Learning from
BEST CLI, BASIL 2 and LIFE BTK for BTK therapy

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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
• Grant/Research Support	• Abbott, Medtronic, BSC
• Consulting (non-compensated)	• Medtronic, Boston Scientific, Abbott, Phillips
• Major Stock Shareholder/Equity	• Primacea, TissueGen, Orchestra, R3 Vascular, Transit Medical, Syntervention, Cagent
• Royalty Income	• None
• Ownership/Founder	• Innovation Vascular Partners, LLC
• Intellectual Property Rights	• None
• Other Financial Benefit	• None

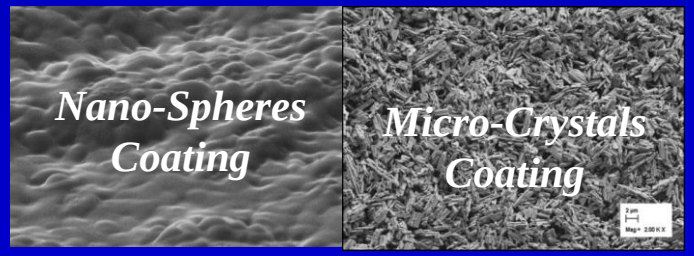
Why is this difficult?

- Unfortunately, the outcomes for ATK seem dependent upon patency and walking difficulties
- BTK data are mired in endpoints, heterogeneity of subjects, non-uniform nature of wound care and type of patient enrolled (RB3 in RB 4-5-6)

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*

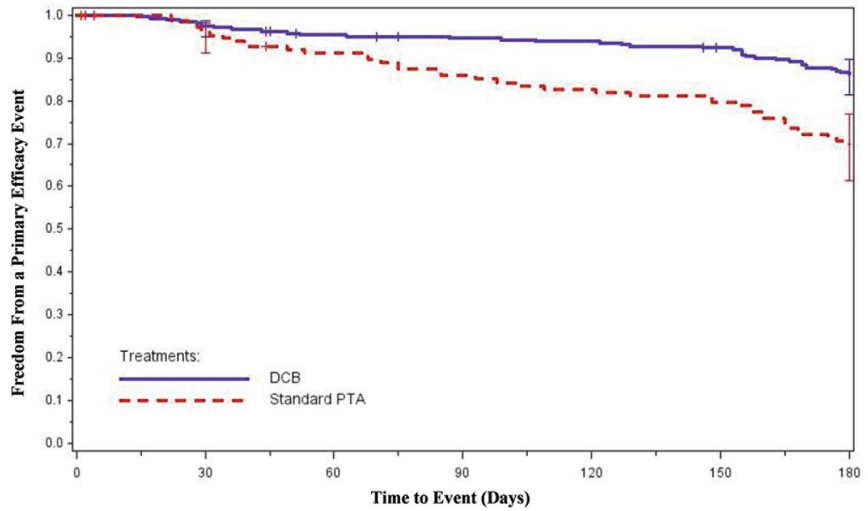
Primary Safety	DEB	PTA	*p*
6-month Death Major Amputation or CD TLR	17.7% (41/232)	15.8% (18/114)	*0.021* (non-inferiority) *0.662 (superiority)*



Zeller T et al JACC 2014
Zeller T et al JACC Interv 2020

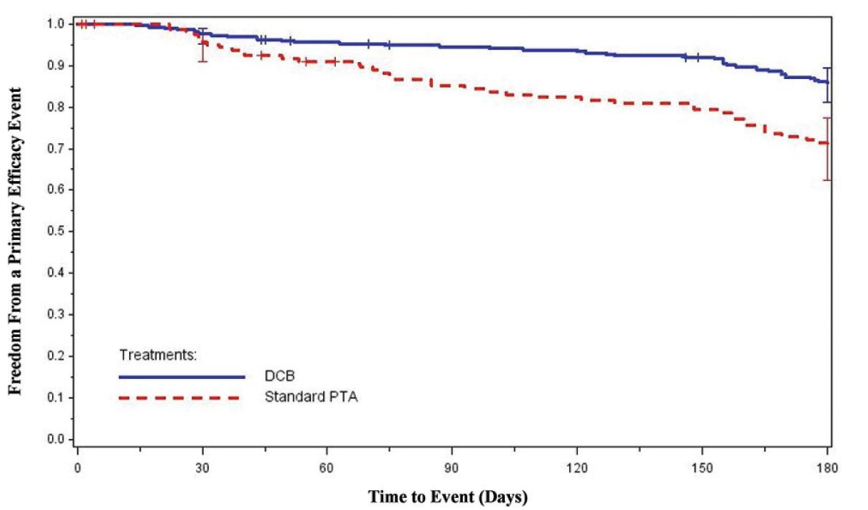
LEVANT BTK

A



180 Days	Survival % [95% CI]	Patients with Events	Patients Censored	Patients Remaining	Difference [95% CI]	P-Value
DCB	86.2% [81.4%, 89.8%]	37	43	224	16.3% [7.1%, 25.6%]	<.001
PTA	69.9% [61.4%, 76.9%]	41	39	92		

B



180 Days	Survival % [95% CI]	Patients with Events	Patients Censored	Patients Remaining	Difference [95% CI]	P-Value
DCB	85.8% [81.1%, 89.3%]	40	49	234	15.1% [6.0%, 24.3%]	<.001
PTA	70.7% [62.4%, 77.4%]	42	45	97		

FDA panel voted 2-15 with one abstention regarding effictiveness

SAVAL

Primary Endpoints

12 Months | Subject-based | Intention-to-treat

- Primary effectiveness endpoint of superior 12-month primary patency rate was not met
  - Lower bound of one-sided 97.5% CI < 0

	DES (N=130 Patients)	PTA (N=71 Patients)	Difference (95% CI)	One-sided lower 97.5% CI	Superiority p-value
Primary Patency	**68.0%** (70/103)	**76.0%** (38/50)	-8.0% (-22.9%, 6.8%)	**-22.92%**	0.8552

Primary patency defined as core lab-adjudicated duplex ultrasound flow at 12 months in the absence of clinically-driven TLR or surgical bypass of the target lesion. The effectiveness endpoint was pre-specified for superiority at a one-sided significance level of 2.5%. Success criterion for the effectiveness endpoint hypothesis was that the lower bound of the one-sided 97.5% CI on the difference was greater than zero.

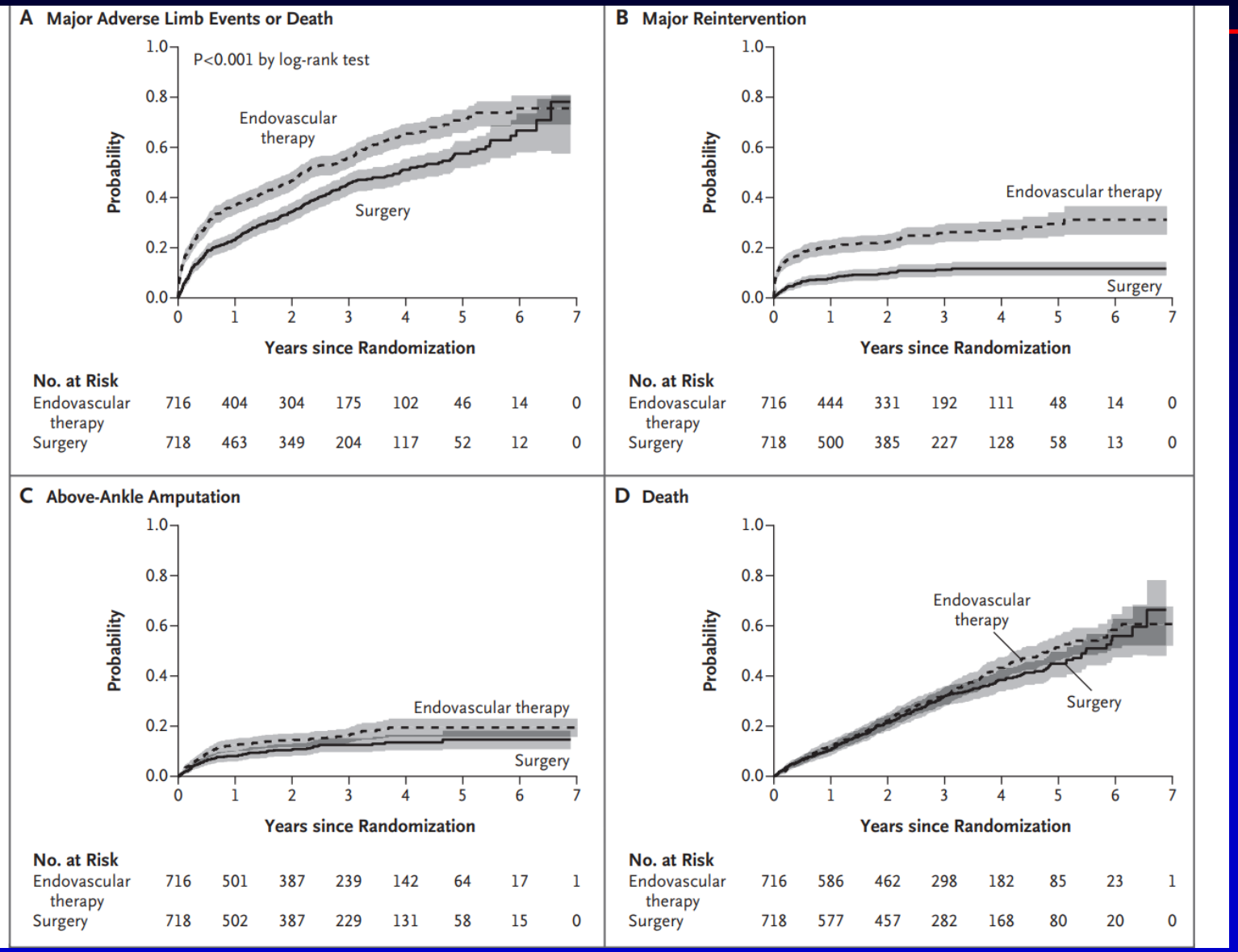
- Primary safety endpoint of non-inferior 12-month MAE-free rate was not met
  - Lower bound of one-sided 97.5% CI < -10%

	DES (N=130 Patients)	PTA (N=71 Patients)	Difference (95% CI)	One-sided lower 97.5% CI	Noninferiority p-value
MAE-free Rate	**91.6%** (109/119)	**95.3%** (61/64)	-3.7% (-10.9%, 3.5%)	**-10.90%**	0.0433

MAEs defined as a composite of above-ankle amputation of the index limb, major re-intervention, and 30-day mortality. Success criterion for the safety endpoint hypothesis was that the lower bound of the one-sided 97.5% CI on the difference was greater than the non-inferiority margin of -10%. P value is 1-sided adjusted for non-inferiority margin of -10%.

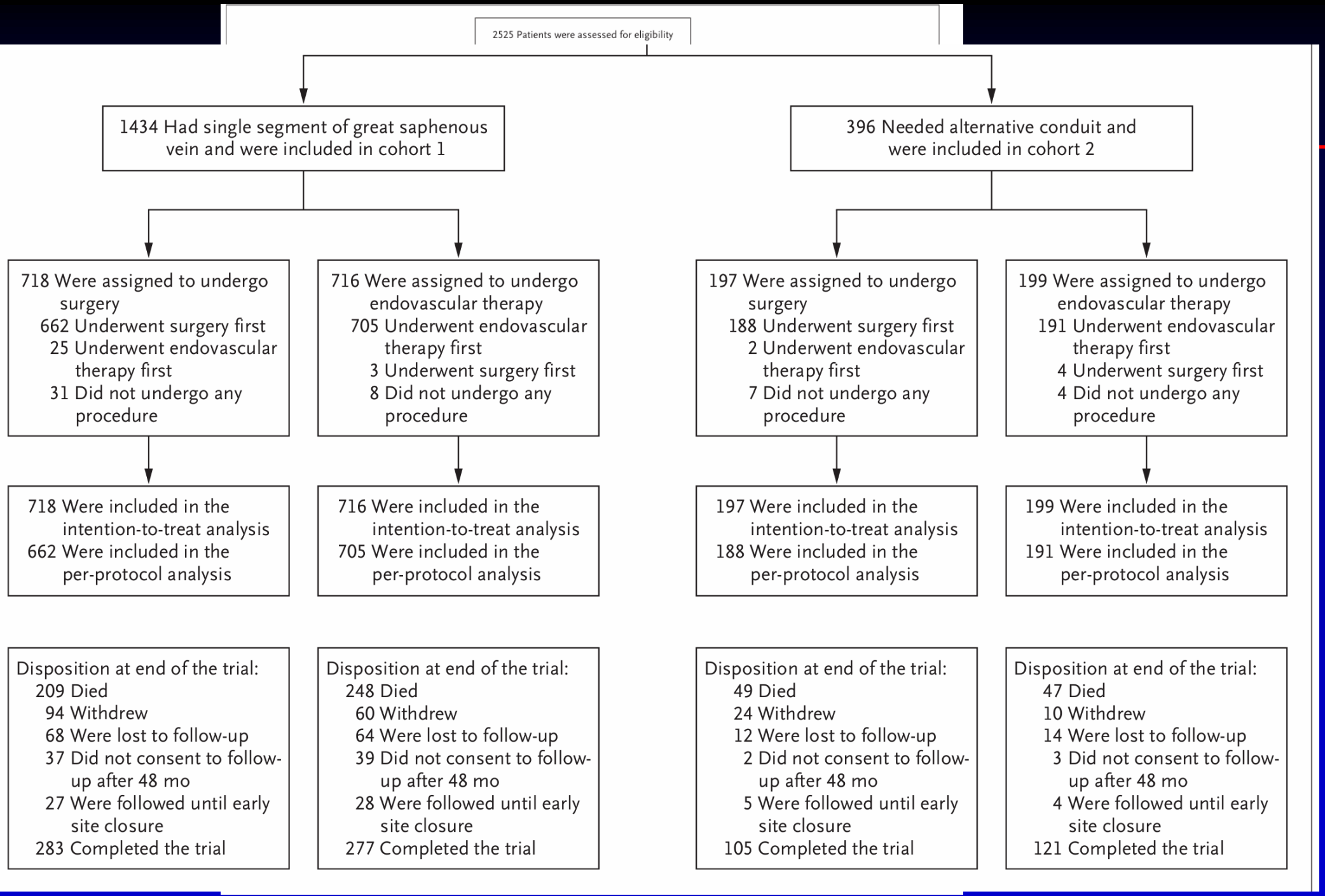
Van OverHagen, CIRSE 2022

BEST CLI



- *5 years to enroll study*
- *18% non-surgeons in the endovascular group, no IMC*
- *38% cross over in the endo group never defined*
- *Primary outcomes major revision, thrombolysis or revision to graft not restenosis*

Farber A et al NEJM 2022


2525 Patients were assessed for eligibility
1434 Had single segment of great saphenous vein and were included in cohort 1
396 Needed alternative conduit and were included in cohort 2
718 Were assigned to undergo surgery
662 Underwent surgery first
25 Underwent endovascular therapy first
31 Did not undergo any procedure
716 Were assigned to undergo endovascular therapy
705 Underwent endovascular therapy first
3 Underwent surgery first
8 Did not undergo any procedure
197 Were assigned to undergo surgery
188 Underwent surgery first
2 Underwent endovascular therapy first
7 Did not undergo any procedure
199 Were assigned to undergo endovascular therapy
191 Underwent endovascular therapy first
4 Underwent surgery first
4 Did not undergo any procedure
718 Were included in the intention-to-treat analysis
662 Were included in the per-protocol analysis
716 Were included in the intention-to-treat analysis
705 Were included in the per-protocol analysis
197 Were included in the intention-to-treat analysis
188 Were included in the per-protocol analysis
199 Were included in the intention-to-treat analysis
191 Were included in the per-protocol analysis
Disposition at end of the trial:
209 Died
94 Withdrew
68 Were lost to follow-up
37 Did not consent to follow-up after 48 mo
27 Were followed until early site closure
283 Completed the trial
Disposition at end of the trial:
248 Died
60 Withdrew
64 Were lost to follow-up
39 Did not consent to follow-up after 48 mo
28 Were followed until early site closure
277 Completed the trial
Disposition at end of the trial:
49 Died
24 Withdrew
12 Were lost to follow-up
2 Did not consent to follow-up after 48 mo
5 Were followed until early site closure
105 Completed the trial
Disposition at end of the trial:
47 Died
10 Withdrew
14 Were lost to follow-up
3 Did not consent to follow-up after 48 mo
4 Were followed until early site closure
121 Completed the trial

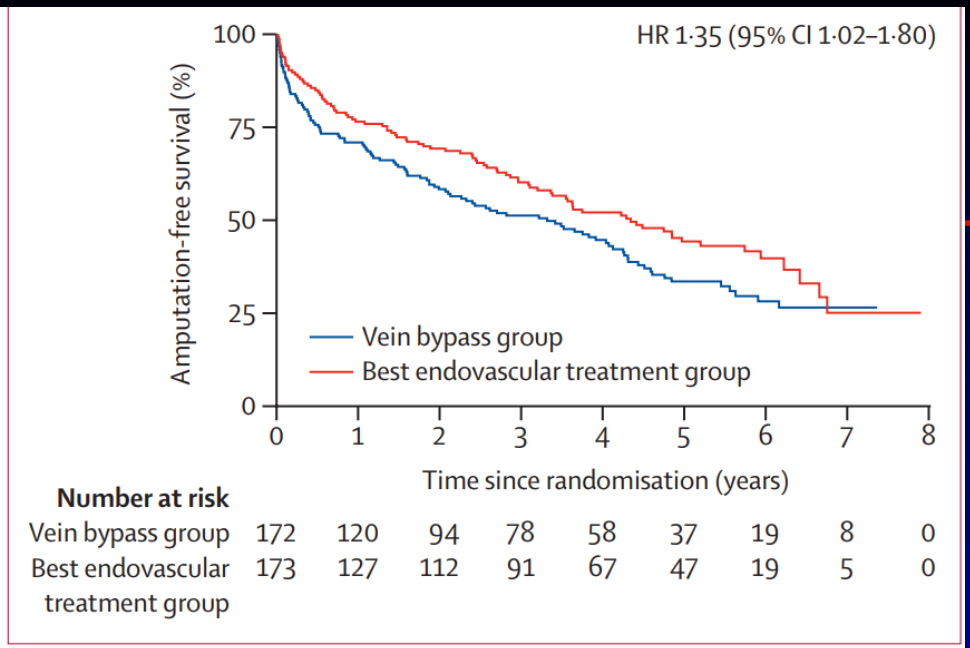
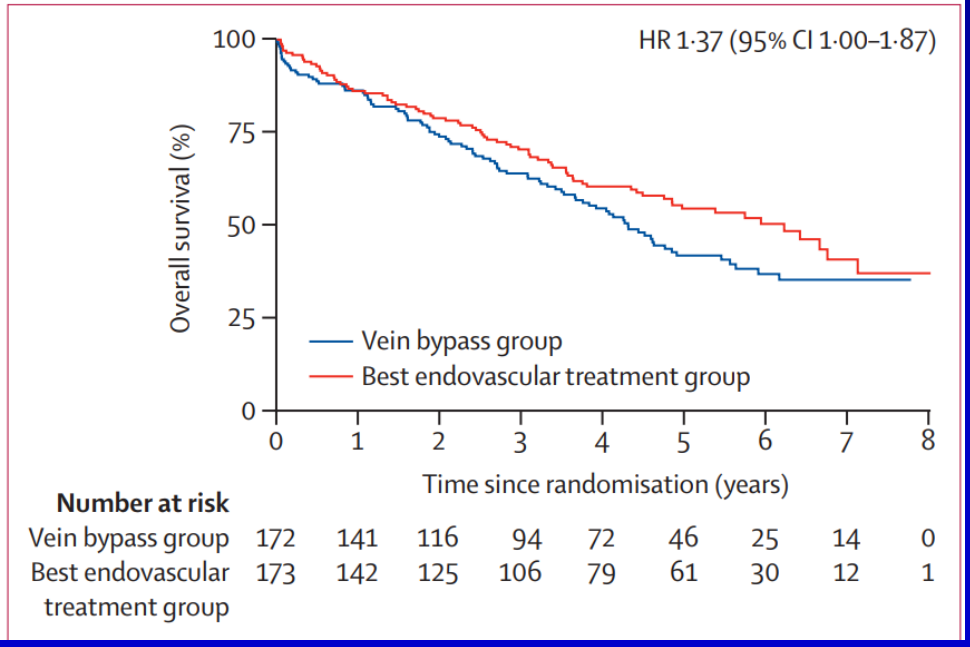


***Figure 2*: Amputation-free survival Kaplan-Meier curve**
HR=hazard ratio.



BASIL 2

- *10 years to enroll study*
- *Similar endpoints MALE etc*
- *However, primary outcome was revision or primary procedural repeat as failure*
- *Endo any restenosis considered failure*
- *Only mortality drove difference between cohorts*

BEST-CLI vs. BASIL-2: trial designs

- BEST-CLI: 150 global centers
  - 1434 subjects over ~5 years (average 2/center/year)
  - Study populations
    - Cohort 1: suitable autologous venous conduit for bypass
    - Cohort 2: need for alternative bypass conduit
  - Excluded if excessive surgical risk
  - Randomized 1:1 in a stratified fashion by anatomy (presence or absence of BTK disease) and clinical (rest pain or tissue loss)

- BASIL-2: 41 primarily UK centers
  - 345 subjects enrolled over 6 years
    - No exclusions for vein suitability
    - No exclusion for bypass suitability
  - Multiple stratifications
  - More bypass:endo cross-over (27%), more reintervention in the endo group (19%)

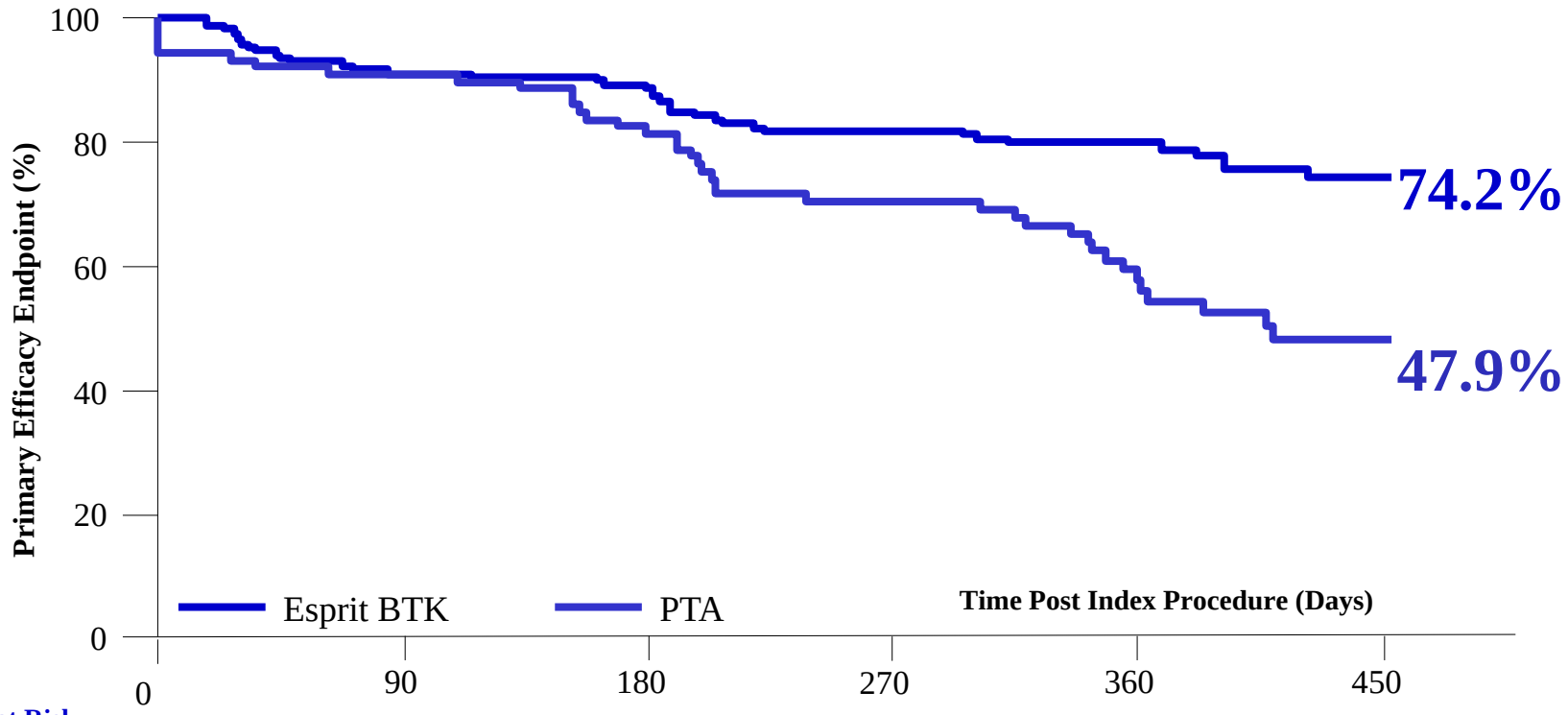
BEST-CLI vs. BASIL-2: Endpoints

- BEST-CLI Primary endpoint:
  - Composite of death and MALE (above ankle amputation, major limb reintervention)
    - ***Reintervention need and timing was determined by site investigator***
    - ***No CD-TLR criteria or independent adjudication***

- BASIL-2 Primary endpoint:
  - Amputation-free survival (AFS) or all-cause death

LIFE-BTK

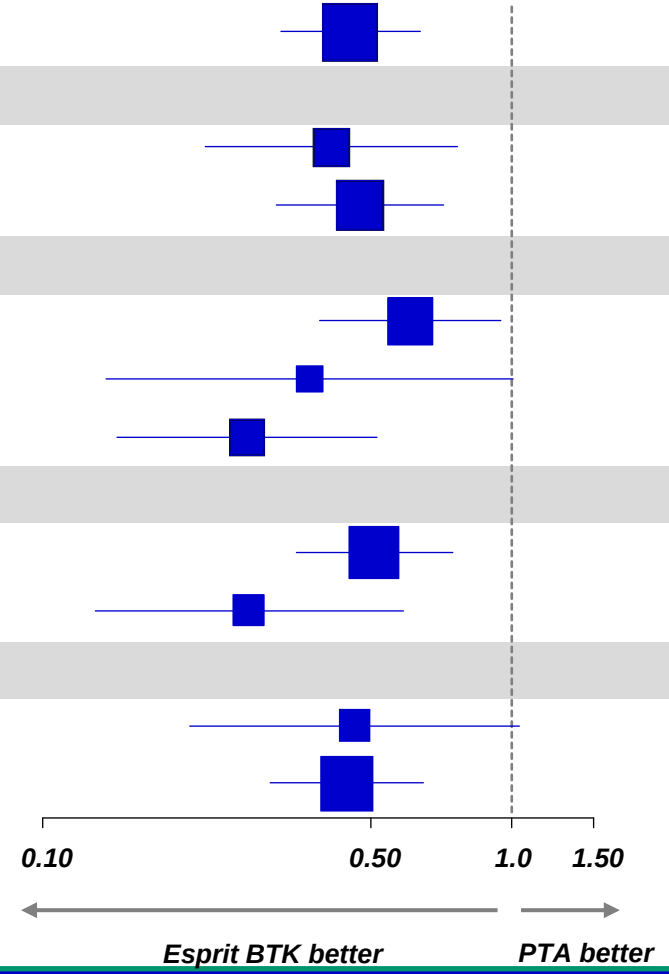
Esprit BTK	PTA	Difference [One-Sided Lower 97.51% CL][2]	P-Value[3]
74.5% (111/149)	43.7% (31/71)	30.8% (17.0%)	<0.0001



No. at Risk						
Esprit BTK	173	163	152	142	95	42
PTA	88	82	78	67	33	15

Subgroup Analyses of Composite Primary Efficacy Endpoint at 1 Year

Subgroup	Esprit BTK (%)	PTA (%)	Relative Risk (CI)	Interaction p value
All patients	38/149 (25.5)	40/71 (56.3)	0.45 (0.32-0.64)	
Sex				**0.7709**
Female	12/51 (23.5)	12/21 (57.1)	0.41 (0.22-0.76)	
Male	26/98 (26.5)	28/50 (56.0)	0.47 (0.31-0.71)	
Race				**0.1055**
White	24/79 (30.4)	22/44 (50.0)	0.61 (0.39-0.95)	
African American	4/18 (22.2)	6/10 (60.0)	0.37 (0.14-1.01)	
Others	10/52 (19.2)	12/17 (70.6)	0.27 (0.14-0.51)	
Region				**0.1247**
US	31/114 (27.2)	32/60 (53.3)	0.51 (0.35-0.75)	
OUS	7/35 (20.0)	8/11 (72.7)	0.28(0.13-0.59)	
Age				**0.6159**
< 65 years old	7/32 (21.9)	9/19 (47.4)	0.46 (0.21-1.04)	
≥ 65 years old	31/117 (26.5)	31/52 (59.6)	0.44 (0.31-0.65)	



Endpoints

	PRIMARY EFFICACY ENDPOINT	PRIMARY SAFETY ENDPOINT
Endpoint	**Limb Salvage + Primary Patency**	**Freedom from MALE + POD**
Definition	Freedom from above ankle amputation in index limb, 100% total occlusion of target vessel, binary restenosis of target lesion, and CD-TLR* at **12 months**	**MALE** = Above ankle amputation in index limb, major re-intervention at **6 months** **POD** = Perioperative mortality at **30 days**
Test	Superiority of Esprit™ BTK against PTA with a 1-sided α of 0.0249	Non-inferiority of Esprit™ BTK against PTA with a 1-sided α of 0.025
	1ST SECONDARY ENDPOINT	**2ND SECONDARY ENDPOINT**
Endpoint	**Binary restenosis of the target lesion at 1 year**	**Freedom from above ankle amputation in index limb, 100% total occlusion of target vessel and CD-TLR at 1 year**
Test	Superiority of Esprit™ BTK against PTA with a 1-sided α of 0.025	Superiority of Esprit™ BTK against PTA with a 1-sided α of 0.025

** Defined as clinically-driven target lesion revascularization*

What’s in the future?

• Serranator (RECOIL)	Cagent
• Magic Touch (LIMES, DEBATE)	Concept Medical
• Luminor DCB (MERLION)	iVASCULAR
• Litos DCB (ACOART II)	Acotec
• IMPACT DEEP redux	Medtronic
• Selution BTK	MedAlliance
• Orchestra	Orchestra

Conclusion(s)

- BTK trials are “in”
- Not one group (industry or Society) and FDA have generalized a singular population or outcome measure
- Unfortunately, difficulties with patients, wounds and endpoints have allowed no one trial to be successful and acceptable
- ***LIFE-BTK has changed this landscape dramatically***
- Patient needs to be very specific and will not answer the question for the cohort we see with CLTI but unfortunately that will be the start
- In this environment, BEST CLI is a remarkable study that unfortunately, missed its mark for the question asked