Glycated hemoglobin (HbA1c) reflects glycemic control over a period of a few months before examination, and thus is commonly used as an indicator and a goal for the treatment of diabetes. Several prospective studies have shown that good glycemic control evaluated by HbA1c could prevent the development and/or progression of diabetic microvascular complications, such as retinopathy and nephropathy. Furthermore, good glycemic control might also prevent macrovascular complications, such as cardiovascular disease, when glycemic control was initiated in the early stages of the development of diabetes. According to these data, the American Diabetes Society proposed that the goal for diabetic control be lower than a HbA1c level of 7.0%. In contrast, several recent studies, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and Veterans Affairs Diabetes Trial (VADT) failed to prove the effect of good glycemic control on the reduction of mortality and macrovascular disease in subjects with type 2 diabetes.

Recently, Craig Currie et al. reported that there was a U-shaped association between HbA1c and the hazard ratio of all-cause mortality in subjects with type 2 diabetes, and the lowest hazard ratio was a HbA1c level of approximately 7.5%. Briefly, the authors obtained data from routine general practice in the UK from a proprietary health data resource: the General Practice Research Database (GPRD) from November 1986 to November 2008, and identified all patients who had a diagnosis of type 2 diabetes and whose treatment history included evidence of a specific escalation of their diabetes treatment. Then, they classified the patients into two groups, one was defined as patients with a newly identified switch from oral monotherapy to a combination oral regimen with a sulfonylurea plus metformin (cohort 1; n = 27,965) and the other was defined as those who were initiated on insulin with or without concomitant oral hypoglycemic agents (cohort 2; n = 20,005). The cohorts were divided into deciles by the rank of the mean of all post-index HbA1c values or yearly values where appropriate. The post-index HbA1c was calculated as the mean of all observations recorded between the index date (first prescription of intensified diabetes therapy) and the respective outcome event (death or large-vessel event) or the censoring point (further switching of treatment or the last recorded database observation). The primary outcome measure was all-cause mortality, and the secondary outcome measure was occurrence of a major cardiovascular event. Mean follow-up was 4.5 and 5.2 years in cohort 1 and 2, respectively.

As the results, unadjusted mortality rates were 16.2 deaths per 1000 person-years of follow-up in cohort 1 and 27.2 deaths in cohort 2. The hazard ratio for all-cause mortality in subjects of cohort 1 (2834 deaths) vs cohort 2 (2035) was 1.49, and there were more deaths in cohort 2. In cohort 1, a significant increase of all-cause mortality was found only in deciles 1 and 10, whereas for cohort 2, significant differences were observed for deciles 1, 2, 3, 9 and 10(Figure 1). Therefore, increased unadjusted mortality was found both in the lowest and highest HbA1c deciles in both cohorts, and patients included in a decile whose median HbA1c of 7.5% had the lowest hazard of death. Similar to the results of all-cause mortality, insulin treatment (cohort 2 vs cohort 1) was associated with an increased risk of progression to first large-vessel disease with an adjusted hazard ratio of 1.36. Taking these results, the authors suggested the revision of the diabetes guidelines include a minimum HbA1c.

From the results of many prospective studies, it is clear that better glycemic control is beneficial for the prevention of the development and progression of diabetic microvascular complications. In contrast, the impact of strict glycemic control on cardiovascular disease and/or mortality has not yet been clarified. The UKPDS, in which glycemic control was initiated at the point of the first diagnosis of type 2 diabetes, proposed the beneficial effect of good glycemic control on cardiovascular events and mortality. Similarly, although the subjects studied were type 1 diabetes, the DCCT/EDIC studies also found that better glycemic control at an early stage of diabetes has beneficial effects on a reduction in cardiovascular disease outcomes. In contrast, the ACCORD study showed that type 2 diabetes subjects (with cardiovascular disease or at least two risk factors for cardiovascular disease or severe atherosclerosis) who underwent intensive glycemic control (target HbA1c < 6.0%) showed rather increased mortality (hazard ratio 1.22) compared with those who received standard glycemic control (target HbA1c 7.0–7.9%), and thus warned of the unexpected risk of strict glycemic control. The results by Currie et al. supported the results of the ACCORD study, and were different from those of UKPDS and DCCT/EDIC. The reason might be explained by the difference in the subjects studied, because the subjects that they investigated were selected from routine general practice and already had high HbA1c levels at baseline (mean HbA1c levels were 7.73 and 8.31% in cohort 1 and 2, respectively), and were more similar to those in the ACCORD study (mean HbA1c was 8.3%), but were different from those in UKPDS (mean HbA1c was 7.1%). The prevalence of previous macrovascular disease was also...
high (22 and 30% in cohort 1 and 2, respectively) and again was similar to that of the ACCORD study (35.2%), but was different from that in UKPDS (2.1%). Therefore, although the proposal by Currie et al. to revise the diabetes guidelines to include a minimum HbA1c level might be used for subjects with type 2 diabetes who already have elevated HbA1c levels and/or have a high risk of macrovascular diseases, it might not be suitable in subjects in early stages of diabetes.

Another observation by Currie et al. was that subjects receiving insulin treatment showed higher hazard ratios for all-causes of death and for progression to first large-vessel disease than those receiving sulfonylurea plus metformin regimen, implying the risk of insulin treatment itself. The U-shaped association was more abundant in cohort 2, and in that cohort, all three deciles lower than a mean HbA1c level of 7.5% showed a significant increase of all-cause mortality. Although the rates of hypoglycemic episodes were not investigated in this study, increased hypoglycemia under insulin treatment might be one reason. It has been suggested that hypoglycemia could increase cardiovascular events for several reasons, such as the enhancement of the adrenergic response and the destabilization of atherosclerotic plaques through the increase of oxidative stress and of other stress responses. However, as the authors discussed in their report, it should be taken in account that there are several differences in the subjects in cohort 1 and 2, such as higher frequency of previous cardiovascular events and of progressed nephropathy in cohort 2. Further investigation to clarify the impact of insulin treatment on mortality with detailed analysis, such as causes of death and frequencies of hypoglycemia, would be necessary.

According to the results from the report by Currie et al. and from the ACCORD study, the proposal to revise the diabetes guidelines to include a minimum HbA1c seems reasonable, especially in subjects with poor glycemic control and a high risk of macrovascular complications who are treated with insulin, but this might not be applicable for subjects at an early stage of diabetes or those with few risks of macrovascular disease. In Japan, a new health check-up system that aimed to prevent and early diagnose lifestyle related diseases including diabetes started in 2008. The Japan Diabetes Society also encourages the early diagnosis of diabetes, and thus included the HbA1c level of 6.5% in the diagnostic criteria of diabetes in 2010 (Journal of the Japan Diabetes Society 2010; 53: 450–467, in Japanese). Because early diagnosis followed by early intervention of diabetes has now been encouraged and been proven to prevent most diabetic complications, careful discussion should be carried out to revise the goal of glycemic control.

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Figure 1 | Hazard ratios for all-cause mortality by HbA1c deciles in type 2 diabetes subjects given oral combination and insulin-based therapies. Hazard ratios for all-cause mortality by HbA1c deciles in type 2 diabetes subjects given (a) sulfonylurea plus metformin regimen and (b) insulin-based regimen are shown. Vertical bars show hazard ratios (HR), and horizontal bars show HbA1c range. Red circle indicates each reference decile. *Truncated value at lower quartile, †truncated value at upper quartile. This figure is reprinted from an article by Currie et al.9 with permission from Elsevier (License number 2491840027075).
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