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COMMENTARY

Low HbA_{1c} and mortality: causation and confounding

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Abstract This commentary provides an overview of the clinically important data linking low or lowered HbA_{1c} to increased total and CVD mortality in the general population, and in patients with diabetes. This sets the scene for a contribution in this issue of *Diabetologia* by Andersson et al (DOI: 10.1007/s00125-012-2584-3) that suggests that BMI might modify the relationship between HbA_{1c} and mortality in patients with type 2 diabetes. The commentary provides a framework for the interpretation of epidemiological data from observational studies and clinical trials, and it addresses the clinical implications of this work. Finally, it highlights new research that is likely to advance this field.

Keywords Cardiovascular disease · HbA_{1c} · Mortality · Type 2 diabetes

Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
CVD	Cardiovascular disease

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The optimal HbA_{1c} target is uncertain for the prevention of death and cardiovascular disease (CVD) in patients with type 2 diabetes. Clinicians reading this commentary will have many high-risk patients with moderately high HbA_{1c} values for whom they are uncertain whether or not to intensify glucose-lowering therapy.

The objective of this commentary is to provide an overview of data relating low or lowered HbA_{1c} to mortality and CVD risk. This sets the scene for a valuable contribution in this issue of *Diabetologia* suggesting that BMI might modify the relationship between HbA_{1c} and mortality in patients with type 2 diabetes [1].

Observational studies, HbA_{1c} and mortality

Observational studies have demonstrated that hyperglycaemia is an important predictor of mortality and CVD risk [2–15], with the majority of studies showing positive linear relationships between HbA_{1c} and mortality or CVD risk [4, 6, 7, 11, 14, 15]. However, several other important studies have suggested non-linear (U- or J-shaped) relationships [3, 5, 8–10, 12, 13, 16]. Thus, the literature is inconsistent, but the issue is important because there are obvious clinical implications if low blood glucose values are the direct cause of the higher mortality risk.

It is unclear why some studies show linear relationships between HbA_{1c} and mortality, whereas others report non-linear relationships. However, it may be that these differences in results are partly explained by variation in study population characteristics and by confounding factors—that is, the presence of an observed or hidden variable(s) associated with both the predictor (low HbA_{1c}) and the outcome (increased mortality). Certainly, the data describing non-

linear relationships [3, 5, 8–10, 12, 13, 16] may have several interpretations, and some of these studies are discussed here.

The first of these studies assessed the relationship between baseline HbA_{1c} and 15-year CVD risk and total mortality in people *without* diabetes in the Atherosclerosis Risk in Communities study [8]. The results of this study showed a J-shaped relationship between HbA_{1c} and mortality, and there was a suggestion of a similar relationship between HbA_{1c} and CVD risk. These data are particularly important because they show that the higher mortality observed with low HbA_{1c} values could not have been related to the presence of diabetes or the effects of its therapy (especially hypoglycaemia). Unfortunately, this study did not explore the potential causes of the J-shaped relationship between HbA_{1c} and mortality. In particular, it did not assess whether these relationships persisted after excluding participants with conditions such as advanced heart or kidney failure and malignancy, which could be important confounders (Fig. 1a).

A similar U-shaped relationship between HbA_{1c} and all-cause mortality was observed in 14,099 participants *without* diabetes who were assessed in the National Health and Nutrition Examination Survey [10]. The higher risk associated with low HbA_{1c} values was attenuated, but remained significant, after adjusting for several suspected confounders, including deaths resulting from liver disease, cancer and other diseases. However, residual confounding through unmeasured variables could still explain the results.

Another important observational study showing a non-linear relationship between baseline or average HbA_{1c} and mortality involved a large cohort of middle-aged and elderly patients with type 2 diabetes [9]. In this study, low HbA_{1c} values were associated with an increased risk of all-cause mortality and CVD events. The HbA_{1c} value associated with the minimum CVD and mortality risk was ~58 mmol/mol (7.5%). Whilst these 'real-life' data are welcome, they too should be interpreted with caution. Hypoglycaemia may have contributed to some of the deaths in those with low HbA_{1c} values, but this is hard to assess because hypoglycaemia and the causes of death were not recorded in the study. The authors explored the effects of differential prescribing of prophylactic CVD drugs by HbA_{1c} level, but they did not adjust for the presence of comorbid conditions that could be important confounders (Fig. 1a).

The impact of comorbidity in these relationships is well-illustrated in a large population-based study of patients with type 2 diabetes, in which low HbA_{1c} values (48 mmol/mol, <6.5%) were associated with a high risk of mortality in those with high levels of comorbidity, but *not* in those with lower levels of comorbidity [17].

Therefore, some [3, 5, 8–10, 12, 13, 16], but not all, prior studies have suggested that there may be a non-linear relationship between HbA_{1c} and mortality or CVD risk. The main concern about these data is confounding by comorbid conditions, some of which are associated with low BMI (Fig. 1a).

In this issue of the journal, Andersson and coworkers report 4-year cardiovascular outcomes and mortality in a large cohort of overweight or obese high-CVD-risk patients with type 2 diabetes enrolled in a trial of sibutramine [1]. One-fifth of the participants had HbA_{1c} values <48 mmol/mol (<6.5%), and therefore the study was adequately powered to assess risks associated with near normal HbA_{1c} values. It is important to note that the study excluded some patients with comorbidities that could be important confounders (advanced heart failure or malignancy). The main finding was that the risks of cardiovascular events (the primary endpoint) and mortality were positively and linearly related to HbA_{1c}. Importantly, there was no evidence of increased risk in individuals with HbA_{1c} values <48 mmol/mol (<6.5%). This is significant because it suggests that overweight and obese patients with type 2 diabetes may be protected from the high mortality or high CVD risk associated low HbA_{1c} values described in some observational studies of type 2 diabetes [9, 12, 13, 16] (Fig. 1a).

Based on these data, it is tempting to speculate that relatively fit, overweight and obese patients with type 2 diabetes might benefit especially from a low HbA_{1c} target. This may be an attractive hypothesis because these individuals may be insulin resistant and, therefore, less likely to experience hypoglycaemia and subsequent cardiac complications [18] compared with normal weight patients.

Data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study showed that compared with normal weight patients, those who were obese and overweight in the standard glycaemic control arm did indeed have a lower risk of hypoglycaemia requiring medical assistance (annual incidence: BMI <25 kg/m^2, 1.2%; BMI 25–29.9 kg/m^2, 0.8%; BMI ≥30 kg/m^2, 0.9%) [19]. However, when an aggressive protocol-driven glucose-lowering regimen was applied, overweight and obese patients appeared to lose their protection from hypoglycaemia, with similar annual rates of hypoglycaemia in all BMI groups (2.7–2.9%) [19]. So, in conclusion, there is little evidence in ACCORD to suggest that BMI may modify the effects of intensive glucose lowering, at least with respect to the risk of hypoglycaemia.

Clinical trials, HbA_{1c} and mortality

The UK Prospective Diabetes Study (UKPDS) demonstrated that, in newly-diagnosed patients with type 2 diabetes, modest HbA_{1c} lowering led to fewer microvascular complications and to a reduced risk of myocardial infarction in overweight metformin-treated patients [20]. There was no evidence of increased mortality associated with glucose

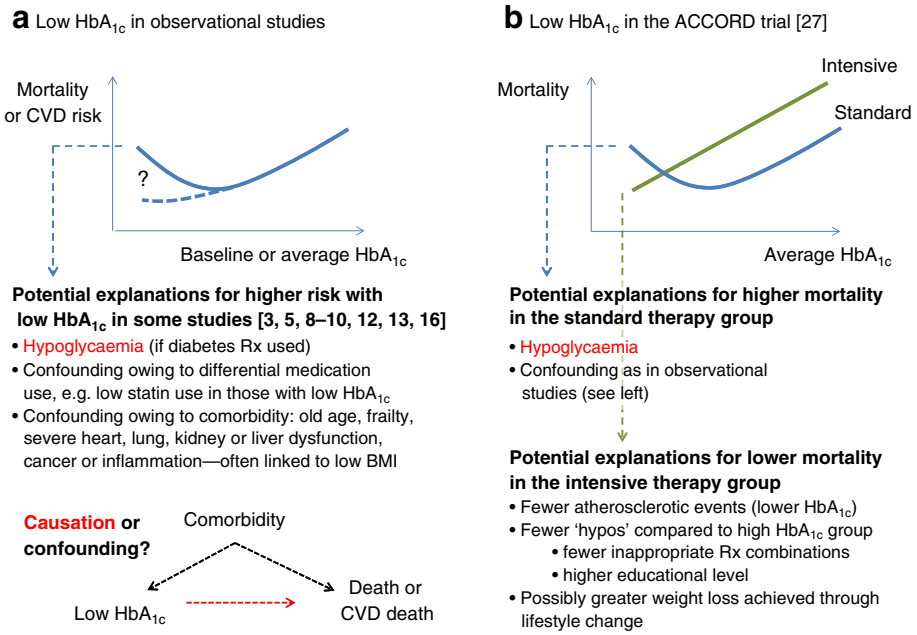

Fig. 1 Epidemiological relationships between HbA_{1c} and mortality in observational studies (**a**) and in clinical trials (**b**) highlighting the higher risk associated with low HbA_{1c} values in some cohorts. Rx, treatment

lowering in this trial. Whilst the early reduction in the risk for myocardial infarction is most likely to be attributable to the beneficial effects of metformin, it may be significant (considering the study by Andersson and coworkers [1]) that this early benefit was observed in overweight or obese individuals. However, in longer term follow-up of UKPDS participants, the mortality and macrovascular benefits were observed in all trial participants and with all glucose-lowering therapies [21].

More recently, three trials that aimed to normalise HbA_{1c} in older, higher-risk patients, showed no overall cardiovascular benefit associated with more aggressive glucose lowering therapy [22–24]. Although there may have been fewer non-fatal myocardial infarctions with aggressive glucose lowering in the ACCORD trial [25], many clinicians were extremely concerned about the increased mortality risk in the intensive therapy group. The cause of this increased mortality is uncertain, but potential explanations included hypoglycaemia, weight gain or the effects of individual drugs or their combinations. For many clinicians, the most likely culprit has been hypoglycaemia, even though several post hoc analyses of ACCORD data have suggested that this is not the case [26, 27] .

What is fascinating about the ACCORD data is that the nature of the intervention changed the epidemiological relationship between average HbA_{1c} and mortality (Fig. 1b) [27]. In the standard therapy group this relationship was similar to the U- or the J-shaped relationships seen in some observational studies [9, 12, 13, 16], and we might speculate that the underlying cause of the higher mortality associated with low HbA_{1c} values might be similar (e.g. hypoglycaemia and comorbidity). However in the intensive therapy group, the relationship between HbA_{1c} and mortality was linear and positive [27]. Patients who were easily able to achieve low HbA_{1c} values with intensive therapy experienced the lowest risk of death, even though intensive therapy was harmful overall.

In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study, severe hypoglycaemia was clearly linked to increased risks for a range of adverse outcomes (CVD, death, microvascular and non-vascular). The authors concluded that comorbid conditions could increase vulnerability to both hypoglycaemia and adverse outcomes in the absence of a direct causal link between the two [28]. In an epidemiological analysis of ADVANCE, non-linear (J-shaped) relationships between average or baseline HbA_{1c} and mortality were suggested both in the standard therapy group and in the intensive therapy group. As the authors were careful to point out, the nature of the relationship between HbA_{1c} and mortality may be different in different populations, it may change over time and it may be modified by other risk factors or therapies [29].

This overview clearly highlights the limitations of using epidemiological data for the purpose of setting clinical HbA_{1c} targets. For example, if we were to use only epidemiological data from the intensive therapy arm of ACCORD, then we might conclude that lower HbA_{1c} values would always be better. But this would ignore the large number of deaths that occurred with intensive glucose lowering in those who had persistently elevated HbA_{1c} values.

So, does the study presented by Andersson and coworkers [1] have any immediate clinical implications? Since these are observational data, it is best viewed as hypothesis-generating, without influencing immediate clinical care. Decisions about optimal clinical HbA_{1c} targets should be guided mainly by the results of clinical trials involving

patients randomised to different HbA_{1c} targets and then followed for important clinical outcomes [30]. The recent ADA/EASD position statement appropriately emphasises the importance of additional factors which should influence HbA_{1c} targets set for individual patients. These include patient attitudes and their expected therapeutic involvement, risk of hypoglycaemia, disease duration, life expectancy, the presence of comorbidity (especially CVD), and patient access to resources and support systems [31].

Where do we go from here?

It may be useful to consider what new research is likely to advance this field. Future studies assessing the relationship between low HbA_{1c} and mortality should aim to collect more comprehensive information about potential confounding factors and perform stratified analyses using this information. Since mortality and CVD event rates are usually low in those with low HbA_{1c} values, a meta-analysis of currently available observational studies, using individual patient-level data, might help to clarify the nature of the relationship between low-range HbA_{1c} and mortality, and determine the patient characteristics that confound the association between low HbA_{1c} values and increased mortality. Similarly, it may be useful to perform a meta-analysis of recent clinical trial data to highlight more patient subgroups (such as those with higher BMI) that might benefit or be harmed by an intensive glucose-lowering regimen. These efforts would be hypothesis-generating and findings would require confirmation in clinical trials.

We need randomised controlled clinical trials to explore the benefits of low HbA_{1c} targets, using agents associated with a low risk of hypoglycaemia and weight gain (metformin and incretin-based therapies) in high-CVD-risk patients with recent-onset type 2 diabetes or non-diabetic hyperglycaemia. Although these clinical trials will be essential, variation in patient characteristics and the number of diabetes therapy combinations available will mean that we will probably never have an appropriate controlled clinical trial to guide clinicians in every possible clinical scenario.

More than ever, clinicians will be expected to integrate the evidence from observational studies and clinical trials, and to combine this with the detailed knowledge of their patients when setting individualised HbA_{1c} targets [31].

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