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**SHORT COMMUNICATION**

**Glycaemic control and the risk of mortality in elderly type 2 diabetic patients (ZODIAC-20)**

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**SUMMARY**

**Aims:** Studies on macrovascular consequences of glucose control in elderly patients (> 75 years) with type 2 diabetes mellitus (T2DM) are lacking. The present study aimed to investigate the relationship between HbA1c and mortality in this specific population. **Methods:** Between 1998 and 1999, 374 primary care patients with T2DM aged older than 75 years participated in the Zwolle Outpatient Diabetes project Integrating Available Care study, a prospective observational study. Early 2009, data on mortality were collected. Updated means for annually measured HbA1c values were calculated after a follow-up time of 10 years. **Results:** In the group with a diabetes duration < 5 years, an increase of 1% in the updated mean HbA1c level was associated with an increase in all-cause and CVD mortality risk of 51% (95% CI 17–95%) and 72% (95% CI 19–148%), respectively. Glycaemic control was not related to mortality for patients with a diabetes duration ≥ 5 years. **Conclusion:** Poor glycaemic control is related to increased all-cause and CVD mortality in patients > 75 years with T2DM of short duration (< 5 years). **Discussion:** Because of the observational study design, our results should be interpreted with caution. Nevertheless, they are suggestive that improving glycaemic control may be beneficial in elderly patients with T2DM, especially in those with recently diagnosed T2DM. Randomised-controlled trials are necessary to investigate whether improving glycaemic control in specific elderly diabetic populations, for example elderly diabetic patients with newly diagnosed T2DM, may be beneficial.

**What's known**

The beneficial effects of improved glycaemic control decrease with longer diabetes duration and with increasing age. However, there are no clinical data on the macrovascular and microvascular consequences of (intensive) glucose control in the very old (patients > 75 years).

**What's new**

Higher levels of HbA1c are related to increased all-cause and CVD mortality in diabetic patients aged older than 75 years, but only in those with diabetes of short duration (< 5 years). Randomised-controlled trials are necessary to investigate whether improving glycaemic control in specific elderly diabetic populations, for example elderly diabetic patients with newly diagnosed T2DM, may be beneficial.

**Introduction**

In a recent response to a meta-analysis of the Collaborators on Trials of Lowering Glucose (CONTROL) Group, the differences between patients with type 2 diabetes mellitus (T2DM) of short and long duration were emphasised (1,2). Based on the heterogeneous results of four large randomised-controlled trials, it seems that intensive glucose control is only beneficial in those with diabetes of short duration (3–6). A meta-analysis, published in 2006, already showed that the beneficial effects of improved glycaemic control decreased with longer diabetes duration and with increasing age (7). Unfortunately, there are no clinical data on the macrovascular and microvascular consequences of (intensive) glucose control in adults older than 75 years. Although guidelines recommend applying less stringent targets to frail older adults and those with limited life expectancy, the level of evidence of this advice is low and mainly based on expert opinion (8). We aimed to explore the relationship between HbA1c and (cardiovascular) mortality, and the role of diabetes duration in this relationship, in a prospectively designed cohort of elderly patients (> 75 years) with T2DM.

**Patients and methods**

**Study population**

This study is part of the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) study; the design and details of which have been presented elsewhere (9). In this study, general practitioners are assisted by hospital-based diabetes specialist nurses in their care of patients with T2DM. At baseline, patients with a very short life expectancy (including...
patients with active cancer) or insufficient cognitive abilities were excluded (~5%). Four patients were excluded because of insufficient baseline data. Nearly 90% (n = 1357) of the remaining patients agreed to participate. For the present study, we selected all patients aged older than 75 years (n = 374).

Data collection
Baseline data were collected in 1998 and 1999, and consisted of a full medical history including macrovascular complications, medication use and tobacco consumption. Patients were considered to have macrovascular complications when they had a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke or transient ischaemic attack. Laboratory and physical assessment data such as HbA1c, lipid profile, serum creatinine, the urinary albumin-to-creatinine ratio, blood pressure, weight and height were collected annually. An updated mean of annually measured HbA1c was calculated for each individual from baseline to the end of the follow-up period by averaging the baseline values with the mean annual values. For example, at 1 year the updated mean HbA1c is the average of the baseline and 1 year values, and at 3 years it is the average of baseline, 1, 2 and 3 year values. This technique is similar to the one used in the United Kingdom Prospective Diabetes Study (UKPDS) (10).

Clinical endpoints
We examined two clinical endpoints in this study: all-cause and cardiovascular disease (CVD) mortality. Early 2009, the vital status and cause of death were retrieved from records maintained by the hospital and the general practitioners. The causes of death were coded according to The International Classification of Diseases, 9th revision (ICD-9).

Statistical analyses
Continuous variables are presented as mean (± standard deviation) for normally distributed values and as median (interquartile range) for non-normally distributed values. Normality was evaluated using Q–Q plots. Nominal variables are presented as the total number of patients (percentage). A Cox proportional hazard model was used to investigate the relationship between the updated mean HbA1c, as a time-dependent covariate, and mortality with and without adjustment for selected confounders. We used two different models. In model 1, only age and gender were taken into account as possible confounders. In model 2, we adjusted for the following variables: age, gender, smoking (yes or no), BMI, duration of diabetes, serum creatinine, macrovascular complications (yes or no), albuminuria (yes or no), systolic blood pressure, total cholesterol–HDL ratio and use of insulin (yes or no). Analyses were repeated in strata according to diabetes duration. The diabetes duration variable at baseline was categorised into tertiles: < 5 (n = 111), 5–11 (n = 139) and ≥ 11 years (n = 124). In order to estimate the possible implications of higher HbA1c levels on mortality, we calculated the population attributable risk per cent (PAR%) of HbA1c levels ≥ 7% for all-cause and cardiovascular mortality (11). In our analyses PAR% can be interpreted as the percentage by which mortality rates could be reduced if all patients would have had HbA1c levels < 7%. The assumption of proportional hazards was checked by inspecting the Schoenfeld residual plots for the baseline predictor variables. All analyses were performed with SPSS version 15.0.1 (SPSS Inc., Chicago, IL).

Ethics statement
The ZODIAC study and the informed consent procedure were approved by the local medical ethics committee. Informed consent was obtained from all patients.

Results
Baseline characteristics of our study population are presented in Table 1. Approximately one-third of our study population was men. Median age (interquartile range) was 80 (78–83) years and median diabetes duration was 8 (4–13) years. Patients with a diabetes duration ≥ 11 years (tertile 3) had lower mean body mass index and were more often smokers compared with patients with shorter diabetes duration. The number of patients treated with only a diet was the highest in the group with a diabetes duration < 5 years (tertile 1); also, use of insulin was the lowest in this group compared with patients with longer diabetes duration. After a follow-up time of 10 years, 304 of 374 patients (81%) had died, of which 127 deaths (42%) were attributable to cardiovascular causes.

Analyses overall group
In multivariate analyses (model 2), an increase of 1% in HbA1c led to an increase in CVD mortality risk by 26% (95% CI 6–49%). The unadjusted hazard ratio, and the age- and gender-adjusted one, were not relevantly different. The relationship with all-cause mortality was not significant in both models.

Analyses stratified according to diabetes duration (Table 2)
In the group with a diabetes duration < 5 years (tertile 1), the level of HbA1c as a continuous variable...
was positively related to both all-cause and CVD mortality. In multivariate analyses, an increase of 1% in HbA1c was associated with an increase in all-cause and CVD mortality risk of 51% (95% CI 17–95%) and 72% (95% CI 19–148%), respectively. All results for patients with a diabetes duration ≥ 5 years were not significant.

### Population attributable risk per cent
The PAR% of HbA1c levels ≥ 7% for all-cause mortality in patients with diabetes of short duration was 23% (95% CI 2–36%). For CVD mortality the PAR% was 39% (95% CI 17–48%). Again, all results for patients with a diabetes duration ≥ 5 years were not significant.

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### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall n = 374</th>
<th>Tertile 1 (&lt; 5 years) n = 111</th>
<th>Tertile 2 (5–11 years) n = 139</th>
<th>Tertile 3 (≥ 11 years) n = 124</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>80 (78–83)</td>
<td>80 (78–83)</td>
<td>80 (77–82)</td>
<td>80 (78–84)</td>
<td>0.887</td>
</tr>
<tr>
<td>Male sex</td>
<td>130 (34.8)</td>
<td>34 (30.6)</td>
<td>57 (41.0)</td>
<td>39 (31.5)</td>
<td>0.148</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.8 (4.4)</td>
<td>28.6 (4.4)</td>
<td>28.0 (4.3)</td>
<td>26.9 (4.2)</td>
<td>0.012</td>
</tr>
<tr>
<td>Duration of T2DM (years)</td>
<td>8 (4–13)</td>
<td>2 (1–3)</td>
<td>7 (6–9)</td>
<td>16 (13–20)</td>
<td>–</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>155.7 (24.7)</td>
<td>153.1 (24.3)</td>
<td>156.8 (24.9)</td>
<td>156.7 (24.9)</td>
<td>0.416</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.4 (1.2)</td>
<td>7.3 (1.3)</td>
<td>7.5 (1.1)</td>
<td>7.4 (1.2)</td>
<td>0.292</td>
</tr>
<tr>
<td>Albuminuria present</td>
<td>206 (55.1)</td>
<td>53 (47.7)</td>
<td>84 (60.4)</td>
<td>69 (55.6)</td>
<td>0.133</td>
</tr>
<tr>
<td>Cholesterol–HDL ratio</td>
<td>4.9 (1.6)</td>
<td>5.2 (1.7)</td>
<td>4.8 (1.6)</td>
<td>4.7 (1.5)</td>
<td>0.099</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>98 (86–115)</td>
<td>95 (82–111)</td>
<td>99 (87–123)</td>
<td>98 (87–111)</td>
<td>0.165</td>
</tr>
<tr>
<td>Macrovascular complications present</td>
<td>162 (43.3)</td>
<td>45 (40.5)</td>
<td>62 (44.6)</td>
<td>55 (44.4)</td>
<td>0.780</td>
</tr>
</tbody>
</table>

Data are means (± SD), medians (interquartile range) or n (%). One-way ANOVA, chi-square, or Kruskal–Wallis test was used where appropriate to test for differences between groups.

### Table 2 Analyses stratified according to diabetes duration. Hazard ratios and the 95% confidence intervals of HbA1c, for all-cause and cardiovascular disease (CVD) mortality

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Model</th>
<th>Tertile 1 (&lt; 5 years) n = 111</th>
<th>Tertile 2 (5–11 years) n = 139</th>
<th>Tertile 3 (≥ 11 years) n = 124</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause</td>
<td>Unadjusted</td>
<td>1.24 (1.01–1.52)</td>
<td>1.01 (0.83–1.24)</td>
<td>0.99 (0.82–1.20)</td>
</tr>
<tr>
<td></td>
<td>Model 1*</td>
<td>1.27 (1.03–1.55)</td>
<td>1.04 (0.85–1.26)</td>
<td>1.03 (0.84–1.26)</td>
</tr>
<tr>
<td></td>
<td>Model 2†</td>
<td>1.51 (1.17–1.95)</td>
<td>1.04 (0.84–1.28)</td>
<td>1.05 (0.85–1.30)</td>
</tr>
<tr>
<td>CVD</td>
<td>Unadjusted</td>
<td>1.35 (1.00–1.81)</td>
<td>1.17 (0.87–1.57)</td>
<td>1.19 (0.91–1.55)</td>
</tr>
<tr>
<td></td>
<td>Model 1*</td>
<td>1.37 (1.02–1.84)</td>
<td>1.19 (0.99–1.15)</td>
<td>1.28 (0.98–1.68)</td>
</tr>
<tr>
<td></td>
<td>Model 2†</td>
<td>1.72 (1.19–2.48)</td>
<td>1.18 (0.87–1.60)</td>
<td>1.16 (0.86–1.58)</td>
</tr>
</tbody>
</table>

*Adjusted for age and gender. †Adjusted for age, gender, smoking (yes or no), BMI, duration of diabetes, serum creatinine level, macrovascular complications (yes or no), albuminuria (yes or no), systolic blood pressure, total cholesterol–HDL ratio and use of insulin (yes or no).
All analyses were repeated with only the baseline HbA1c value as variable of interest (data not shown). Results did not relevantly change. The proportional hazards assumptions were met for all analyses.

Discussion

Poor glycaemic control is related to increased all-cause and CVD mortality in patients with T2DM aged over 75 years, but only in those with diabetes of short duration. In the lowest tertile (duration < 5 years), the all-cause mortality risk was 51% higher for every 1% increase in HbA1c. For CVD mortality, the increase in mortality risk was even 72%.

To our knowledge, the relationship between HbA1c and mortality in elderly patients with T2DM has not been described before. In previous observational and intervention studies elderly patients were either not included or subanalyses were not performed for this specific population. More recently, a large retrospective observational study showed that there seems to be a U-shaped association between HbA1c and mortality (12). Although an estimated 16% of the study population was aged over 75 years, no subanalyses were performed.

It is important to emphasise that the associations found between HbA1c and mortality in this study do not imply causality. Because of the observational nature of our study, we can only speculate about the underlying mechanisms. Firstly, poor glycaemic control itself may indeed affect mortality risk in elderly patients with recently diagnosed diabetes. The heterogeneous results of four large randomised-controlled trials in younger patients already suggested that intensive glucose control may only be beneficial with regard to mortality in those with diabetes of short duration (1,4–6,13). Secondly, it may be possible that our results are influenced by confounders we did not adjust for. For example, the results for all-cause mortality may be confounded by co-morbidities such as cancer or infectious diseases. In order to reduce the impact of reverse causality we performed additional analyses for the overall group, in which we excluded the deaths in the first year of follow-up. This did not relevantly change the results.

Besides its observational design, there are other reasons why our results should be interpreted with caution. Firstly, our study cohort is rather small and only comprises 374 elderly patients with T2DM. As we also stratified our cohort into tertiles, the number in these tertiles is even smaller. Secondly, the heterogeneous health status of elderly patients makes it more difficult to identify the implications of our results for clinical practice. However, additional analyses revealed that for patients with a diabetes duration < 5 years, the all-cause mortality rate could theoretically have been lowered by 23% if all patients had had HbA1c levels < 7%. An important strength of our study is its prospective design. Other strengths of our study are the high number of deaths after 10 years follow-up, the use of the updated mean method and the number of variables we adjusted for in our model.

Although our study is the first study linking higher levels of HbA1c to increased mortality in elderly patients with recently diagnosed diabetes, we do not recommend aiming for intensive glycaemic control for all subjects in this specific patient category. Intensive control may also lead to an increased risk of hypoglycaemia causing possible adverse events such as fall accidents and fractures. Physicians caring for older patients should take co-morbidity, frailty and estimated life expectancy into account when setting treatment goals for individual patients. Confirmation of our results in other cohorts would be interesting, because if confirmed, randomised-controlled trials are necessary to investigate whether improving glycaemic control in specific elderly diabetic populations, for example patients with newly diagnosed T2DM, may be beneficial.

Author contributions

Concept/design: KJJH, GWDL, NK and HJGB; data collection: KJJH, GWDL, NK and ID; data analysis/interpretation: all authors; statistics: KJJH, GWDL and KHG; drafting article: KJJH; critical revision of article: GWDL, NK, ID, KHG, STH and HJB; supervision: NK, STH and HJB; approval of article: all authors.

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