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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

therapeutics letter
January - February 2008

Glycemic Targets in Type 2 Diabetes

Many people with type 2 diabetes mellitus spend a lot of time, effort and money trying to keep their blood glucose down to normal or close to normal. Is there solid evidence for this approach? The Canadian Guidelines posted on the Canadian Diabetes Association website were accessed to find out what evidence is available to answer this question.[1] The Guidelines combine recommendations for type 1 and type 2 diabetes, but for this Letter references and information pertinent to type 1 diabetes have been removed.

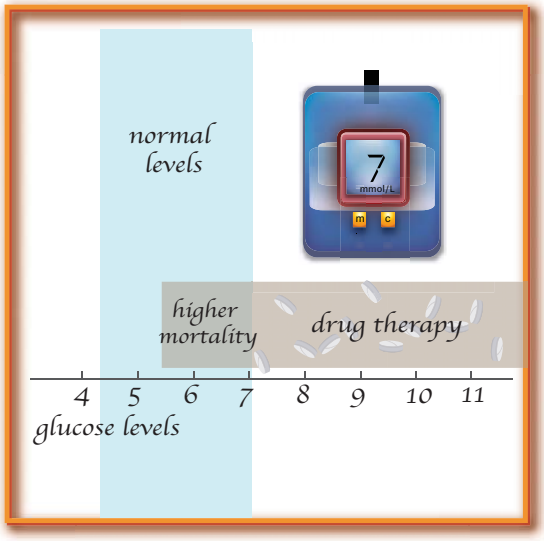
1. *Glycemic targets must be individualized; however, therapy in most patients with type 2 diabetes should be targeted to achieve an A1C ≤7.0% in order to reduce the risk of microvascular (Grade A, Level 1A)[2] and macrovascular complications (Grade C, Level 3).[3]*
2. *To achieve an A1C ≤7.0%, patients with type 2 diabetes should aim for fasting plasma glucose (FPG) or preprandial PG targets of 4.0 to 7.0 mmol/L and 2-hour postprandial PG targets of 5.0 to 10.0 mmol/L (Grade B, Level 2).[2,3]*
3. *If it can be safely achieved, lowering PG targets toward the normal range should be considered (Grade C, Level 3) [3,4]:*
   - *A1C ≤6.0% (Grade D, Consensus);*
   - *FPG/preprandial PG: 4.0 to 6.0 mmol/L (Grade D, Consensus); and*
   - *2-hour postprandial PG: 5.0 to 8.0 mmol/L (Grade D, Consensus)*

What do these guidelines mean for clinicians?

The guidelines caution that these targets must be individualized and will not be appropriate for all patients. At the same time they explicitly advocate these targets for most patients. The guidelines imply that these targets will reduce complications associated with diabetes and that the benefit of this approach outweighs the harm. The targets create serious challenges for physicians and patients, which have significant implications in terms of time, effort and utilization of health care resources.

What is the evidence used to support this approach?

Grade A, Level 1A means that it is based upon *a systematic review of high quality randomized controlled trials or an appropriately designed randomized controlled trial with adequate power to answer the question posed by the investigators.*



In this case the reference used to support a target A1C of <7.0% is the UKPDS 33 trial.[2] This trial randomized 3,687 new patients with type 2 diabetes to drug therapy with oral sulfonylureas or insulin with a target fasting plasma glucose of <6.0 mmol/L or to diet therapy with a target of the best achievable fasting plasma glucose with diet alone. Patients were followed for 10 years and the average A1C levels achieved in the drug and diet group were 7.0% and 7.9%, respectively. Microvascular endpoints were reduced in the drug group as compared to the diet group (ARR 2.4% [95%CI 0.4 - 4.7%], NNT 42 for 10 years). This reduction is entirely explained by the reduction of one of the microvascular endpoints, the need for retinal photocoagulation, ARR 2.7%. Total mortality and macrovascular outcomes were not reduced and major hypoglycemic events were increased (See Therapeutics Letter # 27).[5]

Grade C, Level 3 means that it is based upon *non-randomized controlled trial evidence;* in this case the reference is to a publication reporting observational data from the UKPDS trial relating measures of glucose to outcomes.[3] Grade D recommendations are based upon *a consensus of the experts preparing the report.*

Guideline assumptions

The guidelines above make the following assumptions:

1. physicians can identify the patients for whom it is safe to target A1C at <6% or <7%.
2. the benefit outweighs the harm when the identified patients are treated to A1C targets of <6% or <7% as opposed to higher A1C targets.

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Prior to February 2008 there was no evidence to support these assumptions and since February 2008 there is evidence which places these assumptions in doubt.

ACCORD, a test of the glycemic target hypothesis

The Action to Control CardiOvascular Risk in Diabetes (ACCORD) trial was designed to test whether cardiovascular disease (CVD) events can be reduced in type 2 diabetes patients at high risk of CVD by intensively lowering A1C levels to a target of <6.0%.[6] In this RCT 10,251 patients were randomized to either a target A1C of <6.0% or a target A1C of 7.0-7.9%. Other components of the same RCT randomized patients to systolic BP targets of <120 mmHg or <140 mmHg and to a statin plus a fibrate or a statin alone. The planned completion date of the trial was 2009.

After about 4 years into the trial, in February 2008, the glycemic component of the trial was terminated because mortality was 5.0% in the <6.0% group as compared to 4.0% in the 7.0-7.9% group, RR 1.26 [1.06 - 1.51], ARR 1.0%, NNT 100 for 4 years to cause one death.[7] The achieved average A1C in the <6.0% and 7.0-7.9% groups were 6.4% and 7.5%, respectively. The other components of the trial are continuing. The patients randomized to the intensive glycemic group will be treated to the higher glycemic target for the remainder of the trial. Full details of the trial will be published subsequently.

What does Steno-2 tell us about glycemic targets?

Steno-2 randomized 160 type 2 diabetic patients with persistent microalbuminuria to conventional therapy or to intensified target driven therapy involving multifactorial interventions and focused behavior modification.[8] One of the interventions in this trial was differences in A1C targets, the intensive target was <6.5% and the conventional target was <7.5%.[8] The achieved A1C in the intensive target group averaged 7.9% as compared to 9.0% for the conventional group. However, the intensive group also had many other different interventions: dietary targets, exercise targets, smoking cessation targets, blood pressure targets, lipid profile targets, mandating use of ACE inhibitors and increased use of aspirin prophylaxis. After 8 years follow-up there was a significant reduction in cardiovascular and microvascular outcomes in the multifactorial intervention group and a non-significant reduction in mortality, RR 0.80 [0.40 - 1.60].[9] The recently published 13 year follow-up results of the 8 year Steno-2 trial demonstrate a significant reduction in mortality: 30% in the intensive group versus 50% in the conventional group, RR 0.60 [0.40 - 0.90], ARR 20%, NNT 5 over 8 years.[10] However, it is impossible to attribute the mortality benefit to any one of the multiple interventions and consequently this trial does not tell us anything about which glycemic target is better.

Conclusions

- **A glycemic target of < 6% compared to a target of 7 to 7.9% caused increased mortality in type 2 diabetics who were at high risk of cardiovascular events.**
- **The optimal glycemic target in patients with type 2 diabetes is unknown.**
- **Additional RCTs that test specific glycemic targets are needed for the full spectrum of patients with type 2 diabetes.**

RR = Relative risk
ARR = Absolute risk reduction
NNH = Number needed to harm
NNT = Number needed to treat
CI = Confidence interval

The draft of this Therapeutics Letter was submitted for review to 40 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

References

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