Industry Perspective on Lower Extremity Peripheral Artery Disease

MEDCAC on Lower Extremity Peripheral Artery Disease

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On behalf of Medtronic, Abbott Vascular, Boston Scientific, C. R. Bard, and Gore Medical

Disclosures

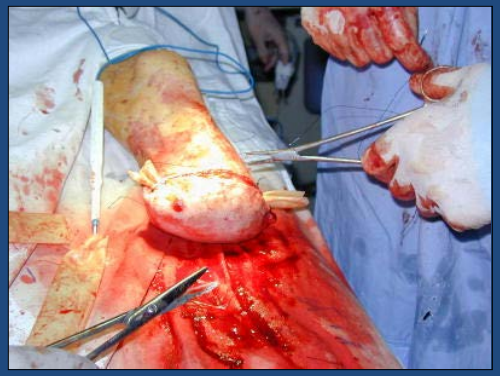
- Medtronic employee and shareholder
- No other conflicts of interest

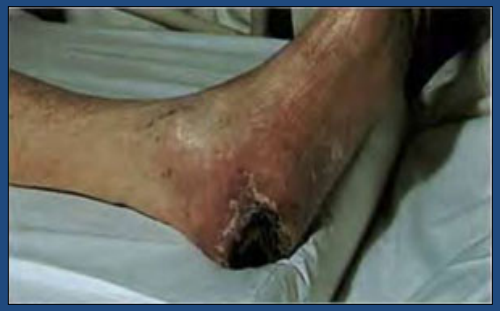
Presentation Overview

- Burden of PAD on patients
- Advancements in endovascular technologies over the past decade & the significant improvements in patient outcomes
- Growing body of level 1 evidence supporting endovascular therapies for PAD patients
- Continued investments in clinical research on advancements in endovascular therapies and treatment of PAD

PAD is a chronic, progressive, and complex disease associated with significant morbidity and mortality

- The burden of PAD falls primarily on the elderly
  - 1 in every 5 people over the age of 70 has the disease[1]
- PAD significantly impacts patients, resulting in rest pain, severe pain when walking, and amputation—and eventually death if left untreated
- For patients with PAD, the goal is to improve blood flow in the leg in order to:
  - Reduce pain
  - Improve functional ability
  - Improve quality of life
  - Prevent amputation
- Patients want the treatment to be as minimally invasive as possible, durable, with limited complications, and not require reintervention



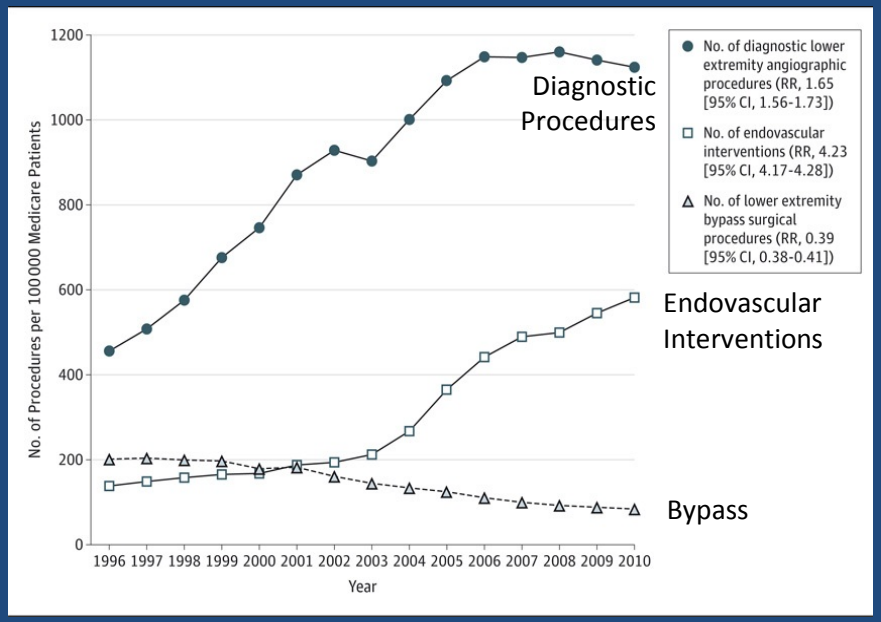


In current practice, a variety of prevention, diagnosis, and treatment modalities—including endovascular interventions—have important roles in managing and treating patients with PAD

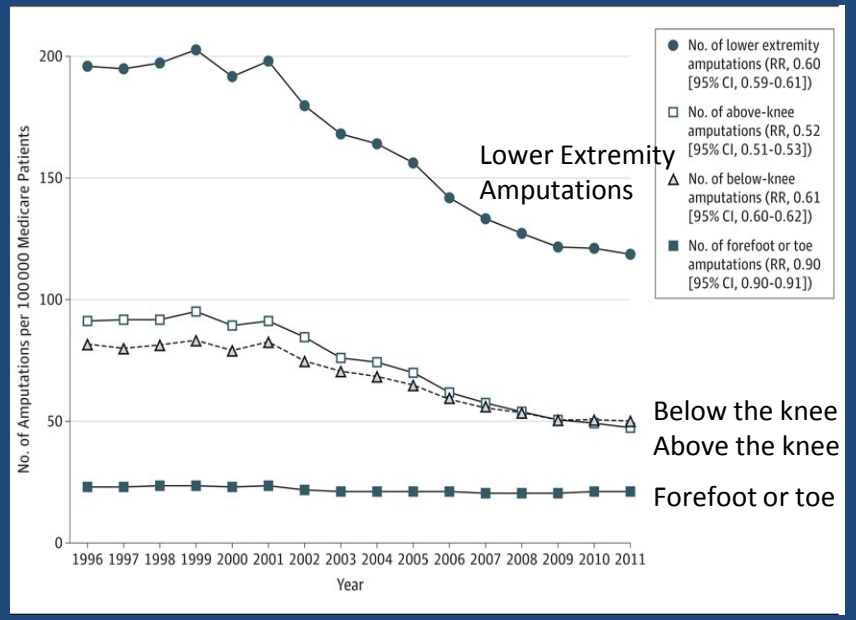
Sources: 1. American Podiatric Medical Association. PAD Fact Sheet. Available here. 2 Alan T. Hirsch et al. Circulation. 2012;125:1449-1472

From 1996-2011, the use of endovascular treatments increased, while amputations decreased by 45%

Trends in Angiography, Endovascular Intervention & LE Bypass in the Medicare Program



Trends in Major Amputation Rates in the Medicare Program



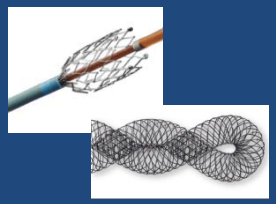
"[W]e recognize that our study presents no direct causative experimental evidence to explain the decrease in amputation risk. However, it is evident that the increasing use of vascular and preventive care, especially among patients with diabetes, has been temporally associated with lower rates of major amputation." – Goodney 2015

Source: Phillip Goodney et al. JAMA Surg. 2015 Jan 1; 150(1): 84–86.

Technology advancement has driven an increase in rigorous clinical studies on PAD therapies

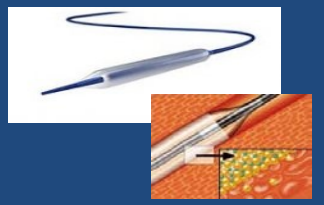
2005
First Stent Graft Approval

2005-2008
Modern Atherectomy Device Approvals



2010-2015
Modern Bare Metal Stent Approvals

2012
First Drug Eluting Stent Approval



2014-2015
First Drug Coated Balloon Approvals

Since the 2013 AHRQ PAD systematic review:

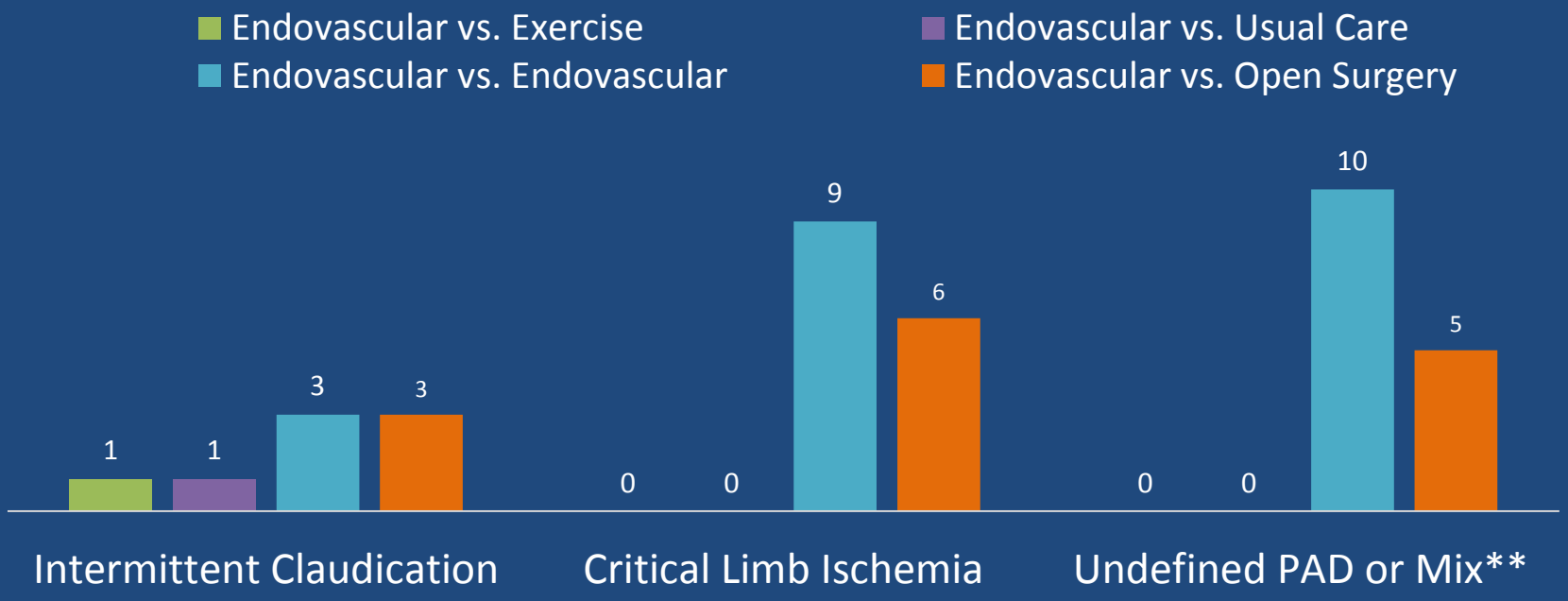
- **35** peer-reviewed, comparative studies published on LE PAD have evaluated endovascular therapy against an active comparator*
- Increasingly complex lesions are being studied, leading to device indications for long lesions, chronic total occlusions, and in-stent restenosis

*Based on internally commissioned study done by Boston Health Economics that applied AHRQ's inclusion criteria from the 2013 AHRQ PAD report to identify published literature on endovascular therapy from August 2012 – May 2015. Of note, unlike the AHRQ 2013 PAD Report, the BHE literature review included comparative endovascular vs. endovascular studies that met the rest of AHRQ's extraction criteria. 2013 AHRQ report available here.

Peer-reviewed literature on endovascular therapies published since 2013 AHRQ PAD Report

Peer reviewed publications on endovascular interventions meeting AHRQ literature extraction criteria (with the inclusion of endo vs. endo trials):*

35 study publications between August 2012 – May 2015



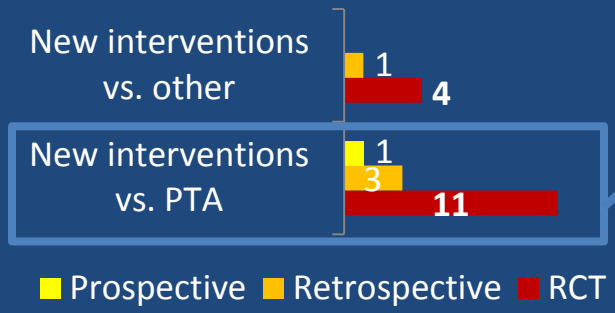
*Based on internally commissioned literature review done by Boston Health Economics (BHE) in June 2015. Unlike the AHRQ 2013 PAD Report, the BHE literature review included comparative endovascular vs. endovascular studies that met the rest of AHRQ's extraction criteria. See the Appendix for the citations of these 35 publications and for an overview of AHRQ's inclusion criteria. No publications evaluating endovascular interventions for asymptomatic PAD patients met AHRQ's inclusion criteria. Publications that included IC and CLI were included in both categories.

**Study classified as meeting on one the following: a mixture of IC and CLI patients (i.e., not separated), vague/broad ailment such as 'lower extremity vascular disease' or 'extremity vascular occlusion'

Since the 2013 AHRQ report, new endovascular treatments have demonstrated improved outcomes over standard PTA

15 of the 20 comparative endovascular studies published since 2013 AHRQ PAD report compare new endovascular interventions to PTA; 11 of the 15 are RCTs

Types of Comparative Endovascular Studies (n=20)



Results of 15 studies of new endo therapies vs. PTA:

- 10 found *statistically significant* improvements in clinical outcomes compared to PTA alone
  - Higher patency rates[5, 18-24]
  - Lower TLR rates, lower restenosis rates, and/or lower adverse event rates[18-24,26]
- 4 of the 15 studies did not find statistical difference[28-31] and 1 found mixed results[32]

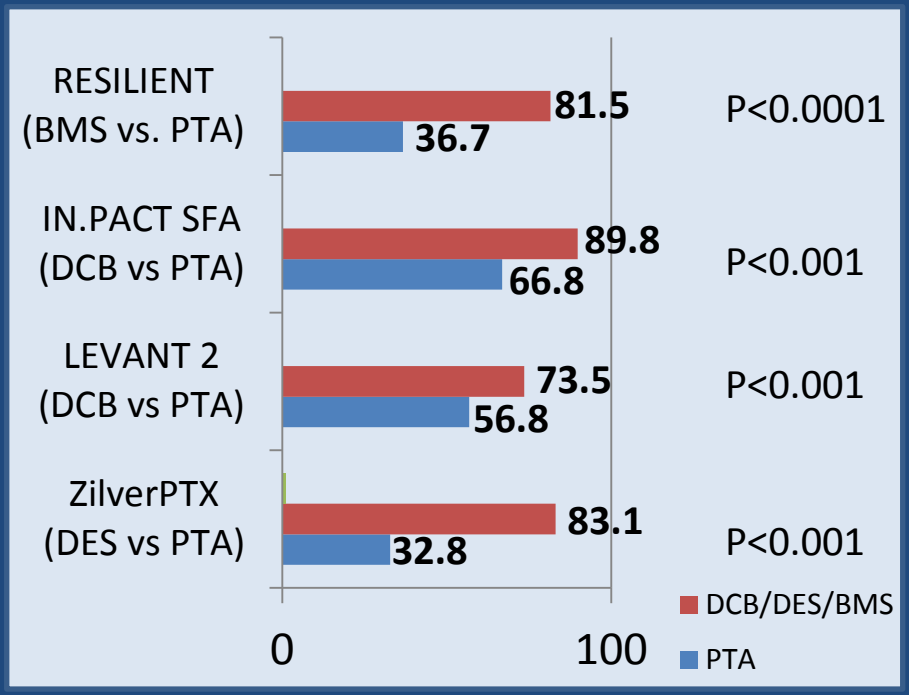
- **Patency** evaluates the ability of the treated artery to remain open for improved blood flow
- **Clinically-driven target lesion revascularization (TLR)** is an important endpoint because a repeat intervention exposes patients to additional procedure risks, morbidity, and more hospitalizations
  - Symptom relief and avoidance of repeat interventions is of chief concern for patients

Note: The exact definitions for primary patency and clinically-driven TLR and the analysis windows are defined in the clinical study protocols and publications and vary from trial-to-trial. Data is presented for illustrative purposes only. See Appendix for more detail.

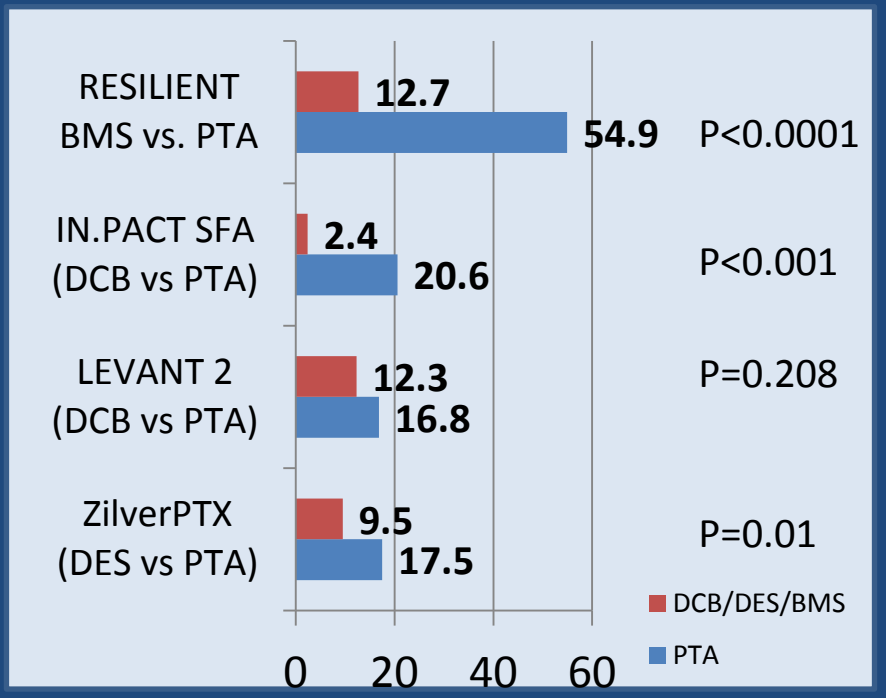
PTA: percutaneous transluminal angioplasty

RCTs comparing newer endo therapies demonstrate significant improvements over PTA alone

Improved Primary Patency (%) by Kaplan-Meier Estimate at 1-Year[1]



Clinically-Driven TLR at 1-Year[1]

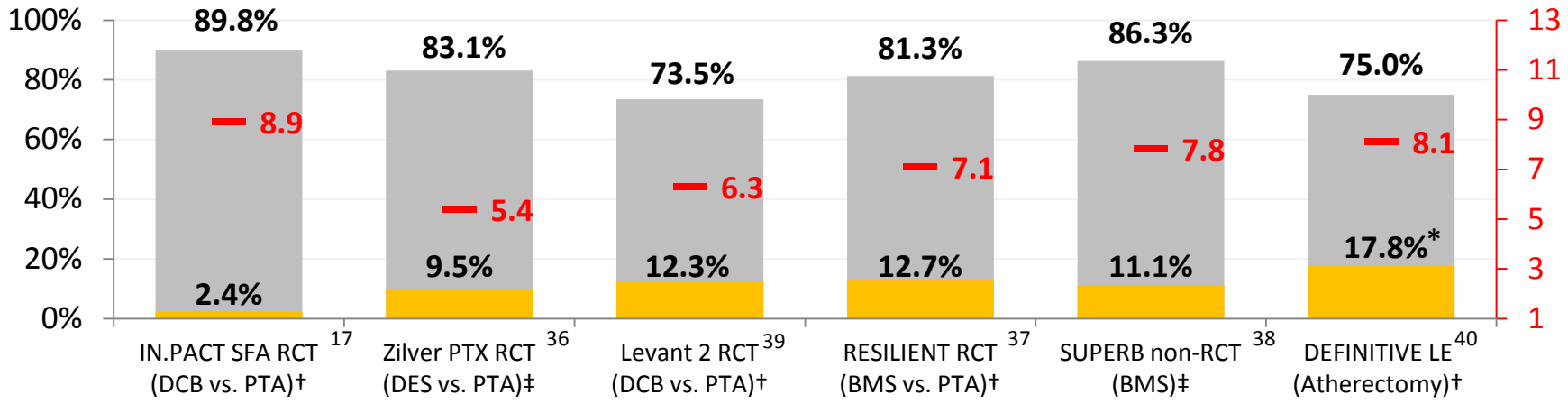


PTA patients required 5 to 8.6 times more interventions to achieve the same level of functional performance as newer endo therapies at 1 year

[1] The definitions for primary patency and clinically-driven TLR and the analysis windows are defined in the clinical study protocols and publications and vary from trial-to-trial. Data is presented for illustrative purposes only. See Appendix for more detail.
IN.PACT SFA - Ref. 17; LEVANT 2 – Ref. 39; Zilver PTX – Ref. 36; RESILIENT – Ref. 37

High patency and low TLR rates seen in studies of complex patients with long, calcified lesions & co-morbidities

Fem-Pop Therapies 12-month Patency and TLR from Multicenter Independently Adjudicated IDE Trials



Primary Patency Survival Estimate at 12-month Follow-up

TLR or Clinically-driven TLR (actual event rates or derived by survival estimates); TVR for DEFINITIVE LE*

Mean lesion length (cm)

Duplex derived Primary Patency based on PSVR ≤2.4 **(†)** or PSVR ≤2.0 **(‡)**

The **percentage of patients with diabetes** in the treatment arms **ranged from 38% to 52%** across all six studies

*17.8% TVR. The DEFINITIVE LE evaluated target vessel revascularization rates (TVRs), rather than target lesion revascularizations (TLRs).
The definitions for primary patency and clinically-driven TLR and the analysis windows are defined in the clinical study protocols and publications and vary from trial-to-trial. Data is presented for illustrative purposes only. See Appendix for more detail.
Fem: Femoral Pop: Popliteal

Significant QoL and functional improvements with newer endo therapies at 1 year

DCB vs. PTA (2 RCTs)[17,39]

- Patients in the DCB arm had **better EQ-5D results** at 6 months and 1 year relative to the baseline than patients in the PTA arm*[17]
  - While gains in walking ability were significantly improved in both arms at 1 year, **8.6 times as many TLRs were required in the PTA arm** to achieve similar outcomes
- WIQ scores favored the DCB arm but only the walking distance was statistically significant (P<0.001)[39]

Modern BMS (Prospective, multi-center, single arm study) [38]

- Patients receiving a modern BMS demonstrated statistically **significant improvements in functional and QoL measures** from baseline that was sustained out to 1 year (SF-12 and peripheral artery questionnaire)

DES vs. PTA (RCT)[36]

- While WIQ scores were significantly improved in both arms at 1 year, almost **twice as many TLRs were required in the PTA arm** to achieve similar outcomes

Atherectomy (Prospective, multi-center, single arm study)[40]

- **QoL measurements revealed statistically significant improvements** from baseline in all categories at 30 day and 1 year (EQ-5D and WIQ)

*At 6 months, the improvement on EQ-5D in DCB arm was statistically significant over PTA. At 12 months, there was a trend toward better EQ-5D results at 12 months for the DCB group vs PTA (p=0.095), but this did not achieve statistical significance.
EQ-5D: Validated patient-reported quality of life (QoL) instrument produced by the EuroQoL Group
WIQ: Walking Impairment Questionnaire
The Peripheral Artery Questionnaire is a clinically validated disease-specific health status questionnaire

IC and CLI patients experience significantly fewer adverse events with endo compared to other treatment modalities

IC Patients

- **Fewer repeat procedures compared to *exercise*** (RCT, 151 patients, 7 years, P=0.014)[1]
- **Fewer CV events compared to *usual care*** (prospective, observational study, 236 patient, 3.33 years, P=0.001)[2]
- **Fewer complications, higher patency rates, lower infection rates, and lower MACE rates compared to *open surgical procedures*** (prospective, observational study, 263 patients, 6 years, P<0.001, P<0.01, P=0.004, P<0.001)[3]

CLI Patients

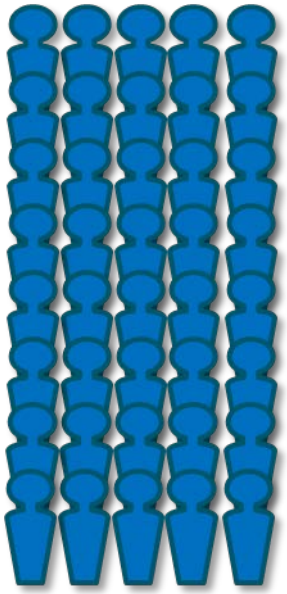
- **Lower all-cause mortality compared to *open surgical procedures*** (retrospective study, 161 patients, 11 years, P<0.05)[7]
- **Better survival rate compared to *open surgical procedures*** (prospective, observational study, 147 patients, 7 years, P=0.005)[10]
- **Lower infection rates compared to *open surgical procedures*** (retrospective analysis of prospectively collected data, 10,547 patients, 5 years, P<0.001)[4]

MACE: major adverse cardiac event

CONTINUED INVESTMENTS IN CLINICAL RESEARCH ON ADVANCEMENTS IN ENDOVASCULAR THERAPIES & TREATMENT OF PAD

Industry continues to invest in multiple clinical trials to further strengthen the evidence for PAD treatments

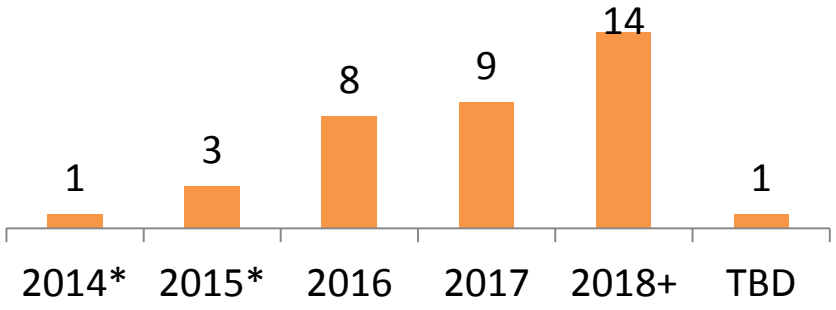
More than 8,800 patients across 36 ongoing studies



Abbott Vascular, Boston Scientific, C.R. Bard, Medtronic, & Gore Medical

- **Of the 36 ongoing studies** evaluating new endovascular therapies…
  - — **23** are **in both the IC and CLI patient populations**
  - — **13** are **in** the **IC patient population**
- **9** of the 36 ongoing studies **are** prospective, multi-center, **RCTs**
- **3.6 years** is the **average duration** of the ongoing studies

Distribution of Ongoing Studies by Estimated Year of Completion (n=36)



*Drafting manuscripts for study completed in 2014 and one of studies that recently ended in 2015

Key takeaways

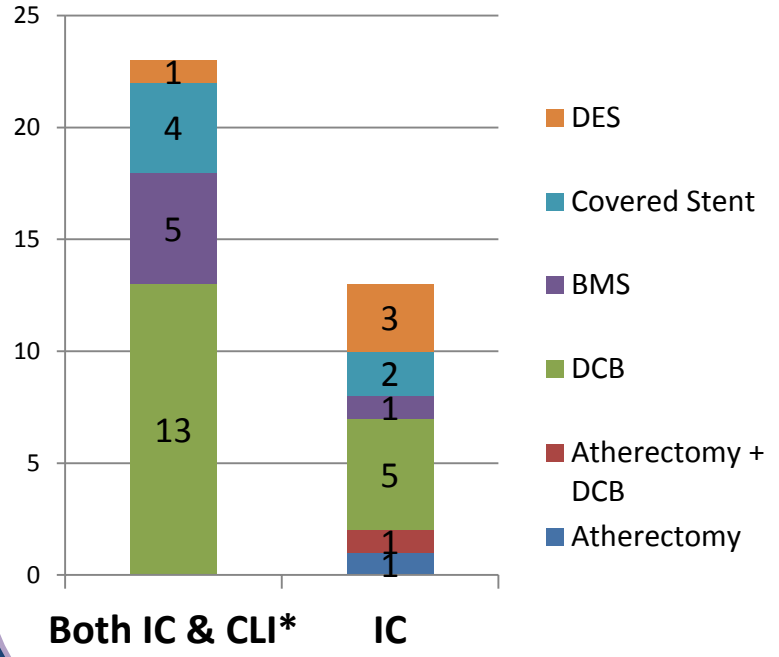
- Based on the expanding evidence base, endovascular therapies have generated significant and sustained clinical improvements for PAD patients
  - ✓ Improved patency rates
  - ✓ Reduced need for reintervention
  - ✓ Reduced complications
  - ✓ Improved quality of life
  - ✓ Improved functional status
- Endovascular therapies are increasingly recommended and used for the treatment of PAD patients by clinicians
- Industry has many clinical studies in progress that will further strengthen the evidence available to PAD patients and their providers and support continued innovation to improve patient outcomes

APPENDIX:

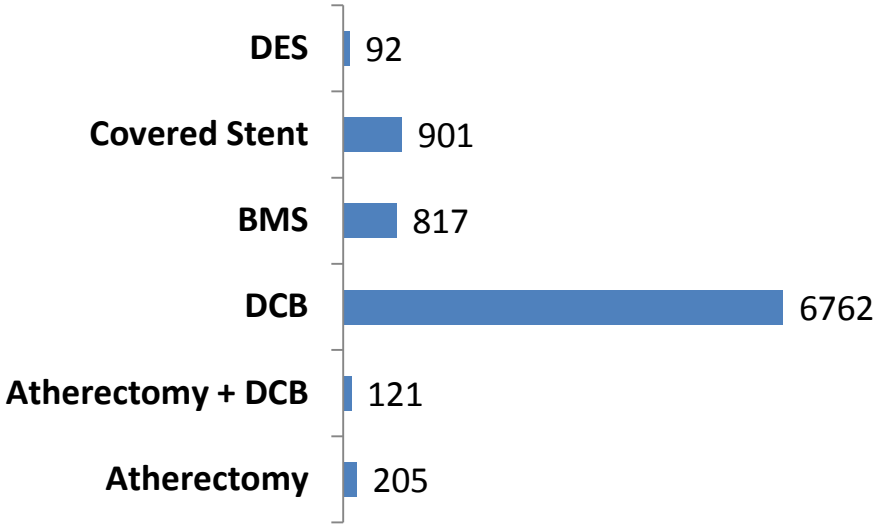
1. Detail on ongoing studies
2. References of the 35 comparative, published studies since 2013 AHRQ PAD review and additional studies cited in slides
3. Study inclusion criteria from 2013 AHRQ PAD Report that was replicated to identify studies published since the report
4. Definitions of key study endpoints in PAD trials

Ongoing studies evaluate a variety of endovascular therapies in the IC and CLI patient populations

Distribution of Ongoing Studies by Therapy Type and Patient Population (n=36)



Number of Patients in Ongoing Studies by Therapy Type (n=8,898)



*Studies included patients with critical limb ischemia (CLI) and intermittent claudication (IC)

DES: Drug eluting stent BMS: Bare Metal Stent DCB: Drug Coated Balloon

13 Ongoing Studies for Patients with IC (1 of 3)

Study Name	Sponsor	Objective	Design	n	Duration	Est. Completion
Atherectomy						
JET Registry[1]	Boston Scientific	To observe the treatment effects of the MEDRAD Jetstream NAVITUS System in long, occluded, diffuse, thrombotic or calcified lesions in PAD of the common femoral, SFA, or popliteal arteries	Prospective, multicenter non-RCT	205	1 year	Jan-2016
Atherectomy + DCB						
DEFINITIVE AR[2]	Medtronic	To evaluate the long-term effect of treating a vessel with plaque excision in combination with DCB compared to PTA alone	Prospective, multicenter, RCT	121	1 year	Jun-2015
DCB						
IN.PACT SFA[3]	Medtronic	To evaluate the long-term effect of the IN.PACT Admiral DCB vs. PTA when used to treat atherosclerotic lesions in the SFA and/or PPA	Prospective, multicenter, RCT	331	5 years	Jun-2018
IN.PACT SFA II Health Economic Study[4]	Medtronic	To evaluate the total costs of DCB vs. PTA through 2 years and cost-effectiveness in terms of cost per repeat revascularization avoided	Prospective, multicenter, RCT	181	2 years	June 2015

13 Ongoing Studies for Patients with IC (2 of 3)

Study Name	Sponsor	Objective	Design	n	Duration	Est. Completion
DCB						
IN.PACT Global[5]	Medtronic	To evaluate the efficacy of the IN.PACT Admiral DCB in the treatment of de novo ISR, long lesions (≥ 15 cm), and CTO (≥ 5 cm)	Prospective, multicenter, non-RCT	1538	5 years	Dec-2020
IN.PACT China[6]	Medtronic	To evaluate the safety and efficacy of the IN.PACT Admiral for the interventional treatment of de novo and non-stented restenotic lesions in SFA and PPA in Chinese patients	Prospective, multicenter, non-RCT	143	1 year	Jan-2017
IN.PACT Japan[7]	Medtronic	To evaluate the safety and efficacy of MDT-2113 for the interventional treatment of de novo and non-stented restenotic lesions in the SFA & PPA compared to standard PTA in Japanese patients	Prospective, multicenter, RCT	100	3 years	Mar-2018
Stents (Bioresorbable)						
ESPIRIT[8]	Abbott Vascular	To evaluate the safety and performance of the ESPRIT BVS in subjects with symptomatic claudication from occlusive vascular disease of the SFA or common or external iliac arteries	Prospective, multicenter, non-RCT	35	3 years	Apr-2017

13 Ongoing Studies for Patients with IC (3 of 3)

Study Name	Sponsor	Objective	Design	n	Duration	Est. Completion
Stents (variety)						
VBL 10-04[9]	Gore Medical	To confirm the safety and performance of the 25 cm GORE® VIABAHN® Endoprosthesis with PROPATEN Bioactive Surface when used in the SFA	Prospective, multicenter, non-RCT	71	3 years	Sept-2015
PI 13-05[10]	Gore Medical	To evaluate the safety and efficacy of PI 13-05 for the treatment of arterial occlusive disease in patients with de novo or restenotic lesions in the common and/or external iliac arteries	N/A	35	3 years	Dec-2017
BES 10-07[11]	Gore Medical	To evaluate the safety and efficacy of the VIABAHN BX for the treatment of arterial occlusive disease in patients with de novo or restenotic lesions in the common and/or external iliac arteries	N/A	135	3 years	Aug-2018
DURABILITY Iliac[12]	Medtronic	To evaluate the clinical efficacy and safety of EverFlex and GPS bare metal self-expanding stents for treatment of lesions in the common and external iliac arteries	Prospective, multicenter, non-RCT	75	3 years	Jan-2016
VISIBILITY Iliac[13]	Medtronic	To evaluate the clinical effectiveness and safety of Visi-Pro bare metal balloon expandable stents for treatment of lesions in the common and external iliac arteries	Prospective, multicenter, non-RCT	75	3 years	Jan-2016

23 Ongoing Studies Evaluating Both IC and CLI (1 of 5)

Study Name	Sponsor	Objective	Design	n	Duration	Est. Completion
DCB						
SAFE-DCB Registry[19]	C.R. Bard	To conduct a post-market evaluation of Lutonix DCB in SFA and popliteal arteries	Single arm	1000	5 years	2020
Levant 2[20]	C.R. Bard	To evaluate the safety and effectiveness trial of Lutonix DCB in SFA/PA	RCT	476	6 years	2020
Levant 2 Continued Access Registry[21]	C.R. Bard	To evaluate the safety and effectiveness trial of Lutonix DCB in SFA/PA	Single arm	576	6 years	2019
Levant 2 Safety Registry[22]	C.R. Bard	To evaluate the safety and effectiveness trial of Lutonix DCB in SFA/PA	Single arm	100	6 years	2019
Global DCB SFA Registry[23]	C.R. Bard	To evaluate thecclinicial use and safety of Lutonix DCB for SFA/PA in a real-world population	Single arm	700	4 years	2016

23 Ongoing Studies Evaluating Both IC and CLI (2 of 5)

Study Name	Sponsor	Objective	Design	n	Duration	Est. Completion
DCB (continued)						
Lutonix DCB in BTK Arteries[24]	C.R. Bard	To evaluate the safety and effectiveness study of Lutonix DCB in treatment of arteries below the knee (BTK)	Prospective, multicenter, non-RCT	320	7 years	2020
Lutonix DCB-Hemodialysis[25]	C.R. Bard	To evaluate the safety and effectiveness of Lutonix DCB in BTK arteries in hemodialysis patients	Prospective, RCT	36	4 years	2019
DCB SFA Long Lesion Registry[26]	C.R. Bard	To evaluate the clinical use and safety of Lutonix DCB in long lesions of SFA/PA	Prospective, multicenter, non-RCT	112	3 years	2016
DCB SFA ISR Registry[27]	C.R. Bard	To evaluate the safety and effectiveness of DCB in in-stent restenotic lesions of SFA	Prospective, RCT	240	7 years	2021
Levant 2 PAS[28]	C.R. Bard	To conduct a post-market evaluation of DCB for SFA/PA disease in women	Prospective, multicenter, non-RCT	150	4 years	Planning / TBD

23 Ongoing Studies Evaluating Both IC and CLI (3 of 5)

Study Name	Sponsor	Objective	Design	n	Duration	Est. Completion
DCB (continued)						
LEG Registry[29]	C.R. Bard	To conduct a post-market, real-world global registry assessing the clinical use and safety of the Lutonix DCB in arteries of the lower extremity	Prospective, multicenter, non-RCT	500	2 years	2017
Levant Japan[30]	C.R. Bard	To demonstrate the safety and efficacy of MD02-LDCB for the treatment of stenosis or occlusion of the femoral and popliteal arteries in the Japanese population	Prospective, multicenter, non-RCT	110	5 years	2017
DCB + Stent						
DCB + LifeStent[31]	C.R. Bard	To evaluate the safety and efficacy of Lutonix DCB with LifeStent Vascular Stent for treatment of long (10—24 cm) lesions in the SFA	Prospective, multicenter, non-RCT	149	4 years	2017

23 Ongoing Studies Evaluating Both IC and CLI (4 of 5)

Study Name	Sponsor	Objective	Design	n	Duration	Est. Completion
Stents (variety)						
SuperNOVA[14]	Boston Scientific	To determine whether the Innova Nitinol Stent System (BMS) shows acceptable performance in long-term (12-month) safety rates and vessel patency when treating femoropopliteal lesions	Prospective, multicenter, non-RCT	299	3 years	Jul-2016
MAJESTIC[15]	Boston Scientific	To determine whether the BSX nitinol DES shows acceptable performance at 9 months when treating SFA and/or PPA lesions up to 110 mm in length.	Prospective, multicenter, non-RCT	57	3 years	Mar-2017
ISR 14-04[16]	Gore Medical	To evaluate post-market safety and effectiveness of GORE® VIABAHN® Endoprosthesis for treatment of in-stent restenosis of the SFA	Prospective, multicenter, non-RCT	108	3 years	Dec-2020
VJH 11-01[17]	Gore Medical	To evaluate the utility of GP1101 vs. surgical bypass in the treatment of Femoral/Popliteal Arterial Symptomatic PAD using bypass data from a retrospective study	Prospective, multicenter, non-RCT	133	3 years	Aug-2018
PCE 09-02[18]	Gore Medical	To evaluate the safety and effectiveness of the TIGRIS Vascular Stent in the treatment of de novo and restenotic atherosclerotic lesions, ≤24cm in length, in the SFA/PPA of patients with symptomatic PAD	Randomized study	269	3 years	Aug-2017

23 Ongoing Studies Evaluating Both IC and CLI (5 of 5)

Study Name	Sponsor	Objective	Design	n	Duration	Est. Completion
Stents (variety, continued)						
BOLSTER[32]	C.R.Bard	To evaluate safety and effectiveness of LifeStream balloon expandable covered stent in treatment of iliac artery occlusive disease	Prospective, multicenter, non-RCT	150	4 years	Dec-2017
CONTINUUM[33]	C.R.Bard	To conduct a post-market evaluation of LifeStent Vasculat Stent System (BMS)	Prospective, multicenter, non-RCT	234	5 years	Sep-2016
REALITY[34]	C.R.Bard	To evaluate the performance of LifeStent vascular stent 5 mm diameter (BMS)	Prospective, multicenter, non-RCT	30	2 years	2014
REALITY 2[35]	C.R.Bard	To evaluate the performance of LifeStent vascular stent 250 mm length (BMS)	Prospective, multicenter, non-RCT	30	2 years	2016
RELIABLE[36]	C.R. Bard	To evaluate the safety and effectiveness of LifeStent in Japan (BMS)	Prospective, multicenter, non-RCT	74	4 years	2017

References for Ongoing Studies

Reference #	Study Name	ClinicalTrials.gov #
1	JET Registry	NCT01436435
2	DEFINITIVE AR - Two-Year Follow-Up Extension Study	NCT02363894
3	IN.PACT SFA	NCT01566461
4	IN.PACT SFA II Health Economics Sub-study	N/A
5	IN.PACT Global	NCT01609296
6	IN.PACT China	NCT02118532
7	IN.PACT Japan	NCT01947478
8	ESPRIT	NCT01468974
9	VBL 10-04	NCT01263665
10	PI 13-05	NCT01961167
11	BES 10-07	NCT02080871
12	DURABILITY Iliac	NCT01400919
13	VISIBILITY Iliac	NCT01402700
14	SuperNOVA	NCT01292928
15	MAJESTIC	NCT01820637
16	ISR 14-04	Not registered yet
17	VJH 11-01	NCT01575808
18	PCE 09-02	NCT01576055

Reference #	Study Name	ClinicalTrials.gov #
19	SAFE-DCB Registry	NCT02424383
20	Levant 2	NCT01412541
21	Levant 2 Continued Access Registry	NCT01628158
22	Levant 2 Safety Registry	NCT01790243
23	Global DCB SFA Registry	NCT01864278
24	Lutonix DCB in BTK Arteries	NCT01870401
25	Lutonix DCB - Hemodialysis	N/A
26	DCB SFA Long Lesion Registry	NCT02013271
27	DCB SFA ISR Registry	NCT02063672
28	Levant 2 PAS	Not registered yet
29	LEG Registry	NCT02043951
30	Levant Japan	NCT01816412
31	DCB + LifeStent	NCT02278991
32	BOLSTER	NCT02228564
33	CONTINUUM	NCT02228564
34	REALITY	NCT01920308
35	REALITY 2	NCT02262949
36	RELIABLE	NCT01746550

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2013 AHRQ PAD Study Inclusion Criteria*

Patient Population

- Adult patients ≥18 years of age with lower extremity PAD (e.g., ABI <0.9 who are asymptomatic or symptomatic [atypical leg symptoms, IC, or CLI])

Studies

- Comparative studies of LE PAD treatment interventions
- Note: for the update, Boston Health Economics included publications comparing endovascular vs. endovascular treatments that met the other search criteria

Timing

- Short-term studies (30 days, intermediate term (31 days to 1 year)
- Long-term (>1 year) studies

Setting

- Inpatient and outpatient

Safety

- Included

Publications

- English-language only
- Peer-reviewed article

Time Period

- 2013 AHRQ report evaluated literature from January 1995 – August 2012. For the update, Boston Health Economics evaluated literature from August 2012 to May 2015

*See Table 3 of the 2013 AHRQ PAD Report for more detail on the inclusion criteria Boston Health Economics replicated in their targeted update

Overview of select study endpoints in PAD trials

- Primary Patency
  - Absence of restenosis, which means a re-narrowing of the artery
  - Patency evaluates the ability of the treated artery to remain open for improved blood
- Restenosis
  - An important measure of effectiveness for endovascular therapy
  - Objective evaluation with post-procedure imaging
- Target lesion revascularization (TLR)
  - Repeat intervention of the same lesion
  - Important clinical end point as it exposes patients to additional procedural risks and discomforts and reflects a further use of medical resources
- Clinically-driven TLR
  - Similar to TLR, but revascularizations had to be based on severity of symptoms or drop in ankle-brachial index (ABI), reflecting reduced hemodynamic status of the limb rater than an angiopgrahic or anatomic measure alone
- Target vessel revascularization (TVR)
  - Repeat intervention within the target vessel
- EQ-5D:
  - Validated quality of life instrument. Domains include Mobility, Pain/Discomfort, Self-Care. Usual Activities, Anxiety/Depression