How The BEST-CLI Trial Will Change Clinical Practice

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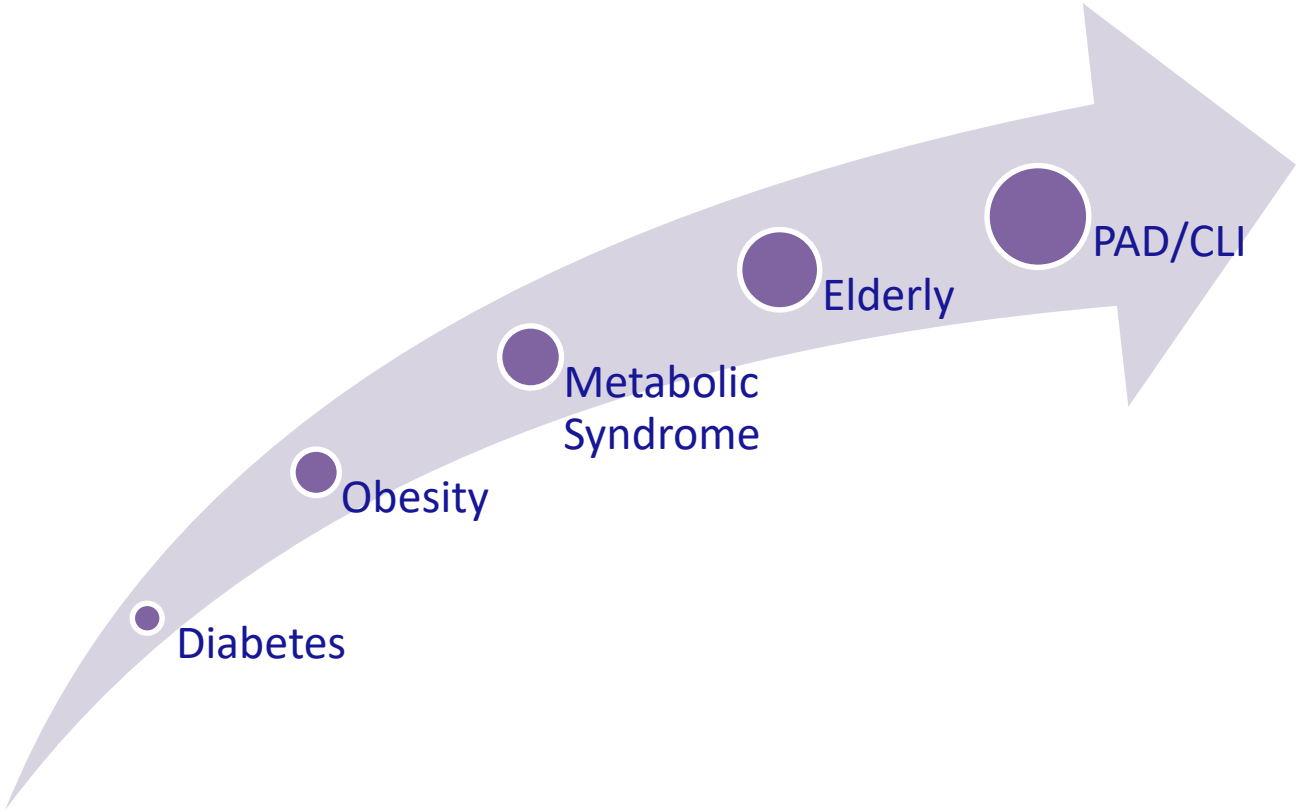
Disclosure Statement of Financial Interest

I, Matthew Menard, DO have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

- ***BEST-CLI Trial Co-Chair***
  - ✧ ***Supported by NHLBI: 1U01HL107407-01A1***
- ***Janssen (SAB)***
- ***Aralez (SAB)***

CLI: A Growing Worldwide Epidemic



An Expensive Problem

National health care costs of peripheral arterial disease in the Medicare population

Alan T Hirsch[1,2], Lacey Hartman[3], Robert J Town[3] and Beth A Virnig[3] *Vascular Medicine* 2008; 13: 209–215

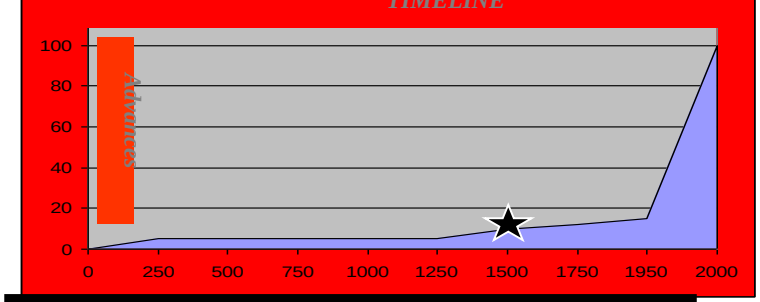
- Medicare expenditure on CLI > $4 billion

  (CHF = $3.9B, Cerebrovascular disease = $3.7B)

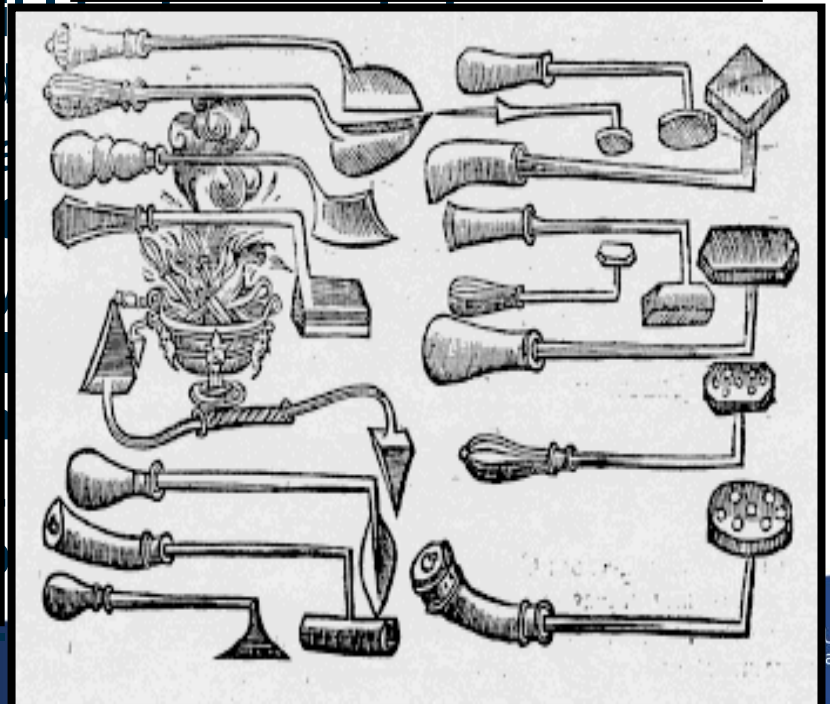
  – 90% inpatient care

  – $1,700 per patient (>2X avg beneficiary)

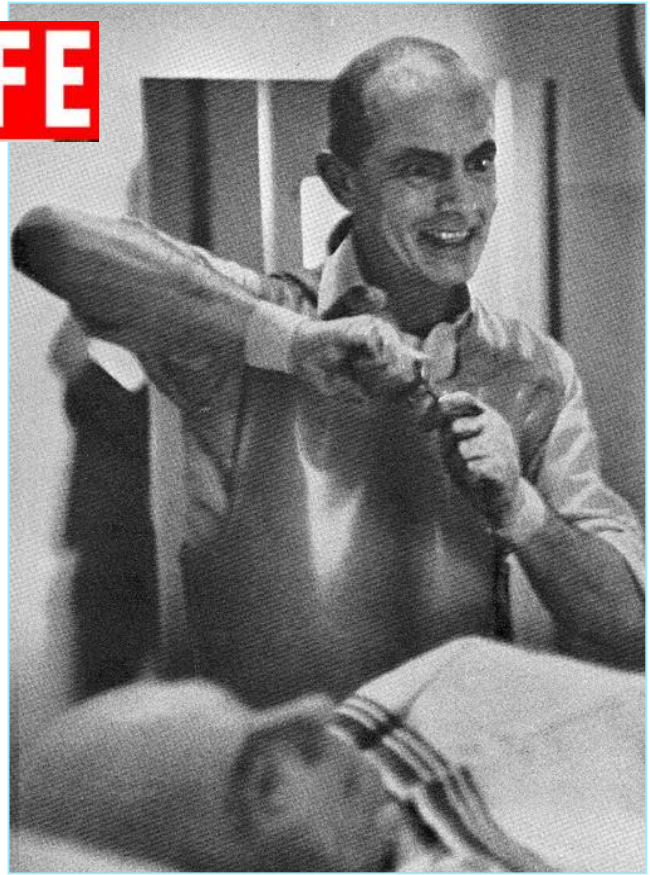
  – 3% of total Medicare budget (THR = 0.9%, TKR 1.7%)



Cautery Devices



Haeger, K. The illustrated History of Surgery, 1988.



1964

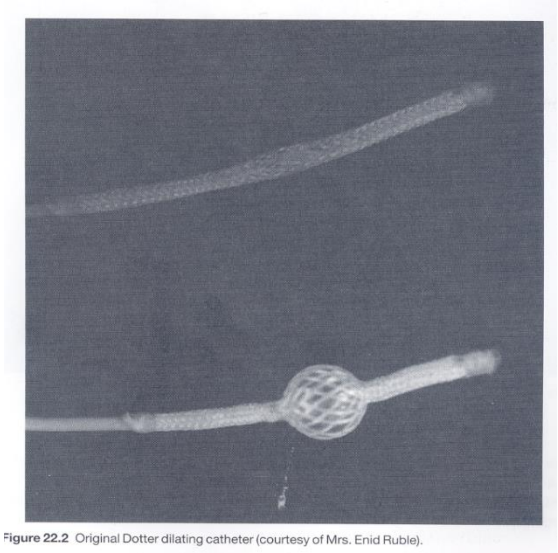
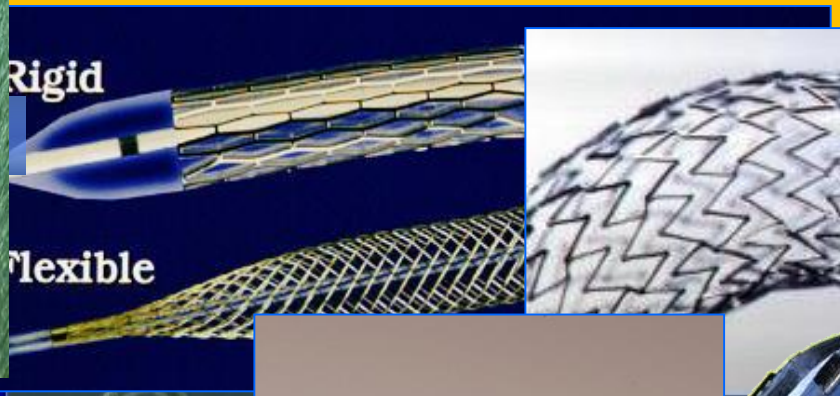
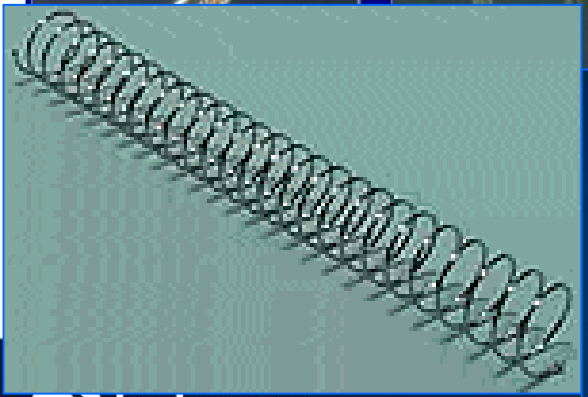
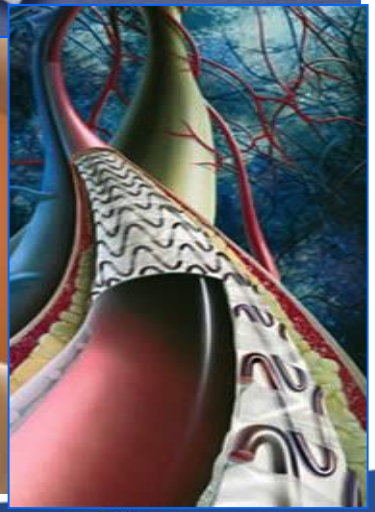


Figure 22.2 Original Dotter dilating catheter (courtesy of Mrs. Enid Ruble).

Endovascular Therapy for CLI



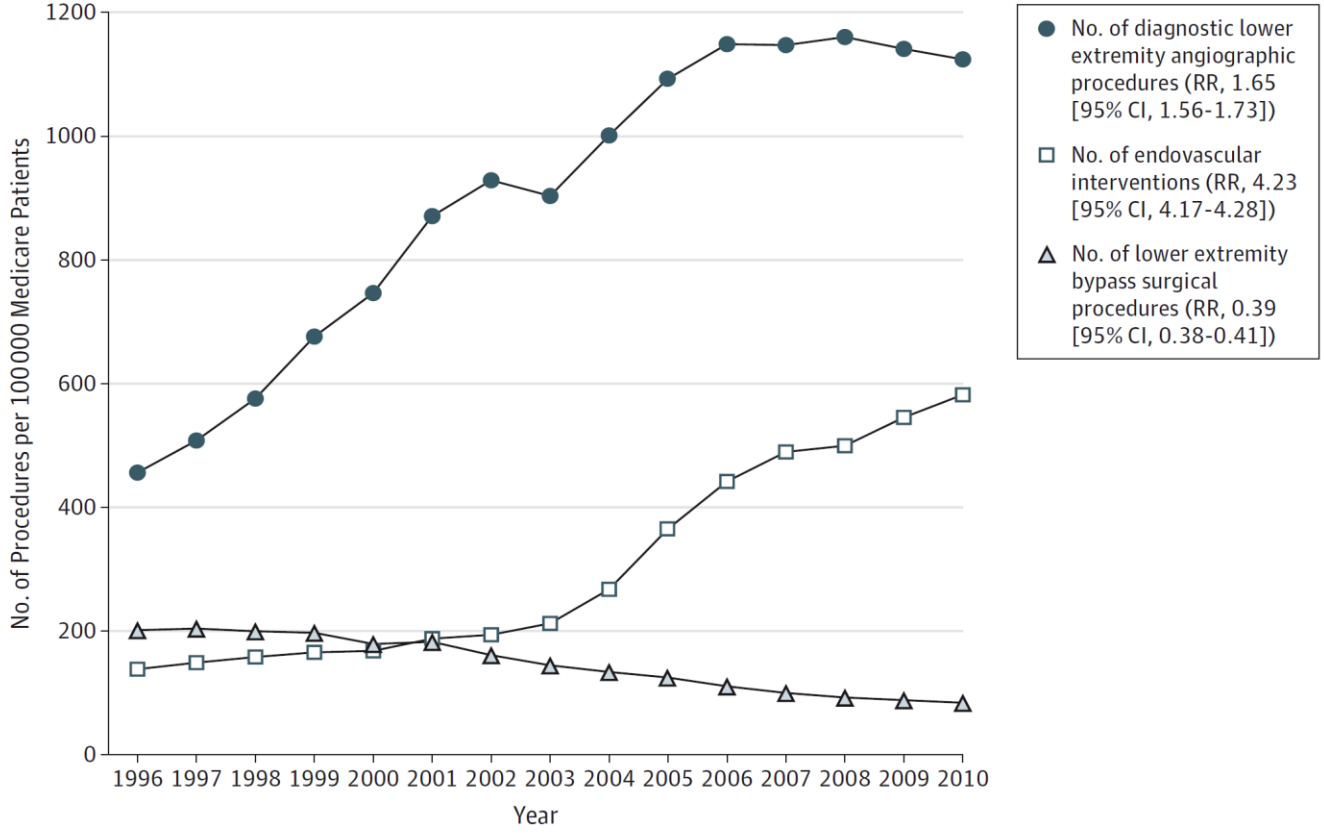




tct2018

Cardiovascular Research Foundation

Figure 2. Trends in Diagnostic Angiography, Therapeutic Endovascular Interventions, and Lower Extremity Bypass Surgery, 1996-2010



Outcomes of Infrainguinal Revascularizations with Endovascular First Strategy in Critical Limb Ischemia

Sjoerd Jens · Anne P. Conijn · Franceline A. Frans · Marieke B. B. Nieuwenhuis · Rosemarie Met · Mark J. W. Koelemay · Dink A. Legemate · Shandra Bipat · Jim A. Reekers

Endovascular-first approach is not associated with worse amputation-free survival in appropriately selected patients with critical limb ischemia

Karan Garg, MD, Patrick A. Kaszubski, BS, Rameen Moridzadeh, BS, Caron B. Rockman, MD, Mark A. Adelman, MD, Thomas S. Maldonado, MD, Frank J. Veith, MD, and Firas F. Mussa, MS, MD, *New York, NY*

Endovascular first strategy for de novo TransAtlantic Inter-Society Consensus C and D femoro-popliteal disease: Mid-term outcomes from a single tertiary referral center

Jeffrey Lorne Grenville[1], Kong Teng Tan[2], Hadas Moshonov[2] and Dheeraj Kumar Rajan[2]

J Cardiovasc Surg (Torino). 2013 Dec;54(6):679-84.

Endovascular first as "preliminary approach" for critical limb ischemia and diabetic foot.

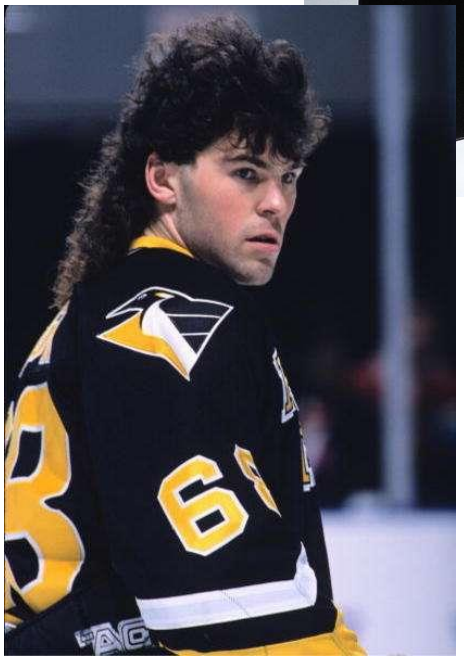
Setacci C[1], Sirignano P, Galzerano G, Mazzitelli G, Sauro L, de Donato G, Benevento D, Cappelli A, Setacci F.

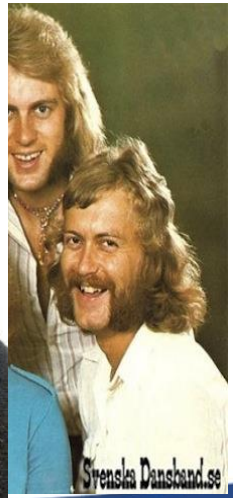
Limb Salvage in Patients With Peripheral Arterial Disease Managed by Endovascular First Approach

Kyin Kyin May, MBBS[1,2], Peter Ashley Robless, FRCS[1,2], Harvinder Raj Singh Sidhu, FRCS[3], Ben Soo Yeng Chua, FRCS[4], and Pei Ho, FRCS[1,2]

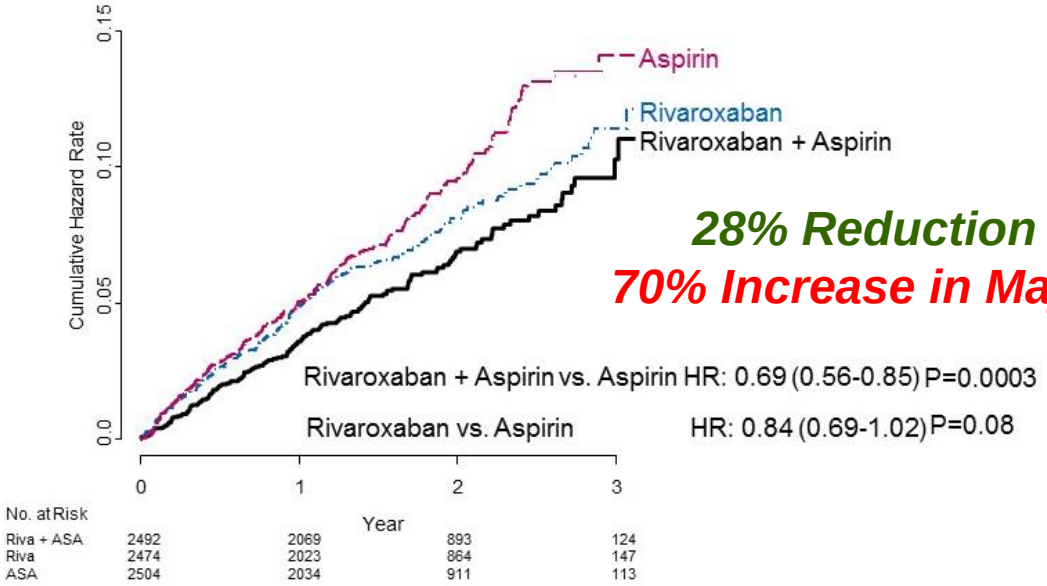
Long-term limb salvage and survival after endovascular and open revascularization for critical limb ischemia after adoption of endovascular-first approach by vascular surgeons

Hasan H. Dosluoglu, MD,[a,b] Purandath Lall, MBBS,[a,b] Linda M. Harris, MD,[b] and Maciej L. Dryjski, MD,[b] *Buffalo, NY*




Svenska Dansband.se

COMPASS Trial PAD+CAD



28% Reduction in MACE

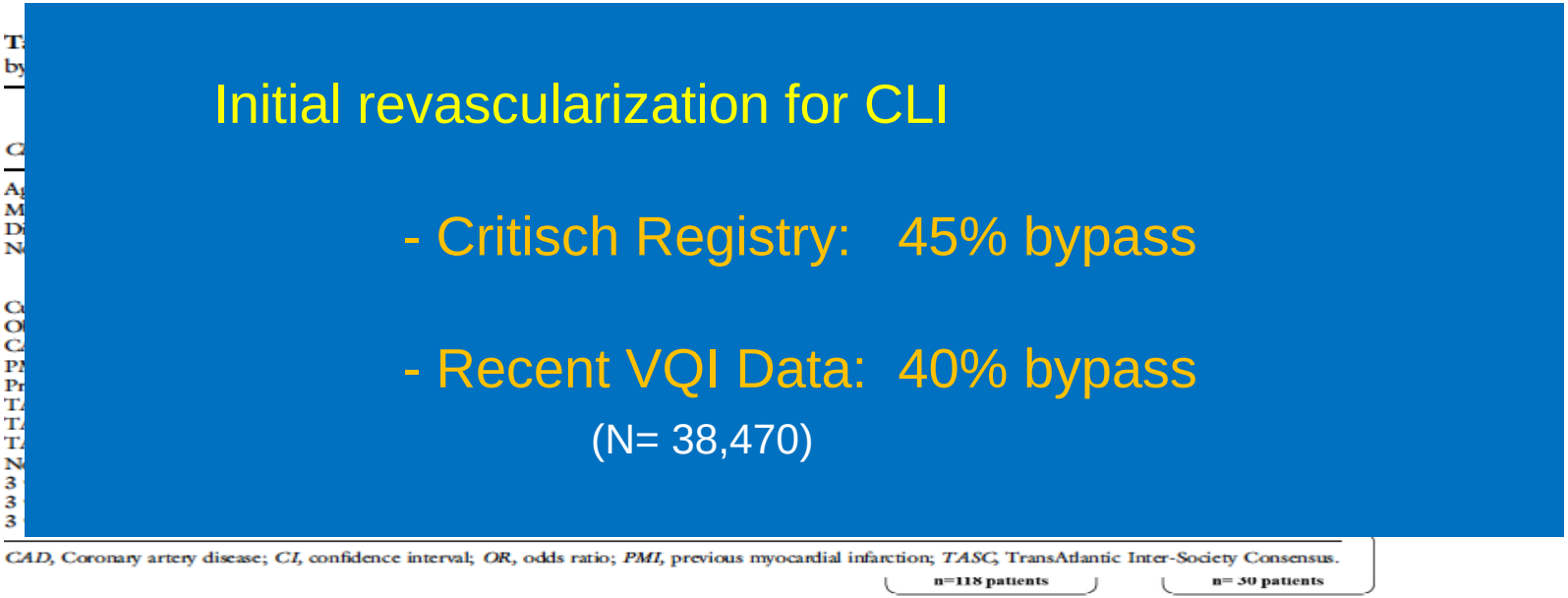
70% Increase in Major Bleeding

Adapted from: N Engl J Med 2007;357:217-27.

>90% with CAD, large subgroup with Concomitant PAD

Current practice of first-line treatment strategies in patients with critical limb ischemia

Theodosios Bisdas, MD,[a] Matthias Borowski, PhD,[b] and Giovanni Torsello, MD,[a] for the First-Line Treatments in Patients With Critical Limb Ischemia (CRITISCH) Collaborators, *Muenster, Germany*

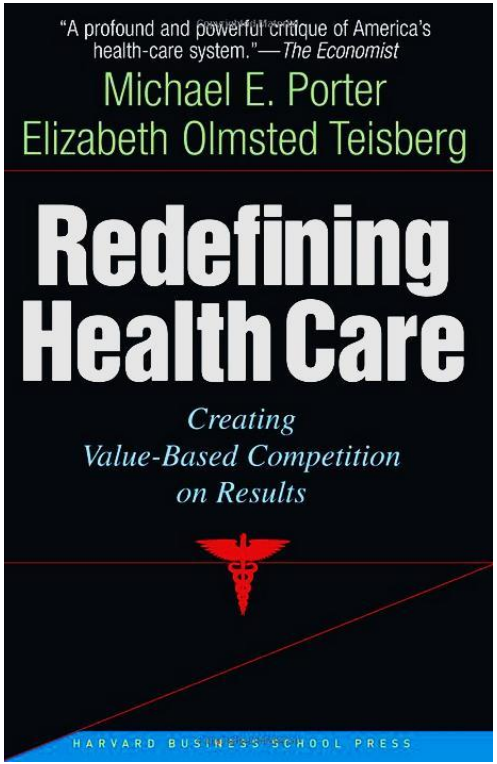


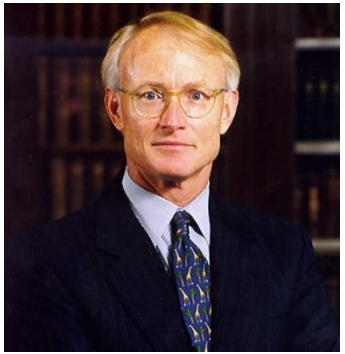
CAD, Coronary artery disease; *CI*, confidence interval; *OR*, odds ratio; *PMI*, previous myocardial infarction; *TASC*, TransAtlantic Inter-Society Consensus.

n=118 patients n= 30 patients

J Vasc Surg 2015; 62:965-73

What Is "Value" in Health Care?





***Value* = dollars spent per health-related outcome**

Which FIRST *Revascularization Option* in CLI Has the BEST Value?

Bypass Surgery

VS

Endovascular Therapy (Endo)

What is current state of evidence

Tunis et al.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

THE USE OF ANGIOPLASTY, BYPASS SURGERY, AND AMPUTATION IN THE MANAGEMENT OF PERIPHERAL VASCULAR DISEASE

SEAN R. TUNIS, M.D., M.SC., ERIC B. BASS, M.D., M.P.H., AND EARL P. STEINBERG, M.D., M.P.P.

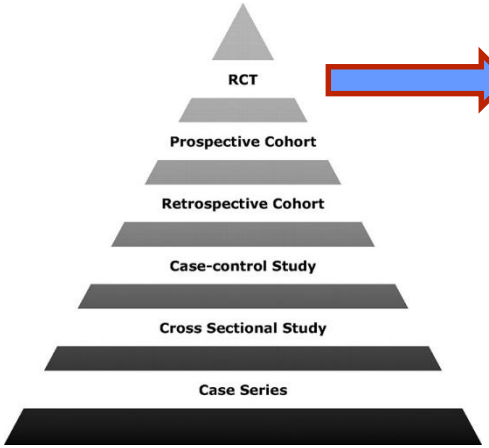
Abstract *Background.* Percutaneous transluminal angioplasty has been adopted widely as a treatment for patients with peripheral vascular disease of the lower extremities. However, the effect of this procedure on the overall management of peripheral vascular disease and on the outcomes of patients has not been clearly delineated. In particular, it is not known whether angioplasty has replaced other treatments for peripheral vascular disease.

Methods. To assess the extent to which angioplasty is used and the associated changes in the surgical management of peripheral vascular disease of the lower extremities, we used data on hospital discharges in Maryland to identify all angioplasty procedures, peripheral bypass operations, and lower-extremity amputations performed for peripheral vascular disease in Maryland hospitals between 1979 and 1989.

Results. We estimate that from 1979 to 1989 the annual rate of percutaneous transluminal angioplasty for peripheral vascular disease of the lower extremities, adjusted for age and sex, rose from 1 to 24 per 100,000 Maryland residents ($P<0.0001$ by linear regression). Despite this increase in the use of angioplasty, the adjusted annual rate of peripheral bypass surgery also rose substantially, from 32 to 65 per 100,000 ($P<0.001$), whereas the adjusted annual rate of lower-extremity amputation remained stable at about 30 per 100,000. Total charges for hospitalizations during which a peripheral revascularization procedure was performed increased from $14.7 million in 1979 (in 1989 dollars) to $30.5 million in 1989.

Conclusions. In Maryland, the adoption of percutaneous transluminal angioplasty for peripheral vascular disease of the lower extremities has been associated with an increase in the use of peripheral bypass surgery and with no decline in lower-extremity amputations. These results could be due to increased diagnosis of peripheral vascular disease, expanded indications for procedural interventions, or an increased number of repeat procedures performed in patients with peripheral vascular disease of the lower extremities. (N Engl J Med 1991; 325:556-62.)

Randomized controlled trials represent the most internally valid forms of evidence



A WELL-DESIGNED TRIAL IDENTIFIES THE OPTIMAL COURSE OF ACTION IN RESEARCH SETTINGS

SOURCE: Ho et al. Circulation 2008;118:1675

Advantages and Disadvantages of Randomized Clinical Trial Design

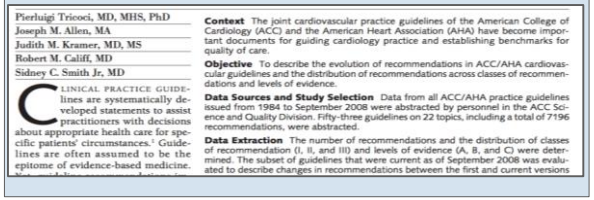
Clinical Trial Design	Advantages	Disadvantages
Randomized Clinical Trial	- eliminates confounding factors - minimizes treatment selection bias -reduces spurious causality -most reliable form of scientific evidence	- time intensive - expensive - generizability

James, S. *et al.* (2015) Registry-based randomized clinical trials—a new clinical trial paradigm *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2015.33

How Often Do We Know What to Do for the Patient?

Cardiovascular Treatment Guidelines

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines



Pierluigi Tricoci, MD, MHS, PhD
Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

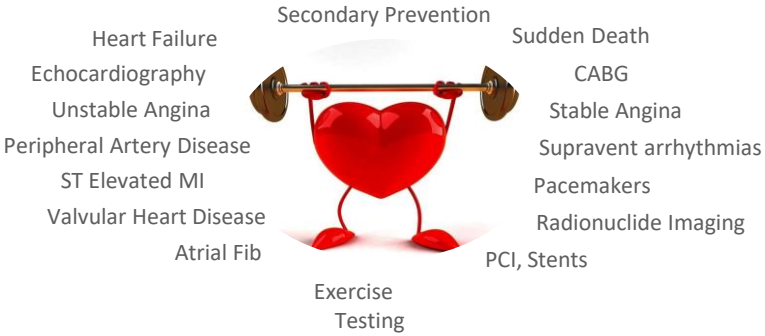
Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.

Data Extraction The number of recommendations and the distribution of classes of recommendation (I, II, and III) and levels of evidence (A, B, and C) were determined. The subset of guidelines that were current as of September 2008 was evaluated to describe changes in recommendations between the first and current versions

CLINICAL PRACTICE GUIDELINES are systematically developed statements to assist practitioners with decisions about appropriate health care for specific patients' circumstances.[2] Guidelines are often assumed to be the epitome of evidence-based medicine.

JAMA. 2009;301(8):831-841



16 **High impact cardiovascular guidelines used to power healthcare decisions by payers, healthcare providers and consumers**

2,711 **Recommendations within these guidelines**

11% **Were based upon enough evidence to warrant the recommendation. The vast majority were based upon *a single trial* and *expert opinion***

Large RCT's for Vascular Disease

- **Carotid Endarterectomy**
  - NASCET, ACAS, ACST, VA Trial, ECST,GALA
- **CEA vs Carotid Stent**
  - ACT I, CREST, CASANOVA,EVA 3s, ICSS, SAPPHIRE, SPACE, CAVATAS
- **AAA**
  - ADAM, UK Small AAA
- **AAA vs EVAR**
  - DREAM I and II, EVAR I and II, OVER, Numerous IDE studies.
- **CLI: Bypass vs Endo**
  - **BASIL**

Peripheral Vascular Disease

Comparative effectiveness of endovascular and surgical revascularization for patients with peripheral artery disease and critical limb ischemia: Systematic review of revascularization in critical limb ischemia

W. Schuyler Jones, MD,[a,b] Rowena J. Dolor, MD,[a,c] Vic Hasselblad, PhD,[a] Sreekanth Vemulapalli, MD,[a,b] Sumeet Subherwal, MD,[a] Kristine Schmit, MD,[a,c] Brooke Heidenfelder, PhD,[a,c] and Manesh R. Patel, MD[a,b]
Durham, NC

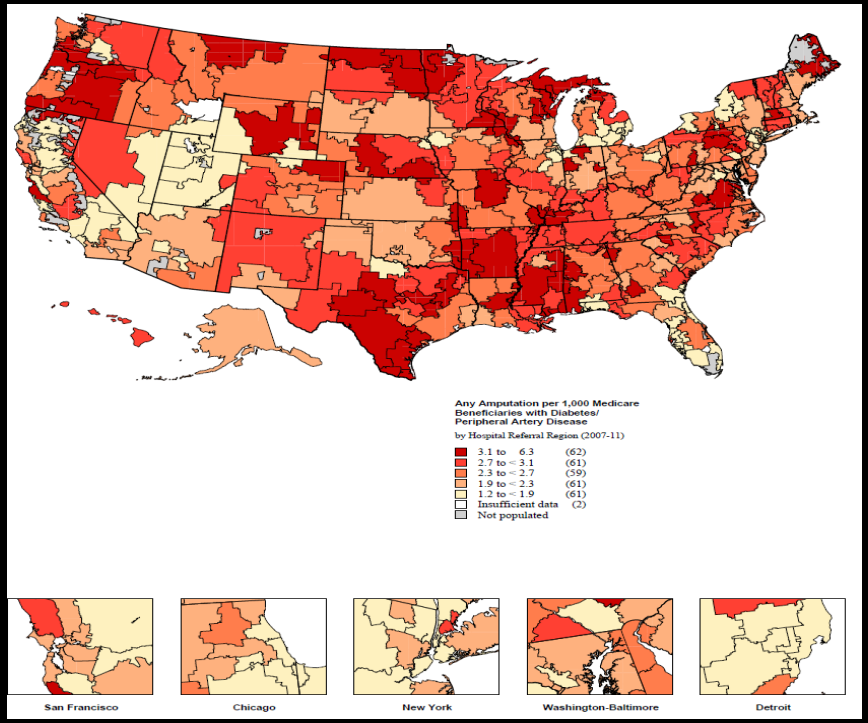
Background For patients with critical limb ischemia (CLI), the optimal treatment to enhance limb preservation, prevent death, and improve functional status is unknown. We performed a systematic review and meta-analysis to assess the comparative effectiveness of endovascular revascularization and surgical revascularization in patients with CLI.

Methods We systematically searched PubMed, Embase, and the Cochrane Database of Systematic Reviews for relevant English-language studies published from January 1995 to August 2012. Two investigators screened each abstract and full-text article for inclusion, abstracted the data, and performed quality ratings and evidence grading. Random-effects models were used to compute summary estimates of effects, with endovascular treatment as the control group.

Results We identified a total of 23 studies, including 1 randomized controlled trial, which reported no difference in amputation-free survival at 3 years (odds ratio [OR] 1.22, 95% CI 0.84-1.77) and all-cause mortality (OR 1.07, 0.73-1.56)

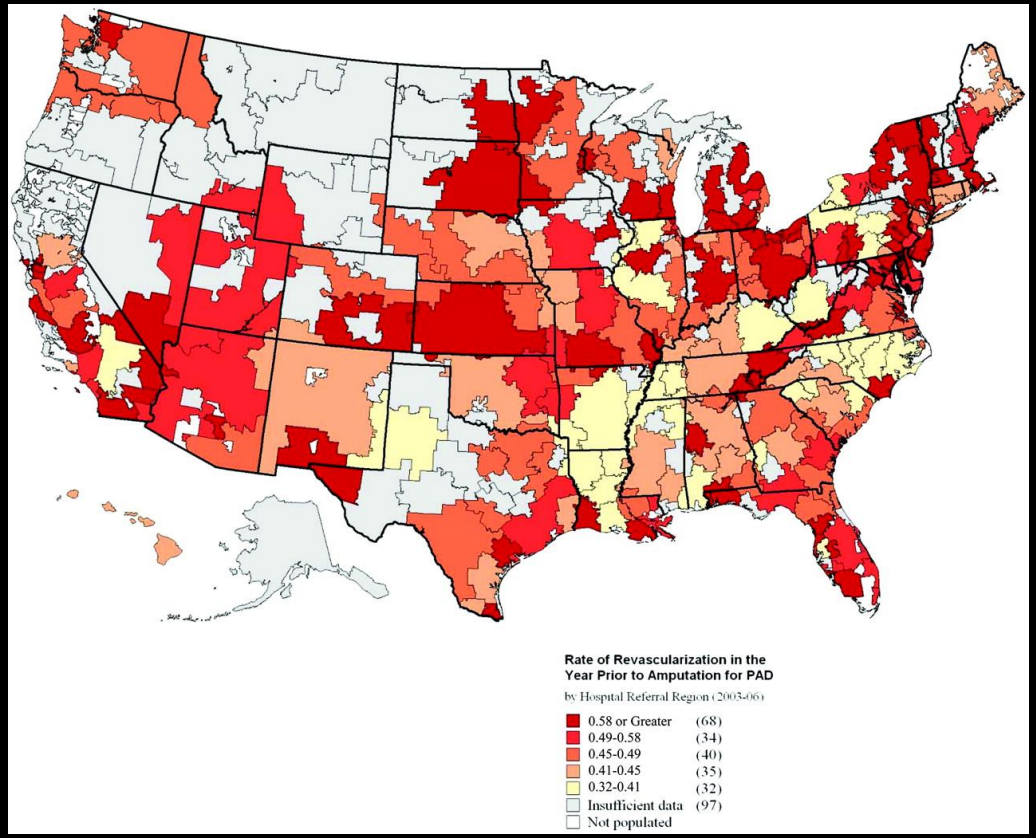
…There is paucity of high-quality data available to guide clinical decision making….

Variation in Amputation Rates Among Patients with CLI



Dartmouth Atlas of Cardiovascular and Thoracic Healthcare Care. Manning Selvage & Lee; 1998

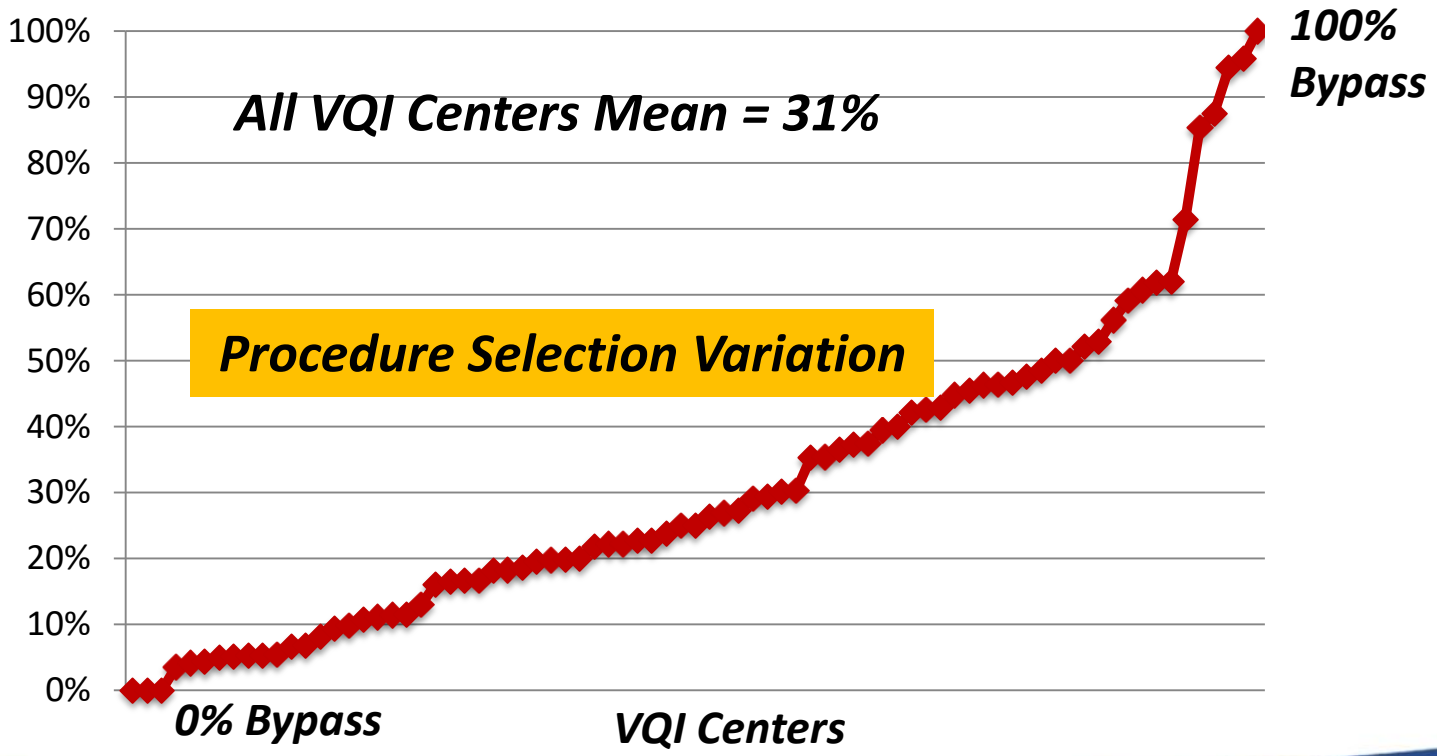
Variation in LE Revascularization



Goodney P et al. Circ Cardiovasc Qual Outcomes. 2012;5:94-102

Equipoise

Critical Limb Ischemia: % Treated by Bypass (vs. PVI)



Limitations of Current Data

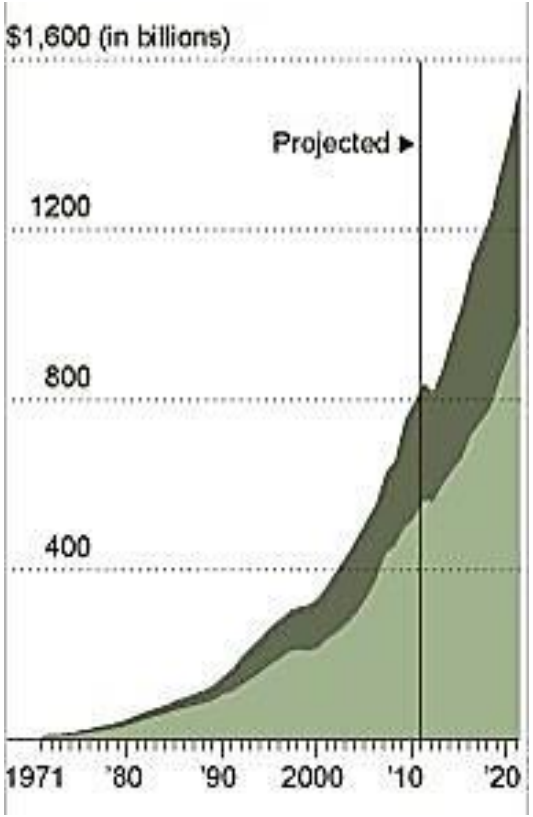
- Retrospective
- Poorly controlled
- Suboptimal endpoints
  - Amputation free survival
  - Target lesion revascularization
  - Target vessel revascularization
  - Patency
- Sponsor bias
- Operator bias
- Inclusion of claudicants
- Short or incomplete follow up

The Exponential Rise in Health Care Expenditures

Federal Spending on Medicare and Medicaid

As budget negotiations continue, lawmakers and White House officials are considering ways to slow the growth of federal spending on Medicare and Medicaid, which is projected to continue rising at a rapid pace.

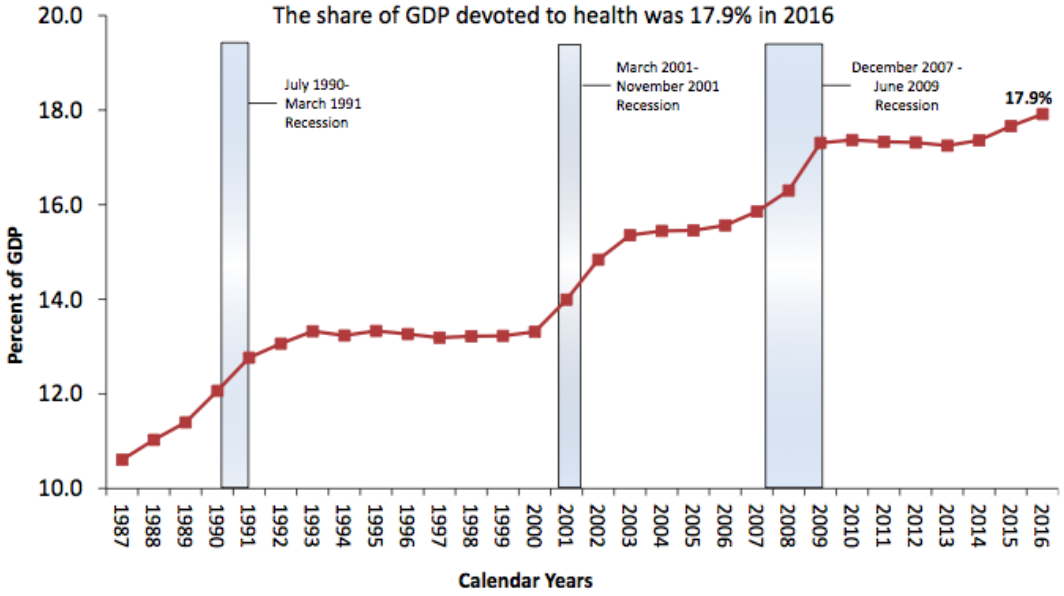
Medicaid **Medicare**



Pear R. Administration Offers Health Care Cuts as Part of Budget Negotiations. New York Times, July 4th, 2011.

We can’t afford every health intervention that is effective

NATIONAL HEALTH EXPENDITURES AS A SHARE OF GDP, 1987-2016



SOURCE: CMS

The mandate for better evidence is compelling

BEST-CLI

Best **E**ndovascular versus Best **S**urgical **T**herapy
in Patients with **C**ritical **L**imb **I**schemia

BEST-CLI Trial: Overview

- **NIH-funded, prospective, randomized, multicenter, multispecialty, pragmatic, open-label superiority trial**
- **2100 patients at 160 clinical sites**

***Goal**: to assess clinical outcomes, quality of life, cost and value in patients who are candidates for both vascular surgery and endovascular therapy*

BEST-CLI Trial Design: Two Cohorts

- **Cohort #1 Patients with adequate single segment great saphenous vein (SSGSV) N=1620**

  Open surgery vs. Endovascular treatment

- **Cohort #2 Patients without adequate SSGSV** (if randomized to OPEN conduit may include arm vein, short saphenous vein, composite vein, cryopreserved vein, and prosthetic conduit) **N=480**

  Open surgery vs. Endovascular treatment

Why Is BEST-CLI Important?

Uniquely positioned to provide level I data for CLI

- Well-powered and designed
- Real-world pragmatic trial

- BASIL: n = 452
- PREVENT III: n = 1405

Novel Primary Endpoint

Major Adverse Limb Event (MALE) – free survival

MALE defined as:

- Above ankle amputation or
- **Major** re-intervention
  - new bypass graft
  - jump/interposition graft revision
  - thrombectomy/thrombolysis

Key Secondary Endpoints

- Re-intervention and Amputation-free Survival (RAS)
- Amputation-free Survival
- MALE-POD

Additional Secondary Endpoints

- Freedom from hemodynamic failure
- Freedom from clinical failure
- Freedom from critical limb ischemia
- Number of re-interventions per limb salvaged
- Freedom from re-interventions (major and minor) in index limb

Optimal Medical Therapy

BEST-CLI Trial Optimal Medical Therapy (OMT) Report Cards

Overview of Site 1005 Optimal Medical Therapy Performance Metrics*

Site	Site Name	Date of Data Freeze	# Randomized	HTN Control	DM Control	Statin Use
1005	Brigham and Women's Hosp.	11/1/2017	17	🟢	🟡	🟡

*Summary of Performance Metrics on Page 3

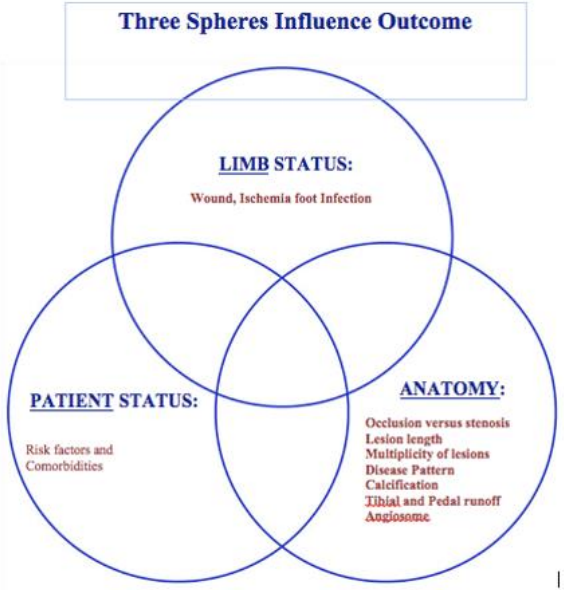
Explanation of Performance Metrics.

Metric	Grade		Explanation
Hypertension (HTN) Control	🟢	Excellent	Greater than 80% of patient visits with subjects either meeting age-specific targets for both SBP and DBP or at least one anti-hypertensive medication reported
	🟡	Fair	Between 60% and 80% of patient visits with subjects either meeting age-specific targets for both SBP and DBP or at least one anti-hypertensive medication reported
	🔴	Poor	Less than 60% of patient visits with subjects either meeting age-specific targets for both SBP and DBP or at least one anti-hypertensive medication reported
	○	NA	Your site did not have any patient visits with data available for this metric
Diabetes (DM) Control	🟢	Excellent	Greater than 80% of patient visits with Hemoglobin A1c <8%
	🟡	Fair	Between 60% and 80% of patient visits with Hemoglobin A1c <8%
	🔴	Poor	Less than 60% of patient visits with Hemoglobin A1c <8%
	○	NA	Your site did not have any patient visits with data available for this metric
Statin Use	🟢	Excellent	Greater than 80% of patient visits with statin use reported
	🟡	Fair	Between 60% and 80% of patient visits with statin use reported
	🔴	Poor	Less than 60% of patient visits with statin use reported
	○	NA	Your site did not have any patient visits with data available for this metric

- Based on percentage of post-baseline visits at which targets are met
- Baseline visits are not considered because they reflect care the subject received before the subject was enrolled in BEST
- One patient can contribute data at more than one visit
- Grades are based on accepted, defined standards and not on comparison with other trial sites

SVS Lower Extremity Threatened Limb Classification - WIfI Index

- **Wound: extent and depth**
- **Ischemia: perfusion/flow**
- **foot Infection: presence and extent**



Risk of Amputation

	Ischemia – 0				Ischemia – 1				H	Ischemia – 2				Ischemia – 3			
W-0	VL	VL	L	M	VL	L	M	H		L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H		L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H		M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H		H	H	H	H	H	H	H	H
	FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3		FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3

Benefit of Revascularization

	Ischemia – 0				Ischemia – 1				Ischemia – 2				Ischemia – 3			
W-0	VL	VL	VL	VL	VL	L	L	M	L	L	M	M	M	H	H	H
W-1	VL	VL	VL	VL	L	M	M	M	M	H	H	H	H	H	H	H
W-2	VL	VL	VL	VL	M	M	H	H	H	H	H	H	H	H	H	H
W-3	VL	VL	VL	VL	M	M	M	H	H	H	H	H	H	H	H	H
	FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3	FI-0	FI-1	FI-2	FI-3

TIDE

The Impact of Diabetes on Revascularization in BEST-CLI

TIDE Ancillary Study Update

Swim with (the) TIDE

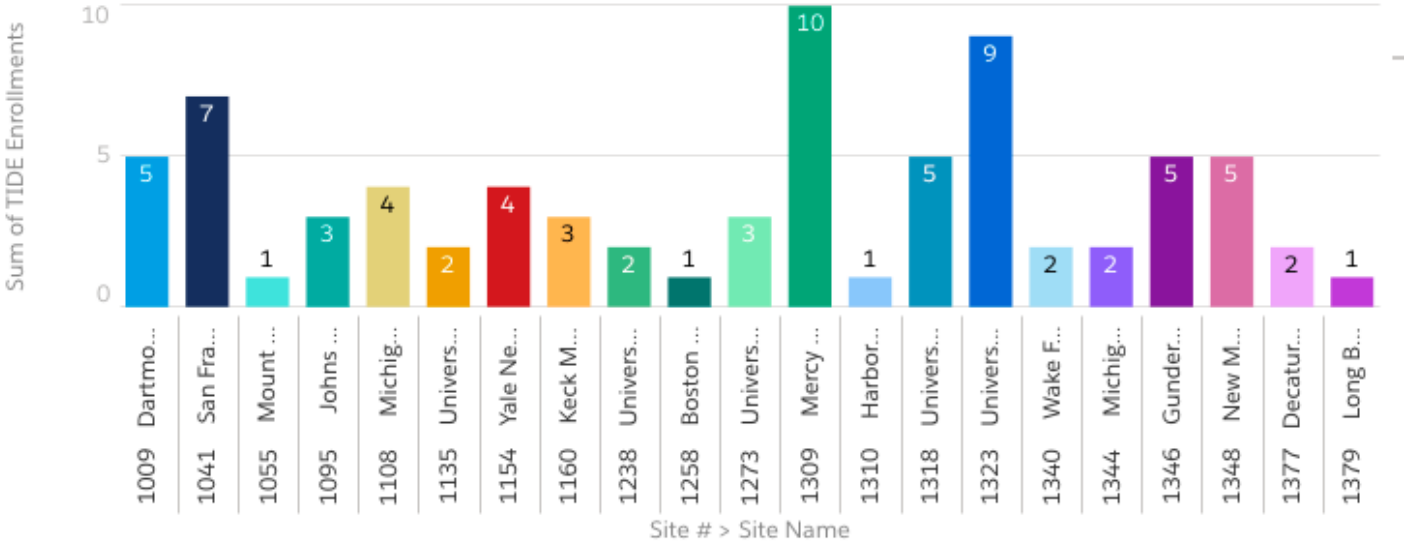
Sponsored by the National Heart Lung and Blood Institute

TIDE: Trial Update

An NHLBI Substudy of BEST-CLI

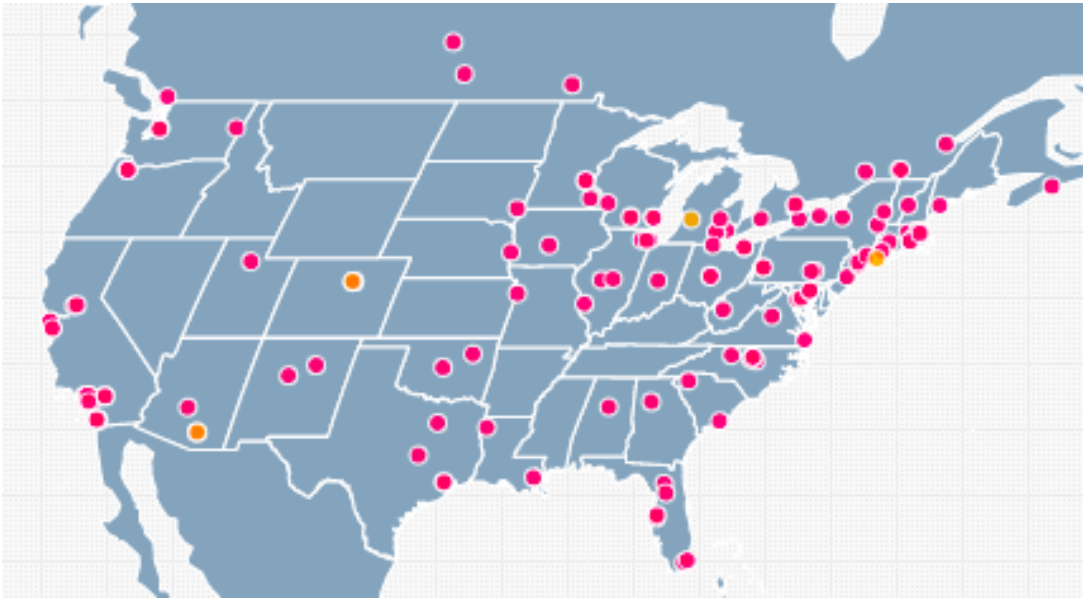
Total TIDE Enrollments
77

TIDE Study Report



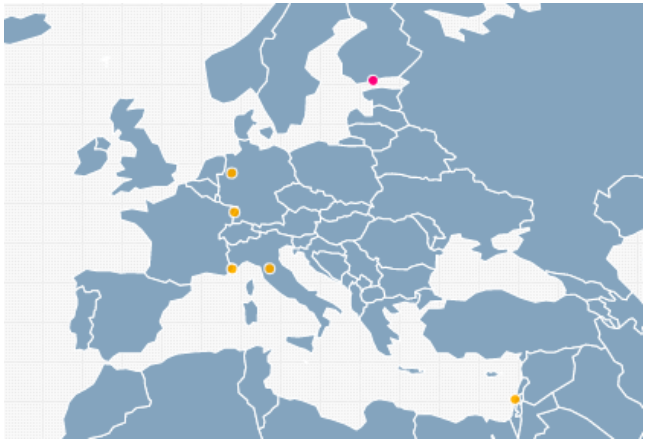
BEST-CLI in North America

130 Active Sites

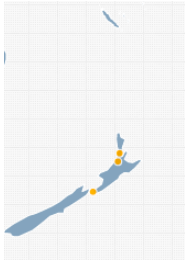


BEST-CLI Global Footprint

Europe



New Zealand



4 Active Sites

New Zealand (3)

Finland (1)

Germany

Italy

Site Investigators

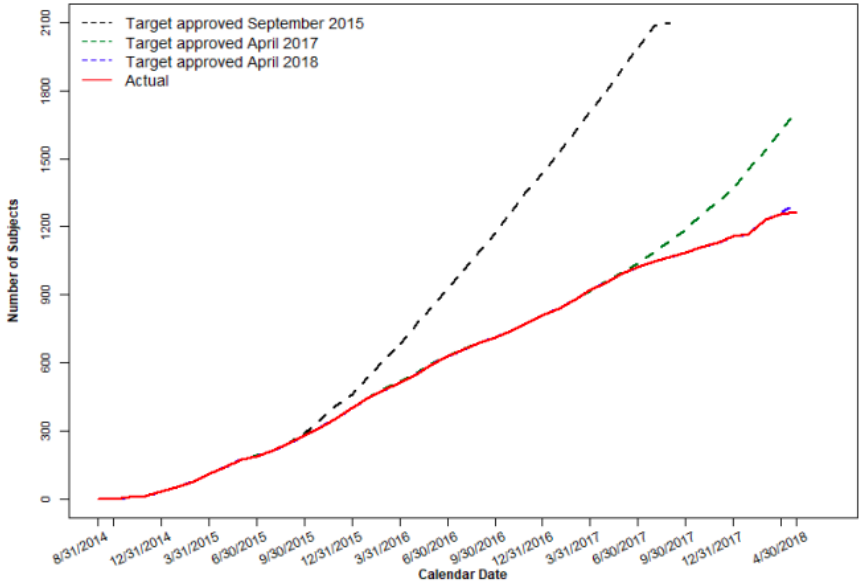
930 Investigators

- 114 Interventional Cardiologists
- 111 Interventional Radiologists
- 3 Vascular Medicine Specialists
- 690 Vascular Surgeons
- 12 Other

Enrollment Update

As of 9/22/2018

- **1,456 subjects randomized**

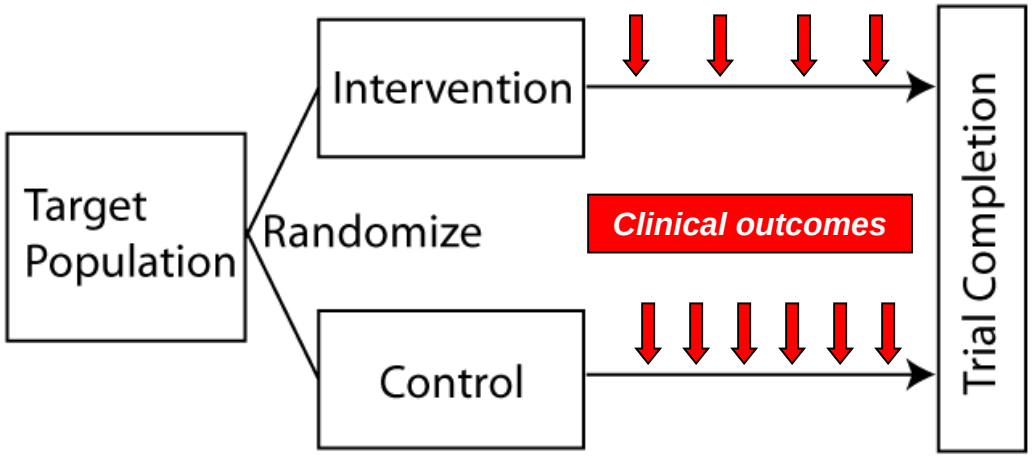


VALUE IN HEALTHCARE

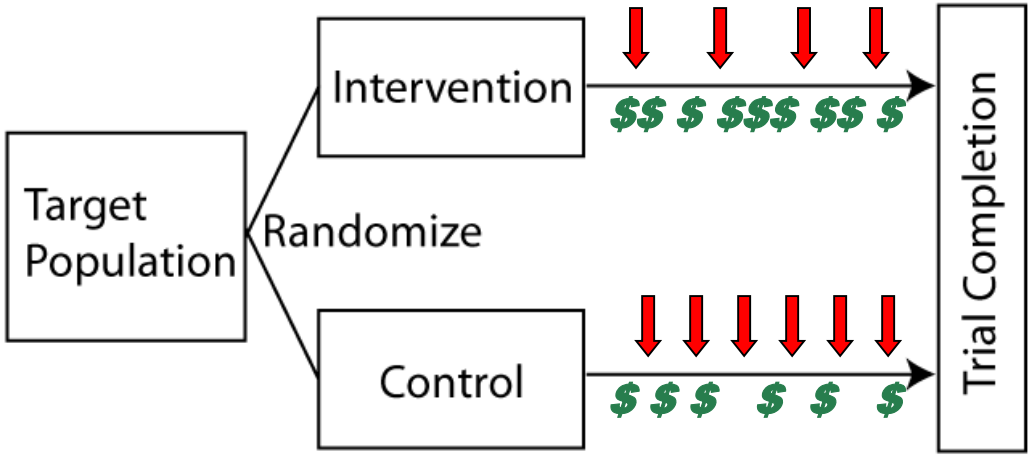
PERSPECTIVE

Christopher J. White, MD, M-SCAI, FACC, FAHA, FESC, FACP

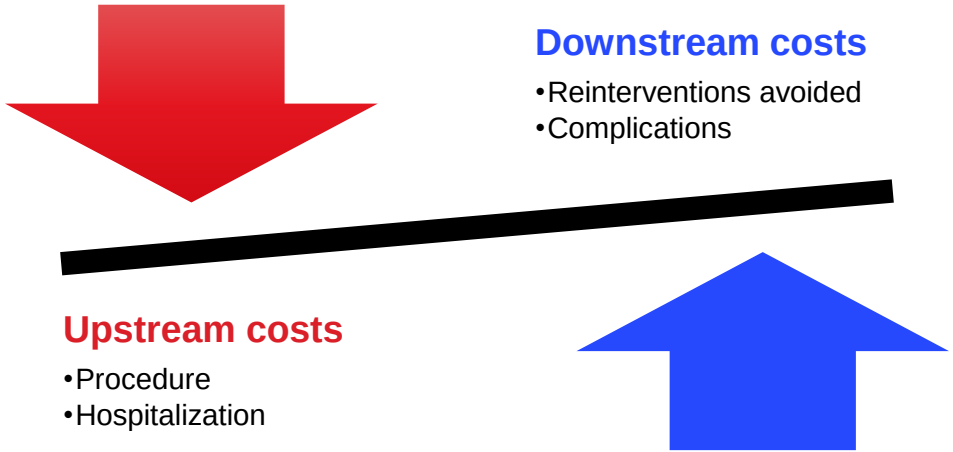
A typical trial



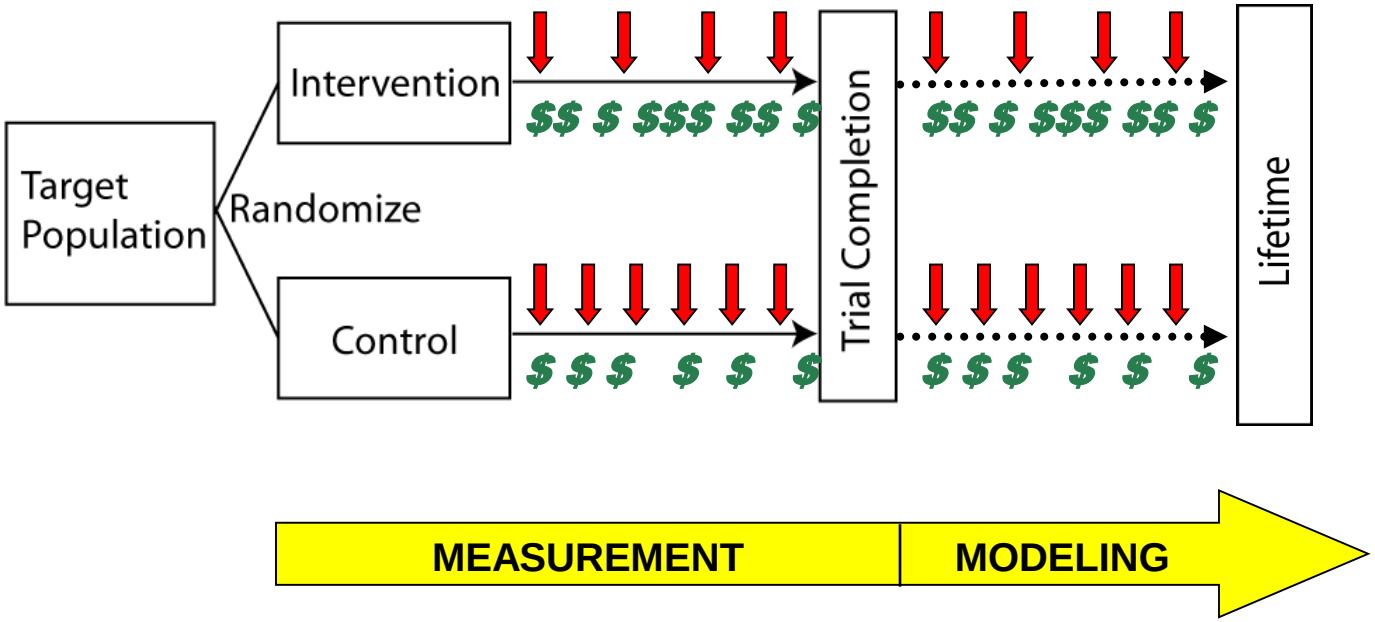
CEA alongside a prospective study



Cost-effectiveness analysis considers the cost of an intervention and its downstream consequences



The approach we're taking in BEST



Incremental cost-effectiveness ratio (ICER)

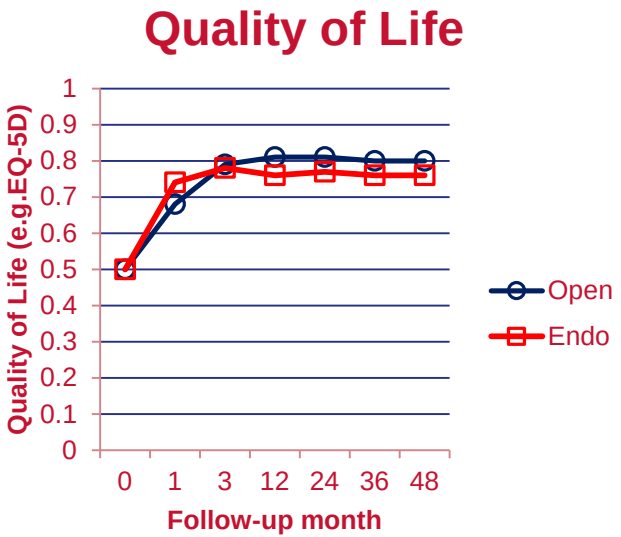
$$ICER = \frac{COST_{TREATMENT\ A} - COST_{TREATMENT\ B}}{EFFECT_{TREATMENT\ A} - EFFECT_{TREATMENT\ B}}$$

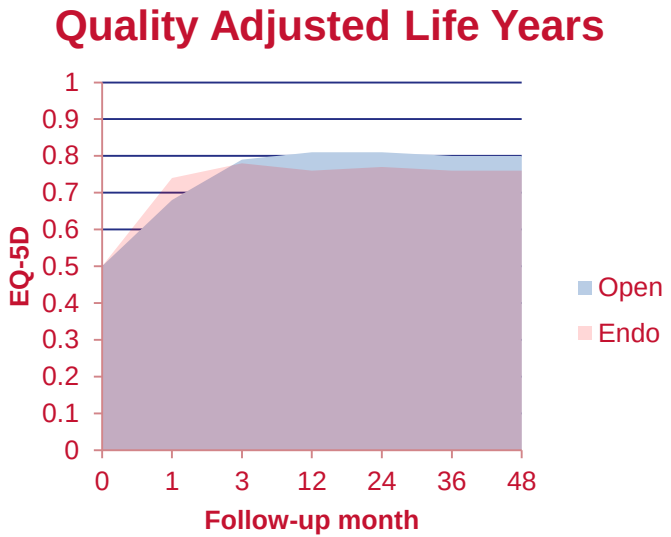
$$= \frac{\Delta COST}{\Delta EFFECT}$$

"HEALTH EFFECT" is often measured in quality adjusted life years (QALYs), a measure that incorporates both length and health-related quality of life

Quality Adjusted Life Years (QALYs)

- Quality Adjusted Life Years (QALYs) will be calculated based on area under the curve of quality of life for each patient. The average QALYs in two intervention arms then will be compared as outcomes.





Interpreting Cost-effectiveness analysis

Adopt new treatment?	Improved Outcomes	Worse Outcomes
Saves money	YES ("dominant strategy")	PROBABLY NOT
Costs money	MAYBE (usually if <$50-100K/QALY)	NO ("dominated strategy")

What could we possibly see in BEST?

HYPOTHETICAL

OUTCOMES	TREATMENT A	TREATMENT B
M.A.L.E.	SUPERIOR	
COMPLICATIONS		SUPERIOR
QUALITY OF LIFE	SUPERIOR	
COSTS		LESS EXPENSIVE

WHICH TREATMENT REPRESENTS BETTER VALUE?

Collaboration and CLI teams

Collaboration within BEST-CLI

Inclusive of everyone who treats CLI:

81% sites are multi-disciplinary

CLI Teams in Action

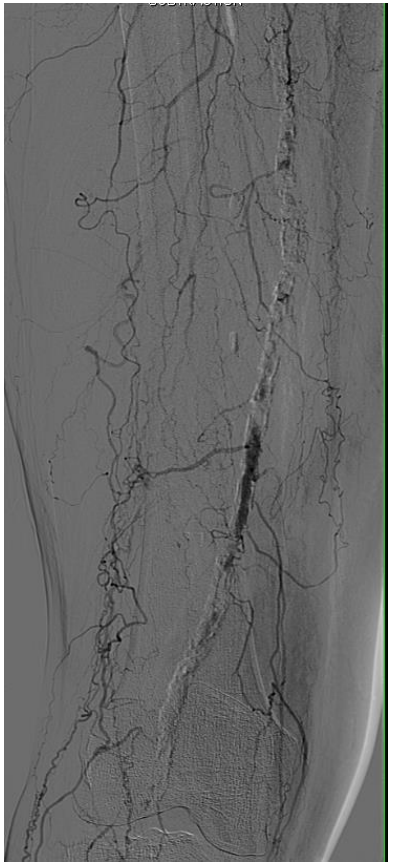
- George Adams
- Sahil Parikh
- Carlos Mena

Collaboration is the *antidote* to bias

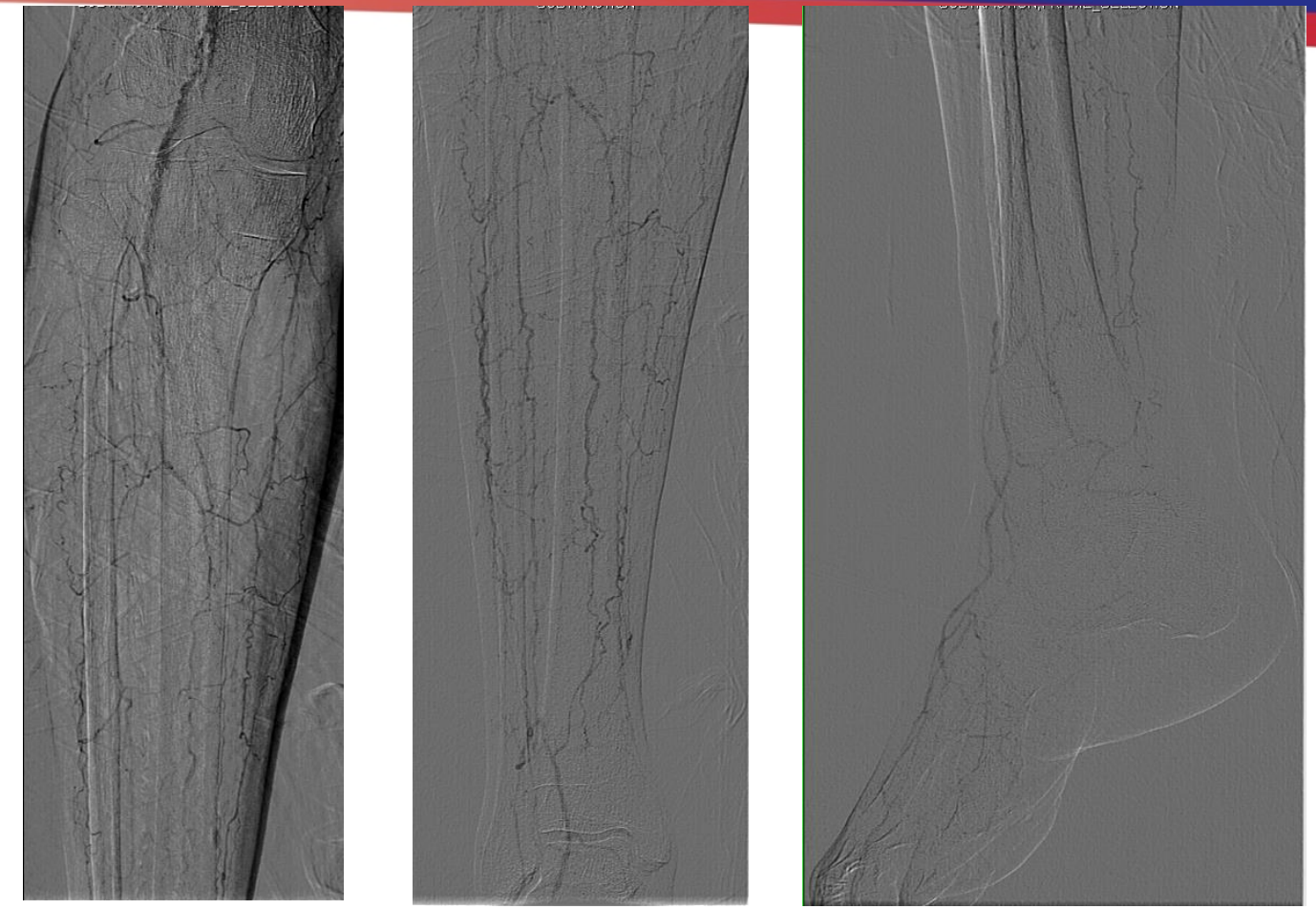
- Peter Soukas
- Rob Lookstein

Case Review

62 yo f with nonhealing toe amputation site, good GSV



Case Review



Summary

- Raise the bar of CLI care

- **Interdisciplinary collaboration and awareness-raising**
- **Everybody wins – especially our patients**

Conclusions

- There is an exceptional knowledge deficit in CLI management cf other areas of clinical therapy.
- Technical success is necessary, but **Value** in CLI care is far more complex
- Systematic data regarding outcomes will be necessary in order to change behaviors and practice patterns, and reduce cost

- **BEST CLI, in synergy with BASIL-2 and BASIL-3, will provide powerful, Level I data that will help to shape a much-needed evidence based approach to CLI.**
- **And set the stage for the next generation of investigations.**