Evidence discussing glycaemic targets that need to be achieved to reduce macrovascular disease risk in type 2 diabetes

Introduction

Type 2 diabetes mellitus (T2DM) is a disease that causes the glucose (sugar) levels in the blood to rise above normal range. High blood sugar destroys both small (microvascular) and large (macrovascular) blood vessels via a process known as clogging of the vessels (Atherosclerosis). When clogging occurs in large vessels, it causes the vessels to narrow thereby reducing blood flow to the muscles of the heart, brain and limbs (extremities) resulting in heart attack, stroke, pain and reduced healing of infection and wounds. People with T2DM have a 2 to 4-fold increased risk of developing diseases of the large vessels and these diseases of the large vessels account for 70% deaths in people with T2DM. This paper thus aims at discussing the disadvantages of high blood sugar and the importance of maintaining a near normal blood sugar level to prevent disease of the large vessels in people with type 2 diabetes (Figure 1).

Coronary heart disease.

Diabetic Patients has 25% lifetime risk of developing foot related complaints and around 6% of diabetes people are affected from diabetic foot disease (Figure 2 & Figure 3).

How does non-optimal blood glucose affect the individual with type 2 diabetes?

Non-optimal blood glucose has shown to have a detrimental effect on the patient’s daily life. In patients without diabetes, their blood sugar is usually maintained between 4mmol/l to 7mmol/l. In diabetic individual with poorly managed diabetes, their blood sugar can rise from 10mmol/l and above. High blood sugar together with other risk factors such as high blood pressure, smoking, alcohol, sedentary lifestyle, obesity and high cholesterol levels can further aggravate the clogging process. This will cause further damage resulting in diseases of the large vessels such as:

- Myocardial infarction (heart attack)
- Cerebrovascular accident (Stroke)
- Peripheral artery disease (diabetic foot ulcers due to reduced blood flow to the extremities)
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When high blood sugar level remains consistently unmanaged over many years, it results in leg ulcers

Lower limb amputation

Swallowing difficulties following a stroke

Pain

Sexual dysfunction

Incontinence

Communication difficulties

Emotional distress/depression

Reduced quality of life

What is glycaemic target?

Glycaemic target is a measurement to determine how effectively an individuals’ blood sugar is being managed. Different guidelines have set different targets for people with type 2 diabetes. The following glycaemic targets are recommended by NICE guidelines:

48mmol/mol (6.5%) or less for individuals whose diabetes is being managed either with healthy diet, and lifestyle modification (smoke cessation, exercise and alcohol abstinence) or diet, lifestyle changes and a single dose of antidiabetic medication that does not cause the blood sugar levels to drop below 4mmol/l.

53mmol/mol (7.0%) for individuals whose antidiabetic medication can cause their blood sugar levels to drop below 4mmol/l and those whose blood glucose level rises to 58 mmol/l (7.5%) or more despite being on one antidiabetic medication. A less tight glycaemic target of less than 64 mmol/mol (8.0%) may be use for individuals with history of severe low blood sugar, elderly patients, patients with advanced large vessels disease, long duration diabetes in whom glycaemic goal cannot be achieve notwithstanding effective self-management education, proper blood sugar monitoring, and effective management with multiple antidiabetic medication including insulin (ADA, 2015). Lowering blood sugar is critical to T2DM management in order to decrease the risk of large and small vessel disease. Lowering glycaemic target should be tailored to individual needs (Table 1 & Table 2).

![Figure 3 Diabetes mellitus.](image)

| Table 1 Glycaemic targets for the management of type 2 diabetes |
|---|---|---|---|
| Organization | HbA1c (%) mmol/mol | FPG (mg/L) | PPG (mg/L) |
| NICE | <6.5 (48 mmol/mol) | <153 |
| IDF – EUROPE | <6.5 (48 mmol/mol) | <100 |
| ADA – EAC | <7.0 (53 mmol/mol) | 70-130 |
| AACE | < or equal 6.5 (48mmol/mol) | <110 |

| Table 2 Glycaemic targets for older adults |
|---|---|
| Group | HbA1c % | HbA1c mmol/mol |
| Functionally independent | 7-7.5% | 53-59 |
| Functionally dependent | 7-8% | 53-64 |
| Frail | Up to 8.5% | Up to 70 |
| Dementia | Up to 8.5% | Up to 70 |
| End of life care | Avoid symptomatic low blood sugar |

Does reduction in glycaemic level reduces the risk of macrovascular complication?

Several studies have investigated the effect of tight glycaemic control on large vessels disease in individuals with type 2 diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) investigated the effect of intensive glycaemic control on large vessels disease in 3687 newly diagnosed T2DM patients with a glycaemic target of 6.0%. After 10 years follow-up period, a glycaemic level of 7.0% was attained in the intensive treatment group compared to 7.9% in the diet group. The intensive treatment group experienced a significant reduction in stroke, heart attack and diabetes related deaths as well as reduction in eye disease, kidney disease and diseases of the lower limbs. Hence supporting glycaemic targets of 7.0% or less in the prevention of disease of the large vessels (Table 3).

The Action to Control Cardiovascular Risk in Diabetes assessed the effect of reducing glycaemic levels to less than 6% on cardiovascular events in 10,251 T2DM patients at high risk of cardiovascular disease. The patients in the intensive treatment achieved a mean HbA1c of 6.5% at six months. The ACCORD study revealed that lower glycaemic levels were related with a reduction in the onset or progression of small vessels disease. Findings from the ACCORD study also suggest that the older adults may require a less stringent glycaemic target(Figure 4 & Figure 5).

The Action in Diabetes and Vascular Disease (ADVANCE) and the Veteran Affairs Diabetes Trial (VADT) looked at whether reducing glycaemic levels to less than 6.5% would have any significant effect in reducing both small and large vessels disease. Both ADVANCE and VADT showed that reducing glycaemic levels had significant effect in preventing the progression of small vessel disease but no changes were seen in major cardiovascular events (Figure 6 & Table 4).

The importance of lowering glycaemic target

Several clinical trials including the UKPDS, ACCORD, ADVANCE and VADT examined whether tight blood sugar levels can reduce the risk of stroke, heart attack and diabetes related deaths.
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in individuals with T2DM. The UKPDS demonstrated that optimal glycaemic control significantly reduces the risk of stroke, heart attack, diabetes-related deaths and all other causes of deaths. A ten-year follow-up of the UKPDS continued to show significant benefits in risk reduction in both small and large vessels disease even when HbA1c had deteriorated later. This is known as the “legacy effect”. Meta-analyses involving 5 studies revealed that lowering glycaemic levels in T2DM patients significantly reduces the occurrence of heart attack and coronary heart disease. Good glycaemic control have also shown to enhance wound healing in individual with T2DM.

Table 3 Findings from the UKPDS

| Metformin intensive | Sulfonylurea/insulin intensive |
|---------------------|-------------------------------|
| Change in risk      | P Value                       | Change in risk | P Value           |
| Stroke              | Reduced by 41%                | NS | Increased by 14% | NS               |
| Heart attack        | Reduced by 39%                | 0.01 | Reduced by 21%   | NS               |
| Diabetes related deaths | Reduced by 42%           | 0.017 | Reduced by 20%   | NS               |
| Other diabetes related endpoints | Reduced by 32%    | 0.0023 | Reduced by 7%    | NS               |
| Small vessels disease | Reduced by 29%            | NS | Reduced by 16%   | NS               |

Table 4 Outcomes: summary of ACCORD, ADVANCE and VADT Study

| Accord | Advance | Vadt |
|--------|--------|------|
| HbA1c Intensive vs standard | 6.4 VS 7.5 | 6.4 VS 7.0 | 6.9 VS 8.4 |
| Nonfatal heart attack Intensive vs standard | 3.6 vs 4.6 | 2.7 vs 2.8 | 6.3 vs 6.1 |
| CV Deaths Intensive vs standard | 2.6 vs 1.8 | 4.5 vs 5.2 | 2.1 vs 1.7 |
| Small vessel disease | Nephropathy reduced by 21% Retinopathy reduced by 5% | Blood sugar control had no effect on CV events |
| Take home | Reduced heart attack | Blood sugar had no effect on CV events but reduced the risk of small vessel disease |

ACCORD Glucose (Action to Control Cardiovascular Risk in Diabetes — Glucose-lowering arm)

National Heart, Lung, and Blood Institute
ACCORD trial began January 1, 2001, February 6, 2008

- **Goal:**
  To test whether an intensive strategy that targets HbA1c levels <6.0% reduces the rate of CV events more than a standard strategy that targets an HbA1c of 7.0% to 7.9%

- **Population and treatment:**
  10,000 patients with type 2 diabetes and either heart disease or two risk factors for heart disease
  Randomly assigned to intensive blood sugar lowering or to standard blood sugar lowering

- **Primary outcome:**
  A composite of fatal and nonfatal major CV events

**Figure 4** ACCORD Glucose.

Is glycaemic target individualized or standard for everyone?

Following findings from UKPDS, ACCORD, ADVANCE and VADT study, guidelines strongly advocates for individualized targets. The ACCORD, ADVANCE and VADT study had elderly patients as well as patients with more than 10 years duration of diabetes. The mortality rate recorded in these studies demonstrate that very tight glycaemic control could be detrimental in the elderly patients and people with very long duration diabetes. When setting glycaemic targets, guidelines strongly emphasized on individual factors such as diabetes duration, age of the individual, lifestyle factors (diet, alcohol, exercise levels, smoking status), the individual’s risk of cardiovascular disease, how well the individual is responding to lifestyle changes and existing antidiabetic medication, and the individual’s current health status.

**How does an individual know they are on the right glycaemic target?**

Individual with T2DM can have their HbA1C monitored every three to six months. The HbA1c gives a record of glycaemic control for the past three months. The HbA1c will determine if the individual is achieving their glycaemic target. Blood glucose self-monitoring can also be used to determine if an individual is achieving their glycaemic target. However, NICE guidelines do not recommend regular self-blood glucose monitoring for individual with type 2 diabetes except they are receiving insulin therapy, or they are on oral antidiabetic medication that can make them prone to low blood sugar levels.

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**ACCORD Glucose: Results**

- The median A1c level achieved in the intensive-treatment group was 6.4%, vs 7.5% in the standard group.
- The trial was stopped early because of an excess of three deaths per 1000 participants per year in the intensive group vs the standard group, over an average of four years of treatment.

### Deaths in the two treatment groups at four years

|               | Standard glycemic control | Intensive glycemic control |
|---------------|---------------------------|---------------------------|
| Deaths, n     | 203 (11’008y)             | 257 (14’000y)             |

**Figure 5 ACCORD glucose results.**

### Adverse Outcomes: ACCORD, ADVANCE and VAHD

|                                | ACCORD* | ADVANCE | VADT |
|--------------------------------|---------|---------|------|
| Severe Hypoglycemia (% per yr)  | 3.0 vs 1.0 | 0.7 vs 0.4 | -    |
| Hypoglycemia requiring assistance (% per year) | 4.6 vs 1.5 | 1.8 vs 0.6 | 2.3 vs 1.1 |
| Weight Gain > 10Kg              | 27.8 % vs 14.1% | 0.0 vs -1.0 | -    |
| Wt gain (Kg) Intensive group    | 3.5     | 0.7     | 6.8  |
| Increased Mortality Rosiglitazone | No      | No      | No   |

**Figure 6 Adverse outcomes.**

What else can an individual with type 2 diabetes do to minimise the risk of macrovascular complication?

Studies have shown that smoke cessation can significantly reduce the risk of cardiovascular mortality and events. People with T2DM who are overweight or obese are advised to lose weight. The Look AHEAD study found that weight reductions of 5-10% was linked with significant improvements in CVD risk factors, and more improvements were seen with a more substantial weight loss. A 5-10% reduction in weight correlated to a 6mmol/mol decrease in HbA1c, a 5-mmHg decrease in both systolic and diastolic blood pressure, a 0.5mmol/l decrease in triglycerides and a 0.293 mmol/l increase in HDL cholesterol. Diet modification, such as eating more fruit and vegetables, oily fish, white meat rather than red, nuts and pulses, wholegrains and reducing saturated fats, dairy products, sugar and salt help to reduce the risk factors associated with CVD. People with T2DM are advised to take at least 150 minutes aerobic exercise weekly and they should also stay in regular contact with their dietitian who can advise on diet that can reduce their blood sugar and cholesterol levels. They can also attend a structured diabetes education program where they can learn about carbohydrate counting and low glycaemic index diet. Furthermore, controlling blood pressure below the target of 140/80mmHg with medication such as ACE Inhibitors can reduce the risk of diabetes complications.

**Conclusion**

High blood sugars in individuals with T2DM can result in diseases of the large vessels. The primary objective in managing high blood sugar and preventing the risk of large vessels disease is early treatment and reduction in HbA1c levels to as near normal as is safely possible. Reduction of HbA1c to individualized safe levels have shown to have long term benefits in reducing the risk of stroke, heart attack and diabetes-related deaths in individuals with T2DM. Beside antidiabetic medications, strategies that reduces blood pressure, cholesterol levels as well as increased physical activity, healthy diet, smoke cessation

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and alcohol abstinence have been effective in reducing HbA1c levels and preventing diabetes complication in individuals with T2DM.

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Conflicts of interest

The author declares there is no conflicts of interest.

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