The Best Ways To Evaluate CLTI Treatment Outcomes:

Physiology (ABIs And PVRs), Wound Healing, Anatomy (Angiography Or Ultrasound), MACE Or MALE: Why It Matters

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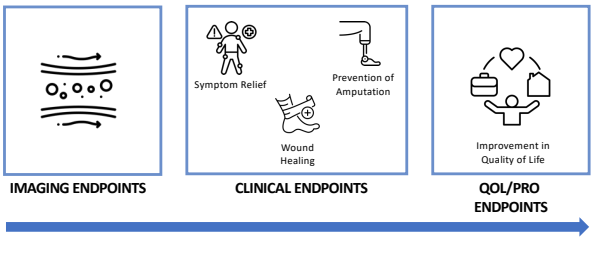
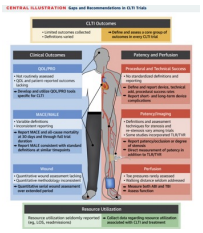
Disclosures

- Boston Scientific
- Medtronic vascular
- Neptune Medical

Potential Endpoints for Study



CLTI Study Outcomes Lacked Uniformity



Objective Outcome Measures for Trials in Patients With Chronic Limb-Threatening Ischemia Across 2 Decades

Analysis and Recommendations

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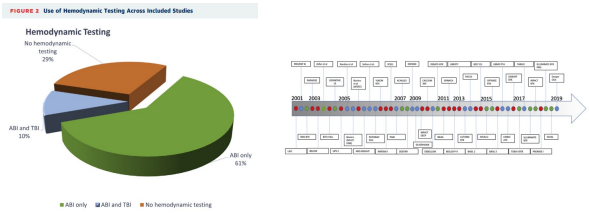
Hemodynamic/Anatomic Outcomes Varied



Individually, Each Category Has Limitations

Imaging Endpoints	Clinical Endpoints	Patient Reported Outcomes/Quality of Life
Pros • Simple measurement • Most objective • Standardized Cons • Vessel status and clinical outcomes are not always concordant • Interpreter variation • Require core lab adjudication	Pros • Essential • Drive treatment Cons • Low frequency (especially in short device trials) • Certain outcomes more difficult to quantify and compare (wound healing). • Variety of factors affect clinical outcomes → comorbitidies	Pros • Most important Cons • Rarely significant statistically • Least specific

Study Design Improves Individual Criteria

Imaging Endpoints	Clinical Endpoints	Quality of Life
• *Solution 1:* Minimize lesion variation (lesion and character) • *Solution 2*: Manage imaging criteria to minimize variation	• *Solution 1*:Extend assessment periods • *Solution 2*:Use sicker patients to increase frequency of events • *Solution 3*: Standardize complex therapies and make outcomes quantitative and objective (wound core lab). • *Solution 4:* Given low number of events, include as part of composite or secondary	• *Solution 1:* Utilize surrogates and secondary endpoints to reflect this.

Standard Composite Endpoint Design: Safety and Efficacy

Safety

Primary Safety Endpoint
- Post-intervention/Surgery
  - Freedom from BTK MALE + POD at 30d
- *Alternatively:* Amputation-free survival

Secondary Safety Endpoints
- Limb salvage
- Major/minor amputations
- Device/procedure related events
- Adverse events

Efficacy

Primary Efficacy
- Composite of Limb Salvage and Primary Patency
- *Alternatively:* Amputation-free survival

Secondary Efficacy Endpoints
- Wound healing
- Change in ABI
- Change in QOL (e.g., EQ-5D)
- Change in WIQ
- Change in Rutherford category

Composite outcomes are conventional, but limiting

✓ Generates Statistical Significant by combining endpoints

X Components weighted equally, **BUT** should not be.

X Least serious event can dominate the composite

X Non-fatal events = fatal events

X More components produce significance, but the value of the finding gets obscured

X The separation of safety and efficacy → increase power requirement/sample size

X Only events are measured. Quantitative and continuous variables are often ignored. QoL is excluded.

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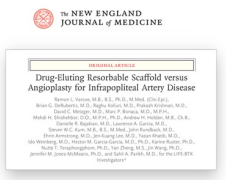
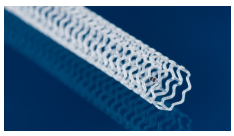
New CLTI devices and trial design

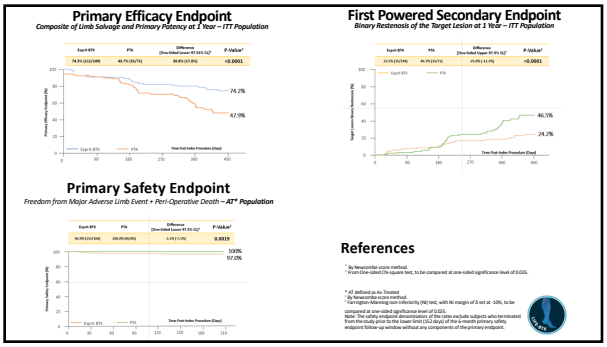


Life BTK Trial

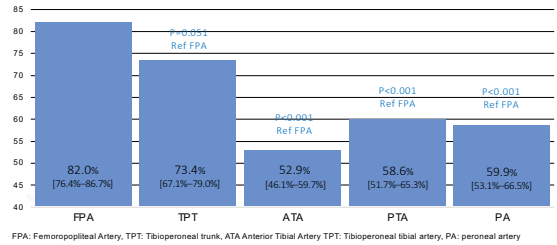


Endpoints for LIFE BTK

	SAFETY	EFFICACY
Primary Endpoint	Freedom from MALE + POD	Limb Salvage + Primary Patency
Secondary Endpoint	2nd Secondary Endpoint: Freedom from above ankle amputation in index limb, 100% total occlusion of target vessel and CD-TLR at 1 year	1st Secondary Endpoint: Binary restenosis of the target lesion at 1 year



Real-world concordance between Duplex and Angiography is limited



FPA: Femoropopliteal Artery, TPT: Tibioperoneal trunk, ATA Anterior Tibial Artery TPT: Tibioperoneal tibial artery, PA: peroneal artery

Tsukizawa. TCT 2024

WIN Ratio Example

1. Each Subject in Treat group compared to each subject in control group

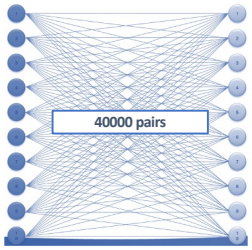
- Interventional arm=200 patients
- Control arm- 200 patients
- Total pairs = 200 x 200 = 40000 pairs

2. Rank the hierarchy based on descending order of importance

- Death>>Amputation>>CD TLR>>Binary Restenosis>>QoL

3. Compare and score each patient to one another at each tier until one of the pairs shows a better outcome

- Win for test Rx
- Loss for test Rx (if control wins)
- Tie if both have event



WIN Ratio: Potential Future CLTI Outcome

Advantages

- ✓Simple. There is a winner or a loser.
- ✓All key events in patients course get included (not just the first).
- ✓Outcomes are prioritized (death more important than restenosis, etc).
- ✓Allows for repeat events.
- ✓Able to incorporate continuous/quantitative variables, like QOL scores.

Limitations

- x Power calculations and sample size determinations are complex and require simulation.
- x Unfamiliar to many.
- x Statistical software requirements

THANK YOU!

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