BEST-CLI Will Not Change My Practice

Matthew T. Finn MD Msc

Cardiovascular Institute of the South

Houma, Louisiana

Cors at the Shore 2023

Disclosures

Consultant:
Akura medical
Truvic

Major Stockholder:

Speaker’s Bureau:
Janssen

Other Support:

Cors at the Shore 2023

BEST-CLI and BASIL-2: Long awaited follow up to BASIL-1 from 2005

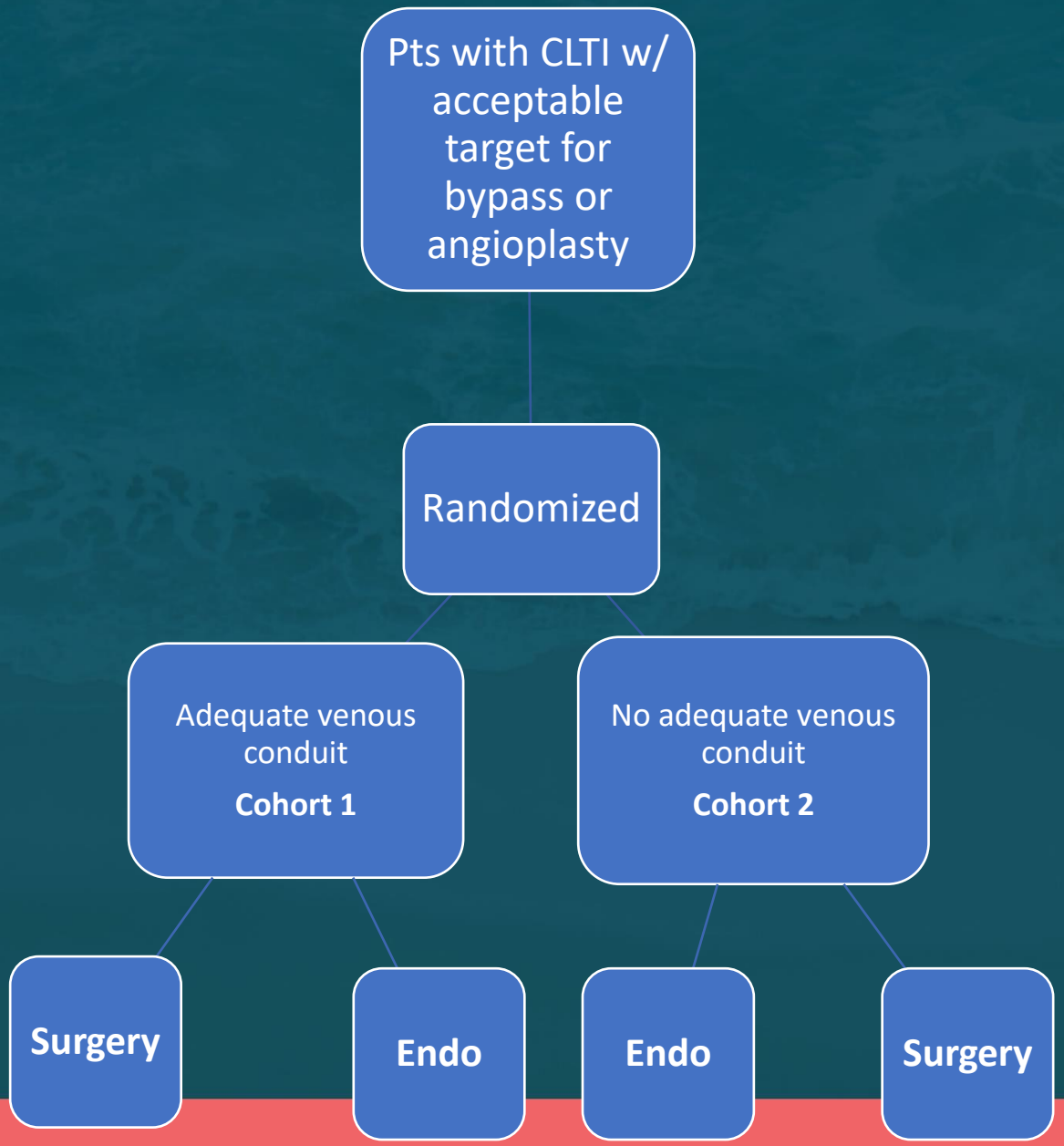
- BASIL-1: Surgical-bypass-first vs. endovascular treatment-first in patients with chronic limb threatening ischemia (CLTI)

- Primary endpoint BASIL-1 was amp free survival at 6 months
  - no significant difference was seen – HR 0.73 95% CI 0.49–1.07

- Primary endpoint BEST CLI was broader than BASIL I & II
    - BEST-CLI used MALE (including major amputation or major limb re-intervention) in combination with all cause death.

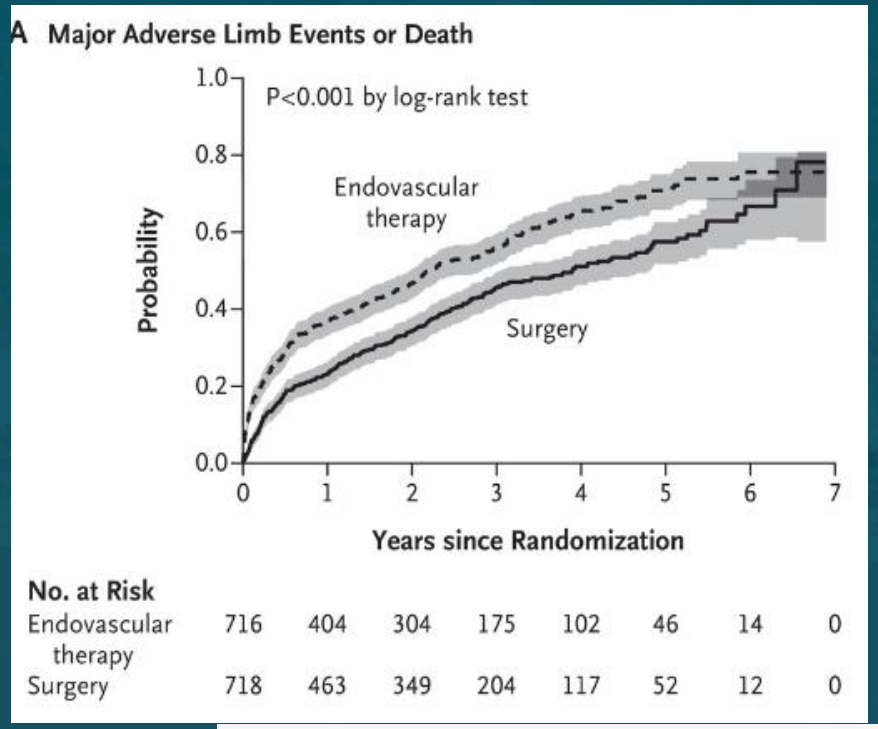
Cors at the Shore 2023

Adam D et al Lancet 2005



Cors at the Shore 2023

Primary Outcome Cohort 1 (adequate conduit available)



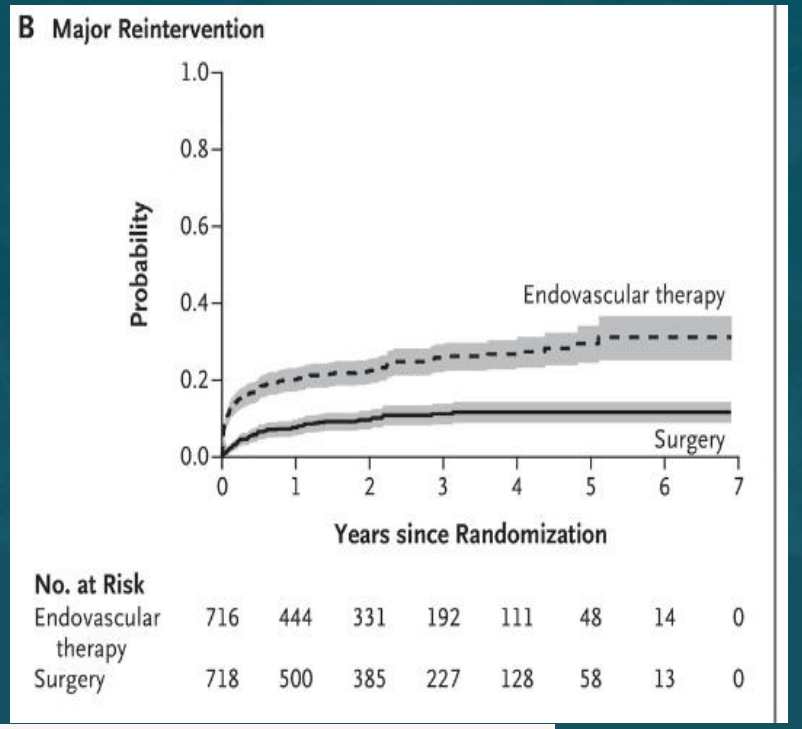


Table 2. Efficacy and Safety Outcomes in Cohort 1.*

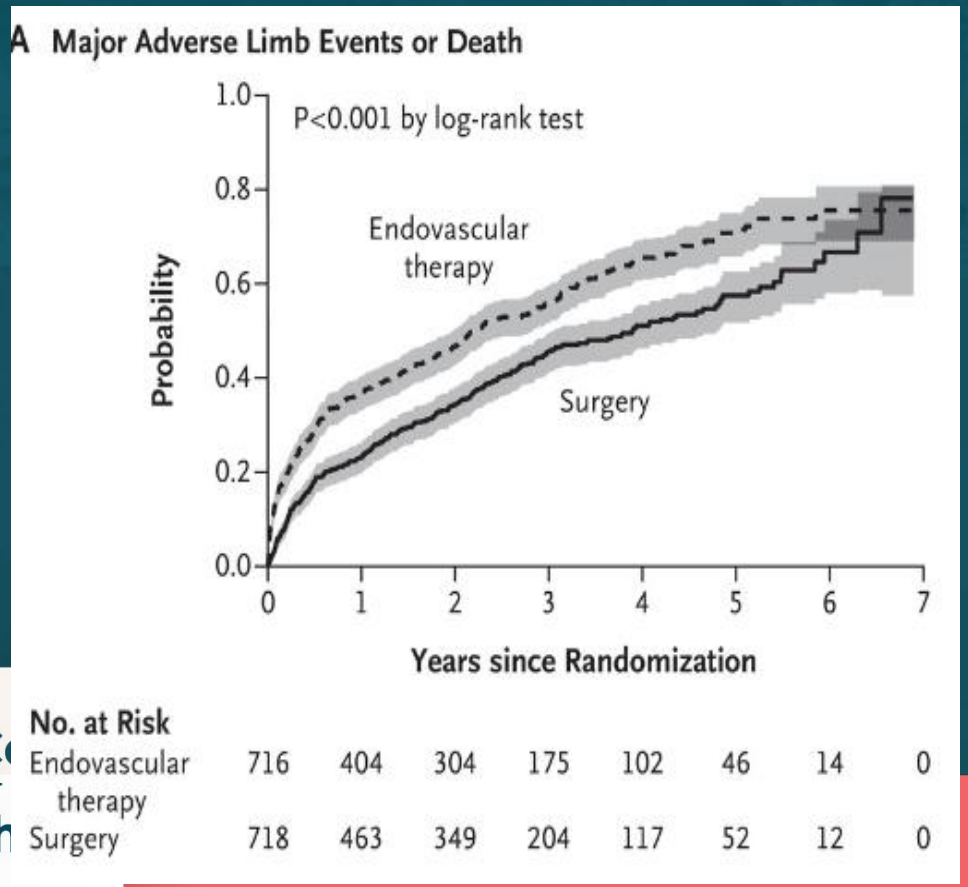
Outcome	Surgery	Endovascular Therapy	Hazard Ratio (95% CI)†	P Value
Efficacy				
Primary outcome: major adverse limb event or death from any cause — no./total no. (%)‡	302/709 (42.6)	408/711 (57.4)	0.68 (0.59–0.79)	<0.001
Secondary outcomes — no./total no. (%)				
Death from any cause	234/709 (33.0)	267/711 (37.6)	0.98 (0.82–1.17)	
Above-ankle amputation of the index limb	74/709 (10.4)	106/711 (14.9)	0.73 (0.54–0.98)	
Intervention in index limb				
Major	65/709 (9.2)	167/711 (23.5)	0.35 (0.27–0.47)	

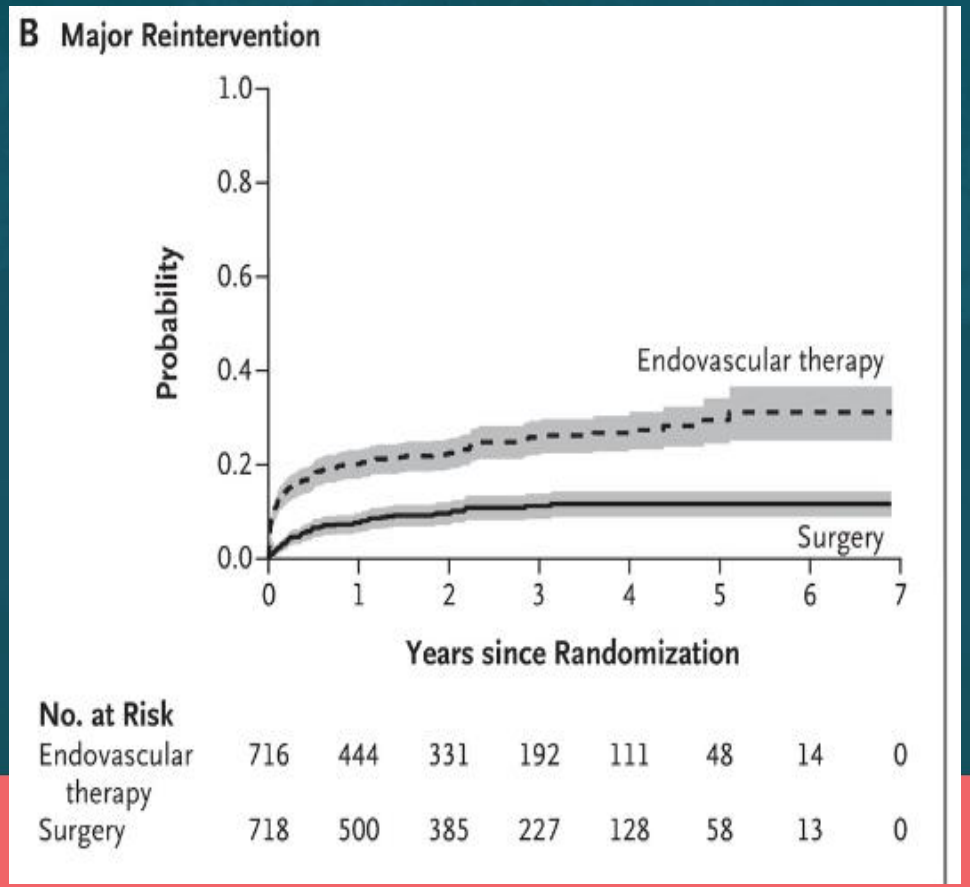
Cors at the Shore 2023

How do we explain this difference in the primary outcome for cohort 1 – Look at the numbers!

- Primary Outcome: 42.6% in the surgical group vs. 57.4% in the endovascular group
  - absolute risk reduction of 14.8%
- This was nearly entirely driven by excess reintervention in the endovascular therapy arm (surgery 9.2% vs. endovascular 23.5%)
  - absolute difference of 14.3%
- These reinteventions were due to excess technical failures in the endo arm 1.7% surgery vs. 15.3% endo in cohort 1
  - This very high endo failure rate is more extreme because these patients had good bypass targets so endo success rates should have been better than contemporary studies not way worse!

This difference also explains the early and constant separation of the KM curves of cohort 1.





Endo arm cohort 1 – more concerns

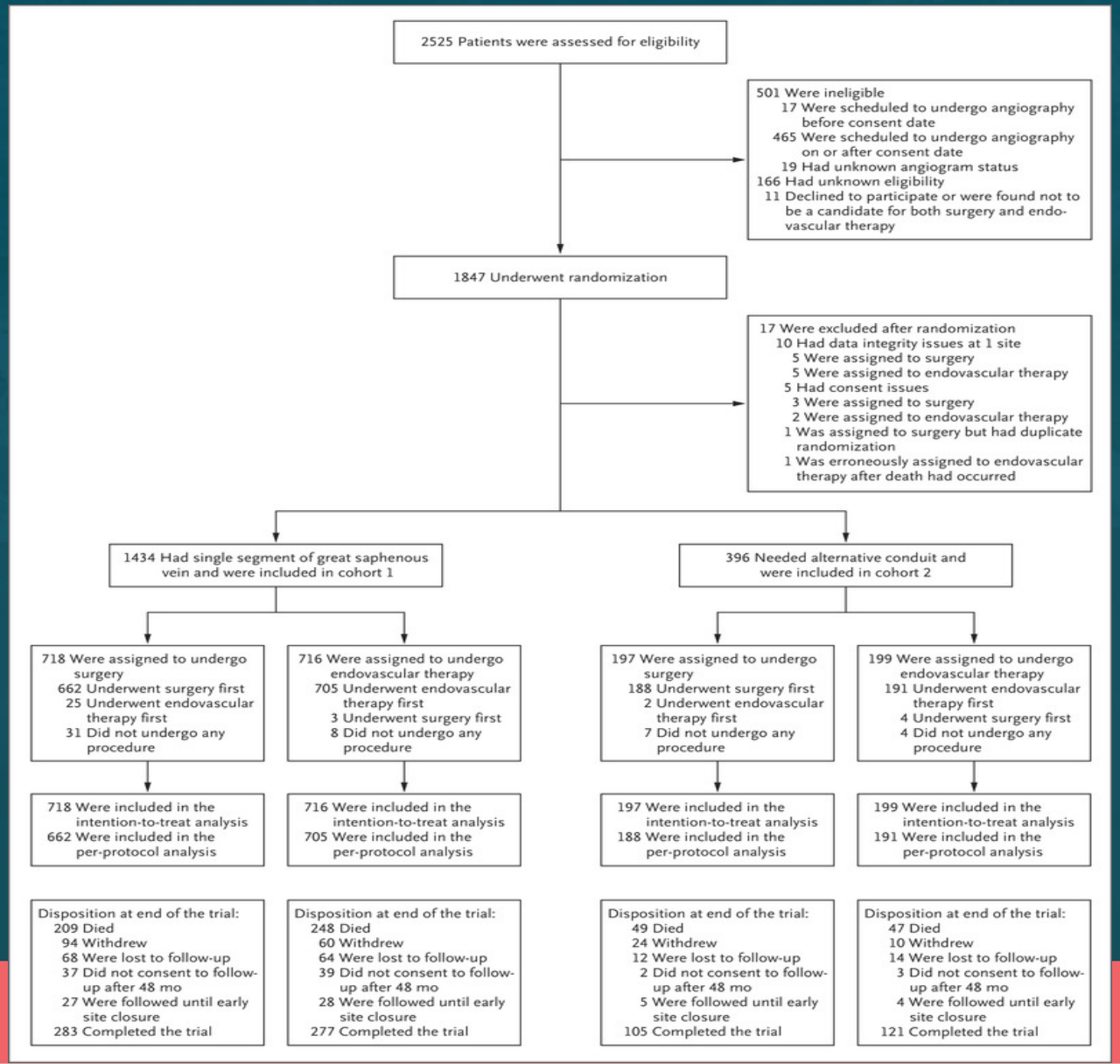
- The primary endpoint was 10% lower in the endo arm of cohort 2 compared to the endo arm of cohort 1 suggesting **selection bias.**
  - **(they should have been similar because received the EXACT same treatment)**

Technical Failures

- BEST CLI fails to explain why the excess rate of endovascular failures (15.3%) in cohort 1 occurred.
- Modern CLI cohorts studying endovascular techniques predict a failure rate of 5% or less.

De Boer SE et al doi:10.3390

Consort diagram = Cluster F*?



Problems with the trial execution limited internal and external validity

Examples:

- 17 patients had data integrity issues so were just excluded after randomization. This shouldn't happen in modern RCTs.
- 1 patient was assigned to endo after dying before the procedure (**this is blatant example of bias in the trial**) before eventually being excluded

Serious problems with trial validity

- Missingness, loss to follow up, data integrity accounted for too much of the study group

	Cohort 1		Cohort 2		Grand total
	Surgery	Endo	Surgery	Endo	
Underwent alternate therapy than randomized	25	8	2	4	
Did not have any procedure	31	8	7	4	
Withdrew	60	60	24	10	
Loss to follow up	68	64	12	14	
Total	218	135	45	32	430

Nearly 1/4th of patients with data issues = NOT A VALID STUDY

- 430/1830 randomized = 23.5% of overall randomized cohort
- This does not include an additional 17 patients excluded due to data integrity and consent issues

TO THE EDITOR

Farber at al. report a lower rate of technical success in the endovascular-therapy group (85%) than in surgical group (98%) in cohort 1 in the BEST-CLI trial. This divergence in success explains almost the entire difference in the primary outcome between the two groups, because technical failure inevitably leads to repeat revascularization attempts. This difference in success rates accounts for the immediate separation of the Kaplan–Meier curves for the primary outcome of major adverse limb events or death from any cause, because the definition of major adverse limb events includes repeat revascularization.

We also note that this trial had an unacceptably high number of patients who were lost to follow-up and a large number of protocol deviations. Across the four trial cohorts, a total of 363 patients were lost to follow-up, withdrew consent, or were excluded due to data issues, which represents 19.8% of the overall analysis cohort.

Matthew T. Finn, M.D.
Pradeep Nair, M.D.
Craig Walker, M.D.
Cardiovascular Institute of the South, Gray, LA

BASIL-2

A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial

Prof Andrew W Bradbury, MD, Catherine A Moakes, MSc, Matthew Popplewell, MD, Lewis Meecham, FRCS, Gareth R Bate, PGDip, Lisa Kelly, PGDip, Prof Ian Chetter, MD, Athanasios Diamantopoulos, PhD, Arul Ganeshan, FRCR, Jack Hall, MSc, Simon Hobbs, MD, Prof Kim Houlind, MD, Hugh Jarrett, MSc, Suzanne Lockyer, MSc, Jonas Malmstedt, MD, Jai V Patel, FRCR, Smitaa Patel, MSc, S Tawqeer Rashid, PhD, Athanasios Saratzis, MD, Gemma Slinn, MPhil, Prof D Julian A Scott, MD, Hany Zayed, MD, Prof Jonathan J Deeks, PhD

The Lancet

DOI: 10.1016/S0140-6736(23)00462-2

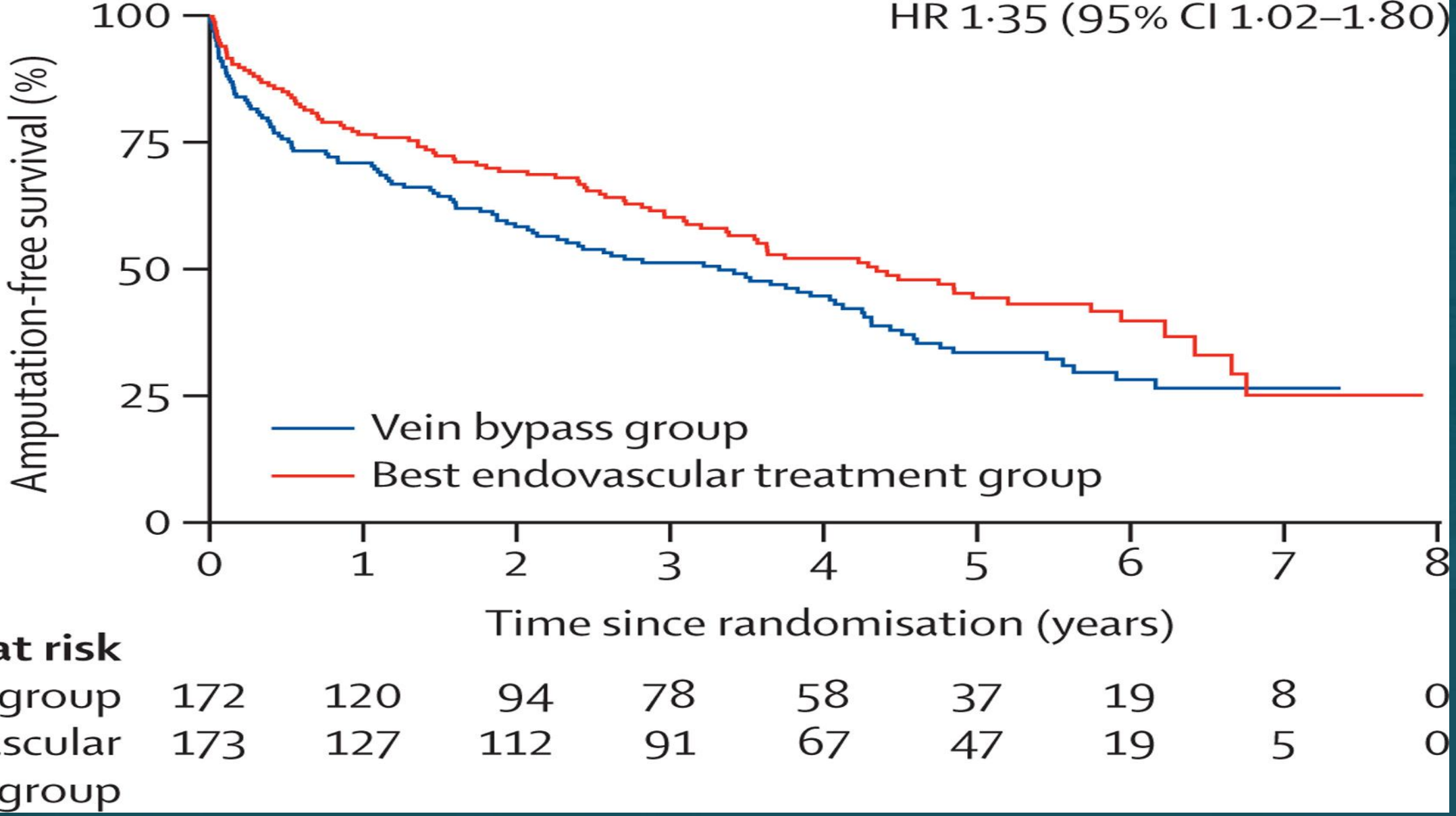
Cors at the Shore 2023

BASIL-2 Design: Surgical bypass first vs. Endo-first for CLTI

- multicenter, open label, randomized control trial performed at 41 sites across the United Kingdom (39 sites), Sweden (1 site) and Denmark (1 site)
- In the surgical arm, any vein deemed suitable by the operating surgeon could be used. If it was discovered that a vein could not be used, a prosthetic or composite graft was allowed.

BASIL-2 Design: Surgical bypass first vs. Endo-first for CLTI

- The study primary endpoint was amputation-free survival (time-to-major amputation or death from any cause with intent-to-treat) with follow-up of at least 24 months.

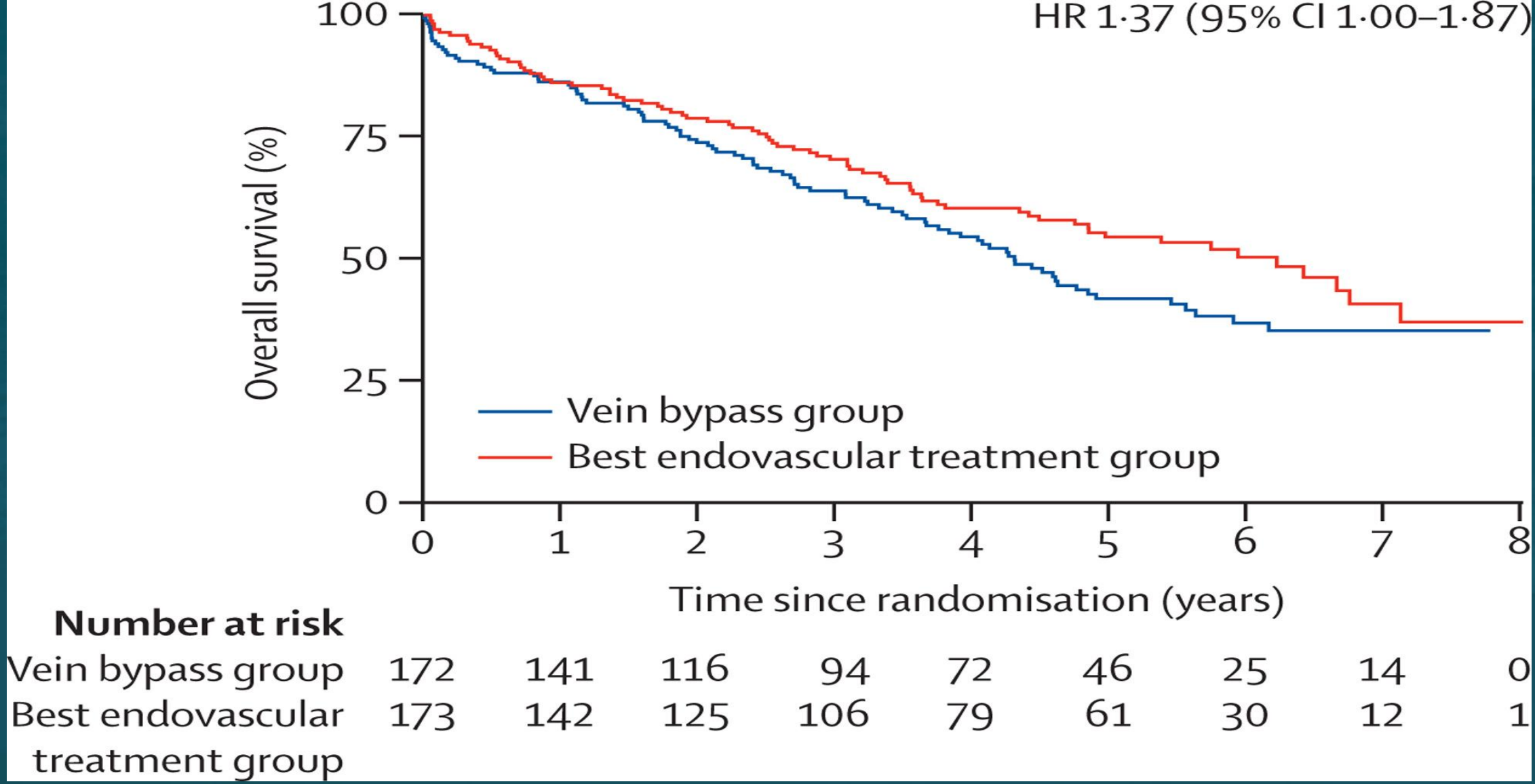


Number at risk

Vein bypass group	172	120	94	78	58	37	19	8	0
Best endovascular treatment group	173	127	112	91	67	47	19	5	0

Cors at the Shore 2023

The primary endpoint of amputation free survival occurred in 63% in the venous bypass arm and 53% in the endovascular treatment arm, adjusted hazard ratio 1.35, 95% CI 1.02–1.80, p = 0.037.



Number at risk

Vein bypass group	172	141	116	94	72	46	25	14	0
Best endovascular treatment group	173	142	125	106	79	61	30	12	1

Cors at the Shore 2023

This was driven by higher rates of death in the venous bypass arm compared to endovascular therapy (53% vs. 45% adjusted HR 1.37 95% CI 1.00-1.87) with the vast majority of the deaths due to cardiovascular causes or respiratory events.

BASIL-2 – Points of Emphasis

A strength of BASIL-2 was the choice of the primary endpoint of amputation-free survival rather than major adverse limb events (which includes revascularization procedures) used in BEST-CLI.

- Amputation-free survival reduces opportunities for bias in BASIL-2 given subjective decisions for revascularization, particularly in the context of high endovascular failure rates.

Difficult and slow enrollment in both BASIL-2 and BEST-CLI may represent current practice patterns and highlight challenges of offering routine bypass

BASIL-2 Detractors Will Say-

1. If patients have an adequate vein for bypass, it remains unknown which treatment strategy is superior as this was not the hypothesis tested in BASIL-2?

- However, only 7 patients randomized in the venous bypass arm had prosthetic or conduit grafts used.

2. The confidence intervals for the primary outcome were wide, making the conclusion of superiority of endovascular treatment over bypass surgery less robust.

    - Nevertheless, the preconceived hypothesis (and conclusion of BEST-CLI) of the superiority of venous bypass over endovascular revascularization is highly unlikely based on these results.

Conclusion - little to be concluded from Best CLI

- Excess technical failures occurred in the endo arm (~15%) accounting for the differences between groups for the primary endpoint
- These patients had at least one good target for bypass so success rates with endo procedure should have been better than contemporary studies (not way worse).
- Modern endo techniques were underutilized or not documented.

BEST- CLI Conclusions continued

- Significant problems occurred with the running of the trial limiting its validity with nearly 25% of randomized patients (n=430) having documented problems with randomization, missingness, loss to follow up, data integrity
- The overall event rates between endovascular cohort 1 and 2 should have been similar (since they had the same treatment); yet, the observed primary event rate for cohort 1 was 10% higher than cohort 2
- Given requirement for adequate conduit for bypass this is not the usual CLI patient which often has limited below the knee vessels (limited external validity aka generalizability)

What additional data could help us try to salvage something from this trial ? None of which were provided in the publication….

- Procedure times by cohort (Did patients get a real attempt at endo prior to bailing out to bypass?)
- Crossing techniques used?
- Alternative access attempts?
- Provide data regarding procedural volumes and case numbers for endovascular and surgical centers to establish basic competencies?
- Sensitivity analysis of rate of the primary endpoint in only those patients with successful index procedures (surgery and endo for both intent to treat and per protocol treatment)
- Fix missingness and add back patients excluded due to missing data (ask sites to provide).

BASIL-2 and BEST-CLI Take home - Little to conclude from BEST-CLI

- Significant issues with trial design and execution limit the applicability of BEST-CLI
- BASIL-2 demonstrated superiority for endovascular treatment over venous bypass (only 7 patients in bypass arm had prosthetic or composite grafts) and endo treatment has the advantage being less invasive with potentially lower resource utilization.
- These results and the less invasive nature of endo treatment should encourage physicians to favor an endovascular first approach.

Thank you

Cors at the Shore 2023

References

1. Bradbury AW, Moakes CA, Popplewell M, et al. A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal revascularisation procedure to restore limb perfusion (BASIL-2): an open-label, randomised, multicentre, phase 3 trial. *Lancet*. Published online 2023. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)00462-2/fulltext

2. Farber A, Menard MT, Conte MS, et al. Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia. *N Engl J Med*. Published online November 7, 2022. doi:10.1056/NEJMoa2207899

3. Adam DJ, Beard JD, Cleveland T, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet*. 2005;366(9501):1925-1934.

4. Shishehbor MH, Powell RJ, Montero-Baker MF, et al. Transcatheter Arterialization of Deep Veins in Chronic Limb-Threatening Ischemia. N Engl J Med. 2023;388(13):1171-1180.