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# The relationship between glycaemic control and mortality in patients with type 2 diabetes in general practice (ZODIAC-11)

Gijs W Landman, Kornelis JJ van Hateren, Nanne Kleefstra, Klaas H Groenier, Rijk OB Gans and Henk JG Bilo

## ABSTRACT

### Background

The relationship between the degree of glycaemic control and mortality remains an important topic of discussion.

### Aim

This study aimed to investigate this relationship.

### Design of study

Prospective cohort study.

### Setting

Primary care.

### Method

A total of 1145 patients with type 2 diabetes were enrolled in the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) in 1998. Their survival status was recorded in September 2004. Mortality ratios were calculated using standardised mortality ratios (SMRs). Associations between haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels and mortality were studied with a Cox proportional hazard model. HbA<sub>1c</sub> levels were studied as continuous and as categorical variables.

### Results

A total of 335 patients died after a median follow-up period of 5.8 years. The SMR (95% confidence interval [CI]) for total mortality was 1.86 (95% CI = 1.66 to 2.06) and 2.24 (95% CI = 1.91 to 2.61) for cardiovascular mortality. For each 1% increase in HbA<sub>1c</sub> there was a 21% increase in the hazard ratio for total mortality. When compared with the target HbA<sub>1c</sub> group (HbA<sub>1c</sub> 6.5–7%), the group with very poor glycaemic control (HbA<sub>1c</sub> >9%) had a hazard ratio of 2.21 (95% CI = 1.42 to 3.42) for total mortality. The group with normal glycaemic control (HbA<sub>1c</sub> <6.5%) had a hazard ratio of 1.00 (95% CI = 0.46 to 2.19) for total mortality.

### Conclusion

HbA<sub>1c</sub> level was associated with mortality and this effect seemed largely attributable to patients who were in really poor glycaemic control. The absence of differences in mortality in the groups with lower HbA<sub>1c</sub> levels supports the position that there is no basis for continually decreasing the therapeutic target HbA<sub>1c</sub> level in patients with type 2 diabetes mellitus.

### Keywords

blood glucose; mortality; type 2 diabetes mellitus.

## INTRODUCTION

Patients with type 2 diabetes mellitus have a two- to fivefold increase in risk for developing cardiovascular disease compared to people without diabetes.<sup>1,2</sup> Between 50% and 75% of all deaths seen in patients with type 2 diabetes are related to cardiovascular complications.<sup>3</sup> Since this excess risk is only partially explained by traditional risk factors, such as obesity, dyslipidaemia, and hypertension, type 2 diabetes is often considered an independent risk factor for cardiovascular morbidity and mortality.

A strong body of evidence links chronic hyperglycaemia to microvascular complications. A meta-analysis of observational studies suggests that hyperglycaemia is also associated with an increased risk for cardiovascular mortality in patients with type 2 diabetes.<sup>4</sup> In the UK Prospective Diabetes Study (UKPDS), a continuous relationship was found between glycosylated haemoglobin

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(HbA<sub>1c</sub>) levels and rates of macrovascular complications. For every 1% decrease in HbA<sub>1c</sub> level, investigators estimated a 14% decrease in myocardial infarction, a 12% decrease in stroke, and a 14% reduction in all-cause mortality.<sup>5</sup> Results from a meta-analysis of all the randomised trials in which glycaemic control and its relationship to macrovascular risk were studied in patients with both type 1 and type 2 diabetes, showed that glucose lowering itself reduces cardiovascular risk.<sup>6</sup>

Three recently performed studies have investigated the role of intensive glycaemic control.<sup>7-9</sup> The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed a significantly higher mortality rate in the intensive treatment group compared to the standard glucose-lowering therapy group.<sup>7</sup> The two other trials, the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial and the Veterans Affairs Diabetes Trial (VADT), found no effect of intensive glycaemic control on the occurrence of major macrovascular events or all-cause mortality compared to the control group.<sup>8,9</sup> The post-trial study from the UKPDS suggested that the effects on mortality of a more intensive strategy to control blood glucose levels in patients with newly diagnosed type 2 diabetes were sustained for up to 10 years after the cessation of randomised interventions.<sup>10</sup> The major difference between the three recently performed studies and the post-trial study from the UKPDS is that in the UKPDS only patients with newly diagnosed type 2 diabetes were included.

In light of these results, the goal of this study was to investigate the relationship between glycaemic control (as indicated by HbA<sub>1c</sub> level) and mortality in patients with type 2 diabetes, in a prospective observational setting.

## METHOD

In 1998, in the Zwolle region (the Netherlands), a large shared-care diabetes project was initiated, the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC). In this project, GPs were assisted in their care of patients with type 2 diabetes by hospital-based nurses specialising in diabetes. As part of this project, the patients with type 2 diabetes in 32 primary care practices consulted (and still consult) these diabetes specialist nurses annually. Patients with a very short life expectancy (including patients with active cancer) or insufficient cognitive abilities were excluded. During the first year of the project, 1664 subjects with type 2 diabetes were identified in these practices. Patients being treated by specialists in internal medicine ( $n = 338$ ) were

## How this fits in

Three recent randomised studies (the ACCORD, ADVANCE, and VADT trials) showed that a low haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) target level does not result in decreased mortality. In this study, HbA<sub>1c</sub> was a significant predictor for mortality. This effect seems largely attributable to poor glycaemic control. The study data suggest that for patients with moderate glycaemic control, it may be better to focus on other risk factors than to keep on lowering the target values for HbA<sub>1c</sub>.

excluded. Fifty-seven patients were excluded by their GPs due to an estimated very short life-expectancy or insufficient cognitive abilities. Of the 1269 patients who were invited to participate, 1149 (91%) agreed. Four patients were excluded due to insufficient baseline data. Details of the ZODIAC study have been published previously.<sup>11</sup>

Baseline data were collected in 1998 and 1999 and involved a full medical history, including the presence or absence of macrovascular complications, medication use, and tobacco consumption. Laboratory and physical assessment data were collected on a yearly basis and included lipid profile, creatinine, (micro)albuminuria, blood pressure, weight, and height. HbA<sub>1c</sub> was measured first at baseline and annually thereafter. An updated mean of annually measured HbA<sub>1c</sub> was calculated for each individual from baseline to the end of the follow-up period. This is in accordance with the technique used in the UKPDS 35.<sup>5</sup> For example, at 2 years the updated mean is calculated using the average of the baseline, 1-year, and 2-year values, and at 4 years, the updated mean is the average of the baseline, 1-year, 2-year, 3-year, and 4-year values.

Records maintained by the hospital and the GPs were used to obtain cause of death information for the patients who died during the study. The causes of death were coded according to The International Classification of Diseases, 9th Revision (ICD-9). To study the incidence of cardiovascular-related mortality, standardised mortality ratios (SMRs) were calculated using general mortality reference rates from the eastern part of the Netherlands.<sup>12</sup> A Cox proportional hazard model was then used to assess the association between updated mean HbA<sub>1c</sub> levels and mortality (all-cause and cardiovascular). The updated mean value was included as a time-dependent covariate to evaluate glycaemic control during follow-up. Using updated mean HbA<sub>1c</sub> levels as a continuous variable, models were developed and applied to determine the all-cause mortality risk associated with a 1% reduction in the HbA<sub>1c</sub> level. Separate analyses were done for HbA<sub>1c</sub> as a grouped variable (<6.5%, 6.5–7%, 7–8%, 8–9%,

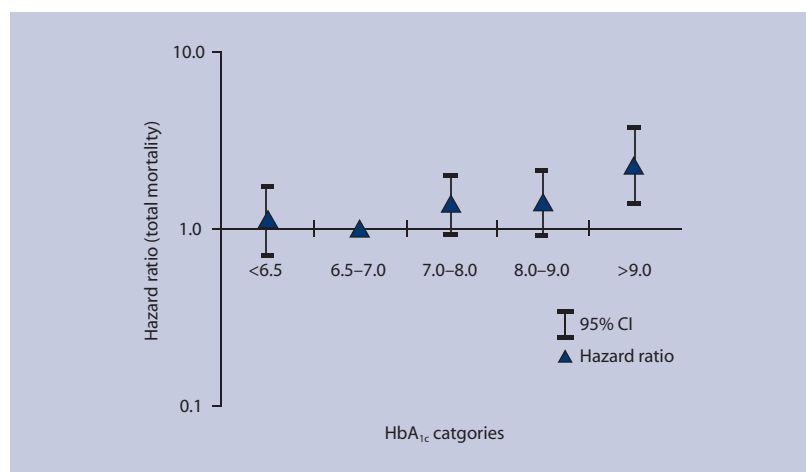
**Table 1. Baseline characteristics.**

| Characteristics                | Total<br>(n = 1145) | Deceased patients<br>(n = 335) | Patients that<br>survived (n = 810) |
|--------------------------------|---------------------|--------------------------------|-------------------------------------|
| Age, years                     | 68.7<br>(±11.5)     | 76.5<br>(±8.7)                 | 65.5<br>(±11.0) <sup>a</sup>        |
| Female, %                      | 54.3                | 58.8                           | 57.5                                |
| Diabetes duration, years       | 7.7<br>(±7.5)       | 9.2<br>(±8.5)                  | 7.1<br>(±7.0) <sup>a</sup>          |
| Smoking, %                     |                     |                                |                                     |
| Never                          | 50.4                | 51.9                           | 49.8                                |
| Former smoker                  | 30.6                | 31.6                           | 30.1                                |
| Current smoker                 | 18.1                | 14.9                           | 19.4                                |
| BMI, kg/m <sup>2</sup>         | 28.9<br>(±4.8)      | 28.3<br>(±5.0)                 | 29.2<br>(±4.7) <sup>b</sup>         |
| Systolic blood pressure, mmHg  | 155.1<br>(±25)      | 154.0<br>(±27)                 | 154.3<br>(±24)                      |
| HbA <sub>1c</sub> , %          | 7.5<br>(±1.3)       | 7.6<br>(±1.3)                  | 7.5<br>(±1.2) <sup>c</sup>          |
| Creatinine clearance, ml/min   | 63.2<br>(±20.0)     | 51.5<br>(±16.7)                | 68.1<br>(±19.2) <sup>a</sup>        |
| Total cholesterol/HDL ratio    | 5.3<br>(±1.60)      | 5.2<br>(±1.7)                  | 5.2<br>(±1.5)                       |
| LDL cholesterol, mmol/l        | 3.4<br>(±1.0)       | 3.3<br>(±1.0)                  | 3.4<br>(±1.0)                       |
| Statin use, %                  | 11.2                | 10.2                           | 12.1                                |
| Insulin use, %                 | 15.4                | 21.2                           | 12.3 <sup>a</sup>                   |
| Microalbuminuria, %            | 41.8                | 55.3                           | 36.6 <sup>a</sup>                   |
| Macroalbuminuria, %            | 5.5                 | 7.9                            | 4.5 <sup>c</sup>                    |
| Macrovascular complications, % | 61.4                | 77.9                           | 54.5 <sup>a</sup>                   |

HDL = high-density lipoprotein. LDL = low-density lipoprotein. Data are means (± standard deviation) or %. <sup>a</sup>P<0.001. <sup>b</sup>P<0.01. <sup>c</sup>P<0.05.

and ≥9%), and the therapeutic target range for HbA<sub>1c</sub> (between 6.5% and 7%) was used as a reference. The following variables were included in the models as possible confounders: age, sex, smoking (never, previous, and current), duration of diabetes, creatinine, body mass index, systolic blood pressure, total cholesterol-HDL (high-density

**Figure 1. Hazard ratio's for total mortality for five HbA<sub>1c</sub> categories, reference category is 6.5–7.0.**



lipoprotein) ratio, macrovascular complications (yes/no), use of statins (yes/no), insulin use (yes/no), and albuminuria (yes/no).

**RESULTS**

The baseline characteristics of the study population are shown in Table 1. A total of 335 (31%) patients died during a median follow-up of 5.8 years. Date and cause of death could not be traced in 6 and 20 patients, respectively. Out of the 315 known causes of death, 51% (n = 161) were attributable to cardiovascular disease, 21% (n = 70) to malignancies, and 10% (n = 34) to respiratory diseases.

The SMR (95% confidence interval [CI]) for total mortality was 1.86 (95% CI = 1.66 to 2.06) and 2.21 (95% CI = 1.42 to 3.42) for cardiovascular mortality.

The hazard ratio (HR) for the updated HbA<sub>1c</sub> mean (continuous variable) was 1.21 (95% CI = 1.07 to 1.36) for all-cause mortality.

HRs for the updated HbA<sub>1c</sub> mean in the categories <6.5% (n = 228), 7–8% (n = 318), 8–9% (n = 208), and ≥9% (n = 144) were 1.11 (95% CI = 0.71 to 1.74), 1.40 (95% CI = 0.99 to 1.97), 1.43 (95% CI = 0.97 to 2.10), and 2.26 (95% CI = 1.39 to 3.67) respectively compared to HbA<sub>1c</sub> 6.5–7% (n = 245) for all-cause mortality (Figure 1). HRs for the updated HbA<sub>1c</sub> mean in the categories <6.5% (n = 228), 7–8% (n = 318), 8–9% (n = 208), and ≥9% (n = 144) were 0.94 (95% CI = 0.47 to 1.91), 1.40 (95% CI = 0.84 to 2.31), 1.71 (95% CI = 0.99 to 2.96), and 3.13 (95% CI = 1.62 to 6.05) respectively, compared to HbA<sub>1c</sub> 6.5–7% (n = 245) for cardiovascular mortality (Figure 2).

**DISCUSSION**

**Summary of main findings**

HbA<sub>1c</sub> seems to be a predictor for mortality in type 2 diabetes mellitus, but whether this predictive value translates to causality is unknown. In the present study cohort, the increased mortality risk, corrected for risk factors including diabetes duration, seems largely attributable to those patients with poor glycaemic control.

Patients with an average HbA<sub>1c</sub> ≥9% have a 2.26 higher total mortality risk and a 3.13 higher cardiovascular mortality risk compared to the group with an HbA<sub>1c</sub> at the current therapeutic target level (6.5–7%). Patients with an average HbA<sub>1c</sub> <9% did not have significantly different risks for total and cardiovascular mortality. A HbA<sub>1c</sub> level <6.5% does not seem to change cardiovascular and all-cause mortality risks when compared with the normal target range of 6.5–7%.

There are several plausible physiological explanations for the effect of chronically elevated glucose levels on cardiovascular disease risk.

Glucose can react with various proteins to form advanced glycation end-products, which may contribute to long-term complications of diabetes, plaque formation, and atherosclerosis. These effects are gradual and likely to be cumulative.<sup>13</sup>

### Strengths and limitations of the study

Because of the observational nature of the study, the associations found do not imply causality. The study population itself presents other limitations. A patient population of 1145 is rather small. Second, it is comprised of patients treated in primary health care, and therefore might represent a population with less overall risk, since many subjects with more complicated disease will be treated in secondary care in the Netherlands. However, approximately 80% of the patients with type 2 diabetes are treated at the primary healthcare level, allowing the study conclusions to be applicable to a majority of patients with type 2 diabetes.

### Comparison with existing literature

The results of this study agree with those reported in the ACCORD,<sup>7</sup> ADVANCE,<sup>8</sup> and VADT<sup>9</sup> studies, that a low HbA<sub>1c</sub> therapeutic target level does not result in decreased mortality. In fact, in the ACCORD trial, increased mortality was seen in the intensive treatment group.<sup>7</sup> It is possible that the use of multiple types of medications in an attempt to achieve normal blood glucose levels in patients with longstanding type 2 diabetes results in increased side-effects, and perhaps also increased mortality.

### Implications for clinical practice

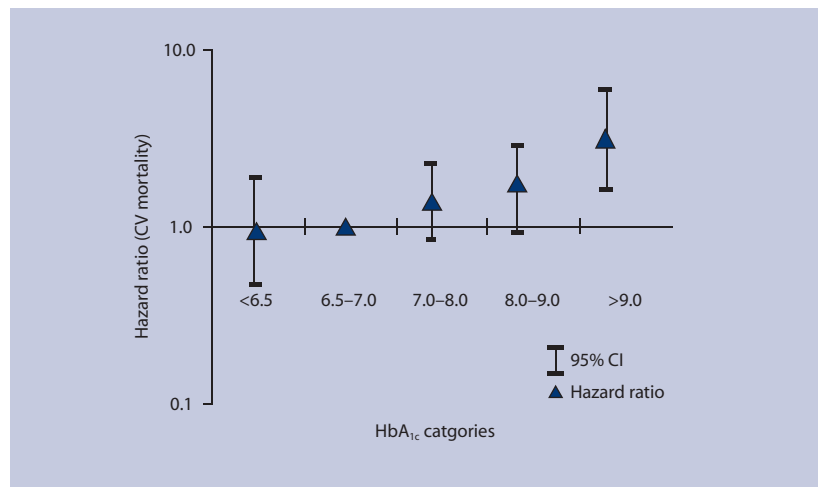
The results of this observational study show that there is not much difference in mortality risk, as long as HbA<sub>1c</sub> levels are below 9%. Postponing death is not the only treatment goal in patients with type 2 diabetes, and the prevention of microvascular complications with strict metabolic control should also be a priority. The study data suggest that, in order to increase the life expectancy in these patients, glycaemic control is important in patients with poor control (HbA<sub>1c</sub> >9%). For patients with moderate glycaemic control and longstanding diabetes, it may be better to focus on other risk factors, such as smoking, high blood pressure, and lipid profile disturbances, than to aim for increasingly lower therapeutic target values for HbA<sub>1c</sub>.

### Ethics committee

The ZODIAC Study was approved by the medical ethics committee, (reference number 03.0316) and all patients provided informed consent.

### Competing interests

The authors have stated that there are none.



**Figure 2. Hazard ratio's for cardiovascular mortality for five HbA<sub>1c</sub> categories, reference category is 6.5-7.0.**

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