Setting glycaemic targets in patients with type 2 diabetes. Where to now?

Distiller LA, BSc, MBCh, FCP(SA), FACE
Centre for Diabetes and Endocrinology, Houghton, South Africa
Correspondence to: Dr Larry Distiller, e-mail: Larry@cdecentre.co.za

Keywords: glycaemic targets; type 2 diabetes; cardiovascular disease; macrovascular disease; microvascular disease; HbA1c; legacy effect; public sector; private sector

Introduction

Results from several randomised controlled trials have demonstrated conclusively that microvascular complications can be reduced in patients with both type 11–2 and type 2 diabetes. These trials have indicated that an HbA1c level ≤ 7% is a reasonable target to aim for if attempts are to be made to reduce or delay the advent of microvascular complications. This target has therefore been incorporated into the American Diabetes Association (ADA)4 and subsequently the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA)5 guidelines. However, cardiovascular disease (CVD) remains the leading cause of both morbidity and mortality in patients with type 2 diabetes and over 65% of deaths in these patients are attributable to heart disease or stroke. Given the known increasing prevalence of type 2 diabetes globally, the CVD burden due to these conditions is expected to continue rising. It is therefore important to understand the relationship between improved glucose control and the occurrence of macrovascular disease.

Are our targets low enough?

Problems have been experienced in demonstrating a meaningful reduction in macrovascular disease (coronary heart disease, stroke and peripheral vascular disease) at the same ≤ 7% target level of HbA1c. This has raised the question as to whether a level of ≤ 7% is low enough. While some meta-analyses have shown a relationship between HbA1c and CVD,6,8 the role of improved glycaemic control in reducing this complication is less clear. The Diabetes Control and Complications Trial (DCCT) did not answer this question satisfactorily, as although there was a trend towards lower risk of CVD events with improved control, this was not statistically significant. However, a post-hoc analysis of the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated a continuous association between myocardial infarction and HbA1c with a statistically significant, 18% reduction, in CVD events for every 1% reduction in HbA1c. There was no threshold for cessation of benefit (i.e. the lower the level of mean HbA1c the better).10 This resulted in a number of Societies, including the American College of Endocrinology11 and the European Association for the Study of Diabetes (EASD)12 recommending a target HbA1c of ≤ 6.5%. This target has also been incorporated into the recommendations of the Joint British Societies Guidance document.13 Recommending a target HbA1c of ≤ 6.5% was, however, a combination of expert opinion and the belief in “the lower the better” without any outcome-based trials to support it.

Evidence for cardiovascular risk reduction?

Into this environment, three landmark trials, namely the ACCORD (Action to Control Cardiovascular Disease in Diabetes),14 ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation)15 and VADT (Veteran Affairs Diabetes Trial)16 were conducted. Both the ADVANCE and VADT found that no effect on intensive glucose control on major cardiovascular events was achieved by aiming for an HbA1c of ≤ 6.5%. The ADVANCE did however demonstrate a significant reduction in nephropathy (Relative Risk Reduction of 21%; p = <.001) with lower HbA1c targets. Paradoxically, the ACCORD trial revealed a significantly increased rate of death from any cause in the intensively treated group (5.0% vs 4.0%; hazard ratio, 1.22; p = 0.04). Interestingly, there were no significant differences in the primary outcomes (a composite endpoint of non-fatal MI, non-fatal stroke and death from cardiovascular causes) between the intensively treated and standard treatment groups in this trial. In the intensive-therapy group, the rate of non-fatal myocardial infarction was significantly lower than in the standard-therapy group (3.6% vs 4.6%; hazard ratio, 0.76; p = 0.004), but the rate of death from cardiovascular causes was higher (2.6% vs 1.8%; hazard ratio, 1.35; p = 0.02). There was no significant difference in the rate of non-fatal stroke (1.3% vs 1.2%;
hazard ratio, 1.06; \( p = 0.74 \)). Thus, although more patients in the intensively treated group died, a significant reduction in non-fatal myocardial infarction was seen in those that survived. A sub analysis of the VADT patients demonstrated a significant reduction in non-fatal myocardial infarction in patients who entered the trial with lower coronary artery calcification scores. A common feature in all three trials was the fact that the patients enrolled had had type 2 diabetes for a considerable time (8–10 years) and were generally regarded as high-risk patients. In the same vein, the HEART2D (Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus) Study\(^{17} \) was performed in an attempt to demonstrate that reducing post-prandial glucose levels in patients with diabetes post myocardial infarction could improve cardiovascular outcomes. Notwithstanding the fact that this trial was underpowered, no difference in risk for future cardiovascular events could be demonstrated.

In contrast to these “negative” studies, the long-term follow-up of the UKPDS\(^{18} \) cohort showed a significant reduction in cardiovascular events and myocardial infarction in the initially intensively treated group after 20 years. Furthermore, this significant reduction in coronary artery events was achieved, despite the fact that during the second decade of follow-up the difference in HbA\(_{1c}\) between the conventional and intensively treated groups had disappeared. This has given rise to the concept of the “legacy effect” of improved glycaemic control. It should be noted that the UKPDS cohort was very different from the patients in the above three trials as the UKPDS cohort had initially been recruited at the onset of type 2 diabetes and not after established macrovascular complications had developed.

**All risk groups are not equal**

Perhaps the most important lesson to be learned from these trials is that intensifying glycaemic control when cardiovascular disease is already present cannot possibly be expected to have a beneficial effect on outcomes. If we are hoping to reduce cardiovascular complications, intensive glycaemic control needs to be introduced very much earlier, probably from the time of diagnosis of the condition and certainly before overt cardiovascular disease is present.

Two more recent large meta-analyses of all cardiovascular trials have been conducted by Kelly et al\(^{18} \) and Ray et al.\(^{20} \) These demonstrated that, when all available trials are analysed together, intensive glucose control does indeed reduce the risk for some cardiovascular disease such as non-fatal myocardial infarction, but did not reduce the risk of cardiovascular death or all-cause mortality. The meta-analyses, not surprisingly, also confirmed the significantly increased risk of hypoglycaemia in intensively treated patients.

Based on these findings, the debate still rages as to whether a target HbA\(_{1c}\) level of \( \leq 7\% \) or \( \leq 6.5\% \) should be recommended. Many authorities are now questioning the advisability of having a single “target” and are recommending individualisation, with \( \leq 7\% \) being recommended for those with long-standing diabetes or with CAD and \( \leq 6.5\% \) for newly diagnosed and relatively younger or healthier subjects. While this appears to be an eminently reasonable approach, there is still no long-term prospective outcomes data to support the contention that younger patients or those with new-onset type 2 diabetes will have a reduction in cardiovascular outcomes if the lower targets are achieved. It is also reasonable to suggest that HbA\(_{1c}\) levels up to 7.5% may be acceptable in the elderly and infirm, those with hypoglycaemia unawareness or those with other unrelated diseases that may limit their longevity. What is clear, however, is that for any one patient, a desirable HbA\(_{1c}\) should be decided upon and set as the target. Treatment should then be intensified slowly but progressively until the target for that patient is reached. At the same time, every attempt should be made to avoid significant hypoglycaemia.

**Real world data**

This all makes sense and these newer approaches appear to be reasonable. However, in the real world it has been repeatedly demonstrated that these targets are difficult to achieve. This may be due to a host of factors, not least being our inability to bring about appropriate lifestyle changes. Even in the STENO-2 trial,\(^{21} \) which required rigorous life-style modification together with highly intensive therapy to be instituted in a small group (80 patients) who were closely monitored and managed, only 15% achieved an HbA\(_{1c}\) below 6.5%. Published surveys\(^{22-24} \) indicate that only between 37 and 44% of type 2 patients world-wide have HbA\(_{1c}\) levels \( \leq 7\% \). Data obtained from the National Health Laboratory Service (NHLS) database and from several private laboratories in South Africa (unpublished data: Personal communication) suggests that in this country not more than 32% of patients in the public sector and 39% of patients in the private sector have HbA\(_{1c}\) levels below 7%. The problem with these surveys are that patients who are eligible to have targets of \( \leq 6.5\% \) or even \( \leq 7\% \) are not distinguished from the elderly, frail and sick in whom one might settle for higher ambient glucose levels.

Perhaps of more relevance, available data from South Africa, obtained from the same sources as mentioned above, suggests that up to four out of five patients with diabetes in the public sector and as many as two in three patients in the private sector do not have their HbA\(_{1c}\) checked more than once a year, if at all.

**Recommendations**

Surely, before setting targets, it is more important to document the prevailing HbA\(_{1c}\) level on a patient in order to have a starting point. The HbA\(_{1c}\) should then be measured serially in order to allow for appropriate and timely intensification of therapy. Furthermore, it has been well demonstrated that any reduction of HbA\(_{1c}\) has beneficial effects with regard to improved outcomes\(^{19} \) and most of the benefit
MORE WITH DIAMICRON MR

ADVANCE
the largest, prospective study ever in 11 140 Type 2 diabetic patients²,³

• Diamicron MR* reduces serious diabetic complications¹
• Diamicron MR* significantly reduces renal events by 21% & macroalbuminuria by 30%¹
• Diamicron MR*: No weight gain & low hypoglycaemia¹

For full prescribing information, refer to package insert approved by the medical regulatory authority.

References:
1. ADVANCE Collaborative Group NEJM 2008;358;2560-72
2. Study rationale and design of ADVANCE. Diabetologia 2001; 44: 1118-1120.

* DIAMICRON MR based strategy.
of glucose lowering occurs from the initial reduction of overtly elevated levels. It seems prudent to aim for that objective first. While reasonable attempts need to be made to achieve internationally accepted targets, this is not attainable in many patients and is not advisable in some. The recent trials have demonstrated how difficult it may be to intensify therapy in order to achieve lower targets without the added problems of polypharmacy, weight gain and more particularly, hypoglycaemia. This is not to say that a target HbA1c of ≤ 7% should not be strived for in the majority of patients. But, it is clear that if we are unable to reach the recommended target levels in a large proportion of patients, the least we can do is to measure the HbA1c regularly and attempt to reduce it from the current level to as low as is practical and achievable.

It must also always be remembered that glycaemic control is but one modifiable risk factor in most of these patients, in whom obesity, dyslipidaemia and hypertension are extremely common co-morbidities. Of these, sustained glycaemic control is probably the most difficult to achieve and should not be addressed without adequate attention to lipid and blood pressure control.

Conclusion

While it is admirable to attempt to achieve glycaemic targets as laid down in various guidelines, this needs to be done with due care, the avoidance of hypoglycaemia and appropriate patient selection, taking due note of the patient’s duration of diabetes, the presence or absence of cardiovascular or other diseases, the patient’s potential longevity and prognosis. Targets should be individualised for each patient considering all these factors. It is reasonable, in the first instance to at least attempt to reduce the HbA1c from the initial level by about 1% irrespective of the starting level. Finally, other risk factors should not be ignored but need to be aggressively managed.

References