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Short Report Collaborative Research

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Short Report

Prospective multicentre observational study evaluating acute lower limb ischaemia (PROMOTE-ALI)

Alexandra Gratl[1], Albert Busch[2], Caroline Caradu[3], Panagiotis Doukas[4], Katariina Noronen[5], Alexandru Predenciuc[6], Lan Tran[7], Christian Zielasek[8], Petar Zlatanovic[9], Florian K. Enzmann[1,*] and the European Vascular Research Collaborative (EVRC)

[1]Department of Vascular Surgery, Medical University of Innsbruck, Innsbruck, Austria
[2]Division of Vascular and Endovascular Surgery, Department of Visceral, Thoracic and Vascular Surgery, Technical University of Dresden and University Hospital Carl-Gustav Carus, Dresden, Germany
[3]Department of Vascular Surgery, Bordeaux University Hospital, Bordeaux, France
[4]Department of Vascular Surgery, European Vascular Centre Aachen-Maastricht, RWTH Aachen, Aachen, Germany
[5]Department of Vascular Surgery, Helsinki University Central Hospital, Helsinki, Finland
[6]Division of Vascular Surgery, Institute of Emergency Medicine, Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Moldova
[7]Department of Vascular Surgery, University Medical Centre Amsterdam, Amsterdam, The Netherlands
[8]Department of Vascular Surgery, Inselspital, Bern University Hospital, Bern, Switzerland
[9]Clinic for Vascular and Endovascular Surgery, University Clinical Centre of Serbia, Belgrade, Serbia

*Correspondence to: Florian K Enzmann, Department of Vascular Surgery, Medical University of Innsbruck, Anichstraße 35, Innsbruck, 6020, Austria (e-mail: Florian.enzmann@i-med.ac.at)

Members of the European Vascular Research Collaborative are co-authors of this study and are listed under the heading Collaborators.

Introduction

Acute lower limb ischaemia (ALI) constitutes a major challenge for vascular specialists. However, clinical guidelines on the management of ALI suggest that robust contemporary data on treatment and outcomes to inform optimal management are lacking[1]. ALI has been previously related to short-term limb loss rates as high as 42% and in-hospital mortality rates up to 20%[2–4].

Endovascular therapy (EVT) is an alternative to open surgical revascularization (OS), as described in four RCTs performed in the 1990s[5–8]. A Cochrane review of these RCTs showed no evidence in favour of either technique in terms of limb salvage or survival[9]. Contemporary data from the USA suggested no difference in survival and limb salvage outcomes between percutaneous and surgical thrombectomy[10]. In contrast, a large registry from Sweden reported that EVT may reduce mortality compared with OS, without any impact on rates of amputation[11]. An alternative revascularization approach is to combine EVT and surgical techniques in hybrid procedures; however, data on hybrid procedures are also scarce[1,12,13].

The aim of this study was to perform a multicentre prospective analysis of patients presenting with ALI to evaluate the current treatment strategies and outcomes for ALI patients, with a special focus on risk factors for loss of amputation-free survival (AFS).

Methods

A prospective multicentre observational study evaluating patients with ALI (PROMOTE-ALI) was conducted by the European Vascular Research Collaborative (EVRC) and registered at ClinicalTrials.gov (NCT05138679). The recruitment interval was from December 2021 to May 2023 and the recorded clinical parameters were based on a Delphi consensus[14]. Patients suffering from unilateral or bilateral ALI according to Rutherford grading were eligible[15]. The primary endpoint was AFS 90 days after the diagnosis of ALI. The detailed study protocol was previously published[16]. Details regarding methods are available in the *Supplementary Methods*.

Results

Some 705 patients presenting with ALI were recruited from 36 vascular centres in 12 European countries (*Table S1*). Chronic kidney disease ($P = 0.028$), smoking ($P = 0.038$), and pre-existing direct oral anticoagulation ($P = 0.020$) were significantly associated with loss of 90-day AFS. The high number of active COVID-19 infections (131 patients, 18.6%) at the time of ALI diagnosis was not associated with inferior AFS ($P = 0.086$). Details regarding demographics and co-morbidities are listed in *Table S2*.

Aetiology and clinical status at diagnosis

ALI presenting after prior revascularization (OS and EVT) was the most common aetiology (219 patients, 31.1%), followed by native artery thrombosis (197 patients, 27.9%) and embolic events (194 patients, 27.5%). Rutherford grade III ALI at admission ($P < 0.001$) and heparinization at the time of diagnosis ($P = 0.041$) were both associated with reduced 90-day AFS (*Table S3*).

Most cases of ALI were localized in the femoral (443 patients, 62.8%) or popliteal (364 patients, 51.6%) arteries. ALI due to arterial occlusion affecting the aorta ($P = 0.001$) or crural vessels ($P = 0.001$) exhibited the strongest correlation with reduced

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90-day AFS (*Fig. S1*). In 329 patients (46.7%), only one arterial segment was occluded and, in 259 (36.7%) patients, two anatomical segmental levels were affected. Patients with three or more levels of occlusion (117 patients, 16.6%) had significantly worse 90-day AFS ($P < 0.001$).

Treatment

A total of 675 patients (95.7%) underwent revascularization and the remaining patients were treated conservatively (25 patients) or with primary amputation (5 patients). OS was the most common treatment modality, followed by hybrid procedures and EVT. A Kaplan–Meier analysis of the three groups did not show any significant differences regarding 90-day AFS (OS 83.2%, EVT 86.6%, and hybrid 81.6%; log rank $P = 0.709$). Revascularized patients had significantly higher 90-day AFS (83.5% *versus* 54.7%; $P < 0.001$). Details regarding performed procedures are shown in *Table 1*.

Clinical outcome

Overall AFS was 86.0% at 30 days and 82.4% at 90 days. A total of 66 major amputations (9.4%) were performed and 55 (7.8%) patients died after 90 days. The most frequent cause of death was multiple organ failure (32 patients, 4.5%). Details regarding primary and secondary endpoints, including clinical outcomes, are shown in *Table S4*.

Risk factors for loss of amputation-free survival

Factors significantly associated with loss of 90-day AFS were included in a multivariable model, highlighting acute kidney injury, no revascularization, Rutherford grade III ALI, and three or more levels of arterial occlusion as independent risk factors for loss of 90-day AFS (*Table 2*).

Discussion

Despite ALI representing a common vascular emergency, high-quality contemporary data on the presentation, treatment, and outcomes are scarce. The present study stands as the largest prospective cohort on ALI to date. Consistent with the findings of the present study, previous research reported 30-day AFS rates between 82.1% and 87.5%[3,11]. The impact of different revascularization techniques on AFS is controversial. Whereas the present study did not identify the type of procedure as a significant factor, previous studies suggested that the choice of revascularization technique may impact the likelihood of major amputation[3,11]. Notably, preoperative and postoperative parameters, such as Rutherford grade III ALI, three or more levels of arterial occlusion, and acute kidney injury, significantly affected AFS in the present study.

Over recent decades, studies have suggested a reduction in the proportion of OS procedures with more favourable results after EVT[3,11,17,18]. Interestingly, the present study revealed a higher-than-expected percentage of patients exclusively treated with OS. Nonetheless, the present study was unable to demonstrate any superiority in terms of AFS of OS, EVT, or hybrid procedures.

Despite guideline recommendations advocating for heparinization of patients awaiting revascularization, it was performed for fewer than two-thirds of patients in the present study.

The revised version of the Rutherford grading system for ALI, though widely utilized, demonstrated limitations in the present study. Rutherford grade III ALI is conventionally defined as irreversible ischaemia predictably requiring major amputation[15] and it was one of the strongest risk factors for loss of AFS in the present study. In total, 9.9% of patients were diagnosed with Rutherford grade III ALI at the time of inclusion, which is remarkably high compared with previous data[11]. Surprisingly, two-thirds of those patients ultimately survived without undergoing major amputation. The role of the Rutherford grading system in patient evaluation and decision-making may be limited and its intended predictive capability regarding clinical outcomes is debatable. Despite its widespread application since 1997, the clinical performance and ability to provide a prognosis have never been validated[1].

Furthermore, acute kidney injury[19] emerged as an independent risk factor for loss of AFS, highlighting the importance of post-procedural surveillance and optimized medical therapy to improve care and outcomes for the ALI population[20].

Table 1 Procedural data

Variables	Overall ($n = 705$)	Patients with 90-day AFS ($n = 595$)	Patients without 90-day AFS ($n = 110$)	P
No revascularization	30	19	11	0.001
Primary amputation	5	–	5	–
Revascularization	675 (95.7)	576 (96.8)	99 (90)	0.001
Open surgery only	393 (55.7)	334 (56.1)	59 (54)	0.629
Endovascular only	135 (19.1)	119 (20.0)	16	0.182
Hybrid procedure	147 (20.8)	123 (20.7)	24	0.786
Detailed procedures*				
Embolectomy	427 (60.1)	359 (60.3)	68 (62)	0.771
Endarterectomy	116 (16.5)	99 (17)	17	0.758
Prosthetic bypass	80 (11)	65 (11)	15	0.411
Vein bypass	58 (8)	50 (8)	8	0.692
PTA only	77 (11)	65 (11)	12	0.996
PTA and stenting	137 (19.4)	120 (20.2)	17 (15.5)	0.252
Aspiration thrombectomy	75 (11)	67 (11)	8	0.213
Thrombolysis	84 (12)	71 (12)	13	0.973
Atherectomy	18	18	0	0.065
Compartment syndrome	73 (10)	58 (10)	15	0.219
Fasciotomy	132 (18.7)	106 (17.8)	26	0.151
During initial procedure	110 (15.6)	87 (15)	23	0.095
As a secondary procedure	22	19	3	0.797

Values are *n* (%). *Multiple procedures possible. AFS, amputation-free survival; PTA, percutaneous transluminal angioplasty.

Table 2 Risk factors for loss of amputation-free survival at 90 days

Risk factor	Univariable analysis		Multivariable analysis*	
	HR (95% c.i.)	P	HR (95% c.i.)	P
Acute kidney injury†	6.68 (4.40,10.13)	<0.001	5.21 (3.40,8.00)	<0.001
Additional revascularization	1.58 (1.00,2.50)	0.051	–	–
Blood transfusion	2.41 (1.29,4.49)	0.006	1.29 (0.67,2.47)	0.450
CKD (eGFR <30 ml/min/1.73 m^2)	2.00 (1.08,3.74)	0.028	–	–
DOACs	1.65 (1.08,2.53)	0.020	–	–
Heparin at diagnosis	1.55 (1.01,2.37)	0.043	–	–
No revascularization	3.56 (1.91,6.65)	<0.001	2.73 (1.41,5.29)	0.003
Occlusion aorta	3.29 (1.81,6.00)	<0.001	1.89 (0.96,3.73)	0.067
Occlusion crural	1.88 (1.27,2.79)	0.002	1.36 (0.85,2.17)	0.197
Re-intervention due to bleeding	2.14 (0.99,4.59)	0.052	–	–
Rutherford grade III ALI	3.07 (1.97,4.80)	<0.001	2.19 (1.36,3.51)	0.001
Smoking (active and previous)	1.58 (1.03,2.45)	0.038	–	–
Traumatic ALI	4.03 (1.28,12.72)	0.017	–	–
Three or more levels of occlusion	2.93 (1.97,4.35)	<0.001	1.94 (1.18,3.16)	0.008
Wound infection	1.74 (0.97,3.10)	0.062	–	–
Wound re-intervention	1.79 (1.08,2.97)	0.024	–	–

*Variables identified in univariable analysis ($P \leq 0.010$) were included in a multivariable Cox proportional hazards model for associations with loss of amputation-free survival at 90 days. †Injury or higher—according to the RIFLE (risk, injury, and failure, sustained loss and end-stage kidney disease) criteria. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (calculated using the CKD-EPI equation); DOACs, direct oral anticoagulants; ALI, acute lower limb ischaemia.

This is the largest prospective study on ALI. No discernible difference could be detected in 90-day AFS between OS, EVT, and hybrid procedures. Rutherford grade III ALI, multi-level arterial occlusions, no revascularization, and acute kidney injury were identified as major risk factors for amputation or mortality within 90 days after ALI diagnosis. This highlights the need for individualized risk- and lesion-adapted revascularization strategies, along with diligent post-procedural surveillance to mitigate adverse events and improve limb salvage and survival in ALI patients.

Collaborators

European Vascular Research Collaborative (EVRC)

Maria-Elisabeth Leinweber (Department of Vascular Surgery, Clinic Ottakring, Vienna, Austria); Ivan Matia (Department of Cardiac and Vascular Surgery, Clinic of Floridsdorf, Vienna, Austria); Ambroise Duprey (Department of Vascular Surgery and Angiology, Reims University Hospital Centre, France); Nicolas Massiot (Department of Vascular Surgery and Angiology, Reims University Hospital Centre, France); François Guimo (Department of Vascular Surgery and Angiology, Reims University Hospital Centre, France); Nabil Chakfé (Department of Vascular Surgery, University Hospital of Strasbourg, France); Salome Kuntz (Department of Vascular Surgery, University Hospital of Strasbourg, France); Adeline Schwein(Department of Vascular Surgery, University Hospital of Strasbourg, France); Jean Sénémaud (Department of Vascular Surgery, Bichat Hospital Paris, France); Yves Castier (Department of Vascular Surgery, Bichat Hospital Paris, France); Leila Dehina (Department of Vascular and Endovascular Surgery, Hospices Civils de Lyon, France); Antoine Millon (Department of Vascular and Endovascular Surgery, Hospices Civils de Lyon, France); Alexandre Pouhin (Department of Vascular Surgery, Dijon University Hospital, France); Joseph Touma (Department of Vascular Surgery, Henri Mondor University Hospital, France); Bahaa Nasr (Department of Vascular and Endovascular Surgery, Brest University Hospital, France); Nicla Settembre (Department of Vascular and Endovascular Surgery, Nancy University Hospital, Université de Lorraine, France); Blandine Maurel (Department of Vascular and Endovascular Surgery, Nantes University Hospital, France); Jeremie Jayet (Department of Vascular and Interventional Surgery, Ambroise Paré University Hospital, Paris, France); Raphael Coscas (Department of Vascular and Interventional Surgery, Ambroise Paré University Hospital, Paris, France); Fabien Lareyre (Department of Vascular Surgery and Vascular Medicine, Hospital of Antibes, France); Alexander Gombert (Department of Vascular Surgery, European Vascular Centre Aachen-Maastricht, RWTH Aachen, Germany); Alexander Oberhuber (Department of Vascular and Endovascular Surgery, University Hospital of Muenster, Germany); Ursula Werra (Department of Vascular and Endovascular Surgery, University Hospital Cologne, University of Cologne, Germany); Jan Paul Bernhard Frese (Department of Vascular Surgery, Charité-Universitätsmedizin Berlin, Germany); Markus Wagenhäuser (Department of Vascular and Endovascular Surgery, University Hospital of Duesseldorf, Germany); Marton Berczeli (Heart and Vascular Center, Semmelweis University Hospital, Hungary); Zoltan Szeberin (Heart and Vascular Center, Semmelweis University Hospital, Hungary); Dumitru Casian (Department of General Surgery, Institute of Emergency Medicine, Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Moldova); Vincent Jongkind (Department of Vascular Surgery, University Medical Center Amsterdam, Netherlands); Martin Teraa (Department of Vascular Surgery, University Medical Center Utrecht, Netherlands); Leszek Kukulski (Department of Cardiac, Vascular and Endovascular Surgery and Transplantology, Medical University of Silesia in Katowice, Silesian Centre for Heart Diseases, Zabrze, Poland); Nebojsa Budakov (Clinic for Vascular and Endovascular Surgery, Clinical Center Novi Sad, Serbia); Nemenja Stepanovic (Clinic of Vascular Surgery, Clinical Center Nis, Serbia); Angelos Karelis (Vascular Center, Department of Thoracic Surgery and Vascular Diseases, Skåne University Hospital, Malmö, Sweden); Salome Weiss (Department of Vascular Surgery, University Hospital of Bern, Switzerland); Basel Chaikhouni (Department of Vascular Surgery, University Hospital of Bern, Switzerland); Mathieu Béguin (Department of Vascular Surgery, University Hospital of Bern, Switzerland); Anna-Leonie Menges (Department of

Vascular Surgery, University Hospital Zurich, Switzerland); Thomas Wyss (Department of Interventional Radiology and Vascular Surgery, Kantonsspital Winterthur, Switzerland); Mariam Darwish (Department of Vascular Surgery, University Hospital Wales, Cardiff, UK); Lewis Meecham (Department of Vascular Surgery, University Hospital Wales, Cardiff, UK); Eshan Mazumdar (Department of Vascular Surgery, University Hospital Wales, Cardiff, UK); Katarzyna Powezka (Department of Vascular Surgery, NHS Lothian, Scotland, UK).

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Author contributions

Alexandra Gratl (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing—original draft), Albert Busch (Conceptualization, Data curation, Investigation, Project administration, Resources, Writing—review & editing), Caroline Caradu (Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Supervision, Validation, Visualization, Writing—review & editing), Panagiotis Doukas (Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Writing—original draft, Writing—review & editing), Katariina Noronen (Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Writing—review & editing), Alexandru Predenciuc (Data curation, Formal analysis, Project administration, Resources, Validation, Writing—review & editing), Lan Tran (Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Writing—review & editing), Christian Zielasek (Data curation, Investigation, Project administration, Resources, Validation, Writing—review & editing), Petar Zlatanovic (Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Validation, Writing—review & editing), Florian K. Enzmann (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing), and the European Vascular Research Collaborative (Data curation, Investigation, Validation, Writing—review & editing)

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

Research data supporting this publication are available directly from the corresponding author on reasonable request.

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