Explaining the Discrepancy Between Lower Patency and Higher Limb Salvage Rates After Revascularization for Critical Limb Ischemia

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ABSTRACT: In patients treated for critical limb ischemia (CLI), limb salvage rates are consistently better than patency rates. This has prompted some to question whether perfusion really matters. In an effort to better explain this very reproducible phenomenon, our analysis suggests that the difference between patency and limb salvage rates can be explained by a number of factors, the most important of which are the effects of reintervention and the severity of tissue loss present in the CLI population under study.

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Key words: critical limb ischemia, peripheral vascular disease, vascular intervention

A tenet of vascular care is that tissue needs adequate perfusion to survive. This is so integral to our thinking about vascular disease that it is only rarely questioned. One exception to this has been in the management of critical limb ischemia (CLI). In patients treated for CLI, limb salvage rates are consistently better than patency rates.1-4 This has prompted some to question whether perfusion really matters. In an effort to better explain this very reproducible phenomenon, our analysis suggests that the difference between patency and limb salvage rates can be explained by a number of factors, the most important of which are the effects of reintervention and the severity of tissue loss present in the CLI population under study. These two factors, along with a few other facets that are unique to this complicated CLI cohort, help to explain the nature of the difference between the higher limb salvage rates and lower patency rates after revascularization.

BACKGROUND

The presence of lower patency rates with discordant higher limb salvage rates in the same patient groups has prompted clinicians in the field to ask why this occurs and even to doubt the value of perfusion in CLI. Limb salvage is much more readily apparent to patients than patency. If perfusion is a prerequisite to healing the threatened limb, it would make more sense if patency correlated well with limb salvage. This variance between lower patency and higher limb salvage rates is not an isolated issue, but rather a strong trend seen in the literature.1-4 A meta-analysis by Romiti et al summarized more than 60% of the articles published between 2000 and 2006 on infrapopliteal angioplasty...
for chronic CLI. The study showed a limb salvage rate of 86% and primary patency rate of 58% at 1 year. These findings are in keeping with more current literature as well. In an effort for the study of CLI to move forward, a practical discussion of this seeming discrepancy is worthwhile.1-4

There is an important caveat in the patency vs limb salvage discussion. Limb salvage is a very clear-cut endpoint: either the patient has undergone a major limb amputation above or below the knee or not. Any broad discussion of patency must include details of the technique of measuring patency. It is extremely variable from study to study. Even common measurement techniques have not been standardized. However, even when combining studies that utilize ankle brachial index (ABI), physical exam, Doppler, duplex, computed tomography angioplasty (CTA), and angiography, the gap may change a bit but the same wide variance between limb salvage and patency rates have been demonstrated.1-5

The efficacy of angioplasty for limb salvage has been confirmed through large clinical trials. The British Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial highlighted the value of angioplasty in limb salvage. The trial enrolled 452 patients with severe limb ischemia due to infrainguinal disease. The investigators found that after several years of follow-up that neither bypass first nor angioplasty first were more successful at limb salvage, although bypass was more expensive.6 This finding has been echoed by multiple other nonrandomized studies. However, in many CLI studies there is likely a significant selection bias in treatment. Patients who are too ill for an infrainguinal bypass will be recommended for angioplasty by default while patients with diffuse, multilevel disease are more likely to be offered a bypass, especially if they have major foot damage.7,8 This selection bias does alter results somewhat but gives little explanation for the issue at hand.

**Limb Salvage Is a Complicated Process**

Limb salvage in CLI is a highly complex process, and its solution is multifaceted. A profound degree of ischemia is usually required to produce CLI but multiple factors must be reversed or at least successfully managed to heal the limb; patency is just one of those. Medical issues such as renal insufficiency, malnutrition, untreated infection, and chronic nonambulatory status are related to poor wound healing, independent of vascular factors. The treatment of any wound requires control of diabetes, proper nutrition, wound care, and various mechanical off-loading techniques.9,10

The discrepancy in limb salvage and patency rates

<table>
<thead>
<tr>
<th>Institution or Study Name (no. patients)</th>
<th>Primary Patency (%)</th>
<th>Limb Salvage (%)</th>
<th>Gap (Primary Patency % - Limb Salvage %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitt3 (111)</td>
<td>33</td>
<td>75</td>
<td>42</td>
</tr>
<tr>
<td>Massachusetts General Hospital11 (409)</td>
<td>64</td>
<td>85</td>
<td>24</td>
</tr>
<tr>
<td>Leipzig1 (62)</td>
<td>33</td>
<td>100</td>
<td>67</td>
</tr>
<tr>
<td>IN.PACT DEEP (358)</td>
<td>60</td>
<td>93</td>
<td>33</td>
</tr>
<tr>
<td>Cornell12 (106)</td>
<td>64</td>
<td>87</td>
<td>23</td>
</tr>
<tr>
<td>Range (%)</td>
<td><strong>33-64</strong></td>
<td><strong>75-100</strong></td>
<td><strong>23-67</strong></td>
</tr>
</tbody>
</table>
is shown in Table 1. Although this fact is broadly identifiable in the literature, for illustrative purposes we selected a sampling of recent, well-performed, representative studies in the field. These studies are from well-known centers in the United States and the European Union that used balloon angioplasty to restore perfusion. Fernandez et al from the University of Pittsburgh evaluated the efficacy of tibial artery endovascular intervention in 111 patients with Rutherford class 4, 5, and 6 CLI. The primary patency at 1 year was 33% and the limb salvage rate was 75%. Conrad et al from Massachusetts General Hospital with 409 patients demonstrated a primary patency rate of 64% with a limb salvage rate of 85%. Meltzer et al from Cornell did a retrospective review of 106 patients with a primary patency of 64%, 23% lower than their limb salvage at 87%. We included the IN.PACT Deep study in the analysis. This was a multicenter study conducted in the European Union that randomized patients to either percutaneous transluminal angioplasty (PTA) or drug coated balloon. Although this was a negative study (no benefit of the drug coated balloon was seen) the overall cohort of 358 patients received the most contemporary and aggressive endovascular interventional care. The overall limb salvage rate in the entire group at 1 year was 93%. In the imaging cohort, the primary patency was 60% at 1 year. The difference between primary patency and limb salvage rates among this small group of studies mirrors the broader literature. Even within this small group of recent studies, the range at 1 year in the gap between limb salvage and patency is anywhere from a low of 23% to a high of 67%. This variance is from trials as diverse as European, American, plain old balloon angioplasty, and drug-coated balloon angioplasty data with enrollment sizes from 62 to over 400 patients. Clues that help explain this discrepancy are found within the complex CLI population.

**IMPACT OF TISSUE LOSS**

Part of the challenge in understanding the patency-limb salvage gap may be the inclusion of Rutherford class 4 (patients with rest pain but without tissue loss) along with Rutherford 5 and 6 patients. The degree of tissue loss correlates with the likelihood of a longer healing time as well as amputation. Patients with rest pain but no tissue loss require significantly less management and reversal of other confounding variables and are significantly less likely to lose a limb in the short term. There are no wounds to heal, there is often no or minimal infection to treat, and a single level of revascularization usually resolves the clinical syndrome. As an added confounder, many patients with diabetes and/or renal failure do not experience a rest pain phase prior to the initiation of tissue loss. Thus, the rest pain cohort may be predetermined to include a less challenging patient population. Studies with larger populations of Rutherford class 4 patients are likely to have different outcomes than studies with a predominance of patients with tissue loss. The Society for Vascular Surgery staging system for CLI patients includes assessment of wound, ischemia, and foot infection criteria (SVS WIfI). In the SVS WIfI scoring system for likelihood of amputation, patients with rest pain are considered at low or very low risk of limb loss. Zhan et al evaluated 201 patients with threatened limbs. They focused on the clinical outcomes of 1-year amputation-free survival (AFS) rate and wound healing time (WHT). Each of the three WIfI categories was
graded from mild to severe, and based on these findings, patients were further divided into stage 1 (very low risk) to stage 4 (high risk). Risk of amputation and WHT increased with advanced stages. This follows what one would expect clinically; patients who present with more severe tissue loss generally do worse clinically. In the 2008 meta-analysis of CLI, studies that included less than 75% of patients with tissue loss had a better patency at 1 year than studies that included more than 75% of patients with tissue loss (52.5% vs 66.0%) and a better limb salvage rate (92.6% vs 86.1%).

Incidentally, among the representative studies in Table 1, the best correlation and the narrowest gap between primary patency and limb salvage was in the study from Cornell, which included only patients with tissue loss. In the representative studies, patients with rest pain comprised up to 29% of the subjects.

Other tissue-related factors that may help to explain the discrepancy between limb loss and patency include degree of infection upon presentation and subsequent wound management. Both of these factors introduce significant variability into the clinical course. Infection associated with tissue loss plays a major role in the risk of limb loss. As noted above, the WIfI scoring system also takes into account the presence of infection, and it is common for patients with major tissue loss to also present with significant infection. In this case, even with adequate perfusion, advancing infection may cause further damage. Wound management is also highly variable from one practice to the next and aggressive and vigilant wound care is required in addition to perfusion to achieve wound healing. Revascularization is not expected to be productive in the face of ongoing or untreated infection. Conversely, excellent wound care using contemporary methods may be successful even if the revascularization is marginal.

**ROLE OF REINTERVENTION**

Another factor contributing to the gap between primary patency and limb salvage is that a significant portion of patients with loss of patency receive reintervention, which results in further opportunities for improved perfusion and limb salvage, but is not reflected in the primary patency data. The use of reintervention, or target lesion revascularization (TLR) within 1 year of the index procedure ranges in the cited studies from 13% to 50% (Table 2). In Table 2, the patency-limb salvage gap from Table 1 is compared with the percentage of patients in each study with rest pain (no tissue loss) and also those requiring reintervention.

<table>
<thead>
<tr>
<th>Institution or Study Name (no. patients)</th>
<th>Gap (Primary Patency % - Limb Salvage %)</th>
<th>Rest Pain</th>
<th>Target Lesion Revascularization (TLR) (%)</th>
<th>Rest Pain + TLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitt³ (111)</td>
<td>42</td>
<td>17</td>
<td>50</td>
<td>67</td>
</tr>
<tr>
<td>Massachusetts General Hospital¹¹ (409)</td>
<td>24</td>
<td>29</td>
<td>25</td>
<td>44</td>
</tr>
<tr>
<td>Leipzig¹ (62)</td>
<td>67</td>
<td>26</td>
<td>50</td>
<td>76</td>
</tr>
<tr>
<td>IN.PACT DEEP² (358)</td>
<td>33</td>
<td>16</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>Cornell¹² (106)</td>
<td>23</td>
<td>0</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Range (%)</td>
<td>23-67 (from Table 1)</td>
<td>0-29</td>
<td>13-50</td>
<td>27-76</td>
</tr>
</tbody>
</table>

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There is a substantial decline in the gap between limb salvage and patency when secondary patency is utilized. In the studies from both Schmidt et al and Fernandez et al, the reintervention rate is 50%. For example, in the clinical study by Fernandez et al, using secondary patency lowers the patency-limb salvage gap from 42% to 19%. In the meta-analysis by Romiti et al, primary patency at 1 year with PTA was 58% and secondary patency was 68%. The absolute difference between patency and limb salvage then declines significantly from 28% to 18%. This could have a major impact on the perceived gap between patency and limb salvage since this patient population very often requires TLR to maintain patency and achieve healing.

When the 2 factors are combined, the use of reinterventions and the inclusion of rest pain (patients without tissue loss), the gap between primary patency and limb salvage at 1 year almost completely disappears from a numerical standpoint. Table 3 demonstrates the comparison between the identified primary patency-limb salvage gap (Table 1) and the results when reintervention and non-tissue-loss patients are accounted for in the analysis of each study. In 4 of the 5 representative studies, the combination of TLR and rest pain is larger than the gap between primary patency and limb salvage. In the IN.PACT Deep study, the limb salvage-patency gap was slightly larger than the combination of TLR and rest pain. It should be noted that the patency figure for the IN.PACT Deep study was derived from an imaging cohort, not from the entire study group. Going forward, our understanding of the patency-limb salvage gap must take into account the role of reintervention and tissue loss.

**Comparing Angioplasty to Bypass Studies**

Patients with severe tissue loss are frequently directed toward bypass rather than angioplasty. After undergoing bypass, patients are less likely to require reintervention, with overall estimates of around 30% as opposed to angioplasty where up to half require reintervention. Bypass series are expected to include more patients with tissue loss and a lower reintervention rate. It follows that bypass should be more likely to have a better correlation between primary patency and limb salvage and this is what is seen in the literature. For instance, in Romiti et al, bypass data show a primary patency rate of 81.5% and a limb salvage rate of 88.5%. Slim et al, in a contemporary bypass series, evaluated 230 patients with infrapopliteal CLI and found a limb salvage rate of 83.0% at 1 year with a patency rate of 87.4%.

**Other Factors**

Another issue is that if the wound heals prior to loss of patency, the patient is at a low risk of limb loss.

### Table 3: Patency-Limb Salvage Gap Compared to Rest Pain Plus Target Lesion Revascularization

<table>
<thead>
<tr>
<th>Institution or Study Name (no. patients)</th>
<th>Gap (Primary Patency % - Limb Salvage %)</th>
<th>Rest Pain + TLR</th>
</tr>
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**Other Factors**

Another issue is that if the wound heals prior to loss of patency, the patient is at a low risk of limb loss.
despite a loss of patency. Although wounds in CLI patients may require many months or even a year to heal, more superficial wounds and ulcers in locations that are easily managed may heal readily with a few weeks or months of revascularization. In many studies, a substantial number of the wounds are healed within 1 year. Because time to wound healing has not been well correlated with patency at the time of healing, the impact of this factor remains unknown. However, it is possible that this is a significant factor in promoting higher limb salvage rates. Some Rutherford class 4 patients may also be misdiagnosed. There is a paucity of data on the rate of potential misdiagnosis of rest pain, but not all studies include objective data proving ischemia along with the pain in these patients. The possible inclusion of patients as Rutherford class 4 who in fact have, for instance, neuropathic pain would skew the findings.

**CONCLUSION**

After revascularization for CLI, limb salvage rates and primary patency rates at 1 year are significantly different, with patency rates being quite a bit lower. This can potentially be explained by considering specific factors such as the effects of both tissue loss and reintervention on the overall results of revascularization.

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