Endovascular Therapy for PAD

Clinical Outcomes, Challenges and Potential for Disease Management

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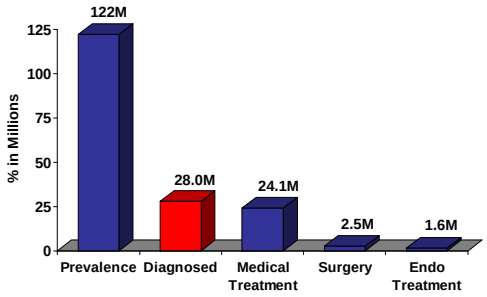
Peripheral Arterial Disease Statistics Worldwide: 2008



Based on Millennium Research Group Data

Current Challenges for Medical/Non-invasive Therapy for Symptomatic PAD

Supervised Exercise Programs

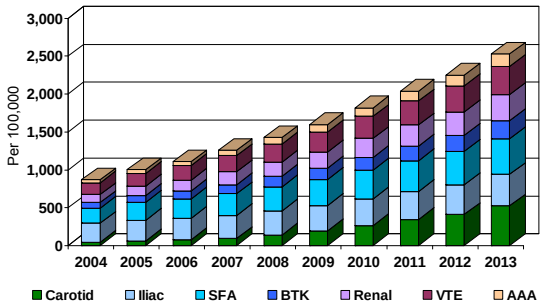
- Trial comparisons limited in study size and number of trials
- Sedentary, unmotivated population often inherent, limiting practicality of exercise
- Cause or symptom effect
- Reimbursement and availability of supervised programs variable
- Concurrent comorbidity (eg, cardiac) may be limiting, and resistance training ineffective
- Most comparisons with EVT not representative of contemporary practice patterns

Current Challenges for Medical/Non-invasive Therapy for Symptomatic PAD

Secondary prevention for CV risk essential, but for medications specific to PAD symptom improvement…

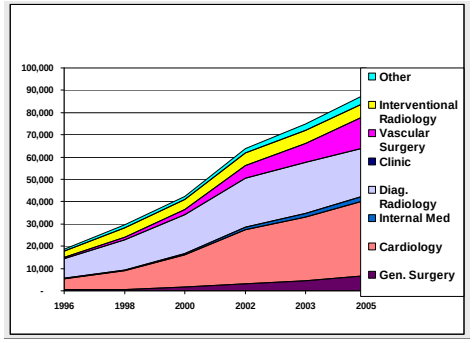
- Trial comparisons with revascularization limited in number, trial design and/or suboptimal medical therapy
- Expense and intolerance
- Most pharmacologic therapies intended to reduce cardiovascular risk rather than alleviate symptoms
- Therapies intended to reduce symptoms do not alter disease progression
  - Cilostazol: concerns in heart failure/advanced cardiomyopathy
- 'Crossover' to revascularization common due to persistent/refractory symptoms

Estimated Number of Endovascular Procedures Worldwide



Based on Millennium Research Group Data, 2008

Peripheral Stent Procedures in Medicare* by Specialty

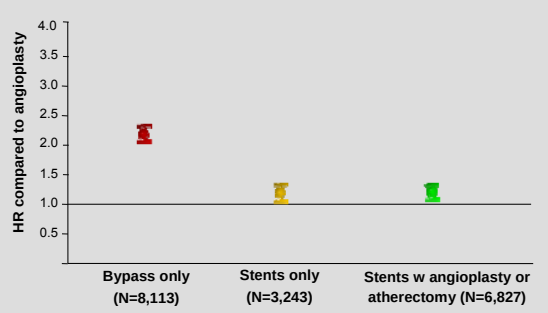


*(CPT Code 37205)

Current Challenges for Endovascular Therapy for Symptomatic PAD

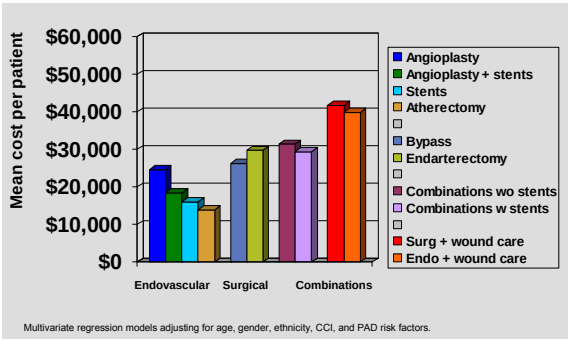
- Many trials, few approved indications
  - *Potential for indication-specific reimbursement*
  - *Inability to promote products/educate clinicians regarding 'off-label' use*
- Evolving regulatory process to raise threshold requirements for approval
- Variability in trial endpoints and design permits broad interpretation of safety and efficacy
- Technologies, technique and outcomes are specific to vascular territory

Risk of Symptom Progression By Revascularization Option (Adjusted): 15 month Follow-up



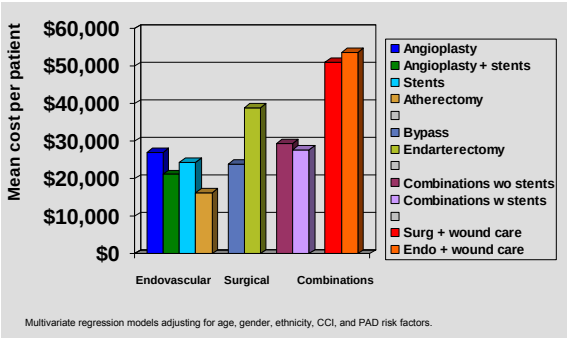
All comparisons are to patients treated with angioplasty (N=20,480).
Hazards ratios from Cox proportional hazards models adjusting for age, gender, ethnicity, CCI, and PAD risk factors.

Risk-adjusted Medical Services Costs
Index Quarter



Multivariate regression models adjusting for age, gender, ethnicity, CCI, and PAD risk factors.

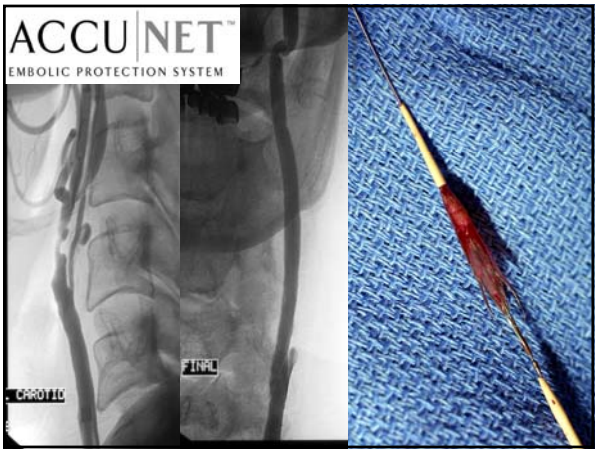
Risk-adjusted Medical Services Costs
4 Quarters Following Index Quarter



Multivariate regression models adjusting for age, gender, ethnicity, CCI, and PAD risk factors.

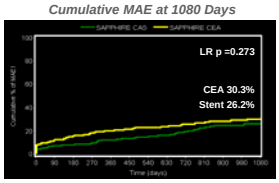
Endovascular Therapies for PAD

- Carotid Stent Revascularization
- Renal Revascularization
- Lower Extremity Revascularization
  - Superficial Femoral Artery Disease
  - Below Knee Disease/Critical Limb Ischemia
- New Technologies and Indications

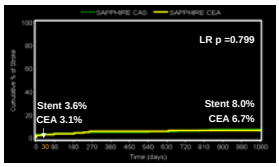


SAPPHIRE Trial: Randomized CAS to CEA in High-Surgical Risk Patients

Cumulative MAE at 1080 Days



Cumulative Stroke to 30 Days plus Ipsilateral Stroke from 31 - 1080 Days

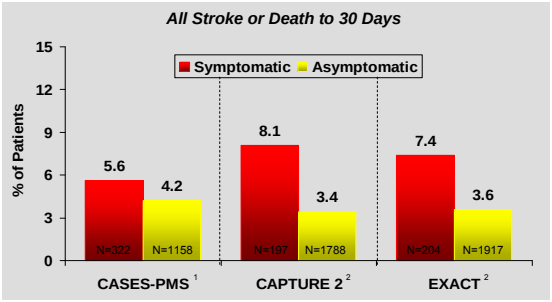


CAS is a durable procedure with similar long-term risk of stroke as CEA (8.0% vs. 6.7%, p=0.799), respectively.

Between 30 days and 3 years the incremental annual risk of ipsilateral stroke for all randomized patients was 1.5% with stenting which was similar to CEA (1.2%)

H.S. Gurm et al., *N Engl J Med* 2008; 358:1572-9.

Post-market Surveillance High-Risk Registries



Clinical outcomes approxmate the 3% and 6% benchmarked rates in recent trials in High-Risk Patients

[1]NEJM 2009, In Press [2]W.A. Gray et al., TCT 2007.

Ongoing RCTs with Standard Risk Patients

CREST Trial

- CAS vs. CEA in standard-risk symptomatic patients with stenosis >50%
- Lead-in phase completed (n=1479)
- 30-day mortality and morbidity with CAS
  - (Symptomatic 6.1%, Asymptomatic 3.9%)[1]

ACT 1

- CAS vs. CEA in standard-risk asymptomatic patients with ≥70 to ≤ 99% stenosis, no octogenarians included
- Lead-in patients completed (n= 118)
- 30-day mortality and morbidity with CAS (1.7%)[2]

[1]G. Roubin, ISET 2007. [2]K. Rosenfield, TCT 2007.

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Renal Artery Stenting Trials

2-Year Follow-up

	ASPIRE-2 [1]	RENAISSANCE [2]
% of Patients with Follow-up	164 (79%)	85 (85%)
Death (%)	0.5	5.3
QMI (%)	0.0	--
TLR (%)	14.4	18.1
Major Embolic Event (%)	6.3	2.3
Overall MAE (%)	19.7*	15.9**
Systolic BP (Baseline)	168	157
Systolic BP (Follow-up)	149	144
Diastolic BP (Baseline)	82	75
Diastolic BP (Follow-up)	77	73
Serum Creatinine (Baseline)	1.36	1.27
Serum Creatinine (Follow-up)	1.46	1.43

*MAE defined as device or procedure related death, QMI, TLR, and significant embolic event causing end organ damage
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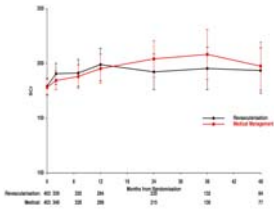
[1]K. Rocha-Singh et al., J *Am Coll Cardiol* 2005; 46: 776-83. [2]M. Jaff et al., ATJ 2007.

ASTRAL Trial (Angioplasty and Stent for Renal Artery Lesions)

Plot of SCr Over Time



Conclusions

- *Currently no evidence of a benefit for revascularization on renal function in the ARVD patients entered into ASTRAL – those in whom clinicians 'uncertain' of whether to revascularize*
- *Also no evidence of differences between the arms for any of the secondary endpoints (i.e. blood pressure, major events, mortality)*
- *No evidence of differences in treatment effect across the various subgroups – for renal functional end-point only*

P. Kalra et al., ACC 2008 Presentation.

CORAL Trial
Cardiovascular Outcomes in Renal Atherosclerotic Lesions

1080 pts with ≥ 60% RAS, SBP ≥155 mm Hg and ≥ **2** antiHTN meds

- Stent w/EDP+medical therapy
- Medical therapy alone

Follow-up 3.5-5 years

1° Endpoint: cardiovascular or renal death, stroke, MI, CHF hospitalization, decline in renal function, need for dialysis

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Endovascular Stent Treatment of Lower Extremities

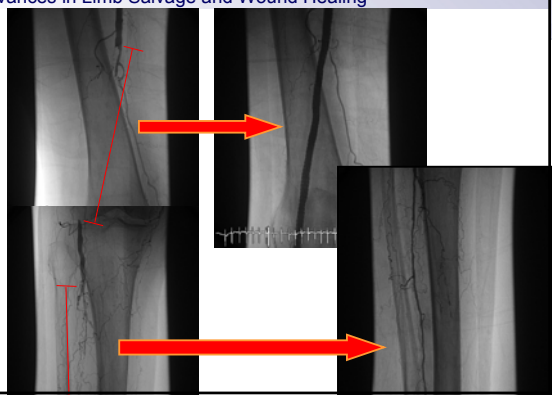
	FAST[1]		VIENNA[2]		RESILIENT[3]		PREVENT III[4]
	PTA n=121	Stent n=123	PTA n=53	Stent n=51	PTA n=72	Stent n=134	FP Bypass n=697
Lesion length (cm)	4.5	4.5	9.3	12.2	5.7	6.2	–
Occlusions (%)	25	37	31	41	19	17	–
Crossover (%)	11	–	32	–	40	–	–
12-month Primary Patency (%)	61	68	37	63	38	80	59.5
No. of Fractured Stents (n)	–	10	–	4	–	9	–

[1]H. Krankenberg, *Circulation* 2007; 116. [2]Schillinger M, *Circulation* 2007; 115:2745-9.
[3]B. Katzen et al., Oral Presentation TCT 2007. [4]Conte, J Vasc Surg 2006;43:742-51.

Critical Limb Ischemia (CLI)
Background and Rationale

- Aggressive revascularization measures have become fundamental in contemporary treatment strategies for pts with lower limb CLI
- Despite initial treatment, most pts experience not only abbreviated survival but impaired functional status, characterized by rest pain and inability to ambulate
- In part due to failed prior revascularization attempts and comorbidity or extensive tissue loss that may preclude revascularization in CLI, major lower extremity amputation remains a commonly performed procedure
  - >100,000/year attributed to PAD
  - Overall amputation rates have not declined
  - Still <1/3 ambulate with a prosthesis following amputation

Critical Limb Ischemia
Advances in Limb Salvage and Wound Healing



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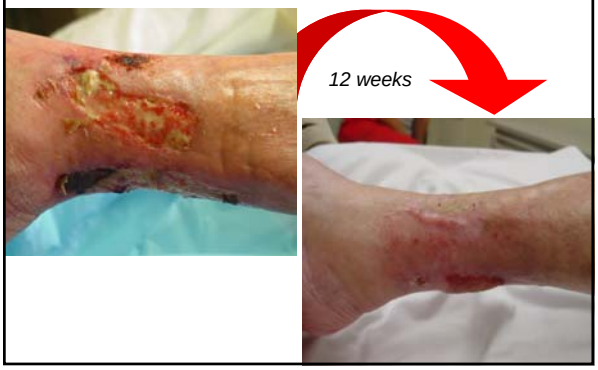

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Novel Endovascular Therapies for PAD
Perspective

Rapid evolution in device technology against background of increasing disease recognition, constant medical therapy

- Self-expanding and drug-eluting stents
- Drug-eluting balloons
- Plaque excision/atherectomy
- Excimer laser
- Cryoplasty
- Cutting balloon angioplasty
- Distal embolic protection
- Chronic total occlusion and re-entry technologies

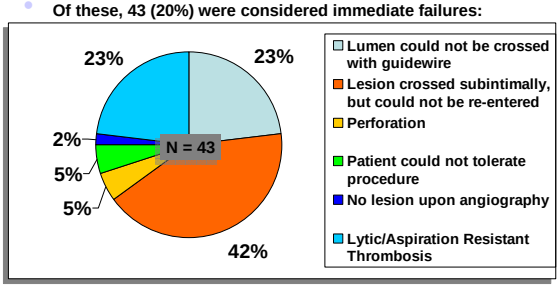
Alternative Therapies for Lower Limb Ischemia

	Claudication			CLI		
	Atherectomy	Laser	Cryo	Atherectomy	Laser	Cryo
Study	**Zeller[1]**	**CELLO[2]**	**CHILL[3]**	**Zeller[4]**	**LACI[5]**	**BTK CHILL[6]**
Centers	**Single**	**20**	**16**	**Single**	**14**	**Multicenter**
Patients	**84**	**85**	**102**	**36**	**145**	**108**
Occlusions (%)	**N/A**	**16.0**	**14.7**	**N/A**	**91.0**	**33.9**
Lesion length (cm)	**9.0 ± 10.6**	**5.6 ± 4.7**	**4.7 ± 2.6**	**4.8 ± 2.8**	**4.0**	**4.1 ± 3.0**
Adjunctive therapy (%)	**>60%**	**N/A**	**8.8**	**~40%**	**>95%**	**N/A**
Follow-up time	**12 mo.**	**6 mo.**	**9 mo.**	**12 mo.**	**6 mo.**	**12 mo.**
Clinical Patency (%)	**84.0**	**84.0**	**82.2**	**76.0**	**N/A**	**84.3**
Primary Patency (%)	**84.0**	**63.0**	**70.1**	**67.0**	**N/A**	**N/A**

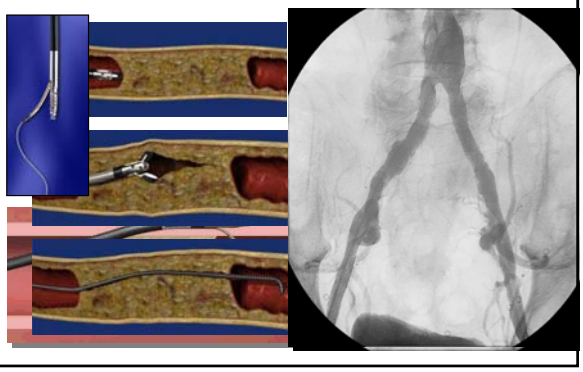
BASIL Trial

Angioplasty Attempts/Immediate Failures

- **Of the 224 patients allocated to angioplasty, 216 underwent attempted angioplasty**
- **Of these, 43 (20%) were considered immediate failures:**

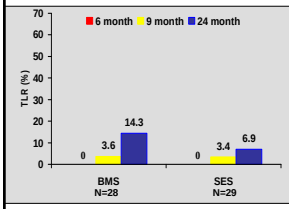


Novel 'Enabling' Technologies
Chronic Total Occlusions

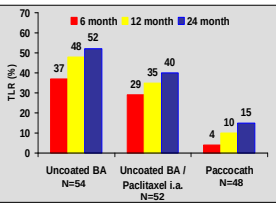


Drug-Eluting Stents & Drug-Coated Balloons in SFA Disease

SIROCCO II: TLR to 2-Years[1]



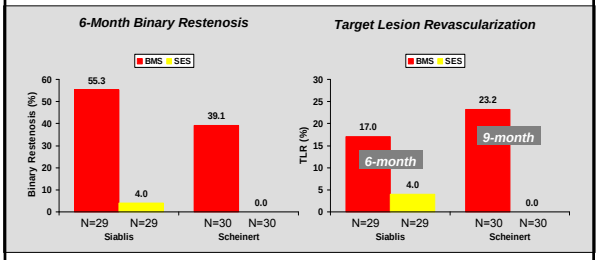
THUNDER: TLR to 2-Years[2]



SIROCCO II:
Bare SMART Nitinol Stent vs. Sirolimus-Eluting SMART Nitinol Stent
Sirolimus 90 µg/cm² (total 1mg/stent)
Co-polymer matrix (sirolimus 30:70 co-polymer)

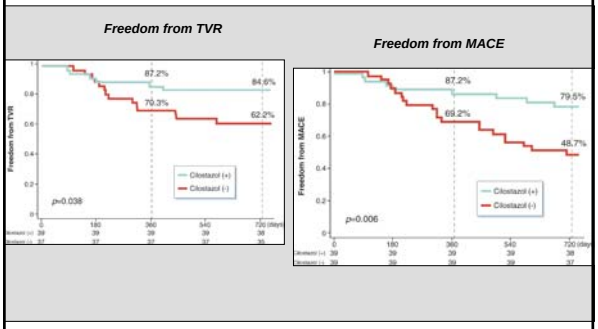
THUNDER Trial:
Uncoated Balloon vs. Uncoated Balloon Iopromid-Paclitaxel* vs. Paclitaxel-Coated Balloon**
** ~17 mg Paclitaxel/100 ml KM*
*** ~3 µg/mm² Paclitaxel*

CYPHER Sirolimus-eluting Coronary Stent Below the Knee

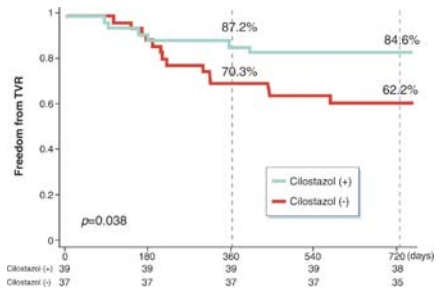


[1]D. Siablis et al., *J Endovasc Ther* 2005; 12:685-95. [2]D. Scheinert et al., *EuroIntervention* 2006; 2:169-74

Pharmacologic Inhibition of Restenosis Cilostazol

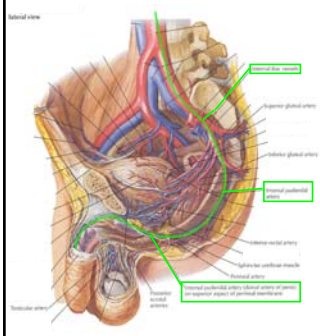


Pharmacologic Prevention of Restenosis Cilostazol



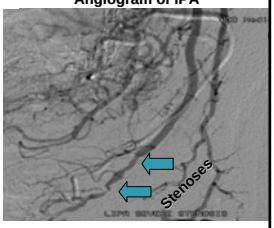
Soga, Y. et al. J Am Coll Cardiol 2009;53:48-53

Feasibility of Percutaneous Revascularization with DES for Erectile Dysfunction



- Cavernosal arteries fed by the internal pudendal artery (IPA)
- Non-tortuous, relatively easy access
- FIM trial for PDE-5 inhibitor resistant patients

Angiogram of IPA



Endovascular Therapy for PAD Summary

- Large patient population with PAD but multiple challenges to establishing a standard of care
- Strategies developing to establish endovascular treatments as first line therapy for revascularization
  - More trials are being conducted to pursue indications specific to PAD
  - Advanced therapies such as a DEB and DES are now being evaluated
- Evolution of novel endovascular therapies has broadened treatment to pts previously without options
  - Improvements in procedural safety and efficacy have lowered interventional threshold for complex PAD, CLI
  - 'Enabling' technologies and techniques have revolutionized treatment paradigm of PAD
- Issue is to focus on not what can be done, but what should be done, with emphasis on modifying cardiovascular risk