The Clinical Rational: Why endpoints for CLI trials should be evaluated at 6 months instead of 1 year

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Disclosures

Consultant:

- Abbott Vascular
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- Boston Scientific
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- Cook Medical
- Medtronic
- Spectranetics
- Terumo Medical
- TVA Medical
Outcomes of Patients With Critical Limb Ischemia

Fate of the patients presenting with chronic critical leg ischemia. CLI – critical limb ischemia

TASC II. (2007). JOURNAL OF VASCULAR SURGERY
Volume 45, Number 1, Supplement S
Caution – Investigational Device, Limited by Federal (USA) Law to Investigational Use
In one year post tx:
75% of CLI patients would have had a major event.

25% dead (via CMS database)

30% major AMP

20% cont. CLI
Why 6 months vs 12 months

- 75% of the CLI patient would be in a form of irreversible damage.

Many trials used the 12 months as a marker for their end point and found failure:

1. 87% of major amputations happened in the 1st 4 months\(^1\)

2. 47% of patients who received bypass graft failed before the 6 months period\(^2\)

\(^1\)Translational-medicine.com
\(^2\)Ann VascSurg 2011;25; 873-877
Why 6 months vs 12 months

3. Autologus bone marrow transplant: early failure rate started at 3 month (40%)\(^1\)

4. shifting into revascularization: an article titled “Endovascular strategies for limb salvage” discussed a broad spectrum of testing and therapeutic methods but NO clear plans on follow up, times of recalculations etc..it is a good start.\(^2,3,4\)

\(^1\)Cell transplantation Vol. 18, pp 371-380 2009
\(^2\)Progress in endovascular disease 54 (2011) 47-60
\(^3\)Translational-medicine.com
\(^4\)Ann VascSurg 2011;25; 873-877
Why 6 months vs 12 months

PREVENT III trial: studied molecular therapy (edifoligide; E2F decoy) for preventing vein graft failure in CLI patients.

Graft surveillance by DUS with primary end point one yr.

30 day and 1 yr surveillance noted. What happened in the 11 months between 1st and 2nd studies?

At the end no benefit from the new drug.

Why 6 months vs 12 months

A trial designed by Goodney\(^1\)
-54% of patients who received major amputations DID NOT receive any peripheral surveillance prior to major amputation AND in the year before.
In the 46% that did have surveillance \(\Rightarrow\) 37.4% received diagnostic angiogram and only 24% of those received PVI.

\(^1\)Goodney et al, Circulation 2011
6 months vs 12 months

• Majority of papers reviewed in prep for FDA request to consider a 6 months primary endpoint vs 12 month showed the following:
  – Most primary failure events happen in the 1st 3 months post revascularization.
  – Also, most secondary patency and repeated intervention happen to be initiated within the 1st 3 months as well
6 months vs 12 months

- In a study done by Gasper et al, they did duplex US at 0, 1, 3, 6, 9, & 12 months on venous bypass grafts looking for clues of early arterialization of the venous graft.
- Interesting: able to predict patency based diameter, vessel early adaptive remodeling which otherwise would not been possible had the rigorous surveillance not been done.

Based on the published data, most studies followed CLI in the same Patterns and expectation from trials for CAD and other PAD conduits.

Today, in daily practice for CLI patients follow up

6 months vs 12 months

Based on the published data, most studies followed CLI in the same Patterns and expectation from trials for CAD and other PAD conduits.

What happens between 1&6 months is essential. Serious data is missing that can alter the course of therapy and possibly outcome for CLI patients.

Most current CLI trials allow Duplex US at 1, 6, 12

Based on the published data, most studies followed CLI in the same Patterns and expectation from trials for CAD and other PAD conduits.

- Most of the data regarding outcomes in the CLI patient will start to reveal itself in the 1st 3 months following therapy.
- At 6 month we will learn whether the treatment was a success or a failure in the majority of patients.
6 months vs 12 months

Course adjustment in CLI patients based on more frequent surveillance

CLI time line in months post PVI

Un-adjusted course of CLI therapy.
Patients tend to do well in the 1st 3 months and then decline.
6 months vs 12 months

Course adjustment in CLI patients based on more frequent surveillance

Adjusted course of CLI therapy. This includes secondary & assisted patency, the KEY is looking and finding the problem before regression begins
The Deadly Reality of CLI
The Deadly Reality of CLI

Image courtesy of J. A. Mustapha

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The Deadly Reality of CLI

Images courtesy of J. A. Mustapha
Breast Cancer

- Estimated New Cases in 2016: 246,660
- % of All New Cancer Cases: 14.6%
- Estimated Deaths in 2016: 40,450
- % of All Cancer Deaths: 6.8%

Percent Surviving 5 Years: 89.7%

2006-2012

www.cancer.gov
Colon Cancer

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<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Estimated New Cases in 2016</td>
<td>134,490</td>
</tr>
<tr>
<td>% of All New Cancer Cases</td>
<td>8.0%</td>
</tr>
<tr>
<td>Estimated Deaths in 2016</td>
<td>49,190</td>
</tr>
<tr>
<td>% of All Cancer Deaths</td>
<td>8.3%</td>
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</tbody>
</table>

**Percent Surviving 5 Years**

65.1%

2006-2012

www.cancer.gov
Pancreatic Cancer

- Estimated New Cases in 2016: 53,070
- % of All New Cancer Cases: 3.1%
- Estimated Deaths in 2016: 41,780
- % of All Cancer Deaths: 7.0%

Percent Surviving 5 Years: 7.7%
(2006-2012)

www.cancer.gov
An example of assisted CLI time line

Image courtesy of J. A. Mustapha
An example of un-assisted CLI time line
Septic $\rightarrow$ BTKA $\rightarrow$ death at month 9

Images courtesy of J. A. Mustapha
References


Thank You

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