What is the best first-line therapy for type 2 diabetes?

In this section, a panel of multidisciplinary team members give their opinions on a recently published paper. In this issue, we discuss which first-line antidiabetes drug is most effective at delaying the need for subsequent treatment intensification.

Initial choice of oral glucose-lowering medication for diabetes mellitus: a patient-centered comparative effectiveness study.

Berkowitz SA, Krumme AA, Avorn J et al (2014) *JAMA Intern Med* **174**: 1955–62

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Rates of treatment intensification following initiation of different oral therapies

1 In this retrospective study of the records of a large US health insurer, the authors compared the effects of treatment initiation with different classes of antidiabetes drugs in terms of subsequent need for treatment intensification.

2 Glucagon-like peptide-1 (GLP-1) analogues were not included in the analysis as they may have been initiated off-label for weight loss, and sodium–glucose cotransporter 2 inhibitors were excluded as they were not licensed in the US at the time.

3 The primary outcome was time to treatment intensification, defined as initiation of another class of glucose-lowering agent (including GLP-1 analogues and insulin), and secondary outcomes included time to major cardiac events and time to hospitalisation for hypoglycaemia.

4 A total of 15 516 people with T2D were evaluated, of whom 57.8% began on metformin, 23.0% on sulphonylureas, 6.1% on thiazolidinediones (TZDs) and 13.1% on dipeptidyl peptidase-4 (DPP-4) inhibitors.

5 Over a median follow-up of around 1 year, 24.5% of people who began on metformin required a second therapy, compared with 37.1% of those who began on a sulphonylurea, 39.6% of those on a TZD and 36.2% of those on a DPP-4 inhibitor ($P<0.001$ for all comparisons with metformin).

6 In adjusted analyses, sulphonylureas (hazard ratio [HR], 1.68), TZDs (HR, 1.61) and DPP-4 inhibitors (HR, 1.62) were all associated with increased risk of treatment intensification compared with metformin, and the latter significantly increased the time to treatment intensification compared with the other agents.

7 Compared with metformin, sulphonylureas were associated with an increased risk of composite cardiac events (coronary heart disease, congestive heart failure [CHF], unstable angina, ischaemic stroke, acute myocardial infarction or a revascularisation procedure; HR, 1.16), CHF (HR, 1.19) and hypoglycaemia (HR, 2.71), whereas the other agents were not.

8 The authors conclude that metformin results in a significant delay in the need for treatment escalation and should be favoured as a first-line therapy, particularly over sulphonylureas, which have a higher risk of adverse events.

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Berkowitz and colleagues performed a retrospective cohort study of individuals with type 2 diabetes who were newly prescribed an oral glucose-lowering medication between 2009 and 2013 and received a second prescription (the latter criterion taken as an indication that the medication was tolerated). The cohort was drawn from fully insured members of a large national health insurer in the US. The purpose was to determine the effect of the choice of first glucose-lowering medication on time to treatment intensification with a second oral agent or insulin, and on short-term adverse events (hypoglycaemia, diabetes-related visits to the emergency department and cardiovascular events).

This was a large cohort including over 15 000 people, of whom 58% started treatment with metformin. Those initially prescribed metformin were less likely to need the addition of a second oral agent, insulin or both. Rates of hypoglycaemia were greatest in those taking a sulphonylurea, as were rates of cardiovascular events and congestive heart failure.

The choice of first-line agent seemed to be dependent on various factors, including gender (women were less likely to receive metformin as a first-line agent), age (younger people were more likely to receive it) and presence of co-morbidities. Those with pre-existing coronary heart disease were less likely to receive metformin as a first-line treatment. Interestingly, there was a fairly even split between the choice of first-line agent in those people with the lowest household income, in spite of a nearly fivefold difference in price between older and newer oral glucose-lowering medications. Rates of adherence were similar between the agents.

The authors present a fair discussion of the strengths and limitations of their study and conclude that, in real-world practice, metformin is superior to other glucose-lowering agents as a first-line treatment for type 2 diabetes. In addition, they highlight that underuse of metformin may result in unnecessary harm and expense to patients.

Whether the results of this study translate to UK clinical practice in the NHS is yet to be determined, but the findings highlight the need for continued education for all healthcare professionals working with people with type 2 diabetes that metformin is the first-line agent of choice. Education of healthcare professionals forms an important part of the service specification for many diabetes services and provides a mechanism for continual reinforcement of these important messages. ■

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This novel study, the aim of which was to determine the effectiveness of glucose-lowering medications by documenting subsequent treatment intensification, gives some interesting insights into the merits of commonly used oral agents. It also raises a number of interesting points not explored in the paper itself.

Just about every clinical guideline recommends lifestyle modification as the initial intervention in type 2 diabetes, with metformin as the first choice of medication. So why were fewer than 60% of this cohort of over 15 000 patients started on metformin as the initial agent for their diabetes? Some may justifiably have been started on other agents because of contraindications to metformin, but increasingly these are seen as relative rather than absolute when weighed against the distinct benefits of the agent. Might the marketing of the newer and more expensive agents have played a role?

For those who did receive metformin, the study provides ample justification for its place as the first drug of choice. It is cheap and safe, and it was the least likely to require add-on therapy. The study also confirms that sulphonylureas confer an increased risk of hypoglycaemia and of subsequent insulin requirement. Furthermore, their use was associated with an increased risk of cardiovascular events and congestive heart failure. Should such data lead to a review of the role of sulphonylureas as a recommended treatment? The other drug classes examined were significantly more expensive and were either less effective (in the case of dipeptidyl peptidase-4 [DPP-4] inhibitors) or have since fallen out of common use because of safety concerns (thiazolidinediones).

It is striking that the superiority of metformin was demonstrated despite "adequate adherence" in only 28.2% of recipients, while the inferiority of DPP-4 inhibitors was demonstrated despite adequate adherence in 41.6%. One cannot help thinking that outcomes would be even better if all patients received education on lifestyle modification to improve glucose control and if effective solutions were identified to improve adherence to metformin. It is conceivable that such a focus would demonstrate even more conclusively that metformin monotherapy is an effective, safe and inexpensive long-term treatment and, furthermore, it might challenge the widely-held view (repeated in the article) that type 2 diabetes is unavoidably progressive, inevitably requiring more treatments. In a world that is trying to address the challenge of nearly 400 million people with diabetes, with the potential to bankrupt families and health systems and disrupt whole economies, that would be very good news indeed. ■