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Traditional and nontraditional glycemic markers and risk of peripheral artery disease: The Atherosclerosis Risk in Communities (ARIC) study

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Abstract

Background and aims—Traditional glycemic markers, fasting glucose and hemoglobin A1c (HbA1c), predict incident peripheral artery disease (PAD). However, it is unknown whether nontraditional glycemic markers, fructosamine, glycated albumin, and 1,5-anhydroglucitol, are associated with PAD and whether these glycemic markers demonstrate particularly strong associations with severe PAD, critical limb ischemia (CLI).

Methods—We quantified the associations of these five glycemic markers with incident PAD (hospitalizations with PAD diagnosis or leg revascularization) in 11,634 ARIC participants using Cox regression models. Participants were categorized according to diabetes diagnosis and clinical cut-points of glycemic markers (nontraditional glycemic markers were categorized according to percentiles corresponding to the HbA1c cut-points).

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Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

N.D. designed the study, analyzed the data, and drafted and revised the manuscript. L.K. performed statistical analysis and interpreted results. S.B., B.J., R.C.H., C.M.B., A.R.S., A.R.F., G.H., M.S., J.C., E.S. interpreted the results and reviewed the manuscript. A.T.H. interpreted the results and reviewed the abstract. K.M. designed the study and analytic plan, interpreted the results, and drafted and revised the manuscript. K.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Results—Over a median follow-up of 20.7 years, there were 392 cases of PAD (133 were CLI with tissue loss). HbA1c was more strongly associated with incident PAD than fasting glucose, with adjusted hazard ratios (HR) 6.00 (95% CI, 3.73–9.66) for diagnosed diabetes with HbA1c 7% and 3.53 (2.39–5.22) for no diagnosed diabetes with HbA1c 6.5% compared to no diagnosed diabetes with HbA1c <5.7%. Three nontraditional glycemic markers demonstrated risk gradients intermediate between HbA1c and fasting glucose and their risk gradients were substantially attenuated after adjusting for HbA1c. All glycemic markers consistently demonstrated stronger associations with CLI than PAD without CLI (p for difference <0.02 for all glycemic markers).

Conclusions—Nontraditional glycemic markers were associated with incident PAD independent of fasting glucose but not necessarily HbA1c. Our results also support the importance of glucose metabolism in the progression to CLI.

Keywords

Peripheral artery disease; Diabetes; Glycemic markers; Foot care

1. Introduction

Peripheral artery disease (PAD) is a condition characterized by atherosclerotic occlusive disease of the lower extremities [1], affecting approximately 8–12 million Americans [2]. Patients with PAD have 3–4 times higher mortality compared with those without [3]. Critical limb ischemia (CLI) is a severe form of PAD, with 10%–40% of patients requiring major amputation within 6 months after its diagnosis [2]. Although amputation rates have recently decreased among patients with PAD [4], ~150,000 legs are still amputated due to PAD annually in the U.S. [5].

Diabetes is known to be particularly strongly associated with PAD, with a relative risk of 3- to 4-fold compared to those not having diabetes [6]. The American Diabetes Association (ADA) recommends annual foot examinations for patients with diabetes [7]. However, the adherence to this recommendation is reported to be ~30% [8], and thus biomarkers that can classify the risk of PAD among diabetic patients may be helpful for targeted foot care.

In this context, traditional glycemic markers, fasting glucose and hemoglobin A1c (HbA1c), would be promising since they are routinely measured in patients with diabetes and are associated with PAD [9]. Previous studies have demonstrated a stronger association of HbA1c with PAD [9] and other cardiovascular outcomes and mortality [10] compared with fasting glucose. However, HbA1c has a few drawbacks, such as not reflecting recent changes in glucose levels and being influenced by red blood cell turnover (e.g., due to anemia) [11]. Also, it requires a whole blood specimen, often precluding its retrospective measurement in a research setting, where serum and/or plasma samples are typically stored.

Some nontraditional glycemic markers—fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG)—may overcome these drawbacks of HbA1c by reflecting glucose levels in the last few weeks, not being affected by red blood cell turnover, and being measurable in serum or plasma samples [12,13]. Recently, these nontraditional glycemic markers have been shown to be associated with coronary heart disease (CHD) and stroke

similarly to HbA1c or to provide additional information beyond HbA1c [14,15]. However, their associations with PAD risk have not been quantified.

Therefore, we comprehensively investigated the associations of traditional (fasting glucose and HbA1c) and nontraditional glycemic markers (fructosamine, glycated albumin, and 1,5-AG) with incident PAD in a community-based cohort, the Atherosclerosis Risk in Communities (ARIC) Study. We also explored whether these glycemic markers have stronger relationships to incident CLI than PAD without CLI because foot monitoring and care would be particularly important for individuals at high risk of the severe form of PAD.

2. Materials and methods

2.1. Study population

The ARIC Study enrolled 15,792 participants aged 45–64 years from four U.S. communities. The first clinic examinations (visit 1) took place from 1987 to 1989, with three short-term follow-up visits (visits 2–4) approximately every three years [16]. A fifth examination was completed from 2011 to 2013. A total of 14,348 participants attended visit 2 in 1990–1992, which was the baseline of this study, given the availability of the glycemic markers of interest. We excluded participants whose race/ethnicity was recorded as other than white or black ($n = 42$); who had missing variables of interest ($n = 1794$); who were fasting <8 h ($n = 374$); or who had prevalent PAD at baseline ($n = 504$), leaving final sample of 11,634.

2.2. Measurement of glycemic markers

Serum glucose was measured in fresh samples at visit 2 using the hexokinase method. HbA1c was measured in whole blood samples collected at visit 2 stored at -80 Celsius degrees using high-performance liquid chromatography with instruments standardized to the Diabetes Control and Complications Trial assay (Tosoh A1c 2.2. Plus Glycohemoglobin in 2003–2004 and Tosoh G7 analyzers 2007–2008) [17]. Fructosamine (Roche Diagnostics Corp, Indianapolis, IN, USA), glycated albumin (Asashi Kasei Lucica GA-L, Tokyo, Japan), and 1,5-AG (GlycoMark, Winston-Salem, NC) were measured in 2012–2013 in stored frozen serum using a Roche Modular P800 system [14,18]. Previous studies have shown these analytes to be reliable in long-term stored samples [19–21].

2.3. Other variables of interest at baseline

Age, gender, race, educational level, alcohol use, and smoking status were self-reported. Education was categorized as advanced (completed college or more), intermediate (high school to less than college), and none or basic (less than high school). Body mass index (BMI) was calculated as body weight (in kilograms) divided by height (in meters) squared. Seated systolic blood pressure (SBP) was measured three times after 5 min of rest using a random-zero sphygmomanometer, and the average of the second and third readings was recorded. Total cholesterol and high-density lipoprotein (HDL) cholesterol were determined using enzymatic methods. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [22]. Medication use over the prior two weeks was verified by reviewing medication containers

that participants brought to the visit. Diagnosed diabetes was defined as a self-reported physician diagnosis of diabetes or current use of glucose-lowering medications. Duration of diagnosed diabetes was categorized as $>\sim 3$ years (diagnosed diabetes at visit 1) and $<\sim 3$ years (no diagnosed diabetes at visit 1). History of CHD was defined by a self-reported history of physician-diagnosed myocardial infarction, prior coronary reperfusion procedure, electrocardiogram evidence of myocardial infarction at visit 1, or subsequent CHD events between visit 1 and visit 2 [23]. History of stroke was defined as a self-reported history of stroke at visit 1 or adjudicated stroke events between visit 1 and visit 2. Prevalent heart failure was defined as self-reported treatment for heart failure, hospitalization for heart failure between visit 1 and 2, or the Gothenburg stage 3, a status with dyspnea due to cardiac causes and under treatment with digitalis or loop diuretics [24,25]. Prevalent atrial fibrillation cases were identified from Electrocardiography and by review of hospital discharge records [26].

2.4. Incident peripheral artery disease

Based on previous literature [27,28], incident PAD was defined as hospitalizations with the following International Classification of Diseases (ICD) codes: atherosclerosis of native arteries of the extremities, unspecified (440.20); atherosclerosis of native arteries of the extremities with intermittent claudication (440.21); atherosclerosis of native arteries of the extremities with rest pain (440.22); atherosclerosis of native arteries of the extremities with ulceration (440.23); atherosclerosis of native arteries of the extremities with gangrene (440.24); other atherosclerosis of native arteries of the extremities (440.29); atherosclerosis of bypass graft of the extremities (440.3); atherosclerosis of other specified arteries (440.8); leg artery revascularization (38.18, 39.25, 39.29, 39.50). Of these, cases based on 440.22, 440.23, and 440.24 as well as PAD cases with coexisting leg amputation (84.1x), lower extremity ulcer (707.1x), and gangrene (785.4) were considered CLI. Participants were followed until incident hospitalized PAD, date of death, date of the last contact, or December 31, 2012, whichever came first.

2.5. Statistical analyses

We first categorized participants into five groups according to the status of diagnosed diabetes and levels of traditional glycemic markers. We used clinical cut-points recommended by the ADA to categorize fasting glucose and HbA1c [29]. Specifically, fasting glucose levels were categorized into <5.6 , $5.6\text{--}6.9$, or ≥ 7 mmol/L with no diagnosed diabetes and <7.2 or ≥ 7.2 mmol/L with diagnosed diabetes. Similarly, HbA1c was categorized into <5.7 , $5.7\text{--}6.4$, or $\geq 6.5\%$ with no diagnosed diabetes and <7 or $\geq 7\%$ with diagnosed diabetes. For nontraditional glycemic markers, we categorized by their percentiles corresponding to HbA1c cut-points since their clinical cut-points are not established. In persons with no diagnosed diabetes, HbA1c values of 5.7% and 6.5% corresponded to the 77th percentile and the 96th percentiles, respectively. In persons with diagnosed diabetes, HbA1c of 7% was equivalent to the 32nd percentile. The cut-points for 1,5-AG were inverted (e.g., 23rd percentile instead of 77th percentile) because lower values indicate hyperglycemia [30].

Baseline characteristics of the study population were compared between participants with and without incident PAD during follow-up. We estimated survival free of PAD using the Kaplan Meier method. We used Poisson regression models with linear splines to evaluate the continuous association between the glycemic markers and incidence rate of PAD with the adjustment of age, sex and race. Cox proportional hazards models were used to quantify the independent associations of categories by glycemic markers and diagnostic status of diabetes with incident PAD beyond potential confounders. We also modeled the glycemic markers as spline terms with knots at the thresholds of categories described above.

We constructed three models for the adjustment of covariates. Model 1 was adjusted for key demographic and clinical factors, age (years), race, sex, education level, BMI, total cholesterol, HDL cholesterol, drinking status (current, former, never), smoking status (current, former, never), SBP, eGFR, antihypertensive medication use, lipid-lowering medication use, aspirin-containing analgesics use, anticoagulants use, antiplatelet medication use, history of atrial fibrillation, heart failure, CHD and stroke, and duration of diabetes. Model 2 was additionally adjusted for each traditional glycemic marker (Model 2a with fasting glucose and Model 2b with HbA1c). We primarily used the category with no diagnosed diabetes and the lowest level of glycemic markers (highest for 1,5-AG but for convenience we do not specify this every time in subsequent sections) as the reference, but in a case of a J-shaped association, we secondarily analyzed the lowest risk group as the reference group. The proportional hazards assumption was visually verified using log-log plots. Seemingly unrelated regression was used to formally compare the strength of associations for each glycemic marker with incident PAD without CLI *vs.* CLI [31].

All statistical analyses were conducted using Stata SE, version 14 (Stata Corp, College Station, TX), and a *p* value of less than 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics by PAD status

Over a median follow-up of 20.7 years, there were 392 cases of PAD (133 were CLI). Baseline characteristics of participants by the status of incident PAD during follow-up are shown in Table 1. Compared to participants who did not develop PAD, those who developed PAD were more likely to be older, male, of black race, less educated, current smokers, and to have poorer risk factor profiles (i.e., higher levels of BMI and SBP, lower eGFR, higher prevalence of using insulin, antihypertensive medication, lipid-lowering medication, aspirin-containing analgesics, anticoagulants, and anti-platelet medication, and higher prevalence of CHD, stroke and heart failure). Regarding diagnosed diabetic status and glycemic markers, participants with incident PAD had ~4-fold higher prevalence of diagnosed diabetes and higher levels of all glycemic markers (lower levels of 1,5-AG) than those without incident PAD. These patterns were more prominent in persons who developed CLI compared with those who developed PAD without CLI. Around half of persons who developed CLI had diagnosed diabetes at baseline.

3.2. Incidence of PAD and CLI by glycemic markers

Participants with diagnosed diabetes and/or higher levels of glycemic markers had lower PAD-free survival (Supplementary Fig. 1). The continuous associations of five glycemic markers with the incidence rate of PAD adjusted for age, sex, and race are shown in Fig. 1. The incidence rate of PAD increased monotonically along with both traditional glycemic markers, although the risk gradient appeared to be steeper for HbA1c (e.g., reaching a PAD incidence rate of 20 per 1000 person-years at 99th percentile in Fig. 1A) than fasting glucose (e.g., PAD incidence rate at the 99th percentile of 15 per 1000 person-years in Fig. 1B). The nontraditional glycemic markers were associated with an increased incidence rate of PAD as well but demonstrated J-shaped associations, although less so for 1,5-AG.

3.3. Relative risk of PAD and CLI according to traditional glycemic markers

After accounting for other potential confounders, both traditional glycemic markers showed significant associations with incident PAD (Model 1 in Table 2). Again, the associations were stronger for HbA1c than for fasting glucose. Specifically, the adjusted hazard ratio (HR) for diagnosed diabetes with HbA1c $\geq 7\%$ (vs. no diagnosed diabetes with HbA1c $<5.7\%$) was 6.00 (95% confidence interval, 3.73–9.66), whereas that for diagnosed diabetes with fasting glucose ≥ 7.2 mmol/L (vs. no diagnosed diabetes with fasting glucose <5.6 mmol/L) was 3.42 (2.11–5.54). In addition, persons with prediabetes, indicated by a HbA1c level of 5.7–6.4%, had ~60% higher risk of PAD compared to those with HbA1c $<5.7\%$. The additional adjustment for fasting glucose modestly attenuated the associations for HbA1c (Model 2a in Table 2), but the general patterns remained consistent. On the other hand, there was no longer a risk gradient by fasting glucose levels after the additional adjustment for HbA1c, with both groups showing HR ~ 1 (Model 2b in Table 2).

For both HbA1c and fasting glucose, adjusted HRs were generally higher for CLI than for PAD. For example, the adjusted HR for CLI for diagnosed diabetes with HbA1c $\geq 7\%$ (vs. no diagnosed diabetes with HbA1c $<5.7\%$) was 10.39 (4.79–22.53) in Model 1 and 6.36 (2.68–15.10) in Model 2a. Based on seemingly unrelated regression, HRs for both traditional glycemic markers were significantly greater for CLI than for PAD without CLI ($p < 0.001$ for HbA1c and $p = 0.015$ for fasting glucose [Supplementary Table 1]). We confirmed similar patterns when we modeled HbA1c and fasting glucose continuously (Supplementary Fig. 2A and 2B).

3.4. Relative risk of PAD and CLI according to nontraditional glycemic markers

The associations of nontraditional glycemic markers with incident PAD were independent of cardiovascular risk factors as well (Model 1 in Table 3). The adjusted HRs appeared to be smaller than those for HbA1c but slightly greater than those for fasting glucose. Specifically, the adjusted HRs for diagnosed diabetes with higher glycemia categories (vs. no diagnosed diabetes with lowest glycemia categories) ranged from 3.6 to 4.3. Given a J-shaped association for fructosamine and 1,5-AG, when their lowest risk category was used as the reference, the corresponding HRs exceeded 4.3 (Supplementary Table 2). The HRs were statistically significant also among those with diagnosed diabetes and lower levels of fructosamine and glycated albumin (Model 1 in Table 3). The adjusted HRs for participants with no diagnosed diabetes and highest glycemia categories reached statistical significance

as well. The further adjustment for fasting glucose (Model 2a in Table 3) attenuated the associations in no diagnosed diabetes with highest glycemic categories, but glycated albumin still showed a significant association. However, when HbA1c was included in place of fasting glucose (Model 2b in Table 3), the risk gradients within the no diagnosed diabetes and diagnosed diabetes groups were not evident for PAD. Similar patterns were seen when we modeled nontraditional glycemic markers continuously (Supplementary Fig. 2C–E).

Similar to fasting glucose and HbA1c, all three nontraditional glycemic markers showed greater HRs for CLI than for overall PAD, with HRs adjusted for conventional cardiovascular factors ranging from 5.4 to 7.6 for diagnosed diabetes with higher levels (vs. no diagnosed diabetes with the lowest levels) (Model 1 in Table 3). HRs for CLI were significantly greater than those for PAD without CLI in seemingly unrelated regression analyses (p for difference <0.001 for all nontraditional glycemic markers [Supplementary Tables 3 and 4]). Nonetheless, in Model 2b further adjusting for HbA1c, all estimates for CLI were not statistically significant, except the highest category of glycated albumin in no diagnosed diabetes (HR 2.23 [95% CI 1.08–4.63]).

4. Discussion

In this community-based prospective study, both traditional (fasting glucose and HbA1c) and nontraditional (fructosamine, glycated albumin, and 1,5-AG) glycemic markers were significantly associated with incident PAD, independently of potential con-founders. The association with incident PAD was particularly strong and robust when persons with and without diagnosed diabetes were stratified by HbA1c. Overall, nontraditional glycemic markers demonstrated a strength of association with PAD in between that of HbA1c and fasting glucose. Of note, all five glycemic markers demonstrated stronger associations with CLI than PAD without CLI.

The independent associations of traditional glycemic markers with PAD were consistent with previous reports mainly among diabetic patients [9,32,33], but our study extended current knowledge in several aspects. First, we confirmed these associations in the general population (particularly for HbA1c). Specifically, we found persons with prediabetes, indicated by a HbA1c 5.7–6.4%, had ~60% higher risk of PAD compared to those with HbA1c $<5.7\%$. Second, HbA1c demonstrated stronger associations with PAD compared to fasting glucose levels, confirming the pattern observed for other cardiovascular outcomes and mortality [10,34,35]. Third, HbA1c demonstrated stronger associations with CLI than PAD. Fourth, while most previous studies were cross-sectional [33] or had a relatively short duration of follow-up (a median of ~6 years) [32], our study explored a long follow-up of over 20 years.

To our knowledge, this is the first study reporting the associations of three nontraditional glycemic markers—fructosamine, glycated albumin, and 1,5-AG—with incident PAD, independent of traditional cardiovascular risk factors. Their associations with PAD were stronger than fasting glucose but not as strong as HbA1c. Once accounting for HbA1c, their associations with PAD were considerably attenuated. These patterns are generally consistent

with previous reports from ARIC for other cardiovascular diseases (CHD, stroke, and heart failure) [14,15].

We found J-shaped associations of nontraditional glycemic markers (particularly fructosamine in both Fig. 1 and Table 3) with incident PAD. Of interest, low levels of fructosamine have been reported to be associated with increased risk of mortality [15,36] and heart failure [15]. Several mechanisms might partly explain these associations. Fructosamine values are lower among those with low concentrations of serum albumin (hypoalbuminemia below 30–35 g/L), as present in protein-losing enteropathy, nephrotic syndrome, or advanced liver diseases like cirrhosis. Increased albumin catabolism also leads to low fructosamine levels [37]. Therefore, the lowest category of fructosamine might include individuals with poor health and low serum albumin levels, who are at high risk of PAD. This mechanism of increased albumin catabolism also results in low glycated albumin levels, which may be related to the observed J-shaped association between glycated albumin and PAD risk.

Although PAD is often considered a disease of large arteries, microvascular disease is known to play an important factor in the development of CLI, by impairing collateral formation and wound healing [38]. Our observation of all five glycemic markers consistently demonstrating stronger associations with CLI than PAD without CLI seems to support the involvement of microvascular disease in the pathophysiology of CLI, since hyperglycemia is known to be more strongly associated with microvascular disease (namely retinopathy, nephropathy, and neuropathy) than macro-vascular disease (e.g., CHD) in general [39]. In addition, intensive glycemic control decreases the risk of microvascular disease but not necessarily macrovascular disease in patients with diabetes [40,41]. Nonetheless, we cannot deny the possibility that glycemic markers may merely reflect the severity of diabetic complications such as neuropathy contributing to non-healing wound, although we accounted for the duration of diabetes. Thus, future studies should explore specific parameters of microvascular disease (e.g., retinopathy) and their associations with CLI vs. PAD.

Our results have several clinical and research implications. First, HbA1c, the central glycemic marker for glucose control in diabetic patients, may be useful for classifying the risk of PAD. Given the low adherence to annual foot care among diabetic patients, HbA1c may be used to identify diabetic patients who would particularly benefit from foot care and monitoring. Second, although intensive glucose control has not consistently shown an evident benefit for reducing overall cardiovascular risk, our results suggest that intensive control may contribute to the reduction of CLI. Third, although the three nontraditional glycemic markers were not more strongly associated with PAD than was HbA1c, there are a few scenarios that these markers may be useful since they showed stronger associations than fasting glucose. For example, fructosamine and glycated albumin can be measured rapidly, easily, precisely, and inexpensively [42]. Therefore, these nontraditional glycemic markers may be useful in clinical practice or research settings with limited resources (e.g., developing countries [37]). In addition, these nontraditional glycemic markers can be assessed with serum and plasma samples, while HbA1c requires whole blood samples. Therefore, when research studies or trials have only stored serum or plasma, these

nontraditional glycemic markers would be reasonable alternatives as useful glycemic markers for PAD.

There are several limitations in our study. First, glycemic markers were based on single measurement at baseline. Second, the definition of PAD (and CLI) relied on hospital discharge diagnostic codes. Although this approach has been used in several studies [27,28], asymptomatic cases or mild cases were unlikely to be captured. However, it is important to study severe PAD, since revascularization procedures and inpatient care account for a majority of medical expenditure related to PAD (e.g., \$3.9 billion for total Medicare paid PAD-related care annually) [43]. Third, we are not able to eliminate the possibility of residual confounding. Finally, we investigated whites and blacks aged 47–70 years, so the results may not be generalizable to other racial or age groups.

In conclusion, traditional and nontraditional glycemic markers are strongly associated with incident PAD, independently of potential confounders. Of the five glycemic markers tested, HbA1c demonstrated the most robust association with PAD. The nontraditional glycemic markers demonstrated stronger associations with PAD than fasting glucose but were no longer associated with PAD after accounting for HbA1c. Of note, all glycemic markers demonstrated stronger associations with CLI than overall PAD. These results suggest the particular usefulness of HbA1c for classifying the risk of PAD and the importance of hyperglycemia in the progression to the severe form of PAD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.atherosclerosis.2018.04.042>.

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Fig. 1. Adjusted incidence rates for baseline glycemic markers with incident PAD

(A) HbA1c, (B) fasting blood glucose, (C) fructosamine, (D) glycated albumin, and (E) 1,5-AG. The graph shows incidence rate per 1000 person-years and 95% CIs (shaded area) of PAD with spline terms of A1c (knots at 5.7, 6.5, and 7%), fasting glucose (knots at 5.0, 5.6, and 7 mmol/L), fructosamine, glycated albumin, and 1,5-AG (knots at the 5th, 35th, 65th, and 95th percentiles) adjusted for age, race, and sex; trimmed at 1% and 99%. Frequency histograms were shown for persons without diabetes (grey bars) and for persons with diabetes (black bars).

Table 1

Baseline characteristics by categories of PAD during follow-up (N = 11,634).

Characteristic	Overall		No PAD		PAD		PAD without CLI		CLI
					All				
n	11,634		11,242		392		259		133
Age, years	56.8 (5.7)		56.8 (5.7)		58.7 (5.5)		58.7 (5.5)		58.5 (5.7)
Female, %	55.8		56.3		43.9		40.5		50.4
Black, %	22.9		22.8		26.5		16.6		45.9
BMI, kg/m ²	27.9 (5.3)		27.9 (5.3)		28.9 (5.4)		28.2 (4.9)		30.1 (6.0)
Education level, %									
No or basic	20.2		19.8		31.6		26.6		41.4
Intermediate	42.1		42.2		38.5		39.0		37.6
Advanced	37.7		38.0		29.8		34.4		21.1
Smoking status, %									
Current smoker	21.1		20.6		36.0		39.4		29.3
Former smoker	38.2		38.2		37.5		39.4		33.8
Drinking status, %									
Current drinker	57.5		57.6		54.6		61.0		42.1
Former drinker	20.3		20.1		26.3		23.9		30.8
Diagnosed diabetes, %	7.2		6.4		28.3		17.8		48.9
Duration of diagnosed diabetes >~3 years, %	5.6		4.9		24.7		14.3		45.1
Fasting glucose, mmol/L	6.2 (2.1)		6.2 (2.0)		8.0 (4.1)		7.0 (3.1)		9.8 (5.0)
HbA1c, %	5.7 (1.1)		5.7 (1.1)		6.8 (2.1)		6.2 (1.5)		7.9 (2.7)
Fructosamine, μmol/L	237.2 (46.0)		236.0 (43.1)		272.9 (89.8)		249.4 (61.7)		318.6 (115.1)
Glycated albumin, %	13.5 (3.6)		13.4 (3.3)		16.4 (7.3)		14.3 (4.7)		20.4 (9.5)
1,5-AG, ug/ml	17.8 (6.6)		17.9 (6.5)		14.9 (9.0)		16.7 (8.1)		11.2 (9.7)
SBP, mmHg	121.1 (18.4)		120.8 (18.2)		129.3 (21.6)		128.1 (20.5)		131.6 (23.4)
Total cholesterol, mmol/L	5.4 (1.0)		5.4 (1.0)		5.6 (1.1)		5.6 (1.1)		5.6 (1.1)
HDL cholesterol, mmol/L	1.3 (0.4)		1.3 (0.4)		1.1 (0.3)		1.1 (0.4)		1.1 (0.3)
eGFR, ml/min/1.73m ²	96.5 (15.3)		96.6 (14.9)		91.3 (22.6)		90.7 (19.0)		92.5 (28.2)
Insulin, %	1.6		1.4		9.2		4.6		18.0

Characteristic	Overall	No PAD	PAD	PAD without CLI	CLI
Antihypertensive medication, %	31.8	30.9	55.9	52.9	61.7
Lipid lowering medication, %	6.3	6.1	12.0	12.4	11.3
Aspirin-containing analgesics, %	51.1	50.8	59.4	59.8	58.6
Anticoagulants, %	0.7	0.7	1.8	1.9	1.5
Antiplatelet, %	0.9	0.8	3.6	3.5	3.8
History of atrial fibrillation, %	0.4	0.4	0.0	0.0	0.0
History of heart failure, %	4.5	4.3	10.5	8.1	15.0
History of CHD, %	5.4	4.9	19.6	22.0	15.0
History of stroke, %	1.6	1.5	4.3	4.2	4.5

Continuous variables are reported as mean (SD), and categorical variables are reported as a percentage.

Table 2

Adjusted HRs (95% CIs) for PAD and CLI by categories of fasting glucose and HbA1c (N = 11,634).

	PAD n = 392		CLI n = 133		Model 1	Model 2a	Model 2b	Model 1	Model 2a	Model 2b
	Events/N	Model 1	Events/N	Model 1						
HbA1c										
No diagnosis of diabetes										
HbA1c <5.7%	167/8360	1 (reference)	33/8360	1 (reference)					1 (reference)	
HbA1c 5.7–6.4%	78/1973	1.56 (1.17–2.06)	20/1973	1.71 (0.96–3.06)					1.66 (0.93–2.96)	
HbA1c 6.5%	36/468	3.53 (2.39–5.22)	15/468	5.21 (2.68–10.14)					4.07 (2.03–8.18)	
Diagnosis of diabetes										
HbA1c <7%	16/259	1.74 (0.94–3.22)	6/259	2.28 (0.81–6.46)					2.07 (0.73–5.86)	
HbA1c 7%	95/574	6.00 (3.73–9.66)	59/574	10.39 (4.79–22.53)					6.36 (2.68–15.10)	
Fasting glucose										
No diagnosis of diabetes										
<5.6 mmol/L	103/4911	1 (reference)	24/4911	1 (reference)					1 (reference)	
5.6–6.9 mmol/L	145/5202	1.03 (0.79–1.33)	33/5202	0.95 (0.55–1.62)					0.86 (0.50–1.46)	
7 mmol/L	33/688	1.58 (1.04–2.38)	11/688	1.80 (0.86–3.80)					0.81 (0.36–1.84)	
Diagnosis of diabetes										
<7.2 mmol/L	13/168	1.90 (0.96–3.75)	4/168	1.61 (0.48–5.44)					1.15 (0.34–3.95)	
7.2 mmol/L	98/665	3.42 (2.11–5.54)	61/665	5.10 (2.29–11.32)					1.20 (0.47–3.11)	

Model 1 was adjusted for age (years), race (black, white), sex (male, female), education level, BMI, total cholesterol, HDL cholesterol, drinking status (current, former, never), SBP, eGFR, antihypertensive medication use, lipid lowering medication use, aspirin-containing analgesics use, anticoagulants use, antiplatelet medication use, history of atrial fibrillation, heart failure, CHD and stroke, and duration of diabetes (<3 years, <3 years, <3 years). Model 2a was adjusted for all variables in model 1 and fasting glucose. Model 2b was adjusted for all variables in model 1 and HbA1c.

Table 3

Adjusted HRs (95% CIs) for PAD and CLI by categories of fructosamine, glycated albumin, and 1,5-AG (N = 11,634).

	PAD n = 392			CLI n = 133		
	Model 1	Model 2a	Model 2b	Model 1	Model 2a	Model 2b
Fructosamine						
No diagnosis of diabetes						
<77th Percentile (<241.8 µmol/L)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
77th–95th Percentile (241.7–270.0 µmol/L)	0.81 (0.57–1.14)	0.77 (0.55–1.09)	0.75 (0.53–1.06)	0.59 (0.28–1.28)	0.57 (0.26–1.22)	0.53 (0.25–1.15)
96th Percentile (≥ 270.1 µmol/L)	1.85 (1.20–2.84)	1.30 (0.81–2.08)	0.94 (0.58–1.54)	3.36 (1.76–6.44)	2.32 (1.16–4.64)	1.43 (0.68–3.00)
Diagnosis of diabetes						
<32nd Percentile (<274.4 µmol/L)	1.90 (1.09–3.30)	1.71 (0.98–2.97)	1.43 (0.82–2.50)	2.57 (1.05–6.29)	2.32 (0.95–5.65)	1.82 (0.74–4.45)
32nd Percentile (≥ 274.4 µmol/L)	3.61 (2.24–5.83)	1.94 (1.11–3.40)	1.09 (0.61–1.94)	5.44 (2.55–11.61)	2.85 (1.23–6.61)	1.33 (0.55–3.24)
Glycated albumin						
No diagnosis of diabetes						
<77th Percentile (<13.6%)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
77th–95th Percentile (13.6–15.5%)	1.03 (0.74–1.45)	1.00 (0.72–1.40)	0.95 (0.68–1.33)	1.24 (0.65–2.36)	1.21 (0.63–2.29)	1.12 (0.59–2.13)
96th Percentile (≥ 15.6%)	2.35 (1.55–3.55)	1.75 (1.11–2.76)	1.23 (0.76–1.97)	4.89 (2.58–9.24)	3.61 (1.83–7.14)	2.23 (1.08–4.63)
Diagnosis of diabetes						
<32nd Percentile (<16.4%)	1.81 (1.03–3.18)	1.64 (0.93–2.88)	1.40 (0.79–2.47)	2.51 (0.98–6.43)	2.32 (0.91–5.92)	1.91 (0.74–4.90)
32nd Percentile (≥ 16.4%)	4.31 (2.67–6.95)	2.59 (1.48–4.53)	1.41 (0.78–2.54)	7.61 (3.58–16.18)	4.53 (1.95–10.52)	2.14 (0.88–5.23)
1,5-AG						
No diagnosis of diabetes						
>23rd Percentile (>14.6 mg/ml)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
5th–23rd Percentile (7.9–14.6 µg/ml)	0.89 (0.64–1.23)	0.88 (0.63–1.22)	0.87 (0.62–1.20)	0.73 (0.36–1.49)	0.73 (0.36–1.48)	0.72 (0.35–1.47)
4th Percentile (≤ 7.8 µg/ml)	1.81 (1.15–2.84)	1.40 (0.87–2.28)	1.05 (0.63–1.73)	3.14 (1.53–6.42)	2.32 (1.08–4.98)	1.41 (0.62–3.21)
Diagnosis of diabetes						
>68th Percentile (>9.7 µg/ml)	1.37 (0.75–2.51)	1.23 (0.67–2.25)	1.06 (0.58–1.95)	1.57 (0.59–4.19)	1.40 (0.52–3.75)	1.14 (0.43–3.07)
68th Percentile (≤ 9.7 µg/ml)	4.18 (2.60–6.71)	2.60 (1.52–4.46)	1.50 (0.85–2.66)	6.20 (2.94–13.06)	3.73 (1.63–8.50)	1.77 (0.73–4.25)

Models are the same as Table 2.