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The impact of diabetes on rapid deterioration in intermittent claudication. A prospective cohort study

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Introduction

Intermittent claudication (IC) is the most common presentation of peripheral arterial disease (PAD) and is manifested as pain, cramping or aching in the calf, thighs or buttocks exacerbated by walking and relieved by rest.[1]

The affected limb is assumed to have a favourable outcome and only 5-10% eventually develop chronic limb-threatening ischaemia (CLTI). [2,3] Although this prognosis is generally accepted, previous studies[4-6] report varied estimates of progression to CLTI among patients with IC ranging from 1.4% per year to 21% within 5 years of diagnosis, suggesting that the evidence is still unclear. Additionally, it has been shown that such estimates probably underestimated the true progression of PAD among IC patients.[7,8,9]

Knowledge about the risk of lower limb deterioration in patients with IC is essential to allow for informed clinical decision making for vascular procedures and other treatment plans. Revascularization is generally recommended for patients with debilitating symptoms or

patients with unsuccessful conservative management.[2] However, for those at risk of deterioration, delayed intervention may lead to poorer outcomes and potential loss of less risky endovascular options. [9,10,11] Accordingly, there is a need for further information on the prognosis of the lower limb and the risk factors associated with rapid deterioration even in the presence of mild IC symptoms.

This study sought to determine the rate of PAD progression for patients diagnosed with IC and to identify independent risk factors associated with rapid development of CLTI.

Materials and methods

Study design

This study employed a prospective observational cohort design, recording haemodynamic assessment and symptom severity at baseline and after two years. Major adverse cardiovascular and cerebrovascular events, lower limb events and mortality were recorded during the study. The Strengthening the reporting of observational studies in epidemiology (STROBE) statement[12] was followed throughout the study.

Ethical approval

Ethical approval was sought and granted from the University Research Ethics Committee. Informed consent was obtained from all participants following the Declaration of Helsinki principles.[13]

Study population

The study population comprised of consecutive patients newly referred over 12 months to the vascular surgery unit in the national hospital. with IC as the reason for referral. Out of 249 referrals, 246 potential participants agreed to participate. Recruitment was confirmed once PAD was diagnosed by haemodynamic analysis. The recruitment period took place over 12 months and was carried out prior to the appointment with the vascular surgeon to ensure allocation concealment[8].

Study protocol

All potential participants were asked to refrain from exercising, smoking or drinking caffeine for at least one hour prior to their appointment.[14] On the day of the appointment, participants were assessed for PAD by haemodynamic analysis (performed by an experienced podiatrist) which included Doppler waveform analysis, ABPI and TBPI. The walking impairment questionnaire (WIQ)[15] was administered by the researcher to assess symptom severity where an increase in WIQ indicated worse symptoms. At baseline current pharmacological therapy, smoking habits and concomitant disease data were retrieved from medical records and blood parameters were recorded prospectively. Patients without PAD as defined in the inclusion criteria (table 1) or who had CLTI were excluded from the study.

Insert table 1

Ankle-brachial Pressure Index measurement

The Dopplex assist (Huntleigh®) was used to assess Doppler waveforms and Ankle-brachial Pressure Index (ABPI) using an 8MHz probe following the protocol proposed by Aboyans et al[19] (Table 2). Due to unreliable ABPI readings associated with medial arterial calcification (MAC),[21,22] participants with calcified infrapopliteal or femoropopliteal arteries diagnosed by duplex scan, an ankle pressure ≥200mmHg, an ABPI ≥1.4[23] or an increase in ABPI >0.15 without revascularisation were classified as having calcified arteries.[1] The ABPI readings of these participants were excluded from follow-up analysis.

Toe-Brachial Pressure Index measurement

The Huntleigh (Huntleigh®) Ankle and toe pressure kit was used to assess toe pressures which has high sensitivity allowing recording of otherwise undetectable waveforms following the protocol in table 2. Considerations taken during Toe-Brachial Pressure Index (TBPI) measurement included toe cuff size (2.5cm),[24] ambient temperature (24 to 25°C),[25] participants lay supine throughout the procedure[26] and rested for 10 minutes prior to measurement.[27] Participants who had an absolute toe pressure ≥150mmHg were classified as having calcified arteries. The TBPI readings of these participants were excluded from follow-up analysis.

Insert table 2

Doppler waveform analysis

Doppler waveform analysis was performed using an 8MHz Doppler probe attached to the Dopplex assist (Huntleigh®) and Aquasonic® ultrasound transmission gel (Parker Laboratories, New Jersey). Doppler waveforms were assessed at the dorsalis pedis and posterior tibial artery. The waveforms were recorded as triphasic, biphasic, monophasic discontinuous, monophasic continuous or absent as defined by Scissons.[28]

The walking impairment questionnaire

Symptom severity was measured using the validated WIQ[15] which focuses on symptom severity assessing four subscales – pain, distance, speed and stairs as perceived by the patient in the previous week and a Likert scale with 1 representing 'no difficulty' and 5 indicating 'unable to do'. The protocol described by Mcdermott[29] was followed for scoring the WIQ.

Outcomes

The following data was recorded at each follow-up:

- ABPI measurement defined as measurement of the ankle-brachial pressure index[19] (Table 2)
- TBPI measurement defined as measurement of the toe-brachial pressure index[25] (Table 2)
- Doppler waveform analysis defined as monophasic -continuous, monophasic, biphasic, triphasic [19,28]
- Symptom severity defined by scores obtained from the Walking impairment questionnaire[15]
- Adverse events and outcomes defined below:

Adverse events and outcomes

The outcomes recorded included:

- **Development of CLI** - defined as ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease.[9,20]

- **Revascularisation** – any revascularisation procedure including angioplasty, bypass and thrombectomy. Participants who underwent lower limb revascularisation procedures[2] were excluded from analysis of PAD progression.

- **Significant haemodynamic deterioration** – a decrease in ABPI by ≥0.15[30] or in TBPI by ≥0.1.[9]

- **Significant deterioration** – for the purpose of this study participants who experienced significant deterioration were those who were referred for revascularisation due to deterioration of PAD and/or due to change in symptom severity (any subsequent operation related to a failed primary procedure was not included as an adverse event).

- **Mild haemodynamic deterioration** – deterioration which is not haemodynamically considered significant, that is, a decrease in ABPI <0.15[30] and / or a decrease in TBPI <0.1 or a change in waveforms[9]

- **Symptom deterioration** –defined as a decrease in walking distance before symptoms of IC develop, [29,31] measured by an increase in WIQ distance score

- **Cerebrovascular event** – defined as transient ischaemic attack or stroke[32]

- **Cardiovascular event** – MI, heart failure, cardiovascular death[33]

- **Mortality** – death reported on the national database

Statistical analysis

A power calculation was performed to determine the sample size of the study using 0.18%[34] for p^0 (incidence of CLTI among the general population) and 3%[1] for p^1 (incidence of CLTI among population with IC). The minimum number of participants required to determine effects hypothesized in the study was N=65.

Continuous variables are presented as means and standard deviations that measure central tendency and dispersion respectively. Categorical variables are presented as frequencies and percentages. The Chi square test and the Mann Whitney U test were used to compare parameters between two independent groups; the Wilcoxon signed ranks test was used to

compare mean parameters between repeated measurements. Binomial logistic regression models were used to identify the significant factors associated with deterioration to CLI and haemodynamic deterioration, expressed as odds ratio (OR) and 95% confidence interval (95% CI). Relative risks (RR) were calculated using the rare disease assumption[35] since the incidence of CLI is 0.24% in the general population.[36-38]

Statistical analyses were performed using SPSS for Mac (Version 26.0, SPSS Inc., IL, USA).

Results

Out of 246 referrals, 93 patients did not have PAD and 3 participants did not respond, therefore 150 participants were eligible and all consented to participate in the study. At baseline the study cohort consisted of 119 men (79.3%) and 31 (20.7%) women. The mean age was 69.7 years (+/- 9.3) and 69.3% were living with diabetes (tables 3 and 4). After 2 years, lower limb outcome data of 145 participants were retrieved (reasons for missing data were: 4 passed away and 1 relocated). Haemodynamic data was recorded in 135 participants. Reasons for non-returners for 24-month follow-up were: 3 hospitalisations, 5 reported transport difficulty and 2 had infectious disease precluding cuff placement.

Insert table 3
Insert table 4

Haemodynamic Outcomes

Within two years 67.3% (n=101) of the participants experienced deterioration of different levels; 23.3% (n=35) deteriorated to CLTI, 27.3% (n=41) experienced significant haemodynamic decline (decline in ABPI by ≥0.15 and/or decline in TBPI by ≥0.1 and/or significant deterioration requiring revascularisation) and 17% (n=25) experienced mild haemodynamic decline. During the study 14 participants developed MAC evident in ABPI and/or TBPI assessments at the first or second follow-up precluding assessment of haemodynamic deterioration in these participants. Seven of these developed CLI and were included in the CLI group. Fifteen participants did not attend for the second follow-up which precluded haemodynamic assessment but 2 developed CLI and are included in that group. During the study period 29 participants (19.3%) demonstrated stable/improved haemodynamic measures. At the 2nd follow-up WIQ scores were recorded in 134 participants

(4 died, 1 relocated and 11 could not walk due to other causes including breathlessness, knee pain and hip surgery). 40% (n=53 of 134) reported stable/improved symptoms according to the WIQ.

Insert figure 1 in colour

Clinical events

Fifty participants underwent revascularisation, 25 (10.7%) due to CLTI (16 endovascular, 1 hybrid and 8 bypass procedures,) and 25 (10.7%) due to IC (21 endovascular, 1 hybrid and 3 bypass procedures). Major adverse cardiovascular and cerebrovascular events were recorded in 12% (n=18) of participants, 3 of which were fatal cardiovascular events. One cause of death was malignant disease.

Baseline characteristics

The group who developed CLTI within 2 years had a mean age of 69.9 years and were predominantly male (74.3%). 29% of the female study cohort developed CLI compared to 22% of the male cohort.

Participants who deteriorated to CLTI had a mean baseline **ABPI** of 0.66 (±0.36) or **0.53** (±0.21) when calcified arteries were excluded and a mean **TBPI of 0.33** (±0.15) at baseline which were significantly lower than those observed in participants who did not deteriorate to CLTI (p=0.002 and p=0.015 respectively). Participants who deteriorated to CLTI were more likely to have **infrapopliteal artery disease** (p=0.03) and **monophasic continuous Doppler waveforms** in the pedal arteries (p=0.04) compared to participants who did not deteriorate to CLTI.

Significant predictors for deterioration

Baseline **ABPI, ABPI ≤0.5, TBPI ≤0.39, infrapopliteal artery (IPA) disease** and high **HbA1c** were identified as significant predictors for deterioration to CLTI. (p<.05, binomial logistic regression). Female gender, IPA disease, lack of antiplatelet therapy, high CRP, lack

of calcium channel blockers and diabetes were identified as significant predictors of significant haemodynamic decline (decline in ABPI by ≥0.15 and/or decline in TBPI by ≥0.1) (p=<.05).

Insert table 5

Participants with baseline TBPI ≤0.39 are 3.6 times more likely to develop CLTI than participants with higher TBPI (RR 3.6, 95%CI 1.21-10.71: p=0.02); with every 1-unit increase in baseline HbA1c the risk of developing CLTI increases by 1.35 times (RR 1.35, 95%CI 1.03-1.78: p=0.03) and with every 0.1-unit decrease in baseline TBPI participants are 3 times more likely to deteriorate to CLTI (RR 3.03, 95%CI 0.003-0.48: p=0.01).

Insert table 6

The results indicate that women are 6.7 times more likely to have a significant deterioration than men (RR 6.73, 95%CI 1.65-27.49: p=0.01); participants with diabetes are 7.7 times more likely to experience a significant deterioration than participants without diabetes (RR 7.7, 95%CI 2.21-27.02: p=<0.01). Participants who lack antiplatelet/anticoagulant therapy are 7.7 times more likely to experience significant deterioration (reciprocal OR 7.7, 95%CI 0.03-0.53: p=<0.01) and with every 1-unit increase in CRP, the risk of deterioration increases by 1.1 times (RR1.1, 95%CI 1.01-1.18: p=0.03).

Participants with IPA disease are 2.75 times more likely to experience significant deterioration within 2 years than participants without IPA disease (RR 2.75, 95%CI 1.04-7.3: p=0.04).

Discussion

The main finding of this study is that CLTI developed in almost a quarter (23.3%) of participants with IC within two years and more than half of the participants (50.6%) experienced significant deterioration in lower limb perfusion.

This study reports specific independent predictors for lower limb deterioration where ABPI ≤0.5, TBPI ≤0.39, infrapopliteal artery disease, high HbA1c have been shown to be predictors of deterioration to CLTI within 2 years. An ABPI of ≤0.5 has been associated with

development of CLTI previously[2] but no studies have assessed TBPI as a predictor and no comparisons can be made. Literature investigating TBPI as a predictor of adverse events is limited to one study investigating TBPI as a predictor of cardiovascular mortality, unrelated to lower limb events.[39] This is therefore the first study to report TBPI as an independent predictor of CLTI in patients with IC and results corroborate the mounting number of reports supporting the use of TBPI for its superior diagnostic capacity to ABPI in patients with and without medial arterial calcification.[40-42]

The identification of IPA disease as a risk factor for CLTI development is also an important finding. This is consistent with previous work where IPA was present in 83% of patients with CLTI.[43] Implicating IPA disease as an independent risk factor for CLTI development is emphasized in the knowledge that isolated tibial arterial disease has a worse prognosis in terms of limb salvage and independent living status compared to patients with infrainguinal arterial disease at other sites.[44] Additionally, diffuse disease of the infrapopliteal arteries in patients with diabetes[45] is more likely to result in worse ischaemia.[44] It is therefore suggested that patients with IC with disease in the IPA segment should be closely monitored due to the increased risk of deterioration shown in the results reported in our study.

These findings challenge previously held views that intermittent claudication is a benign condition with respect to the limb.[23] The commonly accepted rate of disease progression is that 80% experience stable disease, 20% deteriorate, of whom only 5-10% develop CLTI within 5 years.[2,17] The high rates of deterioration to CLTI in >23% within 2 years observed in this study potentially confirm the suggestion that the progression of PAD may be underestimated,[7,8] particularly in the presence of diabetes and IPA disease. In this study 69% of the recruited participants were living with diabetes, a known risk factor of PAD and is associated with 26% increased risk of PAD.[46] This high rate of participants with diabetes may have contributed to the higher rate of deterioration observed in this study since PAD is more aggressive with early large vessels involvement when compared to individuals without diabetes.[1]

Given the high rate of significant haemodynamic decline in over 50% within a relatively short period of time observed in this study, it follows that their cardiovascular risk is also increased since such a deterioration in lower limb perfusion is predictive of future cardiovascular events.[30] These results therefore call for increased awareness that patients with

IC should be monitored by haemodynamic analysis so that any decline can be detected promptly allowing for timely referral to specialists.

In our study haemodynamic improvement/stability was observed in only 19% of the cohort over two years while symptom improvement was reported in 40%. Developing patient-oriented end points is deemed critical when planning treatment strategies for IC,[9] but the discrepancy between the proportions of those who remained haemodynamically stable and those who reported stable symptoms suggests that relying on patient perception of improvement may not be the best measure of disease progression, particularly for those at high risk of deterioration. Early identification of those who are more likely to develop CLTI is required to support clinical decision making both for specialists responsible for the management and the patients themselves.

Strengths and potential limitations of the study

This study had a high rate of recruitment with a near complete follow-up rate, allowing for significant outcome estimates.

Some potential limitations include; firstly, this study presented results from a referral based cohort potentially resulting in overestimation of worse outcomes. Nevertheless, although it is a highly selected group, due to the health system from where the participants were recruited, the study population represented a wide range of IC symptoms and severity of PAD. Further population-based studies would potentially include patients who have milder disease and would not have otherwise sought medical advice.

Secondly, this was a single centre study and external validity cannot be verified, consequently generalizability of results should be interpreted with caution. Our cohort had a high prevalence of diabetes, possibly because it is highly prevalent in the population studied, which may have influenced the outcomes observed. While this needs to be acknowledged, long established notions of disease need to meet population demographic and patient characteristic diversity.

Thirdly, severity of symptoms was not measured objectively. While objective testing of walking distance has less risk of reporting bias, its use is ineffective in patients with known cardiac disease or who limit walking due to other conditions. Symptoms reported by the patient

are considered as the most important stimulus for considering revascularisation in claudication[47] and in this regard the WIQ fulfilled the required need. Furthermore, since this study aimed to assess factors obtained in a real-life clinical setting, self-reported claudication distance using a validated questionnaire was feasible.

Conclusion

The prognosis of the lower limb in patients with IC may be worse than previously assumed. The risk of deterioration in patients with low ABPI and TBPI, uncontrolled diabetes and disease in the infrapopliteal segment increases significantly. Efforts should be made to increase vascular assessment clinics run by trained health professionals for patients with IC and who should be working in liaison with vascular surgeons for fast-track referrals when patients at high risk of deterioration are identified. Closer haemodynamic monitoring of patients with IC may mean fewer adverse lower limb events and reduced morbidity in this population. Further studies assessing the use of identified predictors of deterioration to CLTI in clinical decision making are required.

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Table 1

Inclusion Criteria	Exclusion Criteria
• Newly referred IC patients with PAD defined as abnormal Doppler waveforms (not triphasic, [16,17] ABPI <0.9 or TBPI <0.7[18,19] in the symptomatic limb / limbs[2,19]. PAD was also confirmed following Duplex scan by the vascular surgeon where one or more arteries had >50% stenosis[16]. • Patients with bilateral or unilateral symptoms according to Fontaine classification IIa and IIb.	• Patients with symptoms of IC but who did not have PAD. • Patients who had CLTI defined as rest pain, active ulceration, tissue loss or absolute toe pressure <30mmHg[20]. • Patients who underwent previous lower limb revascularisation. • Patients who had a previous appointment with a vascular surgeon and have been previously diagnosed with IC due to PAD. • Patients with contraindications to cuff placement for ankle, toe or brachial pressure measurements including active digital ulcerations, active leg ulceration, lymphedema, history of deep vein thrombosis, patients with arteriovenous fistula in both arms and patients with vasospastic disorders.

Table 1 Inclusion and exclusion criteria of the study

Table 2

- ***ABPI protocol adapted from Aboyans et al 2012***[19]
- The potential participant lay at rest for 5 to 10 min in the supine position, relaxed, head and heels supported, in the room with a comfortable temperature (19°C–22°C/66°F–72°F).
- The cuff was chosen adequately according to the limb size with the width contouring at least 40% of the limb circumference.
- Any open lesion posing potential contamination was covered with an impermeable dressing.
- The participant was asked to stay still during the pressure measurement.
- The cuff was placed around the ankle using the straight wrapping method and the lower edge of the cuff was placed 2 cm above the superior aspect of the medial malleolus.
- An 8MHz Doppler probe was used and Doppler gel was applied over the sensor.
- After the Doppler device was turned on, the probe was placed in the area of the pulse at a 45° to 60° angle to the surface of the skin and was moved around until the clearest waveforms signal was heard.
- The cuff was inflated progressively up to 20 mmHg above the level of flow signal disappearance and then deflated at 2mmHg per second pressing the deflate button on the Dopplex Assist until the flow signal reappearance. The Dopplex Assist stopped automatically indicating the level of pressure at the first signal. This could also be manually adjusted if deemed necessary such as in cases when the signal was too weak to be automatically detected. The maximum inflation was 300mmHg; if the flow was still detected, the cuff was deflated rapidly to avoid pain.
- The detection of the brachial blood flow during the arm pressure measurement was also done by Doppler.
- The same sequence of limb pressure measurements was used, keeping the same sequence for all participants. In this study the counterclockwise sequence was applied, i.e right arm, right PT, right DP, left PT, left DP, left arm.
- During the sequence of measurement, the first measurement was repeated at the end of the sequence and both results averaged to minimise the white coat effect of the first measurement, except if the difference between the 2 measurements of the first arm

exceeded 10mmHg. In that case, another measurement was taken and accepted if the difference was less than 10mmHg.

- In case of the requirement of repeat measurement of the 4 limb pressures, the measurements were repeated in the reverse order of the first series i.e the clockwise sequence was used starting and ending with the left arm.

- ***TBPI protocol***
- Following ABPI, the PPG sensor was placed on the distal pulp of the hallux or second digit if this was amputated or ulcerated. The sensor was fixed with surgical tape.
- The device automatically increased the sensitivity up to 40 times until a clear signal was obtained. Once this was stable, the 2.5cm toe cuff was placed proximally to the PPG.
- The cuff was inflated until a flat lined PPG signal was shown on the display up to a maximum of 150mmHg.
- The cuff was then slowly deflated at 2mmHg per second as indicated in the display.
- When a constant PPG wave signal returned, the device automatically indicated the pressure of the first return signal. In cases when the return wave was very low and was undetected by the device, the pressure reading of the first return wave was recorded manually by the researcher.
- The TBPI was calculated by dividing the toe pressure by the highest brachial pressure.

Table 2: ABPI and TBPI protocols

Table 3

		Frequency (n=150)	Percentage
Gender	Female	31	20.7%
	Male	119	79.3%
Smoking Status	Current Smoker	55	36.7%
	Ex-smoker	62	41.3%
	Never smoked	33	22%
Symptom Location	Bilateral claudication	86	57.3%
	Unilateral claudication	64	42.7%
Medical History	Ho of Diabetes	104	69.3%
	Ho of hypertension	129	86%
	Ho of hyperlipidaemia	116	77.3%
	Ho of renal disease	47	31.1%
	Ho cardiac disease	61	40.7%
	Prior cardiac intervention	58	38.7%
	Prior MI	29	19.3%
	Prior CVA	15	10%
Medication	Statins	113	75.3%
	Antiplatelet	112	74.7%
	Anticoagulants	12	8%
	On Antiplatelet / anticoagulant	119	79.3%
	Not on Antiplatelet / Anticoagulant	31	20.7%
	ACE inhibitor	72	48%
	Angiotensin receptor blocker	22	14.7%
	Calcium channel blocker	36	24%
	Beta Blocker	12	8%

Table 3 Baseline characteristics – categorical variables

Figure

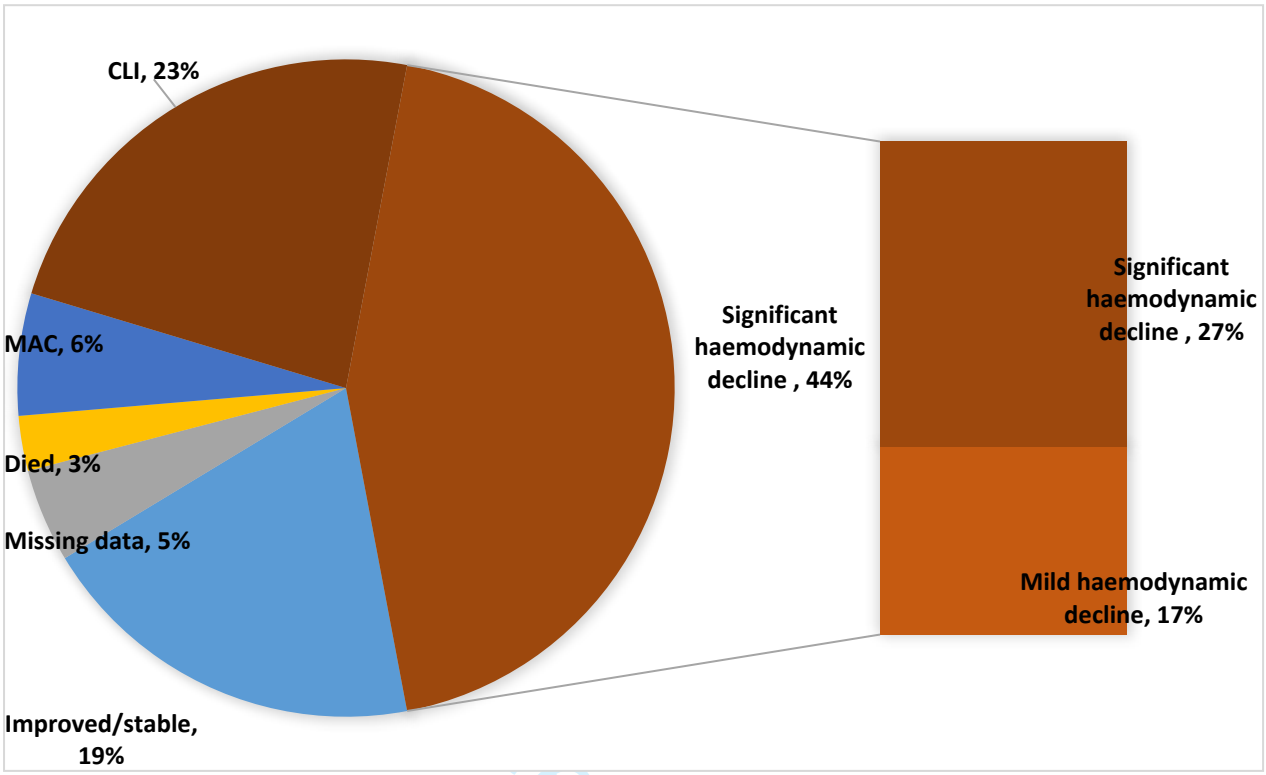

Figure 1: Two-year haemodynamic outcomes (n=150)

Table 4

Characteristic	Mean	SD	Minimum	Maximum
Age (years)	69.7	9.3	38	88
BMI	27.8	4.27	18.9	47.1
ABPI (symptomatic limb)	0.71	0.3	0.4	1.60
ABPI* (excluding calcified arteries) n=125	0.60	0.17	0.4	0.86
TBPI	0.38	0.2	0.21	0.94
Absolute toe pressures (mmHg)	57.4	25.3	38	136
WIQ score	44.9	15.9	28.2	78.8
eGFR (mls/min/1.73m^2) n=150	78.18	31.30	6.0	164.0
Cholesterol (mmol/l) n=150	4.45	1.20	2.41	9.0
Triglyceride (mmol/l) n=150	1.75	1.1	0.15	8.8
HDL Cholesterol (mmol/l) n=150	1.2	1.5	0.63	3.1
Non HDL Cholesterol (mmol/l) n=150	3.23	1.17	1.32	7.49
LDL Cholesterol (mmol/l) n=150	2.41	13.81	0.02	5.85
Total Cholesterol: HDL ratio n=150	3.88	1.33	1.67	7.99
Fasting Glucose (mmol/l) n=115	**8.32**	3.06	4.56	16.85
HbA1c (%) n=150	**6.93**	1.39	4.20	10.91
Creatinine (umol/l) n=150	103.23	74.3	38.0	811
CRP (mg/L) n=139	4.85	7.75	0.10	56.0
ESR (mm 1st hr) n=136	136	16.46	1.00	74.0

Table 4 Baseline characteristics – continuous variables n=150

Table 5

Deterioration to CLI[a]	B	Std. Error	Sig.	Odds ratio	95% CI for OR	
					Lower Bound	Upper Bound
IPA disease	0.81	.413	**0.049**	2.25	1.0	5.04
ABPI	-0.44	1.52	**0.004**	0.647	0.001	0.25
ABPI ≤0.5	1.36	.71	**0.046**	3.89	.97	15.72
ABPI 0.51-0.69	0.67	.59	0.261	1.95	.61	6.25
ABPI 0.7-0.89	-0.16	.71	0.819	.85	.21	3.43
TBPI	-0.33	1.29	**0.011**	0.327	.003	.479
TBPI ≤0.39	1.28	.56	**0.02**	3.60	1.21	10.71
TBPI 0.4-0.69	0.38	.70	.59	1.46	.37	5.78
HbA1c	.30	.14	**.03**	1.35	1.03	1.78

Table 5: Significant predictors for deterioration to CLTI. Binomial logistic regression analysis.

Table 6

Significant haemodynamic decline	B	Std. Error	Sig.	OR	95% CI for OR	
					Lower Bound	Upper Bound
Female	1.91	.72	**0.01**	6.73	1.65	27.49
Calcium channel blocker	-1.61	.64	**0.01**	0.20	.06	.71
Infrapopliteal artery disease	1.01	0.50	**0.04**	2.75	1.04	7.30
Diabetes	2.05	.64	**0.00**	7.73	2.21	27.02
Antiplatelet or anticoagulant	-2.04	.72	**0.00**	0.13	0.03	0.53
Beta blocker	-1.87	1.01	0.06	0.15	0.02	1.12
CRP	.09	0.04	**0.03**	1.09	1.01	1.18

Table 6. Significant predictors for significant deterioration. Binomial logistic regression analysis.