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DIAMACC: protocol of a prospective diagnostic accuracy study of the maximal systolic acceleration to detect peripheral arterial disease in patients with diabetes-related foot ulceration in the Netherlands

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ABSTRACT

Introduction Foot ulcers are one of the most serious complications of diabetes, leading to significant risks on amputation and mortality. Peripheral arterial disease (PAD) is an important factor for the development and the outcome of diabetic foot ulcers (DFU). Although prompt and accurate detection of PAD is critical to reduce complications, its diagnosis can be challenging with currently used bedside tests (such as ankle–brachial index and toe pressure) due to medial arterial calcification. A new and promising bedside test for the detection of PAD is the maximal systolic acceleration (ACC_{max}), measured by duplex ultrasonography (DUS). The primary aim of this study is to assess the diagnostic performance of the ACC_{max} to detect PAD in patients with DFU, in comparison with commonly used bedside tests. Secondary aims include the correlation between diagnostic test accuracy and patient comorbidities. Tertiary objectives focus on collecting (follow-up) data for prognostic evaluation, such as ulcer healing, revascularisation feasibility, amputation risk, cardiovascular events and mortality.

Methods and analysis A multicentre prospective diagnostic accuracy study with 198 patients will be conducted to assess the diagnostic performance of multiple index tests to detect PAD in patients with DFU, with special emphasis on ACC_{max}. A full lower limb arterial DUS will serve as reference test.

Ethics and dissemination Study protocol approval was gained from the Medical Ethical Committee Leiden/Den Haag/Delft and registered at ClinicalTrials.gov. The findings of this study will be reported through peer-reviewed publications and (inter)national conferences.

Trial registration number NCT05646147.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is a multicentre diagnostic accuracy study that enables direct comparisons of various bedside tests to detect peripheral arterial disease.
⇒ Blinded reference standard.
⇒ Clinically relevant endpoints will be collected during follow-up of the participants.
⇒ A potential limitation of this study is that performing duplex ultrasound of crural vessels can be challenging and time-consuming, in which the quality depends on the vascular technician's experience.

INTRODUCTION

The prevalence of diabetes mellitus (DM) is increasing rapidly with patient numbers projected to rise to 783 million people by 2045, making it one of the major causes of morbidity and mortality worldwide.[1] Diabetic foot ulcers (DFU) are one of the most serious complications of diabetes and occur in up to 25% of diabetic patients during their lifetime.[2] Mainly due to the presence of microangiopathy, neuropathy, infection and limb ischaemia, these ulcers are challenging to treat. In fact, the recurrence rate of DFU is as high as 40% within 1 year, leading to a significant risk on gangrene, (major) amputation and mortality.[3 4] Therefore, it is of great importance to pay attention to preventative measures and address underlying treatable causes as soon as possible.

Peripheral arterial disease (PAD) is one of the most important risk factors for the development of DFU and is present in up to 50% of cases.[5 6] Prompt and accurate detection of PAD is paramount, since time to revascularisation is a critical factor for improvement of ulcer healing and limb salvage.[7] However, as shown in previous systematic reviews, the diagnostic performances of current bedside tests to diagnose PAD are less reliable in patients with DM.[8–10] One of the main reasons for the

decrease in diagnostic reliability is the presence of medial arterial calcification (MAC), which is present in approximately one-third of diabetic patients. MAC is a complex systemic vascular disorder that is associated with arterial stiffness and has proven to be an independent predictor of adverse limb events and cardiovascular mortality.[11 12] The increase in arterial wall stiffness can lead to incompressible arteries, hampering bedside tests that rely on (systolic) pressure measurements, such as ankle–brachial index (ABI) and toe pressure (TP). Since reference tests to diagnose PAD, such as CT angiography and digital subtraction angiography (DSA), are invasive, are expensive and carry risks, it is important to explore alternative non-invasive tests.

The maximal systolic acceleration (ACC_{max}) is a new Doppler-derived parameter that could be particularly promising in this patient group. Since external pressure measurements are avoided, its diagnostic performance should theoretically be less susceptible to arterial stiffness (ie, MAC).[13 14] Previous in vitro, in vivo and retrospective studies showed an excellent diagnostic accuracy to diagnose PAD, independent of patients with DM.[15–17] Moreover, these studies revealed a good intraobserver agreement and strong correlation between ACC_{max} and the degree of stenosis. However, prospective assessment is needed to verify these results.

The primary aim of this study is to assess the diagnostic performance of the ACC_{max} to detect PAD in patients with DFU, in comparison with commonly used bedside tests. Secondary aims include comparing the ACC_{max} to currently used bedside tests and examining the correlation between diagnostic test accuracy and patient comorbidities. Tertiary objectives focus on collecting (follow-up) data for prognostic evaluation, such as ulcer healing, revascularisation feasibility, amputation risk, cardiovascular events and mortality.

METHODS AND ANALYSIS

Setting

This study is conducted at a tertiary academic centre and several large peripheral hospitals. Additional Dutch hospitals may be added during the course of the study. The study began on 27 November 2023 and is expected to finish around 1 January 2026.

Ethics and dissemination

The study protocol received approval from the Medical Ethical Committee Leiden/Den Haag/Delft and has been registered at ClinicalTrials.gov. The findings of this study will be disseminated through peer-reviewed publications and (inter)national conferences.

Participants

Patients with a referral by their general practitioner because of a DFU will be screened for eligibility. If eligible for participation, patients will be informed about the study by an attending physician (not the responsible vascular surgeon). It will be emphasised that withdrawment from the study is possible at any given moment. The fundamental concepts outlined in the Declaration of Helsinki will be applied during the study.[18]

Inclusion and exclusion criteria

In order to be eligible to participate in this study, a subject must be 18 years or older, have DM in their medical history and present with a new-onset ulceration on the foot or ankle. Patients unable to provide informed consent will be excluded from the study. During the study period, each patient may only be included once with restriction to one leg. Previous vascular interventions are not an exclusion criterium.

Sample size calculation

In order to compare the ACC_{max} to other bedside tests, such as the ABI, a sample size calculation was performed. The McNemar Test for two correlated proportions was used to calculate the sample size.[19 20] The power of the study was set at 0.90 (beta=0.1) with a significance level (alpha) of 0.05. An effect size with a difference of 0.15 and proportion discordant of 0.25 was used. This resulted in a sample size of 119 patients. Since the expected prevalence of PAD is estimated around 60%, 198 patients will be included in this study. In this way, a 90% power to detect an OR of 4.0 will be achieved.

Patient assessment

A clinical team, comprising multiple vascular surgeons, physicians and vascular technicians, will participate in the study. On the same day, both the index and reference tests will be performed by two randomly assigned vascular technicians. One technician will conduct the index (bedside) tests, whereas the other technician will perform a full lower limb arterial duplex ultrasonography (DUS). Both technicians will be blinded to each other. Ulcer severity will be graded by using the Wound, Ischemia and Foot Infection Score.[21]

Index tests

Multiple bedside tests will be performed during initial presentation, including ABI, toe–brachial index (TBI), TP, visual waveform assessment and waveform assessment measured by DUS (such as ACC_{max}). The anterior and posterior tibial arteries will be used to measure the systolic pressure for ABI, in which the highest result is used to calculate the index. An ABI below 0.9 will be considered as diagnostic for PAD.[22] TBI and TP will be measured by applying an infrared sensor on the hallux (photoplethysmography). A TBI below 0.7 will be classified as abnormal, whereas the TP will be analysed for both 30 and 50 mm Hg thresholds.[23] For visual waveform assessment, both monophasic and biphasic signals will be evaluated for their reliability to diagnose PAD.

Waveform assessment

Waveform assessment with DUS will include acceleration time (AT) and ACC_{max} measurements. The scale (velocity

and time) and sweep will be optimised for each examination. The velocity scale is set slightly higher than the peak systolic velocity (Doppler waveform covering at least three-fourths of the window). The timescale contains a maximum of three to four heartbeats. In case dysrhythmias are present, the most representative waveform for that particular patient will be used. An elaborate explanation of the AT and ACC_{max} can be found in previous articles.[15 17 24] Cut-off values of the ACC_{max} depend on the location of the measurement point (femoral 7.5 m/s^2, popliteal 6.5 m/s^2 and ankle region 5.5 m/s^2), whereas the threshold of the AT is set at 120 ms.

Quality assurance

In total, 40 patients will be evaluated by two vascular technicians to assess interobserver reliability of ACC_{max} measurements. Cohen's kappa test will be used to assess agreement between tests. These values will be interpreted as follows: K=0.21–0.40, fair agreement; K=0.41–0.60, moderate agreement; K=0.61–0.80, substantial agreement and K=0.81–1.00, (almost) perfect agreement.[25]

Reference test

A full lower limb arterial DUS will be performed by a vascular technician as reference test, blinded to the index tests. Although DSA is generally used as a gold standard for detecting PAD, it is expensive and invasive (with risk of complications). DUS has been proven to be a safe alternative to detect a significant stenosis or occlusion and is comparable to DSA in peripheral arteries.[26] Moreover, DUS is also considered as a reliable reference test in several systematic reviews.[8–10] During the study, patients will undergo a full lower limb DUS on the same day as the index tests. PAD will be defined as a stenosis of at least 50% or occlusion of the artery.[22] Every hospital will use its own ultrasound machine to conduct imaging, and measurements will be performed according to vascular laboratory guidelines.

Data collection, validation and management

An electronic case report form (CRF) will be registered in a digital database of Castor EDC. This CRF contains all baseline characteristics, results of index and reference tests and prognostic data (such as wound healing and mortality). Patient data will be coded. Only local investigators will have access to the data.

Data monitoring

The study will be monitored for quality and regulatory compliance by a study-independent monitoring team. Monitoring frequency starts off annually, but may be increased or decreased depending on findings.

Adverse events

All adverse events that occur during the study investigations will be reported. Events that are considered as serious adverse events will also be registered at toetsingonline.nl and Castor EDC.

Statistical analysis

The most recent version of SPSS (version 29.0 - IBM, Armonk, NY: IBM Group) will be used for statistical analysis. Descriptive statistics for patient demographics will be calculated using means for continuous variables and proportions for categorical variables. The diagnostic accuracy of all index tests will be evaluated by calculating sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR). PLR and NLR, which are derived from sensitivity and specificity, represent the effect on the post-test probability of disease. Receiver operating characteristics analysis will be conducted for each bedside test. Separate analyses will be performed to look at the diagnostic accuracy of index tests in relation to patient demographics and comorbidities, such as duration of DM and chronic kidney disease. McNemar testing will be used for comparison between index tests, with a significance threshold set at a p value below 0.05. Tertiary objectives will be assessed by using a multistate approach.[27] Indeterminate results or missing data will be excluded from data analysis. No interim analysis will be performed.

EXPECTED LIMITATIONS AND DIFFICULTIES

A potential limitation of this study is that DUS of crural vessels can be challenging and the quality can depend on the vascular technician's experience. If a reliable assessment is not possible (or significant stenosis missed), the diagnostic performance of the index tests will likely decrease. Furthermore, DFUs are a complex multifactorial problem, in which PAD does not solely predict the clinical outcome. This will impact the prognostic capabilities of bedside tests to predict ulcer healing.

PATIENT AND PUBLIC INVOLVEMENT

Patients or public were neither involved in the development, recruitment nor conduct of this study. The findings of this study will be reported through peer-reviewed publications and (inter)national conferences. If applicable, dissemination of the results will be handled through national patient groups as well.

Full study protocol

The full study protocol can be requested from the corresponding author.

Contributors SW contributed to study design and wrote the study protocol and manuscript. AS and JH contributed to local researching and critical review of the manuscript. JB contributed to principal investigation, study design and critical review of the manuscript. JB is responsible for the overall content as guarantor.

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Competing interests None declared.

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