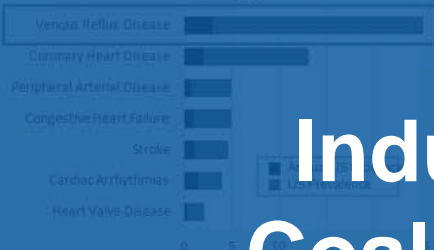


5x More Prevalent Than
Peripheral Artery Disease

Millions



Industry Coalition's Perspective on Chronic Venous Insufficiency

Coalition: Medtronic, Vascular Insights,
Boston Scientific, C. R. Bard, and
AngioDynamics

Medicare Evidence Development
& Coverage Advisory Committee
(MEDCAC)

Lower Extremity Chronic
Venous Disease
July 20, 2016

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Disclosures

- Medtronic employee and shareholder (major)
- No other conflicts of interest

Our Presentation Will Address MEDCAC Voting Question # 1 & Focus on Endovascular Treatments


1. For adults **with varicose veins and/or other clinical symptoms or signs of chronic vein insufficiency**, how confident are you that there is sufficient evidence for an intervention that improves:
 - a) Immediate/near-term health outcomes in patients with symptoms?
 - b) Long-term health outcomes in patients presenting with symptoms?

Intervention of focus: endovascular treatments

Presentation Overview



Burden of chronic venous insufficiency (CVI) to patients and Medicare



The shift from painful stripping to endovascular treatments for CVI



Results of an independent review of the evidence on endovascular treatments for symptomatic CVI



Continued investments to further strengthen the evidence base for appropriate CVI care

Venous Insufficiency and Its Consequences¹

The Pump

Arterial Blood Pump



The Heart

Venous Blood Pump

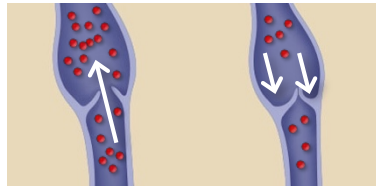
The Foot and Calf



Importance of Vasculature in Leg

The Valves

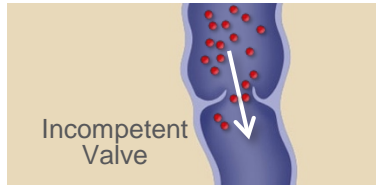
Normal Vein



Valve Open

Valve Closed

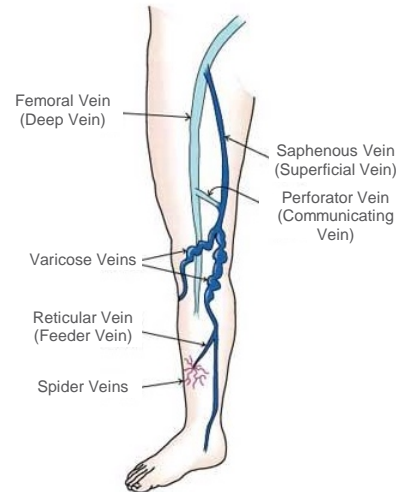
Diseased Vein



Incompetent Valve

Valve Failure Leads to Backward Blood Flow and Pooling in Lower Leg Veins

The Anatomy



Saphenous Vein Insufficiency Most Common Cause

The Condition





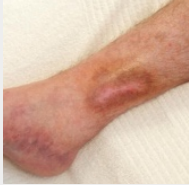
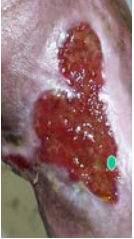


Tired, Aching, Swollen Legs – Progressing in Severity if Untreated

- 5X more prevalent than peripheral arterial disease—affecting 30M in the U.S.²⁻³
- Affects 1 out of 2 people ≥ 50 years and is more common in women⁴
- Up to 72% of leg ulcers are caused by chronic venous disease⁵

CVI Is A Serious, Progressive Disease

Left Untreated, CVI Can Develop Into Debilitating Venous Ulcers

	SIMPLE SPIDER VEINS	SIMPLE VARICOSE VEINS	ANKLE EDEMA OF VENOUS ORIGIN	SKIN DAMAGE	HEALED VENOUS ULCER	OPEN VENOUS ULCER
						
Disease Scoring	CEAP 1	CEAP 2	CEAP 3	CEAP 4	CEAP 5	CEAP 6
% Affected¹		24%	13%	36%	7.3%	2.3%
Treatment Path	"Watch"	Routine Vein Specialist Referral	Rapid Vein Specialist Referral			Urgent Vein Specialist Referral

2.2% is the average annual incidence rate of venous leg ulcers in the Medicare population²

Guidelines Support the Use of Endovascular Treatments in Managing Venous Ulcers

AVF/SVS 2011 Clinical Guidelines: To prevent recurrence, we recommend ablation of the incompetent superficial veins in addition to compression therapy in patients with venous leg ulcer (C6) and incompetent superficial veins (Grade 1B)

The Problem for Patients & Medicare



- The majority of patients with VLUs require assistance with activities of daily living¹
- Medicare beneficiaries with VLUs cost \$6,391 more each year in medical costs than matched non-VLU beneficiaries²

IMPACT of Endovascular Treatment

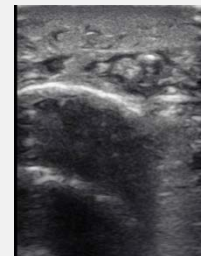
Physiologic Impact

BEFORE



Ulcer Bed

AFTER



Ulcer Bed

Patient Experience

BEFORE



Pre-Procedure

AFTER



11 Months Later

59-Year-Old Male with a History of LLE Persistent Ulcer(s) Since 2003

Minimally Invasive Therapies Have Replaced Painful Surgical Stripping in the Management of CVI

Surgical Intervention



Pre 2000

Highly Invasive
Long Healing Times
Increased Complications

Often Requires General Anesthesia and a Hospital Stay⁵

Endovascular Interventions Today's Standard of Care

Thermal
Tumescent
(Laser and RF)

Non-Thermal
Tumescent

Non-Thermal
Non-Tumescent
Non-Sclerosant

2000-2015

Continued Evolution of Endovascular Care with the Goals of Improving Clinical Outcomes, Quality of Life, and Functional Outcomes in Near- and Long-Term¹⁻⁴

No Need for General Anesthesia and Typically an Office-Based Procedure⁵

In current practice, a variety of treatment modalities have an important role in managing the treatment of patients with CVI

Endovascular Treatments for CVI Are Securely Rooted in Key Societal & Global HTA Recommendations

U.S Professional Societies

AVF/SVS 2011 Clinical Guidelines for Patients with Varicose Veins and Associated CVD:

Recommend endovenous thermal ablation (laser and radiofrequency) for the treatment of saphenous incompetence rather than high ligation and inversion stripping (Grade 1B)¹

AVF/SVS 2014 Venous Leg Ulcer Clinical

Guidelines: To prevent recurrence, we recommend ablation of the incompetent superficial veins in addition to compression therapy in patients with venous leg ulcer and incompetent superficial veins (Grade 1B)²

ACP 2015 Clinical Guideline for Superficial Venous Disease:³

We recommend endovenous thermal ablation (laser and radiofrequency) is the preferred treatment for saphenous and accessory saphenous vein incompetence (Grade 1B)

We suggest mechanical/chemical ablation may also be used to treat truncal venous reflux (Grade 2B)

Global HTA Recommendations

UK NICE 2013 Clinical Guideline: Recommend endothermal ablation (laser and radiofrequency) as an interventional treatment for patients with confirmed varicose veins and truncal reflux. If endothermal ablation is unsuitable, recommend ultrasound-guided foam sclerotherapy⁴

UK NICE IPG 2015: Recommend cyanoacrylate glue occlusion for varicose veins with proper informed consent⁵

UK NICE IPG 2016: Recommend endovenous mechanochemical ablation (MOCA) for treatment of varicose veins on standard arrangements⁶

**Results of an
Independent Review of
the Evidence on
Endovascular
Treatments for
Symptomatic CVI**

Independent Review of Evidence on Endovascular Therapies Mirrored AHRQ's Inclusion Criteria

- Literature search in Embase, PubMed and Cochrane library to identify published original data based on AHRQ literature extraction criteria which included:^a
 - RCTs, prospective and retrospective observational studies with a comparator
 - English-language only
 - Sample size ≥ 20 subjects
 - Published between January 2000 – May 2016
- Among 8546 search results, 256 relevant studies were identified on initial screening
- Further screening of full-text articles identified **126** studies that have been analysed^c
 - Study duration range – 1 week to 10 years follow-up
 - Mean age range^b– 18 to 79 years

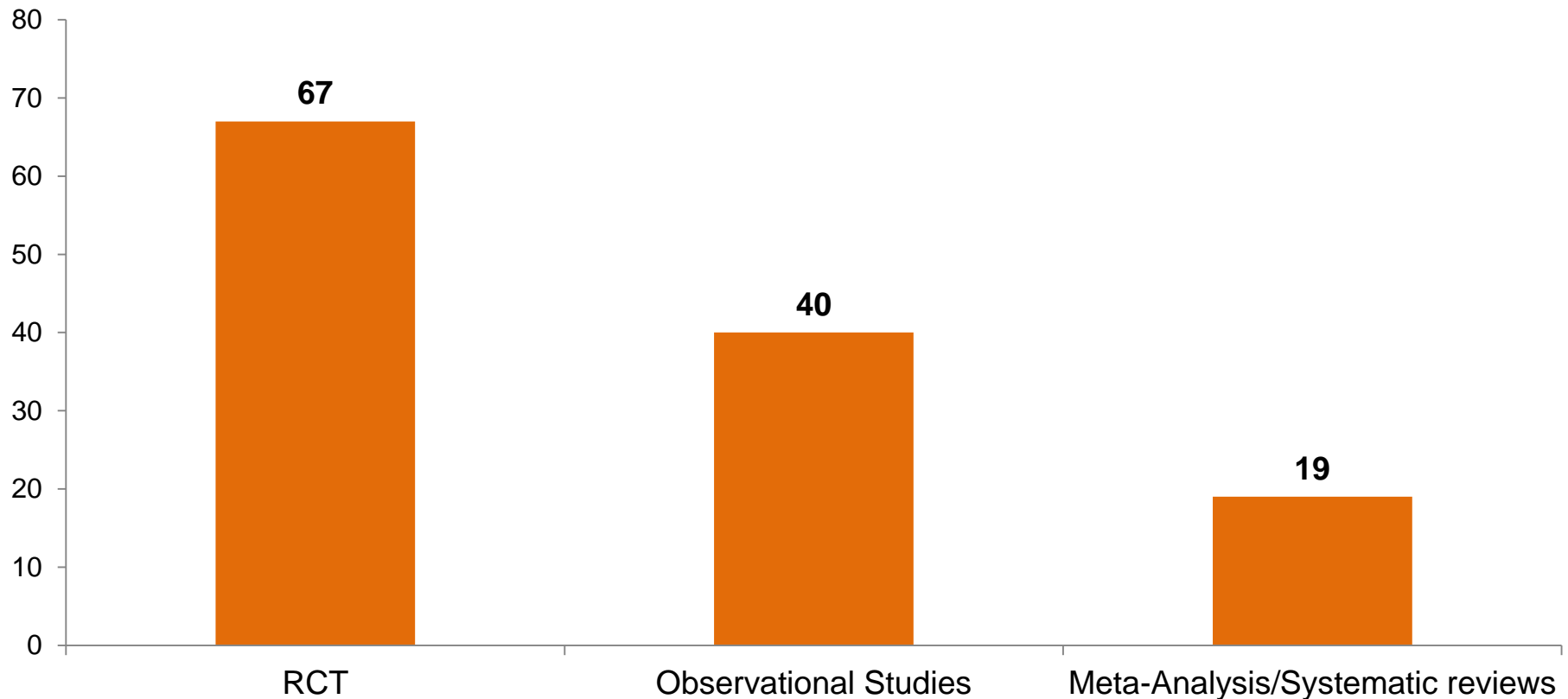
^a Based on internally commissioned literature review done by Indegene Healthcare in May-June 2016. The inclusion criteria Indegene employed is based on AHRQ's Evidence-based Practice Center Systematic Review Protocol for Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease (LECVD) available on AHRQ TAP website [here](#).

^b Studies reporting median age not included to provide mean age range.

^c Excel spreadsheet of all 126 studies available upon request.

A Robust Number of Peer-Reviewed Literature on Endovascular Therapies Published Since 2000

Peer-reviewed publications on endovascular therapies meeting AHRQ literature extraction criteria (Jan. 2000 – May 2016)

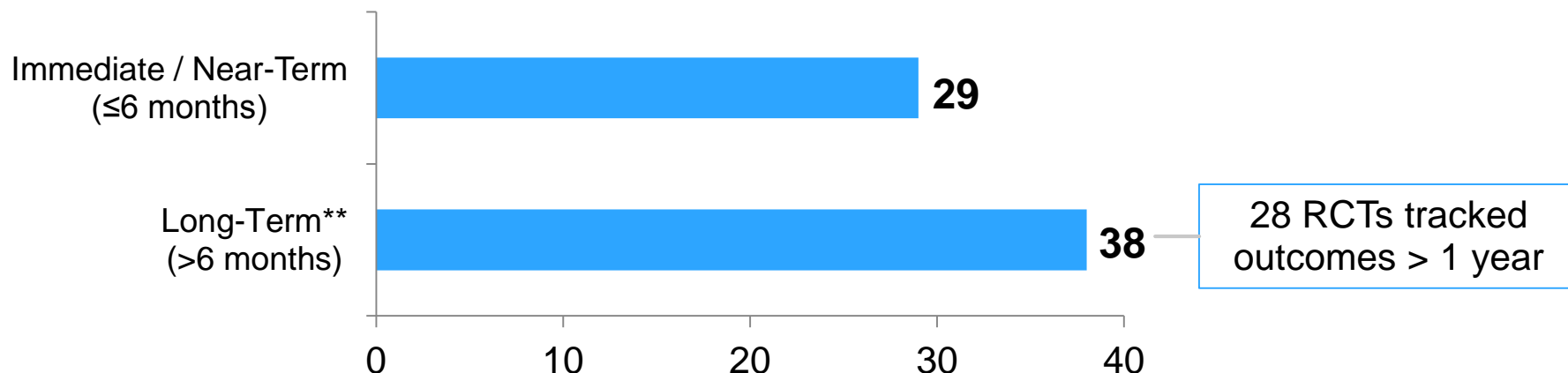


RCT: randomised controlled trial.

Large Number of RCTs Evaluating Near- and Long-Term Outcomes of Endovascular Treatments

Peer-reviewed publications on endovascular therapies meeting AHRQ literature extraction criteria (Jan. 2000 – May 2016)

RCTs of Endovascular Treatments (N=67)



Number of Publications	Observational	Meta-Analysis/ Systematic Review**
Immediate /Near-Term	12	2
Long-Term	28	15

*MEDCAC questions do not define immediate/near-term or long-term, so we employed the definitions from AHRQ's protocol which defines short-term as ≤30 days, intermediate term as 31 days to 6 months and long-term as more than 6 months.

**Durations not explicitly analyzed in 2 of the systematic reviews/ meta-analyses.

Endovascular Therapies Outperform Stripping on Clinical Outcomes in Near- and Long-Term...

HIGHER TREATMENT SUCCESS RATES^a

- In studies of duration ranging from 6 weeks to 2 years ($P \leq 0.02$ in 4 RCTs and 1 observational study, $N = 770$)¹⁻⁵

LOWER POST-OPERATIVE COMPLICATIONS

- Overall complications rate ($P < 0.02$ in 2 RCTs; $N = 265$)^{6,7}
- Neurological complications ($P < 0.05$ in 3 RCTs; $N = 388$)^{1,2,8}
- Wound infection ($P < 0.05$ in 2 RCTs; $N = 429$)^{5,9}
- Hematoma or ecchymosis ($P < 0.05$ in 3 RCTs; $N = 465$)^{7,9,10}

REDUCED RATES OF RECURRENCE AT 5 YEARS

- Different site recurrence in 1 RCT including 400 patients ($P = .002$)¹¹
- Neovascularization (predictor of future recurrence) in 1 RCT including 118 patients ($P = .001$)¹²

MORE COST-EFFECTIVE

- At 6 months and 5 years (RCT and economic modeling evaluation conducted by NHS; $N=627$)

^aDefined by vein occlusion rate, abolition of venous reflux or recanalization/absence of residual fragments in included studies

...And Demonstrate Statistically Significant Quality of Life and Functional Improvements Over Stripping

BETTER QUALITY OF LIFE SCORES^a

- In studies of duration ranging from 1 week to 2 years ($P \leq 0.05$ in 3 RCTs, N = 273)^{7,8,13}

SHORTER RECOVERY TIME TO RESUME WORK & ROUTINE ACTIVITIES

- $P \leq 0.05$ in 9 RCTs and 1 observational study, N = 1901^{1,2,5-9,14-17}

REDUCED PAIN

- $P \leq 0.05$ in 7 RCTs and 2 observational studies, N = 1789^{1,8,9,13-18}

IMPROVED PATIENT SATISFACTION

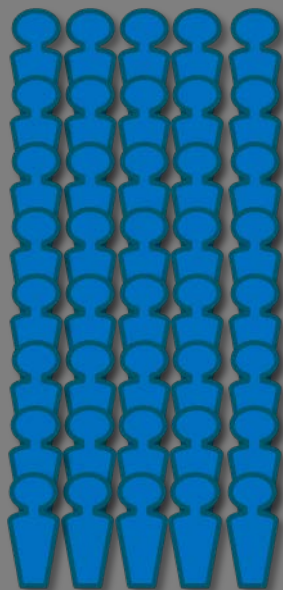
- $P \leq 0.05$ in 2 RCTs, N = 408^{8,9}

^a Measured by VEINES-QoL/Sym questionnaire, CIVIQ2 questionnaire in included studies.

**CONTINUED
INVESTMENTS IN
CLINICAL RESEARCH
ON ENDOVASCULAR
TREATMENTS FOR CVI**

Industry Continues to Invest in Studies to Further Strengthen the Evidence for CVI Treatments

**More than 900 patients
across 5 ongoing studies**



Medtronic, Vascular Insights,
and AngioDynamics

- 5 ongoing studies evaluating the effectiveness of endovascular treatment options for CVI patients
 - 3 track outcomes out to 3 years (1 of 3 out to 5 years)
 - 2 are RCTs against an active comparator
- Support the role post-market studies and registries in generating data on the real-world effectiveness of treatments

Distribution of Ongoing Studies by Estimated Year of Completion



*2015 study completed and awaiting publication of results. April 2016 study completed and awaiting publication of results.

Key Takeaways

- Endovascular therapies have generated significant and sustained clinical and quality of life improvements over stripping in multiple studies
- U.S. clinical guidelines and global HTAs recognize the clinical value of endovascular therapies in managing CVI
- Industry has studies in progress and will continue to make investments that will:
 - Further strengthen the evidence available to CVI patients and their providers and
 - Support continued innovation to improve patient outcomes

APPENDIX

Table of Contents

- Details of ongoing studies
- Slide References
- Study References

5 Ongoing Studies for Patients with Symptomatic CVI (1 of 2)

Study Name	Sponsor	Objective	Design	n	CEAP Score	Duration of Follow-Up	Est. Completion	ClinicalTrials.gov #
VeClose	Medtronic	To demonstrate the safety and effectiveness of VenaSeal Closure System (non Thermal, non Tumescant non-Sclerosant) against radiofrequency ablation for the treatment of incompetent great saphenous veins	Prospective, multicenter RCT	242	C2-4	3 years	Sept-2016	NCT01807585
eSCOPE	Medtronic	To assess the role of the VenaSeal Closure System in closure of incompetent great saphenous veins in a routine clinical setting	Prospective, multi-center, observational post-market study	70	C2-4	3 years	Nov-2015 (awaiting publication)	NCT01570101
MARADONA	Vascular Insights	To compare occlusion rate, post-operative pain and complications between ClariVein (mechano-chemical endovenous ablation) and radiofrequency ablation for the treatment of incompetent great saphenous veins	Prospective, multi-center RCT	460	C2-4b	Up to 5 years	Dec-2019	NCT01936168

5 Ongoing Studies for Patients with Symptomatic CVI (2 of 2)

Study Name	Sponsor	Objective	Design	n	CEAP Score	Duration of Follow-Up	Est. Completion	ClinicalTrials.gov #
WAVES	Lake Washington Vascular Medtronic Research Grant	To assess the efficacy of the VenaSeal Closure System for the treatment of lower extremity superficial truncal veins in a real-world clinical setting. The study will test the hypothesis that VCS a) performed on truncal varicose veins, and b) without mandatory postoperative compression stockings is non-inferior to current therapy (VCS or radiofrequency ablation) of the great saphenous vein (GSV) with use of postoperative compression stockings	Prospective, single-center single-arm trial, with comparison to subject-level historical data from the VeClose Pivotal Trial	50	C2-5	3 Months	Apr-2016 (awaiting publication)	NCT02585726
SeCure	AngioDynamics	To assess the safety and effectiveness of the VenaCure EndoVenous Laser Treatment 400 µm Fiber Kit for treatment of incompetent perforator veins	Prospective, multi-center, single-arm non-blinded clinical trial	86	C4b-C6	3 Months	Oct-2016	NCT02215369

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