

Management of a 50-year-old man with type 2 diabetes, whose blood sugar is suboptimally controlled



Dr Mark Savage discusses the treatment and management of this patient, and the evidence for the different pharmacological options

Your patient is a 50-year-old man with type 2 diabetes. He is currently on metformin and sulphonylurea but is not adequately controlled, with an HbA_{1c} of 7.8%. He is obese, with a body mass index (BMI) of 33 kg/m² and he has metabolic syndrome. His BMI currently excludes exenatide use.

In the UK the quality and outcomes framework (QOF) uses an HbA_{1c} level of 7.5% as a threshold for payment.⁴ This has been interpreted by a lot of clinicians as a set target. However, most international bodies, such as the International Diabetes Federation and NICE, have opted for a lower target of 6.5%.^{5,6}

Introduction

The first major outcome study in patients with type 2 diabetes was the United Kingdom Prospective Diabetes Study (UKPDS).¹ This demonstrated that better glycaemic control reduced microvascular complications,¹ but failed to demonstrate an effect of glycaemic control on cardiovascular (CV) mortality,¹ although metformin was found to reduce mortality and the rate of cardiovascular events in obese patients.² The Steno-2 study showed that an approach that targets multiple risk markers has many benefits.³ Therefore, HbA_{1c} should be lowered in patients with type 2 diabetes primarily to reduce microvascular risk, but also to lower CV risk as part of a multi-risk factor reduction approach.

Type 2 diabetes in context

Consider 100 people with a fasting sugar level of 6.5 mmol/l—none have diabetes. Now imagine another 100 people with a fasting sugar level of 7.5 mmol/l—all have diabetes. Assuming equal blood pressure (BP), weight, and lipids, what is the difference between these cohorts? Their CV risks are essentially identical, but their risks of microvascular disease (retinopathy in particular)⁷ are different. This is because the relationship between blood glucose and cardiovascular disease is linear—there is no cut off value, unlike for microvascular risk, which increases rapidly after a fasting level of 7.0 mmol/l.

Therefore, it is important that we see type 2 diabetes for what it really is—a cardiovascular disease, with

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those who have a long life, or an early diagnosis, being at risk of microvascular complications. It is the so-called type 2 diabetic phenotype of central obesity, abnormal lipid profile, and high BP that is associated with cardiovascular risk—whether or not diabetes is present. Seen together, this combination of abnormalities has been termed ‘the metabolic syndrome’.⁸ This patient is relatively young, so you should be getting his HbA_{1c} as low as practicable and if possible to 6.5% to reduce the risk of retinopathy. This lowering of HbA_{1c} will also contribute to his CV risk reduction.³

A recent study looking into the benefits of lowering HbA_{1c} to levels below 6.0% was stopped early because of excessive deaths in the lower HbA_{1c} group.⁹ Analysis as to why this occurred is still on-going, but it would seem prudent not to lower HbA_{1c} to lower than 6.5% for the present.

If one wants to reduce CV risk effectively and cheaply it is wise to treat hyperlipidaemia and hypertension aggressively.^{10,11} With regard to glycaemic agents, this patient is already on metformin as this is the only traditional oral antiglycaemic with evidence to support its use as a CV-risk reducing agent.² The launch of the thiazolidinediones (glitazones)—pioglitazone and rosiglitazone—gave hope that this might change, as these agents address many of the factors associated with the metabolic syndrome: reducing BP,¹² improving the lipid profile (pioglitazone in particular),^{13–15} and reducing microalbuminuria.¹⁶ Hopefully, the glitazones will reduce CV risk at the same time as treating high glucose levels.

NICE recommendations for glycaemic control

Lifestyle and patient education must not be ignored. A good dietary and exercise history should be taken. Any patient who drinks large volumes of fizzy drinks or fresh orange juice each day should be advised to stop this habit. Walking a small dog for 50 m does not count as exercise, unless it makes the person breathless. The patient being discussed should be enrolled into a local educational programme,⁶ such as Xpert^{®17} or DESMOND^{®18}

Each patient should have an individualised target for HbA_{1c} (a level of 7.8% is almost always too high).

Like the patient in question, most will end up taking metformin and a sulphonylurea, which will work for a time. However, control almost always worsens¹ and a new treatment strategy is required. According to NICE the treatment depends on the individual patient: if they are severely obese (BMI >35 kg/m²) exenatide may be considered; otherwise the choice boils down to insulin or glitazones, one of which should be added to the sulphonylurea/metformin combination already being taken. Glitazones are preferred if the metabolic syndrome is present,⁶ as in this case, but which glitazone?

Rosiglitazone and pioglitazone

This patient is already on metformin and a sulphonylurea. The next stage of therapy for poor glycaemic control would be the addition of another agent to these drugs. Rosiglitazone and pioglitazone are both effective glucose-lowering agents and have positive effects on the metabolic syndrome.^{13,19,20} The manufacturers have undertaken studies with hard endpoints to show whether these agents have effects on mortality and serious CV events. The first study to be published—PROactive—showed significant benefits with pioglitazone with respect to death, myocardial infarction, and stroke;²¹ the RECORD study on rosiglitazone will probably be published in 2010.

Much has been written on the conclusions of the PROactive study, particularly as the use of statins was relatively low (reflecting prescribing habits at the time of enrollment) and because those who took pioglitazone had higher rates of heart failure (the incidence of which was 1.6% higher with pioglitazone than with placebo).^{15,21} No excessive deaths due to heart failure were recorded. Rosiglitazone use is also associated with increased prevalence of heart failure²² and the pragmatic advice is to be aware of heart failure as a contraindication when either glitazone is used.

The debate about which glitazone to use took another twist in 2007, when a meta-analysis by Nissen and Wolski suggested a surprising increased incidence of ischaemic cardiac events in patients who had taken rosiglitazone.²³ A subsequent meta-analysis of pioglitazone studies suggested an opposite (beneficial) effect for pioglitazone on ischaemic heart disease.²⁴

These papers led the European Medicines Agency to issue a warning on the use of rosiglitazone in patients with ischaemic heart disease.²⁵ However, interim results from RECORD on the effects of rosiglitazone in people with ischaemic heart disease showed no significant effect on this condition.²⁶

Newer agents

As far as this patient is concerned, it should be noted that the discussion has revolved around agents that are commonly available, used often, and have been assessed by NICE. The use of the gliptins (sitagliptin and vildagliptin) is also being considered by NICE in an updated version of its guidance on type 2 diabetes.⁶ While these agents seem to be more weight-neutral, or indeed help weight loss, and are, therefore, attractive to the diabetes community, there is no guarantee that the use of these agents will be endorsed.

Conclusion

This patient has both poor glycaemic control and the metabolic syndrome. He is taking two established agents to treat the glycaemia, yet requires more therapy. The choice presently revolves around the addition of insulin or a glitazone. Heart failure (which this patient does not have) would be a contraindication for a glitazone; certain lifestyles or occupations would be relative contraindications for insulin (e.g. heavy goods vehicle driver). The presence of the metabolic syndrome in this patient is a factor in favour of using a glitazone.

There is little to choose between rosiglitazone and pioglitazone in this patient. However, there is presently more evidence in favour of pioglitazone and, moreover, it has a licence for use with insulin, which may need to be added at a later date. My general approach is to use pioglitazone in appropriate patients with the metabolic syndrome who are not reaching their glycaemic target, such as the patient discussed here, while leaving those patients on rosiglitazone if they are already doing well on it.

Summary

To summarise the evidence for the management of this patient, I would:

- enrol the patient in a patient education programme
- aim to treat multiple risk factors
- set individualised targets for HbA_{1c} and BP based on the NICE guidance
- choose between insulin and a glitazone to improve glycaemic control
- select a glitazone as metabolic syndrome is present (most likely pioglitazone, as there is more evidence for benefit with this agent).

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Conflict of interest statement

Dr Mark W Savage was previously an investigator for the PROactive study and was a member of the guideline development group for the NICE guideline on the management of type 2 diabetes. He has received honoraria for educational activities and advisory board attendances from Takeda UK Ltd, as well as other pharmaceutical companies.

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