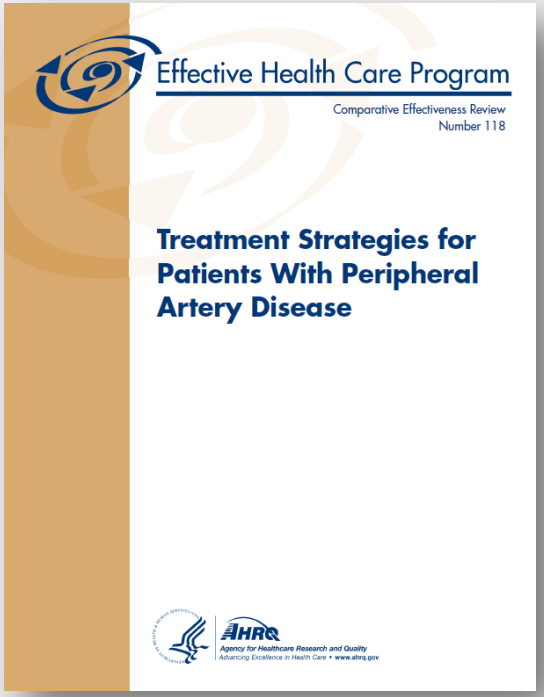
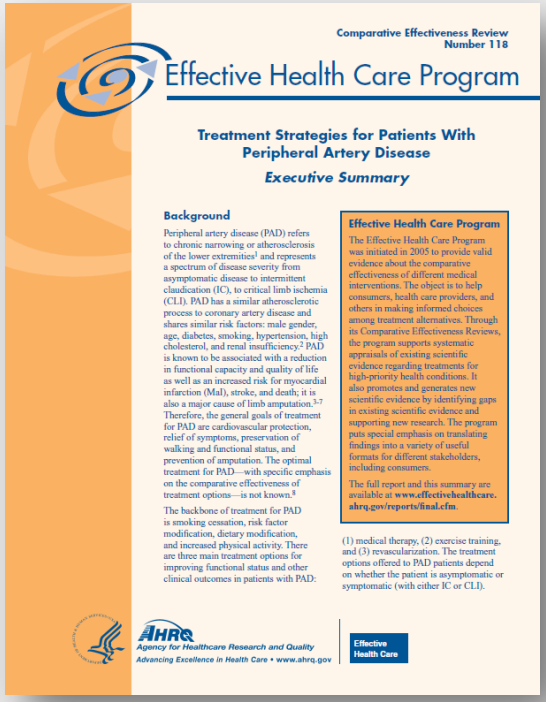
Treatment Strategies For Patients with Peripheral Artery Disease

Schuyler Jones, MD and Manesh Patel, MD

July 22, 2015





Disclosures

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- Research Grants to Institution: AHRQ, American Heart Association, AstraZeneca, Bristol Myers Squibb, Boston Scientific Corporation
- Consultant/Honoraria: American College of Physicians, American College of Radiology
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Other co-authors

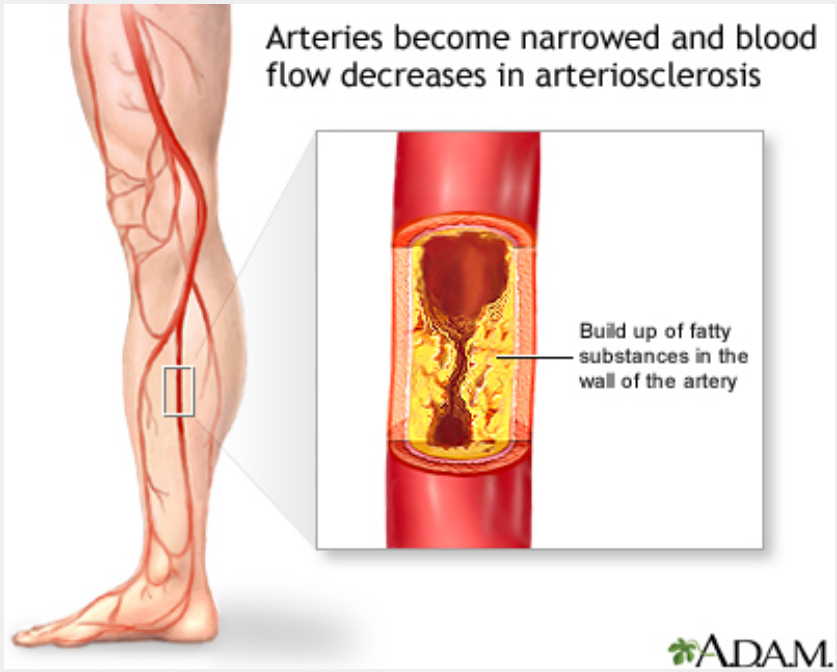
No conflicts of interest to disclose

Note:

- Key Informants (TEP, Peer reviewers) must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained.
- The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

Peripheral Artery Disease (PAD)

- Chronic narrowing or blockage of the arteries of the *lower* extremities.



Symptomatology of PAD

- Asymptomatic
- Intermittent claudication
  - Exercise-induced ischemic leg pain while walking and/or weakness, relieved by rest
  - Mortality rate from stroke and MI two to three times greater than in age-matched controls[1]
- Critical limb ischemia
  - Pain at rest, eventually resulting in gangrene and amputation[2]

[1]*Dormandy JA et al. J Cardiovasc Surg 1989;30:50–57.*
[2]*European Working Group on Critical Leg Ischemia. Circulation 1991;84(Suppl IV):IV1–IV26.*

Clinical Classifications

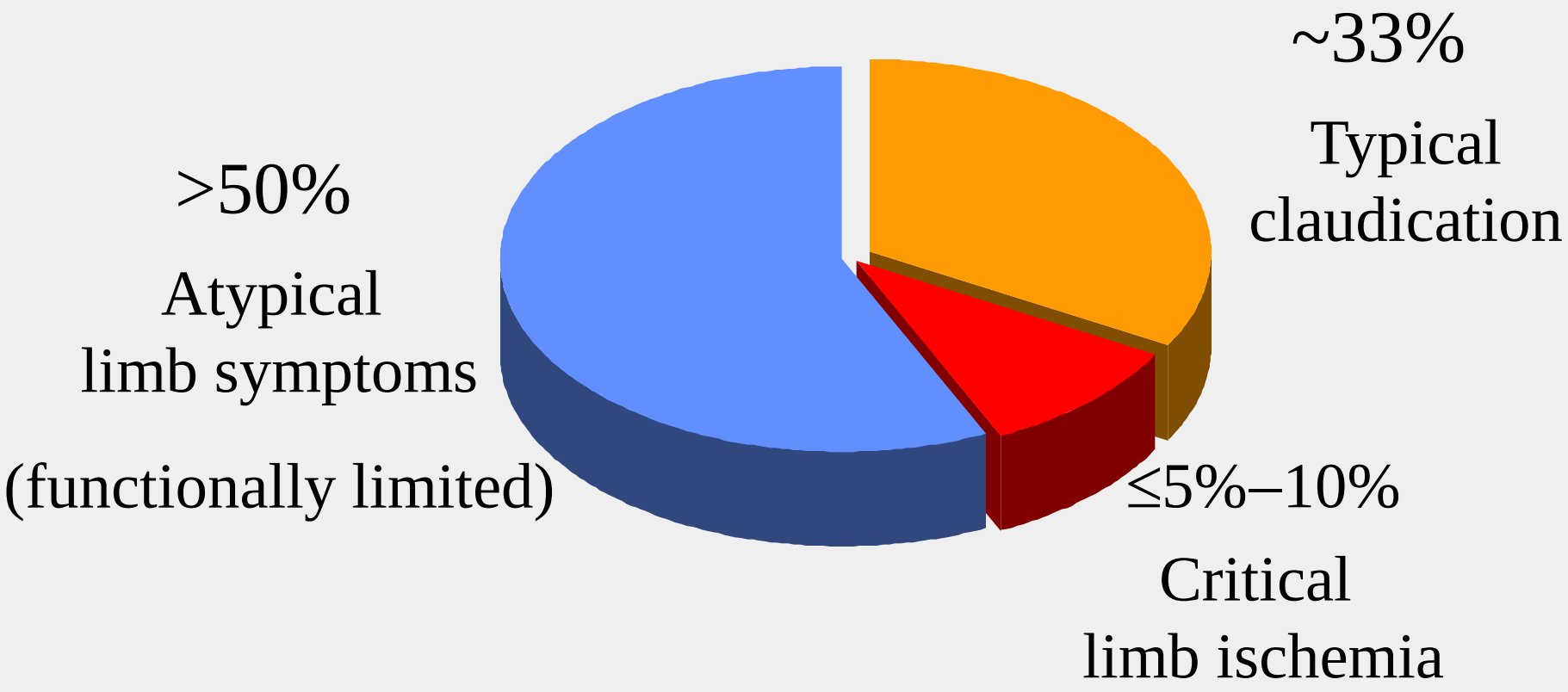
Disease Severity	Fontaine Stage	Rutherford Stage
Asymptomatic	Stage I	Stage 0
Intermittent Claudication or Atypical Limb Symptoms	Stage IIa Stage IIb	Stage 1 Stage 2 Stage 3
CLI	Stage III Stage IV	Stage 4 Stage 5 Stage 6

Table II. Society for Vascular Surgery Lower Extremity Threatened Limb (SVS WIfI) classification system

I. Wound
II. Ischemia
III. foot Infection
W I fI score
W: Wound/clinical category
SVS grades for rest pain and wounds/tissue loss (ulcers and gangrene):
0 (ischemic rest pain, ischemia grade 3; no ulcer) 1 (mild) 2 (moderate) 3 (severe)

(J Vasc Surg 2014;59:220-34.)

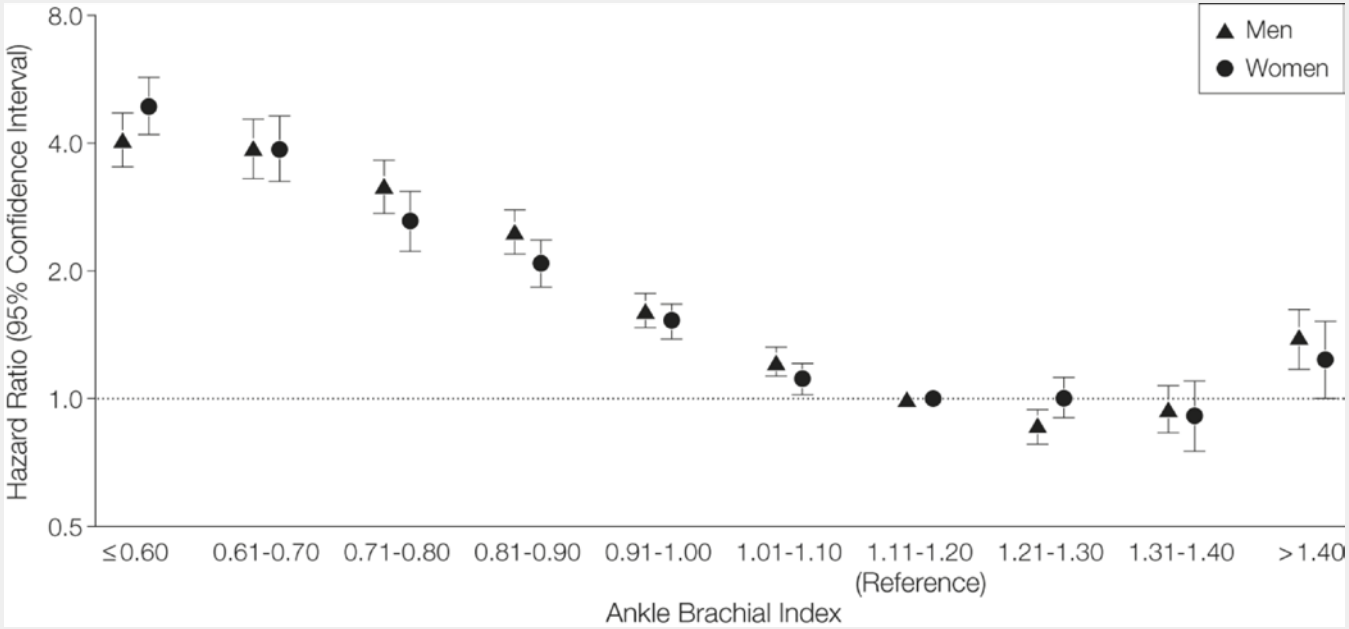
Focusing on Classic Symptoms Misses Majority of Patients



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

Using Ankle Brachial Index (ABI)

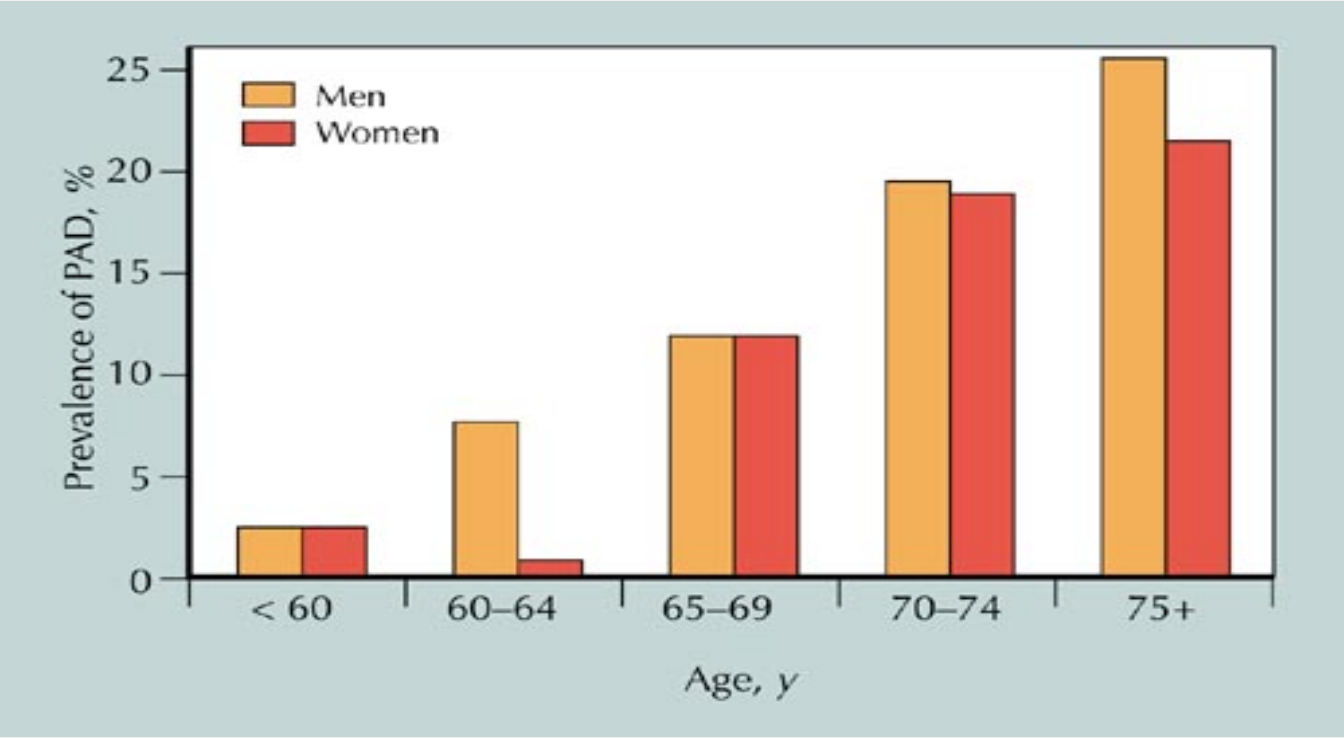
- Mild to moderate PAD = ABI of 0.41 to 0.90
- Severe PAD = ABI ≤ 0.40
- Requires further testing = ABI ≥ 1.30



Fowkes FGR et al. **Ankle Brachial Index Combined With Framingham Risk Score to Predict Cardiovascular Events and Mortality: A Meta-analysis**

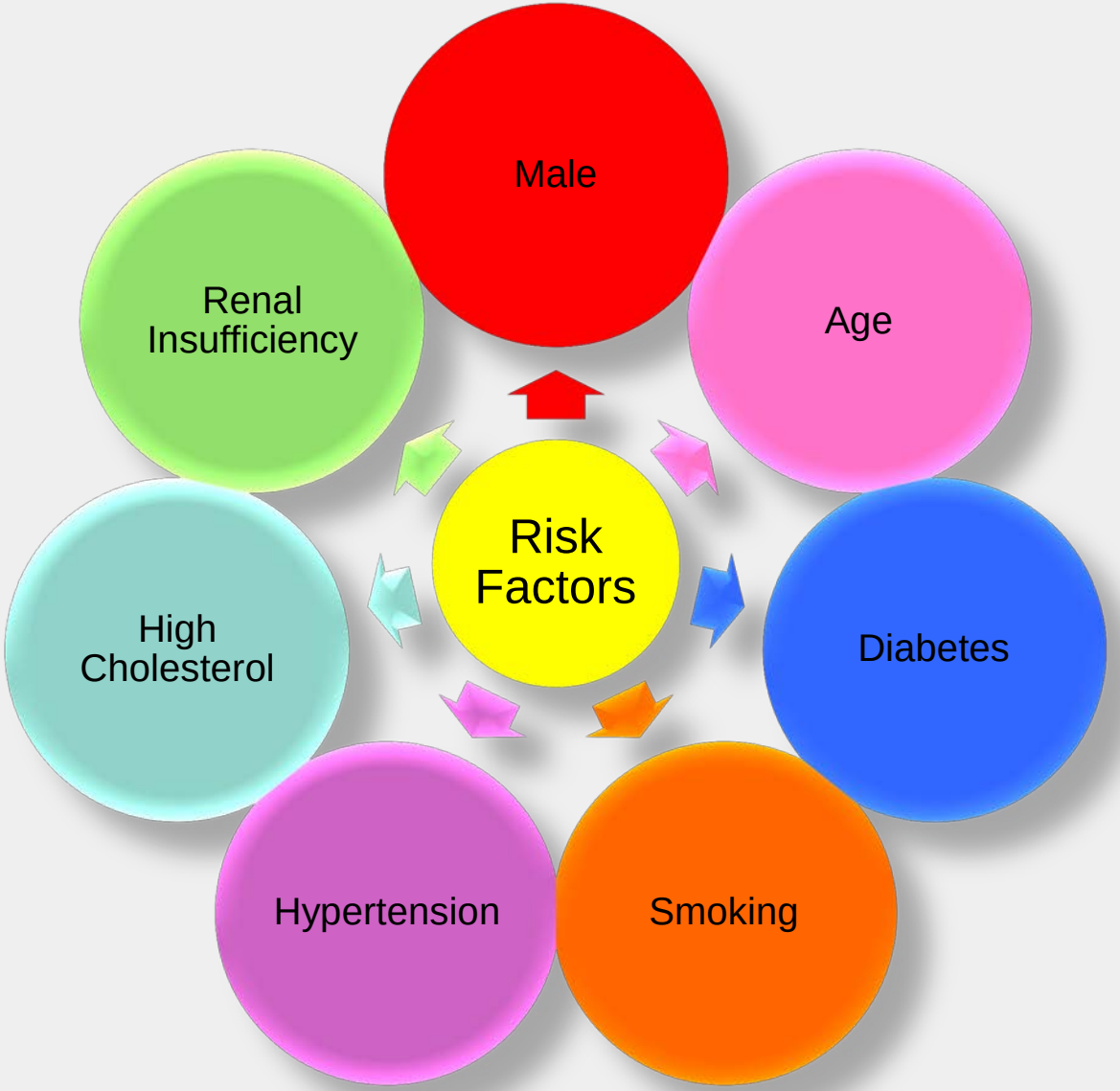
JAMA. 2008;300(2):197-208

Prevalence of PAD

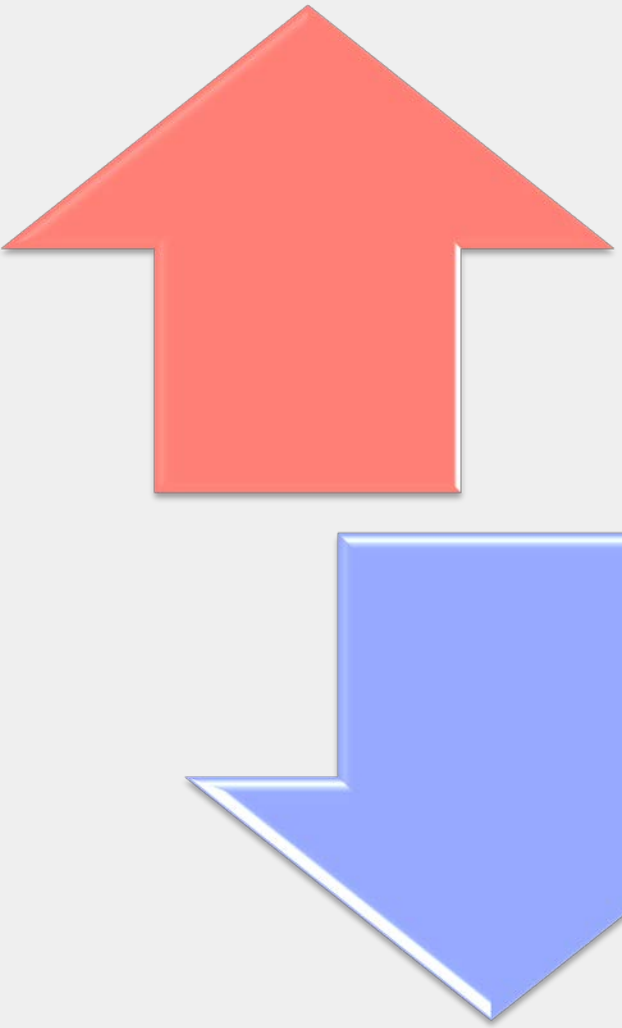


Taken from: Hirsch A. Atlas of Heart Diseases: Vascular Disease. Edited by Eugene Braunwald (series editor), Mark A. Creager. ©2002 Current Medicine, Inc.

Risk Factors for PAD



Consequences of PAD



Amputation/Tissue Loss

Myocardial infarction (MI)

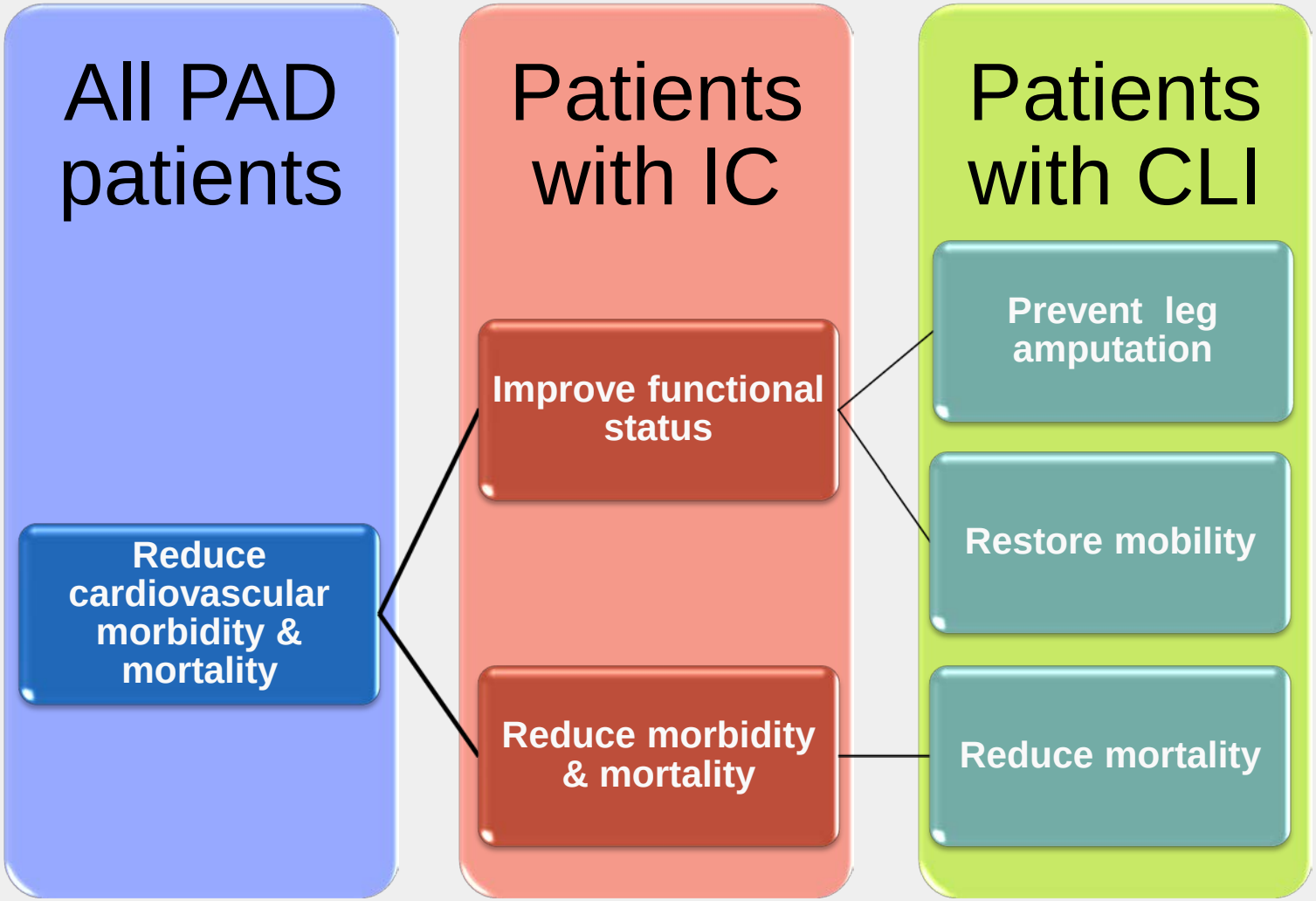
Stroke

Death

Functional capacity

Quality of Life

Goals of Therapies for PAD



Reducing Cardiovascular Morbidity & Mortality

- Prevention includes:
  - Antiplatelet agents
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Management of other risk factors:
    - Tobacco use
    - Diabetes
    - Dyslipidemia
    - Hypertension

Medical Therapy & Functional Capacity

Cilostazol

- Prevents blood clots (antiplatelet effect)
- Widens blood vessels (vasodilator effect)
- Side effects: headache and diarrhea
- Contraindicated in patients with congestive heart failure

Pentoxifylline

- Prevents blood clots (antiplatelet effect)
- Widens blood vessels (vasodilator effect)
- Side effects: nausea and diarrhea

Exercise Training & Functional Capacity

- Exercise therapy
  - Improved endothelial function
  - Reduced systemic inflammation
  - Improved mitochondrial function and skeletal muscle metabolism

Revascularization

- Goals of revascularization
  - Restore blood flow
  - Improve wound healing
  - Prevent amputation
- Revascularization depends on:
  - Patient-specific characteristics
  - Anatomic characteristics
  - Severity of symptoms
  - Need for possible repeat procedure
  - Patient and physician preference

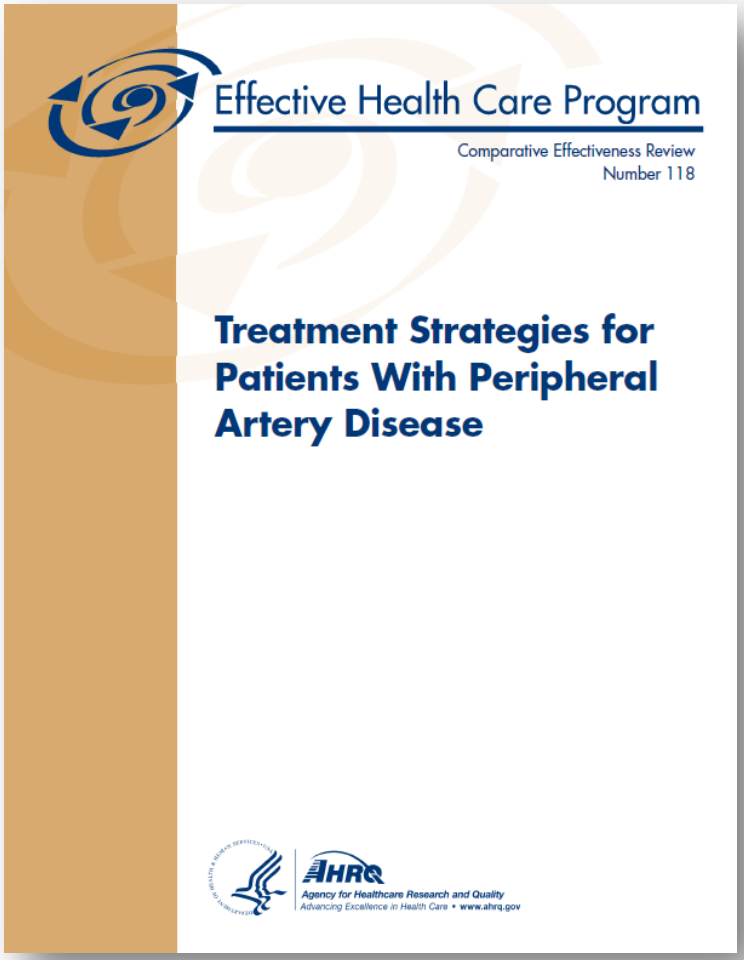
Revascularization: Strategies

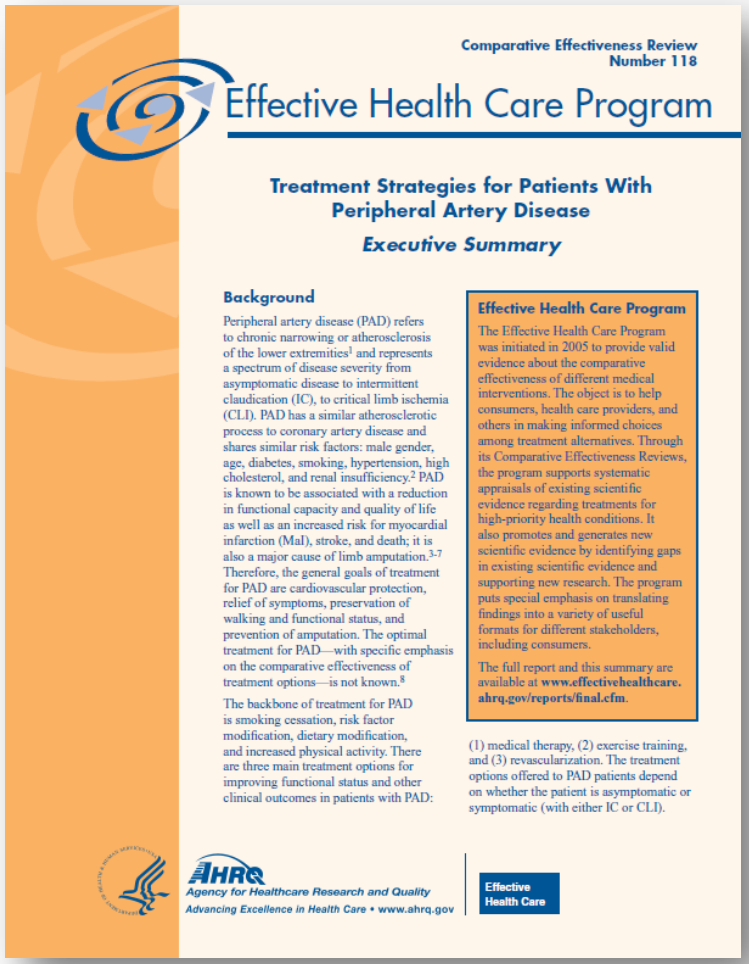
- Surgery
  - Lower extremity bypass (native vein conduit, PTFE graft), endarterectomy
- Angioplasty
  - Cryoplasty, drug-coated, cutting, and standard angioplasty balloons
- Stenting
  - Self-expanding and balloon-expandable; drug-eluting stents are now available
- Atherectomy
  - Laser, directional, orbital, and rotational atherectomy

Revascularization: Endpoints

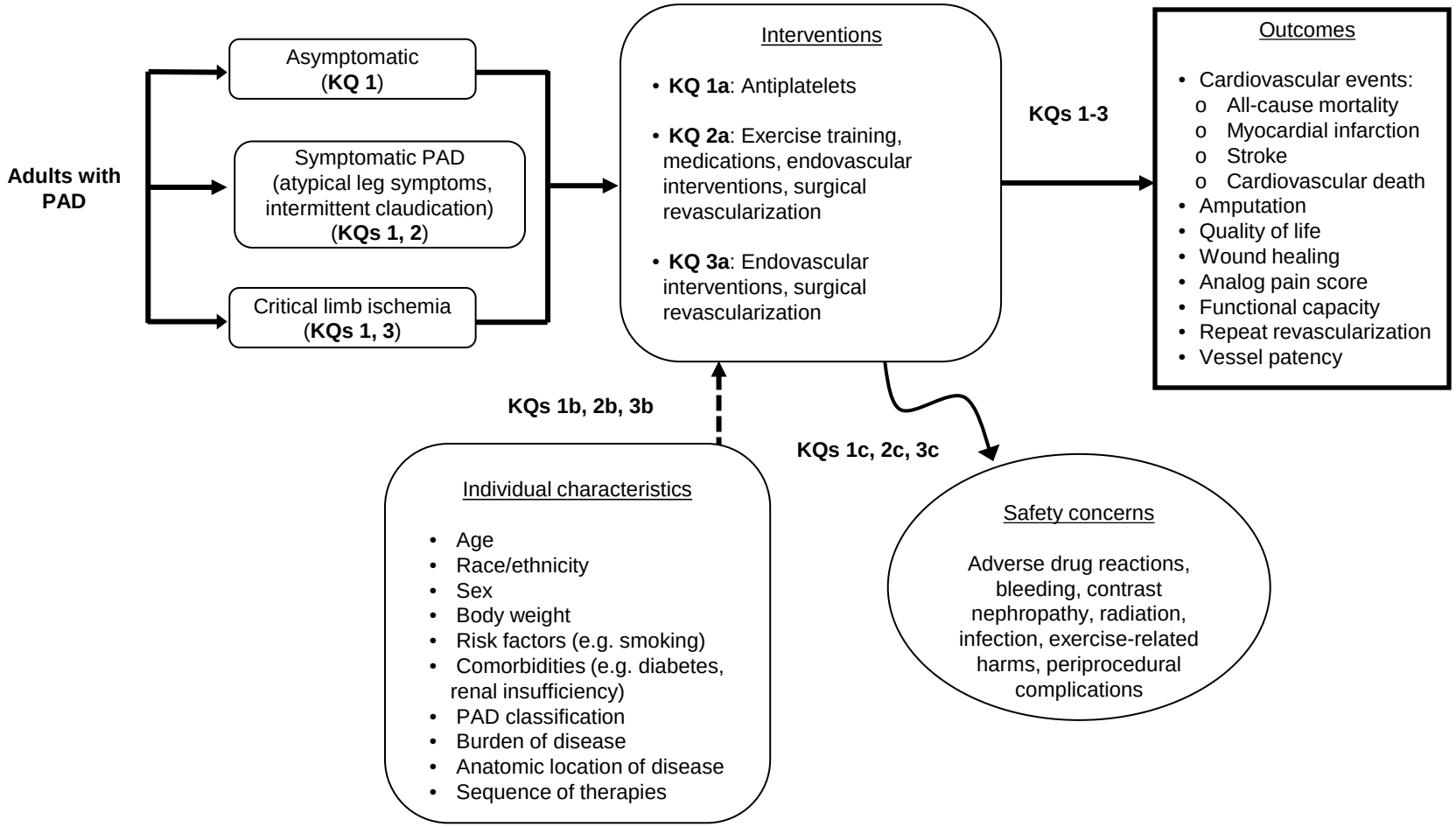
- Cardiovascular:
  - Death (all-cause and cardiovascular), MI, stroke
- Quality of Life
- Limb-specific:
  - Functional capacity
  - Major amputation, amputation-free survival, wound healing, analog pain scale
  - Target limb revascularization, target lesion revascularization, acute limb ischemia
- Surrogate-other:
  - Primary and secondary patency

AHRQ Comparative Effectiveness Review Process and Findings





Analytical Framework



Key Question 1

- In adults with peripheral artery disease (PAD), including asymptomatic patients and symptomatic patients with atypical leg symptoms, intermittent claudication (IC), or critical limb ischemia (CLI):
  a) **What is the comparative effectiveness of aspirin and other antiplatelet agents** in reducing the risk of adverse cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), functional capacity, and quality of life?
  b) **Does the effectiveness of treatments vary** according to the patient's PAD classification or by subgroup (age, sex, race, risk factors, or comorbidities)?
  c) What are the significant **safety concerns** associated with each treatment strategy (e.g., adverse drug reactions, bleeding)? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, or PAD classification)?

Key Question 2

- In adults with symptomatic PAD (atypical leg symptoms or IC):
  a) **What is the comparative effectiveness of exercise training, medications (cilostazol, pentoxifylline), endovascular intervention (percutaneous transluminal angioplasty, atherectomy, or stents), and/or surgical revascularization (endarterectomy, bypass surgery)** on outcomes including cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, quality of life , wound healing, analog pain scale score, functional capacity, repeat revascularization, and vessel patency?
  b) **Does the effectiveness of treatments vary** by use of exercise and medical therapy prior to invasive management or by subgroup (age, sex, race, risk factors, comorbidities, or anatomic location of disease)?
  c) What are the significant **safety concerns** associated with each treatment strategy (e.g., adverse drug reactions, bleeding, contrast nephropathy, radiation, infection, exercise-related harms, and periprocedural complications causing acute limb ischemia)? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, anatomic location of disease)?

Key Question 3

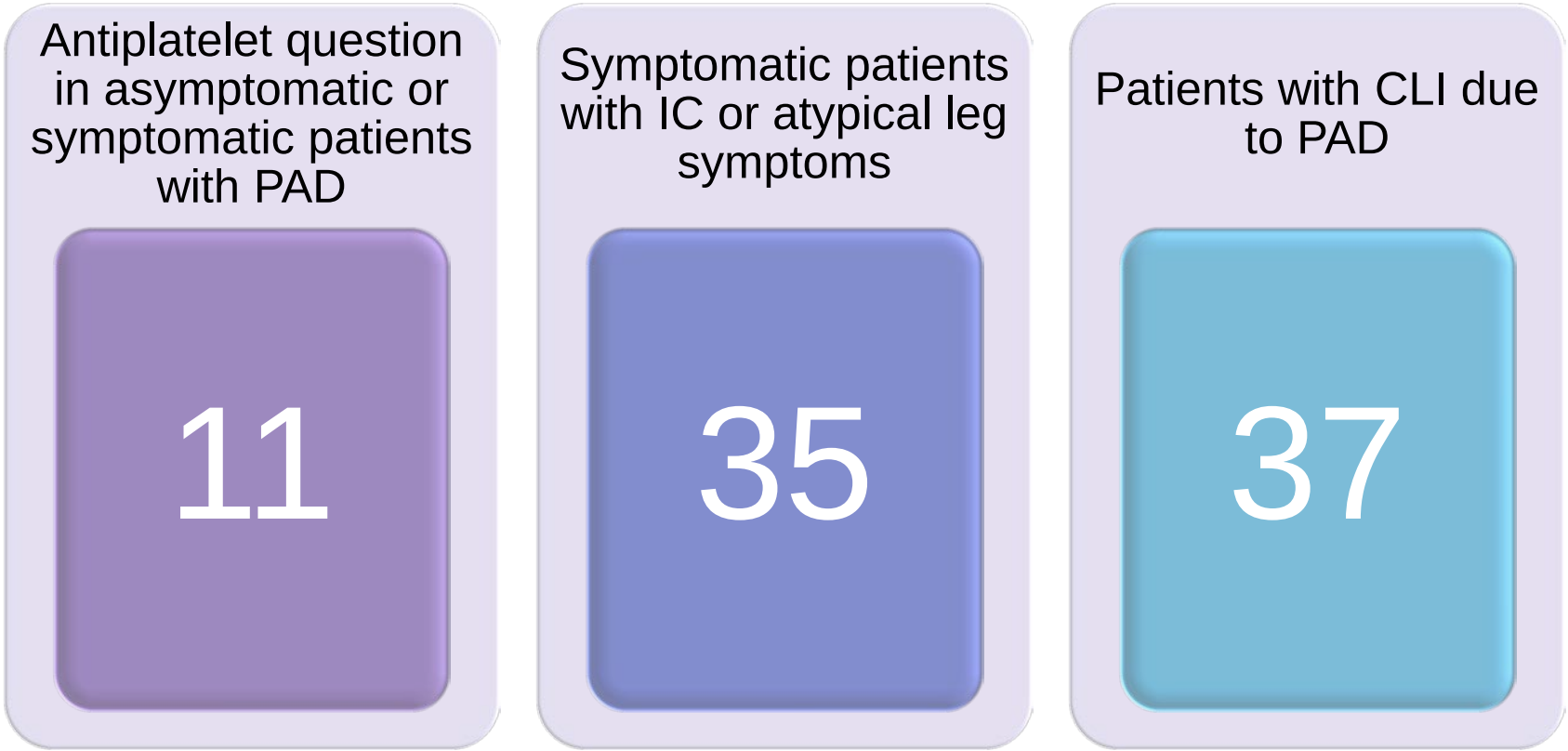
- In adults with CLI due to PAD:
  a) **What is the comparative effectiveness of endovascular intervention (percutaneous transluminal angioplasty, atherectomy, or stents) and surgical revascularization (endarterectomy, bypass surgery)** for outcomes including cardiovascular events (e.g., all-cause mortality, myocardial infarction, stroke, cardiovascular death), amputation, quality of life, wound healing, analog pain scale score, functional capacity, repeat revascularization, and vessel patency?
  b) **Does the effectiveness of treatments vary** by subgroup (age, sex, race, risk factors, comorbidities, or anatomic location of disease)?
  c) What are the significant **safety concerns** associated with each treatment strategy (e.g., adverse drug reactions, bleeding, contrast nephropathy, radiation, infection, and periprocedural complications causing acute limb ischemia)? Do the safety concerns vary by subgroup (age, sex, race, risk factors, comorbidities, or anatomic location of disease)?

Strength of the Evidence

High	• Further research is very unlikely to change the confidence in the estimate of effect.
Moderate	• Further research may change the confidence in the estimate of effect and may change the estimate.
Low	• Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient	• Evidence either is unavailable or does not permit estimation of an effect.

Studies Addressing the Key Questions

Literature Search: January 1995 – August 2012
5,908 citations identified (1,035 duplicate articles)
4,873 abstracts reviewed



Antiplatelet Therapy in Adults with PAD

Antiplatelet Therapy

1) Aspirin vs. placebo/no antiplatelet
2) Clopidogrel vs. aspirin
3) Clopidogrel + aspirin vs. aspirin

Aspirin vs. Placebo

Figure 7. Forest plot for RCTs of aspirin versus placebo: composite vascular events at 2 or more years

Study name	Population	Total N	Hazard ratio	Lower limit	Upper limit	p-Value
Belch, 2008 (POPADAD)	Asym PAD	636	0.98	0.76	1.26	0.88
Fowkes, 2010	Asym PAD	3350	1.00	0.85	1.17	1.00
Catalano, 2007 (CLIPS)	IC	181	0.35	0.15	0.82	0.02

Abbreviations: Asym=asymptomatic; CI=confidence interval; IC=intermittent claudication; PAD=peripheral artery disease.

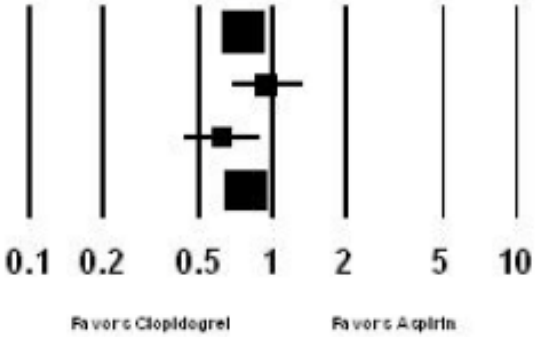
No difference: all-cause mortality, nonfatal MI, composite vascular events
Strength of Evidence: High (asymptomatic), Low (intermittent claudication)

0 studies: functional outcomes, quality of life, safety concerns among subgroups
Strength of Evidence: Insufficient

Clopidogrel vs. Aspirin

Figure 8. Clopidogrel versus aspirin for all outcomes in PAD subgroup of CAPRIE RCT

CAPRIE study outcome	Hazard ratio	Lower limit	Upper limit	p-Value
CV mortality	0.76	0.64	0.91	0.00
Nonfatal stroke	0.95	0.68	1.31	0.74
Nonfatal MI	0.62	0.43	0.88	0.01
Composite CV events	0.78	0.65	0.93	0.01



Abbreviations: CI=confidence interval; CV=cardiovascular; MI-myocardial infarction.

N=6,452

Clopidogrel more effective for reducing nonfatal MI, cardiovascular mortality, and composite vascular events.

Strength of Evidence: Moderate

0 studies: all-cause mortality, functional outcomes, quality of life, modifiers of effectiveness, general safety or among subgroups

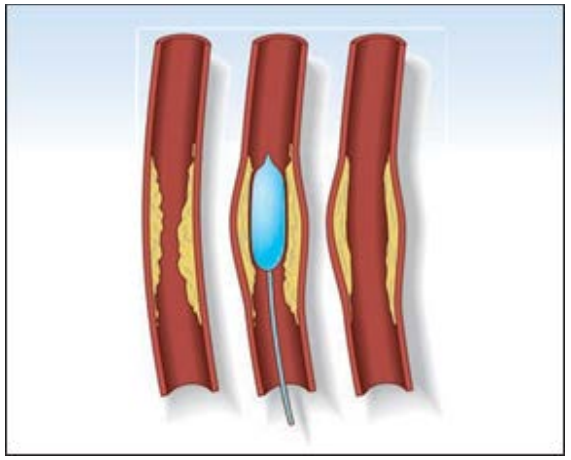
Strength of Evidence: Insufficient

Clopidogrel + Aspirin vs. Aspirin

4 total studies:

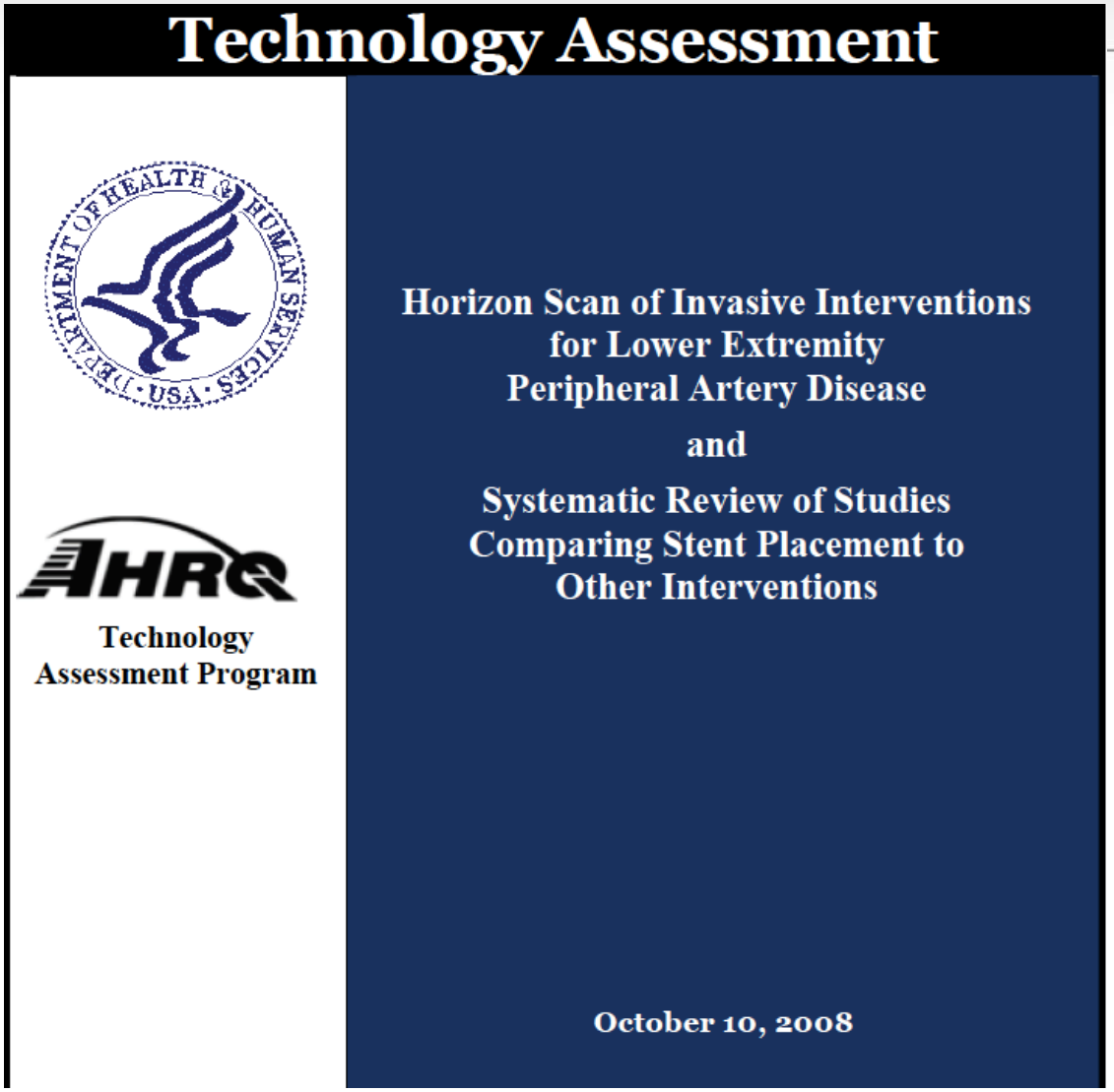
1. CHARISMA (N=3,096)—PAD subpopulation; 92% intermittent claudication
2. CASPAR (N=851)—IC/CLI mixed population undergoing bypass surgery
3. MIRROR (N=80)—IC population undergoing peripheral vascular intervention
4. Cassar et al (N=103)—safety evaluation; platelet inhibition study

1. No difference: all-cause mortality, composite cardiovascular events
    A. Strength of Evidence: Moderate
2. Dual therapy may reduce nonfatal MI
3. No difference: nonfatal stroke, cardiovascular mortality
    A. Strength of Evidence: Low
4. Minor bleeding significantly higher (34.4%) with dual therapy vs. aspirin (20.8%)
    A. Strength of Evidence: Insufficient



Exercise, Medications, and Endovascular and Surgical Revascularization for Claudication

Same Treatment Strategy Comparisons



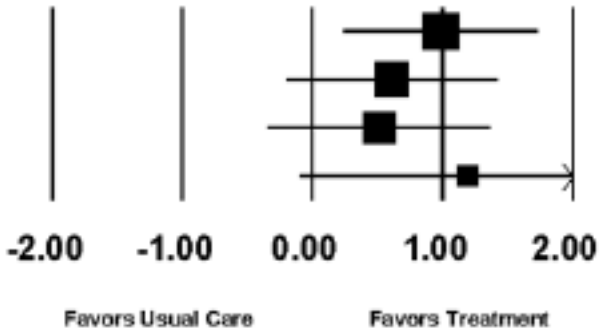
- Prior reports have investigated effectiveness and safety of endovascular and surgical revascularization technology
- Same treatment strategy comparisons were not included in the scope of Duke's CER for KQ2 (claudication) or KQ3 (critical limb ischemia)

Exercise, Medications, and Revascularization: Adults with IC

Comparison	Number of Studies	Number of patients
Cilostazol vs. placebo	10	4,103
Exercise training vs. usual care	12	754
Endovascular intervention vs. usual care	9	1,593
Surgical revascularization vs. usual care	1	427
Endovascular intervention vs. exercise training	9	1,005
Surgical revascularization vs. exercise + medical therapy	1	127
Endovascular vs. surgical revascularization	3	836

Maximal Walking Distance or Absolute Claudication Distance

Treatment	Statistics for each treatment			
	Std diff in means	Lower limit	Upper limit	p-Value
Exercise training	0.98	0.23	1.74	0.01
Cilostazol	0.61	-0.20	1.42	0.14
Endovascular intervention	0.51	-0.35	1.37	0.25
Endovascular intervention & exercise	1.20	-0.11	2.50	0.07

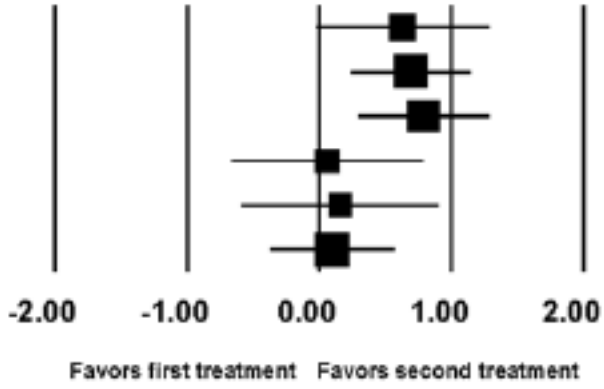


- Supervised Exercise Training and the combination of Endovascular Revascularization + Exercise Training resulted in **Large** improvements in Maximal Walking Distance (when compared with usual care). Strength of Evidence: Moderate
- Cilostazol and Endovascular Revascularization resulted in **Moderate** improvements in Maximal Walking Distance (when compared with usual care). Strength of Evidence: Low
- When network meta-analysis was performed, no individual treatment was found to have statistically significant effect when compared to the others.

Initial Claudication Distance or Pain-Free Walking Distance

Treatment comparison	Std diff in means	Lower limit	Upper limit	p-Value
Usual Care vs Cilostazol	0.631	-0.024	1.286	0.059
Usual Care vs Exercise training	0.691	0.230	1.152	0.003
Usual Care vs Endovascular intervention	0.789	0.292	1.286	0.002
Cilostazol vs Exercise training	0.059	-0.668	0.786	0.874
Cilostazol vs Endovascular intervention	0.158	-0.593	0.909	0.680
Exercise vs Endovascular intervention	0.098	-0.376	0.572	0.685

Statistics for each study

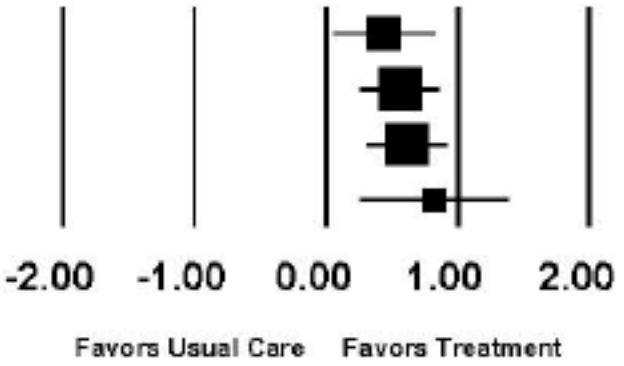


- Exercise Training and Endovascular Revascularization were found to have **moderate to large** effects on ICD/PFWD. Strength of Evidence: Low
- Cilostazol was found to have **no** statistically significant effect on ICD/PFWD. Strength of Evidence: Low
- When network meta-analysis was performed, no individual treatment was found to have statistically significant effect when compared to the others.

Quality of Life
SF-36 Physical Functioning

Figure I. Network meta-analysis of treatment effects versus usual care on quality of life in IC patients

Treatment comparison	Std diff in means	Lower limit	Upper limit	p-Value
Cilostazol	0.4400	0.0479	0.8321	0.0278
Exercise	0.5630	0.2559	0.8701	0.0003
Endovascular	0.6120	0.2989	0.9251	0.0001
Surgical	0.8230	0.2560	1.3900	0.0044

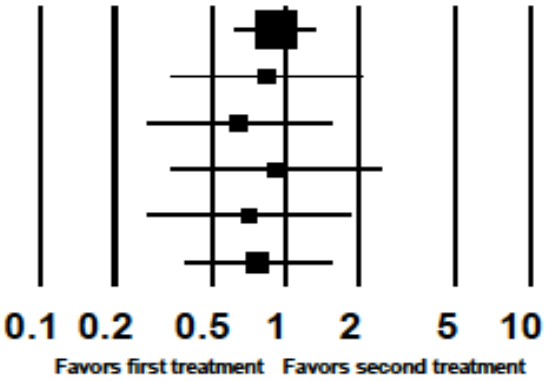


- Cilostazol, Exercise Training, Endovascular Revascularization, and Surgical Revascularization were all found to have **moderate to large** effects on QOL (when compared with usual care). Strength of Evidence: Low
- When network meta-analysis was performed, no individual treatment was found to have statistically significant effect when compared to the others.

Network Meta-analysis comparing all treatment strategies on mortality for IC

Figure 11. Network meta-analysis of treatment effects versus usual care and each other on mortality in IC patients

Treatment comparison	Odds ratio	Lower limit	Upper limit	p-Value
Cilostazol vs. Control	0.91	0.62	1.35	0.65
Exercise vs. Control	0.84	0.34	2.07	0.70
Exercise vs. Cilostazol	0.65	0.27	1.55	0.33
Endovascular vs. Control	0.91	0.34	2.45	0.86
Endovascular vs. Cilostazol	0.71	0.27	1.84	0.48
Endovascular vs. Exercise	0.77	0.39	1.54	0.47



Abbreviation: CI=confidence interval.

When compared to each other, no specific treatment was found to have a significant effect on mortality in patients with intermittent claudication.

Cilostazol, Exercise Training, and Endovascular Revascularization in Intermittent Claudication

- Inconclusive evidence: nonfatal MI, nonfatal stroke, amputation, modifiers of effectiveness, general safety

  Strength of Evidence: Insufficient

- 0 studies: composite cardiovascular events, wound healing, pain, safety (subgroups)

  Strength of Evidence: Insufficient

Supervised vs. Home Exercise

Peripheral Vascular Disease

Supervised vs unsupervised exercise for intermittent claudication: A systematic review and meta-analysis

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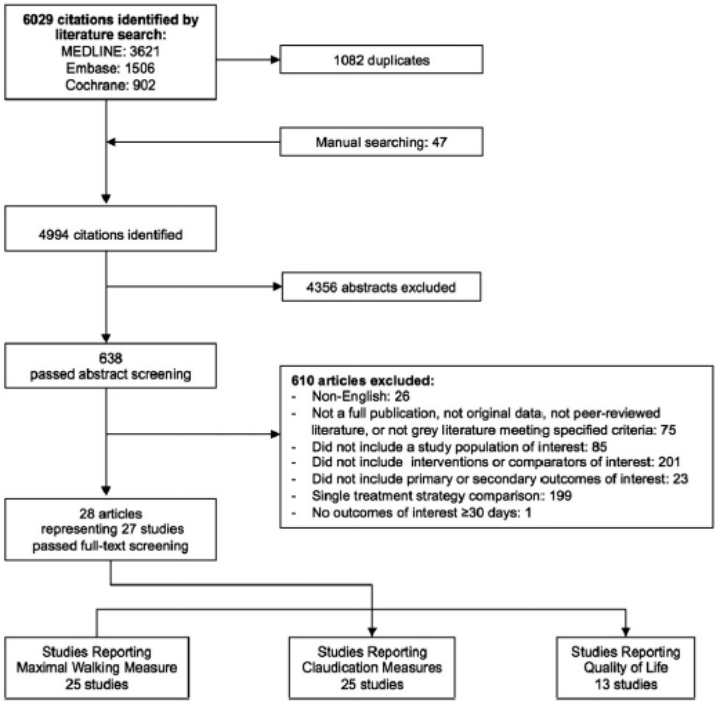
- 6,029 initial abstracts
- 4,994 abstracts screened
- 27 studies included in final report



* Not part of AHRQ original report
** No external funding

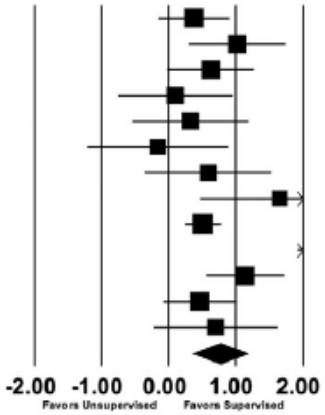
MWD and ICD

Panel A= 6 month outcome
Panel B= 12 month outcome

Maximal Walking Distance

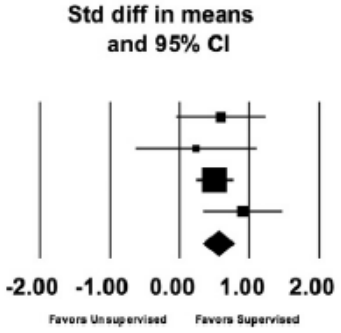
A

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Patterson, 1997	0.38	-0.16	0.91	0.17
Pinto, 1997	1.02	0.30	1.74	0.01
Tisi, 1997	0.62	-0.02	1.27	0.06
Savage, 2001	0.10	-0.76	0.96	0.82
Kakkos, 2005	0.32	-0.55	1.19	0.47
Hobbs, 2006	-0.16	-1.21	0.89	0.77
Hobbs, 2007	0.59	-0.36	1.53	0.22
Treat-Jacobson, 2009	1.66	0.46	2.85	0.01
Nicolai, 2010	0.51	0.24	0.78	<0.001
Gardner, 2012	2.39	1.93	2.86	<0.001
Murphy, 2012	1.14	0.56	1.72	<0.001
Schalger, 2012	0.47	-0.08	1.01	0.09
Parmenter, 2013	0.70	-0.23	1.63	0.14
	0.77	0.36	1.17	<0.001



B

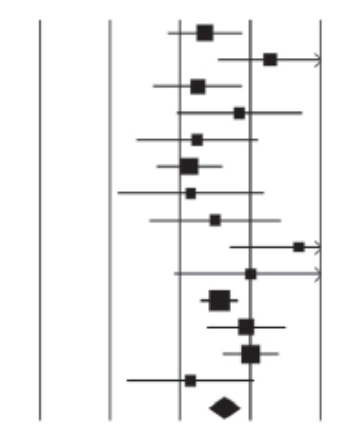
Study name	Std diff in means	Lower limit	Upper limit	p-Value
Tisi, 1997	0.59	-0.06	1.24	0.07
Kakkos, 2005	0.23	-0.63	1.10	0.60
Nicolai, 2010	0.50	0.24	0.77	<0.001
Schlager, 2012	0.91	0.34	1.47	<0.001
	0.56	0.34	0.77	<0.001



Initial Claudication Distance

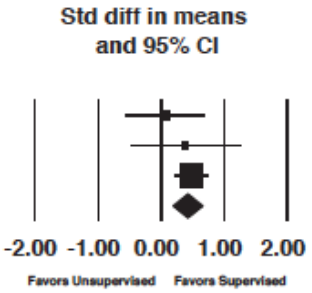
A

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Patterson, 1997	0.35	-0.18	0.89	0.19
Pinto, 1997	1.28	0.54	2.03	<0.001
Tisi, 1997	0.25	-0.39	0.88	0.44
Savage, 2001	0.85	-0.05	1.74	0.06
Kakkos, 2005	0.24	-0.62	1.11	0.58
Zwierska, 2005	0.14	-0.33	0.61	0.56
Hobbs, 2006	0.15	-0.90	1.20	0.78
Hobbs, 2007	0.50	-0.44	1.44	0.30
Stewart, 2008	1.70	0.70	2.70	<0.001
Treat-Jacobson, 2009	1.01	-0.08	2.10	0.07
Nicolai, 2010	0.56	0.29	0.83	<0.001
Murphy, 2012	0.94	0.37	1.51	<0.001
Gardner, 2012	1.01	0.61	1.40	<0.001
Parmenter, 2013	0.14	-0.76	1.05	0.76
	0.63	0.40	0.85	<0.001



B

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Tisi, 1997	0.06	-0.57	0.70	0.84
Kakkos, 2005	0.38	-0.49	1.26	0.39
Nicolai, 2010	0.48	0.21	0.75	<0.001
	0.41	0.18	0.65	0.001



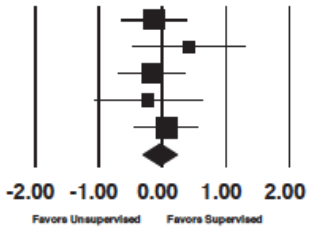
SE is more effective at improving MWD and ICD than HE

Quality of Life

General QOL (SF-36)

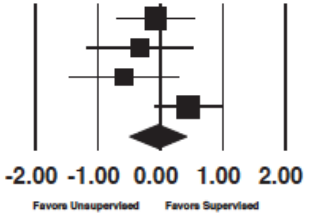
A

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Patterson, 1997	-0.13	-0.66	0.40	0.63
Regensteiner, 1997	0.41	-0.47	1.30	0.36
Pinto, 1997	-0.16	-0.69	0.37	0.55
Savage, 2001	-0.22	-1.08	0.64	0.61
Gardner, 2011	0.06	-0.43	0.56	0.80
	-0.04	-0.31	0.23	0.77



B

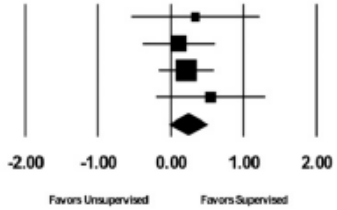
Study name	Std diff in means	Lower limit	Upper limit	p-Value
Pinto, 1997	-0.08	-0.71	0.56	0.81
Savage, 2001	-0.33	-1.19	0.53	0.45
Kakkos, 2005	-0.58	-1.47	0.30	0.19
Murphy, 2012	0.45	-0.10	1.00	0.11
	-0.05	-0.50	0.41	0.84



Walking Impairment Questionnaire

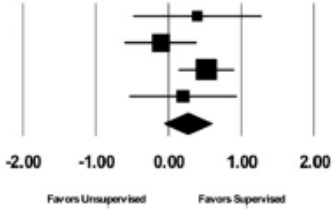
A

Study name	Std diff in means	Standard error	Lower limit	Upper limit	p-Value
Regensteiner, 1997	0.34	0.45	-0.54	1.22	0.45
Gardner, 2011	0.11	0.25	-0.38	0.61	0.66
Gardner, 2012	0.21	0.19	-0.17	0.59	0.27
Guidon, 2013	0.55	0.38	-0.20	1.30	0.15
	0.24	0.14	-0.03	0.50	0.08



B

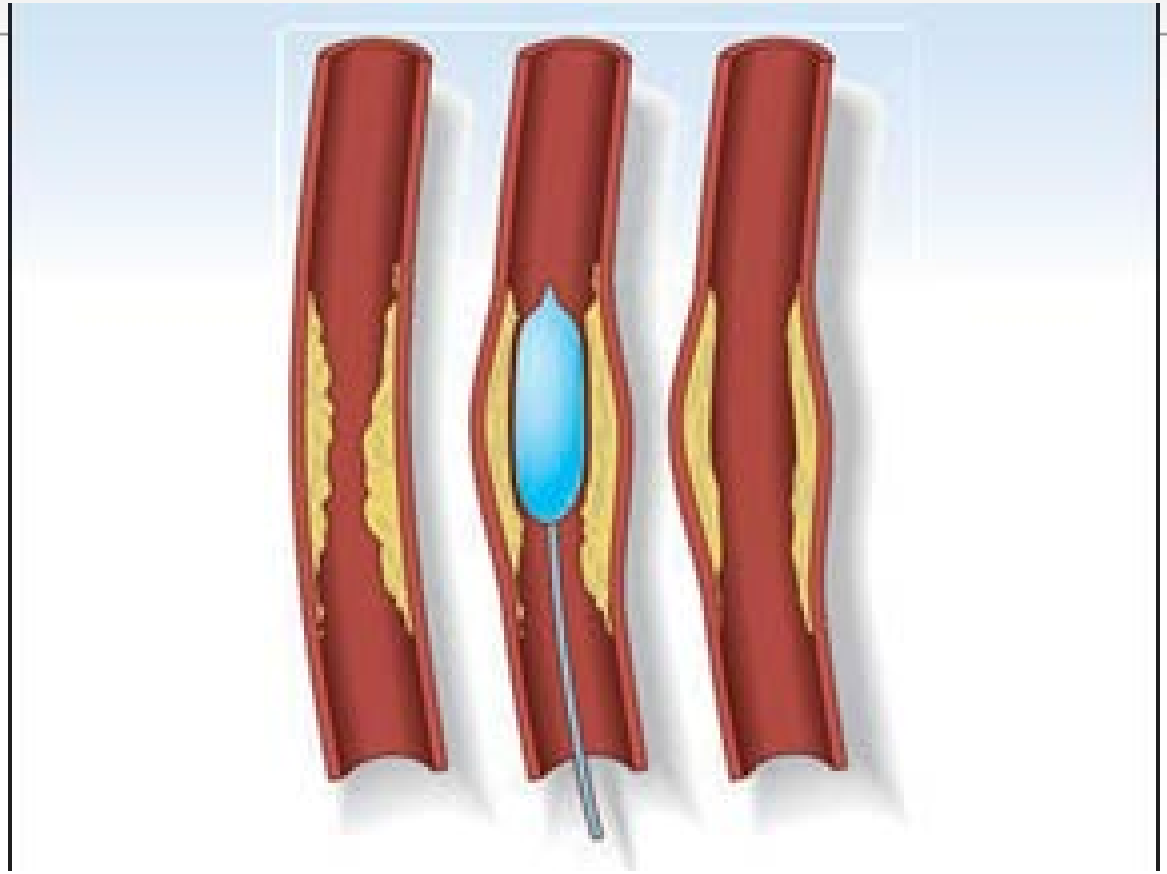
Study name	Std diff in means	Standard error	Lower limit	Upper limit	p-Value
Regensteiner, 1997	0.40	0.45	-0.49	1.28	0.38
Gardner, 2011	-0.11	0.25	-0.60	0.39	0.67
Gardner, 2012	0.52	0.20	0.14	0.90	0.01
Guidon, 2013	0.20	0.38	-0.54	0.94	0.60
	0.26	0.17	-0.06	0.59	0.11



Panel A = 3 month outcome

Panel B = 6 month outcome

No difference in QOL between SE and HE



Endovascular and Surgical Revascularization in Adults with CLI due to PAD

Endovascular and Surgical Revascularization for CLI

Endovascular vs. Usual Care

- Population: CLI only or IC-CLI mixed
- 4 Studies

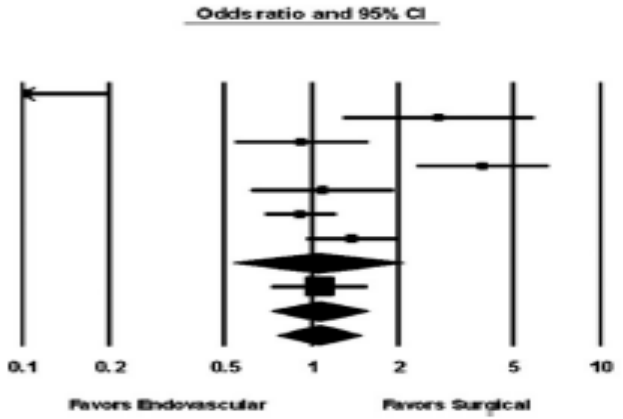
Endovascular vs. Surgical

- Population: CLI only
- 23 studies
- 12, 779 patients

Endovascular vs. Surgical Revascularization: CLI

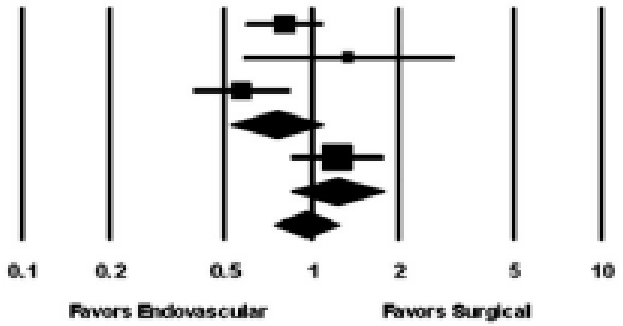
All-Cause Mortality at 2-3 years

Group by Population	Study name	Statistics for each study				Death / Total	
		Odds ratio	Lower limit	Upper limit	p-Value	Endovascular	Surgical
CLI - Obs	Wolfe, 2000	0.10	0.05	0.20	0.00	21 / 84	95 / 125
CLI - Obs	Taylor, 2006	2.75	1.28	5.89	0.01	33 / 65	15 / 57
CLI - Obs	Kudo, 2006	0.92	0.54	1.57	0.77	80 / 153	45 / 84
CLI - Obs	Ah Chong, 2009	3.92	2.32	6.61	0.00	79 / 100	178 / 364
CLI - Obs	Sultan, 2009	1.10	0.62	1.93	0.75	41 / 190	24 / 119
CLI - Obs	Soderstrom, 2010	0.91	0.69	1.21	0.54	143 / 262	431 / 761
CLI - Obs	Korhonen, 2011	1.37	0.96	1.97	0.08	122 / 241	103 / 241
CLI - Obs		1.05	0.54	2.06	0.88		
CLI - RCT	Adam, 2005 (BASIL)	1.07	0.73	1.56	0.74	84 / 224	82 / 228
CLI - RCT		1.07	0.73	1.56	0.74		
Overall		1.06	0.76	1.48	0.72		



Amputation-Free Survival at 2-3 years

Group by Population	Study name	Statistics for each study				Amputation / Total	
		Odds ratio	Lower limit	Upper limit	p-Value	Endovascular	Surgical
CLI - Obs	Soderstrom, 2010	0.80	0.59	1.09	0.16	114 / 262	212 / 431
CLI - Obs	Varela, 2011	1.34	0.58	3.11	0.50	26 / 42	27 / 49
CLI - Obs	Korhonen, 2011	0.57	0.39	0.84	0.00	145 / 241	175 / 241
CLI - Obs		0.76	0.53	1.09	0.13		
CLI - RCT	Adam, 2005 (BASIL)	1.22	0.84	1.77	0.29	128 / 224	119 / 228
CLI - RCT		1.22	0.84	1.77	0.29		
Overall		0.96	0.74	1.24	0.73		



Endovascular vs. Surgical Revascularization: CLI

- At 1 year, no difference in primary patency

  Strength of Evidence: Moderate
- Endovascular revasc may reduce all-cause mortality (≤ 6 mos), improve secondary patency at > 1 yr
- No difference: all-cause mortality (> 1 yr); amputation (all timepoints); amputation-free survival (>1 yr) Strength of Evidence: Low
- Inconclusive evidence: nonfatal MI, wound healing, primary patency (> 2 yrs), length of stay, modifiers of effectiveness

Published Data since AHRQ Review

- Updated literature search dates:
  - August 2012 – March 2015
- 1700+ citations included after literature search for abstract review
- 61 abstracts were included for full text review
- 25 individual, full-text articles were available for qualitative review

KQ1 – Antiplatelet question
Published Data since AHRQ Review

7 total studies
Only 4 are good quality studies

Author	Population	Type of study	Comparison	N	Results
Antiplatelet Studies					
Bonaca et al, 2013 TRA2°P-TIMI 50	Claudication, abnormal ABI, or prior revascularization	RCT	Vorapaxar vs. placebo	3,787	No difference in CV death, MI, stroke Reduction in limb events
Patel et al, 2014 PLATO	Subgroup analysis of PAD patients with ACS	RCT	Ticagrelor vs. clopidogrel in addition to aspirin	1,144	Consistent results in PAD subgroup when compared with overall trial
Shigematsu et al, 2012 COOPER	History of claudication & abnormal ABI, or prior revascularization	RCT	Clopidogrel vs. ticlopidine	431	Clopidogrel >> ticlopidine for cumulative incidence of safety endpoints
Strobl et al, 2013	Symptomatic patients undergoing PVI	RCT	ASA + Clopidogrel vs. ASA + Placebo	80	Improved TLR rates at 6 months; no improvement at 12 months

Published Data since AHRQ Review

KQ2 (intermittent claudication): 13 studies; 1 good quality study

Author	Population	Comparison	N	Results
Intermittent Claudication				
Murphy et al, 2014 CLEVER 18 month results	Intermittent claudication in patients with aorto-iliac stenosis	Endovascular revasc vs. supervised exercise training vs. optimal medical therapy	79	PWT improved with ER and SET vs OMT QOL improved with ER and SET vs OMT

KQ3 (critical limb ischemia): 8 studies; 0 good quality studies

Author	Population	Comparison	N	Results
Critical Limb Ischemia				

*3 included studies had mixed IC/CLI population

Limited impact of updated evidence for KQ2 and KQ3 results

Conclusions for KQ1

Aspirin vs. placebo

- No benefit for preventing vascular events in asymptomatic PAD (SOE: High)
- Aspirin favored for reducing nonfatal MI and combined vascular events in IC patients (SOE: Low)

Clopidogrel monotherapy vs. aspirin monotherapy

- Clopidogrel favored for reducing adverse cardiovascular outcomes in PAD subgroups (SOE: Moderate)

Dual antiplatelet therapy vs. aspirin monotherapy

- No difference in reducing stroke or cardiovascular mortality in PAD subgroup, IC or CLI patients (SOE: Moderate)
- Dual therapy favored for reducing nonfatal MI (SOE: Moderate)

Conclusions for KQ2 and KQ3

Exercise or Endovascular Revasc vs. usual care (intermittent claudication)

- Favors exercise training for improving walking distance (Large effect; SOE=Moderate)
- Favors endovascular revasc for improving walking distance (Moderate effect; SOE=Low)

Supervised exercise vs. Home exercise (intermittent claudication)

- Favors endovascular intervention for functional improvement but not quality of life (Moderate effect; SOE=High)

Endovascular + exercise vs. exercise or endovascular intervention alone (intermittent claudication)

- Endovascular intervention + exercise improved both maximal walking distance (Large effect; SOE=Moderate) and initial claudication distance (Moderate effect; SOE=Low)

Conclusions for KQ3

Endovascular revascularization vs. surgical revascularization (critical limb ischemia)

- Limited evidence for the effectiveness of surgical vs. endovascular revascularization
- No difference in all-cause death (> 1yr), amputation (all time points), and amputation-free survival (>1 yr); SOE: Low

Limitations of the Evidence-base

- Few published large-scale RCTs comparing antiplatelets in PAD
- Few direct comparisons of treatment strategies in patients with IC.
- Same-treatment strategy comparisons studied previously and excluded from Duke's CER.
- No studies comparing a majority of treatment strategies in patients with atypical leg pain.
- Unable to stratify analysis by disease severity, risk, or symptoms.

Challenges in Evaluating the Existing Literature in PAD patients

- Population differences
- Endpoint differences
- Length of follow-up
- Evolution of revascularization
- Crossover between surgical and endovascular therapies

Recent Data

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Peripheral Vascular Disease

Temporal Trends and Geographic Variation of Lower-Extremity Amputation in Patients With Peripheral Artery Disease

Results From U.S. Medicare 2000–2008

W. Schuyler Jones, MD,*† Manesh R. Patel, MD,*† David Dai, PHD,*
Sumeet Subherwal, MD, MBA,*† Judith Stafford, MS,* Sarah Calhoun, BS,*
Eric D. Peterson, MD, MPH*†
Durham, North Carolina

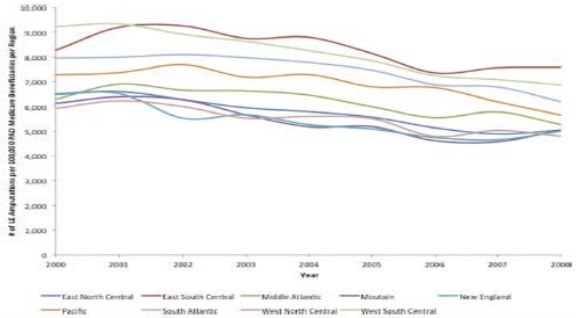

Figure 2 Temporal Trends in Lower-Extremity Amputation by U.S. Census Bureau

Graph showing the temporal patterns of performance of LE amputation by U.S. Census Bureau. LE = lower extremity.

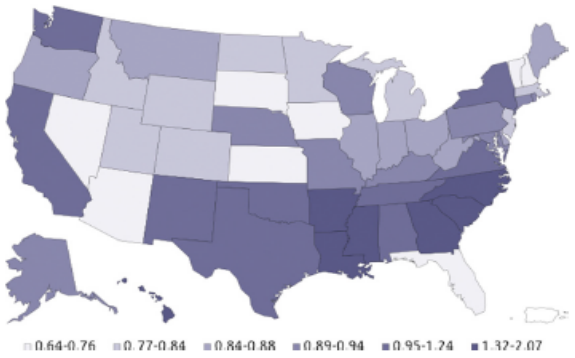

Figure 1 Geographic Variation in Use of Lower-Extremity Amputation

Geospatial map showing the ratio of rates of LE amputation per state compared with the national average. LE = lower extremity.

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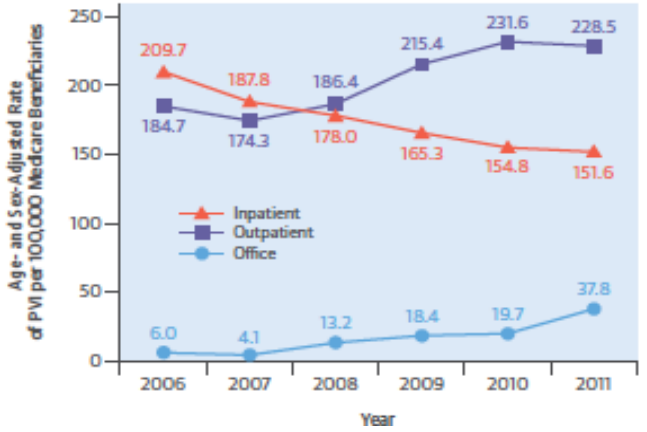
Trends in Settings for Peripheral Vascular Intervention and the Effect of Changes in the Outpatient Prospective Payment System

W. Schuyler Jones, MD,*† Xiaojuan Mi, PHD,* Laura G. Qualls, MS,* Sreekanth Vemulapalli, MD,*†
Eric D. Peterson, MD, MPH,*† Manesh R. Patel, MD,*† Lesley H. Curtis, PHD*†

CENTRAL ILLUSTRATION Trends in PVI Among Medicare Beneficiaries



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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Evaluation and Treatment of Patients With Lower Extremity Peripheral Artery Disease

Consensus Definitions From Peripheral Academic Research Consortium (PARC)

Manesh R. Patel, MD,* Michael S. Conte, MD,† Donald E. Cutlip, MD,‡§ Nabil Dib, MD,‖ Patrick Geraghty, MD,¶ William Gray, MD,#** William R. Hiatt, MD,†† Mami Ho, MD, PhD,‡‡ Koji Ikeda, PhD,§§ Fumiaki Ikeno, MD,‖‖ Michael R. Jaff, DO,¶¶ W. Schuyler Jones, MD,* Masayuki Kawahara, MD,‡‡ Robert A. Lookstein, MD,## Roxana Mehran, MD,# ## Sanjay Misra, MD,*** Lars Norgren, MD,††† Jeffrey W. Olin, MD,## Thomas J. Povsic, MD, PhD,* Kenneth Rosenfield, MD,‡‡‡ John Rundback, MD,§§§ Fadi Shamoun, MD,‖‖‖ James Tcheng, MD,* Thomas T. Tsai, MD,¶¶¶ Yuka Suzuki, PhD,### Pascal Vranckx, MD,**** Bret N. Wiechmann, MD,†††† Christopher J. White, MD,‡‡‡ Hiroyoshi Yokoi, MD,§§§ Mitchell W. Krucoff, MD*

ABSTRACT

The lack of consistent definitions and nomenclature across clinical trials of novel devices, drugs, or biologics poses a significant barrier to accrual of knowledge in and across peripheral artery disease therapies and technologies. Recognizing this problem, the Peripheral Academic Research Consortium, together with the U.S. Food and Drug Administration and the Japanese Pharmaceuticals and Medical Devices Agency, has developed a series of pragmatic consensus definitions for patients being treated for peripheral artery disease affecting the lower extremities. These consensus definitions include the clinical presentation, anatomic depiction, interventional outcomes, surrogate imaging and physiological follow-up, and clinical outcomes of patients with lower-extremity peripheral artery disease. Consistent application of these definitions in clinical trials evaluating novel revascularization technologies should result in more efficient regulatory evaluation and best practice guidelines to inform clinical decisions in patients with lower extremity peripheral artery disease. (J Am Coll Cardiol 2015;65:931–41) © 2015 by the American College of Cardiology Foundation.

UPCOMING/ONGOING STUDIES

Original Article

Clinical Trials in Peripheral Vascular Disease

Pipeline and Trial Designs: An Evaluation of the ClinicalTrials.gov Database

Sumeet Subherwal, MD, MBA; Manesh R. Patel, MD; Karen Chiswell, PhD; Beth A. Tidemann-Miller, MS; W. Schuyler Jones, MD; Michael S. Conte, MD; Christopher J. White, MD; Deepak L. Bhatt, MD, MPH; John R. Laird, MD; William R. Hiatt, MD; Asba Tasneem, PhD; Robert M. Califf, MD

Conclusions—PVD studies represent a small group of trials registered in ClinicalTrials.gov, despite the high prevalence of vascular disease in the general population. This low number, compounded by the decreasing number of PVD trials in the United States, is concerning and may limit the ability to inform current clinical practice of patients with PVD. (***Circulation*. 2014;130:00-00.**)

****Updated Search Results:**
Only 2 between-treatment comparison studies planning to enroll > 500 patients

EUCLID (Examining Use of Ticagrelor in PAD)

- Double-blind randomized controlled comparison of ticagrelor vs. clopidogrel in symptomatic PAD (ABI < 0.80 or prior revascularization)
- Primary endpoint: CV death, MI, ischemic stroke
- ClinicalTrials.gov Identifier: NCT01732822

Estimated Enrollment:	13500
Study Start Date:	August 2012
Estimated Study Completion Date:	July 2016
Estimated Primary Completion Date:	July 2016 (Final data collection date for primary outcome measure)

BEST-CLI (Best Endovascular vs. Best Surgical Therapy in Patients With Critical Limb Ischemia)

- Open label, randomized controlled trial of endovascular and surgical revasc in patients with CLI
- Primary endpoint: Time to major adverse limb event or death
- ClinicalTrials.gov Identifier: NCT02060630

Estimated Enrollment:	2100
Study Start Date:	August 2014
Estimated Study Completion Date:	December 2018
Estimated Primary Completion Date:	December 2018 (Final data collection date for primary outcome measure)