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CME ARTICLE

What is my ideal diabetes target?

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You are reviewing the laboratory results that have just arrived at your clinic. The first report reads: "Yeo Siok Hoon, HbA1c 10.0%." You remember Madam Yeo, who had recently retired after working 45 years as an accounts clerk. A regular patient of yours, Madam Yeo has an anxious personality and a special sensitivity to numbers. You can already hear her asking you, "Doctor, what is my ideal diabetes target?"

HOW COMMON IS THIS IN MY PRACTICE?

The prevalence of diabetes mellitus (DM) is increasing worldwide in a two-pronged fashion – among the ageing population with longer life expectancy and among the younger population with a rising trend toward obesity.

HOW RELEVANT IS THIS TO MY PRACTICE?

DM is diagnosed and managed in the community, and thus knowledge of its diagnostic and treatment targets are essential to all family physicians. This article highlights the evidences that have shaped our current treatment targets for type 2 diabetes mellitus.

For decades, the diagnostic criteria for DM had remained unchanged, until 1997, when an expert committee on the diagnosis and classification of DM revised the diagnostic criterion of fasting glucose to 7 mmol/dL. This was based on the observations from three cross-sectional epidemiologic studies that suggested the association between fasting glucose levels and retinopathy.[1]

About ten years later, in June 2008, the treatment targets of DM came under siege when the Action to Control Cardiovascular Risk in Diabetes (ACCORD)[2] and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE)[3] groups published two contradictory conclusions from their interim analyses in the *New England Journal of Medicine*. Both studies recruited participants with type 2 DM, randomised them to standard treatment versus tight blood glucose control treatment, and followed up on the participants' cardiovascular and other outcomes.

The ACCORD study, with a mean follow-up period of 3.5 years, reported in its interim data analysis that the all-cause deaths in the tight-control arm of the study (with physicians targeting glycated haemoglobin levels [HbA1c] below 6.0% and patients achieving a median HbA1c of 6.4%) was significantly higher than the standard-treatment group (with physicians targeting HbA1c of 7%–7.9%, and patients achieving a median HbA1c of 8.1%).[2] These results were consistent even with stratification by previous cardiovascular events or multiple cardiovascular risk factors. The study also analysed the speed of reduction in HbA1c levels, percentage change within the first four months (1.4% in the intensive-therapy group and 0.6% in the standard-therapy group), changes in drug regimens, medication side effects of hypoglycaemia attacks and undetected drug interactions at high doses, but did not isolate any conclusive reasons for the excess number of deaths.

The ADVANCE study group released the results of their interim analysis the following week, bearing reverse conclusions and supported the prevailing clinical practice. Their strategies, which targeted intensive glucose control (with HbA1c value at 6.5%), yielded a 10% relative reduction in the combined outcome of major micro- and macrovascular events. There was a significant 21% relative rate reduction in renal complications.[3] They also analysed their results to address the finding of increased deaths by the ACCORD study and presented no significant effects by the type of glucose control on deaths from cardiovascular or any other causes. In 2009, the Veterans Affairs Diabetes Trial (VADT) study group also published their findings in the same journal, reporting no significant increase in mortality in their intensively controlled group. Similarly, this study did not find significant difference in the reduction of micro- or macrovascular complications in the tight glucose control group.[4]

The five main observed differences between ACCORD and the ADVANCE and VADT studies were: (a) the overall magnitude of the reduction in HbA1c; (b) the speed of reduction in HbA1c within the first four months; (c) the difference in drug regimes in the intensive arm (further subanalyses were unable to attribute the increased rates of deaths to any single drug or drug class); (d) the observed rates of hypoglycaemia; and (e) the postulated adverse drug interactions among the various drug classes at higher doses.

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WHAT SUPPORTS OUR CURRENT PRACTICE?

The United Kingdom Prospective Diabetes Study (UKPDS) on glucose control had established that intensive glucose therapy (with sulfonylurea, insulin or metformin in obese patients) leads to lower microvascular (renal and retinal) complications compared to dietary modifications alone. The ten-year follow-up analysis showed that the intensively controlled group had fewer micro- and macrovascular complications despite the lack of sustained difference in HbA1c levels after ten years.[5]

As type 2 DM often coexists with other metabolic conditions that result in the same cardiovascular complications and death, it is increasingly difficult to identify the contributory protection from these complications. The Diabetes Control and Complication Trial Research Group (DCCT) for type 1 DM, which followed their study population over a long period of time, has established the role of intensive glucose control (to normal physiological control) in the reduction of micro- and macrovascular complication rates.[6]

Another large retrospective cohort study in the United Kingdom with 27,965 type 2 DM patients on oral treatment and 20,005 type 2 DM patients on insulin, all of whom were above 50 years of age, monitored the patients over time for their all-cause mortality.[7] The HbA1c levels with the lowest hazard had a median HbA1c of 7.5% (interquartile range [IQR] 7.5%–7.6%). The hazard ratios in the lowest HbA1c (6.4%; IQR 6.1–6.6) and the highest HbA1c (10.5%; IQR 10·1%–11·2%) were 1.52 and 1.79, respectively. These figures supported a general U-shaped association. The authors proposed that future studies were required to define the optimal HbA1c value for all-cause mortality in treated diabetic patients.[7]

WHAT SHOULD I DO NEXT?

In this era of evidence-based medicine, new clinical information is available every day, pointing practices in many different directions. In the midst of medical uncertainty, family physicians must examine the information available and decide on what is best for our patients. Although there are no clear answers, patients with DM will benefit from individualised treatment targets. The most appropriate target for glycaemic control should be one that would reduce microvascular events to ensure a better quality of life while mitigating the identified risks of increased mortality.

Type 2 DM with HbA1c control below 6%, observed in normal physiological levels and the tight control arm of the DCCT trial, will likely have long-term benefits and protection against microvascular complications. Patients who are not on medications should be complimented on their diet and lifestyle control. In patients treated with medications, existing complications such as nephropathy may support the benefits of continuation of tight glucose control targets. Uncertainties concerning the increased risk of mortality[2,6] should be communicated to patients and treatment targets should also be agreed upon by patients.

One of the hypotheses for increased mortality was the dropping of glucose levels "too fast" and "too much" in the context of a clinical trial. However, the overall magnitude and short timeline are unique, and should be important considerations when formulating treatment plans and titrating the regime of hypoglycaemic medication or insulin therapy. This must also be balanced with findings from the ten-year follow-up of the UKPDS, which shows that despite the lack of sustained differences, initial intensive glucose control after the completion of the trial continues to show benefits ten years later. In addition, patients on very high doses of medications should be monitored for possible unknown drug-drug interactions that may only exist at these concentrations. Any suspicion should be actively reported for further confirmation.

Madam Yeo attended your clinic and you explained to her the laboratory results. In response to the question on her ideal diabetes target, you highlighted to her the current clinical practice guidelines and explained the benefits of long-term tight glycaemic control. You also encouraged the patient to achieve 150 minutes of physical activities a week and download a nutrition tracking application to monitor her daily calorie intake in order to lower her body weight. You ended your consultation by arranging for Madam Yeo to have her annual diabetic retinal photography and foot screening done at a nearby community health centre.

TAKE HOME MESSAGES

1. DM targets need to be individualised.
2. The optimal treatment targets for DM as effective treatment for other metabolic conditions in reducing the risk of cardiovascular complications have been questioned.
3. It is beneficial to have good and early glycaemic control, as it reduces potential complications.
4. "Too fast" and "too much" reduction of HbA1c, hypoglycaemia and possible adverse drug-drug interactions at high doses are the postulated dangers in tight glycaemic control strategies.

ABSTRACT Diabetes mellitus is common in our increasingly affluent and ageing population. Although it is an old friend of practising family physicians, there is a need to be familiar with and up to date about the disease. As patients become more informed and receptive to current medical information, family physicians also need to stay current. This article highlights the evidences that have shaped our current treatment targets for type 2 diabetes mellitus.

Keywords: family medicine, treatment target, type 2 diabetes mellitus
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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

(Code SMJ 201212A)

	True	False
1. The prevalence of diabetes mellitus has been increasing worldwide, mainly due to an ageing population with longer life expectancy.	☐	☐
2. The current criteria of diagnosis and classification of diabetes mellitus (fasting glucose level of 7 mmol/dL) was based on the observations from three cross-sectional epidemiologic studies.	☐	☐
3. The association between a fasting glucose level of 7 mmol/dL and nephropathy led to the criteria for the diagnosis of diabetes mellitus in 1997.	☐	☐
4. In the ACCORD study, the all-cause mortality in patients with tight diabetic control (HbA1c below 6.0%) was lower than that in patients in the standard treatment group (target HbA1c 7.0%–7.9%).	☐	☐
5. The results of the ACCORD study were consistent even with stratification by previous cardiovascular events or multiple cardiovascular risk factors.	☐	☐
6. In the ACCORD study, the speed of reduction in HbA1c levels was found to be associated with a higher mortality rate in the tight diabetic control group as compared to the standard treatment group.	☐	☐
7. The ADVANCE study, released a week later than the ACCORD study, bore the reverse conclusions and supported the prevailing clinical practice.	☐	☐
8. In the ADVANCE study, a 10% relative rate reduction in the combined outcome of major macrovascular and microvascular events was attained in the intensive glucose control group (HbA1c 6.5%).	☐	☐
9. No relative rate reduction in renal complications was found between the intensive glucose control group and the standard glucose control group in the ADVANCE study.	☐	☐
10. In the VADT study, a significant increase in mortality rates was found in the intensive glucose controlled group as compared to the standard controlled group.	☐	☐
11. No significant difference in the reduction of macrovascular or microvascular complications was found in the intensive glucose controlled group in the VADT study.	☐	☐
12. The UKPDS showed that intensive glucose therapy with sulfonylurea, insulin or metformin in obese patients led to lower microvascular complications compared to dietary modifications alone.	☐	☐
13. A ten-year follow-up analysis in the intensively controlled group showed fewer macrovascular and microvascular complications despite a lack of sustained differences in HbA1c levels after ten years in the UKPDS study.	☐	☐
14. Type 2 diabetes mellitus often coexists with other metabolic conditions that result in similar cardiovascular complications and death, making the identification of contributory protection of good diabetes control difficult.	☐	☐
15. In type 1 diabetics, intensive glucose control as compared to normal physiological control has been shown to reduce the rate of macrovascular and microvsacular complications.	☐	☐
16. A large cohort study in the United Kingdom demonstrated that the HbA1c level with the lowest hazard ratio of all-cause mortality had a median HbA1c of 7.5%.	☐	☐
17. The same study showed that the hazard ratio of all-cause mortality was highest in patients with the lowest HbA1c of 6.4%.	☐	☐
18. A general U-shaped association has been found between low (HbA1c 6.4%) and high (HbA1c 10.5%) mean HbA1c values with increased all-cause mortality and cardiac events.	☐	☐
19. One of the proposed hypotheses for increased mortality is the speed of HbA1c reduction in the study setting, which should be considered when formulating a treatment plan for diabetic patients.	☐	☐
20. It is important to individualise treatment targets for all diabetic patients in order to reduce microvascular events, while mitigating identified risks of increased mortality.	☐	☐

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