Relationship between HbA_{1c} levels and risk of cardiovascular adverse outcomes and all-cause mortality in overweight and obese cardiovascular high-risk women and men with type 2 diabetes

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Abstract

Aims/hypothesis The optimal HbA_{1c} concentration for prevention of macrovascular complications and deaths in obese cardiovascular high-risk patients with type 2 diabetes remains to be established and was therefore studied in this post hoc analysis of the Sibutramine Cardiovascular Outcomes (SCOUT) trial, which enrolled overweight and obese patients with type 2 diabetes and/or cardiovascular disease. **Methods** HRs for meeting the primary endpoint (nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest or cardiovascular death) and all-cause mortality were analysed using Cox regression models. **Results** Of 8,252 patients with type 2 diabetes included in SCOUT, 7,479 had measurements of HbA_{1c} available at baseline (i.e. study randomisation). Median age was 62 years

(range 51–86 years), median BMI was 34.0 kg/m² (24.8–65.1 kg/m²) and 44% were women. The median HbA_{1c} concentration was 7.2% (3.8–15.9%) (55 mmol/l [18–150 mmol/l]) and median diabetes duration was 7 years (0–57 years). For each 1 percentage point HbA_{1c} increase, the adjusted HR for the primary endpoint was 1.17 (95% CI 1.11, 1.23); no differential sex effect was observed ($p=0.12$ for interaction). In contrast, the risk of all-cause mortality was found to be greater in women than in men: HR 1.22 (1.10, 1.34) vs 1.12 (1.04, 1.20) for each 1 percentage point HbA_{1c} increase ($p=0.02$ for interaction). There was no evidence of increased risk associated with HbA_{1c} $\leq 6.4\%$ (≤ 46 mmol/l). Glucose-lowering treatment regimens, diabetes duration or a history of cardiovascular disease did not modify the associations.

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Conclusions/interpretation In overweight, cardiovascular high-risk patients with type 2 diabetes, increasing HbA_{1c} concentrations were associated with increasing risks of cardiovascular adverse outcomes and all-cause mortality.

Keywords Cardiovascular outcomes · HbA_{1c} · Macrovascular complications · Type 2 diabetes

Abbreviation

SCOUT Sibutramine Cardiovascular OUTcomes

Introduction

Patients with type 2 diabetes have a well-established high risk of cardiovascular disease and mortality, compared with the general population [1–4]. For a long while it was anticipated that tight normalisation of blood glucose would reduce cardiovascular and all-cause mortality, but recently this dogma has been questioned after some studies reported low normal HbA_{1c}, as well as high HbA_{1c}, levels to be associated with an increased risk of mortality (i.e. a J-shaped curve) [5, 6]. The reason for the excess mortality risk associated with low HbA_{1c} levels is not clear but may include risks associated with hypoglycaemia as well as a direct adverse effect of some pharmacological glucose-lowering agents. On the other hand, no increased risk of mortality associated with low HbA_{1c} values has been observed in other studies [7–11]. To further our scientific understanding of the relationship, we analysed a large population of middle-aged and elderly overweight patients with type 2 diabetes who were at high risk of cardiovascular adverse events at study baseline. Our aim was to evaluate the outcomes associated with differing HbA_{1c} levels and to consider whether indices of the burden of comorbidity, age and agents used for lowering glucose levels could explain the conflicting predictions derived from blood glucose and HbA_{1c} measurements.

Methods

The Sibutramine Cardiovascular OUTcomes (SCOUT) trial (trial registration: ClinicalTrials.gov NCT00234832) was a randomised, double-blind, placebo-controlled, multicentre study conducted in 16 countries with the purpose of comparing the centrally acting anti-obesity drug sibutramine (a noradrenaline [norepinephrine] and serotonin reuptake inhibitor) and lifestyle modification with placebo and lifestyle modification on cardiovascular outcomes in overweight and obese cardiovascular high-risk patients. Most patients enrolled into the SCOUT trial would have been contraindicated for sibutramine use according to the label because

of their pre-existing cardiovascular disease. A full study description is available elsewhere [12]. The original scientific SCOUT hypothesis was that a decrease in weight would outweigh the small sympathomimetic effect of sibutramine; however, the primary analysis showed that patients receiving sibutramine had statistically increased risk of major cardiovascular adverse events compared with those receiving placebo [12].

Patients enrolled in the SCOUT trial were ≥55 years of age, with a BMI of 27–45 kg/m², or a BMI of 25–27 kg/m² with a waist circumference of ≥102 cm in men and ≥88 cm in women. Furthermore, for enrolment in the trial, all patients were required to have a history of coronary artery disease, stroke, peripheral arterial occlusive disease and/or type 2 diabetes with an additional cardiovascular risk factor (diabetic nephropathy, smoking, dyslipidaemia or hypertension). Patients thought unlikely to be able to follow the study protocol due to chronic conditions such as active cancer or advanced heart failure (New York Heart Association class III–IV) were excluded. Due to a lower than expected event rate, inclusion criteria were revised 15 months after first enrolment, so that patients enrolled after that point needed to have both type 2 diabetes and a history of cardiovascular disease. The SCOUT trial was conducted between January 2003 and March 2009, with a maximum follow-up of 72 months. The primary endpoint comprised the first occurrence of nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest or cardiovascular death. Mortality from any cause was a secondary endpoint.

Before randomisation, a full medical history and clinical examination, including anthropometric measurements, vital signs and samples for blood biochemistry and urine analysis, were obtained from all patients. Measurements of HbA_{1c} were obtained at randomisation (baseline) and at years 2, 3, 4 and 5 for patients with type 2 diabetes at baseline. All blood samples were analysed in a certificated laboratory. For the present analysis, all patients with available measurements of HbA_{1c} at study baseline were included (i.e. patients without diabetes were not considered).

Ethics All volunteers gave their written, informed consent before participating. The trial was approved by the relevant local ethical committees and was conducted in the conformity with Declaration of Helsinki.

Statistics Patients were grouped according to selected values of baseline HbA_{1c}. Discrete variables were compared using the Cochran–Armitage trend test and continuous variables were compared using the Kruskal–Wallis test. Analyses of the prognostic importance of baseline HbA_{1c} were performed with Cox proportional hazard regression models. All Cox models were adjusted for sex, age, randomised treatment assignment, diabetes duration, history of arterial

hypertension, congestive heart failure, history of cardiovascular disease, history of revascularisation, ethnicity, tobacco use, systolic and diastolic blood pressure, heart rate, BMI, HDL-cholesterol and LDL-cholesterol concentrations, urinary albumin/creatinine ratio (as a measure of the degree of renal impairment, because conventional estimations of glomerular filtration rates have been shown to be unreliable in obesity [13]) and use of insulin, metformin, sulfonylureas and thiazolidinediones. To further investigate the association between HbA_{1c} values and outcomes, a time-dependent Cox analysis was performed as a sensitivity analysis, allowing for an update on changes in BMI and HbA_{1c} levels at years 2, 3, 4 and 5, when HbA_{1c} levels were measured. Statistical tests were two-tailed and were conducted at the 0.05 level of statistical significance.

Results

Of the 9,804 participants randomised to study treatment, 8,252 had type 2 diabetes and 7,479 had measurements of HbA_{1c} available at study baseline and formed the present study population. Median age was 62 years (range 51–86 years) and 44% were women. The median HbA_{1c} was 7.2% (3.8–15.9%) (55 [18–150] mmol/mol) and median diabetes duration was 7.1 years (0.0–56.9 years). In total 2,255 participants were treated with insulin, 2,732 were treated with sulfonylureas, 4,928 were treated with metformin and 283 were treated with thiazolidinediones at study baseline. Table 1 presents baseline characteristics of patients grouped according to selected HbA_{1c} values. Patients within the lower HbA_{1c} categories were observed to have a lower adverse cardiovascular risk profile with, for example, higher HDL-cholesterol, lower albumin/creatinine ratio, lower systolic blood pressure and heart rate, and lower BMI than patients within the higher HbA_{1c} categories. The duration of diabetes and use of glucose-lowering agents (in particular the use of insulin) were also found to be associated with increased levels of HbA_{1c}.

Median follow-up time was 4.3 years (interquartile range 3.6–4.9 years). Figures 1 and 2 present crude incidence rates and adjusted HRs for the primary endpoint (Fig. 1) and all-cause mortality endpoint (Fig. 2) associated with the different HbA_{1c} categories. As shown, increasing HbA_{1c} levels tended to be associated with increased HRs for both endpoints. Analyses that included HbA_{1c} as a continuous variable provided similar results. For each 1 percentage point HbA_{1c} increase, HRs for primary outcome events and all-cause mortality were increased by 1.17 (95% CI 1.11, 1.23) and 1.16 (1.09, 1.23), respectively. Use of sibutramine did not modify these relationships ($p>0.9$ for interactions between HbA_{1c} levels and sibutramine, for both endpoints). Baseline BMI was found not to significantly influence the

association between HbA_{1c} and endpoints ($p>0.1$ for interactions, for both endpoints).

Particular subgroups The prognostic importance of baseline HbA_{1c} on the risk of all-cause mortality was found to be greater in women (mean±SD age 63±6 years, HbA_{1c} level 7.6±1.5% [60±8 mmol/mol]) than in men (age 63±6 years, HbA_{1c} level 7.5±1.4% [58±7 mmol/mol], $p=0.02$ for interaction). For each 1 percentage point increase in baseline HbA_{1c}, the HRs increased by 1.22 (95% CI 1.10, 1.34) in women and by 1.12 (1.04, 1.20) in men. No such differential prognostic importance of HbA_{1c} was evident for the primary endpoint ($p=0.12$ for interaction between sex and HbA_{1c}).

The prognostic importance of baseline HbA_{1c} values was similar in insulin-treated and non-insulin-treated individuals ($p=0.6$ and 0.7 for interaction, for primary endpoint and all-cause mortality, respectively), sulfonylurea and non-sulfonylurea users ($p=0.4$ and 0.8), metformin and non-metformin users ($p=0.1$ and 0.9), and across all ages ($p=0.6$ and 0.6). The prognostic importance of baseline HbA_{1c} was not dependent on diabetes duration ($p=0.6$ and 0.3), urine albumin/creatinine ratio ($p=0.2$ and 0.09), HDL-cholesterol ($p=0.9$ and 0.07), LDL-cholesterol ($p=0.3$ and 0.4) or history of cardiovascular disease, revascularisation or congestive heart failure ($p=0.4$ and 0.6) (history of cardiovascular disease [$p=0.8$ and 0.2], history of revascularisation [$p=0.2$ and 0.8], history of congestive heart failure [$p=0.2$ and 0.3]).

Changes in HbA_{1c} levels over time During the first 4 years after randomisation, mean±SD HbA_{1c} values were found to increase in patients within the lowest baseline HbA_{1c} categories and decrease in patients within the highest HbA_{1c} categories: 0.62±0.80% (6.7±8.7 mmol/l), 0.57±1.14% (6.3±12.5 mmol/l), 0.16±1.21% (1.7±13.2 mmol/l), −0.22±1.44% (−2.4±15.8 mmol/l), −0.75±1.49% (−8.2±16.3 mmol/l) and −1.96±2.87% (−21.4±20.4 mmol/l) in the ≤6.4%, 6.5–7.4%, 7.5–8.4%, 8.5–9.4%, 9.5–10.4% and ≥10.5% HbA_{1c} subgroups, respectively (for subgroup categories in mmol/l, please see the legend to Fig. 1). Increasing levels of HbA_{1c} during follow-up were associated with a trend towards increased HRs for meeting the primary endpoint (HR 1.06 [95% CI 0.98, 1.14]), as well as the all-cause mortality endpoint (HR 1.07 [0.98, 1.16]), for each 1 percentage point HbA_{1c} increase. These associations were not found to be dependent on baseline HbA_{1c} levels ($p=0.8$ and 0.9 , respectively, for interactions between baseline HbA_{1c} values and changes in HbA_{1c}), sex ($p=0.4$ and 0.5 for interactions), diabetes duration ($p=0.8$ and 0.2 for interactions) or baseline BMI ($p=0.6$ and 0.5 for interactions). The HRs associated with baseline HbA_{1c} values remained unchanged when including changes in HbA_{1c} levels in the Cox models. There was no differential prognosis associated with changes in

Table 1 Characteristics of the participants at baseline divided according to their initial HbA_{1c} level

Baseline characteristic	HbA _{1c} level						<i>p</i> value for trend
	≤6.4% (≤46 mmol/mol)	6.5–7.4% (48–57 mmol/mol)	7.5–8.4% (58–68 mmol/mol)	8.5–9.4% (69–79 mmol/mol)	9.5–10.4% (80–90 mmol/mol)	≥10.5% (≥91 mmol/mol)	
No. (%)	1,844 (25)	2,333 (31)	1,631 (22)	883 (12)	477 (6)	311 (4)	
Sex, male (%)	57	58	55	54	54	48	0.63
Age (years)	63.3 (6.3)	63.4 (6.1)	63.6 (6.2)	63.0 (6.0)	62.1 (5.8)	61.5 (5.3)	<0.0001
Randomised to sibutramine (%)	51	51	49	47	49	56	0.3
Diabetes duration (median [interquartile range] years)	3.6 (1.2–7.7)	6.0 (2.7–11.2)	9.5 (5.2–15.2)	11.1 (6.5–17.9)	11.7 (7.3–18.4)	11.8 (6.7–17.4)	<0.0001
Weight (kg), men	99.6 (14.6)	100.4 (14.7)	101.5 (15.5)	100.4 (15.5)	102.8 (15.9)	101.4 (16.6)	0.3
Weight (kg), women	90.3 (14.1)	91.1 (14.1)	91.7 (14.8)	90.0 (14.3)	93.1 (14.9)	90.8 (16.2)	0.2
BMI (kg/m ²)	34.3 (4.5)	34.6 (4.5)	34.8 (4.6)	34.7 (4.7)	34.4 (4.7)	34.9 (5.0)	<0.0001
History of cardiovascular disease (%)	78	77	77	79	80	75	0.8
Arterial hypertension (%)	91	91	91	89	93	92	0.7
Congestive heart failure (%)	7	8	9	10	10	14	0.02
Ethnicity (% white)	97	97	96	94	94	91	0.002
History of revascularisation (%)	38	35	33	35	36	32	0.003
Use of alcohol, current or previous (%)	62	62	59	56	56	53	<0.0001
Use of tobacco, current or previous (%)	54	59	57	57	57	52	0.4
Blood biochemistry							
HDL-cholesterol (mmol/l)	1.23 (0.31)	1.19 (0.29)	1.18 (0.29)	1.17 (0.28)	1.12 (0.25)	1.11 (0.27)	<0.0001
LDL-cholesterol (mmol/l)	2.86 (0.97)	2.81 (0.98)	2.77 (0.95)	2.84 (1.00)	2.87 (1.01)	2.84 (0.95)	0.08
Triacylglycerols (mmol/l)	2.11 (1.22)	2.22 (1.17)	2.33 (1.46)	2.52 (1.78)	2.80 (1.79)	3.21 (2.48)	<0.0001
Creatinine (μmol/l)	90 (24)	92 (26)	92 (27)	93 (30)	94 (31)	93 (31)	0.15
Urinary albumin/creatinine ratio (mg/mmol)	4.5 (21.4)	8.2 (34.0)	10.9 (43.4)	14.4 (44.5)	21.1 (69.1)	17.1 (53.0)	<0.0001
Vital signs							
Systolic blood pressure (mmHg)	138 (12)	138 (12)	139 (13)	140 (13)	139 (13)	139 (14)	<0.001
Diastolic blood pressure (mmHg)	79 (8)	78 (8)	77 (8)	77 (8)	77 (9)	78 (9)	<0.0001
Heart rate (bpm)	70 (10)	71 (10)	73 (10)	73 (10)	75 (10)	75 (10)	<0.0001
Medication							
Insulin (%)	7	23	41	55	57	54	<0.0001
Metformin (%)	41	54	62	60	59	61	<0.0001
Sulfonylureas (%)	29	38	40	38	38	42	<0.0001
Diuretics (%)	48	49	52	50	49	55	0.13
Fibrates (%)	9	10	10	12	15	18	0.03
Statins (%)	64	66	67	65	68	59	0.1
Aspirin (%)	75	76	78	76	77	75	0.3
Calcium-channel blockers (%)	37	37	40	40	40	37	0.3
Beta blockers (%)	64	60	57	58	58	60	<0.0001

Continuous data are presented as mean (SD)

HbA_{1c} between participants with and without a history of cardiovascular disease ($p=0.9$ and 0.8 , respectively, for interactions), or with and without heart failure ($p=0.8$ and 0.8 , respectively, for interactions). On pooling a history of revascularisation, cardiovascular disease and heart failure, there was still no differential prognosis found for patients with and without these conditions ($p=0.9$ for interactions).

A significant interaction ($p=0.04$) was found between change in BMI and increases in HbA_{1c} on the risk of mortality; in participants who decreased their BMI, a 1 percentage point increase in HbA_{1c} was associated with an HR of 1.11 (95% CI 1.01, 1.22), whereas a 1 percentage point increase in HbA_{1c} was associated with an HR of 0.97 (0.83, 1.14) in those whose BMI increased. No similar differential effect of a

Fig. 1 Adjusted HRs (squares) and crude incidence rates (bars) for primary outcome events associated with HbA_{1c} concentrations at baseline. Error bars represent 95% CIs. The number of participants meeting the endpoint was 133, 246, 178, 124, 80 and 66 in the ≤6.4% (≤46 mmol/mol), 6.5–7.4% (48–57 mmol/mol), 7.5–8.4% (58–68 mmol/mol), 8.5–9.4% (69–79 mmol/mol), 9.5–10.4% (80–90 mmol/mol) and ≥10.5% (≥91 mmol/mol) HbA_{1c} subgroups, respectively. *p < 0.05 for difference between reference group (HbA_{1c} ≤6.4%) and actual group. Adjusted analysis included sex, age, randomised treatment assignment, diabetes duration, history of arterial hypertension, history of congestive heart failure, history of cardiovascular disease, history of revascularisation, ethnicity, tobacco use, systolic and diastolic blood pressure, heart rate, BMI, HDL-cholesterol concentration, LDL-cholesterol concentration, urine albumin/creatinine ratio and use of insulin, metformin, thiazolidinediones and sulfonylureas

change in HbA_{1c} according to a change in BMI was found for the primary event (*p* = 0.2 for interaction). Thus, for patients losing weight, a 1 percentage point decrement in HbA_{1c} was associated with an HR of 0.91 (0.83, 0.99) for the all-cause mortality endpoint and 0.93 (0.85, 1.02) for the primary endpoint. For participants not losing weight, each 1 percentage point decrease in HbA_{1c} was associated with an HR of 1.00 (0.88, 1.15) for the all-cause mortality endpoint and 1.00 (0.88, 1.14) for the primary endpoint.

Discussion

Based on more than 7,000 overweight and obese patients with type 2 diabetes and either cardiovascular disease or additional cardiovascular risk factors, the present analysis demonstrated increases in risk of the primary endpoint (nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest and cardiovascular mortality) and all-cause mortality with increasing levels of HbA_{1c} values. Contrary to the findings from a recent retrospective study of a large and unselected cohort of individuals with type 2 diabetes from the UK general practice database (age being comparable to the present cohort) [5], no excess risk was found for patients in the lowest HbA_{1c} groups in the present cohort.

The relationship between HbA_{1c} levels and outcomes may be more complex than previously recognised and elevated levels of HbA_{1c} may function both as a risk marker and as a risk factor depending on the population studied (i.e. its particular lifetime expectancy and degree of comorbidity) [14]. In this context patients with, for example, cancer or heart failure frequently have elevated blood glucose levels, despite cachexia [15]. Furthermore, as a physiological response to high adrenergic tone, hepatic gluconeogenesis is increased and skeletal muscle glucose uptake is decreased in patients with stress due to any cause [16]. In the present cohort (comprising middle-aged and elderly, overweight and obese, high-risk patients), followed for approximately 4 years, elevated HbA_{1c} levels may therefore have served both as a risk marker and a risk factor. Conversely, in cohorts with a low prevalence of comorbidity, an elevated HbA_{1c} level may mainly act as a risk factor for long-term disease and mortality; in more heterogeneous cohorts of patients with various degrees of comorbidities [5] it is possible that those with the greatest comorbidity and who have developed diabetes (e.g. due to stress, cancer or impaired peripheral blood flow) could confound the findings of increased risks associated with low HbA_{1c} levels [17–19].

The SCOUT trial was designed to investigate the importance of weight loss with sibutramine treatment, diet and exercise on the risk of cardiovascular disease and although the main study found an increased risk of cardiovascular

Fig. 2 Adjusted HRs (squares) and crude incidence rates (bars) for all-cause mortality associated with HbA_{1c} concentrations at baseline. Error bars represent 95% CIs. In total 115 (6%), 187 (8%), 141 (9%), 93 (11%), 54 (11%) and 52 (17%) participants in the ≤6.4% (≤46 mmol/mol), 6.5–7.4% (48–57 mmol/mol), 7.5–8.4% (58–68 mmol/mol), 8.5–9.4% (69–79 mmol/mol), 9.5–10.4% (80–90 mmol/mol), and ≥10.5% (≥91 mmol/mol) HbA_{1c} subgroups died, respectively. *p < 0.05 for difference between reference group (HbA_{1c} ≤6.4%) and actual group. Adjusted analysis included sex, age, randomised treatment assignment, diabetes duration, history of arterial hypertension, history of congestive heart failure, history of cardiovascular disease, history of revascularisation, ethnicity, tobacco use, systolic and diastolic blood pressure, heart rate, BMI, HDL-cholesterol concentration, LDL-cholesterol concentration, urine albumin/creatinine ratio and use of insulin, metformin, thiazolidinediones and sulfonylureas

morbidity for the sibutramine arm, post hoc analyses revealed a significant beneficial effect of intentional weight loss on outcomes in patients not receiving sibutramine [20]. In the present analysis we found a beneficial effect associated with decreasing HbA_{1c} levels on the all-cause mortality endpoint among those experiencing weight loss, but no effect associated with lowered HbA_{1c} levels among those not experiencing weight loss. These data may therefore support previous ideas about the importance of how glycaemic control is improved and to what extent weight is increased with intensified glycaemic control. For example, in this context, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which randomised >10,000 cardiovascular high-risk patients to achieve a target HbA_{1c} level of either <6.0% (42 mmol/l) or 7.0–7.9% (53–63 mmol/l), was stopped prematurely because of an unexpected increase in mortality risk for the intensive treatment group [6]. Interestingly, post hoc analyses indicated that the risk was not associated with low HbA_{1c} as such, but was rather driven by a high risk for those who failed to achieve a low HbA_{1c}, which may have been due to factors such as weight gain; this is nevertheless not well investigated [21]. Several other studies, including two recent meta-analyses, have likewise failed to demonstrate any reduction in risk of mortality for intensified glucose control in patients with established type 2 diabetes and various degrees of cardiovascular disease [22–25].

The influence of hypoglycaemia on the risk of adverse outcomes [26] has gained increasing attention and may contribute to the neutral or even increased risk of mortality in prospective studies that aim to improve glycaemic control. Our study population may have differed from those in studies primarily concerning diabetes treatment and this could explain our finding of a lack of increased risk associated with very low HbA_{1c} levels. The SCOUT patients with obesity and cardiovascular disease might have been at lower risk of hypoglycaemia than other individuals with type 2 diabetes because of, for example, their higher adrenergic tone [27]. It is also possible that the lower glucose levels seen in our study cohort were more likely to have been achieved by improved diet, increased exercise and/or weight loss rather than by increasing use of glucose-lowering medications.

Current ADA guidelines recommend target levels of HbA_{1c} <7% (53 mmol/l) in patients with type 2 diabetes. Data from the present analysis support these recommendations and, furthermore, suggest that achievement of HbA_{1c} levels <6.5% (48 mmol/l) would translate into even better outcomes [28]. Although this study does not inform as to whether or not an actively intensified regimen of glycaemic control might translate into a more favourable outcome, the findings raise the possibility that in obese cardiovascular high-risk patients there may be benefit from maintaining good glycaemic control and that high HbA_{1c} levels are likely to increase risk.

Although it may have been due to chance (i.e. we did not adjust for the number of tests performed), we found a sex difference in the prognostic importance of high HbA_{1c} levels on the risk of all-cause mortality; it was greater in women than in men, in agreement with the findings from a Framingham sub-study, and previous large cohort studies of heart failure patients and myocardial infarction patients, where diabetes was found to carry a worse prognosis in women than in men [29–31]. What may underlie these findings is not clear, but they may relate to a higher prevalence of high HbA_{1c} values as was found in women from the SCOUT trial. This perhaps reflects the general clinical misconception that women do not require as intensive glucose control as men, or that the lower mortality rate in women with cardiovascular disease (even allowing for postmenopausal status in SCOUT) translates into higher relative risk associated with diabetes in women [32, 33]. In this context, one previous study reported that the prognostic importance of a low HbA_{1c} level was limited to patients with low comorbidity and a long life expectancy [14]. However, in our middle-aged and elderly cardiovascular high-risk population we did show a favourable prognosis for low HbA_{1c} values and that this was not dependent on factors such as heart failure, coronary artery disease, age or impaired renal function, indicating that efforts to achieve low HbA_{1c} are clinically relevant in high-risk populations.

Strengths and limitations The present analysis was based on a large cohort of overweight and obese cardiovascular high-risk individuals with type 2 diabetes. Although the analyses for the present paper were considered post hoc, longitudinal data (median follow-up 4 years) were collected prospectively and measurements were available for a wide range of prognostic variables. The main limitation for interpretation of the present analyses was the lack of data on hypoglycaemic events. Also, the analyses did not account for changes in medication during follow-up and although several variables were included in the Cox models, it cannot be excluded that some residual confounding might have been present. Finally, it should be noted that the participants were overweight or obese individuals recruited to a weight-loss trial and therefore this may reduce the capacity to make generalisations based on the findings.

Conclusions and clinical implications In overweight and obese cardiovascular high-risk individuals with type 2 diabetes, a high baseline HbA_{1c} concentration was associated with increasing cardiovascular and all-cause mortality risks.

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