

Can The BEST-CLI Trial Tell Us Whether Saving A Limb Also Prolongs Survival?

Peter A. Schneider, MD
University of California San Francisco

Peter A. Schneider Disclosures

Consulting:
Surmodics, Medtronic, Boston Scientific, Phillips, Cagent, Acotec, Abbott, Endologix, Shockwave, Silk Road, Healthcare Inroads, Inari, BD

Is there a survival benefit to limb salvage?

- One goal of CLTI treatment is amputation prevention.
- When the limb is not salvageable, a secondary goal is to proceed to major amputation expeditiously to prevent systemic infection and assist the patient in becoming as physically functional as possible without the limb.
- The loss of the limb has significant repercussions on the patient's health, mobility, independence, financial status, and almost always impacts the patient's family.
- CLTI management requires the significant expenditure of time, energy and resources by the patient, family, healthcare team, and healthcare system.

CLTI has a higher mortality rate than many cancers

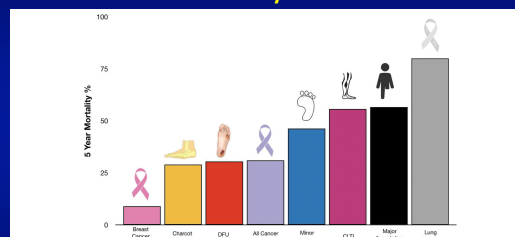
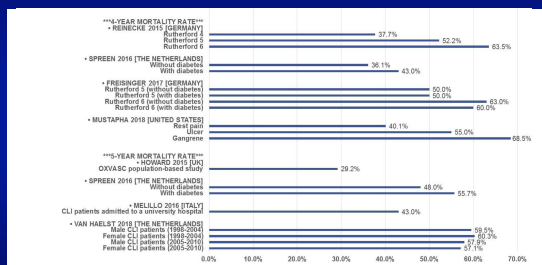


Fig. 1 Five Year Mortality of Diabetic Foot Complications and Cancer. Diabetic foot complications compared to cancer: CLTI = diabetic foot ulcers [11] = 30.5%, Charcot = Charcot neuroarthropathy of the foot amputation [14], All Cancer = pooled 5 year survival of all cancers [1], CLTI = chronic limb threatening ischemia [28, 29], Major Amputation = above foot amputation [20-22, 26, 27], Minor Amputation = foot level amputation [17, 27]

Armstrong et al. J Foot Ankle Research 2020;13:16

CLTI: Long-term Mortality

4 to 5 year mortality up to 68.5%

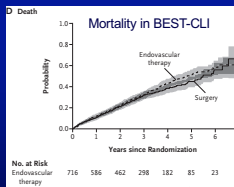


Duff et al. Vascular Health and Risk Management 2019;15:187

Mortality in BEST-CLI and BASIL-2

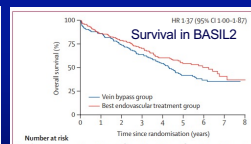
Mortality	BASIL-2 Perioperative	BEST-CLI Perioperative
Bypass	6%	1.7%
Endovascular	3%	1.3%

Mortality	BASIL-2 at 40 months	BEST-CLI at 2.7 years
Bypass	53%	33%
Endovascular	45%	38%



No. at Risk
Endovascular: 716, 586, 462, 298, 182, 85, 23, 1
Surgery: 718, 577, 457, 282, 168, 80, 20, 0

Farber et al. NEJM 2022



Number at Risk
Best endovascular treatment group: 177, 141, 110, 94, 72, 65, 25, 14, 0
Best bypass group: 173, 142, 125, 106, 79, 61, 30, 12, 1

Figure 3: Overall survival Kaplan-Meier curve (HR: hazard ratio).

Redberg A, et al. Lancet. 2023;DOI: 10.1016/S0140-6736

Comparisons: BASIL-2 and BEST CLI

	BASIL-2	BEST CLI Cohort 1
Enrolled participants	345	1434
Age	73yrs	67yrs
Tissue loss	88%	80%
Tibial disease	100%	67%
Endo technical success	87%	85%
Crossover: endo to bypass	19%	23.5%

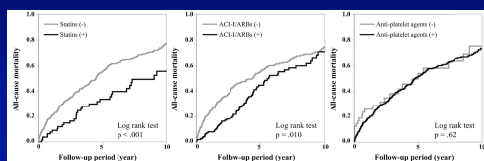
BASIL-2 patients are older, sicker, more tibial disease.

	BEST-CLI	BASIL-2
Aspirin usage	67-71%	76-80%*
Statin usage	70-79%	75-80%
Smoking	35-37%	19-22%

*any antiplatelet

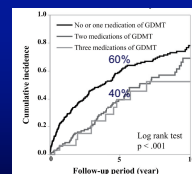
Impact of Guideline-Directed Medical Therapy on 10-Year Mortality after Revascularization for Patients with Chronic Limb-Threatening Ischemia

Hata et al. J Atheroscler Thromb 2023;30:683

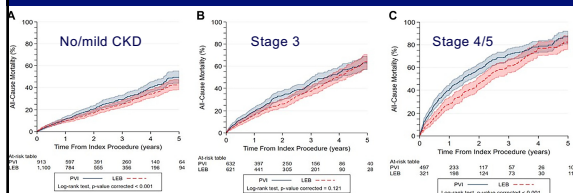


459 CLTI patients underwent revascularization

Absolute mortality at 5 years was 20% less among patients taking 2 or more medications.



Impact of Chronic Kidney Disease



VQI patients underwent bypass or intervention
5-year survival in 4084 Propensity matched CLTI patients
No/mild CKD: 42-49%
Stage 3: 63-64%
Stage 4/5: 82-87%

Cleman et al. J Vasc Surg 2024;80:480

Mortality After Major Amputation

A Meta-analysis of Long-term Mortality and Associated Risk Factors following Lower Extremity Amputation

Stern et al. Ann Vasc Surg 2017;42:322

Table III. Weighted mortality rates

Author	1 year	2 years	3 years	5 years	Total
Abela	—	—	21.8	—	21.8
Barnes	24.1	29.8	—	—	29.8
Carmona	38.3	52.1	—	—	77.4
Chin	—	—	—	—	18.8
Forington	44	—	—	—	77
Hambleton	31	—	—	—	56
Heikkinen	43.9	54	—	—	80.2
Hersikovitz	46.2	—	—	—	46.2
Icks	34.8	—	—	—	64.3
Izumi	—	—	—	—	34.3
Jindeel	9.1	—	—	—	25.6
Jones	48.3	61.4	70.9	—	70.9
Jordan	—	—	—	—	75.4
Kalbaugh	23.3	37.4	51.9	64.2	64.2
Rosen	44	—	—	—	44
Scott	35.7	—	—	—	35.7
Shah	30	40	—	—	40
Sheahan	16.1	—	—	—	56.5
Stone	53	—	—	—	77
Taylor	—	—	—	—	13.6
Tseng	21.5	—	—	—	59.8
Total (weighted)	48.0	61.3	70.6	62.2	70.1

Mortality After Major Amputation

Long-term Mortality After Nontraumatic Major Lower Extremity Amputation: A Systematic Review and Meta-analysis

36,037 Above ankle amputations

Total Weighted Mortality at 5 Years

Overall: 64.4%
Above-the-knee: 69.8%
Below-the-knee: 56.6%

Country	1 Year (%)	5 Years (%)
United States	31.6	63.1
United Kingdom	33.6	49.1
The Netherlands	32.5	69.7
Sweden	40.1	69.7

Meskin et al. J Foot and Ankle Surg 2021;60:567

Is there a survival benefit to limb salvage?

- Historical therapeutic nihilism in the management of CLTI: asserts that many CLTI presentations are unsalvageable, little can be done, and patients would be better served by primary amputation and rehabilitation rather than complex efforts at limb preservation.
- Our decision-making process would be substantially improved by understanding whether amputation prevention extends life.

Survival Decreased After Amputation

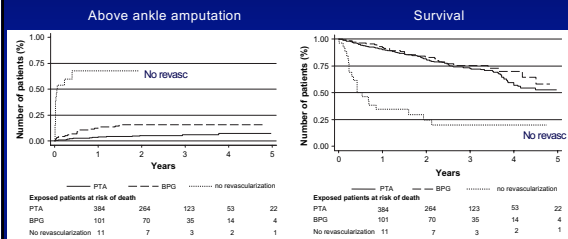


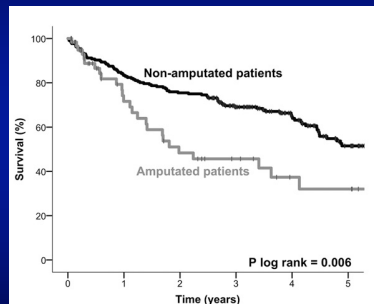
Fig. 1. Kaplan-Meier above-the-ankle amputation estimates in PTA, BFG and non revascularized patients.

Fig. 2. Kaplan-Meier survival estimates of PTA, BFG and non revascularized patients.

Faglia et al. Eur J Vasc Endovasc Surg 2008;32:484

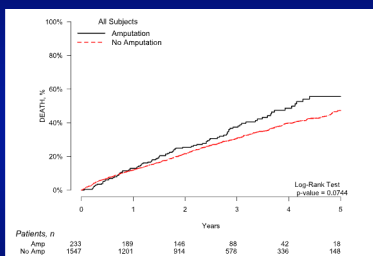
Survival Decreased After Amputation

281 CLTI patients: pooled PADI Trial and JUVENTAS Trial subjects



Spreen et al. Diabetes Care 2016;39:2058

Survival Decreased After Amputation



BEST-CLI: Patients with major amputation during the first year (n=233) versus limb salvage (n=1547)

Can The BEST-CLI Trial Tell Us Whether Saving A Limb Also Prolongs Survival?

Conclusion

Limb salvage may extend life, but we have only indirect evidence. Our decision-making process would be substantially improved by understanding whether amputation prevention improves survival. No RCT of primary amputation will ever be performed. BEST-CLI patients will be propensity matched to gain insight into the survival question

Can The BEST-CLI Trial Tell Us Whether Saving A Limb Also Prolongs Survival?

Peter A. Schneider, MD
University of California San Francisco