HbA1c predicts long-term postoperative mortality in patients with unknown glycemic status at admission for vascular surgery: An exploratory study

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Highlights
- Mortality during a 9-year follow-up of patients with peripheral arterial disease was 40%.
- HbA1c is a useful marker in preoperative risk assessment of patients with unknown glycemic status at admission for vascular surgery.

Abstract
Background: Peripheral arterial disease (PAD) and diabetes mellitus (DM) represent major public health challenges and are tightly associated. To facilitate early diagnosis, HbA1c has been implemented as the preferred diagnostic tool for the diagnosis of type 2 DM. In this study, we compared and evaluated HbA1c, fasting plasma glucose (FPG), and 2-hour post-load glucose values to determine which test best predicted mortality in patients with PAD.

Methods: In all, 273 PAD patients with unknown glycemic status admitted to Haukeland University Hospital for elective surgery between October 2006 and September 2007 were included in the study. All 273 patients underwent a standard oral glucose tolerance test (OGTT) in addition to determination of HbA1c; patients were then grouped into those with DM, intermediate hyperglycemia, and normoglycemia according to World Health Organization and International Expert Committee criteria.

Results: All-cause mortality was 40% over a 9-year follow-up period. After adjusting for age, sex, and relevant medication, HbA1c was a predictor for mortality (hazard ratio [HR] 1.54; 95% confidence interval [CI] 1.03-2.32; P = 0.04). The association did not achieve statistical significance in a fully adjusted Cox regression model, although the effect estimation of HbA1c on all-cause mortality remained largely unchanged (HR 1.39; 95% CI 0.92-2.09; P = 0.13). The OGTT was not a predictor of long-term mortality.

Conclusions: The results indicate that HbA1c is a useful marker in the preoperative screening of patients of unknown glycemic status at the time of admission for vascular surgery, and may identify people at high risk of long-term mortality following surgical treatment for PAD.

Keywords
diabetes, HbA1c, mortality, peripheral arterial disease
Peripheral arterial disease (PAD) and diabetes mellitus (DM) are tightly associated. Based on fasting plasma glucose (FPG) levels, an oral glucose tolerance test (OGTT), or a self-reported DM diagnosis, patients with PAD are reported to have a higher prevalence of DM compared with general populations and populations at risk of developing DM. In Norwegian vascular surgery patients, a 55% prevalence of hyperglycemia and a DM frequency of 29% were found as defined by FPG and an OGTT.

The diagnostic criteria for DM have changed over time along with the development and improvement in biochemical tests. The diagnosis of diabetes is currently based on either an FPG ≥7.0 mmol/L, a 2-hour post-load glucose (2hPG) ≥11.1 mmol/L, or HbA1c ≥48 mmol/mol (6.5%). Studies have shown that FPG, 2hPG, and HbA1c levels primarily define different groups of patients as having DM. In addition, patients with PAD and DM, defined by FPG or an OGTT, have higher mortality than patients with PAD alone.

It is of major importance to investigate the consequences of unknown DM in PAD patients when using the current three diagnostic criteria for the DM diagnosis. The aim of the present study was to compare HbA1c, FPG and 2hPG values and to evaluate which test best predicts long-term mortality in patients with PAD.

2 METHODS

This study is a prospective cohort study of patients with unknown glycemic status at the time of admission for vascular surgery.

2.1 Study population

Initially, 465 patients admitted to Haukeland University Hospital for elective surgery between October 2006 and September 2007 were invited to participate in the study. Twenty-one patients died before deciding whether to participate, 66 declined to undergo an OGTT, and 33 did not have an OGTT performed due to logistic reasons. Furthermore, a DM diagnosis had been previously established in 67 patients. Thus, complete data on HbA1c, FPG, and 2hPG values from 273 vascular surgery patients were included for statistical analyses in the present study with unknown glycemic status (Figure 1). The vascular pathologies were carotid stenosis, abdominal aortic aneurysm (AAA), iliac occlusive disease (IOD) including lesions in the common femoral artery, and infragenual occlusive disease. Informed written consent was obtained from all participants. The research protocol was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REK vest 14109).

2.2 Inclusion and exclusion criteria

All patients admitted for elective vascular surgery due to atherosclerotic disease and competent to give consent to participate in the study were considered eligible for inclusion. Patients admitted for emergency procedures, patients with non-atherosclerotic conditions, patients with dementia or mental disability, and patients with known DM were excluded from the study.

2.3 Diagnostic tests

Throughout this paper, the term “OGTT” refers to the measurements of both FPG and 2hPG, unless stated otherwise. The OGTT was performed according to World Health Organization (WHO) guidelines. Plasma glucose concentrations were measured in a fasting state and again 2 hours after the administration of a 75-g glucose load. Diet recommendations were not given prior to the OGTT and HbA1c measurements. Plasma glucose concentrations were primarily assayed using Modular P analytical system (Roche Diagnostics). The HbA1c values were measured in samples of venous whole blood and analyzed using a Variant II HPLC system (Bio-Rad). The diagnostic tests have been described in detail elsewhere.

The OGTT results were categorized according to 2006 WHO criteria, whereas HbA1c results were categorized...
The estimated glomerular filtration rate (eGFR). Reduced renal function was defined as eGFR <60 mL/min per 1.73 m². Reduced renal function was defined as eGFR <60 mL/min per 1.73 m².

2.4 Other variables
Baseline data on age, sex, smoking habits, vascular bed affected, cholesterol levels, medication, and comorbidities were obtained from patients' medical records. The Modification of Diet in Renal Disease equation was used to calculate the estimated glomerular filtration rate (eGFR). Reduced renal function was defined as eGFR <60 mL/min per 1.73 m².

2.5 Endpoints and follow-up
Study participants were followed from the date of surgical intervention either to the date of death or to the date of study closure on 30 August 2016. Data on all-cause mortality were obtained from the Norwegian civil registry. Death of any cause was used as the primary endpoint. An autopsy was performed only on one-third of patients who died during the follow-up period; hence, causes of death were not recorded in the present study.

2.6 Statistical analysis
Data were analyzed using IBM (Armonk, New York) SPSS Statistics 24 and R version 3.4.0 for Windows (R Foundation for Statistical Computing, Vienna, Austria).

Data are presented as the mean ± SD for continuous variables and as counts with percentages for categorical variables. The significance of differences in patient baseline characteristics for patients alive at end study and patients who died during follow-up was explored using $\chi^2$ tests for categorical data and independent samples $t$ tests for continuous data.

Cox regression models were used to estimate all-cause mortality hazard ratio (HR) with 95% confidence intervals (CIs) for HbA1c, FPG, and 2hPG values at baseline. Multivariate Cox regression analysis was performed using HbA1c, FPG, and 2hPG values as continuous variables. A Firth regression model was used to estimate all-cause mortality HRs according to different vascular pathologies and glycemic categories based on both HbA1c and OGTT results. Event-free time was the time from study inclusion until death or censoring. All patients were monitored from enrolment until death or until 30 August 2016. Based on the selection of appropriate covariates according to known risk factors associated with DM and PAD, three models were constructed to evaluate the effect of possible confounding. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, and the use of platelet inhibitors, statins, and antihypertensive medication. Model 3 was a fully adjusted model that included low-density lipoprotein cholesterol, smoking status, a history of coronary artery disease (CAD), a history of cerebrovascular disease and a history of reduced renal function in addition to the covariates included in Models 1 and 2. Model fit was examined by a global test of the proportional hazards assumption. Complete-case analyses were used for all survival models. The variance inflation factor was used to test for multicollinearity.

A power calculation was not performed prior to the recruitment of patients to the study and this study should therefore be considered exploratory. However, the number of events per variable was within an acceptable level.

3 RESULTS

3.1 Glycemic status
Baseline characteristics of the study population based on glycemic status are presented in Table 1. The prevalence of newly diagnosed DM was 12% based on OGTT results and 15% based on HbA1c levels (Figure 2; Supporting Information Table S1). The HbA1c values and OGTT results largely classified different patients as having newly diagnosed DM. Twenty-five of 40 patients (63%) with HbA1c ≥6.5% had a non-DM OGTT result. In addition, 22% of patients categorized with prediabetes based on OGTT results had an HbA1c ≥6.5%.

3.2 Mortality
All-cause mortality was 40% (n = 110) among the 273 vascular surgery patients with unknown glucose status at baseline, and higher for patients with AAA (55%) and infrarenal occlusive disease (45%) than for those with carotid stenosis (24%) and IOD (15%); (Supporting Information Table S2). Mortality in patients with known DM at baseline (n = 67) was 79%. Patients who died during follow-up had significantly higher mean HbA1c at baseline than patients who were alive at the end of the study. Patients who died during follow-up were also older, had a higher prevalence of reduced renal function, and more often had a history of CAD (Table 2). Patients who were alive at the end of the study were more often treated with antiplatelet therapy than those who died during follow-up. The mean follow-up time was 2805 days and the median follow-up time was 3296 days (range 0-3779 days). Independent variables for
TABLE 1  Baseline characteristics of study participants (n = 273) by glycemic status (follow-up ended on 30 August 2016 = 7.8 years)

| Characteristics          | Reference population* | HbA1c (%) | OGTT b |
|--------------------------|-----------------------|-----------|--------|
|                          |                       | 6.0-6.4   | ≥6.5   | PreDM c | DM d |
| No. participants         | 70 (26)               | 122 (45)  | 40 (15) | 90 (34) | 33 (12) |
| Age (years)              |                       |           |        |         |       |
| Mean                     | 67.6                  | 70.3      | 71.6   | 71.5*   | 71.1  |
| Range                    | 49-87                 | 35-88     | 54-89  | 48-89   | 59-88 |
| Sex                      |                       |           |        |         |       |
| Female                   | 21 (30)               | 38 (31)   | 8 (20) | 15 (17) | 8 (24) |
| Male                     | 49 (70)               | 84 (69)   | 32 (80)| 75 (83) | 25 (76)|
| BMI (kg/m²)              |                       |           |        |         |       |
| Mean ± SD                | 25.2 ± 4.3            | 25.2 ± 4.4| 27.7 ± 4.4* | 26.4 ± 4.4 | 27.0 ± 3.3 |
| Range                    | 16.7-35.8             | 16.4-38.9 | 18.5-36.1 | 17.7-38.9 | 22.2-32.9 |
| No. of cases with missing data | 36 | 55     | 13    | 37    | 12   |
| Vascular pathology       |                       |           |        |         |       |
| Carotid stenosis         | 11 (16)               | 17 (14)   | 8 (20) | 10 (11) | 6 (18) |
| AAA                      | 16 (23)               | 25 (21)   | 8 (20) | 25 (28) | 7 (21) |
| IOD                      | 18 (26)               | 22 (18)   | 2 (5)  | 6 (7)  | 3 (9)  |
| InOD                     | 23 (33)               | 57 (47)   | 21 (53)* | 48 (53)* | 16 (49) |
| Peripheral arterial aneurysms | 2 (3) | 1 (1) | 1 (3) | 1 (1) | 1 (3) |
| Smoking status           |                       |           |        |         |       |
| Non-smoker               | 8 (11)                | 24 (20)   | 6 (15) | 10 (11) | 9 (27) |
| Former or current smoker | 57 (81)               | 94 (77)   | 33 (83)| 77 (86) | 21 (64) |
| No. of cases with missing data | 3 (7) | 4 (3) | 1 (3) | 3 (3) | 3 (9) |
| Renal function*          |                       |           |        |         |       |
| Normal                   | 60 (86)               | 87 (71)   | 25 (63) | 56 (62) | 24 (73) |
| Reduced                  | 10 (14)               | 34 (28)*  | 13 (33)* | 32 (36)* | 9 (27) |
| No. of cases with missing data | 0 | 1 (1) | 2 (5) | 2 | 0 |
| Medical history          |                       |           |        |         |       |
| Antihypertensive treatment|                       |           |        |         |       |
| No                       | 21 (30)               | 26 (21)   | 4 (10) | 14 (16) | 6 (18) |
| Yes                      | 49 (70)               | 96 (79)   | 36 (90)* | 76 (84) | 27 (82) |
| CAD                      |                       |           |        |         |       |
| No                       | 55 (79)               | 99 (81)   | 28 (70) | 71 (79) | 23 (70) |
| Yes                      | 15 (21)               | 23 (19)   | 12 (30) | 19 (21) | 10 (30) |
| FPG (mmol/L)             |                       |           |        |         |       |
| Mean ± SD                | 5.2 ± 0.5             | 5.5 ± 0.6* | 6.6 ± 1.3** | 5.9 ± 0.5** | 7.1 ± 1.4** |
| Range                    | 4.1-6.0               | 4.2-7.3   | 4.8-9.8 | 4.4-6.7 | 5.2-10.5 |
| 2hPG (mmol/L)            |                       |           |        |         |       |
| Mean ± SD                | 5.4 ± 1.2             | 7.0 ± 3.4** | 10.2 ± 3.5** | 8.3 ± 1.9** | 13.2 ± 4.7** |
| Range                    | 2.4-7.6               | 2.9-31.8  | 3.8-18.8 | 2.3-10.9 | 3.0-31.8 |
| No. of cases with missing data | 0 | 0 | 2 | 0 | 2 |
TABLE 1  (Continued)

| Characteristics | Reference populationa | HbA1c (%) | OGTTb | PreDMc | DMDd |
|----------------|-----------------------|-----------|-------|--------|------|
|                |                       | 6.0-6.4   |       |        |      |
| HbA1c (%)      |                       | 6.2 ± 0.1** |       |        |      |
| Mean ± SD      | 5.7 ± 0.2             | 6.8 ± 0.5** |       |        |      |
| Range          | 5.1-5.9               | 6.0-6.4   | 6.5-8.8 | 5.0-7.2 | 5.2-8.8 |
| Total cholesterol (mmol/L) | | | | | |
| Mean ± SD      | 4.6 ± 1.0             | 4.3 ± 1.0 | 4.5 ± 1.1 | 4.4 ± 1.0 |
| Range          | 2.5-6.9               | 2.3-6.7   | 2.0-9.1 | 2.3-6.8 |
| No. of cases with missing data | 1       | 0         | 0        | 0      |
| LDL-C (mmol/L) |                       | 2.8 ± 0.9 | 2.5 ± 0.9 | 2.7 ± 1.1 | 2.7 ± 0.9 |
| Mean ± SD      | 1.1-5.1               | 0.9-5.5   | 1.0-4.7 | 0.9-7.4 | 1.1-5.0 |
| Range          | 1                    | 1         | 0         | 0      |
| No. of cases with missing data | 2       | 1         | 0         | 0      |

Abbreviations: AAA, abdominal aortic aneurysm; BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; InOD, infrainguinal occlusive disease; IOD, iliac occlusive disease; LDL-C, low-density lipoprotein cholesterol.

Unless indicated otherwise, data are given as n (%).
*P < 0.05; **P < 0.001 compared with the reference population. The P-values given in the table refer to the association between patients grouped in different glycemic categories compared with the reference population and were determined using the Chi-squared test for categorical variables and ANOVA for continuous variables.

TABLE 2  Baseline characteristics according to alive/dead status at the end of the follow-up period

| Characteristics | All patients | Died during follow-up | Alive at end of study | P-value |
|----------------|--------------|-----------------------|-----------------------|---------|
| Total (%)      | 273 (100)    | 110 (40)              | 163 (60)              |         |
| Age (years)    |              |                       |                       | <0.001a |
| Mean           | 69.6         | 74.1                  | 66.5                  |         |
| Range          | 35-89        | 53-89                 | 35-87                 |         |
| Sex            |              |                       |                       | 0.07b   |
| Female         | 73 (26.7)    | 23 (21)               | 50 (31)               |         |
| Male           | 200 (73.3)   | 87 (79)               | 113 (69)              |         |
| BMI (kg/m²)    |              |                       |                       | 0.05*   |
| Mean ± SD      | 25.7 ± 4.3   | 24.9 ± 4.6            | 26.2 ± 4.0            |         |
| Range          | 16.4-38.9    | 16.4-36.1             | 18.5-38.9             |         |
| No. of cases with missing data | 112 (41) | 46 (42) | 66 (40) |         |
| Vascular pathology |          |                       |                       |         |
| Carotid stenosis | 42 (100)    | 10 (24)               | 32 (76)               |         |
| AAA            | 60 (100)     | 33 (55)               | 27 (45)               |         |
| IOD            | 47 (100)     | 7 (15)                | 40 (85)               |         |
| InOD           | 119 (100)    | 58 (49)               | 61 (51)               |         |
| Peripheral arterial aneurysms | 5 (2) | 2 (40) | 3 (60) |         |
| Smoking status |              |                       |                       | NSa     |
| Non-smoker     | 42 (15.5)    | 20 (18)               | 22 (14)               |         |
| Former or current smoker | 219 (80) | 87 (79) | 132 (81) |         |
| No. of cases with missing data | 12 (4.5) | 3 (3) | 9 (6) |         |
| Renal functionc |          |                       |                       | 0.007b  |
| Normal         | 199 (73)     | 71 (65)               | 127 (78)              |         |
| Reduced        | 71 (26)      | 39 (36)               | 33 (20)               |         |
| No. of cases with missing data | 3        | 0                    | 3 (2)                |         |
| Medical history |              |                       |                       | NSb     |
| CVD            |              |                       |                       |         |
| No             | 212 (78)     | 84 (76)               | 131 (80)              |         |
mortality were age, male sex, and lack of treatment with platelet inhibitors.

Differences in survival between glycemic categories are shown in Figure 3. Patients diagnosed with DM according to HbA1c values had significantly higher mortality during follow-up than patients with normal HbA1c (P = 0.015). Patients diagnosed with intermediate hyperglycemia based on OGTT results, but not fulfilling the criteria for DM, had significantly higher mortality than normoglycemic patients (P = 0.001).

In crude analysis, as well as in the age- and sex-adjusted Cox regression model (Model 1), HbA1c was significantly associated with all-cause mortality (P = 0.01; Table 3). The association remained statistically significant after adjusting for age, sex, and the use of platelet inhibitors, statins, and antihypertensive medication (P = 0.04; Model 2, Table 3). In a fully adjusted Cox regression model, the effect size of HbA1c on all-cause mortality remained largely unchanged, but the association was no longer significant (P = 0.13; Model 3, Table 3). Fasting plasma glucose and 2hPG values

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**TABLE 2** (Continued)

| Characteristics | All patients | Died during follow-up | Alive at end of study | P-value |
|-----------------|--------------|-----------------------|-----------------------|---------|
| Yes             | 61 (22)      | 26 (24)               | 32 (20)               |         |
| No              | 180 (66)     | 50 (46)               | 113 (69)              | <0.0001b|
| No. of cases with missing data | 0 | 0 | 0 |         |
| CAD             |              |                       |                       |         |
| Yes             | 93 (34)      | 60 (55)               | 50 (31)               |         |
| No              |              |                       |                       |         |
| No. of cases with missing data | 0 | 0 | 0 |         |
| Medical treatment |             |                       |                       |         |
| Antihypertensives |              |                       |                       |         |
| No              | 142 (52)     | 17 (16)               | 43 (26)               | 0.03b   |
| Yes             | 131 (48)     | 93 (85)               | 120 (74)              |         |
| No. of cases with missing data | 0 | 0 | 0 |         |
| Statins         |              |                       |                       | 0.05b   |
| No              | 30 (11)      | 17 (16)               | 13 (8)                |         |
| Yes             | 243 (89)     | 93 (85)               | 150 (92)              |         |
| No. of cases with missing data | 0 | 0 | 0 |         |
| Antiplatelet agents |          |                       |                       | <0.0001b|
| No              | 37 (14)      | 28 (26)               | 9 (6)                 |         |
| Yes             | 236 (86)     | 82 (75)               | 154 (95)              |         |
| FPG (mmol/L)    |              |                       |                       |         |
| Mean ± SD       | 5.7 ± 0.9    | 5.8 ± 1.1             | 5.6 ± 0.7             | NSa     |
| Range           | 4.1-10.5     | 4.2-10.5              | 4.1-9.4               |         |
| 2hPG (mmol/L)   |              |                       |                       |         |
| Mean ± SD       | 7.3 ± 3.3    | 7.8 ± 3.7             | 7.0 ± 2.9             | 0.04a   |
| Range           | 2.3-31.8     | 2.3-31.8              | 2.4-18.3              |         |
| HbA1c (%)       |              |                       |                       |         |
| Mean ± SD       | 6.1 ± 0.5    | 6.2 ± 0.5             | 6.0 ± 0.4             | 0.003a  |
| Range           | 5.0-8.8      | 5.1-8.8               | 5.0-7.9               |         |
| Total cholesterol (mmol/L) |         |                       |                       |         |
| Mean ± SD       | 4.5 ± 1.1    | 4.4 ± 1.0             | 4.6 ± 1.1             | NSa     |
| Range           | 2.0-9.1      | 2.0-7.5               | 2.5-9.1               |         |
| LDL-C (mmol/L)  |              |                       |                       |         |
| Mean ± SD       | 2.8 ± 1.0    | 2.7 ± 1.0             | 2.8 ± 1.1             | NSa     |
| Range           | 0.9-7.4      | 0.9-5.1               | 1.0-7.4               |         |
| Abbreviations: 2hPG, 2-hour post-load glucose; AAA, abdominal aortic aneurysm; BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; FPG, fasting plasma glucose; InOD, infrainguinal occlusive disease; IOD, iliac occlusive disease; LDL-C, low-density lipoprotein cholesterol. Note, percentages in the table may not add up to 100 due to rounding. Unless indicated otherwise, data are given as n (%). The P-values given in the table refer comparisons between patients who died during follow-up and those who were alive at the end of the study. a Independent samples t test. b Chi-squared test. c Renal function was classified as normal if the estimated glomerular filtration rate (eGFR) was >60 mL/min/1.73 m² and as reduced if eGFR was <60 mL/min/ 1.73 m².
were not independent predictors for mortality in any of the three models (Table 3). The proportional hazards assumption was fulfilled for all variables. No variables were found to be highly correlated. The number of events per variable was 110/10 = 11.

Additional analyses of HRs for death according glycemic categories in the different vascular pathologies were performed (Supporting Information Table S3). Results from a fully adjusted Firth regression model were not available for patients with IOD due to a small number of events combined with a high number of adjustment variables.

### 3.3 Medical treatment

At the time of inclusion, 243 of 273 patients (89%) were receiving statins, 236 (86%) were receiving antiplatelet
therapy, 22 (8%) were receiving warfarin, and 213 (78%) were receiving antihypertensive treatment. Fifty-four (25%) of the 213 patients who received antihypertensive treatment were being treated with three or more antihypertensives. Nine of the 33 (27%) patients with newly diagnosed DM based on OGTT results received antidiabetic therapy at the end of the study and 13 (39%) died during follow-up. Of the 13 patients who died during follow-up, two patients received medical treatment for DM and 11 did not use antidiabetic medication at study closure.

4 | DISCUSSION

The findings of this study indicate that HbA1c is a useful marker in the preoperative screening of patients of unknown glycemic status admitted for vascular surgery. The results of HbA1c testing may identify people at high risk of long-term mortality following surgical treatment for PAD. Thus, HbA1c results may be of importance for preoperative risk assessment in this group of patients.

To the best of our knowledge, the present study is the only long-term follow-up study to have evaluated HbA1c and OGTT as predictors of mortality in patients with PAD.

Five year all-cause mortality in patients with PAD has been reported to be in the range 19% to 37%, 19–21 and 10-year all-cause mortality has been reported to range from 42% to 54%. 20,22 In accordance with these studies, the total mortality in the present study, when including patients with known DM, was 48%. Research has shown that approximately one-third of patients with type 2 DM are unaware of their DM diagnosis, and are hence untreated and at high risk of developing vascular complications. 23 Similarly, one-third of patients with PAD and DM in the present study were unaware of their DM diagnosis.

Several previous studies have aimed to compare mortality in patients with PAD and with or without established DM. Those studies concluded that individuals with PAD and DM had significantly higher mortality than individuals with PAD only. 1,24–26 In those studies, patients with known DM had been diagnosed using FPG and/or 2hPG values. The studies did not provide information about mortality in patients with newly diagnosed DM. Due to variations in the definition of glycemic status, variations in the vascular pathology studied, and variations in the groups of patients selected for comparison, it is difficult to interpret results from studies investigating mortality and glycemic status in patients with vascular disease. In the present study, patients with established PAD and unknown glycemic status were tested for DM using both HbA1c and OGTT criteria. When categorizing patients as DM, intermediate hyperglycemia, or normoglycemia, patients with newly diagnosed DM based on HbA1c values had significantly higher mortality in crude analysis than patients with normal HbA1c. Results from the OGTTs showed that patients with intermediate hyperglycemia, but not patients with DM, had significantly higher mortality in crude analysis than patients with normal OGTT, as also reported by van Kuijk et al. 25 The present study was not designed to explore causality for the association of glycemic status with all-cause mortality. However, several possible explanations may be discussed. Patients with intermediate hyperglycemia based on OGTT results were more likely to be former or current smokers than DM patients. This may have affected the association of OGTT status with all-cause mortality.

Another possible explanation could be the discordance in classification into glycemic categories when using OGTT results compared with HbA1c results. Twenty (22%) of the patients with intermediate hyperglycemia based on OGTT results were categorized as having DM according to HbA1c results.

Patients with DM according to HbA1c and patients with prediabetes based on OGTT results shared some baseline features, which may explain, in part, the similarities in mortality between the two groups. Patients in both categories were significantly older and were more likely to have reduced renal function, a medical history of CAD, and infragenual occlusive disease at baseline than participants with normal HbA1c, FPG, and 2hPG values (reference population).

Further, patients with DM based on OGTT results were informed about their DM diagnosis. However, at the time of inclusion in the study, HbA1c was not yet implemented as a diagnostic criterion for DM. Hence, patients with HbA1c ≥6.5% and a non-DM OGTT result were not informed of

### Table 3: Hazard ratios for death during follow-up according to HbA1c, fasting plasma glucose and 2-hour post-load glucose values

|             | HbA1c | FPG | 2hPG |
|-------------|-------|-----|------|
|             | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Crude       | 1.75 (1.24-2.46) | 0.01 | 1.13 (0.93-1.38) | 0.21 | 1.07 (1.01-1.12) | 0.01 |
| Model 1     | 1.67 (1.15-2.44) | 0.01 | 1.12 (0.90-1.40) | 0.31 | 1.03 (0.96-1.09) | 0.43 |
| Model 2     | 1.54 (1.03-2.32) | 0.04 | 1.12 (0.89-1.41) | 0.35 | 1.03 (0.97-1.10) | 0.35 |
| Model 3     | 1.39 (0.92-2.09) | 0.13 | 1.10 (0.87-1.39) | 0.44 | 1.03 (0.96-1.10) | 0.42 |

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; HR, hazard ratio.

Model 1 was adjusted for age and sex.

Model 2 was adjusted for age, sex, and the use of platelet inhibitors, statins, and antihypertensive medication.

Model 3 was the fully adjusted model, adjusted for low-density lipoprotein cholesterol, smoking status, history of coronary artery disease, history of cerebrovascular disease and history of reduced renal function in addition to the covariates included in Models 1 and 2.
their results. Consequently, treatment for newly diagnosed DM may vary between these groups, which may represent a confounding factor in this study. Conversely, only nine patients (27%) with newly diagnosed DM based on OGTT results, of whom five also had DM according to HbA1c values, received medical treatment for DM at the end of the study, reducing the difference in treatment between the groups. Mean HbA1c values in patients with DM categorized based on OGTT results was 6.5%, which is below the recommended target value of HbA1c in the treatment of DM. This may be a possible explanation for the low treatment rate of newly diagnosed DM in this study population.

It has been reported that HbA1c and the OGTT largely define different groups of patients as having DM.11–13,23 This is in accordance with previous published results from the present study population.16 Oral glucose tolerance test and HbA1c values represent different metabolic expressions. The OGTT is a stress test of pancreatic islet cell functioning, whereas HbA1c represents long-term exposure to plasma glucose. Sustained hyperglycemia may induce non-enzymatic glycation of lipoproteins and thereby start a cascade of changes in the endothelial cells that may lead to endothelial dysfunction.27 Thus, HbA1c may, to a greater extent than OGTT results, express the degree of macro- and microvascular inflammation. This could possibly explain the association between HbA1c and all-cause mortality in the present study. However, the present study was not designed to provide an answer to this assumption. Further studies on the association between HbA1c and inflammation are needed to explore whether this association could be a possible target in future research regarding treatment of patients with PAD and DM.

Studies have shown that both OGTT (FPG and 2hPG) and HbA1c levels are associated with future risk of developing DM.11,28 Of note is the high number of patients categorized as having prediabetes according to HbA1c results in the present study (Figure 2). This study does not provide data on the development from prediabetes into DM during the follow-up period. However, one could speculate that a higher number of patients in the prediabetes group based on HbA1c results may develop DM during the follow-up period than in the prediabetes group based on OGTT results. If so, this would support the conclusion on the association between HbA1c and long-term mortality in the present study. In contrast, recent research has shown that the conversion rate from prediabetes to DM in patients with prediabetes is higher based on OGTT than HbA1c results.29 Hence, we cannot exclude the possibility that the association between OGTT results and mortality in the present study may be underestimated.

In the present study, HbA1c was a predictor for all-cause mortality in crude analysis, as well as after adjustment for age, sex, and medical treatment. The association of HbA1c with all-cause mortality did not achieve statistical significance in multivariate analysis, although the effect estimation of HbA1c on all-cause mortality remained primarily unchanged. This could be explained by a lack of statistical power due to sample size, and by the possibility of multicollinearity. Hence, this study should be considered an exploratory study. The results from subanalyses of HRs for death according to glycemic categories in patients with different vascular pathologies indicate that the association of HbA1c with all-cause mortality remained significant for patients with carotid stenosis and AAA. No statistically significant association of HRs for death with different glycemic categories was seen for patients with peripheral occlusive disease, although the effect estimation was 1.45 in Model 2. However, the results are affected by a low statistical power in this subanalysis. A larger study is needed to enable solid conclusions to be reached for each of the vascular pathologies.

O’Sullivan et al30 investigated 30-day morbidity and mortality, as well as 6-month mortality, in 122 PAD patients without DM and found a significant association between HbA1c and 30-day morbidity. In contrast with the findings of the present study, O’Sullivan et al30 did not find an association of HbA1c with mortality. Fifty-eight percent of patients without DM had HbA1c values of 6.0% to 6.9%, and nine patients died during a follow-up period of 6 months.30 The results of O’Sullivan et al30 were affected by a small sample size, a short follow-up time, and selection bias regarding glycemic status.

In accordance with the results of the present study, data on general populations in both Western countries and Asian populations have demonstrated a positive association of HbA1c levels with morbidity and mortality of cardiovascular disease in people without DM.31–33

Due to an established outpatient program at the Department of Vascular Surgery, Haukeland University Hospital, no patients were lost during follow-up. However, the fact that 66 patients declined to participate in the study and a further 21 patients died before deciding to participate may have introduced a selection bias. Of the 66 who declined to take part in the study, 50% were male. Therefore, a selection bias regarding sex cannot be excluded. However, mean FPG values and the prevalence of newly diagnosed DM based on FPG values alone were the same in the 66 patients as in the study participants. The 21 patients who died had high morbidity and were older than the study population, and are therefore not necessarily comparable to the participants in the present study. Thus, selection bias is believed to have had only a minor effect on overall conclusions, although it cannot be excluded.

Finally, an autopsy was only performed on one-third of patients who died during the follow-up period. Hence, only all-cause mortality was recorded in the present study.

5 CONCLUSION

The present exploratory study suggests that HbA1c is a useful marker in the preoperative screening of PAD patients...
with unknown glycemic status at the time of admission for vascular surgery. The HbA1c results may identify people at high risk of long-term mortality following surgical treatment for PAD. Clinicians should consider including HbA1c for preoperative risk assessment in PAD patients.

A large-scale study should be performed to confirm the results reported herein and to evaluate whether the conclusion holds for different vascular pathologies. Further, an intervention study targeting glucose control should be considered to explore possible implications on mortality and relapse of the vascular pathology.

In addition, the possible association of HbA1c with hyperinsulinemia and inflammatory markers in patients with PAD should be investigated as a potential target in the treatment of patients with PAD and abnormal glucose metabolism.

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DISCLOSURE

The authors have no conflicts of interest to disclose.

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