patients with lifestyle-limiting claudication and hemodynamically significant <u>femoropopliteal</u> disease (190,197-200,205,206).
IIb	C-LD	The usefulness of endovascular procedures as a revascularization option for patients with claudication due to isolated <u>infrapopliteal</u> artery disease is unknown (211-213).
III: Harm	B-NR	Endovascular procedures should not be performed in patients with PAD solely to prevent progression to CLI (186-189,214-216).

# Guideline statements: Surgical

## Recommendations for Surgical Revascularization for Claudication

COR	LOE	RECOMMENDATIONS
I	A	When surgical revascularization is performed, bypass to the popliteal artery with <u>autogenous vein</u> is recommended in preference to prosthetic graft material (226-234).
IIa	B-NR	Surgical procedures are reasonable as a revascularization option for patients with lifestyle-limiting claudication with inadequate response to GDMT, acceptable perioperative risk, and technical factors suggesting advantages over endovascular procedures (190,230,235-237).
III: Harm	B-R	Femoral-tibial artery bypasses with prosthetic graft material should not be used for the treatment of claudication (238-240).
III: Harm	B-NR	Surgical procedures should not be performed in patients with PAD solely to prevent progression to CLI (186-189,241).



## Preventing Death

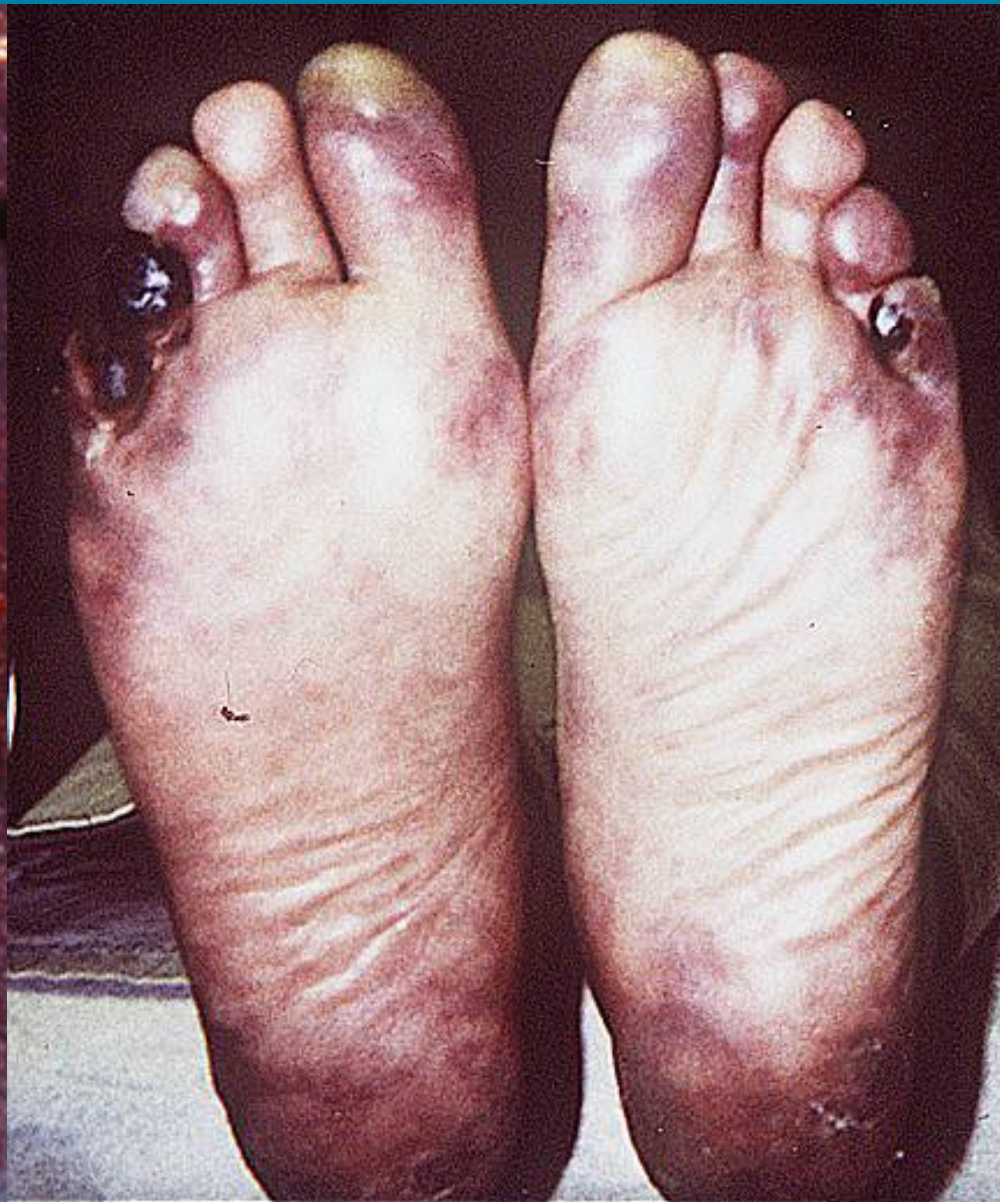
- Antiplatelets
- Cholesterol lowering: “statins”
- ACE inhibitors
- Beta Blockers

## Reducing Symptoms

- Exercise
- Cilostazol
- Catheter-based interventions
- Reconstructive surgery

## Saving Limbs

- Catheter-based interventions
- Reconstructive surgery



- Atherosclerosis is a “pan-vascular” process
- PAD is underappreciated, but confers profound cardiovascular morbidity
- Early recognition, treatment, and risk reduction are critical
- Endovascular strategies rival longstanding surgical paradigm for revascularization