NICE National Institute for Health and Care Excellence

Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Intensive glucose control in people with type 2 diabetes

A 15-year observational follow-up study of participants who were previously enrolled in a large randomised control trial based in the US, found that 5.6 years of intensive glucose control did not significantly decrease the long-term risk of cardiovascular disease compared with standard glucose control in people with type 2 diabetes. This supports the NICE guideline on type 2 diabetes in adults which recommends an individualised approach to agree an appropriate HbA1c target, balancing the risk of hypoglycaemia with the risk of future cardiovascular and diabetes complications. Furthermore, the management of cardiovascular risk in people with type 2 diabetes is multifactorial and not focused solely on blood glucose targets.

Overview and current advice

The NICE guideline on type 2 diabetes in adults recommends that people with type 2 diabetes should be involved in decisions about their individual glycated haemoglobin (HbA1c) target and be supported to achieve and maintain this. For adults with type 2 diabetes that is managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia, the guideline recommends supporting the person to aim for an HbA1c level of 48 mmol/mol (6.5%). If HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher, advice about diet, lifestyle and adherence to drug treatment should be reinforced. The person should be supported to aim for an HbA1c level of 53 mmol/mol (7.0%), and drug treatment should be intensified (taking into account principles of individualised care).

When intensification of drug treatment is needed the guideline recommends that additional treatments should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug. The target HbA1c level can be relaxed on a case-by-case basis, with particular consideration for people who are older or frail, those with a reduced life expectancy, those for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia, and those for whom intensive management would not be appropriate, such as people with significant comorbidities. The NICE patient decision aid for adults with type 2 diabetes can support the implementation of the guideline recommendations on the individualised agreement of HbA1c targets.

The original randomised control trial (RCT), by Duckworth et al. 2009, randomised 1,791 military veterans to receive either standard glucose control which was defined as a HbA1c level between 8 and 9% or intensive glucose control, defined as a goal HbA1c level more than 1.5% lower than the standard therapy group. After 5.6 years there was no significant difference in cardiovascular risk between intensive treatment and standard treatment. However, in a 9.8 year follow-up study by Hayward et al. 2015 there was a significant reduction in cardiovascular risk in the intensive therapy

group compared with standard therapy (hazard ratio 0.83, 95% confidence interval 0.70 to 0.99, p=0.04).

The NICE Pathway on type 2 diabetes in adults brings together everything NICE has said on type 2 diabetes adults in an interactive flowchart. NICE has also published a quality standard on diabetes in adults, which provides a concise set of prioritised statements designed to drive measurable quality improvements within this area.

New evidence

A large, 15-year follow-up, observational study of 1,655 adults with type 2 diabetes who were previously enrolled in Duckworth et al. 2009 (RCT), was conducted to determine the long-term effects of intensive glucose control compared with standard glucose control (Reaven et al. 2019). The mean age (standard deviation) of participants was 60.5 (8.7) years, most were male (97.2%) and the mean (SD) duration of diabetes was 11.6 (7.5) years. The primary outcome was major cardiovascular events and secondary outcomes included major diabetes events, death and quality of life.

There was no significant difference in major cardiovascular events between the intensive therapy group compared with the standard therapy group (47.3/1000 vs 51.8/1000, HR 0.91, 95% CI 0.78 to 1.06, p=0.23). There was no significant difference in the secondary outcomes of risk of any major diabetes events and death from cardiovascular causes (HR 0.90, 95% CI 0.78 to 1.04; HR 0.94, 95% CI 0.73 to 1.20, p-values not reported, respectively). Health related quality of life was measured on a scale from 1-100, higher scores indicating a better quality of life; the mean (SD) score in the intensive therapy group was 63.8 (17.2) compared with 62.2 (17.6) in the standard therapy group, a non-significant mean difference of 1.6 (−0.7 to 3.9).

A major limitation of this study was that the population was almost exclusively male, thus limiting the generalisability of the findings to women with type 2 diabetes. Participants were enrolled to the original RCT between 2000 and 2003, since then there are newer treatment options for type 2 diabetes and the medicines used in this study may not reflect current practice. The intensification of glucose control was only conducted over the initial 5.6 years of the RCT and, although the separation of HbA1c levels between the two groups was maintained for 7.1 years, it is not possible to estimate the effects of continuing intensified blood glucose control from this study.

Commentary

Commentary provided by NICE

The findings of this study (Reaven et al. 2019) are important because, although the initial findings by Duckworth et al. didn't find a significant difference in cardiovascular events after a median follow-up of 5.6 years, the findings of Hayward et al. after a median follow-up of 9.8 years did find a small improvement, and it wasn't known whether further benefits would be realised over a longer time frame This study shows that intensive blood glucose control at a HbA1c level of 6.9% for 5.6 years did not reduce the incidence of major cardiovascular events over a median follow-up of 13.6 years. The authors conclude that the reduction in cardiovascular risk was only realised during the 7.1 years of follow-up, when the HbA1c levels were lower in the intensive therapy group compared with the standard therapy group, and suggest that intensive blood glucose control needs to be maintained to reduce cardiovascular risk.

The authors also commented that other cardiovascular risk factors were well managed in the study cohort and that intensive glucose control may only be effective in reducing cardiovascular risk when other cardiovascular risk factors, such as cholesterol and blood pressure, are not adequately managed. The findings of this study support NICE's recommendations in the type 2 diabetes in adults guideline, where the management of cardiovascular risk is multifactorial and not focused solely on

blood glucose targets. The findings also support NICE's recommendation to involve people with type 2 diabetes in decisions about their individual HbA1c target and to relax the HbA1c target for people who may not benefit from or may be at risk from intensive glucose lowering, the most notable risk being hypoglycaemia and its associated complications. The NICE patient decision aid for adults with type 2 diabetes can help with this conversation.

Study sponsorship

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