Best approach for BTK intervention?

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
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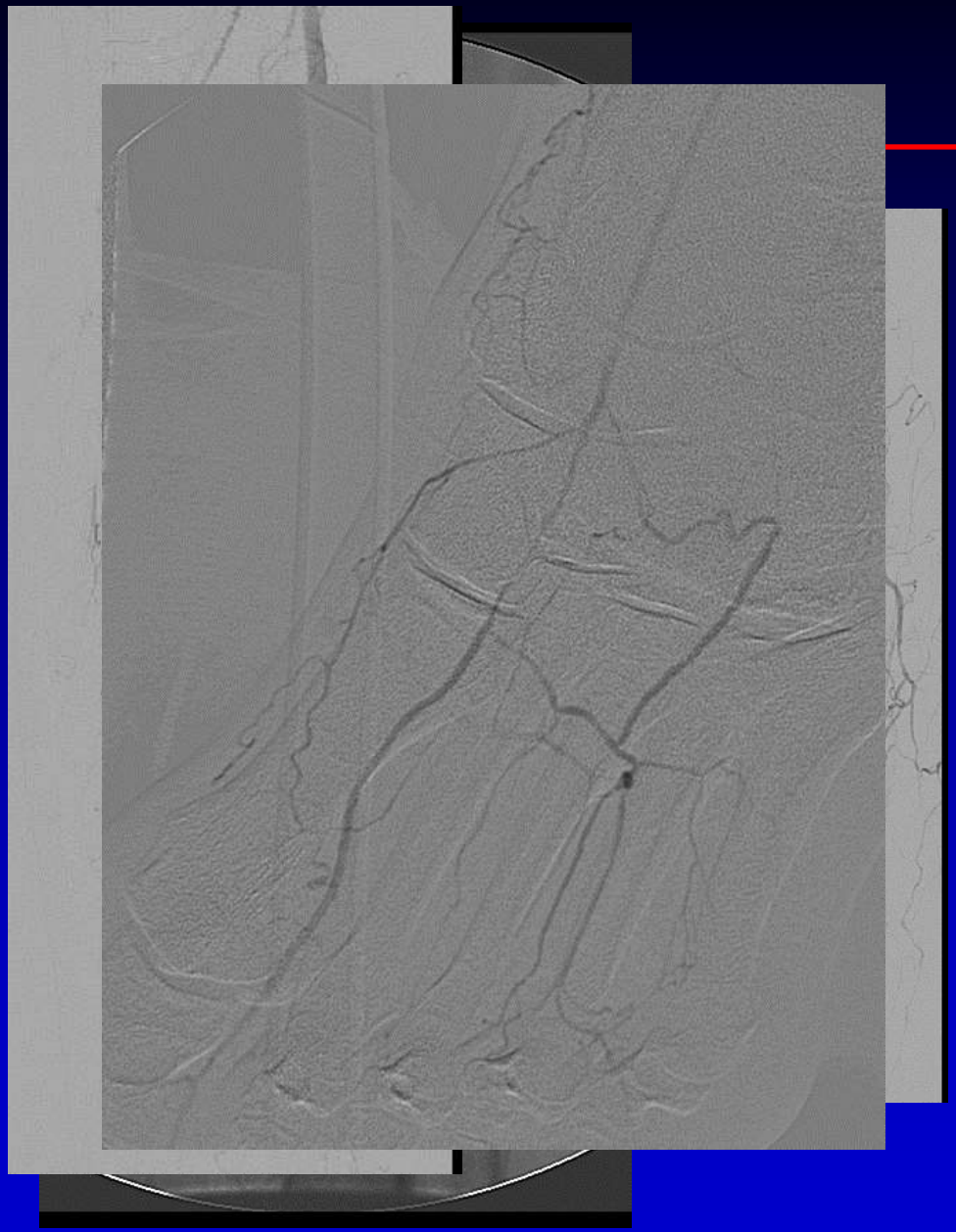
• Other Financial Benefit	• None

Infra-popliteal revascularization

- Short vessel
  - popliteal
- Long vessels
  - tibials
- Generally angled proximally and distally
- Usually calcified
- Total occlusions
- Generally critical limb
  - Outcomes based on AFS

Below the Knee

- Almost all studies deal with infra-popliteal revascularization are for CLI
  - PTA
  - BMS
  - Atherectomy
  - DCB
  - DES
- Data primarily driven with amputation free survival (AFS) as a metric
- Primary patency is harder to find though newer studies use this endpoint in addition to wound healing
- All studies remain incredibly heterogeneous so comparisons are impossible



Angioplasty

- Simple
- Fast
- Lesion length
  - Short
  - Longer
  - Distal
- Outcome driven
  - AFS
  - Wound healing

BASIL

- Between 1999 and 2004
- 452 patients with critical limb ischemia were considered requiring immediate revascularization
- 228 for bypass and 224 for angioplasty
- Follow-up is at 3-7 years and outcome is amputation free survival and operative survival

No difference in outcome either in AFS or OS between surgery or PTA alone

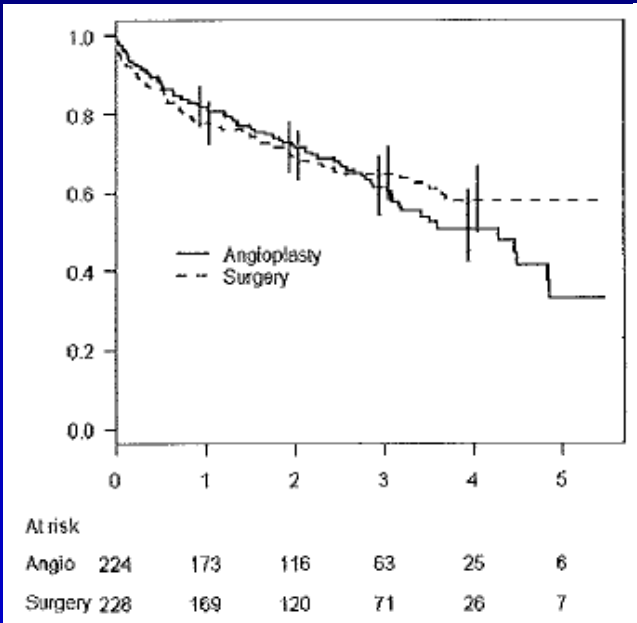


Figure 4 All-cause mortality following bypass surgery (BSX) and balloon angioplasty (BAP) by intention to treat (2005 analysis).

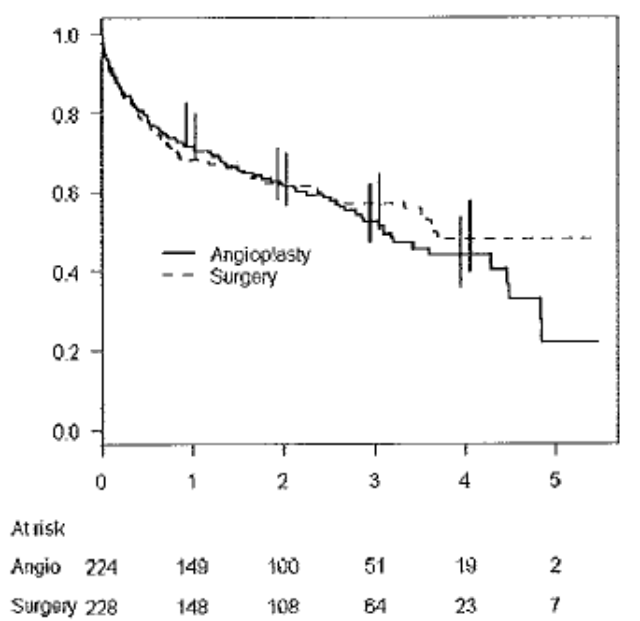
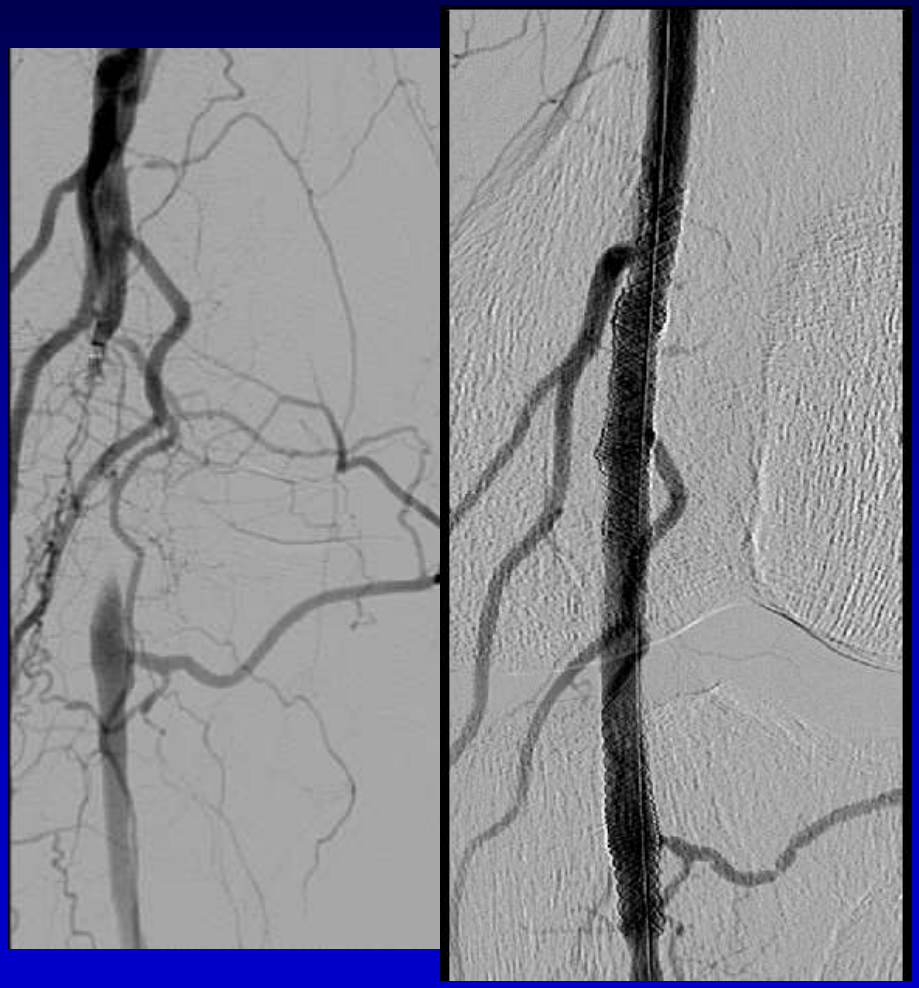


Figure 3 Amputation free survival following bypass surgery (BSX) and balloon angioplasty (BAP) by intention to treat (2005 analysis).

Stenting (BMS)



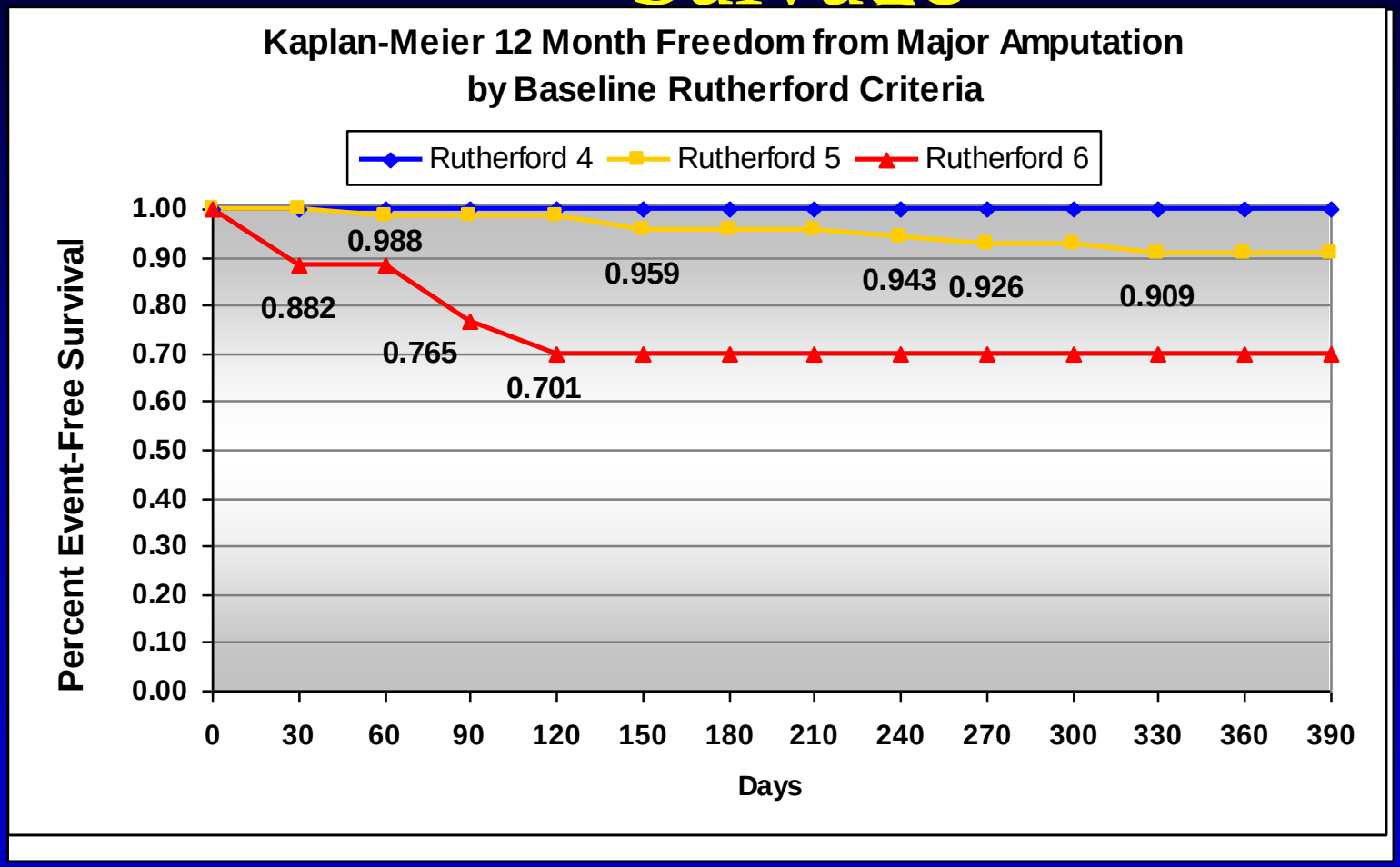
- Generally longer lesions
- Goal wound healing
- Patency less important long term

EXCELL: Core Lab Lesion Baseline Characteristics

Lesion Characteristics	N=140 Lesions/N=120 Patients
Lesion Length, cm	
Overall	4.7 ± 4.2
Stenosis ≤ 99% (95 lesions)	3.6 ± 3.5
Occlusions (42 lesions)	7.1 ± 4.5
Lesions / Patient	1.2 ± 0.4
RVD	2.8 ± 0.7
Pre – stenosis, % (in-lesion)	81.1 ± 16.5
Pre – MLD, mm (in-lesion)	0.5 ± 0.5
Post – stenosis, % (in-stent)	12.3 ± 13.2
Post – MLD, mm (in-stent)	2.4 ± 0.6

Values indicate mean ± SD of the lesion characteristic.

Freedom From TLR/Limb Salvage



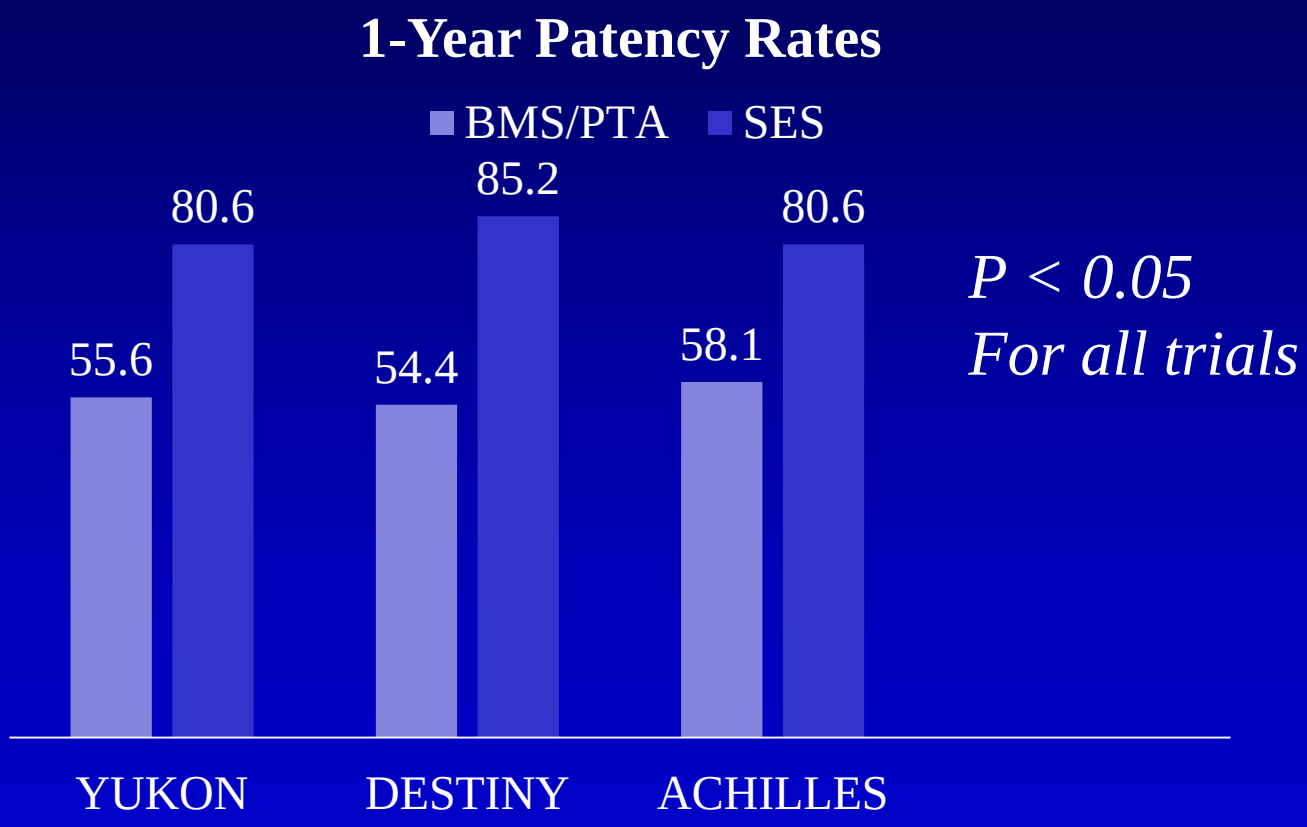
Stenting DES

- Short focal lesions by data set
- Goal wound healing
- Primary patency and long term patency very good

CURRENTLY PRESENTED OR PUBLISHED TRIALS ON DES IN BTK LESIONS

- YUKON-BTK—LL 27mm
  - Sirolimus eluting polymer free vs. bare metal stent (Yukon),Translumina. PI: T. Zeller
- DESTINY—LL 15-19 mm
  - Everolimus eluting stent (Xience V) vs. bare metal stent (Multilink vision), Abbott Vascular. PI: M. Bosiers
- ACHILLES
  - Sirolimus stent with polymer coating (Cypher select) vs. POBA, Cordis. PI: D. Scheinert

YUKON, DESTINY & ACHILLES Trials (n=515)
Primary Patency



P < 0.05
For all trials

Rastan et al. EHJ 2011
Scheinert et al. LINC 2011
Bosiers et al. JVS 2011

Debulking Therapies

- Laser
- Rotational devices
- Directional atherectomy

- All generally registries
- All have AFS primary outcomes
- To a lesser degree is primary patency

Atherectomy

- DA-DEFINITIVE LE
  - CLI cohort 71% overall (PSVR 2.4)
    - SFA 8.6 cm
    - Popliteal 5.4 cm
    - Tibial 6.0 cm
- CSI-LIBERTY 360
  - CLI RB 4/5 and separate RB 6
  - Core lab adjudication-angio/US
- Pathway-JETSTREAM
  - Ongoing registry (currently on hold) includes RB 4 only

The LACI Studies

The LACI Trial: 6 Month Results

- Laird et al
- 145 pt, 155 critical ischemic limbs
- 423 lesions
- 41%SFA, 15% Popliteal, 41% Infrapop
- 70% of Pts had combo occlusion and stenosis
- 29% Rutherford Class 4
- 71% Rutherford Class 5 or 6
- Limb salvage 92% at 6 months

Directional atherectomy

SilverHawk

Primary Patency in Subgroups

Subgroup	Claudicants (n=743)		CLI (n=279)	
	Patency (PSVR ≤ 2.4)	Lesion Length (cm)	Patency (PSVR ≤ 2.4)	Lesion Length (cm)
All (n=1022)	78%	7.5	71%	7.2
Lesion type				
Stenoses (n=806)	81%	6.7	73%	5.8
Occlusions (n=211)	64%	11.1	66%	10.3
Lesion Location				
SFA (n=671)	75%	8.1	68%	8.6
Popliteal (n=162)	77%	6.0	68%	5.4
Infrapopliteal (n=189)	90%	5.5	78%	6.0

Primary IN.PACT DEEP Outcomes

Primary Efficacy	DEB	PTA	*p*
12-month LLL (mm) [1]	0.61 ± 0.78	0.62 ± 0.78	*0.950*
12-month CD-TLR [2]	9.2% (18/196)	13.1% (14/107)	*0.291*

Primary Safety	DEB	PTA	*p*
6-month Death Major Amputation or CD TLR	17.7% (41/232)	15.8% (18/114)	*0.021* (non-inferiority) *0.662 (superiority)*

1. *Angio Cohort, Corelab adjudicated. Angiogaphic Imaging 12-month FU compliance = 70.9% (DEB) vs. 71.4% (PTA)*
2. *Clinically driven TLR of the target lesion in the (major) amputation free surviving subjects at 12 months. "Clinically driven TLR" defined as any TLR of the target lesion associated with: a) deterioration of RC and / or b) Increase in size of pre-existing wounds and / or c) occurrence of a new wound(s), with b) and c) adjudicated by the Wound Healing Core lab*

BioLux

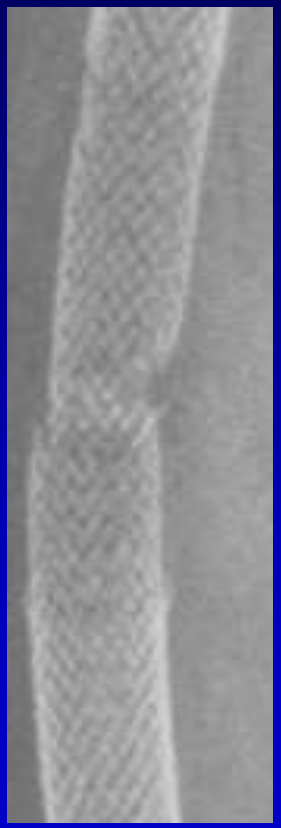
- 104 (50 DCB, 54 POBA) subjects, RB 2-5
- Safety: 30 days
- Efficacy: 6-month primary patency
- 30-day event: 0% DCB vs 5.8% POBA
- 6-month efficacy: 84% DCB vs 76% POBA (P=0.3)

LEVANT BTK

- 455 patients in 55 global sites
- Safety endpoint
  - Amputation
  - Major reintervention
- Efficacy
  - Limb salvage
  - Primary patency 12 months
- Indication for BTK possible after this data set release

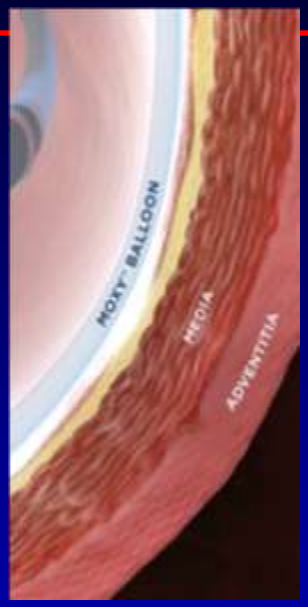
Why Bioabsorbable Stents?

- Advantages
  - No permanent device left behind, no need for stent scaffold later
  - Decrease flow-limiting dissection
  - May allow treatment of areas not suitable for a permanent stent
  - No long-term dual antiplatelet regimen needed
  - Maintain natural anatomic activity of vessel



- **Disadvantages**
  - **Inflammation**
  - **Embolization of material**
  - **Unknown time of support need**

Emerging Platforms PVD



Device	PTA	BMS	DES	DEB	What's Next?
12-mo * patency	33%	80%	82%	LLL 0.4mm	Bioabsorbable Stent?
*results not comparable	VIVA opc	Resilient	Zilver PTX	Thunder #	

Dake M, et al. Circ Cardiovasc Interv. 2011;4:495-504.
*Table adapted from trials *, #*

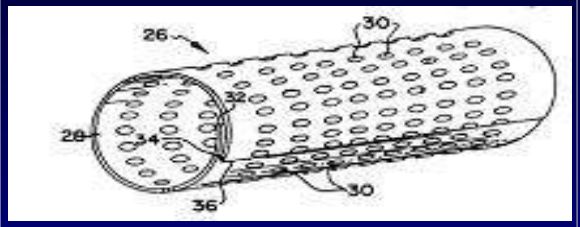
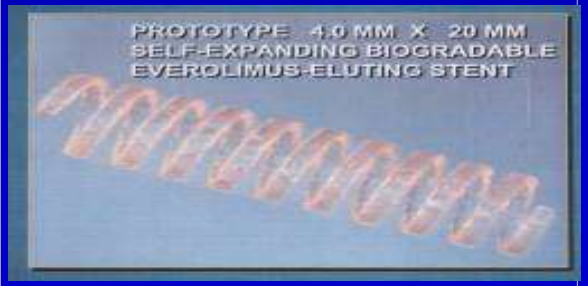
Technology Comparison

Device	Long-term DAPT	Fracture	Expansive Remodeling	Radial Strength	Distal Material Embolization
PTA balloon	No	No	Yes	No	No
DEB	No	No	Yes	No	Yes
Stent-Bare/DES	Yes	Yes	No	Yes	Yes
Bioabsorbable Stent	No	No	Yes	No	Yes

*Avoidance of DAPT and addition of expansive remodeling AND **maintenance of vasomotor tone** are distinct advantages of bioabsorbable stents*

Adapted from Euro Intervention. 2009;5 (Supplement F) F72-F79.

Bioresorbable Stents 2015

Company	Picture	Polymer/Drug	Features
Abbott (BVS)		*All biodegradable polymers (PLLA) with everolimus*	*Self-expanding and balloon-expandable designs*
Igaki-Tamai		*PLLA; Transilast*	*Zigzag design deployed with a heated balloon FIM Trial; 50 pts*
Reva Medical		*Poly (DTE carbonate) with Iodine for radiopacity*	*Design has ratchet links for deployment*
Biosensors		*Poly (L or DL) lactide with BA9*	*Self-expanding stent with a retractable sheath delivery catheter*

Bioresorbable Scaffolds: Clinical Trials

Device	Study	Lesions	n	Outcome
 Igaki-Tamai	Igaki-Tamai FIM	coronary	50	18% restenosis @ 12-mos.
	PERSEUS	SFA	45	50% restenosis @ 6-mos.
 AMS	PROGRESS AMS	coronary	63	48% restenosis @ 12-mos.
	BIOSOLVE-1	coronary	47	4.7% TLR @ 12-mos.
	BEST BTK	infrapopliteal	20	73% primary patency @ 12-mos
	AMS INSIGHT	infrapopliteal	117	68% restenosis @ 6-mos.
 REVA	RESORB	coronary	30	67% TLR @ 6-mos.
 Absorb	ABSORB Cohort A	coronary	30	12% restenosis @ 6-mos.
	ABSORB Cohort B	coronary	45	2.4% restenosis @ 6-mos.
			56	3.5% restenosis @ 12-mos.

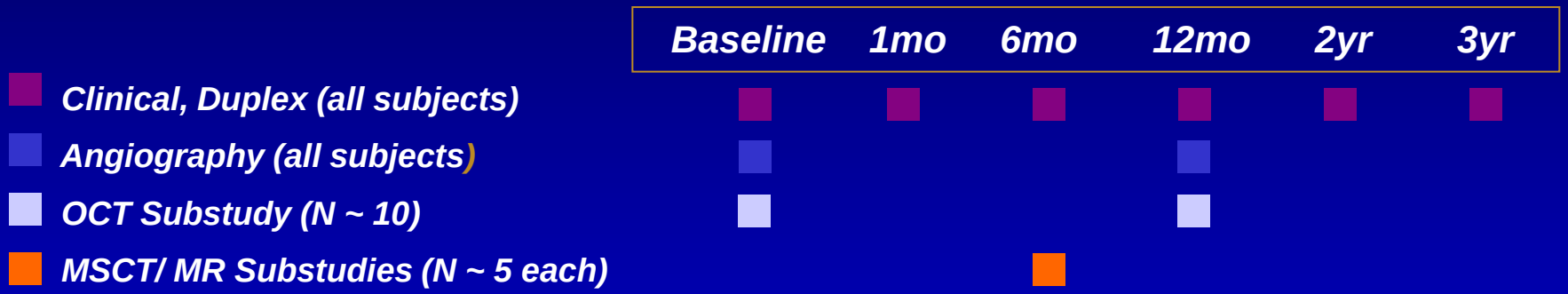
ABSORB BTK

Up to 2 *de novo* lesions in separate tibial vessels, length ≤24 mm, in patients with critical limb ischemia (CLI)

- Prospective, single-arm, multicenter trial
- One target lesion treated with a single 3.0 x 28 mm Absorb BVS
- Up to one non-target lesion treated with commercial device

90 Subjects
• 80 evaluable
• 10 roll-in

Up to 10 sites in EU & New Zealand



Study Objective:	**First-in-man study, safety and performance of the Absorb BVS in subjects with CLI from occlusive vascular disease of the tibial arteries**
Primary Endpoint:	**Freedom from major adverse limb events (major amputation or major reinterventions) occurring within one year or periprocedural (30-day) death (MALE+POD)**
Secondary Endpoints:	**Procedural, clinical, hemodynamic, angiographic, and functional endpoints in hospital & at each FU visit**

What is the best approach?

- All interventions afford AFS
- BMS primary patency poor
- Focal DES excellent primary patency compared with BMS
- Non-stent technologies
  - Directional atherectomy (DEFINITIVE LE) reported outcomes for popliteal and infra-popliteal disease in both claudicants and/or CLI
  - Rotational devices (CSI) OASIS claudicant group—LIBERTY forthcoming
- DCB (IN-Pact DEEP)failed in largest trial for below knee use
  - Principal studies using DCB still may be appealing but given the data (?)
- BVS very early data set and currently not indicated though if proven may provide an excellent early and long term therapy for a difficult location
- Current review of data supports revascularization for infra-popliteal disease though choice is at discretion
- Combined therapies for longer lesions seem appealing though larger trials currently pending