

# Population-Based Study of Incidence, Risk Factors, Outcome, and Prognosis of Ischemic Peripheral Arterial Events

## Implications for Prevention

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**Background**—There are few published data on the incidence and long-term outcomes of critical limb ischemia, acute limb ischemia, or acute visceral ischemia with which to inform health service planning, to monitor prevention, and to enable risk prediction.

**Methods and Results**—In a prospective population-based study (Oxfordshire, UK; 2002–2012), we determined the incidence and outcome of all acute peripheral arterial events in a population of 92 728. Risk factors were assessed by comparison with the underlying population. A total of 510 acute events occurred in 386 patients requiring 803 interventions. Two hundred twenty-one patients (59.3%) were  $\geq 75$  years of age, and 98 (26.3%) were  $\geq 85$  years old. Two hundred thirty patients (62.3%) were independent before the event, but 270 (73.4%) were dead or dependent at the 6-month follow-up, and 328 (88.9%) were dead or dependent at 5 years. The 30-day survival was lowest for patients with acute visceral ischemia (28.2%) compared with acute limb ischemia (75.3%) and critical limb ischemia (92.6%;  $P < 0.001$ ). Risk factors (all  $P < 0.001$ ) were hypertension (age- and sex-adjusted risk ratio, 2.75; 95% confidence interval, 1.95–3.90), smoking (adjusted risk ratio, 2.14; 95% confidence interval, 1.37–3.34), and diabetes mellitus (adjusted risk ratio, 3.01; 95% confidence interval, 1.69–5.35), particularly for critical limb ischemia (adjusted risk ratio, 5.96; 95% confidence interval, 3.15–11.26). Two hundred eighty-eight patients (77.2%) had known previous cardiovascular disease, and 361 (96.8%) had vascular risk factors, but only 203 (54.4%) were on an antiplatelet and only 166 (44.5%) were on a statin. Although 260 patients (69.7%) were taking antihypertensives, 42.9% of all blood pressures recorded during the 5 years before the event were  $> 140/90$  mmHg. Of 88 patients (23.6%) with incident cardioembolic events, 62 had known atrial fibrillation (diagnosed before the event), of whom only 14.5% were anticoagulated despite 82.3% having a CHA<sub>2</sub>DS<sub>2</sub>VASC score  $\geq 2$  without contraindications.

**Conclusions**—The clinical burden of peripheral arterial events is substantial. Although the vast majority of patients have known vascular disease in other territories and multiple treatable risk factors, premorbid control is poor. (*Circulation*. 2015;132:1805–1815. DOI: 10.1161/CIRCULATIONAHA.115.016424.)

**Key Words:** epidemiology ■ patient outcome assessment ■ peripheral vascular diseases ■ risk factors

Vascular disease is the leading cause of death and disability worldwide.<sup>1–3</sup> Peripheral arterial disease (PAD) has a poor prognosis<sup>4,5</sup> but has been neglected in terms of both research and early detection and primary prevention.<sup>6,7</sup> Previous epidemiological studies have concentrated on the prevalence of stable PAD (intermittent claudication or subclinical disease),<sup>8–19</sup> and studies of critical limb ischemia (CLI) have been limited to selected cohorts<sup>20–22</sup> or based on hospital coding data of interventions or amputation outcome,<sup>23–27</sup> cross-sectional surveys,<sup>28</sup> or randomized,

interventional trials with various inclusion/exclusion criteria.<sup>29–31</sup> Epidemiological studies of acute limb ischemia (ALI) and acute visceral ischemia (AVI) are lacking, with current estimates of incidence and outcome being based on hospital registries,<sup>31,32</sup> interventional trials,<sup>33,34</sup> and autopsy studies.<sup>35,36</sup> The comparative epidemiology and relative clinical burdens of all acute PAD syndromes have not been determined in the same population.

### Clinical Perspective on p 1815

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PAD events also tend not to be reported as outcomes in cardiovascular disease prevention trials,<sup>37</sup> or reporting is limited.<sup>38–40</sup> Of the 91 largest blood pressure (BP)–lowering treatment trials, only 11 included PAD as a discrete outcome (Table I in the online-only Data Supplement). However, several strategies for primary and secondary prevention of PAD events in at-risk groups are evidence based, including antiplatelet, statin, and antihypertensive therapy; smoking cessation; and supervised exercise program.<sup>41–43</sup> In addition, anticoagulation is highly effective in the prevention of atrial fibrillation–related peripheral embolic events.<sup>44</sup> Population-based data on the incidence, outcome, risk factors, and current levels of preventive treatment are needed to improve the prevention of PAD events, to enable risk stratification, to inform patients about risks and prognosis, to facilitate health service planning, and to direct future research.

We prospectively ascertained all acute PAD events in patients presenting to medical attention, regardless of age, in a population of 92 728 in Oxfordshire, UK, during 2002 to 2012 (Oxford Vascular Study [OXVASC])<sup>45</sup> and determined the incidence, outcome, risk factors, premorbid preventive treatment, and long-term prognosis.

## Methods

The OXVASC study population comprises all individuals (10-year average, 92 728), regardless of age, registered with ≈100 family physicians in 9 primary care practices in Oxfordshire, UK.<sup>45,46</sup> In the United Kingdom, the vast majority of individuals register for primary health care, which provides a lifelong record of all medical consultations and details of medications, BP measurements, and investigations. All participating practices held accurate age/sex patient registers and allowed regular searches of their computerized diagnostic coding systems. All practices refer patients to only 1 major secondary care center.

The OXVASC study population is 94% white, 3.1% Asian, 1.5% Chinese, and 1.4% Afro-Caribbean.<sup>46</sup> On the basis of the Index of Multiple Deprivation,<sup>47</sup> the electoral wards covering our population are less deprived than the rest of England (mean Index of Multiple Deprivation score, 8.69 versus 16.98; *t* test,  $P < 0.001$ ) but have a broad range of deprivation, with 22% of wards ranking in the lower third nationally. OXVASC was approved by our local research ethics committee.

Case ascertainment was by prospective daily searches for acute events in hospital (hot pursuit), supplemented by searches of discharge and primary care diagnostic coding data (cold pursuit). Full details are given in Methods in the online-only Data Supplement. A study clinician assessed patients acutely in hospital (or at home if ascertained late). Informed consent was sought when possible, or assent was obtained from a relative. Standardized clinical history and examination were recorded, with details of medication, history, and all investigations and interventions occurring subsequent to the event. All diagnoses were reviewed by a vascular surgeon. If a patient died before assessment or was identified only by cold pursuit, eyewitness accounts were obtained and relevant records reviewed. If death occurred outside the hospital or before investigation, autopsy results were reviewed. Clinical details were sought from primary care physicians or other clinicians on all deaths resulting from a possible vascular cause.

Cardiovascular examination included assessment of the peripheral pulses, the Buerger test, and absolute ankle pressure and ankle-brachial pressure index recordings. For patients with incompressible ankle signals, pressures were estimated by pole test. For patients in whom clinical vascular assessment was not possible by the study clinician before urgent revascularization or death, the assessments made by the admitting clinician were used.

All survivors were followed up by a research nurse at 6 months and subsequently by their family doctor, with recurrent events also

identified by the ongoing study ascertainment. If a vascular event was suspected, the patient was reassessed by a study physician. Premorbid disability and disability on follow-up were assessed with the modified Rankin Scale.<sup>48</sup>

To assess key vascular risk factors and levels of premorbid control, we extracted individual data from primary healthcare records for all cases and compared these data with group average data for the underlying unaffected population. The accuracy of these data was tested in cases through direct questioning of patients and relatives and review of records. All premorbid BP measurements were extracted from primary care records of incident cases. BP was generally taken with automated sphygmomanometers by a primary care physician or practice nurse. A cutoff value of 140/90 mmHg was used to define hypertension.

All patients with acute PAD events from April 1, 2002, to March 31, 2012, from the study registered practices were included. Events were defined as any acute arterial event that affected a limb or an organ other than the heart or the brain/eye and led to hospital assessment/admission or caused death in the community. The likely cause (atherosclerotic/in situ thrombosis, embolic, diabetic microvascular disease, iatrogenic, graft/stent thrombosis, or multifactorial) was determined by a vascular surgeon taking into account clinical findings and subsequent investigations.

ALI was defined as an arterial event of sudden onset and <2 weeks in duration resulting in symptomatic limb ischemia.<sup>5</sup> Degree of limb ischemia was graded by the Rutherford classification of severity as viable, threatened-marginal, threatened-immediate, or irreversible.<sup>49</sup> AVI was defined as acute arterial events of sudden onset and <2 weeks in duration resulting in symptomatic visceral ischemia (including bowel, liver, spleen, and renal end-organ compromise). Severity of ischemia was graded by the presence or absence of lactic acidosis on admission. CLI has several overlapping diagnostic classification systems.<sup>5,41,49,50</sup> The original Fontaine and Rutherford classification systems describe symptoms persisting for >2 weeks and delineate intermittent claudication from ischemic rest pain and ulceration. More recent defining criteria from the European Union,<sup>50</sup> Society of Vascular Surgery (United States),<sup>49</sup> and Trans-Atlantic Inter-Society Consensus (TASC) steering committee<sup>5</sup> require both clinical and objective assessment of absolute ankle pressure, ankle-brachial pressure index, or toe pressure (eg, plethysmographic or laser Doppler techniques). As pointed out in the latest TASC consensus statement,<sup>5</sup> strict objective criteria exclude some patients with imminently threatened ischemic limbs in need of urgent revascularization. We therefore included all patients whose symptoms had been present for >2 weeks with ischemic rest pain or tissue loss of sufficient severity to warrant urgent hospital admission and thought to be secondary to large- or small-vessel arterial disease. Objective measurements, although performed, were not required for inclusion. Incidence was compared on the basis of all current diagnostic criteria.

## Analysis

Event rates were defined as the total number of PAD events that led to separate clinical presentations during the study period. Individual patients could have multiple separate events in the same arterial territory. All events were categorized as first-ever incident or recurrent and specific to territory. An incident event implied the first-ever event of that type that a patient experienced in a given vascular territory. A patient could theoretically have 1 incident event of each type (AVI, CLI, and ALI). However, second events of the same type were always classified as recurrent, even if affecting a different limb.

Patients who had an event while temporarily away from Oxfordshire were assessed on their return and included in the analysis, but visitors to Oxfordshire who were not registered with one of the study practices were excluded. The underlying study population was based on the mean of the 10 midyear population age/sex structures. Age-, sex-, and risk factor–specific rates (per 100 000 population per year) were calculated for all incident events of each type. Analyses were done with SPSS (version 20.0; SPSS Inc, Chicago, IL). Numerical data were expressed as means (standard deviations) or proportions as appropriate. Group differences in continuous

parametric variables (eg, age) were examined with the Student *t* test or 1-way ANOVA as appropriate. Group differences in categorical variables were examined with the Fisher exact test or  $\chi^2$  test as appropriate. Risk ratios were adjusted for age and sex and corrected for overdispersion. Odds ratios were calculated by univariable and multivariable binary logistic regression analyses. In multivariable analysis, odds ratios were adjusted for all other risk predictors that were assessed. Outcome was reported in terms of functional status, amputation, amputation-free survival, and overall survival by Kaplan-Meier analysis. Values of  $P < 0.05$  were considered statistically significant.

## Results

A total of 510 acute PAD events occurred in 386 patients requiring 803 interventions. Of 373 incident events, 202 were incident CLI events (22 per 100 000 per year; 95% confidence interval [CI], 19–25; median age, 75.2 years; 54.0% male), 93 were incident ALI events (10 per 100 000 per year; 95% CI, 8–12; age, 76.3 years; 52.7% male), and 78 were incident AVI events (8 per 100 000 per year; 95% CI, 7–11; age, 79.8 years; 35.9% male; Tables II and III in the online-only Data Supplement). Event incidence and distribution did not vary significantly across the practices over the 12-year period.

Twenty-two patients had incident events of differing types (3 had an incident CLI event during follow-up after an incident ALI event, 12 had an ALI event after a previous CLI event, and 7 had an AVI event after a CLI event.) The remaining events were episodes of the same type as the first event and thus were classified as recurrent (many were CLI events in the contralateral lower limb). Lower-limb ischemia was significantly more common than upper-limb ischemia (78:15 for ALI and 202:0 for CLI). Of 373 patients, 94 (25.2%) underwent emergency intervention within 48 hours, 14 (18.1%) of whom had multiple interventions (Table IV in the online-only Data Supplement).

Table 1 shows the demographics, risk factors, and causes of all incident events by type and sex. Mean age at event was similar for both ALI and CLI at 76.3 years (SD, 11.9 years) and 75.2 years (SD, 10.9 years), respectively, but higher for AVI events at 79.8 years (SD, 14.1 years;  $P = 0.02$ ). Age at event was significantly higher for women than for men for all types of event (79.3 years [SD, 10.8 years] versus 73.6 years [12.5 years];  $P < 0.001$ ; Table 1). Incidence rates for all event types increased steeply with age, with 221 events (59.3%) occurring at  $\geq 75$  years of age and 98 (26.3%) at  $\geq 85$  years of age (Figure 1 and Table II in the online-only Data Supplement).

For CLI, the Society of Vascular Surgery consensus criteria were the strictest and resulted in the lowest age-specific incidence (Figure 2), particularly in the older age groups, whereas the 2007 Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) clinical criteria are similar to the OXVASC inclusion criteria and thus resulted in similar incidence rates. Routine hospital episode and death coding data missed 192 of 373 incident events (51.5%; Figure 3) and 165 of 346 events (47.7%) apparently identified by routine coding were not acute PAD events (They were either elective admissions for stable disease such as intermittent claudication or incorrectly coded admissions for sepsis or venous disease).

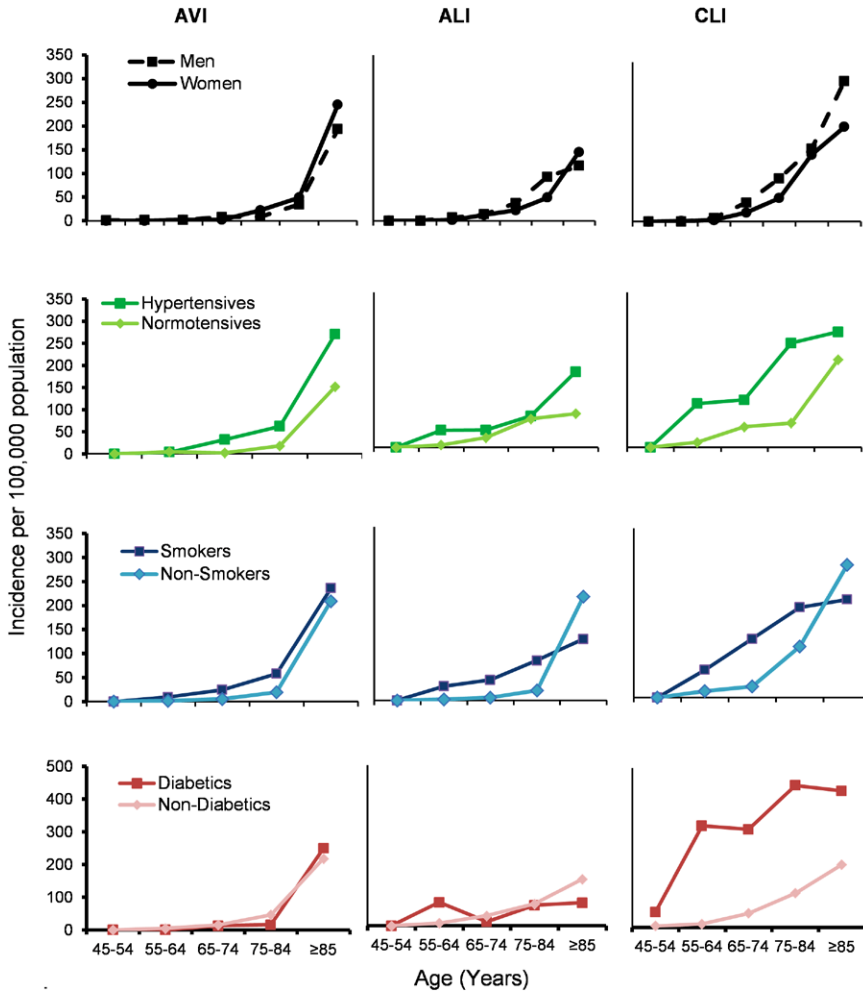
Overall, 288 patients (77.2%) with incident PAD events had previous vascular disease in any territory, with stable

PAD being most common in those with CLI events (70.8%) versus ALI (41.9%) and AVI (20.5%) events ( $P < 0.001$ ; Table 1). Three hundred sixty-one patients (96.8%) had known vascular risk factors. Risk factors for atherosclerosis (hypertension, smoking, diabetes mellitus, hyperlipidemia, and male sex) were most prevalent in patients with CLI events ( $\geq 3$  risk factors: 61.9% for CLI, 44.9% for AVI, and 39.8% for ALI;  $P = 0.001$ ). In contrast, previous atrial fibrillation was most common in patients with AVI and ALI events and least prevalent in those with CLI events (37.2% for AVI, 38.7% for ALI, and 20.8% for CLI events;  $P = 0.001$ ; Table 1 and Table III in the online-only Data Supplement). The most prevalent underlying cause was embolism for AVI and ALI events (55.1% and 46.2%) and atherosclerosis for CLI events (70.6%; the remainder being multifactorial, most commonly [18.8%] atherosclerosis plus diabetic microvascular disease; Table 1 and Table III in the online-only Data Supplement).

**Table 1. Demographics, Pathogenesis, and Risk Factors for Incident Events in All Territories**

	AVI, n (%)	ALI, n (%)	CLI, n (%)
Total	78 (100)	93 (100)	202 (100)
Mean (SD) age, y	79.8 (14.1)	76.3 (11.9)	75.2 (10.9)
Previous symptomatic vascular disease			
Coronary artery disease	27 (34.6)	27 (29.0)	77 (38.1)
Cardiac failure	26 (33.3)	18 (19.4)	42 (20.9)
Stroke/TIA	15 (19.2)	25 (26.9)	43 (21.3)
Peripheral arterial disease	16 (20.5)	39 (41.9)	143 (70.8)
Any	48 (61.5)	69 (74.2)	171 (84.7)
Risk factors			
Current smoker	13 (16.7)	21 (22.6)	58 (28.7)
Ever smoked	53 (67.9)	64 (68.8)	143 (70.8)
Hypertension	54 (69.2)	57 (61.3)	143 (70.8)
Diabetes mellitus	9 (11.5)	12 (12.9)	89 (44.1)
Hyperlipidemia	36 (46.2)	33 (35.5)	112 (55.4)
Atrial fibrillation	29 (37.2)	36 (38.7)	42 (20.8)
Any	72 (92.3)	92 (98.9)	197 (97.5)
Primary pathogenesis			
Embolic	43 (55.1)	43 (46.2)	2 (1.0)
Atherosclerotic/in situ thrombosis	26 (33.3)	22 (23.7)	146 (72.3)
Diabetic microvascular disease	0 (0)	0 (0)	15 (7.4)
Multifactorial	9 (11.5)	19 (20.4)	38 (18.8)
Occluded stent-graft/other	0 (0)	9 (9.7)	1 (0.5)
Medications			
Statin	36 (46.2)	29 (31.2)	101 (50.0)
Antiplatelet	34 (43.6)	42 (45.2)	127 (62.9)
Warfarin	3 (3.8)	9 (9.7)	17 (8.5)
Antihypertensives	57 (73.1)	59 (63.4)	144 (71.3)
Any	61 (78.2)	70 (75.3)	175 (86.6)

ALI indicates acute limb ischemia; AVI, acute visceral ischemia; CLI, critical limb ischemia; and TIA, transient ischemic attack.

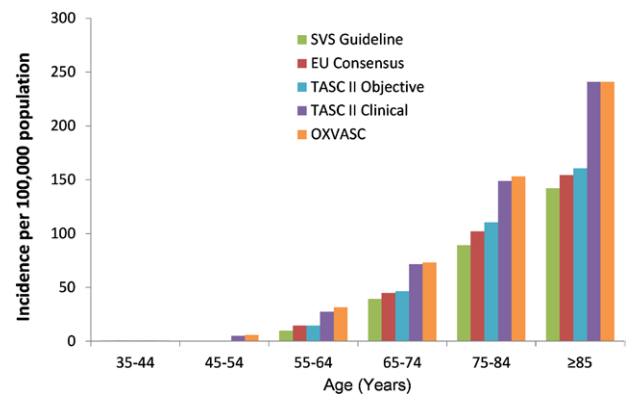


**Figure 1.** Age-, sex-, and risk factor-specific rates per 100 000 population (2002–2012) for all incident acute peripheral arterial events. ALI indicates acute limb ischemia; AVI, acute visceral ischemia; and CLI, critical limb ischemia.

Compared with the underlying study population, incident PAD events were associated with known previous hypertension (risk ratio, 2.75; 95% CI, 1.95–3.90;  $P < 0.001$ ), ever smoking (risk ratio, 2.14; 95% CI, 1.37–3.34;  $P < 0.001$ ), and diabetes mellitus (risk ratio, 3.01; 95% CI, 1.69–5.35;  $P < 0.001$ ; Table 2, Figure 1, and Figure I and Table V in the online-only Data Supplement). Previous diabetes mellitus was more prevalent in those with CLI events (44.1%) compared with ALI (12.9%) and AVI (11.5%) events ( $P < 0.001$ ). Mean age at the incident event was highly correlated with the number of underlying atherosclerotic risk factors, especially for CLI. Patients with CLI with  $>3$  risk factors had events  $\approx 8$  years younger than those with  $<2$  risk factors ( $P = 0.007$ ; Table 3).

Despite the high prevalence of cardiovascular risk factors and known arterial disease, only 203 patients (54.4%) were on an antiplatelet drug, 166 (44.5%) were on a statin, and 260 (69.7%) were on antihypertensive medication. Of 373 patients (93.0%) with incident events, 347 had premorbid BP measurements taken in primary care with a mean of 22.6 (SD, 20.4) readings per patient. Of all BPs recorded in all patients during the 5 years before the incident event, 42.9% (SD, 36.1%) were  $>140/90$  mmHg (43.7% [SD, 32.6%] for AVI; 42.1% [SD, 38.6%] for ALI; 43.0% [SD, 36.4%] for CLI;  $P = 0.96$ ). During the 15 years before the event, 56.1% (30.8) of readings were  $>140/90$  mmHg, with a greater proportion

of hypertensive readings in women (60.7% [SD, 27.9%] versus 51.3% [SD, 32.9%] in men;  $P = 0.004$ ). Mean systolic BP was greatest for ALI cases (151.2 mmHg [SD, 17.3 mmHg] compared with 139.7 mmHg [SD, 37.1 mmHg] for AVI and 142.2 mmHg [SD, 33.7 mmHg] for CLI) and was greater in women (148.2 mmHg [SD, 27.5 mmHg] versus 139.3 mmHg [SD, 34.9];  $P = 0.008$ ). Among those patients who had been started



**Figure 2.** Comparative age-specific rates for incident episodes of critical limb ischemia as defined by current recognized classification systems. EU indicates European Union; OXVASC, Oxford Vascular Study; SVS, Society for Vascular Surgery; and TASC II, Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease.

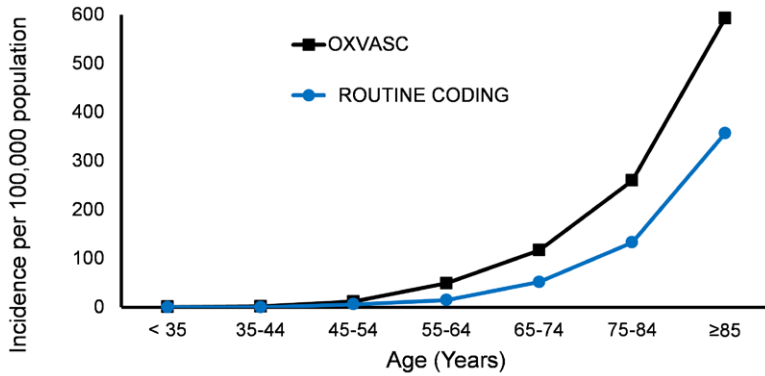


Figure 3. The efficacy of routine coding (hospital discharge, hospital death, and primary care death coding) in identifying ischemic peripheral arterial events compared with Oxford Vascular Study (OXVASC) ascertainment.

	CODING - Underlying Diagnosis	OXVASC Ascertainment
Total events identified	346	373
Correctly identified incident events N (%)	181 (52.3%)	373
Incorrectly identified incident events N (%)	165 (47.7%)	0
Sensitivity (%)	181/373 (48.5%)	373/373
Specificity (%)	152/317 (47.9%)	125/125
Positive Predictive Value (%)	52.3%	100%
Negative Predictive Value (%)	44.2%	100%

on antihypertensive treatment, 50.2% of subsequent BP readings still exceeded 140/90 mmHg despite the majority being on combination therapy (30.0% monotherapy, 34.2% dual therapy, 35.8% triple or greater therapy).

Of 88 patients (23.6%) with incident cardioembolic events (Table VI in the online-only Data Supplement), 62 had known atrial fibrillation (diagnosed before the event), of whom only 9 (14.5%) were anticoagulated despite 51 (82.3%) having CHA<sub>2</sub>DS<sub>2</sub>VASC scores ≥2 without contraindications to anticoagulation.

Figure 4 and Table VII in the online-only Data Supplement show the premorbid and 6-month postevent disability status. Premorbid levels of disability (modified Rankin Scale score >2) was similar for AVI (43.6%), ALI (40.7%), and CLI (34.0%; P=0.24). Of 230 of 369 patients (62.3%; modified Rankin Scale score missing in 4 cases) who were independent before the event (modified Rankin Scale score ≤2), only 99 (26.6%) remained alive and independent at 6 months and only 41 (11.1%) at 5 years after the event, with outcomes being worst for AVI.

Table 2. Age- and Sex-Adjusted Risk Ratios for the Presence of Key Risk Factors in Those With Acute Events Compared With the Remaining Underlying Study Population (Controls) Stratified by Event Type

	Ever Smokers		Nonsmokers		RR	95% CI	P Value
	Cases	Controls	Cases	Controls			
ALI	64	32 223	25	60 505	2.07	1.22–3.50	0.007
AVI	53	32 223	23	60 505	2.03	1.13–3.63	0.02
CLI	143	32 223	56	60 505	2.22	1.31–3.76	0.002
All	260	32 223	104	60 505	2.14	1.37–3.34	<0.001
	Hypertension		Normotension				
ALI	57	11 051	36	81 677	2.04	1.18–3.53	0.01
AVI	54	11 051	24	81 677	2.54	1.33–4.84	0.005
CLI	143	11 051	59	81 677	3.28	2.12–5.09	<0.001
All	254	11 051	119	81 677	2.75	1.95–3.90	<0.001
	Diabetes Mellitus		No Diabetes Mellitus				
ALI	12	3 125	81	89 603	1.04	0.44–2.47	0.93
AVI	9	3 125	69	89 603	0.85	0.44–1.66	0.64
CLI	89	3 125	112	89 603	5.96	3.15–11.26	<0.001
All	110	3 125	262	89 603	3.01	1.69–5.35	<0.001

Rrs were corrected for overdispersion. Smoking status was not established for 9 patients (2.4%); diabetic status was not established for 1 patient (0.3%). ALI indicates acute limb ischemia; AVI, acute visceral ischemia; CI, confidence interval; CLI, critical limb ischemia; and RR, risk ratio.

**Table 3. Mean Age at Event Stratified by the Presence of Multiple Atherosclerotic Risk Factors (Smoking History, Hypertension, Diabetes Mellitus, Hyperlipidemia, and Male Sex)**

Study	n	Mean Age, y	SD	P Value
AVI				
≤1	20	77.7	20.4	0.88
2	23	80.0	14.9	
3	25	81.2	8.9	
≥4	10	80.0	8.2	
ALI				
≤1	22	82.7	12.2	0.02
2	34	73.7	12.0	
3	24	76.8	11.4	
≥4	13	71.5	8.1	
CLI				
≤1	24	80.1	10.9	0.007
2	53	76.0	13.8	
3	52	76.6	9.8	
≥4	73	72.1	8.4	

Group differences in age assessed using one-way ANOVA. ALI indicates acute limb ischemia; AVI, acute visceral ischemia; and CLI, critical limb ischemia.

Figure 5 and Figure II in the online-only Data Supplement show amputation rates, amputation-free survival, and overall survival. In patients with CLI and ALI events, there was a significant risk of future limb loss, which was similar at 1 year (6.6% and 7.5%, respectively) but greater for CLI events at 5 years (43.4% versus 16.9%;  $P=0.01$ ). Amputation-free survival was initially lower for ALI compared with CLI at 3 months (59.1% versus 75.7%;  $P=0.001$ ), but by 5 years, the curves had crossed (36.7% versus 27.1% for CLI). Overall survival at 30 days and 5 years was lowest for AVI events (28.2% and 24.4%) compared with ALI (75.3% and 55.9%) and CLI (92.6% and 70.8%;  $P<0.001$ ). The out-of-hospital death rates (deaths in the community before hospital admission) were low but were higher for patients with AVI events (6.4%) compared with those with ALI (5.4%) and CLI (0.0%) events ( $P=0.002$ ).

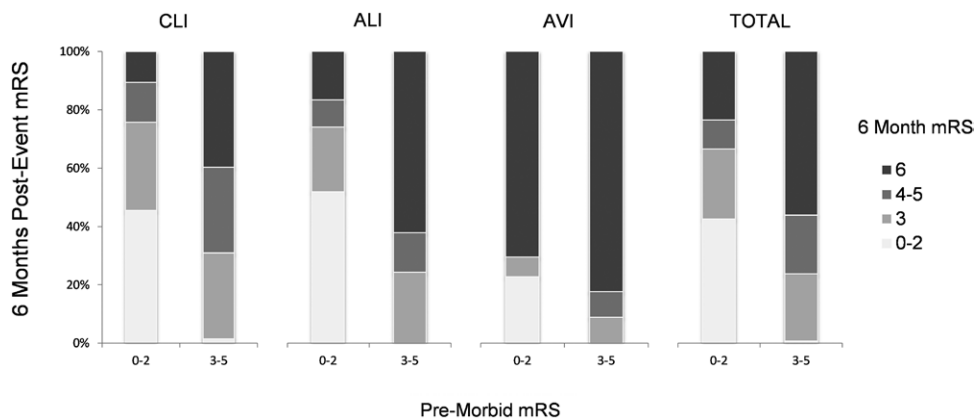
Severity of ischemia on admission was associated with 30-day amputation or death and 1-year mortality for all

event types (Table 4 and Table VIII in the online-only Data Supplement). For patients with ALI, male sex, renal dysfunction, and previous coronary artery disease were independently associated with 30-day amputation or death, and age and renal dysfunction were associated with 1-year mortality. For AVI, age and hypertension were associated with 1-year mortality, whereas for CLI, previous heart failure and renal dysfunction were related. In addition, for CLI, admission ankle-brachial pressure index was associated with 1-year amputation-free survival (risk ratio, 2.4; 95% CI, 1.7–8.6;  $P=0.04$ ). The 30-day amputation-free survival rate stratified by severity of ischemia was 100% for viable, 79.5% for threatened, and 4.8% for irreversible ischemia for ALI and 100% for rest pain only (Rutherford 4), 83.7% for minor tissue loss (Rutherford 5), and 41.7% for major tissue loss (Rutherford 6; Table IX in the online-only Data Supplement) for CLI. The severity of event and 1-year fatality increased significantly with age for all event types (Table X in the online-only Data Supplement). AVI has the highest 1-year fatality of all acute vascular events (Figure III in the online-only Data Supplement).

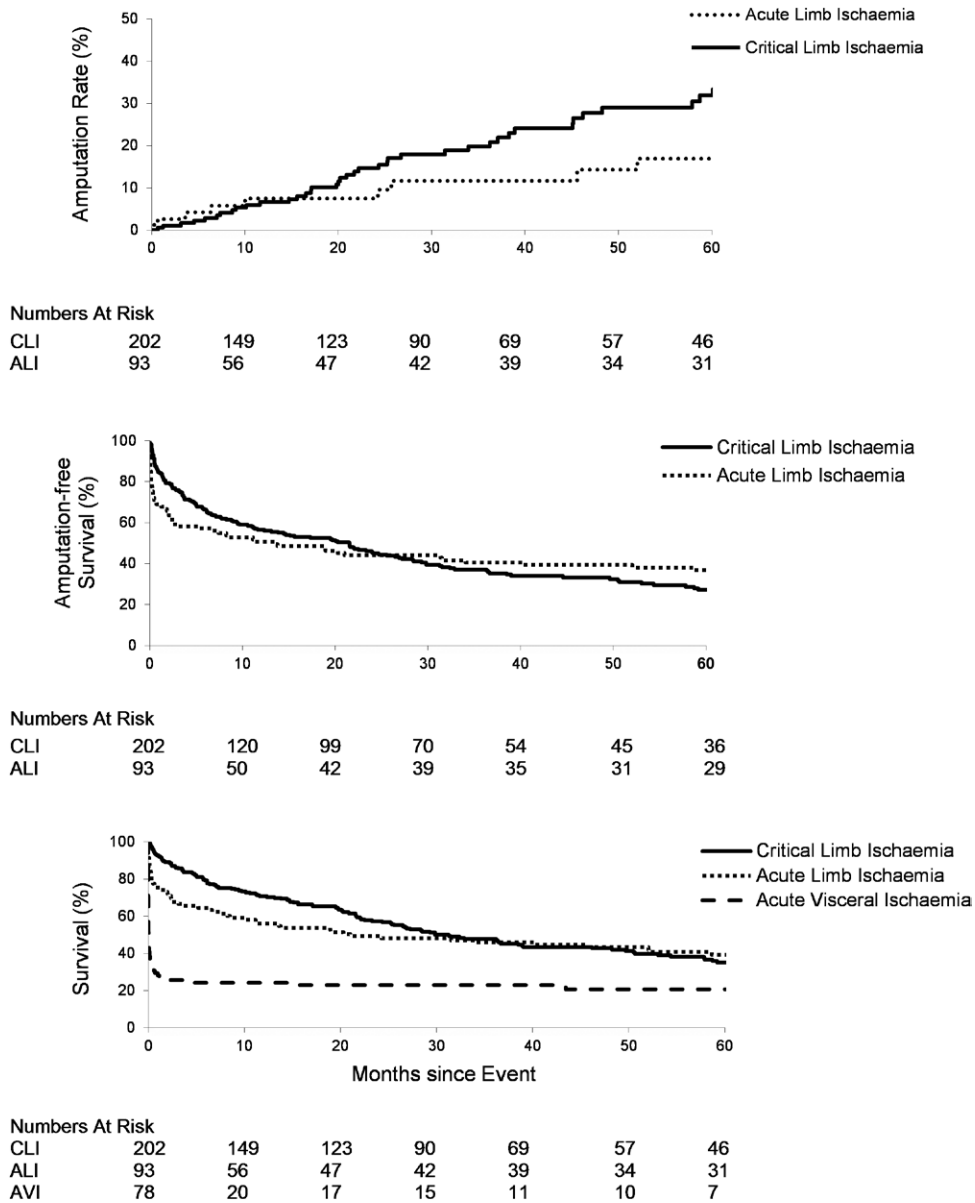
## Discussion

OXVASC is a comprehensive, population-based study of all acute vascular events without exclusion of patients by age or sex,<sup>45</sup> including the first-ever large-scale prospective study of all acute ischemic PAD events. We showed that prospectively collected incidence data are substantially more accurate than routine hospital episode and death coding data. Because there is no *International Classification of Diseases, 10th Revision* code for CLI, previous estimates of incidence have been limited to codes that include stable vascular disease (intermittent claudication) or outcome codes such as amputation and death. In addition, our access to the lifelong medical records allowed us to reliably assess premorbid risk factors and their control.

We have several main findings. First, acute PAD events are a substantial disease burden with high case fatality, poor functional outcome, and high rates of emergency and subsequent vascular intervention to prevent death or limb loss. Second, AVI, ALI, and CLI differ with respect to risk factors, functional outcomes, and survival. Third, age of onset is correlated with degree of atherosclerotic risk factor burden. Fourth, major adverse outcomes (amputation and death) are associated with



**Figure 4.** Changes in disability status for patients with incident acute events stratified by event type. ALI indicates acute limb ischemia; AVI, acute visceral ischemia; CLI, critical limb ischemia; and mRS, modified Rankin Scale.



**Figure 5.** Five-year rates of major amputation, amputation-free survival, and overall survival for incident acute peripheral arterial events by subtype with numbers at risk tabled below. ALI indicates acute limb ischemia; and CLI, critical limb ischemia.

severity of disease-grading criteria and comorbidities such as renal dysfunction, diabetes mellitus, and premonitory cardiac failure. Finally, the vast majority of patients presenting with acute events had preexisting vascular disease or known vascular risk factors, highlighting a great potential for early recognition of risk and prevention.

The overall incidence of CLI was approximately twice that of ALI and AVI, but age trends in rates were similar for all event types, with the majority of events occurring at  $\geq 75$  years of age. Unlike coronary artery disease and acute aortic disease, the incidence of acute peripheral arterial events was similar in men and women, although women had events at an older age. However, the majority of patients were independent before the event, but only a quarter remained so at 6 months after the event. Early mortality increased with age for all event types.

The high rates of previous vascular disease in individuals presenting with acute peripheral vascular events

suggest that limb ischemia and visceral ischemia are usually late-stage manifestations of vascular disease and that individuals suffering PAD events are highly likely to have systemic atherosclerosis affecting other vascular beds. There is therefore great potential for early recognition of risk. Risk factors strongly associated with atherosclerosis and previous atherosclerotic vascular diseases (acute coronary syndrome and intermittent claudication) were most prevalent in patients with CLI events, whereas previous atrial fibrillation was prevalent in those with AVI and ALI. Degree of atherosclerotic risk factor burden was also associated with prematurity of disease. For acute events of cardioembolic origin and known atrial fibrillation, premonitory levels of anticoagulation were very low despite the vast majority of patients being at high risk for thromboembolism ( $CHA_2DS_2VASC$  scores  $\geq 2$ ) without contraindications to anticoagulation.

**Table 4. Potential Risk Factors for 30-Day Amputation/Organ Loss/Death and 1-Year Mortality Stratified by Event Type (Multivariable Analysis)**

Study	30-Day Amputation/Organ Loss/Death			1-Year Mortality		
	OR	95% CI	P Value	OR	95% CI	P Value
<b>ALI (n=93)</b>						
Age	1.02	0.96–1.08	0.58	1.08	1.01–1.14	0.02
Male sex	0.29	0.08–1.01	0.05	2.04	0.62–6.69	0.24
Smoking history	2.09	0.50–8.70	0.31	2.20	0.59–8.27	0.24
Diabetes mellitus	1.48	0.19–11.41	0.71	2.47	0.41–15.03	0.33
Hypertension	3.34	0.85–13.11	0.08	3.30	0.92–11.84	0.07
Hyperlipidemia	0.26	0.06–1.20	0.08	0.37	0.09–1.46	0.15
Atrial fibrillation	1.04	0.28–3.82	0.96	1.48	0.45–4.95	0.52
Heart failure	0.77	0.18–3.35	0.72	2.20	0.51–9.58	0.29
Previous coronary artery disease	4.61	1.07–19.77	0.04	1.17	0.32–4.31	0.82
Previous stroke/TIA	2.42	0.68–8.65	0.17	1.26	0.38–4.18	0.71
Previous PAD	2.65	0.72–9.72	0.14	0.92	0.29–2.91	0.89
Renal function (CKD stage 1–5)*	1.08	0.41–2.84	0.88	2.66	1.00–7.08	0.05
Severity of ischemia on admission†	7.91	1.87–33.42	0.01	3.65	1.17–11.43	0.03
<b>AVI (n=78)</b>						
Age	1.10	1.02–1.18	0.01	1.12	1.03–1.22	0.01
Male sex	7.24	0.84–62.55	0.07	1.11	0.20–6.08	0.90
Smoking history	0.85	0.13–5.37	0.86	4.01	0.55–29.37	0.17
Diabetes mellitus	0.79	0.05–13.33	0.87	...	...	...
Hypertension	0.62	0.06–6.33	0.68	0.06	0.00–0.77	0.03
Hyperlipidemia	0.27	0.04–1.97	0.20	0.22	0.02–1.98	0.18
Atrial fibrillation	0.57	0.09–3.47	0.54	1.52	0.26–9.03	0.65
Heart failure	3.28	0.36–29.60	0.29	11.13	0.74–166.7	0.08
Previous coronary artery disease	2.13	0.25–17.88	0.49	1.15	0.11–11.63	0.91
Previous stroke/TIA	1.66	0.15–18.14	0.68	0.99	0.11–9.21	1.00
Previous PAD	10.74	0.81–141.94	0.07	4.44	0.46–42.53	0.20
Renal function (CKD stage 1–5)*	1.22	0.38–3.91	0.73	6.68	0.62–72.24	0.12
Severity of ischemia on admission†	22.60	2.16–236.41	0.01	14.17	1.79–112.3	0.01
<b>CLI (n=202)</b>						
Age	1.00	0.96–1.05	0.86	1.04	1.00–1.08	0.07
Male sex	1.06	0.45–2.49	0.89	0.78	0.38–1.63	0.51
Smoking history	1.16	0.43–3.16	0.77	0.94	0.42–2.15	0.89
Diabetes mellitus	1.21	0.49–3.01	0.68	0.70	0.33–1.50	0.36
Hypertension	0.51	0.20–1.32	0.16	1.86	0.76–4.53	0.17
Hyperlipidemia	0.72	0.28–1.85	0.50	0.91	0.42–1.97	0.80
Atrial fibrillation	1.23	0.46–3.28	0.69	0.61	0.26–1.45	0.27
Heart failure	1.40	0.54–3.67	0.49	3.88	1.71–8.82	<0.001
Previous coronary artery disease	1.41	0.57–3.45	0.46	1.26	0.59–2.71	0.56
Previous stroke/TIA	0.91	0.31–2.63	0.85	0.96	0.41–2.25	0.93
Previous PAD	2.05	0.73–5.70	0.17	0.69	0.31–1.54	0.37
Renal function (CKD stage 1–5)*	1.55	0.99–2.43	0.05	2.02	1.33–3.05	0.001
Severity of ischemia on admission†	...	...	...	3.38	1.16–9.81	0.03

Multivariable ORs adjusted for all variables analyzed. ALI indicates acute limb ischemia; AVI, acute visceral ischemia; CI, confidence interval; CKD, chronic kidney disease; CLI, critical limb ischemia; OR, odds ratio; PAD, peripheral arterial disease; and TIA, transient ischemic attack.

\*CKD is based on the calculated estimated glomerular filtration rate (<http://www.renal.org>).

†For AVI, this is measured by the presence/absence of lactic acidosis; for CLI, this is tissue loss vs rest pain alone; and for ALI, this is Rutherford grade I/IIA vs IIB/III.



AVI events had a 30-day and 1-year survival of only 28.2% and 24.4%, respectively. ALI and CLI also have a significant mortality at 1 year, and in surviving patients, there is a significant risk of amputation in both forms of limb disease, being greatest for CLI cases at 5 years (43.4%). The 30-day major amputation or death rate and 1-year mortality rate were associated with severity of ischemia on admission, renal dysfunction, previous cardiac failure, and age, whereas diabetes mellitus was associated with both short- and long-term risk of limb loss. These factors could be used to inform clinical management, particularly for diabetic patients who are at high risk of future amputation, so more aggressive early intervention may be warranted.

The potential limitations of OXVASC have been previously noted.<sup>45</sup> First, by not recording the prevalence of patients with stable intermittent claudication, we are unable to estimate the total burden of PAD, although all acute events in such patients were studied. Second, the OXVASC population is predominantly white, so it is difficult to extrapolate the results to other ethnic groups. Third, the population has relatively lower deprivation indexes than the UK average. However, the general practices within OXVASC include the full range of deprivation. Fourth, for some specific age/sex subgroups, there were a limited number of cases. This will limit the ability to precisely estimate the incidence rates in these groups. Finally, we purposely avoided the use of objective measurements to exclude patients with possible CLI from the study and instead included all patients with documented limb ischemia with rest pain or tissue loss of sufficient severity to warrant urgent hospital admission. On one hand, this may have led to an overestimation of CLI incidence compared with studies using strict consensus criteria, but on the other, this has enabled us to perform the first fully inclusive population-based study of all acute peripheral vascular events.

## Conclusions

The clinical burden of peripheral arterial events is substantial, with high case fatality, poor functional outcome, and high rates of emergency and subsequent vascular intervention to prevent death or limb loss. However, although premorbid function is good in the majority of patients and although the vast majority have known vascular disease in other territories and multiple treatable risk factors, premorbid control of risk factors is poor. It is likely that much of the current clinical burden of acute PAD is preventable by more effective use of existing preventive treatments.

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## Disclosures

None.

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### CLINICAL PERSPECTIVE

This is the first prospective, population-based study of all acute ischemic peripheral arterial events over a 10-year period in a population of 92 728 in Oxfordshire, UK. We have shown that the clinical burden of peripheral arterial events is substantial, with high case fatality, poor functional outcome, and high rates of emergency and subsequent vascular intervention to prevent death or limb loss. However, although premorbid function is good in the majority of patients and although the vast majority have known vascular disease in other territories and multiple treatable risk factors, premorbid control of risk factors is poor. It is likely that much of the current clinical burden of acute peripheral arterial disease is preventable by more effective use of existing preventive treatments.

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