



## Glycated hemoglobin and long-term prognosis in patients with suspected stable angina pectoris without diabetes mellitus: A prospective cohort study



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### ABSTRACT

**Objective:** Associations of glycated hemoglobin A1c (HbA1c) levels to incident coronary and cardiovascular events among non-diabetic patients with coronary artery disease are unclear. We investigated relations of HbA1c to long-term prognosis in such patients.

**Methods:** A prospective cohort of 2519 patients undergoing elective coronary angiography for suspected stable angina pectoris (SAP) was divided into pre-defined categories according to HbA1c (%) levels (<5.0, 5.0–5.6 (reference), 5.7–6.4), and followed for median 4.9 years. The primary end-point was major coronary events (including non-fatal and fatal acute myocardial infarctions, and sudden cardiac death). Secondary end-points were death from cardiovascular disease (CVD) and all-cause mortality. Hazard ratios (HRs) (95% confidence intervals [CIs]) were obtained by Cox regression.

**Results:** Median age at inclusion was 62 years, 73% were males, median HbA1c was 5.6% and random plasma-glucose 5.4 mmol/L. After multivariate adjustment, HbA1c levels within the pre-diabetic range were not associated with risk of major coronary events, HR (95% CI): 1.13 (0.79–1.62);  $P = 0.49$ , death from CVD or all-cause mortality HR (95% CI): 0.95 (0.55–1.66) and 1.04 (0.70–1.53), respectively;  $P \geq 0.85$ . Similarly, there was no significant association between HbA1c values within the lowest category and risk of study outcomes, ( $P \geq 0.18$ ).

**Conclusion:** In non-diabetic patients with suspected SAP, there was no overall association between HbA1c levels and prognosis, questioning an independent role of glycemia in the pathogenesis of atherosclerotic complications in these patients.

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### 1. Introduction

Hemoglobin A1c (HbA1c) is a marker of glycemia, reflecting the average plasma glucose concentration over the previous 8–12 weeks [1]. It has been extensively applied for the monitoring and control of diabetes mellitus and was recently introduced as a diagnostic test defining a pre-diabetic state and overt diabetes, at 5.7% and 6.5%, respectively [1].

The INTERHEART study of multiple ethnicities, showed a strong dose–response relationship between HbA1c and risk of acute myocardial infarction (AMI), independent of the presence of self-reported diabetes [2]. Further, elevated HbA1c levels, even within the pre-diabetic range, have been associated with increased risk of all-cause mortality and cardiovascular disease (CVD) in general populations [3,4]. However, it is not established whether the associations to macrovascular disease reflect glucose levels per se, or is related to the frequent co-occurrence of pre-diabetes with the metabolic syndrome [5]. Interestingly, low HbA1c levels have also been associated with increased risk of mortality [4,6], although results have been inconsistent [7] and underlying mechanisms remain unknown.

The prognostic implications of HbA1c levels in patients without diabetes, but with pre-existent coronary artery disease (CAD) have not been extensively evaluated. Associations of HbA1c to all-cause mortality have been demonstrated in such patients [8], but it is not clear whether the unfavorable prognosis is attributable to CVD [9].

We therefore aimed to evaluate the relations of HbA1c levels with risk of major coronary events, CVD mortality and all-cause mortality in a large cohort of patients without diabetes, referred to coronary angiography for suspected stable angina pectoris (SAP).

## 2. Methods

### 2.1. Study population

The source population consists of 4164 adults who underwent elective coronary angiography for suspected SAP in either of two Norwegian university hospitals between 2000 and 2004 [10]. A total of 2573 (61.8%) were originally included in the Western Norway B-Vitamin Intervention Trial (WENBIT; ClinicalTrials.gov Identifier: NCT00354081) [11].

For the present prospective cohort study, 1603 (38.5%) patients with diabetes, defined according to American Diabetes Association criteria [1], and 42 (1.0%) patients with missing HbA1c measurements were excluded, leaving 2519 (60.5%) participants eligible for the final analyses.

The study fulfilled the Declaration of Helsinki and was approved by The Regional Committee for Medical and Health Research Ethics (approval number 2010/1880) and The Norwegian Data Protection Authority. All participants provided written informed consents.

### 2.2. Baseline data

Information on medical history, cardiovascular risk factors and current medication were provided through a self-administered questionnaire completed by each patient, as previously reported [11]. Trained study personnel validated completed questionnaires against medical records. Fasting referred to not having ingested any food or beverage 6 h prior to blood sampling. Left ventricular ejection fraction, angiographic extent of CAD and smoking status was assessed as previously described [10]. Body mass index (BMI) was calculated by dividing weight by height squared ( $\text{kg}/\text{m}^2$ ).

### 2.3. Biochemical analyses

Standard blood laboratory parameters were analyzed in fresh samples according to routine protocols at the referring hospitals. Study specific samples were collected together with routine blood samples before coronary angiography, and stored at  $-80\text{ }^\circ\text{C}$  until analysis. Reagent kits of type Tina-quant<sup>®</sup> were used for measurement of apolipoprotein A-I and apolipoprotein B. C-reactive protein (CRP) (latex, high sensitive assay) were obtained from Roche Diagnostics (GmbH, Mannheim, Germany) and serum measurements

on these parameters were done on the Hitachi 917 system (Roche Diagnostics). HbA1c was determined by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry [12] and plasma cotinine by liquid chromatography/tandem mass spectrometry at BEVITAL AS, Bergen, Norway [13]. We measured serum cardiac troponin T using a high sensitive cardiac troponin T assay on Modular E170 (Roche Diagnostics), with 3 ng/L as the lower detection limit. Cobalamin was measured using a microbiological assay [14]. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [15].

### 2.4. Follow-up and clinical end-points

Information on study end-points was collected as described previously [16]. The primary end-point was major coronary events, which included non-fatal and fatal AMIs, and sudden cardiac death (diagnoses coded I21, I46 and R96 according to the International Statistical Classification of Diseases, 10th version [ICD-10]). Secondary end-points were CVD mortality (causes of death coded I00–I99 according to the ICD-10 system), and all-cause mortality.

Patients were followed up until they experienced an event, or throughout December 31, 2006.

### 2.5. Statistical analyses

The total cohort was divided into pre-defined categories according to HbA1c levels (%):  $<5.0$ ,  $5.0$ – $5.6$  and  $5.7$ – $6.4$  [17]. Baseline continuous and categorical variables are listed as median (25th, 75th percentile) and counts (%), respectively. The linear trends across HbA1c categories were tested by median quantile regression models [18] for continuous variables and logistic regression for categorical variables.

The associations between HbA1c and risk of study outcomes were explored by Cox proportional hazard regression with the HbA1c range  $5.0$ – $5.6\%$  as the reference category. In addition, generalized additive modeling was performed to assess potential risk associations on a continuous scale. The simple model included age and sex as independent variables. Additional covariates for the multivariate model were selected on the basis of clinical relevance and included: current smoking (dichotomous), hypertension (dichotomous), number of significantly stenosed coronary arteries (0–3), left ventricular ejection fraction (continuous), revascularization following angiography (none, percutaneous coronary intervention or coronary artery bypass graft surgery: 0–1), previous AMI (dichotomous), eGFR (continuous), CRP (continuous), BMI (continuous), apolipoprotein A-I (continuous), apolipoprotein B (continuous), and treatment with statins or aspirin (both dichotomous). Additional adjustments for circulating levels of hemoglobin, cobalamin, alanine aminotransferase and aspartate aminotransferase, self-reported weekly alcohol consumption and use of beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor-blockers did not appreciably alter the results and were not included in the final model. We performed log–log plots and plotted Schoenfeld residuals [19] to ensure that the assumption of proportional hazards was not violated.

Statistical power was assessed on the basis of a two-tailed  $\chi^2$  test comparing an HbA1c of  $\geq 5.7\%$  versus  $<5.7\%$  (SamplePower 2.0, SPSS Inc., Chicago, IL). At  $\alpha = 0.05$ , a power of 97% was obtained for an increase in event rate from 10% to 15% (relative risk 1.5) for the primary end-point major coronary events.

All probability values are two-tailed, with a 5% significance level. Statistical analyses were performed with R 3.0.2 (The R-Foundation for Statistical Computing, Vienna, Austria) [20], the R-packages ‘survival’ [21] and ‘quantreg’ [22], and IBM SPSS Statistics 21 (SPSS IBM, NY, USA).

### 3. Results

#### 3.1. Patient characteristics at baseline

For the total cohort, median (25th, 75th percentile) age was 62 (53, 67) years, 1841 (73%) were men, 809 (32%) were current smokers and 750 (30%) had previously undergone a coronary artery revascularization procedure. Median (25th, 75th percentile) random plasma-glucose was 5.4 (5.0, 6.1) mmol/L, HbA1c 5.6 (5.0, 6.0) % and BMI 26.0 (23.9, 28.4) kg/m<sup>2</sup>. Baseline characteristics according to the pre-defined HbA1c categories are shown in Table 1.

As compared to the reference category, the proportion of women was higher among those having HbA1c levels within 5.7–6.4%, and the frequency of significant CAD and triple-vessel disease was lower. Correspondingly, a smaller proportion received revascularization therapy following baseline coronary angiography. Furthermore, trends were observed for lower left ventricular ejection fraction and less frequent use of aspirin and statins in the pre-diabetic category.

A total of 295 (11.7%) and 33 (1.3%) patients reported to have chronic pulmonary disease and cancer, respectively, at baseline,

with no differences in prevalences according to HbA1c levels. Similarly, median values of BMI, serum triglycerides, cardiac troponin T, hemoglobin, and aminotransferases showed no substantial variation across categories of HbA1c (Table 1). Neither were there any differences in self-reported weekly alcohol consumption (data not shown), although information on the latter parameter was only available for 2011 (80%) of the participants.

#### 3.2. Clinical outcomes according to HbA1c levels

During a median (25th, 75th percentile) follow-up of 4.8 (3.7, 5.8) years, 178 (7.1%) patients experienced a major coronary event. CVD accounted for 75 (3.0%) deaths and 155 (6.2%) participants died from any cause. The age and gender adjusted relationships between the pre-defined HbA1c categories and end-points are shown in Table 2. Compared to the reference category (HbA1c 5.0–5.6%), multivariate hazard ratios (HRs) and 95% confidence intervals (CIs) for the HbA1c range 5.7–6.4% were 1.13 (0.79–1.62) for major coronary events, 0.95 (0.55–1.66) for CVD mortality, and 1.04 (0.70–1.53) for all-cause mortality (all  $P \geq 0.49$ ). Similarly, there were no significant increases in risk of clinical outcomes

**Table 1**  
Baseline characteristics of the study population (n = 2519) according to HbA1c categories.

	HbA1c (%)			P for trend
	<5.0%	5.0–5.6%	5.7–6.4%	
	n = 637	n = 771	n = 1111	
HbA1c (%)	4.6 (4.2, 4.8)	5.4 (5.2, 5.6)	6.1 (5.9, 6.3)	–
Age (years)	61 (54, 68)	62 (55, 69)	62 (55, 70)	0.20
Males [N (%)]	498 (78.2)	556 (72.1)	787 (70.8)	0.002
BMI (kg/m <sup>2</sup> )	26.0 (24.1, 28.1)	25.9 (23.7, 28.4)	26.2 (24.0, 28.6)	0.23
Left ventricular ejection fraction (%)	67 (60, 70)	65 (60, 70)	66 (60, 70)	0.02
Fasting [N (%)]	141 (22.1)	199 (25.8)	303 (27.3)	0.07
Random glucose (mmol/L)	5.4 (4.9, 6.0)	5.5 (5.0, 6.1)	5.5 (5.0, 6.1)	0.02
Triglycerides (mmol/L)	1.40 (1.09, 2.00)	1.46 (1.04, 2.07)	1.46 (1.07, 2.00)	0.27
Apolipoprotein A-I (g/L)	1.32 (1.14, 1.47)	1.30 (1.15, 1.49)	1.30 (1.14, 1.48)	0.36
Apolipoprotein B (g/L)	0.89 (0.75, 1.05)	0.87 (0.72, 1.06)	0.87 (0.72, 1.04)	0.04
Serum CRP (mg/L)	1.63 (0.79, 3.06)	1.65 (0.83, 3.33)	1.71 (0.86, 3.69)	0.39
eGFR (mL/min)	91 (79, 100)	91 (80, 100)	91 (79, 99)	1.00
Hgb (g/dL)	14.4 (13.6, 15.2)	14.4 (13.5, 15.1)	14.3 (13.4, 15.0)	0.25
ALT (IU/L)	28 (21, 39)	28 (21, 38)	27 (19, 37)	0.26
AST (IU/L)	25 (21, 31)	25 (21, 30)	25 (21, 30)	1.00
Cobalamin (pmol/L)	352 (273, 444)	358 (269, 445)	363 (274, 468)	0.18
Cardiac troponin T	4 (3, 9)	4 (3, 9)	4 (3, 9)	1.00
<i>Cardiovascular history and risk factors [N (%)]</i>				
Current smoking	212 (33.3)	250 (32.4)	347 (31.2)	0.36
Previous AMI	260 (40.8)	312 (40.5)	420 (37.8)	0.18
Previous PCI	138 (21.7)	137 (17.8)	188 (16.9)	0.02
Previous CABG	75 (11.8)	96 (12.5)	116 (10.4)	0.32
Hypertension	266 (41.8)	334 (43.3)	513 (46.2)	0.06
Cancer	5 (0.8)	10 (1.3)	18 (1.6)	0.15
Chronic pulmonary disease	61 (9.6)	97 (12.6)	137 (12.3)	0.12
<i>Baseline coronary angiography [N (%)]</i>				
No significant stenosis	120 (18.8)	196 (25.4)	316 (28.4)	<0.001
One-vessel disease	170 (26.7)	189 (24.5)	238 (21.4)	0.01
Two-vessel disease	141 (22.1)	170 (22.0)	265 (23.9)	0.36
Three-vessel disease	206 (32.3)	216 (28.0)	292 (26.3)	0.009
<i>Baseline coronary intervention [N (%)]</i>				
None or medication only	264 (41.4)	355 (46.0)	520 (46.8)	0.04
PCI	210 (33.0)	261 (33.9)	361 (32.5)	0.77
CABG	152 (23.9)	141 (18.3)	209 (18.8)	0.02
<i>Medications at discharge [N (%)]</i>				
Statins	530 (83.2)	620 (80.4)	869 (78.2)	0.01
Aspirin	547 (85.9)	652 (84.6)	884 (79.6)	<0.001
Dual anti-platelet therapy <sup>a</sup>	103 (16.2)	133 (17.3)	151 (13.6)	0.09
β-blocker	472 (74.1)	577 (74.8)	780 (70.2)	0.05
ACE inhibitor and/or ARB	161 (25.3)	208 (27.0)	354 (31.9)	0.002

Abbreviations: HbA1c, glycated hemoglobin A1c; BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hgb, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

<sup>a</sup> Dual anti-platelet therapy, any two anti-platelet agents.

**Table 2**  
Risk associations between HbA1c categories and clinical outcomes in the study population (n = 2519).

End-point	HbA1c category	Events	Simple model <sup>a</sup> HR (95% CI)	P	Multivariate model <sup>b</sup> HR (95% CI)	P
Major coronary event	5.7–6.4%	79	1.13 (0.79–1.61)	0.50	1.13 (0.79–1.62)	0.49
	5.0–5.6%	50	Ref.		Ref.	
CVD mortality	<5.0%	49	1.19 (0.80–1.76)	0.39	1.16 (0.78–1.73)	0.46
	5.7–6.4%	33	1.09 (0.63–1.88)	0.77	0.95 (0.55–1.66)	0.86
All-cause mortality	5.0–5.6%	21	Ref.		Ref.	
	<5.0%	21	1.22 (0.67–2.24)	0.51	1.23 (0.66–2.26)	0.52
All-cause mortality	5.7–6.4%	67	1.11 (0.76–1.64)	0.59	1.04 (0.70–1.53)	0.85
	5.0–5.6%	42	Ref.		Ref.	
	<5.0%	46	1.33 (0.88–2.03)	0.18	1.33 (0.87–2.04)	0.18

Abbreviations: HbA1c, glycated hemoglobin A1c; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease.

<sup>a</sup> Adjusted for age and gender.

<sup>b</sup> Adjusted for age, gender, current smoking, hypertension, number of significantly stenosed coronary arteries (0–3), left ventricular ejection fraction, revascularization following angiography (none, percutaneous coronary intervention or coronary artery bypass graft surgery), previous acute myocardial infarction, estimated glomerular filtration rate, C-reactive protein, body mass index, apolipoprotein A-I, apolipoprotein B, and treatment with statins and aspirin.

associated with the lowest HbA1c category ( $P \geq 0.18$ ; Table 2). Further, multivariate generalized additive regression, with HbA1c as a continuous parameter, did not reveal significant risk associations to the primary end-point, major coronary events ( $P \geq 0.16$ ; Fig. 1), or the secondary end-points ( $P \geq 0.20$ ).

In a supplementary analysis, we included the subjects classified with diabetes mellitus (n = 1603) at baseline [1] to the study population. Notably, these patients were at significantly increased risk of major coronary events, as well as CVD – and all-cause mortality, with similar HRs in age and gender adjusted as in multivariate analyses (Supplemental Table 1).

## 4. Discussion

### 4.1. Principal findings

In this large cohort of suspected SAP patients without diabetes, we observed no overall association between HbA1c levels and risk

of incident coronary events or mortality during nearly 5 years of follow-up.

### 4.2. HbA1c levels and disease risk in previous studies

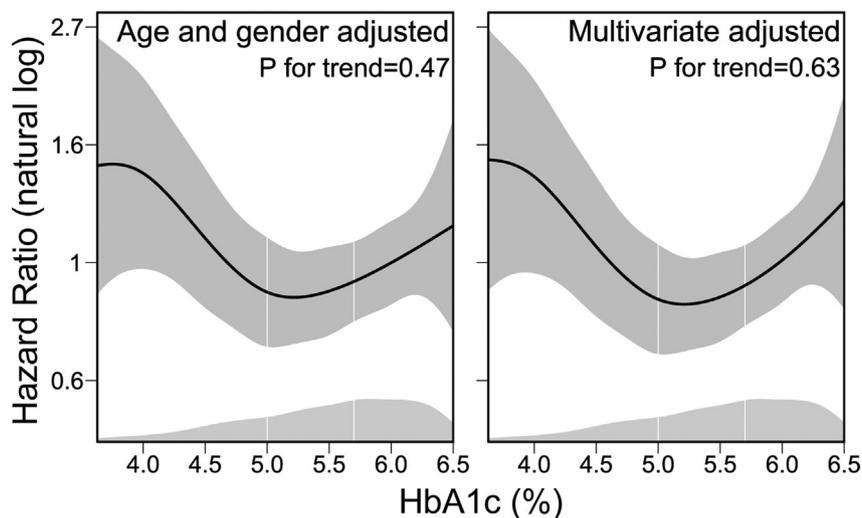
HbA1c correlates with micro- and macrovascular complications in patients with diabetes [1]. HbA1c >8.0% as compared to <7.0% have been reported to increase the long-term risk of all-cause mortality in such patients [23]. On the other hand, intensive glucose-lowering treatment (target HbA1c <6.0%) has also been associated with all-cause mortality [24].

In initially healthy populations, elevated HbA1c was associated with increased risk of all-cause mortality, new onset diabetes and CVD [3,4,7,25], but added little value to CVD risk prediction models containing traditional risk factors [25]. Regarding the lower end of the HbA1c distribution both J-shaped [4,6,25] and no relations [26] to all-cause mortality have been found. The studies are not easily comparable, however, as a variety of cut-off levels were applied.

The prognostic value of HbA1c in CAD patients without diabetes has not been extensively evaluated. Prior studies, including patients with acute coronary syndrome [8,9,27], showed that elevated levels predicted increased risk of all-cause mortality. One of these cohorts also demonstrated associations of elevated HbA1c levels to CVD- and cancer mortality. However, patients with newly diagnosed type 2 diabetes were not excluded from the study population [27], which may explain the discordance from our results.

### 4.3. Interpretation of findings

HbA1c has low intra-, but high inter-individual variability and a number of non-glycemic determinants [28,29]. Heritability of HbA1c levels may be in the range of 40–60% [29], but genetic variants associated with HbA1c levels among patients without diabetes, have not been found to influence mortality [30]. In addition to glucose concentrations, HbA1c levels can be affected by conditions associated with changes in erythrocyte life span, like hemoglobinopathies, vitamin B12 or iron deficiencies, liver or kidney disease [31,32]. In addition, HbA1c values may be reduced as a consequence of heavy alcohol consumption [33].



**Fig. 1.** Plasma HbA1c levels and risk of major coronary events in 2519 non-diabetic patients with suspected coronary artery disease. The association between glycated hemoglobin (HbA1c) levels (%) and risk of major coronary events obtained by generalized additive regression. The simple model (left panel) is adjusted for age and gender. The multivariate model (right panel) is additionally adjusted for current smoking, hypertension, number of significantly stenosed coronary arteries (0–3), left ventricular ejection fraction, revascularization following angiography (none, percutaneous coronary intervention or coronary artery bypass graft surgery), previous acute myocardial infarction, estimated glomerular filtration rate, C-reactive protein, body mass index, apolipoprotein A-I, apolipoprotein B, and treatment with statins and aspirin. The solid lines denote hazard ratios and the shaded areas the 95% confidence interval. Density plots show the distribution of HbA1c, and vertical lines denote values of 5.0% and 5.7%.

In the present cohort, levels of hemoglobin, cobalamin, liver enzymes and eGFR were basically equally distributed across categories of HbA1c, and adjustment for these variables had only minor effects on the risk estimates. In addition, we found no association between self-reported alcohol consumption and HbA1c. Hence, in our cohort of clinically stable CAD patients, with a low frequency of other co-morbidities, glycemia is probably the main determinant of HbA1c levels.

According to the most recent diagnostic guidelines, an HbA1c cut-off at 5.7% defines a pre-diabetic state [1]. Individuals with pre-diabetes were found to have increased intima media thickness of the carotids, an early marker of atherosclerosis [34]. Pre-diabetes has also been associated with risk of diabetes development as well as future microvascular, and macrovascular complications [5]. However, a substantial proportion of subjects classified with pre-diabetes will regress to normo-glycemia [35]. It is currently not established whether the increased CVD risk is confined to the subset that eventually develops overt diabetes mellitus [36].

Insulin resistance is a key pathophysiologic feature of pre-diabetes [37], which is characterized by reduced insulin sensitivity in hepatocytes and muscle cells, accompanied by increased insulin secretion from the pancreas. According to prevailing theories, insulin resistance and the compensatory hyperinsulinemia promote hypertension and dyslipidemia, as well as a pro-thrombotic and pro-inflammatory state [38]. Correspondingly, the prevalence of pre-diabetes overlaps substantially with the metabolic syndrome [39]. The frequent co-occurrence with other CVD risk factors complicates the isolation of vascular effects from intermediate hyperglycemia in epidemiological studies [5]. Hence, whether pre-diabetes per se is causally related to atherosclerosis and its complications is still uncertain [5]. Interestingly, insulin resistance may also be present in normo-glycemic patients [36], and is shown to be particularly prevalent in individuals at high CVD risk [36] and in patients with established CAD [38].

In the present cohort, we found no differences in BMI or levels of lipoproteins and CRP across categories of HbA1c. There was only a weak tendency towards a higher prevalence of hypertension in patients with pre-diabetes, and elevated HbA1c levels were actually associated with less extensive CAD at coronary angiography. Notably, however, risk estimates were similar in age and gender adjusted as in multivariate analyses, suggesting that confounding factors are unlikely to explain the lack of associations between HbA1c levels and clinical outcomes.

A community based prospective study, showed an adverse prognostic effect from the diagnosis of pre-diabetes, which was related to subclinical myocardial damage, evaluated by cardiac troponin T levels [40]. In the present cohort, however, baseline troponin T values were similar across HbA1c categories in the non-diabetic range. Notably, these results are in accordance with prior cross-sectional findings [41].

The fact that HbA1c showed no relation to CVD prognosis in a patient population without diabetes, but with a high burden of other risk factors, adds to the evidence that moderate hyperglycemia is not an independent mediator of atherosclerotic complications [5]. However, randomized clinical trials are needed to provide definite answers to this question. Prior studies have indicated that hypoglycemic agents can delay the conversion of pre-diabetes to diabetes [42], but showed no effects on surrogate markers of atherosclerosis [43]. However, earlier trials have not been sufficiently powered to determine any effect on long-term risk of clinical CVD events [42].

Studies from the general population [4,6], as well among patients with diabetes [44] have demonstrated increased risk of mortality among subjects with low HbA1c values, although it remains unclear whether these associations partly reflected residual

confounding [45]. Similar findings were not apparent in the present cohort. However, our study was not designed to detect potential adverse prognostic implications from HbA1c levels in the overt hypoglycemic range.

#### 4.4. Strengths and limitations

The strengths of our work include its prospective design, the large sample size and detailed description of patient characteristics at baseline, as well as the thorough evaluation of clinical outcomes. As in any observational study, we cannot exclude the possibility of unmeasured confounders. Neither can we rule out that some under-reporting of clinical outcomes may have occurred, since the collection of end-points was based on registry data. However, we do not suspect that any misclassification differed according to HbA1c levels.

Blood samples were stored at  $-80^{\circ}\text{C}$ , and HbA1c concentrations were analyzed in samples that had been thawed twice. Notably, however, HbA1c measurements were shown to be highly reliable for up to 18 years of storage at  $-70^{\circ}\text{C}$  [46], and levels were stable even after several thawing–freezing cycles [47]. In the present study, HbA1c values were only determined at baseline, but repeated analyses of HbA1c does not seem to improve CVD prediction beyond a single measurement for individuals without diabetes [48].

In addition to being classified based on HbA1c levels, pre-diabetes can be diagnosed from fasting glucose concentrations or oral glucose tolerance tests [1]. Unfortunately, these measures were not available for our study population. Hence, we were not able to compare the prognostic implications from different definitions of pre-diabetes [49].

All the included patients underwent elective coronary angiography for suspected stable CAD, and the majority received medications for CVD risk reduction, including aspirin and statins. Consequently, our findings may not necessarily be generalizable to other patient groups or to healthy individuals. Racial disparities regarding HbA1c values have been reported [50]. As our cohort consists almost exclusively of Caucasians, our results are unlikely to be confounded by ethnicity, but may not necessarily apply to non-Caucasian populations.

## 5. Conclusion

In a large cohort of suspected SAP patients without diabetes, there were no overall associations between HbA1c and long-term risk of coronary events or mortality. Thus, HbA1c measurements appear to have a limited value for clinical risk evaluation of such patients. Moreover, our data add to prior works questioning an independent role of intermediate hyperglycemia in mediating acute atherosclerotic complications.

## Disclosure statement

The authors declare that there is no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.atherosclerosis.2015.02.053>.

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