Ruolo dei prostanoidi nel trattamento della CLI

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Terapia medica nelle PAD

Claudicatio

Ischemia critica
Conservative treatment in patients with PAD

Aim
- improve symptoms, i.e. increase walking distance and comfort.

Two strategies
- exercise therapy
- pharmacotherapy
Medical therapy & claudication

Drugs:
- Antiplatelet
- Anti-hypertensive
- Statin
- Pentoxifylline
- Naftidrofuryl
- Cilostazol

Objective documentation is often lacking or limited.

In terms of walking distance improvement, the benefits, if any, are generally mild to moderate, with wide confidence of intervals.
Cilostazol

15 RCTs (3,718 patients):
maximal walking distance increased
- on average by 35 m with cilostazol 50 mg/day
- almost twice (70 m) with the 100 mg dose.

Terapia medica nelle PAD

Claudicatio

Ischemia critica
Iloprost: Indicazioni terapeutiche

- Trattamento dell'ischemia critica degli arti inferiori, in pazienti a rischio di amputazione e quando non è indicato un intervento chirurgico o di angioplastica.

- Trattamento della tromboangioite obliterante (Morbo di Bürger) in stadio avanzato con ischemia critica degli arti quando non è indicato un intervento di rivascolarizzazione.

- Trattamento del fenomeno di Raynaud secondario a sclerodermia.
Paziente con CLI non rivascolarizzabile

- Minor invasività tecniche endovascolari
- Nuove opzioni endovascolari con focus BTK and BTA (pedal plantar loop, retrograde access)
Effect of PTA & Stenting on endothelium
Effetti dell’angioplastica sull’endotelio (imaging alta risoluzione)

OCT
(omoaxial resolutoin 10 μ)

Stump

Ricanalizzaz + PTA
Effetti della manipolazione chirurgica sull’endotelio

- Clampaggio
- Manipolazione endotelio
- Alterazioni emodinamiche /shear stress
Hemodynamic changes / shear stress
Terapia medica adiuvante

- Controllo fattori di rischio ATS
- Antiaggregazione piastrinica
- Statina
- Antiipertensivi

• Doppia antiaggregazione piastrinica
• Terapia anticoagulante (eparina/dicumaroli)
• Cilostazolo
• Iloprost
Iloprost: effetti farmacologici

**Stimulation**

**IP Receptor**

**Adenylate cyclase**

**Iloprost**: effetti farmacologici

**Induction of gene transcription (PPAR δ)**

**Cell membrane**

**Modulation of gene transcription (PPAR δ)**

**Iloprost**

**Prostacyclin**

**IP Receptor**

**Gₐ**

**Adenylate cyclase**

**ATP**

**cAMP**

**PDE**

**5’AMP**

**ILOPROST**

**PROSTACYCLIN**
Iloprost: effetti farmacologici

Iloprost

*Inibitory action on reuptake of adenosin*
*lowering expression of adesin on the endothelium surface*

Platelets
- Antiplatelet effect
- Antithrombotic action

Smooth muscle cell
- Inhibitory action on reuptake of adenosin
- Lowering expression of adesin on the endothelium surface

Microcirculation
- Improved perfusion
Iloprost: effetti farmacologici

Platelets
- Antiplatelet effect
- Antithrombotic action

Smooth muscle cell
- Suppression of vascular smooth muscle cell proliferation
- Vascular dilatation

Microcirculation
- Improved perfusion
Iloprost: effetti farmacologici

Platelets
- Antiplatelet effect
- Antithrombotic action

Smooth muscle cell

Microcirculation
- Improved perfusion
Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)

L. Norgren,a W.R. Hiatt,b J.A. Dormandy, M.R. Nehler, K.A. Harris, and F.G.R. Fowkes on behalf of the TASC II Working Group, Örebro, Sweden and Denver, Colorado

Recommendation 28
Use of prostanoids in critical limb ischemia (CLI)

- Previous studies with prostanoids in CLI suggested improved healing of ischemic ulcers and reduction in amputations [A].
- However, recent trials do not support the benefit of prostanoids in promoting amputation-free survival [A].
- There are no other pharmacotherapies that can be recommended for the treatment of CLI [B].
Studio randomizzato, controllato in doppio cieco
31 pazienti III-IV stadio sottoposti a ricostruzione femoro distale

**Iloprost** = 3.000 ng diluiti in 15 ml di fisiologica per 2 min

**Placebo** = 3.000 ng diluiti in 15 ml di fisiologica per 2 min

End-point:
• Variazione del flusso ematico tramite doppler
Iloprost migliora il flusso ematico femoro-distale dopo iniezione in bolo.

Miglioramento del flusso ematico nel trapianto dopo trattamento con iloprost o placebo

Andamento del flusso ematico nel trapianto, valutato dopo 7 giorni dal bypass femoro-distale, dopo trattamento con iloprost o placebo

Studio prospettico, randomizzato vs placebo

517 pazienti allo stadio III (34%) e stadio IV (66%)

OBIETTIVO:

Effetto di un ciclo perioperatorio di iloprost (3 gg) sulla pervietà del by-pass femoro distale nell’ arco di 12 mesi di follow-up
Inizio interv: Iloprost e.v. per 1 h
Bolo 3000 ng nel bypass
1h post-op - 3° gg iloprost e.v.

Indice di pervietà in pazienti con by-pass protesico

- Inizio interv: Iloprost e.v. per 1 h
- Bolo 3000 ng nel bypass
- 1h post-op - 3° gg iloprost e.v.
The IIaIL Study: Illoprost as Adjuvant to Surgery for Acute Ischemia of Lower Limbs

A Randomized, Placebo-Controlled, Double-Blind Study by the Italian Society for Vascular and Endovascular Surgery

Gaetano de Donato, MD,∗ Gualberto Giassoni, MD, PhD; Gianmarco de Donato, MD;‡ Giuseppe Maria Andreozzi, MD,§ Erminio Bonizzi, PhD;‖ Antonio Mazzoni, MD,¶ Attilio Odero, MD,∥ Giovanni Paroni, MD;∥∥ Carlo Setacci, MD;∥∥ Piergiorgio Settembrini, MD;∥∥ Fabrizio Veglia, PhD,§§ Romeo Martini, MD,§ Francesco Setacci, MD,† and Domenico Palombo, MD]]

Summary Background Data: High rate of complications has been reported following recanalization for acute limb ischemia (ALI). No adjuvant pharmacologic treatment, apart from anticoagulation and standard periprocedural care, has been shown clinically effective. Objective: Aim of this study was to evaluate the effects of the prostacyclin analog illoprost as adjuvant to surgery for ALI. Methods: A total of 300 patients were randomly assigned to receive periprocedural illoprost (subcutaneous bolus of 3000 ng plus intravenous infusion of 0.5–2.0 ng/kg/min for a bolus of 4–7 days following surgery, or placebo. The primary endpoint was the combined incidence of death and amputation at 3-month follow-up. Secondary endpoints were the incidence of each single major complication, total event rate, symptomatology, and tolerability. Results: The combined incidence of death and amputation was 19.9% in the placebo and 14.1% in the illoprost group (relative risk, 1.36; 95% confidence interval, 0.89–2.75; P = 0.12; Cox regression analysis). A statistically significant lower mortality (4.7%) was reported in patients receiving illoprost, compared with controls (10.6%; relative risk, 2.61; 95% confidence interval, 1.07–6.37; P = 0.03). The overall incidence of fatal plus major cardiovascular events was 33.1% and 22.8% in placebo and illoprost groups, respectively (relative risk, 1.43; 95% confidence interval, 1.04–2.09; P = 0.03). No serious adverse reactions occurred after illoprost administration, nor differences in the incidence of bleeding or hypotension between treatment groups. Conclusion: Although at lower levels than previously reported, our results confirm the severity of ALI. Iloprost as adjuvant to surgery significantly reduced mortality and overall major event rate. Further data are needed to support this finding, and to face a still open medical issue.

(Am Surg 2006;72: 969–970)

Acute limb ischemia (ALI) is a serious medical emergency heading to high rate of complications, being not only limb- but even life-threatening, often despite early successful recanalization.1 Improvements in surgical techniques and periprocedural patient care may have reduced the incidence of major complications in ALI patients over the years, but the results of trials published recently seem to document a persistent high risk, with reported 30-day amputation rate of 5% to 12%, mortality risk at 10% to 35%, combined incidence of amputation and death of 25% to 37.5%, at 1- to 6-month follow-up.2-7 Consequences of underlying diseases, the metabolic derangement that seems as a result of the acute insult, and a possible reperfusion injury following recanalization may account for this severe prognosis.8 Only anticoagulation, fasciotomy (when indicated), and periprocedural supportive treatment are established strategies in ALI patients.8,9 Possible benefit from cardiovascular active therapies has recently been suggested in patients undergoing peripheral recanalization or noncardiac major surgical intervention.10,11 Moreover, several categories of compounds, potentially acting on one or biological mechanisms of ischemia-reperfusion syndrome, have been tested in experimental models, but none of them...
Acute Limb Ischemia in Elderly Patients: Can Iloprost be Useful as an Adjuvant to Surgery? Results from the ILAILL Study

Fig. 1. Incidence (%) and Hazard Ratios (HR) of major events in the two treatment groups.

Table 4. Cox regression model analysis for the primary study endpoint (combined death and amputation). HR = Hazard Ratio; CV = cardiovascular; TE = thromboembolectomy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effect</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Placebo vs Iloprost</td>
<td>1.99</td>
<td>1.05–3.75</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous CV event</td>
<td>Yes vs No</td>
<td>0.55</td>
<td>0.29–1.02</td>
<td>0.06</td>
</tr>
<tr>
<td>Duration of ischemia</td>
<td>&gt; 24 vs ≤ 24 hours</td>
<td>1.60</td>
<td>0.82–3.15</td>
<td>0.17</td>
</tr>
<tr>
<td>Class of ischemia</td>
<td>≥ IIb vs &lt; IIb</td>
<td>3.15</td>
<td>1.44–6.89</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>TE vs Other</td>
<td>0.42</td>
<td>0.21–0.87</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Eur J Vasc Endovasc Surg 34, 194–198 (2007)
Prostanoids for critical limb ischaemia (Review)

Long-term survival of patients with critical limb ischemia treated with iloprost: response rate and predictive criteria. A retrospective analysis of 102 patients

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1Cardiothoracic and Vascular Department, Angiology Unit, University of Pisa, Pisa, Italy
2Cardiothoracic and Vascular Department, Vascular Surgery, University of Pisa, Pisa, Italy
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4Internal Medicine Unit, Santi Cosma e Damiano Hospital, Pescia, Italy
5Internal Medicine Unit, Santa Maria Annunziata Hospital, Florence, Italy

Abstract. - OBJECTIVE: Critical limb ischemia (CLI) patients have poor long-term prognosis. We showed that iloprost improves outcomes (major amputation and survival) up to a 5-year follow-up, but it is not known if in this length of time the survival curves, of clinical responders and non-responders, differ.

METHODS: A retrospective study enrolling 102 consecutive patients between 2004-2008, with clinical and instrumental (ultrasound, angiography, transcutaneous tonometry of oxygen TcPO2, and carbon dioxide TcPCO2, in the affected and contralateral limbs) diagnosis of critical ischemia. All patients received the best medical therapy. Iloprost was administered (0.5-2 ng/kg/min 6 hours/day for 2-4 weeks) in all patients initially considered unsuitable for revascularization, repeating it regularly in every six-twelve months in the case of positive response. The minimum expected follow-up was 4 years.

RESULTS: 71.5% of patients were treated with iloprost and the responder rate was 71.2%. Most of the patients were regularly retreated with repeated cycles. Initial median supine TcPCO2 in symptomatic limb was higher in untreated patients than those treated (58 vs. 49 mmHg; \( p < 0.05 \)) and in non-responders compared to responders (60 vs. 49 mmHg; \( p < 0.05 \)). TcPO2 directly and significantly correlated with the highest risk of mortality and seems to represent a new accurate prognostic criterion of unfavourable short and long-term response to prostanoïd. In iloprost group, major amputations were significantly reduced. Revascularization was significantly higher in non-responders (57.1% vs. 11.5%; \( p < 0.05 \)). There was a significantly higher prevalence of subsequent myocardial infarction in the non-iloprost group (27.6% vs. 9.6%; \( p < 0.05 \)).

The survival rate of non-responders was higher than untreated up until the second year (76.2% vs. 62%; \( p < 0.05 \)). At 4 years we found higher survival in patients treated with iloprost (64.3% vs. 41% in untreated; \( p < 0.05 \)) and in responders (76% vs. 38.1% in non-responders; \( p < 0.05 \)).

CONCLUSIONS: Our results confirm the favourable role of iloprost on the long-term outcome in patients with CLI. In particular, the maximum benefit is obtained in responder patients treated with multiple cycles of infusion.

Key Words: Critical limb ischemia, iloprost, Prostanoïd, Responder rate, Transcutaneous tonometry

Introduction

Critical limb ischemia (CLI) is a major healthcare issue, involving approximately 500-1000 people per million of the population and characterized by a poor long-term prognosis. At one year from diagnosis, when untreated, major limb amputation is required in 30% of patients, and overall mortality is 25%-12. The treatment goals are, therefore, not only to relieve ischemic pain and heal ulcers, but also prevent limb loss, improve patient function and quality of life, and, primarily, prolong survival. The most consolidated approaches consist of surgical or endovascular revascularization as a first choice, but many CLI patients are often not eligible for such procedures: compared to the past patients tend to be older, present greater comorbidities and severe
## Table II. Clinical characteristics and outcomes in responders and non-responders to iloprost.

<table>
<thead>
<tr>
<th></th>
<th>Iloprost responders No. = 52</th>
<th>Iloprost non-responders No. = 21</th>
<th>Significant differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD; years)</td>
<td>76.2 ± 9.3</td>
<td>75.2 ± 8.1</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>36.5% (n = 19)</td>
<td>61.9% (n = 13)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>50% (n = 26)</td>
<td>33.3% (n = 7)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>67.3% (n = 35)</td>
<td>66.6% (n = 14)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>86.5% (n = 45)</td>
<td>71.4% (n = 15)</td>
<td></td>
</tr>
<tr>
<td>Smokers (active)</td>
<td>1.9% (n = 1)</td>
<td>9.5% (n = 2)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Smokers (previous)</td>
<td>36.5% (n = 19)</td>
<td>71.4% (n = 15)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Previous surgery/PTA</td>
<td>32.7% (n = 17)</td>
<td>14.2% (n = 3)</td>
<td></td>
</tr>
<tr>
<td>Previous contralateral amputation</td>
<td>1.9% (n = 1)</td>
<td>4.7% (n = 1)</td>
<td></td>
</tr>
<tr>
<td>Stage Leriche-Fontaine III</td>
<td>19.2% (n = 10)</td>
<td>14.2% (n = 3)</td>
<td></td>
</tr>
<tr>
<td>Stage Leriche-Fontaine IV</td>
<td>80.7% (n = 42)</td>
<td>85.7% (n = 18)</td>
<td></td>
</tr>
<tr>
<td>TcPO₂ median in symptomatic limb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine mmHg (range)</td>
<td>3 (0-30)</td>
<td>2 (0-10)</td>
<td></td>
</tr>
<tr>
<td>Dependent mmHg (range)</td>
<td>40 (0-59)</td>
<td>30 (5-52)</td>
<td></td>
</tr>
<tr>
<td>TcPCO₂ median in symptomatic limb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine mmHg (range)</td>
<td>49 (36-140)</td>
<td>60 (47-110)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Dependent mmHg (range)</td>
<td>40 (35-55)</td>
<td>40 (37-70)</td>
<td></td>
</tr>
<tr>
<td>Iloprost treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 cycle</td>
<td>34.6% (n = 18)</td>
<td>81% (n = 17)</td>
<td></td>
</tr>
<tr>
<td>2-3 cycles</td>
<td>26.9% (n = 14)</td>
<td>19% (n = 4)</td>
<td></td>
</tr>
<tr>
<td>&gt; 3 cycles</td>
<td>38.4% (n = 20)</td>
<td>0% (n = 0)</td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>94.2% (n = 49)</td>
<td>81% (n = 17)</td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td>86.5% (n = 45)</td>
<td>76.2% (n = 16)</td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td>82.7% (n = 43)</td>
<td>57.1% (n = 12)</td>
<td></td>
</tr>
<tr>
<td>4 years</td>
<td>75% (n = 39)</td>
<td>38.1% (n = 8)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Subsequent procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major amputations</td>
<td>0% (n = 0)</td>
<td>4.7% (n = 1)</td>
<td></td>
</tr>
<tr>
<td>Minor amputation</td>
<td>9.6% (n = 5)</td>
<td>14.3% (n = 3)</td>
<td></td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>11.5% (n = 6)</td>
<td>57.1% (n = 12)</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

PTA: percutaneous transluminal angioplasty; SD: standard deviation; TcPO₂: transcutaneous tissue oxygen tension; TcPCO₂: transcutaneous tissue carbon dioxide tension.

Sopravvivenza

Tutti i pazienti

Iloprost responders vs. non-responders

* p<0.05

Figure 1. Survival curves in patients treated vs. untreated with iloprost.

Figure 2. Survival curves in patients treated with iloprost: responders vs. non-responders.

Iloprost come adiuvante post rivascolarizzazione

Intra-arterial injection of iloprost reduces the risk of early recoil after balloon angioplasty of below-the-knee vessels in patients with critical limb ischemia

TROISI N, Farina A, Chisci E, Ercolini L, Frosini P, Pigozzi C, Guidotti A, Michelagnoli S.

<table>
<thead>
<tr>
<th></th>
<th>PRESENT STUDY (n=32)</th>
<th>BAUMANN 2014 (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>79.6</td>
<td>76.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>78.1%</td>
<td>50%</td>
</tr>
<tr>
<td>Rutherford classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0%</td>
<td>40.0%</td>
</tr>
<tr>
<td>V</td>
<td>59.4%</td>
<td>36.7%</td>
</tr>
<tr>
<td>VI</td>
<td>40.6%</td>
<td>23.3%</td>
</tr>
<tr>
<td>Mean BTK lesion length, mm</td>
<td>144.1</td>
<td>83.8</td>
</tr>
<tr>
<td>Iloprost treatment</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Elastic recoil</td>
<td>43.8%</td>
<td>97%</td>
</tr>
<tr>
<td>Mean luminal compromise</td>
<td>21.4%</td>
<td>29%</td>
</tr>
</tbody>
</table>

J Cardiovasc Surg 2016
REGISTRO ITALIANO DI VAlUTAZIONE DEGLI OUTCOMES CLINICI DOPO INTERVENTO DI RIVASCOLARIZZAZIONE DEGLI ARTI INFERIORI IN PAZIENTI CON ISCHEMIA CRITICA

• Registro Osservazionale
• Promotore dello studio: SICVE
• Centri di Chirurgia Vascolare
• Rivalutazione dei fattori prognostici per I pz con CLI
Rivalutando update

• Definizione del protocollo: Agosto 2015

• Presentazione protocollo: SIVEC & SICVE 2015

• Inizio arruolamento: Ott 2015

• Centri di chirurgia vascolare invitati: 30

• Centri attivi nel reclutamento: 17
Rivalutando update

- Pazienti arruolati: 450
- Valutazione outcomes a 1 anno nel 2018
- Results & report
Iloprost come adiuvante in chirurgia vascolare: schema posologico

-3 -2 -1 0 +1 +2 +3 +4 +5 +6 +7 +14 +21 3-6 mesi

Bolo intra-arterioso intra-operatorio di 3000 ng (in 1-3 minuti)

Infusione post-operatoria: 0,5-2 ng/kg/min, anche sino a 16 ore/die, per 4-7 giorni

Infusione pre-operatoria: 0,5-2 ng/kg/min, per 6 ore/die, per 1-3 giorni

Proseguimento post-operatorio: 0,5-2 ng/kg/min, per 6 ore/die, fino a 14-21 giorni

Ciclo di richiamo in caso di peggioramento o risposta non soddisfacente: 0,5-2 ng/kg/min, per 6 ore/die, per 14-28 giorni
Contatti

sicve.rivalutando@gmail.com
LINEE GUIDA TASC II 2007

Studi precedenti con prostanoidi hanno suggerito un miglioramento della guarigione delle ulcerie ischemiche e una riduzione delle amputazioni nella CLI [A]. Non ci sono altre farmacoterapie che possono essere raccomandate per il trattamento della CLI [B].

LINEE GUIDA ESC EASD 2007

L’unico trattamento farmacologico che abbia fino ad ora dimostrato in modo convincente di influenzare positivamente la prognosi dei pazienti con ischemia critica degli arti è la prostaciclina sintetica (iloprost), da somministrare quotidianamente e.v. per un periodo di 2-4 settimane. In una metanalisi il dolore a riposo e la dimensione delle ulcerie sono migliorate in confronto con placebo. La probabilità di sopravvivenza con entrambe le gambe sane a 6 mesi era del 65% nel gruppo trattato con iloprost rispetto al 45% nel gruppo trattato con placebo.

LINEE GUIDA ACCP 2012

Per i pazienti con arteriopatia obliterante periferica (AOP) sintomatica e ischemia critica degli arti inferiori/dolore a riposo, che non sono candidabili all’intervento vascolare, si suggerisce l’utilizzo di prostanoidi in aggiunta alle terapie antitrombotiche precedentemente raccomandate (aspirina 75-100 mg/die o clopidogrel 75 mg/die) [Grado 2C].

LINEE GUIDA EULAR 2009

Due studi clinici controllati randomizzati indicano che i prostanoidi e.v. (in particolare iloprost e.v.) sono efficaci nella guarigione delle ulcerie digitali in pazienti con sclerodermia. I prostanoidi e.v. (in particolare iloprost) dovrebbero essere considerati nel trattamento delle ulcerie digitali attive nei pazienti con sclerodermia. [Classe I; Livello di Evidenza: A]

LINEE GUIDA AIUC 2012

La terapia infusione di iloprost è il trattamento standard delle ulcerie digitali sclerodermiche ischemiche.
ILoprost in Acute Ischemia of Lower Limbs

Randomised, double-blind, placebo-controlled, multicenter phase III study to evaluate the effects of iloprost on clinical outcome after surgical revascularization in patients with acute ischemia of lower extremities
ILAILL Study Group

- C. Bertoglio - Imperia
- G. Biasi - Cinisello B.mo
- P.G. Cao - Perugia
- R. Chiesa - Milano
- G. de Donato - Napoli
- G.P. Deriu - Padova
- H. Ebner - Bolzano
- M. Ferrari - Pisa
- S. Ferrero - P. Colotto - Genova
- A. Ippoliti - Roma
- A. Martino - Palermo
- R. Mattassi - Garbagnate M.se
- F. Nessi - Torino,
- C. Novali - Cuneo
- D. Palombo - Torino, Genova
- G. Paroni - S. Giovanni Rotondo
- F. Ponzio - Torino
- C. Pratesi - Firenze
- G. Regina - Bari
- C. Setacci - Siena
- P.G. Settembrini - Milano
- C. Spartera - L’Aquila
- F. Spinelli - Messina

Steering Committee
- G. de Donato - Chairman
- G. Paroni
- C. Setacci
- P.G. Settembrini

Safety Committee
- E. Bonizzoni
- A. Mazzone
- A. Odero
**ILAILL - Iloprost as adjuvant to surgery in ALI**

- **Surgical revascularization + bolus**
- Start 4-7 days drug infusion

- Iloprost 3000 ng/i.a
- Placebo

- 0, 1 month FU
- 30, 90 days
- 1-month FU
- 3-month FU
**Strategy on patients with PAD**

**Surgery & medical therapy**

<table>
<thead>
<tr>
<th>Stade</th>
<th>Clinics</th>
<th>Antiplatelet</th>
<th>Statin</th>
<th>Cilostazol</th>
<th>Iloprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>Claudicatio intermittens</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>Claudicatio intermittens (severe)</td>
<td></td>
<td></td>
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<tr>
<td>III</td>
<td>Rest pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Ulcer and gangrene</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Revascularization**

- **Surgery/ endovasc / hybrid**

**Iloprost**
- **Stade IIb** (Studio IIb Pilot)
- **Acute limb ischemia** (RCT ILAIII)

**Cilostazol**
- **After peripheral intervention**
  (Study STOP-IC, Warner, Neel etc.)

**Graphical Representation**

- **Iloprost**
  - 10 gg
  - 3 mo

- **Cilostazol**
  - 3 mo
Iloprost:
Analogo stabile della Prostaciclinina naturale

Sbilanciamento tra fattori protettivi e dannosi

↓ Prostaciclinina
↓ EDRF
↓ EDHF

Trombossano A₂ ↑
Endotelina ↑
PDGF ↑
Molecole di adesione ↑
PAF ↑
Serotonina ↑

Ripristino dell’equilibrio tra fattori protettivi e dannosi

ILOPROST

AZIONE SUL RECETTORE DELLA PROSTACICLINA
EDRF
EDHF

Trombossano A₂
Endotelina
PDGF
Molecole di adesione
PAF
Serotonina

PAF: Platelet-Activating Factor; EDRF: Endothelium-derived relaxing factor; PDGF: Platelet-derived growth factor; EDHF: Endothelium-Derived Hyperpolarizing Factor
Benefici di iloprost nel trattamento dell'ischemia arteriosa cronica grave degli arti inferiori, stadio Fontaine III-IV non operabile

<table>
<thead>
<tr>
<th>OBIETTIVO TERAPEUTICO</th>
<th>RISULTATI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riduzione del dolore a riposo</td>
<td>Significativa riduzione del dolore a riposo (dopo almeno 2 settimane di trattamento)</td>
</tr>
<tr>
<td>Guarigione dell’ulcera</td>
<td>Significativo miglioramento dell’ulcera (dopo almeno 3-4 settimane di trattamento)</td>
</tr>
<tr>
<td>Salvataggio dell’arto</td>
<td>Significativa riduzione delle amputazioni a 6 mesi dal trattamento</td>
</tr>
<tr>
<td>Sopravvivenza</td>
<td>Significativo incremento dei pazienti vivi senza amputazione a 6 mesi dal trattamento</td>
</tr>
</tbody>
</table>

Effect of cilostazol on restenosis

Coronaries
Efficacy of cilostazol on platelet reactivity and cardiovascular outcomes in patients undergoing percutaneous coronary intervention: insights from a meta-analysis of randomised trials

Sripal Bangalore, Amita Singh, Bora Toklu, James J DiNicolantonio, Kevin Croce, Frederick Feit, Deepak L Bhatt

- 34 randomised trials, until May 2014
- 14,119 patients undergoing PCI

- Dual antiplatelet therapy (ASA + CLOP)
  vs.
  Triple antiplatelet therapy (ASA + CLOP + CILO)
<table>
<thead>
<tr>
<th>Study</th>
<th>TAPT Group</th>
<th></th>
<th></th>
<th>IRR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES</td>
<td>Events</td>
<td>N</td>
<td>Events</td>
<td>N</td>
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<tr>
<td>ABCD</td>
<td>4</td>
<td>315</td>
<td>6</td>
<td>314</td>
<td>0.65 (0.15, 2.35)</td>
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<tr>
<td>ACCEL-AMI</td>
<td>0</td>
<td>30</td>
<td>0</td>
<td>00</td>
<td>2.03 (0.04, 100.76)</td>
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<tr>
<td>ACRIF-HR-RESISTANCE</td>
<td>0</td>
<td>311</td>
<td>0</td>
<td>311</td>
<td>1.11 (0.11, 11.41)</td>
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<tr>
<td>CDES</td>
<td>7</td>
<td>141</td>
<td>15</td>
<td>139</td>
<td>0.46 (0.16, 1.33)</td>
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<tr>
<td>CILON-T</td>
<td>30</td>
<td>477</td>
<td>32</td>
<td>463</td>
<td>0.95 (0.50, 1.80)</td>
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<tr>
<td>CLEAR</td>
<td>1</td>
<td>87</td>
<td>2</td>
<td>88</td>
<td>0.62 (0.06, 6.41)</td>
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<tr>
<td>DECLARE-DMLong</td>
<td>19</td>
<td>450</td>
<td>41</td>
<td>450</td>
<td>0.46 (0.27, 0.80)</td>
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<tr>
<td>DECLARE-LONG-2</td>
<td>13</td>
<td>239</td>
<td>23</td>
<td>249</td>
<td>0.62 (0.26, 1.47)</td>
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<tr>
<td>Cao W et al</td>
<td>5</td>
<td>213</td>
<td>11</td>
<td>215</td>
<td>0.68 (0.16, 2.52)</td>
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<tr>
<td>HOST-ASSURE</td>
<td>4</td>
<td>1876</td>
<td>5</td>
<td>1876</td>
<td>0.60 (0.21, 2.57)</td>
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<tr>
<td>Kum US et al</td>
<td>3</td>
<td>312</td>
<td>/</td>
<td>312</td>
<td>0.71 (0.20, 2.24)</td>
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<tr>
<td>LONG-DES II</td>
<td>6</td>
<td>260</td>
<td>16</td>
<td>260</td>
<td>0.31 (0.11, 0.86)</td>
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<tr>
<td>Suh J et al</td>
<td>1</td>
<td>61</td>
<td>22</td>
<td>82</td>
<td>0.09 (0.01, 0.45)</td>
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<tr>
<td>D+L Subtotal (l-squared = 1.8%, p = 0.430)</td>
<td></td>
<td></td>
<td></td>
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<td>0.57 (0.44, 0.74)</td>
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<tr>
<td>I-Y Subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.67 (0.44, 0.74)</td>
</tr>
<tr>
<td>BMS</td>
<td>Events</td>
<td>N</td>
<td>Events</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Chen YD et al</td>
<td>3</td>
<td>60</td>
<td>10</td>
<td>80</td>
<td>0.30 (0.06, 1.60)</td>
</tr>
<tr>
<td>Min PK et al</td>
<td>4</td>
<td>31</td>
<td>4</td>
<td>28</td>
<td>0.90 (0.23, 3.61)</td>
</tr>
<tr>
<td>D+L Subtotal (l-squared = 23.2%, p = 0.264)</td>
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<td>0.61 (0.17, 1.48)</td>
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<tr>
<td>I-Y Subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.00 (0.10, 1.20)</td>
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<tr>
<td>D+L Overall (l-squared = 6.0%, p = 0.498)</td>
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<td>0.67 (0.44, 0.73)</td>
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<tr>
<td>I-Y Overall</td>
<td></td>
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<td>0.57 (0.44, 0.73)</td>
</tr>
</tbody>
</table>

**TLR (re-intervention)**

-43%
Conclusions

How to make medical therapy effective

1. Correct risk factors
2. Improve exercise therapy
3. Revascularization when indicated & medical tx (cilostazol) to prevent restenosis
Pazienti, studio retrospettivo

<table>
<thead>
<tr>
<th>Table 1. Clinical characteristics and outcomes of CLI population.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall population</strong> No. = 102</td>
</tr>
<tr>
<td>Age (mean ± SD; years)</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Smokers (active)</td>
</tr>
<tr>
<td>Smokers (previous)</td>
</tr>
<tr>
<td>Previous surgery/PTA</td>
</tr>
<tr>
<td>Previous contralateral amputation</td>
</tr>
<tr>
<td>Stage Leriche-Fontaine III</td>
</tr>
<tr>
<td>Stage Leriche-Fontaine IV</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Previous stroke</td>
</tr>
<tr>
<td>TcpO₂, median in symptomatic limb</td>
</tr>
<tr>
<td>Supine mmHg (range)</td>
</tr>
<tr>
<td>Dependent mmHg (range)</td>
</tr>
<tr>
<td>TcpCO₂, median in symptomatic limb</td>
</tr>
<tr>
<td>Supine mmHg (range)</td>
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<tr>
<td>Dependent mmHg (range)</td>
</tr>
<tr>
<td>Iloprost treatment</td>
</tr>
<tr>
<td>1 cycle</td>
</tr>
<tr>
<td>2-3 cycles</td>
</tr>
<tr>
<td>&gt; 3 cycles</td>
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<tr>
<td>Survival</td>
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<tr>
<td>1 year</td>
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<td>2 years</td>
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<td>3 years</td>
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<td>4 years</td>
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<tr>
<td>Subsequent procedures</td>
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<tr>
<td>Major amputations</td>
</tr>
<tr>
<td>Minor amputation</td>
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<tr>
<td>Vascular surgery</td>
</tr>
</tbody>
</table>

PTA: percutaneous transluminal angioplasty; SD: standard deviation; TcpO₂: transcutaneous tissue oxygen tension; TcpCO₂: transcutaneous tissue carbon dioxide tension; COPD: chronic obstructive pulmonary disease.