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Study Protocol of a Prospective Multicenter Observational Study Evaluating Acute Lower Limb Ischemia

Alexandra Gratl, MD, FEBVS,[a,*] *and the European Vascular Research Collaborative (EVRC)*

[a] *Department of Vascular Surgery, Medical University of Innsbruck, Innsbruck, Austria*

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ABSTRACT

Introduction: Acute lower limb ischemia (ALI) is a limb- and potentially life-threatening condition which requires urgent evaluation and treatment. Contemporary data on optimal therapy and prognosis of ALI are lacking, while surgical, hybrid, and foremost endovascular techniques have rapidly evolved over the past decades. Available clinical guidelines are not based on high-level evidence and do not fully reflect day-do-day practice. Contemporary data on etiology, procedural strategies as well as patient outcomes in ALI are urgently needed to improve care and prevent limb loss. The current study was initiated by the European Vascular Research Collaborative (EVRC), established by young European vascular specialists, and aims to provide insight into contemporary treatment strategies in ALI and its clinical results within Europe. In this manuscript we report the rationale and a detailed study protocol.

Material and Methods: The proposed study is a prospective, international, multicenter, observational study on ALI (PROMOTE-ALI) (ClinicalTrials.gov - NCT05138679). Patients with ALI (Rutherford classification grade I -III) of one or both lower extremities will be included in the study. The primary endpoint of the study is amputation-free survival (AFS) at 30 d. Secondary endpoints are freedom from target limb reintervention, freedom from complications, clinical outcome of the index leg, and limb salvage and survival at 30 and 90 d after diagnosis of ALI.

Conclusions: ALI remains a challenging condition and due to the heterogeneous etiology, clinical presentation and treatment strategies, a large multicenter study on this topic is needed to gain contemporary data on clinical outcomes and prognosis, especially for modern endovascular techniques. PROMOTE-ALI is expected to provide these data and set a benchmark for future randomized controlled trials (RCTs).

* *Corresponding author*. Department of Vascular Surgery, University Hospital of Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria. Tel.: +43 50504 80804.

E-mail address: Alexandra.gratl@i-med.ac.at.

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Introduction

Acute lower limb ischemia (ALI) is caused by a sudden decrease in arterial limb perfusion, due to acute thrombosis or embolization of lower limb arteries, which can result in major amputation or death. ALI is defined as the duration of ischemic symptoms of less than 2 wk. Clinical manifestations of limb ischemia lasting longer than 2 wk are defined as chronic limb ischemia.[1] The actual contemporary incidence of ALI is largely unknown as clinical presentation and treatment are heterogenous and most literature is outdated.[1] Epidemiological studies from the US report a decrease in hospital admission rate due to ALI over the last years with reported current incidences of 23.3 to 26.0 per 100.000 person-years.[2,3] This observation might be contributed to the improvement in oral anticoagulative therapy in patients with atrial fibrillation.

According to the widely used clinical classification of Rutherford *et al*, the degree of sensory loss and motor weakness defines the clinical severity of ALI.[4] Depending on the clinical stage of disease, urgent evaluation and management are necessary to achieve limb salvage.

Different invasive approaches are available to restore blood flow. Over the past decades, endovascular techniques have evolved rapidly and gradually replaced traditional open surgical strategies (e.g., embolectomy, bypass surgery). Endovascular procedures include aspiration thrombectomy, catheter-directed thrombolysis, and transluminal angioplasty with or without stenting. Combinations of open and endovascular techniques may also be used. With the evolution of endovascular treatment options over the last decades, several authors initiated randomized controlled trials (RCTs) to compare thrombolysis to standard surgical procedures. These studies have been limited by the small number of patients recruited and their heterogeneity with respect to the investigated thrombolytic technique and patient population. The latter is a general problem of clinical studies on ALI as the ALI population is very diverse. These studies,[5–10] on which current clinical guidelines are based, were published more than 20 y ago.[1] Over the last years, endovascular procedures have evolved with lower rates of technical failure and consequent improvement in clinical outcome parameters; however, reliable data from RCTs are lacking. In ALI, time from ischemic symptom onset to revascularization should be as short as possible to reduce the risk of reperfusion injury, subsequent compartment syndrome, and systemic sequelae such as acute kidney injury or myocardial instability. Frail patients with severe comorbidities, who are unlikely to survive any revascularization procedure may benefit from primary amputation. This may be as many as 24% of patients referring to historic data, however contemporary data are lacking.[11]

In recently published European Society for Vascular Surgery (ESVS) guidelines on the management of ALI, several unsolved issues on diagnosis and treatment are listed that require further research.[1] Additionally, the impact of COVID-19 infections and vaccination status on ALI have not been sufficiently investigated.[12] Multicentric studies are needed to answer several of the pending questions defined by the ESVS guidelines on the management of ALI.[1] They include:

- The current prognosis and its relation with the commonly used Rutherford classification.
- The optimal treatment strategy
- The optimal thrombolytic dose or agent in case of thrombolysis.
- Current prognosis.
- And most importantly, a benchmark to compare future therapies with.

A multicenter observational study design has the potential to include a large number of patients treated in different centers with several treatment regimens and will be valuable to fill several of the aforementioned knowledge gaps. In contrast, a randomized controlled study would not be feasible as the heterogeneity of patients would lead to limitations in patient recruitment and the treatment options that can be investigated.

Therefore, the European Vascular Research Collaborative (EVRC) has initiated the "Prospective Multicenter Observational Study Evaluating Acute Lower Limb Ischemia (PROMOTE-ALI)". The EVRC has been established by young vascular researchers across Europe.[13] This collaborative aims to enable internationally coordinated multicenter trials on vascular diseases. PROMOTE-ALI is the inaugural project and aims to provide contemporary data on outcomes and prognosis of ALI, especially for the newer endovascular techniques, hence providing benchmark data for future studies.

Material and Methods

This is the study protocol of PROMOTE-ALI. The study was registered on ClinicalTrials.gov (NCT05138679). Ethical approval has been obtained by the leading ethics committee of the Medical University of Innsbruck, Austria (EK Nr. 1220/2021). Additionally, ethical approval will be sought by each recruiting center from the competent local ethics committee as required by national regulations. The study will be carried out according to the standards of good clinical and scientific practice in accordance with the declaration of Helsinki as well as with the STrengthening the Reporting of OBservational studies in Epidemiology guidelines for reporting observational studies.[14] Outcome parameters have been defined using available reporting standards published by Rutherford *et al*.[4]

Inclusion and exclusion criteria

All patients with acute lower limb ischemia (Rutherford category I - III, symptom duration of less than 2 wk) of one or both lower limbs will be included into the study. Patients with an age <18 y will be excluded.

Eligibility and informed consent

The screening visit will be performed by a vascular specialist to verify the diagnosis of ALI. If the patient fulfills the inclusion criteria and all exclusion criteria are absent, informed consent is obtained according to local regulations, and the patient is included in PROMOTE-ALI.

Endpoints of the study

The primary endpoint is amputation-free-survival (AFS) 30 d after diagnosis of ALI. Secondary endpoints are freedom from target limb reintervention, freedom from complications (compartment syndrome, major bleeding, acute kidney injury, and multiorgan failure), clinical outcome of the index leg (change in Rutherford category), limb salvage and survival 30 and 90 d after diagnosis of ALI. According to available reporting standards, AFS is achieved if major amputation is avoided.[4]

First visit (day of diagnosis of ALI)

Demographic data including country of admission, age, sex, and body mass index are collected. The presence of cardiovascular risk factors (arterial hypertension, diabetes mellitus, dyslipidemia, and smoking status) as well as other relevant comorbidities (atrial fibrillation, coronary artery disease, chronic kidney failure, and chronic obstructive pulmonary disease) are recorded. Details on previous COVID-19 infection as well as vaccination status and type of vaccine will be obtained. Risk factors for ALI (peripheral arterial disease and previous revascularization procedures, any kind of arterial aneurysms, history of arterial embolization, history of malignant disease, or history of stroke, thrombophilia) will be evaluated. Concomitant medication focused on anticoagulation and/or antiplatelet therapy, including potential recent switching or stopping for any reason will be recorded. Patients will undergo a detailed physical examination including ankle brachial index, pulse status, and clinical stage of ischemia will be graded using the Rutherford classification system for ALI.[4] The anatomical level of the index occlusion of the arterial system (iliac, femoral, popliteal, and crural), the imaging modality used for diagnosis of ALI, the etiology of ALI as well as heparin application at diagnosis of ALI will be documented.

Second visit (early phase—day 1 ± 5)

Within the second visit, details on performed therapies, including conservative management with anticoagulation, primary amputation as well as any kind of revascularization procedure will be collected. For revascularization procedures, date and type of procedure as well as time interval between the onset of clinical ALI symptoms, until reperfusion is achieved, will be obtained. If fasciotomy is performed to prevent or treat compartment syndrome due to reperfusion of the affected limb, details about this procedure are documented (prophylactic or therapeutic; open or subcutaneous fasciotomy). Physical examination will be repeated as described within the first visit. Outcome parameters will be evaluated including sensory and/or motor deficit, need for vascular or wound-related reinterventions, presence of major bleeding complications, hemorrhage and/or infection at vascular access sites. Organ complications (acute kidney failure, major adverse cardiac events, and pulmonary complications) will be documented as well.

Third visit (intermediate phase—day 30 ± 5)

Within the third visit, patients will be asked about their concomitant anticoagulative and/or antiplatelet medication with special focus on any switch and/or stop of medication. Outcome parameters will be obtained according to the second visit with additional evaluation of maximal walking distances.

Final visit (follow-up visit—day 90 ± 5)

Data being collected during the final visit are in accordance with data being collected during the third visit. A graphical illustration of the study protocol is given in Figure.

Rationale for recorded parameters

The definition of recorded clinical parameters is based on the recommendations for registry data collection for revascularization of acute limb ischemia, a Delphi Consensus from the International Consortium of Vascular Registries.[15] The detailed case report form is available as supplementary data.

Data collection and statistics

Data will be collected by an electronic case report form using the ePRO software provided by Castor EDC (Amsterdam, the Netherlands). Due to the unknown true incidence of ALI and the heterogeneous clinical presentation, treatment, and outcome of affected patients,[1] a power calculation was not feasible. A minimum of 500 patients will be recruited to enable covariate analysis being predictable for the defined outcome of AFS. Statistical analysis will be carried out using SPSS (International Business Machines Corporation, Armonk, NY, USA). Continuous data will be shown as median with interquartile ranges using a Wilcoxon test for analysis of significant differences, categorical data as frequencies and percentages. Kaplan-Meier curves will be performed to analyze survival of patients. Univariate analyses of binary and nominal variables will be performed using crosstabulations. Multivariate logistic regression will be performed using patient characteristics, indication, and outcome measures as covariates. A P-value of $<0,05$ is defined to be statistically significant.

Discussion

ALI remains challenging for clinicians due to its etiologic and clinical heterogeneity and lack of current data on effectiveness of different treatment strategies. Besides the existence of numerous different open surgical and endovascular techniques used to treat ALI, strategies also depend on local availability and preferences of the treating physicians. As a consequence, data generated by a real-world observational study seem to be more practical at this stage than an RCT on this complex topic.

Recommendations of current clinical guidelines are based on data obtained decades ago.[1] A meta-analysis on five RCTs comparing thrombolysis to standard surgery reported increased rates of hemorrhagic complications in thrombolysis

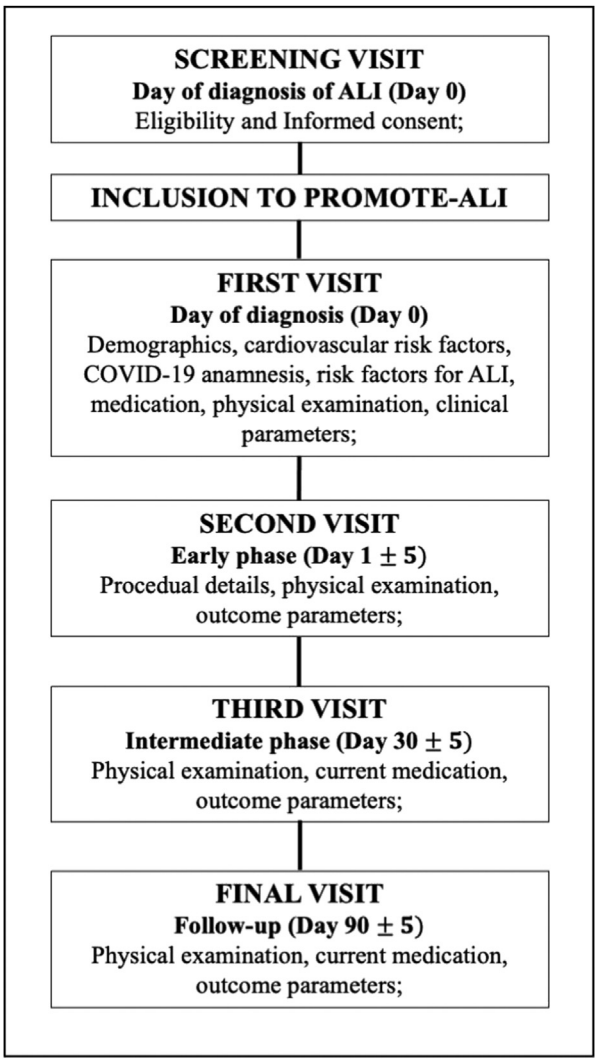

Fig – Graphical illustration of the Study Protocol of PROMOTE-ALI. ALI–Acute limb ischemia.

patients. This led to the conclusion that bleeding risk during thrombolysis should be balanced against the periprocedural risks of surgery.[5] The studies included in this meta-analysis were published in the 1990s and are therefore regarded to be outdated.[1] Further interrogation revealed that two of the included studies had an uncommonly high rate of technical failure of thrombolysis.[6,7] Endovascular treatment is currently an established option to treat ALI in many centers and technical improvements with lower technical failure rates may lead to improved clinical outcomes, but reliable data are scarce. Furthermore, the comparison of different thrombolytic regimens with high *versus* low doses of intra-arterial thrombolytic agents have also been studied in RCTs during the 1990s.[8–10,16] However, the quality is also limited by low sample sizes. A multicenter observational study design has the advantages of including various patients with ALI without the strict boundaries and smaller focus of an RCT, which would otherwise be limited by the heterogeneity of ALI patients. A high number of included patients has the potential to generate data on the impact of numerous factors (patient and treatment related factors) on clinical outcomes in ALI. Data being collected in this observational study were defined using the Delphi Consensus from the International Consortium of Vascular Registries.[15] These recommendations mainly include clinical factors being relevant in the diagnosis, treatment, and prognosis of ALI. Laboratory values are not considered to be relevant within data collection for ALI as there is no clear marker available that predicts risk of amputation or clinical outcome after ALI. The relevance of clinical factors such sensory or motor deficit as well as duration of ischemia were highlighted within this consensus paper and are therefore incorporated within the presented study protocol. Despite being defined as "clinically relevant but not practicable" by the Delphi Consensus group, EVRC decided to include the etiology of ALI to data collection. Different etiologies of ALI (embolic or local thrombotic) on clinical outcome are of great interest as pre-existing manifestations of atherosclerosis or even pre-existing vascular reconstructions might have an impact on clinical outcome. Also the use of heparin in the emergency setting might be of interest, especially as authors reported about a beneficial effect of heparin administration regarding amputation rates following ALI.[17] With the observational study design of PRMOTE-ALI, EVRC defined a study protocol being able to include all factors being defined as relevant in diagnosis, treatment and outcome of ALI and as the Delphi consensus paper as well as the ESVS clinical guidelines emphasized, collection of new data on ALI will be enabled.[1,15]

This observational study has several limitations due to its broad focus and inclusion of various ALI patients in vascular centers all over Europe. This may lead to a high number of subgroups confining the generalizability of clinical findings. It is possible that very ill patients treated conservatively or with primary amputation will be underrepresented, as these patients may sometimes not be referred to a specialized vascular center. However, PROMOTE-ALI will reflect current real-world management and outcomes of ALI at vascular centers across Europe and will provide much needed prospective contemporary data on ALI.

Conclusions

Data obtained by PROMOTE-ALI will address several of the previously identified unresolved issues regarding the management of ALI. They will serve as a benchmark for further studies and as a basis to design focused RCTs on more specific clinical questions in the future.

Supplementary Materials

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jss.2022.09.023.

Author Contributions

AGr and FE drafted the manuscript and coordinated the initiation of the study and the submission process. AB, PD, FE, AGo, AGr, BJ, VJ, FL, LM, MT, SW and PZ made a substantial contribution to the concept of the study protocol, revised the manuscript and approved the version to be published. GdB and RH supervised the process of conception of the study protocol, initiation of the study and the process of manuscript writing. Both critically revised the manuscript and approved the version to be published.

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