

Peripheral Artery Disease MEDCAC Panel

July 22, 2015

Michael R. Jaff, DO

President

VIVA Physicians



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ADVANCES

Michael R. Jaff, D.O.

Conflicts of Interest

Consultant

- Abbott Vascular (non-compensated)
- Boston Scientific (non-compensated)
- Cardinal Health
- Cordis Corporation (non-compensated)
- Covidien (non-compensated)
- Janacare, Inc
- Medtronic (non-compensated)
- Micell, Inc
- Novella (DSMB)
- Primacea

Equity

- Access Closure, Inc
- I.C.Sciences, Inc
- Janacare, Inc
- MC10
- Northwind Medical, Inc.
- PQ Bypass, Inc
- Primacea
- Sano V, Inc.
- Vascular Therapies, Inc

Board Member

- VIVA Physicians (Not For Profit
501(c) 3 Organization)
 - www.vivapvd.com
- Intersocietal Accreditation Commission
- CBSET

VIVA Physicians

www.vivaphysicians.org

- 501 (c) 3 not-for-profit education and research organization
- Board of 15 physician members
 - Interventional Cardiology
 - Vascular Surgery
 - Vascular Radiology
 - Vascular Medicine
- I am representing VIVA as the President of the Board
- All officers and board members receive stipends for their service to the organization based on documentation of specific hours worked.

Founder and Medical Director VasCore, the Vascular Ultrasound Core Laboratory

- VasCore has participated in over 170 clinical trials in 66 countries
 - Many PAD trials which will be discussed today
- VasCore is owned by the Massachusetts General Physicians Organization
- All agreements for services provided are between the sponsor and the MGPO
- My salary is not tied in any way to the number of trials or performance of VasCore

Voting Questions

For each voting question, please use the following scale identifying your level of confidence - with a score of 1 being low or no confidence and 5 representing high confidence.

1 — 2 — 3 — 4 — 5
Low Intermediate High
Confidence Confidence

1. For adults with asymptomatic lower extremity PAD, how confident are you that there is sufficient evidence for an intervention that improves:

- a. Immediate/near-term health outcomes?
- b. Long-term health outcomes?

Discussion:

- o If intermediate confidence (≥ 2.5), please identify the specific intervention(s) and associated outcome(s).
- o Considering the heterogeneity of the Medicare population, discuss which subgroups of the Medicare population the evidence shows are likely to benefit or likely not to benefit from intervention.

2. For adults with lower extremity **intermittent claudication (IC)**, how confident are you that there is sufficient evidence for an intervention that improves:

- a. Immediate/near-term health outcomes?
- b. Long-term health outcomes?

Discussion:

- o If intermediate confidence (≥ 2.5), please identify the specific intervention(s) and associated outcome(s).
- o Considering the heterogeneity of the Medicare population, discuss which subgroups of the Medicare population the evidence shows are likely to benefit or likely not to benefit from intervention.

3. For adults with lower extremity critical limb ischemia (CLI), how confident are you that there is sufficient evidence for an intervention that improves:

- a. Immediate/near-term health outcomes?
- b. Long-term health outcomes?

Discussion:

- o If intermediate confidence (≥ 2.5), please identify the specific intervention(s) and associated outcome(s).
- o Considering the heterogeneity of the Medicare population, discuss which subgroups of the Medicare population the evidence shows are likely to benefit or likely not to benefit from intervention.

Additional Discussion Topics

4. Discuss the important evidence gaps that have not been previously or sufficiently addressed.

5. Discuss any apparent lower extremity PAD treatment disparities and how they may affect the health outcomes of Medicare beneficiaries.



Intermittent Claudication

Major Impact on Patients

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graph TD; A[Major Impact on Patients] --> B[Functional Limitations]; A --> C[Longevity]
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Functional Limitations

Longevity



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Longevity

- Every study looking at the natural history of patients with PAD suggests that the survival of patients with intermittent claudication is ~75% at 5 years
- Mortality due to atherosclerosis in the coronary, cerebrovascular, aortic beds

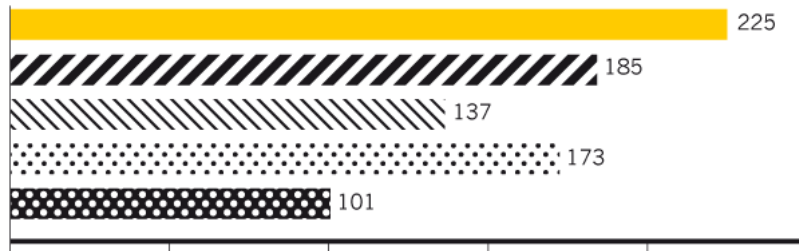


Vascular Disease as the Cause of Death is a BIG Deal. Anywhere.

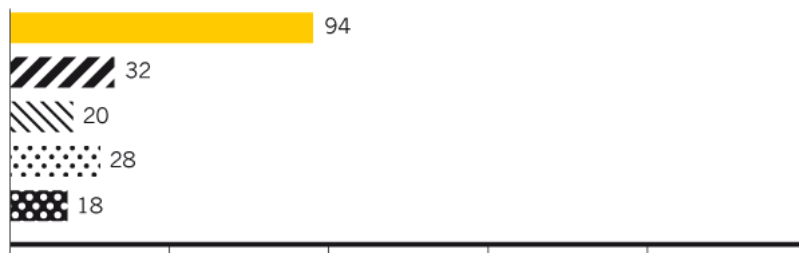
TOP CAUSES OF DEATH

The MDS determined that the four most significant causes of death for Indians aged 30–69 are vascular disease, chronic respiratory disease, tuberculosis and cancer. Some of these burdens look very different in other regions of the world.

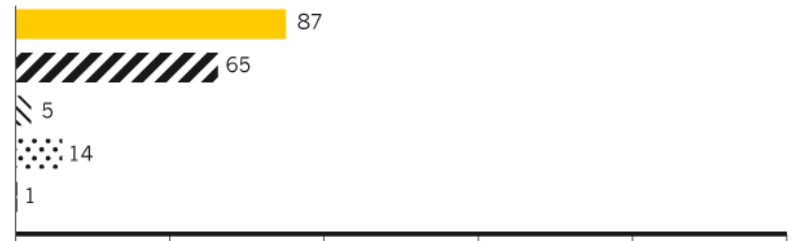
ALL VASCULAR



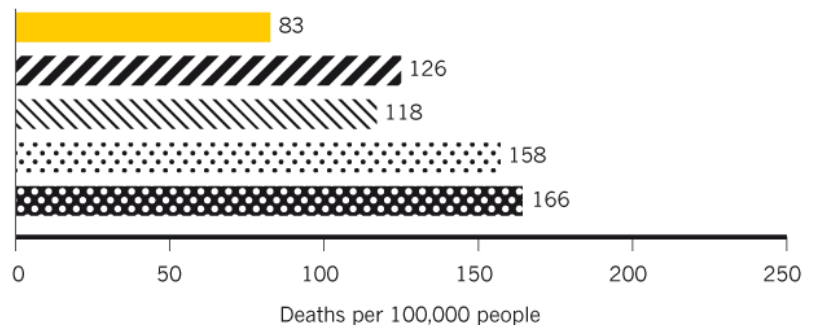
CHRONIC RESPIRATORY DISEASE



TUBERCULOSIS



CANCER



India Sub-Saharan Africa Latin America and Caribbean
East Asia and Pacific High-income countries

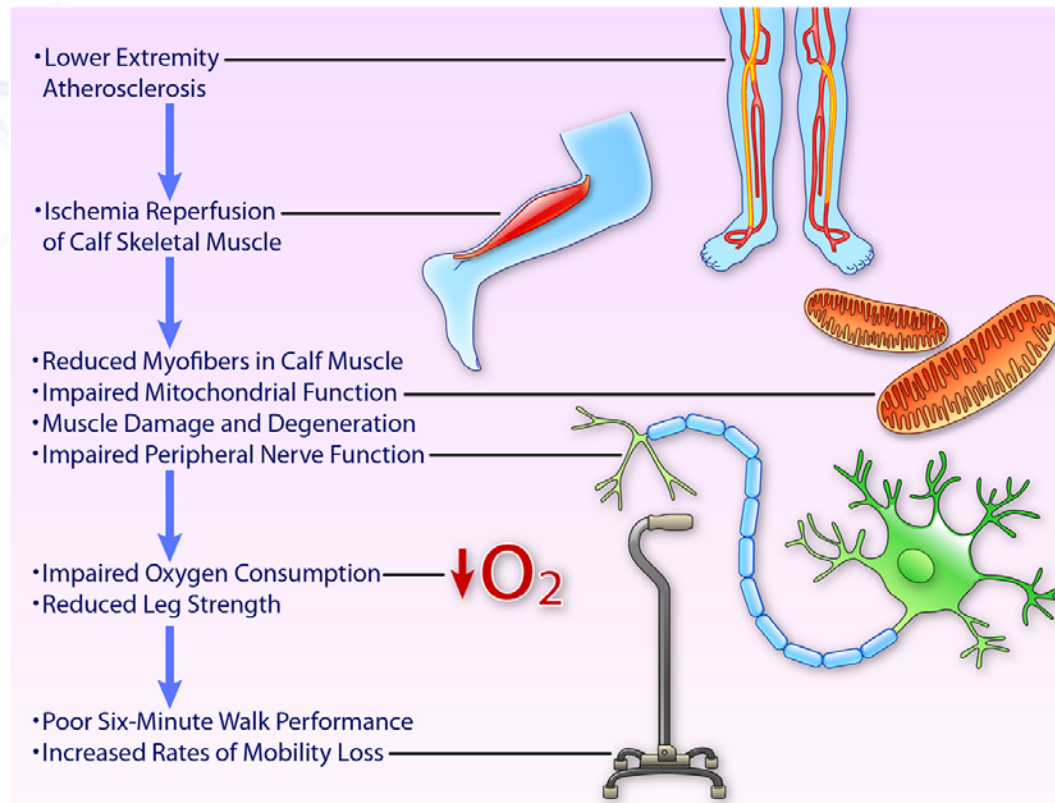
Million Death Study. Nature. Dec 2013.

<http://www.nature.com/news/global-health-one-million-deaths-1.14269>



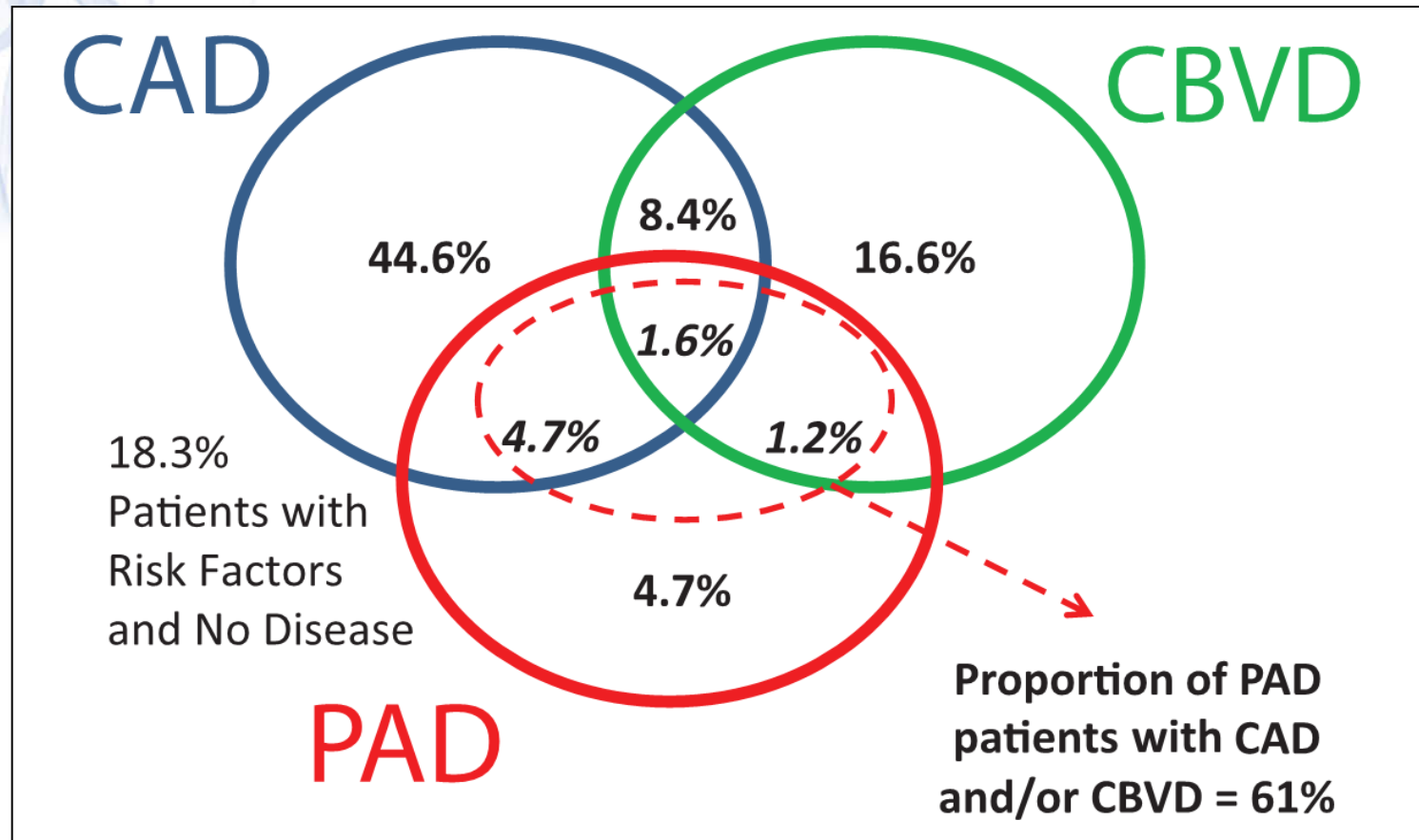
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There is More to PAD than 'Artery Blockages'

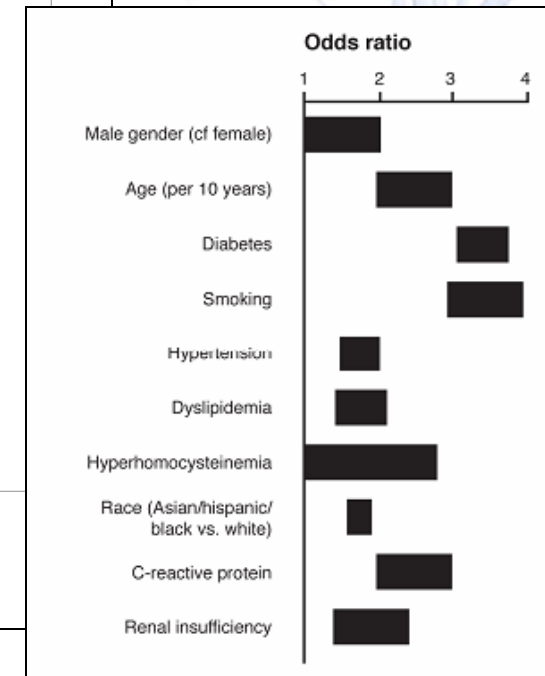
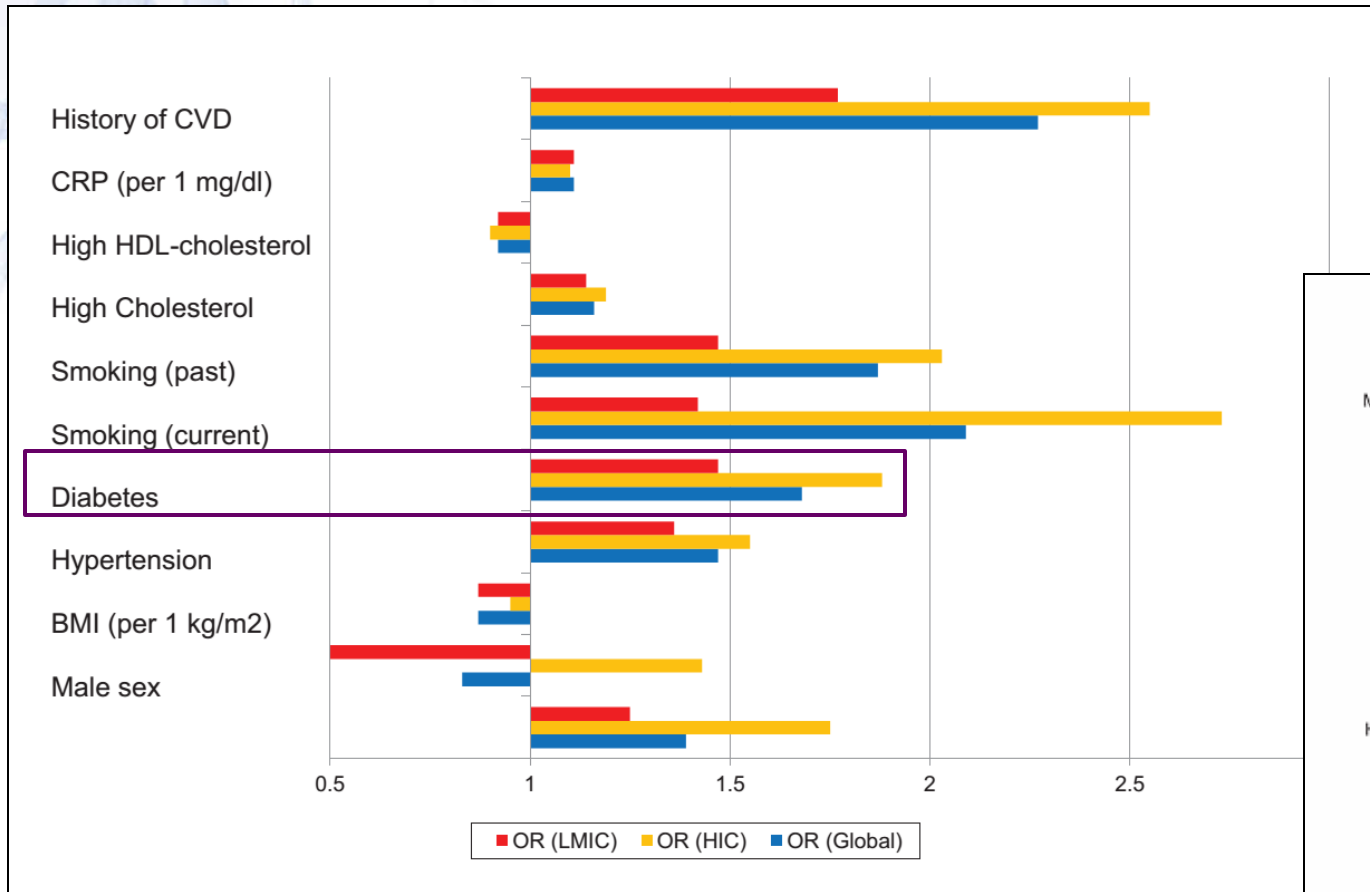


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PAD is Associated with Coronary Artery Disease and Cerebrovascular Disease



Cardiovascular Risk-Factors Suggest Atherosclerosis



J Vasc Surg. 2000 Jan;31(1 Pt 2):S1-S296
Circ Res. 2015 Apr 24;116(9):1509-26a



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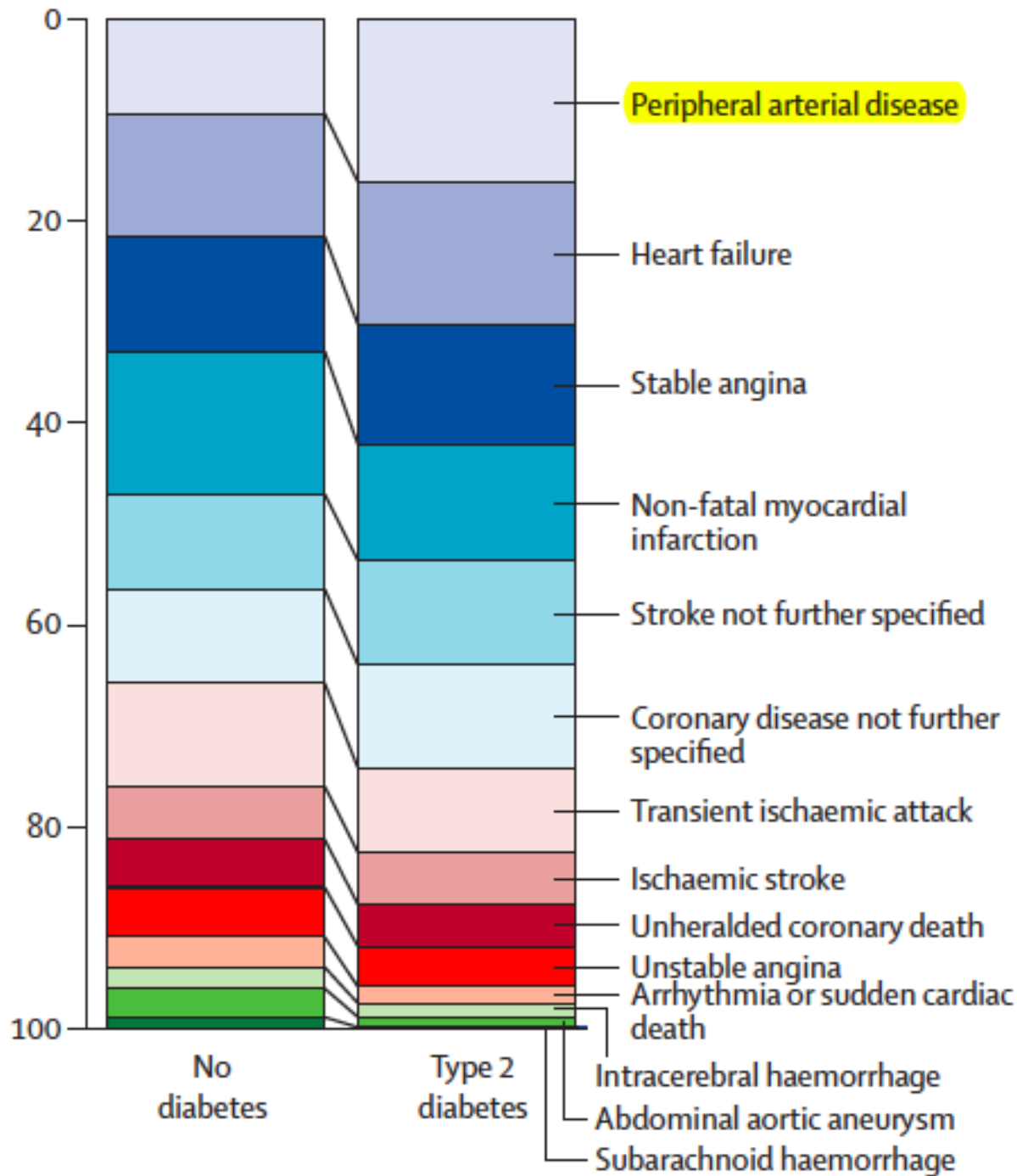
Type 2 diabetes and cardiovascular disease: a cohort study

Anoop Dinesh Shah, Claudiu Adam Timmis, Harry Hendry

Summary

Background The contribution of type 2 diabetes to cardiovascular disease has not been compared in a large cohort study.

Initial presentations of cardiovascular disease (%)



Lancet Diabetes Endocrinol 2014

Published Online
November 11, 2014



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Is There Sufficient Evidence That Intervention Improves Immediate/Near-Term/Long-Term Outcomes?

Absolutely....
If we are talking about
improvement in functional ability



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Exercise Training—The Cornerstone of Treatment for IC

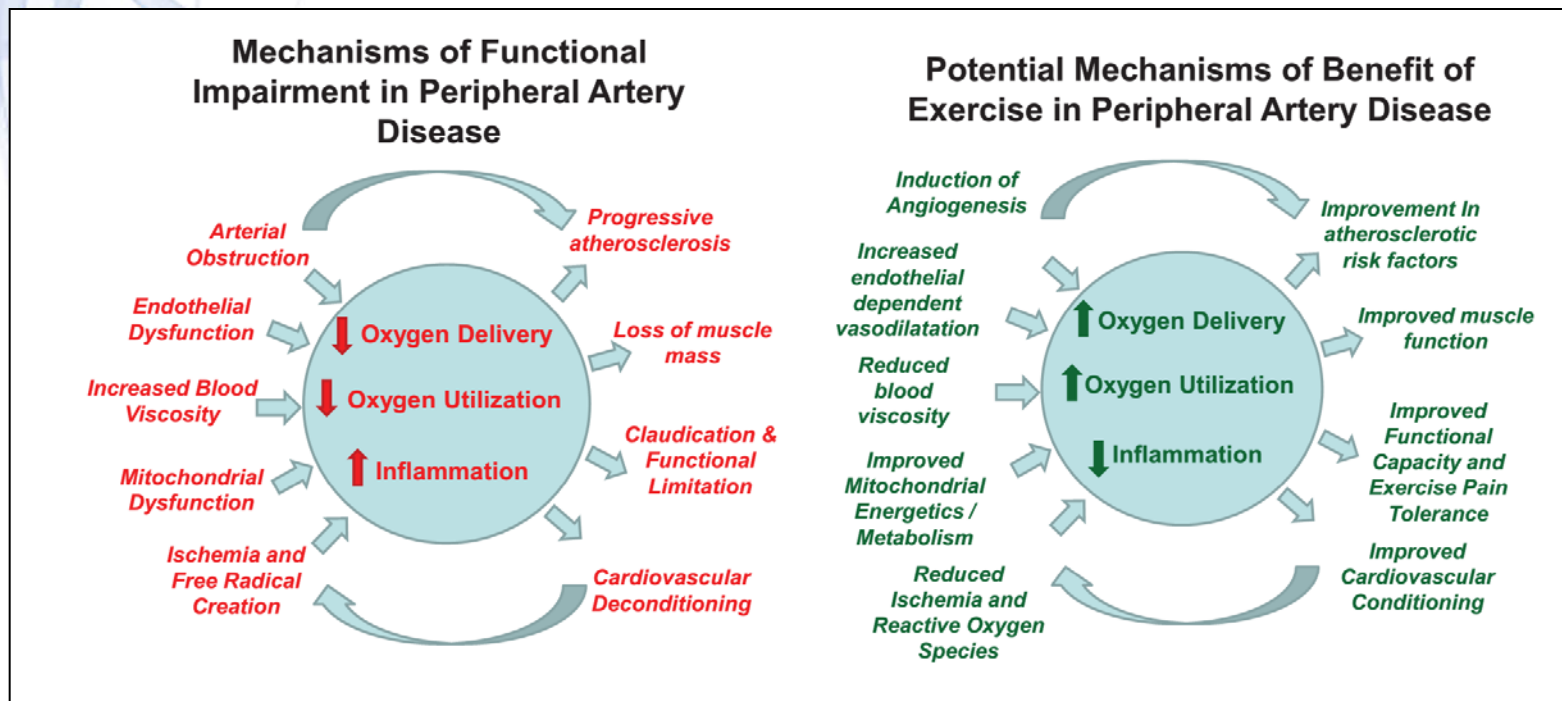
- Cochrane review of 22 RCT
- Significant improvement in
 - Maximum walking time (5.12 minutes)
 - Pain-free walking distance (82.2 m)
 - Maximum walking distance (113 m)

Watson L, et al. Cochrane Database Syst Rev. 2008;4:CD000990.

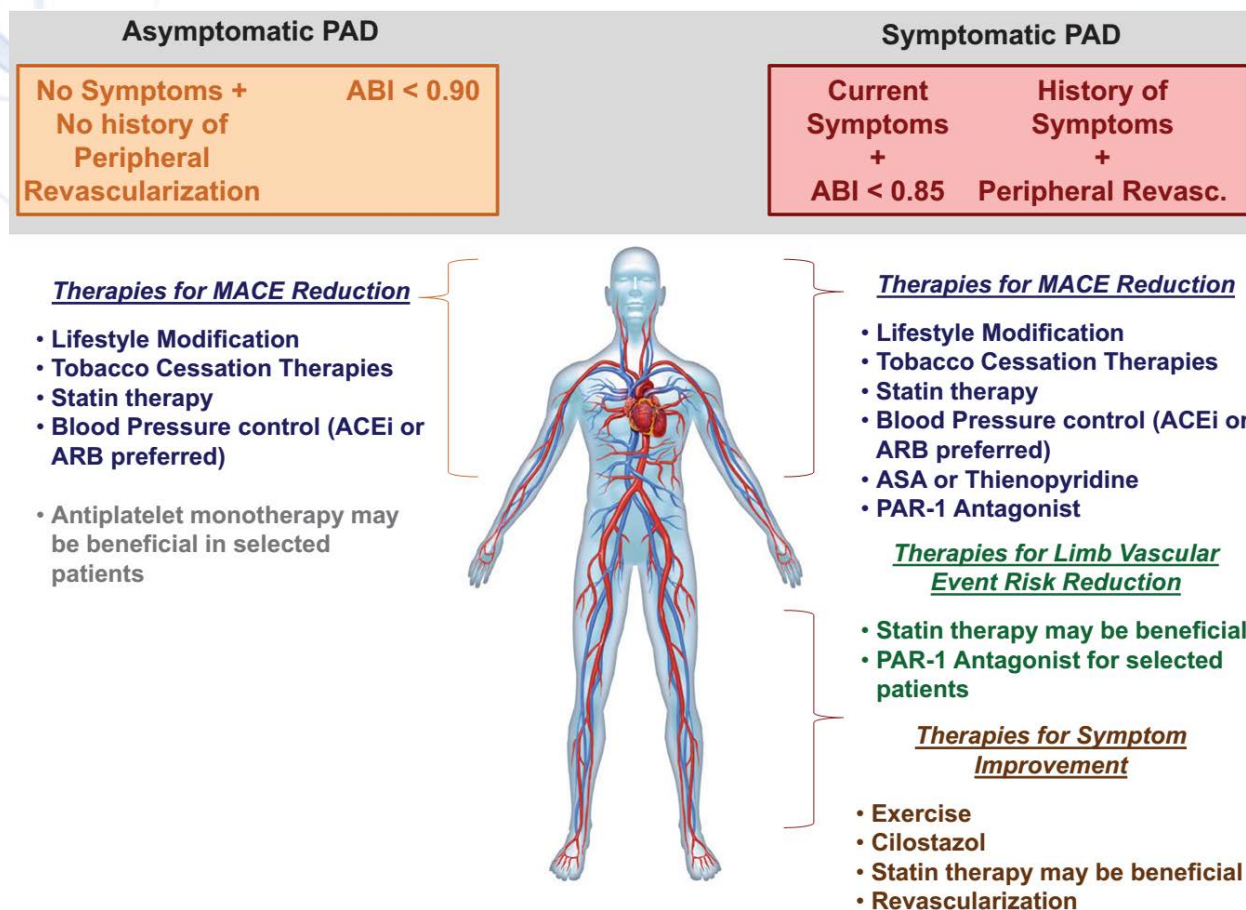


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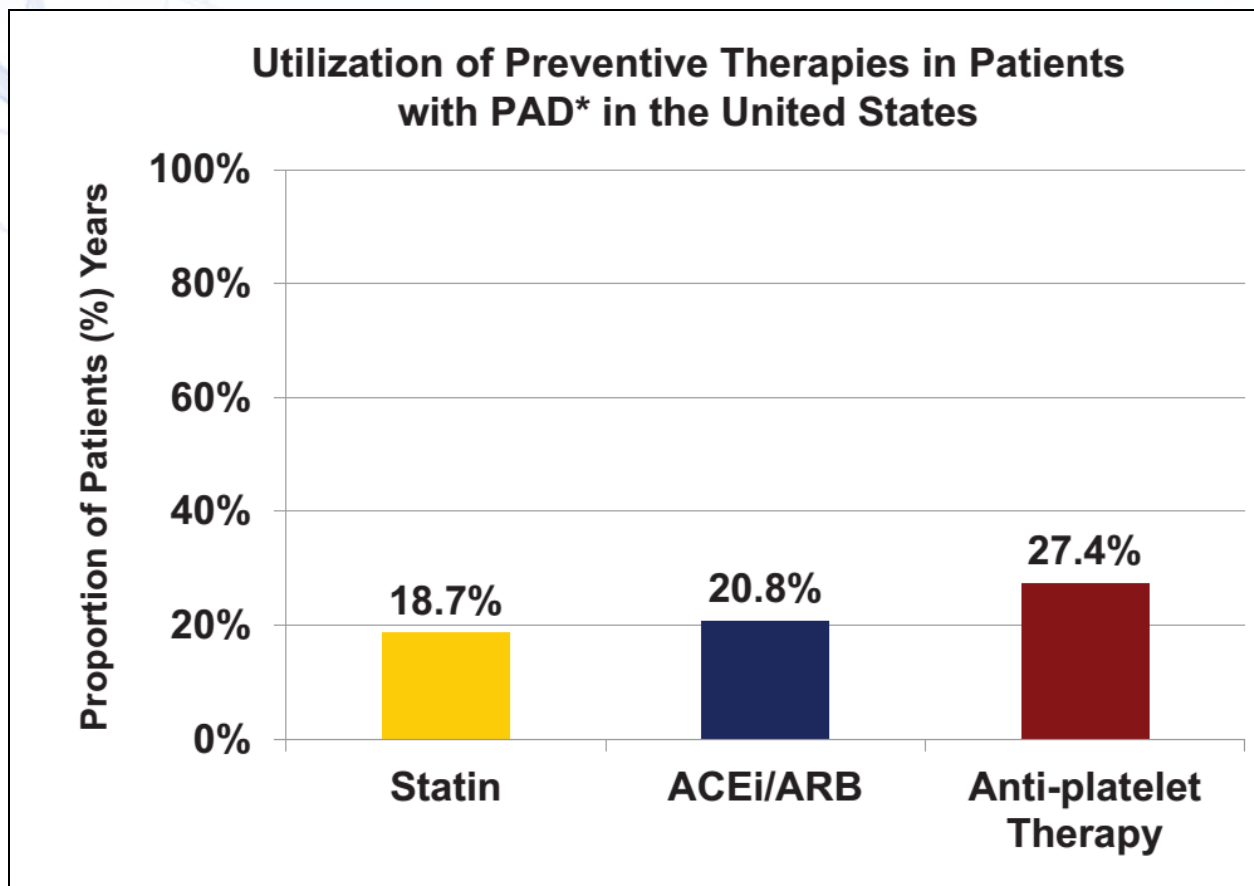
Exercise has Many Benefits for PAD Functional Status



Recommended Medical Treatment of PAD



And yet... Poor Adherence to Guidelines





Effective Health Care Program

Treatment Strategies for Patients With Peripheral Artery Disease *Executive Summary*

Background

Peripheral artery disease (PAD) refers to chronic narrowing or atherosclerosis of the lower extremities¹ and represents a spectrum of disease severity from asymptomatic disease to intermittent claudication (IC), to critical limb ischemia (CLI). PAD has a similar atherosclerotic process to coronary artery disease and

as well as an increased risk for myocardial infarction (MI), stroke, and death; it is also a major cause of limb amputation.³⁻⁷ Therefore, the general goals of treatment for PAD are cardiovascular protection, relief of symptoms, preservation of walking and functional status, and prevention of amputation. The optimal treatment for PAD—with specific emphasis on the comparative effectiveness of treatment options—is not known.⁸

The backbone of treatment for PAD is smoking cessation, risk factor modification, dietary modification, and increased physical activity. There are three main treatment options for improving functional status and other clinical outcomes in patients with PAD:

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through

also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

(1) medical therapy, (2) exercise training, and (3) revascularization. The treatment options offered to PAD patients depend on whether the patient is asymptomatic or symptomatic (with either IC or CLI).

Published May 2013



Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective
Health Care

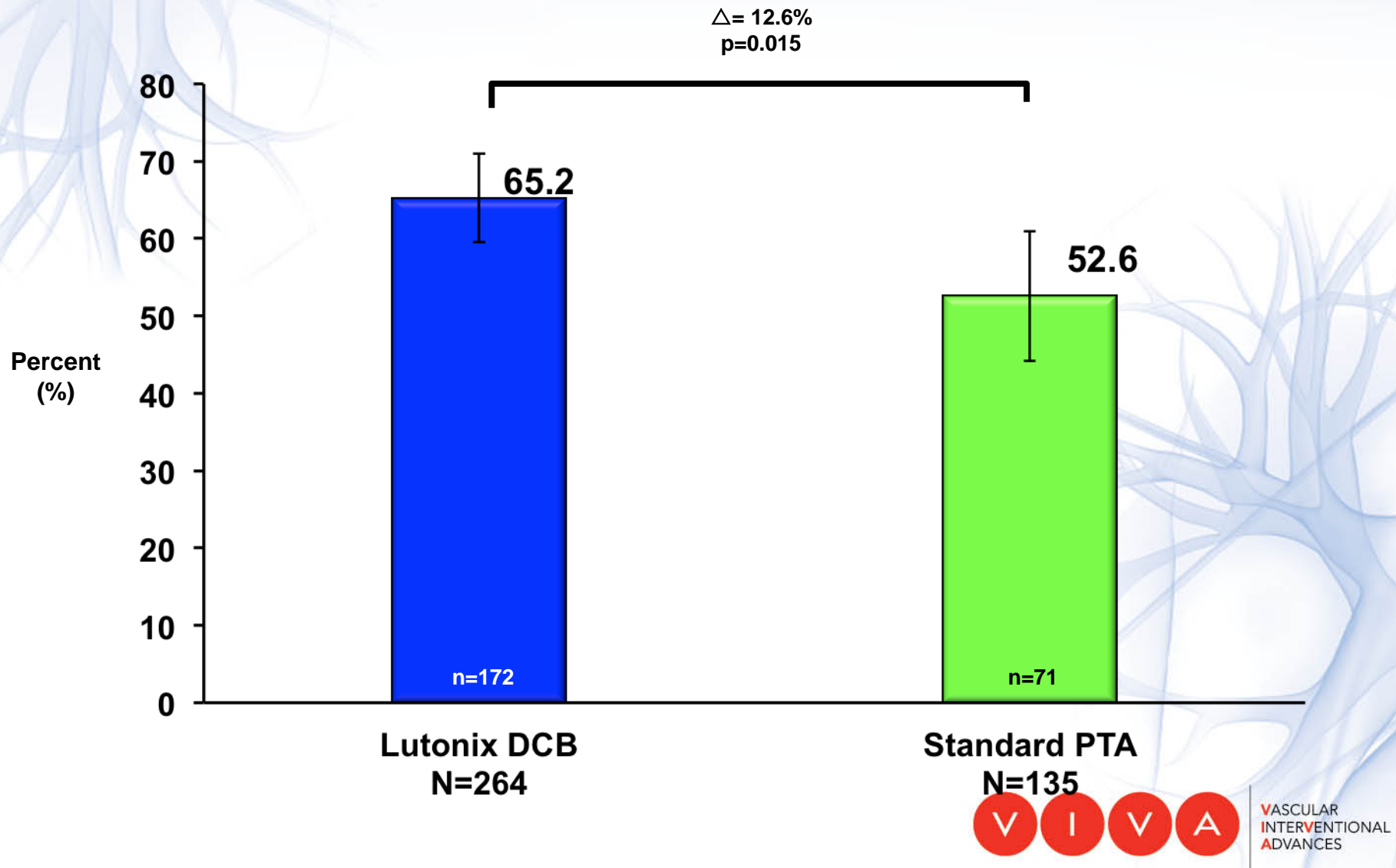


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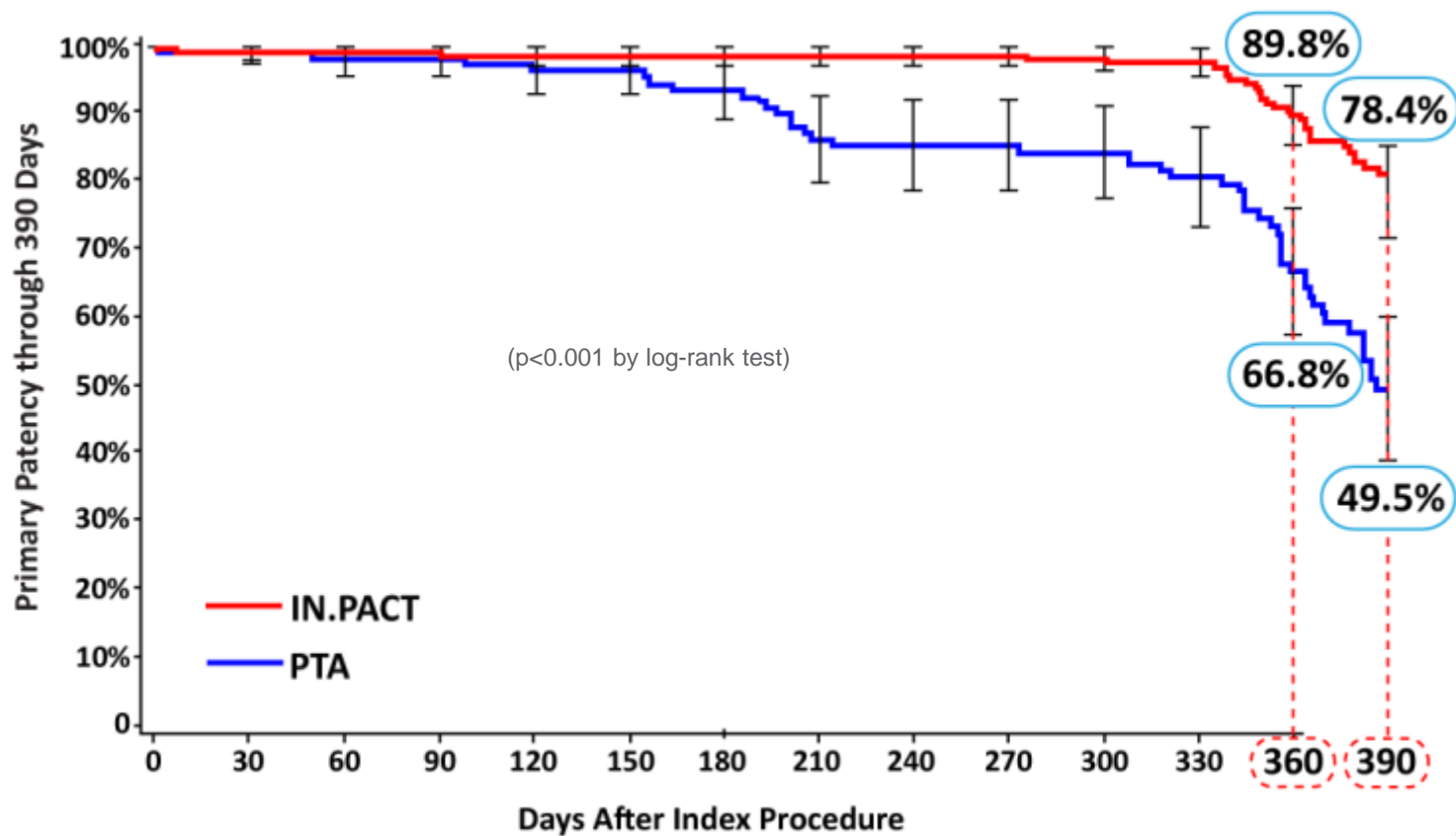
What was Not Included in the AHRQ May 2013 Document?

- Drug Coated Balloon Trials
 - Randomized, blinded to core labs, multicenter, prospective
 - LEVANT 2
 - In.PACT SFA 1.2
- Drug Eluting Stent Trials
 - Randomized, multicenter, prospective now with 5 year follow up
 - Zilver PTX

LEVANT 2: Efficacy Endpoint of Primary Patency Achieved



In.PACT SFA: Substantially Improved Primary Patency: DCB Compared to PTA



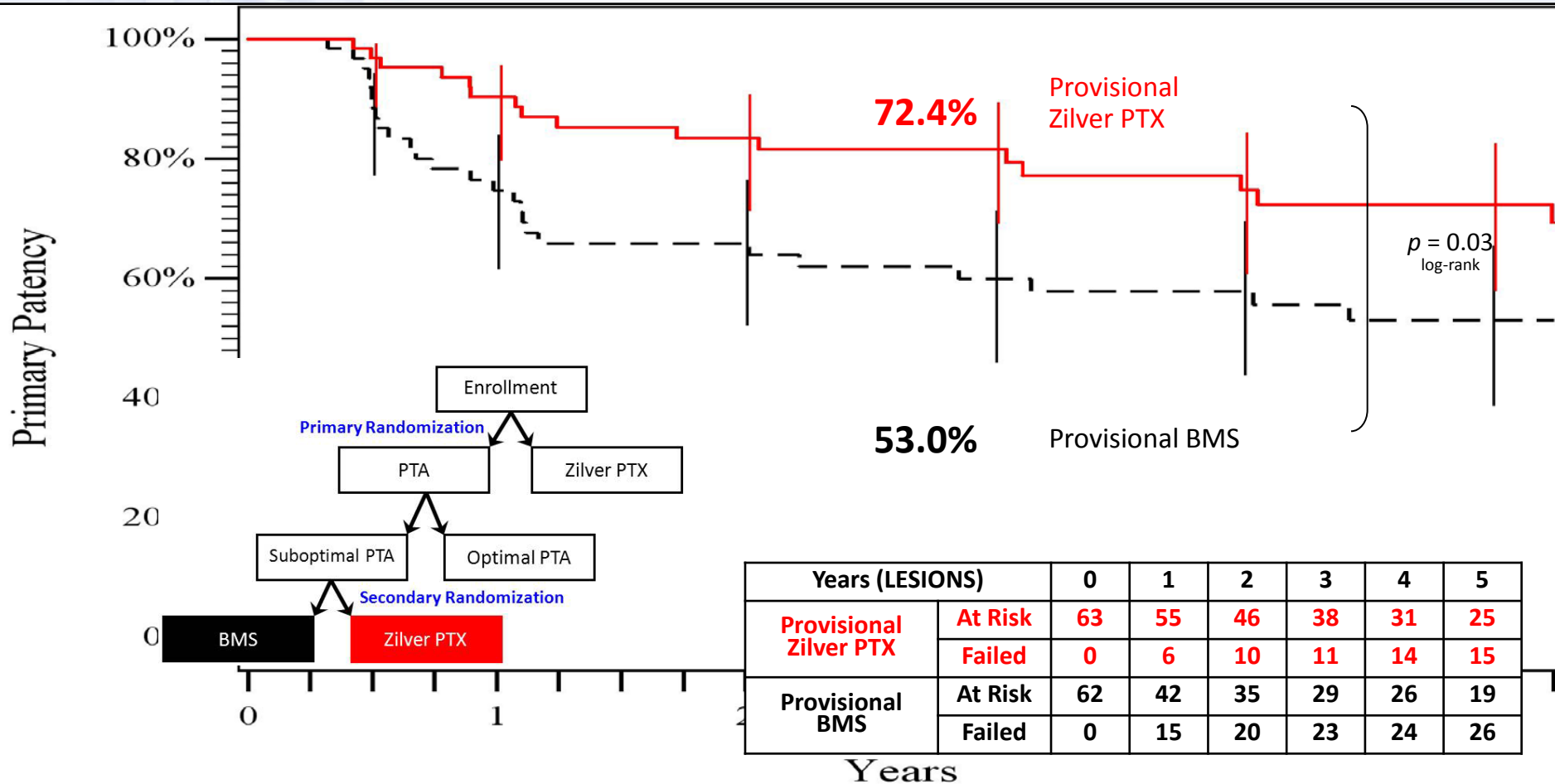
1. Primary patency is defined as freedom from clinically-driven TLR and freedom from restenosis as determined by duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) ≤ 2.4

What was Not Included in the AHRQ May 2013 Document?

- Drug Coated Balloon Trials
 - Randomized, blinded to core labs, multicenter, prospective
 - LEVANT 2
 - In.PACT SFA 1.2
- Drug Eluting Stent Trials
 - Randomized, multicenter, prospective now with 5 year follow up
 - Zilver PTX

5-year Primary Patency (PSVR < 2.0)

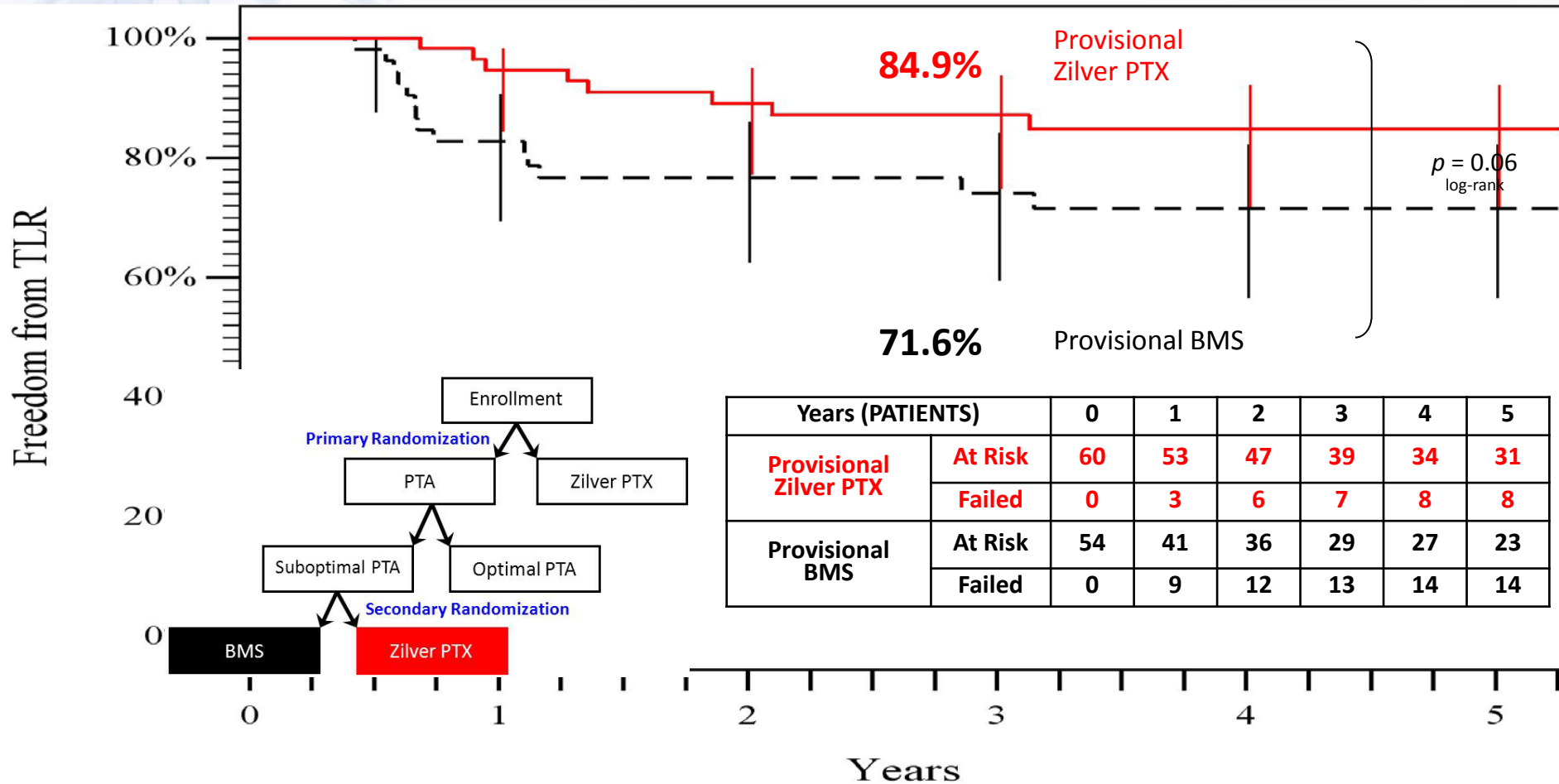
Provisional Zilver PTX vs. BMS



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

5-year Freedom from TLR

Provisional Zilver PTX vs. BMS



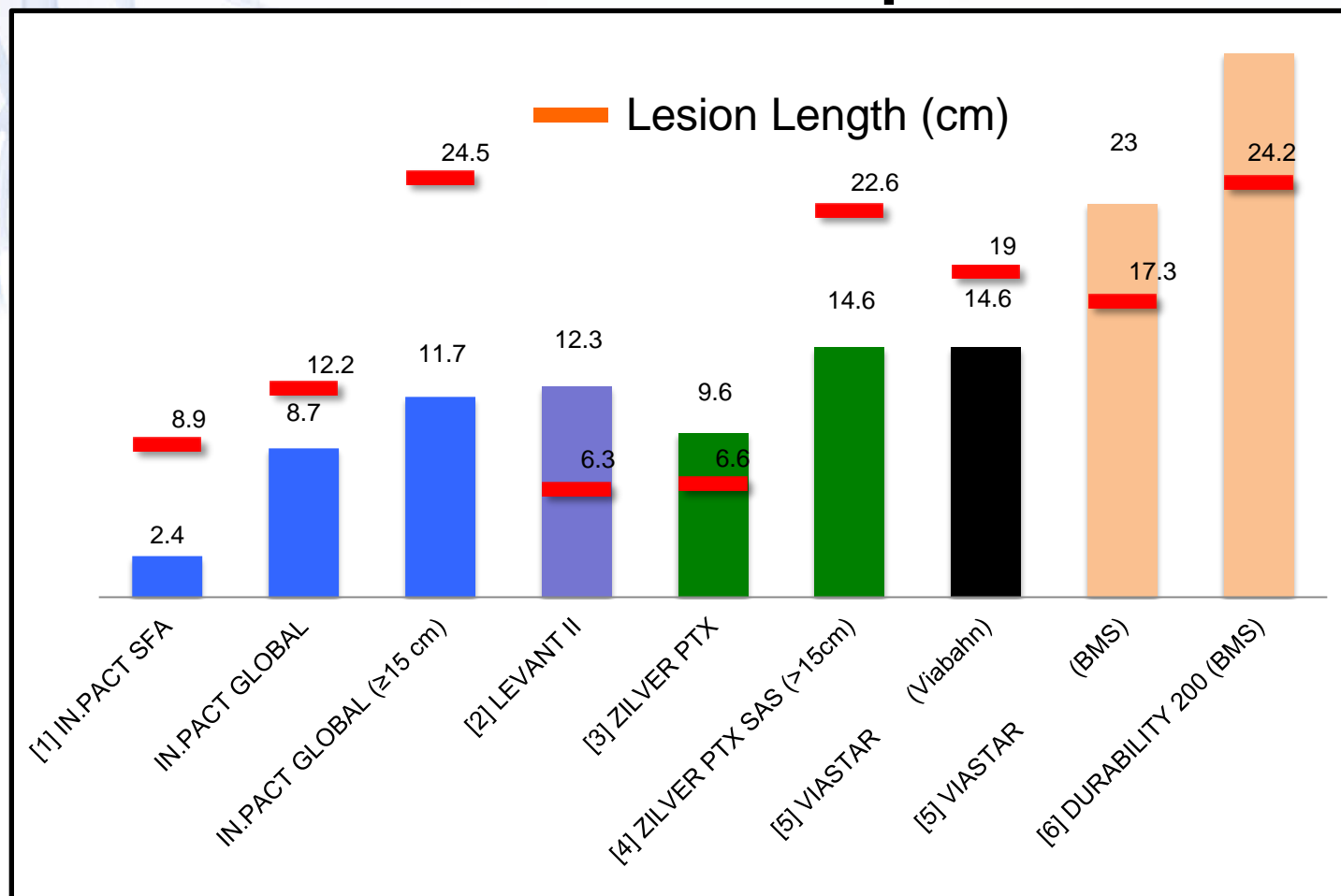
At 5 years, Zilver PTX demonstrates a 47% reduction in reintervention compared to BMS

What was Not Included in the AHRQ May 2013 Document?

- Large Prospective Multicenter Core Lab Adjudicated Registries
 - Nitinol Self-Expanding Stents
 - RESILIENT, SUPERB, STROLL, DURABILITY II
 - Atherectomy
 - DEFINITIVE LE

SFA Trial Comparison

TLR Rates

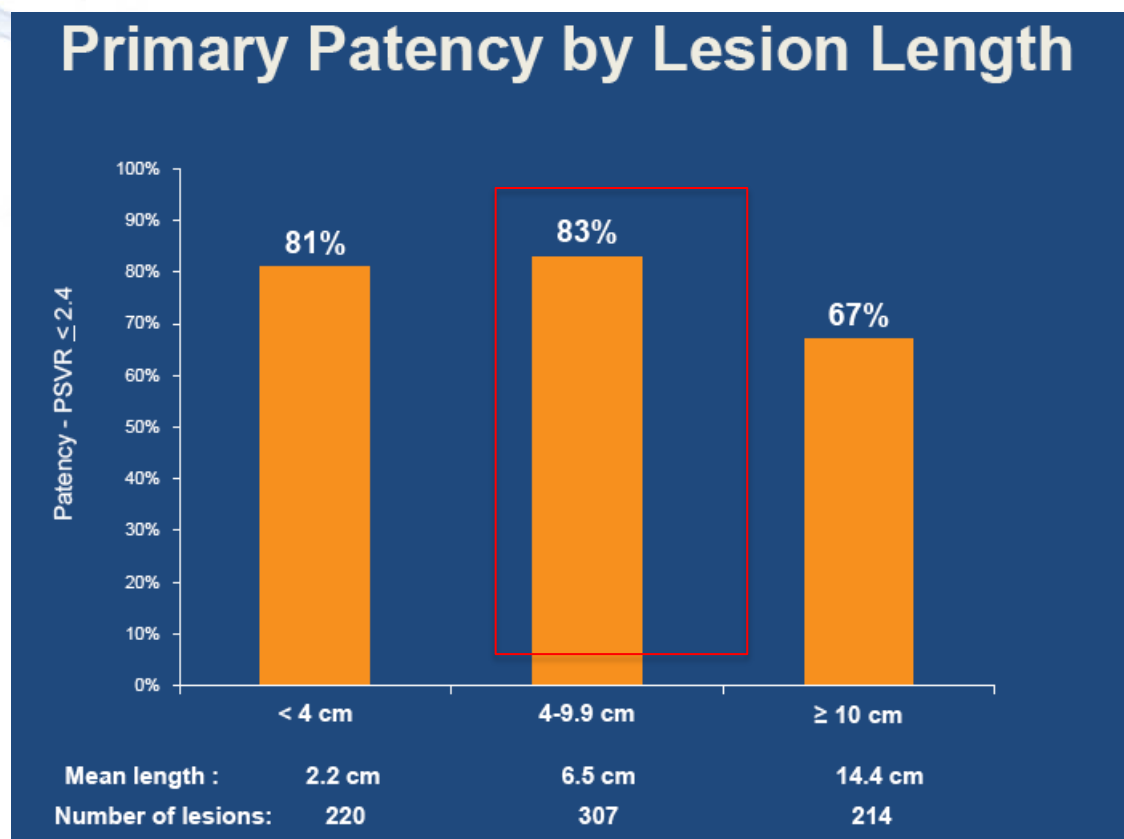


[1] Circulation. 2014 Dec 3 [Epub]; [2] Lutonix FDA Panel Presentation; June 12 2014;
 [3] Circ Cardiovasc Interv. 2011;4:495-504; [4] J Cardiovasc Surg (Torino). 2013 Feb;54(1):115-22;
 [5] J Am Coll Cardiol. 2013 Oct 8;62(15):1320-7; [6] J Vasc Surg 2011 Oct;54(4):1042-50



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Large Multicenter Atherectomy Registry: Definitive LE



McKinsey et al JACC Cardiovasc Interv. 2014;7:923-33



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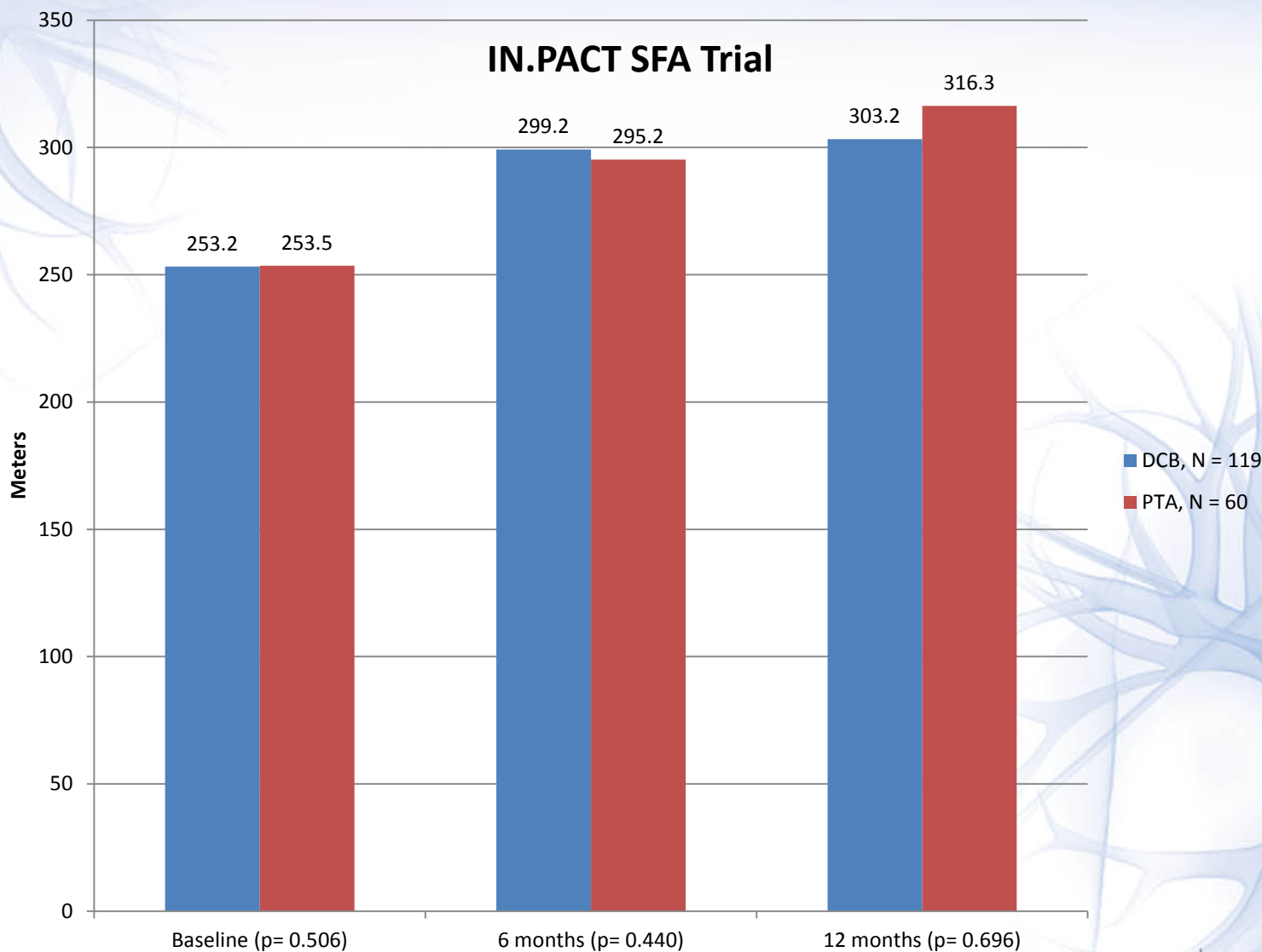
Does Improved Patency and Reduced TLR Result in Improved Functional Performance?



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12-month Functional Outcomes: 6MWT (m, mean \pm SD)

DCB patients achieved the same level of function with 88% fewer re-interventions



All ITT subjects from IN.PACT SFA II only



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What was Not Included in the AHRQ May 2013 Document?

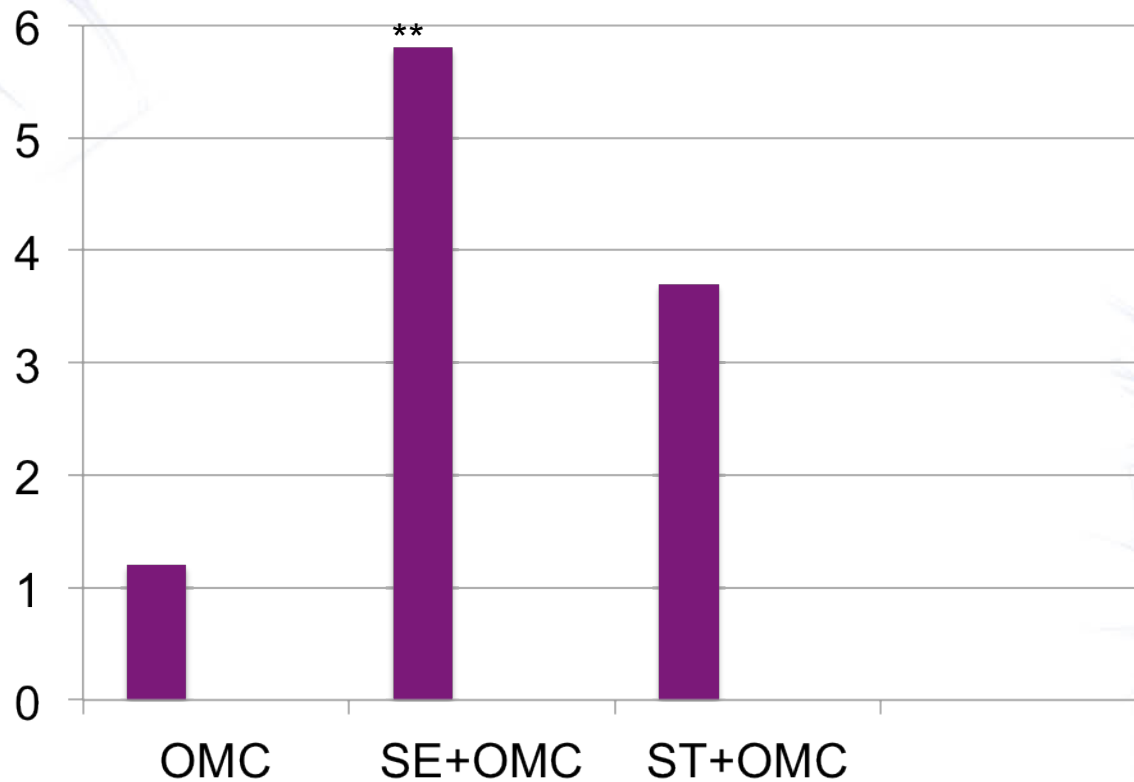
- Comparative Trials of Intervention vs Exercise Training and Optimal Medical Therapy

Supervised Exercise Versus Primary Stenting for Claudication Resulting From Aortoiliac Peripheral Artery Disease Six-Month Outcomes From the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) Study

Timothy P. Murphy, MD; Donald E. Cutlip, MD; Judith G. Regensteiner, PhD; Emile R. Mohler, MD;
David J. Cohen, MD; Matthew R. Reynolds, MD, MSc; Joseph M. Massaro, PhD;
Beth A. Lewis, PhD; Joselyn Cerezo, MD; Niki C. Oldenburg, Dr. PH.; Claudia C. Thum, MA;
Suzanne Goldberg, MSN; Michael R. Jaff, DO; Michael W. Steffes, MD; Anthony J. Comerota, MD;
Jonathan Ehrman, PhD; Diane Treat-Jacobson, RN, PhD; M. Eileen Walsh, RN, PhD;
Tracie Collins, MD; Dalynn T. Badenhop, PhD; Ulf Bronas, PhD;
Alan T. Hirsch, MD; for the CLEVER Study Investigators

CLEVER—Primary Endpoint

Change in PWT from Baseline to 6-Months



CLEVER—Quality of Life

Measure	OMC (n=20)	SE+OMC (n=38)	ST+OMC (n=41)	P, SE vs OMC	P, ST vs. OMC	P, SE vs ST
Change from baseline to 6 mo						
SF-12 physical	1.2±11.0	5.9±10.1	6.6±8.5	0.047	0.023	0.958
SF-12 mental	-2.4±8.0	-2.2±11.5	-1.7±9.9	0.810	0.713	0.862
WIQ pain severity	16.3±34.7	26.3±36.3	40.4±43.9	0.251	<0.001	0.014
WIQ walking distance	-0.5±26.0	25.1±27.6	43.8±42.2	0.007	<0.001	0.029
WIQ walking speed	1.47±15.69	16.5±19.7	30.8±31.0	0.007	<0.001	0.007
WIQ stair climbing	10.2±29.3	24.0±20.9	29.3±39.1	0.071	0.051	0.539
PAQ physical limitation	0.6±22.5	16.2±19.2	28.1±30.9	0.012	<0.001	0.043
PAQ symptoms	1.0±17.2	16.3±21.4	29.2±27.4	0.008	<0.001	0.002
PAQ social limitation	-10.6±29.6	8.8±30.0	17.6±30.2	0.016	<0.001	0.156
PAQ treatment satisfaction	-8.1±19.1	4.6±20.7	4.0±25.9	0.013	0.010	0.323
PAQ quality of life	0.8±26.7	17.3±20.8	30.4±28.3	0.011	<0.001	0.006
PAQ summary	-3.1±18.6	13.8±17.0	28.0±26.4	0.001	<0.001	0.002

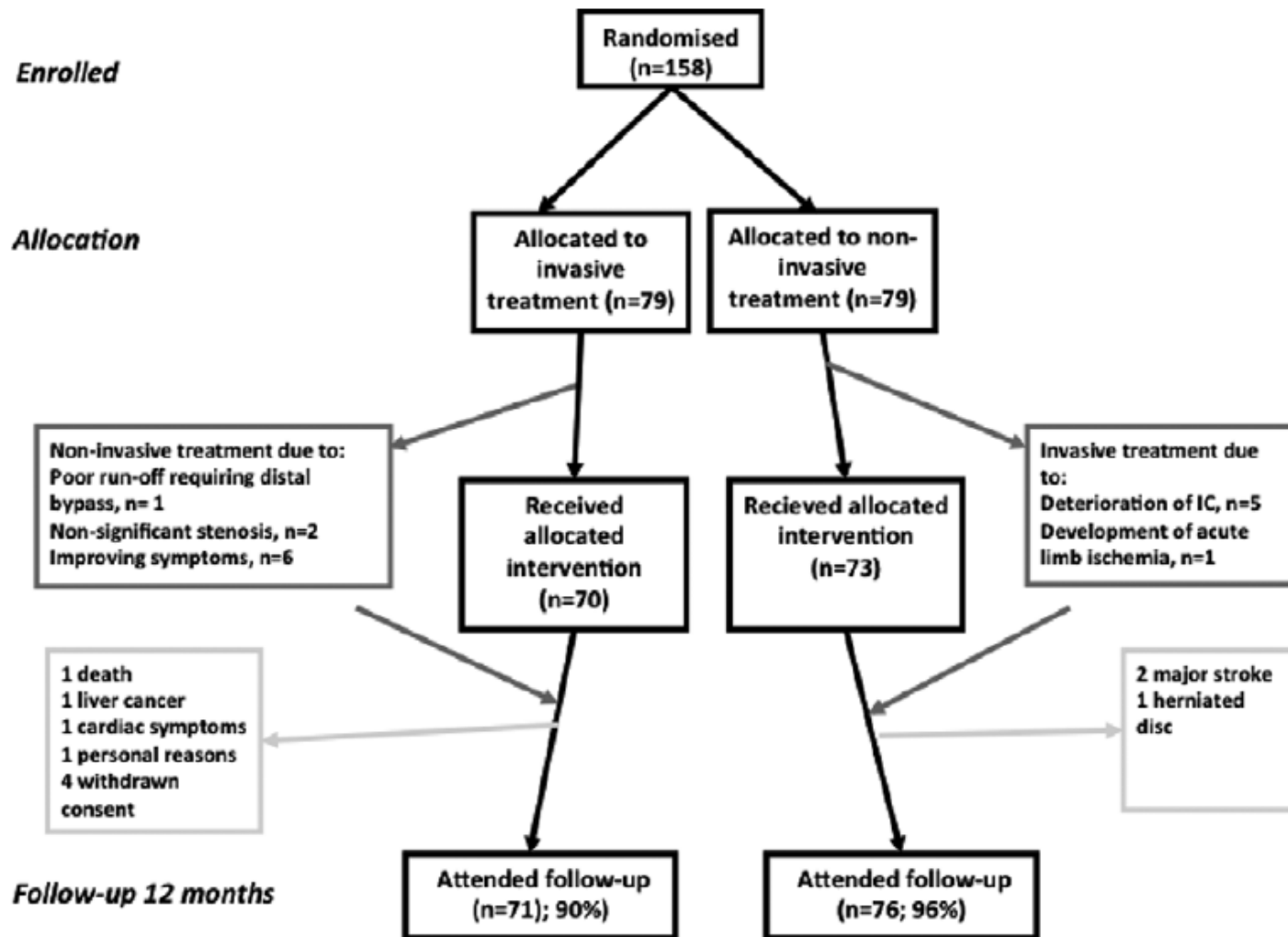
The IRONIC Trial

Improved Quality of Life After 1 Year With an Invasive Versus a Noninvasive Treatment Strategy in Claudicants

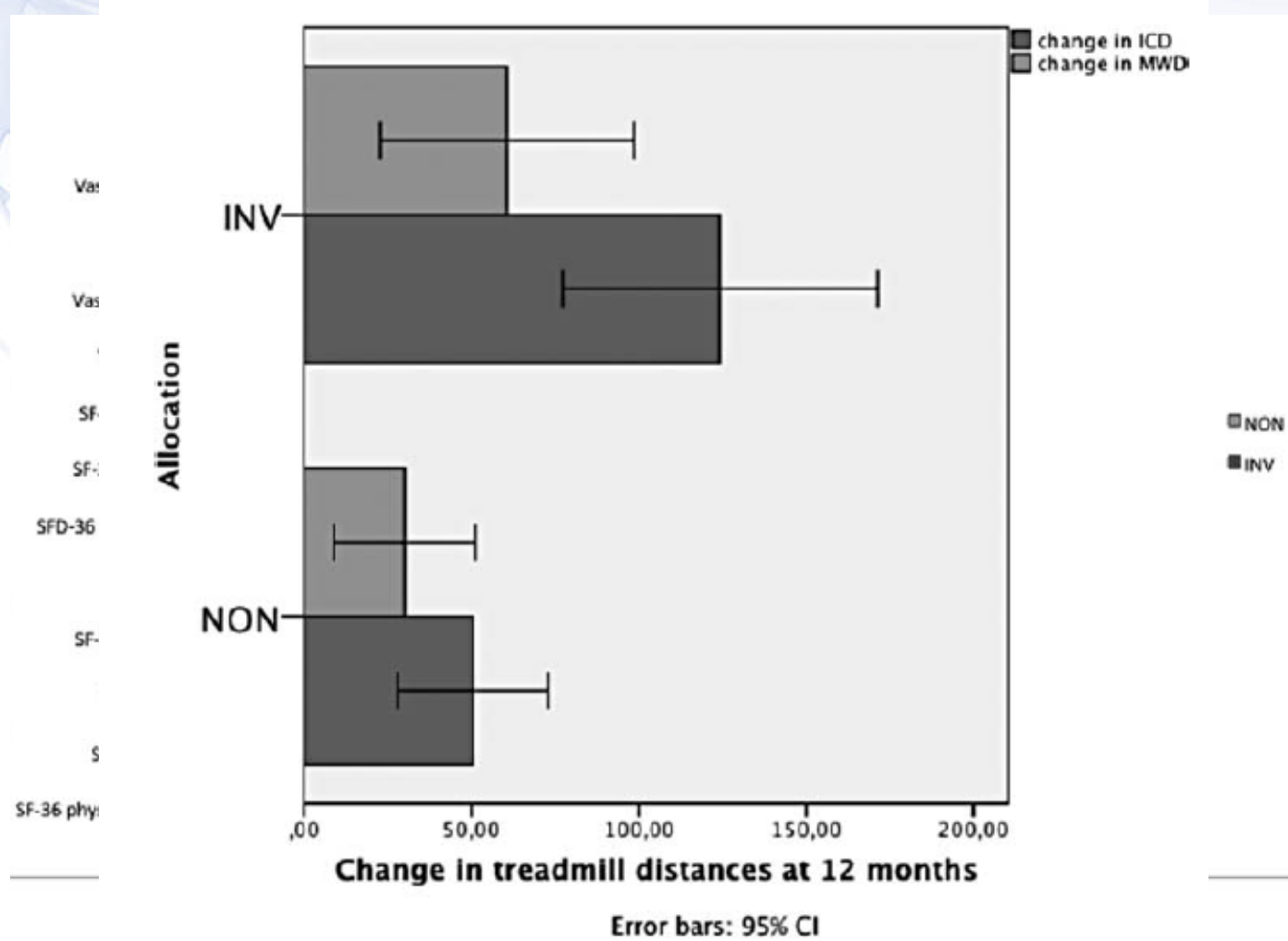
One-Year Results of the Invasive Revascularization or Not in Intermittent Claudication (IRONIC) Trial

- 79 pts with IC randomized to medical therapy
- 79 pts with IC randomized to revascularization
 - 18 out of 75 procedures were surgical

The IRONIC Trial



The IRONIC Trial



Supervised Exercise, Stent Revascularization, or Medical Therapy for Claudication Due to Aortoiliac Peripheral Artery Disease



The CLEVER Study

Timothy P. Murphy, MD,* Donald E. Cutlip, MD,†† Judith G. Regensteiner, PhD,§ Emile R. Mohler III, MD,|| David J. Cohen, MD, MSc,¶ Matthew R. Reynolds, MD,‡ Joseph M. Massaro, PhD,‡# Beth A. Lewis, PhD,** Joselyn Cerezo, MD,* Niki C. Oldenburg, DRPH,†† Claudia C. Thum, MA,‡ Michael R. Jaff, DO,†† Anthony J. Comerota, MD,§§ Michael W. Steffes, MD,†† Ingrid H. Abrahamsen, MS,‡ Suzanne Goldberg, MSN,||| Alan T. Hirsch, MD††

ABSTRACT

BACKGROUND Treatment for claudication that is due to aortoiliac peripheral artery disease (PAD) often relies on stent revascularization (ST). However, supervised exercise (SE) is known to provide comparable short-term (6-month) improvements in functional status and quality of life. Longer-term outcomes are not known.

OBJECTIVES The goal of this study was to report the longer-term (18-month) efficacy of SE compared with ST and optimal medical care (OMC).

METHODS Of 111 patients with aortoiliac PAD randomly assigned to receive OMC, OMC plus SE, or OMC plus ST, 79 completed the 18-month clinical and treadmill follow-up assessment. SE consisted of 6 months of SE and an additional year of telephone-based exercise counseling. Primary clinical outcomes included objective treadmill-based walking performance and subjective quality of life.

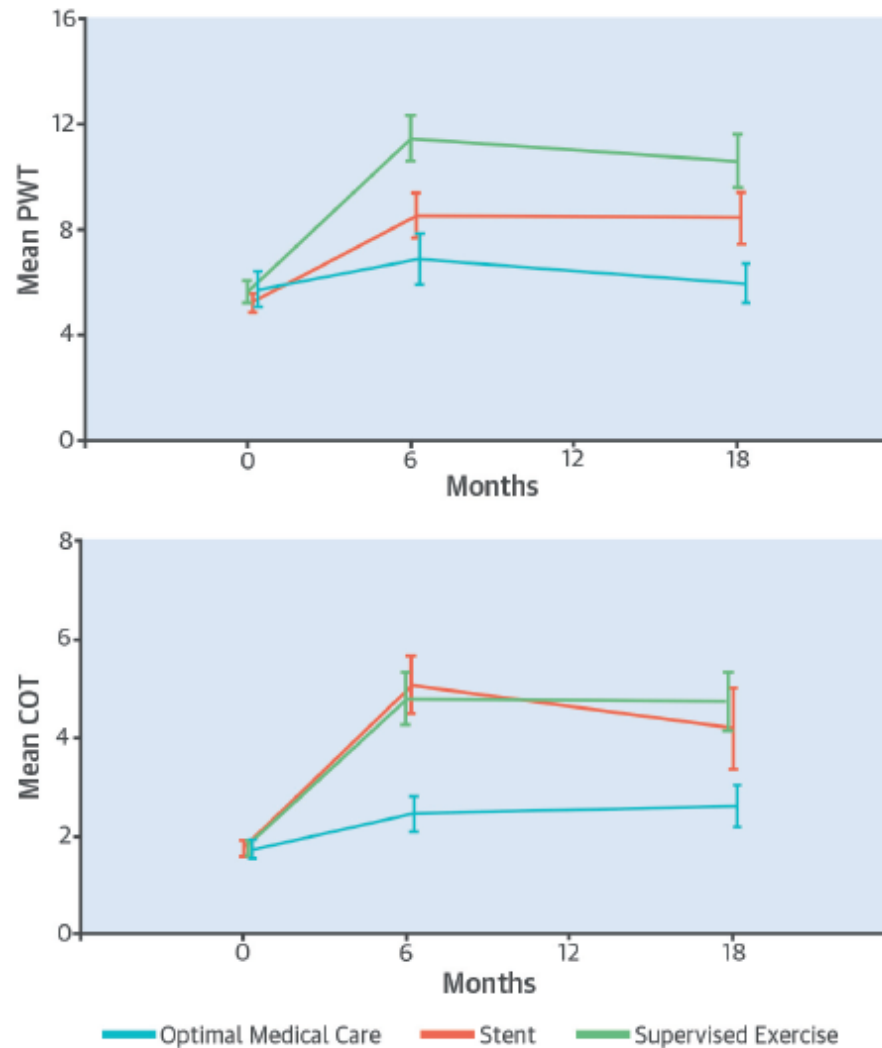
RESULTS Peak walking time improved from baseline to 18 months for both SE (5.0 ± 5.4 min) and ST (3.2 ± 4.7 min) significantly more than for OMC (0.2 ± 2.1 min; $p < 0.001$ and $p = 0.04$, respectively). The difference between SE and ST was not significant ($p = 0.16$). Improvement in claudication onset time was greater for SE compared with OMC, but not for ST compared with OMC. Many disease-specific quality-of-life scales demonstrated durable improvements that were greater for ST compared with SE or OMC.

CONCLUSIONS Both SE and ST had better 18-month outcomes than OMC. SE and ST provided comparable durable improvement in functional status and in quality of life up to 18 months. The durability of claudication exercise interventions merits its consideration as a primary PAD claudication treatment. (Claudication: Exercise Versus Endoluminal Revascularization [CLEVER]; [NCT00132743](#)) (*J Am Coll Cardiol* 2015;65:999–1009) © 2015 by the American College of Cardiology Foundation.

CLEVER

point

CENTRAL ILLUSTRATION Exercise or Intervention for Claudication Due to Aortoiliac PAD: PWT and COT

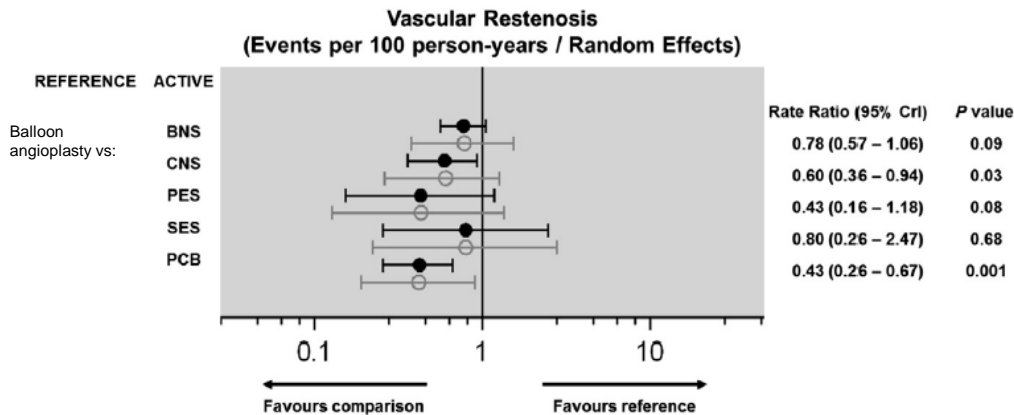


Murphy, T.P. et al. J Am Coll Cardiol. 2015; 65(10):999-1009.

(Upper panel) PWT. Patients with 18-month follow-up visit only. **(Lower panel)** COT. COT = claudication onset time on a graded treadmill test; PAD = peripheral artery disease; PWT = peak walking time on a graded treadmill test.

Comparing Outcomes of Treatments for Femoropopliteal Arterial Disease

- Katsanos et al performed a network meta-analysis of RCTs of endovascular treatment
- Compared plain balloon angioplasty, paclitaxel-coated balloons, drug-eluting stents, bare nitinol stents, and covered nitinol stents
 - Vascular restenosis lowest with paclitaxel-eluting stent and paclitaxel-coated balloon
 - TLR lowest with paclitaxel-coated balloon and paclitaxel-eluting stent



Conclusions

- Quality of data in peripheral artery trials has dramatically improved, even in the past 2 years
- We advocate coverage for supervised peripheral artery rehabilitation programs
 - Cardiac Rehab
 - Heart Failure Rehab
- We now know that advanced technologies for endovascular intervention improve outcomes and quality of life
- We need data on cost effectiveness and objective improvement in physical functioning

