Optimising glycaemic control is still important, especially early in type 2 diabetes

Tight early glycaemic control must remain a priority, according to this evidence review of the role of glycaemic control in optimising type 2 diabetes outcomes published in *Diabetologia*. The global expert group, led by Kamlesh Khunti and Francesco Zaccardi of the Leicester Diabetes Centre, evaluated the historical and current evidence base to identify whether glycaemic control is still as important in type 2 diabetes care or whether the benefits of newer drugs demonstrated in cardiovascular and renal outcome studies should take priority. The authors recommend a two-pronged approach: (1) ensuring early tight glycaemic control, often requiring more than one glucose-lowering agent, to achieve the significant "legacy effect" identified by the UK Prospective Diabetes Study; and (2) ensuring that target-organ protection with SGLT2 inhibitors or GLP-1 receptor agonists is introduced promptly when cardiorenal risk increases and this additional protection is indicated (even if this is at diagnosis). The authors provide a useful comparison of the key features of the cardiovascular/renal outcome trials versus the intensive glucose-lowering trials, and the factors impacting treatment adherence and potential causes of therapeutic inertia. It is hoped that, by using simple searches to evaluate how well we are implementing these two parallel strategies, we can reduce therapeutic inertia in our own practice and, thus, improve care delivery and outcomes for people with type 2 diabetes.

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Previously, diabetes care focused on the management of glucose, the so-called "glucocentric approach". However, following the demonstration that SGLT2 inhibitors and GLP-1 receptor agonists have significant cardiorenal benefits, focus has shifted to prioritising organ-specific effects with these newer drugs. Whether this is the correct strategy to optimise benefits in all groups remained uncertain and prompted Professor Kamlesh Khunti and Dr Francesco Zaccardi to lead a panel of primary and specialist care global diabetes experts to review, discuss and summarise the current evidence around the effects of glucose control on long-term type 2 diabetes outcomes. Their findings are published in the "For debate" feature in *Diabetologia*.

The evidence base

The expert group highlighted that at least 50% of those newly diagnosed with type 2 diabetes remain at low cardiorenal risk and would not have met the inclusion criteria for the cardiovascular and renal outcome trials of the newer drugs and, hence, would not be expected to gain the same level of benefit when treated with these drugs as those at higher risk. Indeed, more than 60% of people with type 2 diabetes would not meet the recommendations for early initiation of an SGLT2 inhibitor or GLP-1 RA according to the American Diabetes Association's Standards of Care.

In contrast, there is strong evidence from the UKPDS (UK Prospective Diabetes Study) that such individuals would benefit from intensive glycaemic control. This 20-year trial compared intensive glucose lowering with sulfonylureas or insulin, or with metformin in those who were overweight or obese, aiming for an 11 mmol/mol (1.0%) difference in HbA_{1c} between the control (diet-managed) group versus the intensive groups. The UKPDS 35 report highlighted that in those recently diagnosed with type 2 diabetes, each 11 mmol/mol reduction in mean HbA_{1c} was linked to a 21% reduction in any diabetes-related endpoint, a 21% reduction in diabetes-related mortality, a 14% reduced risk of myocardial infarction and a 37% reduced risk

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Table 1. UKPDS at 44 years – legacy benefits in those randomised to intensive glycaemic control.

	Relative risk reduction	Absolute risk reduction
Sulfonylurea or insulin group		
All-cause mortality	10%	2.7%
Myocardial infarction	17%	3.3%
Microvascular disease	26%	3.5%
Metformin group		
All-cause mortality	20%	4.5%
Myocardial infarction	31%	6.2%

of microvascular complications (Stratton et al, 2000). Following the active (randomised) part of the study, glucose control rapidly equalised in the intensive and control groups, and this persisted over the long term. Follow-up at 10 years demonstrated a so-called "legacy effect" in those who were initially in the tight control groups, who saw persisting and emerging reductions in both microvascular and macrovascular complications and mortality.

Shortly afterwards, data from three randomised controlled trials in older people with more long-standing type 2 diabetes, many of whom already had diabetes complications, demonstrated differing results from UKPDS, resulting in confusion and causing many clinicians to believe that tight glycaemic control was unsafe. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, multiple drugs were used to rapidly reduce glucose levels towards normal, resulting in no cardiovascular disease (CVD) reduction and an increased risk of death, whilst, in the Veteran Affairs Diabetes Trials, intensive glycaemic control did not reduce the risk of CVD, cardiovascular or all-cause mortality, or microvascular complications. However, in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) study, more gradual glucose reduction did reduce the risk of a combined microvascular and macrovascular endpoint.

UKPDS long-term legacy effect

Recently, post-trial monitoring results at 24 years following the original UKPDS 20-year randomised controlled trial were published, using routinely collected clinical and mortality data for almost 1500 participants (Adler et al, 2024). As reported previously in *Diabetes Distilled*, this analysis confirmed that early glycaemic control with either of the two intensive regimens continued to demonstrate a beneficial legacy effect on mortality and myocardial infarction, as well as reducing microvascular complications amongst those initially treated with a sulfonylurea or insulin (see *Table 1*).

There were no significant reductions in stroke or peripheral arterial disease in either of the intensively treated groups, either during or after the trial, and no significant risk reduction in microvascular disease for metformin.

Implications for practice

This paper advocates a clear, two-pronged approach involving tight early glycaemic control around diagnosis (usually using more than one glucose-lowering therapy), and prompt use of cardiorenal organ protection with SGLT2 inhibitors and GLP-1 RAs as soon as this is required (including at diagnosis if risk is already high enough).

Many readers will not have been practising when UKPDS was published and so may be unaware of the huge impact the study had, highlighting as it did the benefits of tight early glycaemic control on all diabetes outcomes even if glycaemia later deteriorates, and spurring the switch to using metformin as first-line therapy. I hope this update and the publicity around the 44-year results of UKPDS will remind both ourselves and the people we support of the benefits of early glycaemic control combined with cardiorenal benefit from the newer drugs.

A recent systematic review of observational studies demonstrated that between 45% and 93% of people had what the authors described as "poor glycaemic control" (Bin Rakhis et al, 2022). Sadly, when we look at our own practices or services, we are likely to find a significant proportion of people not meeting the glycaemic (and blood pressure and lipid) goals we have agreed or not receiving organ-protecting glucose-lowering therapies when they are clearly appropriate. Khunti et al provide concise guidance on what may affect treatment adherence, along with an analysis of provider,

individual and system-based causes of therapeutic inertia, which can help us identify these in our own practice.

Up to half of people newly diagnosed with type 2 diabetes will already have complications and many will meet the criteria for dual therapy with metformin and an SGLT2 inhibitor, but only a small number are started on dual therapy as soon as the metformin has been titrated and tolerance confirmed, as recommended by NICE NG28. If we have questions about whether an individual is suitable for an SGLT2 inhibitor then the interactive tool from the Improving Diabetes Steering Committee can help us make safe decisions and counsel effectively.

In the clinic, it can be disheartening to witness the low priority that many people with diabetes put on their condition and its care, including arranging blood tests and attending for reviews. It is good to ask ourselves regularly what more we can do to help with education and sharing knowledge to reduce all aspects of therapeutic inertia. Simple searches can help us find and support those early in their diabetes journey to achieve optimal glycaemic control, as well as alerting us to people whose cardiorenal risk warrants additional organ-protecting therapies such as SGLT2 inhibitors and GLP-1 RAs at any time.

This two-pronged approach, regular reviews, individualised care, and doing everything we can to reduce the impact of social determinants of health and to inspire people to care for their diabetes will hopefully minimise disease burden and mortality. Let's refocus on reducing therapeutic inertia. ■

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Glycaemic control is still central in the hierarchy of priorities in type 2 diabetes management

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