Rate and Predictors of Disease Progression in Patients with Conservatively Managed Intermittent Claudication: A Systematic Review

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Background: Intermittent claudication (IC) is a common pathology, affecting 4.5% of the United Kingdom population, and is associated with significant health burden if disease progresses to chronic limb-threatening ischemia (CLTI). The natural history of conservatively managed IC remains poorly described, and this study aimed to examine the rate and predictors of progression from IC to CLTI.

Methods: Systematic review (PROSPERO ID: CRD42023401259) in accordance with Preferred Reporting Items for Systematic reviews and Meta-analyses guidelines of available literature using Scopus, World of Science, Medline, Embase, and CINAHL databases. Adult patients with IC managed conservatively were included. Progression rate was defined as percentage of IC patients developing CLTI at follow-up. Predictors identified from univariate and multivariate analyses were included. A quantitative synthesis was planned if studies depicted homogeneity.

Results: Search terms yielded 6,404 unique reports. Nine studies (7 retrospective and 2 prospective cohorts) on a total of 4,115 patients were included in the primary synthesis. Women constituted 22.7% on average (0−30.1%) of patients included within studies. All included studies were non-randomized cohort designs with expected limitations in terms of determining causal effect. The risk of bias was assessed as "moderate" in 5, and "serious" in 4 of the 9 included studies. 1.1−36.7% of claudicants from studies included developed CLTI by end of follow-up (mean 5.4 ± 2.72 years). A pooled progression rate of 15.26% at maximal (10 years) follow-up did not reach significance ($P = 0.67$) in meta-analysis and is likely unreliable, demonstrating 99% heterogeneity ($P < 0.01$). Predictors of progression were advanced age, diabetes, hemodialysis, smoking, serum low-density lipoprotein, HbA1c, and baseline severity of ischemia (Ankle-brachial index, Toe-brachial index and claudication distance) in univariate analysis. Diabetes, smoking and hemodialysis were predictors of progression in multivariate analysis. Only three studies investigating biomarkers of peripheral arterial disease (PAD) progression were found.

Conflict of interest: BM − Advisory boards, speakers fees Abbott, Philips, Cook, Cydar Medical. No other conflicts to declare.

Funding: Supported by British Heart Foundation Senior Fellowship (FS/17/24/32596) and British Heart Foundation Programme Grant (RG/F/24/110126).

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Ann Vasc Surg 2025; 112: 183–192
https://doi.org/10.1016/j.avsg.2024.12.009
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Manuscript received: August 22, 2024; manuscript accepted: December 3, 2024; published online: 16 December 2024

Conclusions: Diabetes, renal failure, and smoking are significant predictors of PAD progression. Poor quality evidence and data heterogeneity preclude conclusive estimates of progression rates. Women are underrepresented among studies. Future structured, prospective prognostic studies addressing the progression of conservatively managed IC are needed to inform personalized management strategies.

INTRODUCTION

Peripheral arterial disease (PAD) is a global health burden affecting >200 million people worldwide and accounting for 20% of individuals >75 yrs old. Between 2000 and 2013, there was a 23% increase in the prevalence of PAD, and this is expected to rise.[1] >40,000 patients/year require management for limb ischemia in the United Kingdom (UK), a figure that is set to double by 2050.[2] Symptomatic PAD manifests as intermittent claudication (IC) and chronic limb-threatening ischemia (CLTI). IC represents the most common form of symptomatic PAD, with a prevalence of approximately 7% in over 60-year-olds.[3] Early manifestation of symptomatic PAD is IC, which is exercise-induced pain (usually in the calf, posterior thigh and/or buttocks) relieved by rest. A proportion of patients will progress to CLTI. However, progression rates to CLTI are not well-described in the current literature. CLTI is characterized by rest pain, tissue loss or gangrene[4] and is associated with a significant degree of morbidity and mortality, including limb loss in up to a third of patients.[5] Surgical revascularization (open or endovascular) is needed to restore perfusion to the limb; however, some CLTI patients are unsuited to revascularization and will require amputation procedures.[5,6]

Given that the majority of IC patients do not go on to develop CLTI,[7,8] current management strategies adopt a conservative approach, focusing on improving exercise tolerance, and reducing cardiovascular risk factors. Patients are given lipid lowering medications, antiplatelet therapy and counseled on lifestyle modification (e.g. smoking cessation) and provided with exercise-therapy.[9] However, it remains uncertain which factors predict progression of IC to CLTI in patients managed conservatively. Identifying the patients most at risk of progression to CLTI would aid clinicians in risk stratifying patients and targeting high-risk presentations where early intervention might mitigate the risk of adverse outcomes associated with CLTI.[10]

Previous attempts at collating literature informing IC progression include a meta-analysis of progression rate, acknowledging the limitation of significant study heterogeneity, with both invasively and conservatively managed patients included.[8] IC progression was found to be more aggressive than previously thought, with 21% of patients (12–29%) progressing to CLTI over 5 years and amputation rates at 5-year follow-up of 4–27%,[8] with the caveat that this analysis included patients that had surgical/endovascular intervention. Results for patients divided into invasive and conservative management groups are unavailable. Emergent evidence suggests unnecessary intervention in claudication may precipitate progression to CLTI.[11] The identification of predictors for progression of PAD has been addressed in previous reviews.[8,10] However, more studies addressing this topic have been published in recent years, and thus there is need for an up-to-date review of the literature, given recent adaptations in medical, exercised-based, and conservative management strategies. This review aims to synthesize evidence on progression rate and predictors of progression from conservatively managed IC to CLTI. The association of biomarkers and IC progression is not yet well-defined within the literature; relevant, select work is included in discussion outside of our primary synthesis.[12–14]

METHODS

A systematic review of the literature was carried out in line with the Cochrane Collaboration protocol[15] and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guideline.[16] Our study protocol was submitted to the International prospective register of systematic reviews (PROSPERO ID: CRD42023401259).

Inclusion and Exclusion Criteria

Studies of adult patients with IC receiving conservative treatment were included. Predictors of IC progression, as well as observed progression rate were included in synthesis. Studies where participants were not already diagnosed with IC at the outset were excluded. Studies including surgical/invasive management, where patients were followed-up postoperatively, were excluded, as this cohort diverges from the ''natural history'' of IC. Non-English language reports were excluded.

Studies with mixed participant populations (such as asymptomatic patients or patients managed invasively) where some participants underwent intervention were excluded. Conservative intervention was defined as any or a combination of conservative, medical, exercise-based, or expectant management. Prognostic analyses from trial data were considered for inclusion. Protocols, editorials, and conference abstracts were excluded.

The primary outcome (progression to CLTI) was defined as the development of a major adverse limb event, which included the development of rest pain or tissue loss, limb-related hospitalization, revascularization, and amputation. Secondary outcomes included progression of PAD, deterioration in claudication distance or a decrease in Ankle-brachial index (ABI) compared to baseline.

Search Strategy and Screening

The search strategy (terms included in full in supplementary material) set out in PROSPERO was actioned on August 1, 2023 for Scopus, World of Science, Medline, Embase, and CINAHL. Search terms were modified for format in line with each database's convention. To facilitate efficient screening, search results were uploaded to rayyan.ai,[17] which automatically removed duplicate reports. Duplicates were re-checked manually to ensure none were removed erroneously. Nonduplicated records were screened by title and abstract, independently, by 2 reviewers (ML and JF). Search results were evaluated for inclusion using the PICO (population, intervention, comparator, outcome) model. The authors subsequently screened the full texts of the included articles from initial screening. Common reasons for exclusion were non-PAD cohorts, endpoints other than progression such as major adverse cardiovascular events (MACE) and death, and surgical intervention for PAD. Disagreement on inclusion following full text screening was resolved by discussion with a third reviewer (AW).

Data extracted included lead author, study year, study design, sample size, participant demographic details, follow-up duration, predictors of IC progression, progression rate/time to CLTI, quantitative measure of progression rate, and outcome measures. Outcome measures included were heterogenous, including odds ratio (OR), relative risk (RR), hazard ratio (HR), and β co-efficient. The risk of bias in nonrandomized studies of interventions tool (ROBINS-I)[18] was utilized to assess the quality of the included studies. Assessment was performed by 2 reviewers working independently (JF and ML). Disagreement was addressed through discussion until resolution was reached.

Meta-analysis of proportions was undertaken, acknowledging the limitation of high heterogeneity. Statistical analyses were conducted using R (version 4.3.2; GNU General Public Licence Version 3), RStudio (version 2023.12.1 + 402; RStudio Inc., GNU Affero General Public License Version 3). Event frequencies (CLTI) were pooled and displayed as event rates in meta-analysis of proportions. Confidence intervals (CIs) were reported at 95%. The I^2 test was utilized to assess statistical heterogeneity in meta-regression. A random-effects model was pursued given the varying real-world treatment of PAD and displayed as a progression percentage at maximal follow-up (10 years).

RESULTS

A total of 8,930 studies were identified from Scopus (n = 2,725), Web of Science (n = 1,247), Medline (n = 3,391), Embase (n = 1,160), and CINAHL (n = 407). The rayyan.ai screening program removed 2,526 duplicate records, leaving 6,404 studies for title and abstract screening. Following title and abstract screening, 117 full-text articles were considered, of which 9 met the inclusion criteria. 8 studies were included unanimously, with 1 further study included after author discussion to resolve conflicts in screening.[19] The screening process is set out in Figure 1 as a PRISMA flowsheet.

Study Characteristics

Population characteristics, follow-up period and reporting of outcomes varied significantly between included studies (Table I). Study dates spanned 1984 and 2023. A total of 4,115 patients were included, overall, with populations varying from 91 to 1,244. Follow-up ranged between 2 and 10 years. Representation of women ranged from 0 to 30.1% of participants. Neither the retrospective cohort study by Aquino et al.[21] nor Cronenwett et al.[23] included any female participants. All studies quantified PAD progression using ABI deterioration, with the addition of different modalities (Toe-brachial index and Duplex scans) in 2 cases and symptom-severity questionnaires in 2 further cases. Five studies were conducted in the USA,[20–23,26] with 1 study from the UK,[25] Sweden,[19] Japan,[24] and Malta, respectively. Seven were retrospective cohort studies,[19–23,25,26] and 2 prospective cohort studies.[24,27] The most common primary outcome reported was PAD progression, in all 9 studies, with varying definitions of progression by ABI cutoffs.

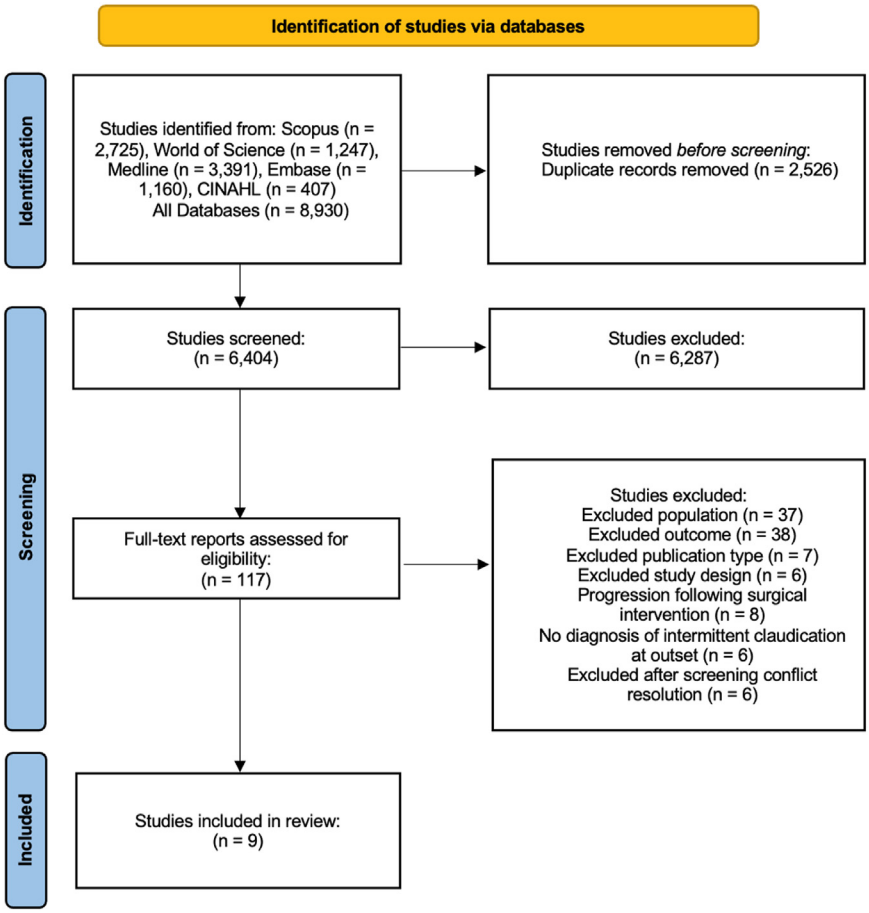

Fig. 1. PRISMA flow diagram of search methodology.

Rates of IC progression to CLTI were reported by clinical outcome (rest pain and tissue loss) in 7 studies[19,21,23–27] (Table II). Predictors for progression were reported in all 9 studies (Table I). Statistical reporting of outcomes was heterogenous, displayed in Table I, precluding meta-analysis.

Study Quality

The included studies were formally assessed for risk of bias using the ROBINS-I tool for nonrandomized studies (Fig. 2). Due to the nonrandomized nature of the included studies, there was an inherent risk of bias (particularly selection bias) because of the observational study designs. Five of the 9 included studies were at moderate risk of bias. Four studies were at serious risk of bias.[19,22,23,26]

Predictors of Progression

8 studies, including 4,024 patients, described predictors for progression to CLTI. One further study including 91 patients, found no indicators of statistical significance[23] (Table I). Diabetes was the most reported predictor, with significant hazard or risk ratios in 4 of the included studies.[21,22,24,27] In multivariate analysis in the 2 included prospective studies, diabetes was associated with a significant HR (5.730 (95% CI 1.102−29.79) $P = 0.038$)[24] and high HbA1c represented an increased OR (1.35 (95% CI 1.03, 1.78) $P = 0.03$).[27] One study found, in multivariate analysis, that the relative risk of ischemic rest pain (RR 1.735 (1.19, 2.53 95% CI) $P = 0.004$) and ischemic ulcers (RR 2.932 (2.12, 4.06) $P = 0.001$) to increase significantly in diabetic patients requiring oral medication.[21]

One study divided PAD into large-vessel and small-vessel disease and concluded that risk factors for each subset differ.[20] In multivariate analysis diabetes represented a significant risk factor for the small-vessel subgroup, only (HR 2.65 (1.03−6.77 95% CI) $P = 0.042$). Smoking represented the most significant predictor of progression in the large-vessel subgroup (HR 3.20 (1.51−6.80 95% CI) $P = 0.003$).[20] Lipid profile was also shown be

Table I. Summary of characteristics for predictors of peripheral arterial disease progression, including quantitative measure, and outcome measure of included studies

Study	Study design	Sample size	Sex M/F (%)	Follow-up (years)	Predictors of PAD progression	Quantitative measure	Outcome measure
Aboyans et al. 2006[20]	Retrospective cohort study	403	87.1/12.9	10	Active smoking HR 3.20 (95% CI 1.51, 6.80 $P = 0.003$). High ratio of low-density lipoprotein HR 1.35 (95% CI 1.05,1.73 $P = 0.019$)	ABI, TBI, Duplex, Symptom questionnaire	HR
Aquino et al. 2001[21]	Retrospective cohort study	1244	100/0	10	Diabetes RR 1.735 (95% CI 1.19, 2.53 $P = 0.004$) and ABI RR 0.788 (95% CI 0.72, 0.86 $P = 0.001$) for ischemic rest pain. Diabetes RR 2.932 (95% CI 2.12, 4.06 $P = 0.001$) and ABI RR 0.833 (95% CI 0.77, 0.90 $P = 0.001$) for ischemic ulcers.	ABI	RR
Bird et al. 1999[22]	Retrospective cohort study	508	87/13	5	Age (years) β −0.029 (95% CI −0.049, −0.009 $P = 0.004$). Diabetes β −0.423 (95% CI −0.805, −0.042 $P = 0.029$). Rose claudication β −1.004 (95% CI −1.503, −0.504 $P = 0.001$). Contra-lateral leg LV-PAD β −0.844 (95% CI −1.301,−0.388 $P = 0.001$)	ABI, San Diego Claudication Questionnaire	β co-efficient
Cronenwett et al. 1984[23]	Retrospective cohort study	91	100/0	2	None of statistical significance	ABI	RR
Jonason and Ringqvist 1986[19]	Retrospective cohort study	151	29/71	5	Initial ABI, smoking, duration of claudication, location of stenoses	ABI	Regression co-efficient
Kumakura et al. 2017[24]	Prospective observational cohort study	1107	70.6/29.4	5	Diabetes HR 5.730 (95% CI 1.102−29.79 $P = 0.038$). Hemodialysis HR 19.56 (95% CI 1.724−222.0 $P = 0.016$).	ABI	HR
Mizzi et al. 2022[10]	Prospective observational cohort study	150	69.7/30.1	2	HbA1c OR 1.35 (95% CI 1.03,1.78 $P = 0.03$). TBPI <0.39 OR 3.60 (95% CI 1.21, 10.71 $P = 0.02$). ABPI <0.5 OR 3.89 (95% CI 0.97, 15.72 $P = 0.046$)	ABI, TBI, Duplex, Symptom questionnaire	OR
Ravindhran et al. 2023[25]	Retrospective cohort study	266	68.8/31.2	6	Hemoglobin, self-reported claudication distance, ABPI, IHD	ABI	Not reported
Rosenbloom et al. 1988[26]	Retrospective cohort study	195	83/17	8	Lowest ankle-brachial index, greatest percentage decrease in ankle-brachial index after exercise ($P = 0.01$)	ABI	Not reported

Table II. Summary of study reported rates of progression from intermittent claudication to chronic limb-threatening ischemia, including outcome definition and point of follow-up

Study	Follow-up point (years)	Rate of progression to CLTI	CLTI	*n*	Outcome definition
Aquino et al. 2001[21]	10	26.5%	330	1244	Ischemic rest pain (30%) or ulceration (23%)
Cronenwett et al. 1984[23]	2	12.1%	11	91	Surgical intervention for rest pain (6.6%) or tissue loss (5.5%)
Jonason and Ringqvist 1986[19]	5	6%	9	151	Surgical intervention for rest pain
Kumakura et al. 2017[24]	5	1.1%	15	1107	Clinical critical limb ischemia
Mizzi et al. 2022[10]	2	23.3%	35	150	Ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease
Ravindhran et al. 2023[25]	6	36.7%	36	98	Ischemic rest pain lasting for 2 or more weeks, nonhealing wounds, or gangrene that was attributable to objectively proven arterial occlusive disease.
Rosenbloom et al. 1988[26]	8	4.8%	29	600	Rest pain or tissue loss

associated with progression, with ratio of total cholesterol to HDL cholesterol (per unit) representing a significant predictor for the small-vessel subgroup in multivariate analysis (HR 1.35 (1.05–1.73 95% CI) $P = 0.019$).[20]

Lower baseline ABI was reported as a predictor,[21,25,27] potentially representing patients with more severe PAD at study start. Increasing age was reported as a significant predictor of progression in 2 studies,[21,22] and major adverse cardiovascular and limb events (MACLE) during follow-up were more commonly reported in older patients.[24] Low hemoglobin level, presence of ischemic heart disease and self-reported claudication distance were reported as predictors in the most recent study included.[25] The most significant HR reported for any predictor variable following multivariate analysis among the studies was for hemodialysis (HR 19.56 (1.724–222.0 95% CI) $P = 0.016$),[24] but this was not replicated elsewhere. Only 15 patients out of the 1,107 included in the study progressed to CLTI, of which 13 were diabetics and 11 required hemodialysis.

Progression Rate

Seven studies including 3,204 patients used established clinical endpoints for CLTI[19,23,24,26,27] (Table II), defined as the syndrome of ischemic rest pain or ischemic ulcers. In 1 case, the surrogate outcome of need for invasive management for CLTI is used (revascularization or amputation).[19] The 2 included prospective studies of 1,257 patients,[24,27] report notably different progression rates; Kumakara et al. reported 1.1% of patients progressing to CLTI per 5 years and Mizzi et al. reported 23.3% of participants progressing to CLTI over 2 years. Two similar studies on 242 IC patients from the 1980's reported that 12.1%[23] and 6%[19] of patients required invasive management for CLTI over 2 and 5 years, respectively. One study divided patients into individual limb events, with 4.8% of limbs progressing to CLTI within 8 years of follow-up.[26] One study cohort, including 2 cohorts of patients who did/did not complete supervised exercise therapy, was included in composite (36.7%) as both arms were conservative.[25]; results were derived from displayed bar chart format as patient % experiencing cardiovascular events.

Three studies, on 2,155 patients, reported rates by establishing ABI cutoffs for ''significant'' deterioration.[20–22] In 1 study, this was defined as a decrease of >0.3 on ABI, with 11% of patients affected at 4.6 years follow-up.[20] Over the same follow-up interval, another study reported a mean total ABI

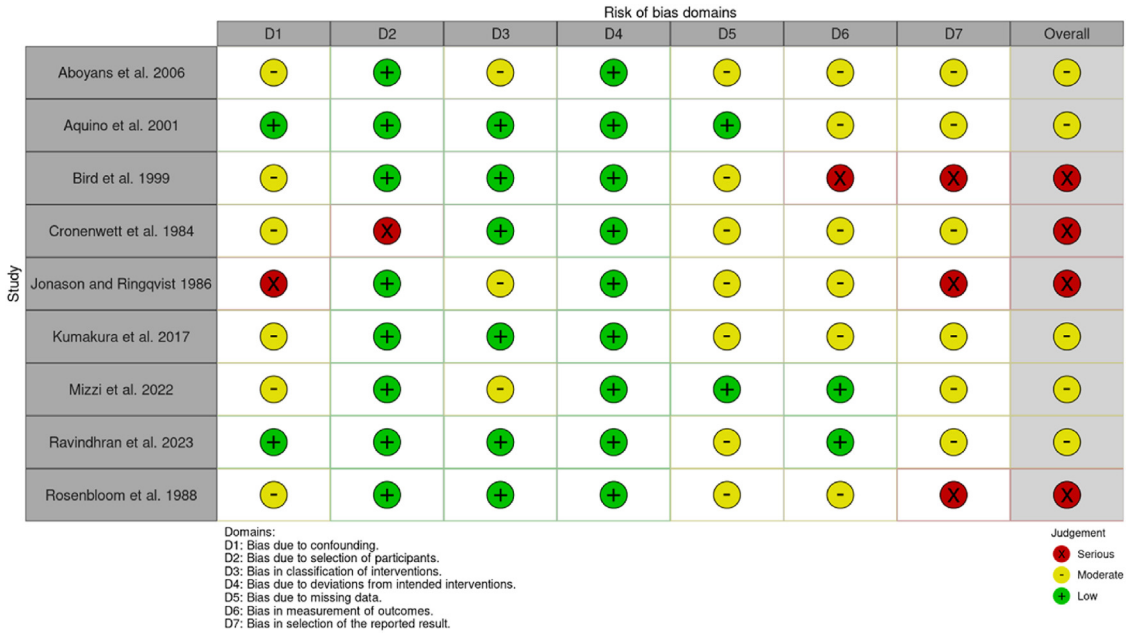

Fig. 2. The risk of bias in nonrandomized studies of interventions tool (ROBINS-I) assessment of included studies.

decrease of 0.02.[22] The third such study reported a higher rate of annual decrease as 0.014.[21]

Medical Regimens

Medical management is reported in five of the included studies.[20,21,23,24,27] Antihypertensives, lipid-lowering medication and oral hypoglycemic medications are collected. Calcium channel blockers and antiplatelet/anticoagulants are reported as significant predictors of ''significant progression'' in ABI, but not to CLTI.[27] Statin therapy prescription increases over time in 1 prospective study[24] and a reduction in MACE, but not CLTI, is reported. One study includes compliance with smoking cessation within population characteristics.[25] No data are available on adherence to medications.

Biomarkers

Three studies were identified that addressed the association between laboratory biomarkers and progression of IC, and therefore were included in a secondary synthesis. No studies addressed clinical outcomes for CLTI. Tzoulaki et al. published 2 manuscripts[12,13] on biomarkers and in multivariate analysis in a cohort of 1,592 patients, a significant mean ABI change, adjusted for baseline ABI and risk factors, was associated with CRP (−0.018 (−0.034, −0.004 95% CI)), IL-6 (−0.019 (−0.031, −0.007 95% CI)) and ICAM-1 (−0.014 (−0.024, −0.003 95% CI)). Only 1L-6 was found to be significantly associated with ABI decrease in their second study which replicated their methodology[13] (IL-6 (−0.018−0.034, −0.002 95% CI $P \leq 0.05$)). Schahab and colleagues found that levels of myeloperoxidase were 3.68 times higher in patients who went on to have MACE ($P < 0.0001$).[14]

DISCUSSION

Our systematic review highlights the paucity of knowledge on the progression of conservatively managed IC to CLTI. This is driven mainly by a low to moderate quality of existing studies and a heterogeneity of methodologies inhibiting quantitative analyses, as supported by previous reviews on this topic.[7,8,10] Our stringent search strategy of including only conservatively managed IC, necessitates the exclusion of previous literature examining long-term outcomes of invasively managed IC. The majority of patients with IC will be managed conservatively, and thus inclusion as the primary research question is warranted, with the aim of reducing potentially confounding factors and differences in pathogenesis introduced by invasive intervention.

The inadequate design and reporting identified in the examined studies may have introduced bias and undermined the robustness of the data. Common sources of bias included selection bias due to inadequate allocation concealment, insufficient methodological detail, incomplete information regarding

attrition or nonconsent, and survival selection bias. Despite ongoing research efforts in this population, literature often prioritises mortality and cardiovascular risk over limb involvement in IC. Consequently, there is limited understanding of PAD prognosis and progression rates in IC patients, with no established criteria enabling clinicians to predict individual outcomes.

Studies on rate of progression to CLTI yielded highly varied data, ranging from 1.1% to 36.7% over 2-10 years of follow-up (average 5.4 years), reflecting differences in methodologies. Acknowledging the expected heterogeneity of the data, meta-analysis of progression to CLTI was undertaken in an attempt to improve the quality of evidence for the consensus of expert opinion that progression rates are in the region of 1% per year, and to reconcile the variance of follow-up duration. The pooled rate of 15.26% at maximal (10-year) follow-up from these studies is nonsignificant and clearly underscores the need for future high-quality research.

A systematic review, examining PAD progression in symptomatic patients, highlighted that while the TransAtlantic Inter-Society Consensus for the Management of PAD cites a 1−3% amputation rate after 5 years for patients with IC, a more aggressive PAD progression may result in a significantly higher amputation rate. ABI cutoffs are utilized in all included studies for PAD progression. However, within the context of the clinical syndrome of CLTI, ABI represents a surrogate endpoint which requires clinical correlation. Inter-provider variability, minimal changes and nondiagnostic readings (e.g. from noncompressible vessels) further complicate the application of ABI as a standalone modality. This notwithstanding, noninvasive tools, such as ABI, hold potential to monitor patient-specific PAD progression within the context of symptom burden.

Increased understanding of the importance of best medical therapy over the 40-year span of the included studies is reflected in the inclusion of medications as predictors for progression in 2 more recent studies.[24,27] Consequently, raising the possibility of temporal bias in the reported increased prescription rate of statin therapy.[24] More comprehensive medical regimens could reasonably be expected to decrease progression rates. However, the 2 most contemporary studies report rates at the higher end of the range for progression to CLTI.[25,27] None of the included studies report adherence rates to prescribed medical regimens, limiting comparison of real-world versus pharmaceutical trial data. Changing thresholds for invasive intervention for IC over time necessitates caution in interpreting these findings, and for this reason we opted to exclude invasively managed/mixed cohorts, acknowledging the limitation of reducing the available literature, in an effort to minimise confounding and examine the ''natural history'' of PAD.

The role of demographics in affecting outcomes of IC may be overlooked in current literature. An important finding from our review was the underrepresentation of women among studies. Women constituted 22.7% of study populations on average. The recently published 2024 European Society for Vascular Surgery guidelines on management of asymptomatic PAD and IC highlight the need for research equity. A higher enrollment of women in clinical trials is necessary to reach the appropriate statistical power and map sex-specific differences in PAD risk factors, presentation, and consequences.[28] Women may decline faster in terms of functional ability once PAD is established[29] and men have historically been more frequently selected for revascularization,[30,31] which may represent inherent biases in management strategies for IC. This represents an important inclusion for future research.

Findings from studies reporting on the predictors of progression reflect the significant role of organ dysfunction (namely diabetes and renal failure), which is widely accepted, and therefore fails to inform more personalized treatment strategies. With evolving health-care strategies aiming for more precision and personalization of care, this review highlights the need for omics-based studies such as biomarkers of disease progression and big-data. Currently, no big-data studies exist on IC despite it being the most common manifestation of PAD and a debilitating condition affecting quality of life. Furthermore, studies on biomarkers of IC deterioration are infrequent and their translational capability to clinical management is yet to be confirmed. Inadequate monitoring of IC patients and delayed invasive intervention may result in more extensive PAD burden, higher-risk interventions, and poorer long-term outcomes.

CONCLUSION

Diabetes, renal failure, and smoking are widely established, significant, predictors of PAD progression. Estimates of progression rates using meta-analysis are inconclusive, due to poor quality evidence and data heterogeneity. Male participants were more represented than female participants, overall. Current knowledge limits the development

of robust predictive tools for identifying deterioration risk in individuals with IC. Consideration of larger contemporary datasets and a detailed focus on demographics, comorbidities, patient reported outcomes and biomarkers, may aid accurate prediction and improve outcomes of conservatively managed IC.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Joseph Louis Jervis Froud: Writing — review & editing, Writing — original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Madeleine Landin:** Writing — review & editing, Writing — original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Arsalan Wafi:** Writing — review & editing, Writing — original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sarah White:** Writing — review & editing, Resources, Formal analysis, Data curation, Conceptualization. **Lindsay Bearne:** Writing — review & editing, Validation, Supervision, Methodology, Data curation, Conceptualization. **Ashish Patel:** Writing — review & editing, Supervision, Conceptualization. **Bijan Modarai:** Writing — review & editing, Writing — original draft, Supervision, Conceptualization.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.avsg.2024.12.009.

REFERENCES

1. Lin J, Chen Y, Jiang N, et al. Burden of peripheral artery disease and its attributable risk factors in 204 countries and territories from 1990 to 2019. Front Cardiovasc Med 2022;9:868370.
2. Song P, Rudan D, Zhu Y, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Health 2019;7:e1020—30.
3. Sigvant B, Wiberg-Hedman K, Bergqvist D, et al. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. J Vasc Surg 2007;45:1185—91.
4. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. Eur J Vasc Endovasc Surg 2019;58:S1—109.e33.
5. Farber A, Menard MT, Conte MS, et al. Surgery or endovascular therapy for chronic limb-threatening ischemia. N Engl J Med 2022;387:2305—16.
6. Kim TI, Mena C, Sumpio BE. The role of lower extremity amputation in chronic limb-threatening ischemia. Int J Angiol 2020;29:149—55.
7. McDermott MM, McCarthy W. Intermittent claudication. The natural history. Surg Clin North Am 1995;75:581—91.
8. Sigvant B, Lundin F, Wahlberg E. The risk of disease progression in peripheral arterial disease is higher than expected: a meta-analysis of mortality and disease progression in peripheral arterial disease. Eur J Vasc Endovasc Surg 2016;51:395—403.
9. Peripheral arterial disease: diagnosis and management: NICE guideline [CG147]. 2020. Available at: https://www.nice.org.uk/guidance/cg147/chapter/recommendations. Accessed August 21, 2024.
10. Mizzi A, Cassar K, Bowen C, et al. The progression rate of peripheral arterial disease in patients with intermittent claudication: a systematic review. J Foot Ankle Res 2019;12:40.
11. Kim TI, Kiwan G, Mohamedali A, et al. Multiple reinterventions for claudication are associated with progression to chronic limb-threatening ischemia. Ann Vasc Surg 2021;72:166—74.
12. Tzoulaki I, Murray GD, Lee AJ, et al. C-reactive protein, interleukin-6, and soluble adhesion molecules as predictors of progressive peripheral atherosclerosis in the general population: Edinburgh Artery Study. Circulation 2005;112:976—83.
13. Tzoulaki I, Murray GD, Price JF, et al. Hemostatic factors, inflammatory markers, and progressive peripheral atherosclerosis: the Edinburgh Artery Study. Am J Epidemiol 2006;163:334—41.
14. Schahab N, Mansuroglu S, Schaefer C, et al. Prognostic value of myeloperoxidase in patients with peripheral artery disease. Vascular 2021;29:363—71.
15. Higgins JPT, Thomas J, Chandler J, et al. eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Chichester (UK): Cochrane, 2024. Available at: www.training.cochrane.org/handbook. Accessed December 29, 2024.
16. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol 2021;134:178—89.
17. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016;5:210.
18. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
19. Jonason T, Ringqvist I. Changes in peripheral blood pressures after five years of follow-up in non-operated patients with intermittent claudication. Acta Med Scand 1986;220:127—32.
20. Aboyans V, Criqui MH, Denenberg JO, et al. Risk factors for progression of peripheral arterial disease in large and small vessels. Circulation 2006;113:2623—9.
21. Aquino R, Johnnides C, Makaroun M, et al. Natural history of claudication: long-term serial follow-up study of 1244 claudicants. J Vasc Surg 2001;34:962—70.
22. Bird CE, Criqui MH, Fronek A, et al. Quantitative and qualitative progression of peripheral arterial disease by noninvasive testing. Vasc Med 1999;4:15—21.

23. Cronenwett JL, Warner KG, Zelenock GB, et al. Intermittent claudication. Current results of nonoperative management. Arch Surg 1984;119:430–6.
24. Kumakura H, Kanai H, Hojo Y, et al. Long-term survival and fate of the leg in de novo intermittent claudication. Eur Heart J Qual Care Clin Outcomes 2017;3:208–15.
25. Ravindhran B, Lim AJM, Kurian T, et al. Supervised exercise therapy for intermittent claudication: a propensity score matched analysis of retrospective data on long term cardiovascular outcomes. Eur J Vasc Endovasc Surg 2023;67:480–8.
26. Rosenbloom MS, Flanigan DP, Schuler JJ, et al. Risk factors affecting the natural history of intermittent claudication. Arch Surg 1988;123:867–70.
27. Mizzi A, Cassar K, Bowen CJ, et al. The impact of diabetes in intermittent claudication: a prospective cohort study. Int J Low Extrem Wounds 2022:15347346221142189. https://doi.org/10.1177/15347346221142189.
28. Nordanstig J, Behrendt CA, Baumgartner I, et al. Editor's choice – European society for vascular surgery (ESVS) 2024 clinical practice guidelines on the management of asymptomatic lower limb peripheral arterial disease and intermittent claudication. Eur J Vasc Endovasc Surg 2024;67:9–96.
29. Singh N, Liu K, Tian L, et al. Leg strength predicts mortality in men but not in women with peripheral arterial disease. J Vasc Surg 2010;52:624–31.
30. Behrendt CA, Sigvant B, Kuchenbecker J, et al. Editor's choice - international variations and sex disparities in the treatment of peripheral arterial occlusive disease: a report from vascunet and the international consortium of vascular registries. Eur J Vasc Endovasc Surg 2020;60:873–80.
31. Sigvant B, Kragsterman B, Falkenberg M, et al. Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization. J Vasc Surg 2016;64:1009–1017.e3.