Type 2 diabetes: does intensive blood glucose control improve renal outcomes?

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A systematic review and meta-analysis has summarised the effects of intensive versus conventional blood glucose control on renal outcomes in patients with type 2 diabetes. Intensive blood glucose control reduced the risk of the surrogate outcomes of microalbuminuria and macroalbuminuria. However, there was no reduction in the more clinically important outcomes of doubling of serum creatinine, end-stage renal disease or death from renal disease and clinicians should continue to follow the NICE clinical guideline on type 2 diabetes.

Overview and current advice

The NICE clinical guideline 87 on type 2 diabetes states that the management of patients with type 2 diabetes is complex, requiring an individualised, multifactorial approach1. Controlling blood glucose requires a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia. NICE guidance recommends that patients should be involved in setting their individualised HbA1c target level, which may be above the general target of 48 mmol/mol (6.5%). Pursuing highly intensive management to HbA1c levels below 48 mmol/mol (6.5%) should be avoided.

Trial evidence suggests small absolute benefits of intensive compared with conventional blood glucose control in people with type 2 diabetes on some macrovascular outcomes, but by no means all2. Intensive control reduces coronary heart disease, but not stroke, death from cardiovascular disease or death from all causes. This needs to be balanced against the increased risk of severe hypoglycaemia with intensive blood glucose control. Previous studies and meta-analyses have also shown a reduction in certain microvascular events with intensive blood glucose control. However, results have been inconsistent, and some end points were disease-oriented, surrogate outcomes rather than patient-oriented, clinical outcomes3.

See the NHS Evidence topic page on type 2 diabetes for a general overview of the condition. The NICE Pathway: diabetes brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.
New evidence

This systematic review and meta-analysis summarised the effects of intensive versus conventional blood glucose control on both surrogate and clinical renal outcomes in patients with type 2 diabetes\(^4\). It included data from seven randomised controlled trials (RCTs) involving 28,065 patients who were monitored for between two and 15 years.

Intensive* versus conventional blood glucose control reduced the risk of surrogate renal outcomes (microalbuminuria: relative risk [RR] 0.86, 95% confidence interval [CI] 0.76 to 0.96; macroalbuminuria: RR 0.74, 95%CI 0.65 to 0.85). However, there was no reduction in clinical renal outcomes (doubling of serum creatinine: RR 1.06, 95%CI 0.92 to 1.22; end-stage renal disease: RR 0.69, 95%CI 0.46 to 1.05; death from renal disease: RR 0.99, 95% CI 0.55 to 1.79)\(^4\).

* The HbA1c targets for intensive control varied in all studies. The highest HbA1c target in the intensive arms of the trials was 7.1% and the lowest was less than 6%\(^4\).

Commentary

Commentary provided by Prof Roger Gadsby MBE
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This meta-analysis found intensive blood glucose control reduced surrogate renal outcomes, such as micro or macroalbuminuria, but not clinically important renal outcomes, such as doubling of serum creatinine, end-stage renal disease or death from renal causes.

The analyses are limited by the low absolute rate of these clinically important, patient-oriented renal outcomes. For example, the pooled cumulative incidence of end-stage renal disease in the conventional treatment group of all trials that reported this outcome was only 1.6%\(^4\). Such low incidences could mean that the analyses were not adequately powered to detect a clinically-important treatment effect if there was one. However, on the other hand, given the known risks of severe hypoglycaemia and limited benefit on cardiovascular outcomes with intensive blood glucose control\(^**\), even if a treatment effect is assumed, the low incidence of these clinically-important renal outcomes may render intensive control hard to justify. As an accompanying editorial points out, the cumulative incidences of end-stage renal disease and cardiovascular disease should be considered\(^5\). In a recent Danish cohort study of patients with diabetes (either type 1 or type 2), there were about 50 cardiovascular-related deaths for every one end-stage renal disease-related death\(^6\).

The authors of this study\(^4\) and a second accompanying commentary\(^7\) discuss several reasons why intensive glycaemic control may not have shown a benefit on clinically important renal outcomes in this meta-analysis. There is an argument that intensive control may have started too late in the course of disease to prevent the development of advanced renal complications in these patients. Additionally, the duration of treatment and/or follow-up in these studies may have been too short to see improvements in progressive chronic kidney disease.

Overall then, clinicians should continue to follow the NICE clinical guideline on type 2 diabetes. As the accompanying editorial concludes, for many patients with type 2 diabetes, the potential benefits of multidrug intensive glucose control regimens (which are only marginally supported by current evidence) must be weighed against the potential risks of such therapy as well as the potentially larger benefits of focussing clinical attention on other areas such as blood pressure lowering, lipid control and smoking cessation\(^5\).

\(^**\) The CONTROL meta-analysis found intensive control to reduce HbA1c by an additional 0.9 percentage points over conventional control significantly reduced the risk of coronary heart disease (by approximately six fewer events per 1,000 patients over 4.4 years) but not stroke, death from cardiovascular disease or death from all causes. Intensive blood glucose control increased the risk of
severe hypoglycaemia (requiring the assistance of a third party), by approximately 42 extra events per 1,000 patients over 4.4 years.

References
1. Type 2 diabetes – The management of type 2 diabetes. NICE clinical guideline 87 (2009)
3. Implementing key therapeutic topics: 3, Type 2 diabetes. MeReC Bulletin Vol 22, No 5, March 2012

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