Critical limb ischemia and diabetic foot
The incidence of critical limb ischemia (CLI) and diabetic foot (DF) has progressively increased and currently constitutes one of the major features of generalized arterial atherosclerotic disease, considering that every year more than one million people suffer a lower limb amputation.

The aims of CLI treatment are pain relief, ulcer healing, infection treatment and, obviously, limb salvage.

A patient affected by CLI and DF needs a multidisciplinary approach, which could consist of all available tools from medical, surgical or endovascular therapy.

The general plan of medical management is to achieve maximal improvement of cardiac, renal and diabetic status before proceeding with non-invasive or invasive examination and endovascular or classic revascularization. Present-day medical treatment of CLI comprises antiplatelet drugs, defibrinating agents, vasoactive substances, prostanoids, etc.

In many Vascular Centers distal bypass surgery with autogenous vein remains the therapy of choice; in fact, the long-term results of distal popliteal, crural and pedal vein grafts justify an aggressive approach in patients with CLI and DF.

Nevertheless, CLI treatment has undergone a gradual shift over the last years to incorporate a greater portion of endovascular treatment. Not only does this include patients who now undergo endovascular therapy rather than surgery, but also patients who in the past would have been offered supportive treatment only, due to factors such as being medically unfit for surgery, lacking sufficient donor vein for bypass grafting.

New developments in basic research, technologies and techniques offer every day new solutions in CLI and DF treatment. Guidelines and clinical judgements are continuously changing, and specialists are involved in a lifelong learning in order to offer the best treatment to every patient, every day.

In 2013 we can assert that the advent of a lot of new devices and techniques and the growing experience of the vascular specialist in endovascular therapy are responsible for making the endoapproach the first line therapy of CLI and, moreover, of DF in many institutions, but we could expect to change our mind in the next future.

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Critical limb ischemia (CLI) is the most advanced stage of arterial disease involving the lower limbs and is associated with significant morbidity, poor survival and requires a major burden of resources for its treatment. Revascularization, when feasible, is recognized to achieve leg salvage in about 88% of cases at one year. However, CLI is associated with significant early and late mortality rates, which in subsets of high risk patients can jeopardize any attempt to lower limb revascularization.

During the last two decades most of studies focused on demonstrating the efficacy and continuous improvements of revascularization procedures for CLI, but little is known on the epidemiology of CLI. Indeed the prevalence of this severe condition has not been properly evaluated in population-based studies. Estimation and identification of subjects with or at risk for CLI issues are issues of great importance because planning of early and adequate treatment of CLI are of key importance for successful treatment of this condition. Furthermore, an undefined number of patients diagnosed with CLI are treated conservatively and data on their outcome are scarce. Recent evidence on the potential efficacy of cellular therapy for CLI may expand the therapeutic range in this patient population. Knowledge of the outcome of unreconstructed leg with CLI may be of help in planning future studies evaluating the efficacy of these new non-invasive treatment methods. The present study was planned to pool currently available data on the prevalence, incidence and natural history of CLI.

Materials and methods

An electronic search was undertaken using the PubMed and Scopus databases on July 2013. The search for studies evaluating the prevalence and incidence of CLI in the general population used the terms “peripheral artery disease, “peripheral arterial disease”, “peripheral vascular disease”. Furthermore, the search for studies evaluating the treatment strategy and natural history of CLI used the terms “critical leg ischemia”, “critical leg ischemia”, “critical lower limb ischemia” along with the terms “placebo”, “medical treatment” and/or “conservative”. Abstracts of the identified articles were then scrutinized to determine eligibility for inclusion in the present analyses. Studies evaluating the prevalence of CLI were included if they were of
prospective nature and included subjects from the general population. The definition criteria of CLI were expected to be heterogeneous and possibly these studies were not planned to primarily identify patients with CLI. Therefore, after scrutiny of the retrieved studies, we accepted any criteria such as Fontaine stages III-IV, ankle blood pressure <70 mmHg and/or ankle brachial index <0.60 to define severe chronic lower limb ischemia. We excluded from the present analysis those studies evaluating the prevalence of CLI in patients with any major cardiovascular risk factor such as diabetes, hypertension, coronary artery disease and/or cerebrovascular disease. On the contrary, in order to estimate the incidence of CLI, only studies reporting on this condition were included in this analysis.

Studies evaluating the natural history of CLI were included if they were either retrospective or prospective, reported on leg salvage, i.e., freedom from major lower limb amputation, included only patients with any definition of CLI, reported on at least 10 patients, included patients who did not undergo any revascularization since the date of entering the study and data on the outcome at one year were available. We included in the present analysis only those studies reporting actuarial data on leg salvage, survival and survival freedom from major lower limb amputation after conservative treatment of CLI. This was made in order to take into account the rates of loss to follow-up. Data on patient demographics and comorbidities were extracted from each study.

Statistical analysis

Statistical analysis were performed using the freely downloadable software Open Meta-analyst. The results were presented as pooled proportions (%) with 95% confidence interval (95%CI). We did not use the Freeman-Tukey arcsine transformation as a preliminary analysis provided similar results to that of proportion analysis. Survival rates were extracted from available survival curves. Pooled analysis of aggregate late survival data was performed by calculating the number of patient at risk during the study intervals by using a spreadsheet developed by Tierney et al.6 Because of the observational nature of the included studies and the expected heterogeneity, we performed random effects analyses of retrieved data. Heterogeneity across studies was evaluated using the $I^2$. When $I^2$<30%, heterogeneity was considered as non significant. Meta-regression was performed by using random effects analysis. A $P<0.05$ was considered statistically significant.

Results

Prevalence of severe lower limb ischemia

Beside a large individual patient data meta-analysis by the Ankle Brachial Index Collaboration study group7 which reported on the prevalence of subjects with ABI <0.60, other five large studies (Park I, Jeon YS, Kim JY et al. Prevalence of peripheral vascular diseases of elderly men in Korea: population-based screening results of 2189 subjects, submitted)8-11 reported on the prevalence of severe lower limb ischemia/CLI in the general population. The pooled prevalence of severe lower limb ischemia among 82,923 subjects was 0.8% (95%CI 0.3-1.4%, $I^2$ 99%) with a marked heterogeneity between studies (Figure 1.1). It is worth noting that the study by
Jensen et al. was the only reporting on the prevalence of CLI as defined by Fontaine grades III and IV criteria. However, this study may have underestimated the prevalence of this condition by excluding subjects aged 70 years or more.

Incidence of critical limb ischemia

We identified two studies providing data on the incidence of CLI in the British and North American population. Researchers of the Oxford Vascular Study,12 a study prospectively evaluating acute vascular events and retrospectively evaluating hospital-care and primary-case administrative and diagnostic codes of vascular events in 91,106 subjects of any age who were residing in Oxfordshire, UK, estimated an incidence of CLI of 22 cases per 100,000 population per year (95% CI 17-28). The incidence per year in subjects aged 65-74 years was 67 cases, in subjects aged 75-84 years was 168 cases and in subjects aged ≥85 years was 171 cases per 100,000 population per year. During a three-year periods 44 CLI cases occurred among 12,886 subjects aged ≥65 years, giving a rough incidence of CLI of 113 cases per 100,000 population per year in these elderly patients.

Baser et al.13 used the 100% Medicare inpatient, outpatient and denominator files to estimate the incidence of CLI in US subjects ≥65 years old. CLI patients were identified using the ICD-9CM codes for rest pain, ulceration and gangrene. They reported an incidence of CLI of 200 per 100,000 population per year, which was 50 cases per 100,000 population for Fontaine stage III and 150 cases per 100,000 population for Fontaine stage IV.

Treatment strategy

We identified nine studies reporting on the treatment strategy in 2144 legs with CLI.14-22 The pooled rate of any revascularization procedure was 70.4% (95% CI 63.4-77.4%, I² 92%), of primary amputation was 8.4% (95% CI 3.9-12.9%, I² 96%) and conservative treatment was 20.3% (95% CI 14.4-26.3%, I² 92%). The rates of conservative treatment did not decrease along with the mid-date of the studies included (P=0.740).

Natural history of critical limb ischemia

Ten studies14, 23-31 reported on at least one year outcome of 734 legs undergoing conservative treatment (Table 1-I). Pooled analysis showed that conservative treatment for CLI was associated with a one-year pooled leg salvage rate of 57.4%
CRITICAL LIMB ISCHEMIA AND DIABETIC FOOT

Table 1-I.—Characteristics of patients who underwent conservative treatment of critical limb ischemia.

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication year</th>
<th>Type of study</th>
<th>Study period</th>
<th>Inclusion criteria</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>Females (%)</th>
<th>Ulcer/gangrene (%)</th>
<th>Diabetes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jivegård</td>
<td>1995</td>
<td>PR</td>
<td></td>
<td>Fontaine stages III-IV</td>
<td>26</td>
<td>73</td>
<td>-</td>
<td>-</td>
<td>19</td>
</tr>
<tr>
<td>Lepäntalo</td>
<td>1996</td>
<td>R</td>
<td>1988-1992</td>
<td>Fontaine stages III-IV, AP ≤50 mmHg, TP ≤30 mmHg, ABI ≤0.35</td>
<td>105</td>
<td>75</td>
<td>55</td>
<td>-</td>
<td>51</td>
</tr>
<tr>
<td>Ubbink</td>
<td>1999</td>
<td>P</td>
<td>1991-1994</td>
<td>Fontaine stages III-IV, AP ≤50 mmHg, ABI ≤0.35</td>
<td>109</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Klomp</td>
<td>1999</td>
<td>PR</td>
<td>1991-1996</td>
<td>Fontaine stages III-IV, AP ≤50 mmHg, incompressible vessels in diabetics</td>
<td>60</td>
<td>72</td>
<td>38</td>
<td>68</td>
<td>38</td>
</tr>
<tr>
<td>Amann</td>
<td>2003</td>
<td>PR</td>
<td>1999-2002</td>
<td>Fontaine stages III-IV, AP &lt;70 mmHg, TP &lt;40 mmHg</td>
<td>39</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Marston</td>
<td>2006</td>
<td>R</td>
<td>1999-2005</td>
<td>Fontaine stage IV, AP &lt;70 mmHg, TP &lt;40 mmHg, ulcer Wagner grade 1-4</td>
<td>86</td>
<td>71</td>
<td>58</td>
<td>-</td>
<td>70</td>
</tr>
<tr>
<td>Belch</td>
<td>2011</td>
<td>PR</td>
<td>2007-2009</td>
<td>Fontaine stage IV, AP &lt;70 mmHg, TP &lt;40 mmHg or TcPO2 &lt;30 mmHg</td>
<td>259</td>
<td>69</td>
<td>30</td>
<td>100</td>
<td>54</td>
</tr>
<tr>
<td>Benoit</td>
<td>2011</td>
<td>PR</td>
<td></td>
<td>Rutherford class 4 and 5, AP &lt;50 mm Hg or ABI &lt;0.4; TP &lt;40 mm Hg or TBI &lt;0.4; TcPO2&lt;20 mmHg</td>
<td>14</td>
<td>66</td>
<td>36</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>Powell</td>
<td>2012</td>
<td>PR</td>
<td>2007-2010</td>
<td>Fontaine stages III-IV; rest pain and/or foot ulcer or gangrene; TP ≤50 mm Hg or AP ≤70 mmHg</td>
<td>24</td>
<td>67</td>
<td>42</td>
<td>67</td>
<td>63</td>
</tr>
<tr>
<td>Losordo</td>
<td>2012</td>
<td>PR</td>
<td>2007-2010</td>
<td>Rutherford class 4 and 5; AP &lt;60 mmHg or TP &lt;40 mmHg</td>
<td>12</td>
<td>67</td>
<td>50</td>
<td>58</td>
<td>42</td>
</tr>
</tbody>
</table>

P: prospective; PR: prospective, randomized; R: retrospective; ABI: ankle brachial index; TBI: toe brachial index; AP: ankle pressure; TP: toe pressure.

(95%CI 45.1-69.7, I² 89%, after Freeman-Tukey arcsine transformation: 57.3%, 95%CI 45.6-68.6%, estimated number of patients at risk 569, Figure 1.2). Univariate meta-regression showed a trend toward better leg salvage in recent years (P=0.142, Figure 1.3). It is worth noting that there were two missing mid-dates, one from a study published in 1995 and the other in 2011: these were replaced with a mid-date dating 3 years back.

Figure 1.2—Pooled one year leg salvage proportion after conservative treatment of critical limb ischemia.
Four studies reported actuarial data on one year survival and the pooled rate was 75.4% (95%CI 59.2-91.6, I² 92%). Five studies reported actuarial data on one year major lower limb amputation-free survival and the pooled rate was 51.4% (95%CI 32.7-71.2, I² 91%).

Discussion

This pooled analysis showed that, despite four decades of active research in the field of lower limb ischemia and its treatment, not much is known about the epidemiology of CLI. Indeed, previous estimates of 50-100 CLI per 100,000 Western population per year were from indirect calculations and might possibly overestimate the real incidence of this condition. The difficulties in exactly defining these figures is due to the fact that identification of CLI (rest pain, ulcer or gangrene related to lower limb ischemia along with objective hemodynamic parameters) needs expertise not available when evaluating large number of patients in the setting of epidemiological study. So far the Oxford Vascular Study is the only to provide a valid estimate of the incidence of CLI, but still with the lack of a strict definition of this condition in the general population. According to this study the incidence of CLI was of 22 cases per 100,000 general population per year. The Oxford Vascular Study along with the one by Baser evaluating the US Medicare population, indicate that the incidence of CLI in subjects >65 years old may range from 113 to 200 cases per 100,000 population per year. These figures indicate that the expected dramatic increase in the proportion of elderly during the next three decades may be associated with a significant increase in the burden of CLI and, therefore, in the need of prompt and effective revascularization and medical treatment in order to avoid leg loss and its related clinical, social and economical consequences. Herein we estimated a pooled prevalence of severe lower limb ischemia (ABI <0.60, ankle pressure <70 mmHg or Fontaine III-IV) of 800 cases per 100,000 adult population. Such a high prevalence suggest that screening for peripheral vascular disease by
measurement of the ankle brachial index, particularly in subjects at high risk of cardiovascular events, may be a valid measure to identify a large number of individuals at high risk to develop CLI and other severe cardiovascular events and therefore treat their modifiable risk factors.7

In this analysis we showed that only a few studies have described the current treatment strategy in patients presenting with CLI. This pooled analysis demonstrated that about 70% of patients underwent any revascularization procedure. However, this figure may be too optimistic as a large study on US Medicare population indicate that, among 68,074 patients with newly diagnosed CLI in 2007, the incidence of first leg revascularization was 34%, of second revascularization 6.5% and of third revascularization was 1.3%.13 This means that the revascularization rate for CLI in the real world may be lower than 50%. We were not able to include this study in our meta-analysis as it failed to provide details on the type of amputation and on clear number of patients conservatively treated. However, this figure may be realistic as we do know that a number of patients with CLI initially treated conservatively do not undergo angiography34 and only later on may undergo revascularization.35 We recognize that conservative treatment may succeed in a number of patients, but lower limb revascularization along with the best medical and local wound treatment should be regarded as the treatment of choice in CLI as it may achieve leg salvage rates at one year higher than 80%.2 Furthermore, bypass surgery is considered the most cost effective alternative to wound care alone in patients CLI and tissue loss.36

The recent evidence of a certain success of autologous bone marrow-derived cell therapy in patients with critical limb ischemia5 has brought new important insights on the natural history of patients with CLI in whom revascularization is not feasible. Data from control groups of such prospective randomized studies as well as those of previous series were recently pooled by Benoit et al.37 and achieved markedly better one-year estimates of leg salvage (66%), survival (80%) and amputation-free survival (55%) than the present ones. However, we included in the present analysis only actuarial data in order to take into account for the censored patients/legs. Therefore we had to exclude from this analysis a number of studies otherwise included in the analysis of Benoit et al.37 In fact, we were able to estimate the amputation free survival only from data of five studies. This prevented meta-regression analysis for this end-point and we were not able to confirm the finding of improved amputation-free survival rates in the most recent series. However, our adjusted analysis for mid-date of studies showed a trend toward better one year leg salvage in the most recent series (Figure 1.3). Even if this finding did not reach statistical significance, we may expect that prompter diagnosis and treatment of CLI as well as improvements in the medical treatment of comorbidities and in local wound care in the most recent series have led to better outcome in this fragile patient population.

Conclusions

In conclusion, the incidence of CLI in the elderly currently is rather high and it is expected to significantly increase with the increase of proportion of the elderly population. Series reporting on treatment strategies in these patients showed that a revascularization is attempted in 70% of cases, but US Medicare data indicate that revascularization rate may be much lower. Conservative treatment in patients with unreconstructable CLI, high operative risk and/or refusing any revascularization
seems to achieve acceptable leg salvage rate at one year. However, leg salvage in these patients is significantly lower than in those undergoing leg revascularization. The results of this pooled analysis indicate a trend toward better leg salvage after conservative treatment in the most recent series. These results are likely related with improvements in the referral pathway as well as in the medical treatment and local wound care. These results may possibly improve by using promising alternative non-invasive procedures such as autologous bone marrow-derived cell therapy.

References


