Glycaemic control and cardiovascular safety in patients with type-2 diabetes

As new therapies become available for type-2 diabetes, healthcare professionals will not only have to make difficult clinical decisions but also cope with the demands from patients for these treatments.

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In 2010 the Commission for Human Medicines (CHM) recommended the withdrawal of the anti-diabetes drug rosiglitazone amidst concerns about its cardiovascular safety. The decision followed an extensive investigation into the studies involving rosiglitazone by the European Medicines Agency (EMA). Association between rosiglitazone and increased risk of cardiovascular disease was first reported in a meta-analysis by Nissen et al in June 2007. The paper reported a 43% increased risk of myocardial infarction (MI) in patients treated with rosiglitazone and a possible increased risk of death from cardiovascular disease. The debate that followed resulted in publication of a number of other meta-analysis and observational reports examining the cardiovascular safety of rosiglitazone and pioglitazone (another drug of the same class). Although the findings of these studies could not establish a definitive link between rosiglitazone and cardiovascular disease, a trend towards increased cardiovascular risk was noted with rosiglitazone treatment prompting the Food and Drug Administration (FDA) to issue a boxed warning restricting its use in patients with known or increased risk of heart disease.

The RECORD study

An interim analysis and subsequently the full results of the RECORD study (the only prospective randomised controlled trial designed to assess the cardiovascular safety of rosiglitazone) reported that the risk of hospitalisation or cardiovascular death with rosiglitazone was comparable to that seen with metformin or sulfonylurea. Treatment with rosiglitazone was, however, associated with increased risk of heart failure and a higher hazard ratio in those with known ischaemic heart disease. The findings of the RECORD study were limited due to fewer events for primary endpoint and imbalance between the treatment groups in the use of other cardiovascular disease modifying agents such as statins. Rosiglitazone was also used extensively in the ACCORD, VADT and BARI2 trials. Although no additional risks were attributed to rosiglitazone in these studies, questions about its cardiovascular safety still remained. Investigation by the EMA following further reports linking rosiglitazone with increased cardiovascular risk including one that compared rosiglitazone with pioglitazone resulted in recommendation of its withdrawal in September 2010.

Alternative to rosiglitazone

Thiazolidinediones (TZDs) have been used extensively in the treatment of type-2 diabetes over the past 10 years. The potent glucose lowering effect of TZDs and the low risk of hypoglycaemia as compared to sulfonylureas favoured TZDs as the preferred add on therapy to metformin. Following the withdrawal of rosiglitazone and the introduction of newer anti-diabetes agents, the choice of second line agents, has once again been left wide open. Attributes of an ideal anti-diabetes drug include its ability to lower blood glucose and not cause hypoglycaemia or weight gain. In addition it must be well tolerated with proven cardiovascular safety, convenient to administer and cost effective. Evidently, most of the existing drugs do not meet all these requirements. In the absence of direct head to head studies comparing the efficacy
of several of these agents, conclusions of about relative efficacy can only be derived from indirect comparisons. A recently published meta-analysis compared all approved non-insulin therapies and found that when added to metformin, the efficacy of most of these agents was comparable and differences existed only in non-glycaemic outcomes such as weight loss and hypoglycaemia.\textsuperscript{14}

Several options may be considered when choosing the appropriate alternative to rosiglitazone. Given their proven efficacy, long-standing experience and the cost effectiveness, sulfonylureas remain the preferred agents as add on therapy to metformin.\textsuperscript{15,16} These benefits must be balanced against the increased risk of hypoglycaemia and weight gain, frequently seen with sulfonylureas. Hypoglycaemia is two to three times more common in patients treated with sulfonylureas, but serious hypoglycaemia requiring hospitalisation is less common. The risk of hypoglycaemia, however, is greater among the elderly and frail and in these patients a choice of alternative agents would be more appropriate.

Where sulfonylureas are not preferred, a simpler alternative would be to switch to pioglitazone.\textsuperscript{15} Pioglitazone, the only drug in its class currently licensed for use has been shown to be highly effective when used as monotherapy as well as in combination with metformin and may be preferred over sulfonylurea in insulin-resistant patients. Pioglitazone treatment is also associated with low risk of hypoglycaemia and favourable changes in lipids.\textsuperscript{5,17} Although belonging to the same class as rosiglitazone, current evidence suggests that pioglitazone does not share its adverse cardiovascular profile.\textsuperscript{12,17,18} Pioglitazone treatment, however, is associated with fluid retention and increased risk of heart failure.\textsuperscript{18,19} Weight gain is also common with pioglitazone and in postmenopausal women there is additional risk of fractures. Therefore, while use of pioglitazone in individuals with no prior history of cardiovascular disease (and where weight gain is not a major concern) may be justifiable, its use in elderly individuals must be carefully evaluated against the increased risk of heart failure and fractures.

**Newer agents**

Recently, many new anti-diabetes drugs have been approved for use in patients with type-2 diabetes.\textsuperscript{20} These include the DPP4 inhibitors (sitagliptin, vildagliptin and saxagliptin) and GLP-1 (Glucagon Like Peptide-1) mimetics (exenatide and liraglutide). GLP-1 is an incretin hormone secreted by the L cells of intestine. GLP-1 is released in response to a meal and lowers blood sugar through stimulation of insulin secretion, glucagon suppression, increased satiety and delayed gastric emptying.\textsuperscript{21} Natural GLP-1 is rapidly cleared from circulation (half life 1.5—2 minutes) by the enzyme DPP4 making it unsuitable for therapeutic use.\textsuperscript{21} Efforts to exploit the actions of GLP-1 for treatment of diabetes have resulted in two major approaches — inhibition of the enzyme DPP4 and development of analogues of GLP-1 resistant to DPP4 enzyme. Three DPP4 inhibitors are currently available in the UK. Sitagliptin is licensed for use as monotherapy, add on to metformin, triple therapy and as add on to insulin. Vildagliptin and saxagliptin are licensed for combination therapy only. When used as monotherapy, these agents lower HbA1c on average by 0.7% and this benefit persists even when used in combination with metformin and sulfonylurea.\textsuperscript{20,22-25} When used in combination with metformin, studies comparing DPP4 inhibitors with sulfonylurea have shown similar efficacy but less weight gain and a lower incidence of hypoglycaemia. In addition, DPP4 inhibitors can be administered orally which makes them preferable to other injectable therapies.\textsuperscript{25} Currently two GLP-1 mimetics (exenatide and liraglutide) have been approved for use in patients with type-2 diabetes as third-line agents. Both exenatide and liraglutide are licensed for use in obese individuals (BMI>35 kg/m$^2$) and poorly controlled on combination treatment.\textsuperscript{15} In patients with BMI less than 35 kg/m$^2$, they are indicated if therapy with insulin will have significant occupational implications or where weight loss would benefit other obesity-related morbidities.\textsuperscript{15} In general these agents lower HbA1c by 1% and improve both fasting and post-prandial blood sugars.\textsuperscript{26} Both exenatide and liraglutide have been shown to be effective when used in combination with metformin, sulfonylureas and pioglitazone.\textsuperscript{27,28} Exenatide is administered twice daily while liraglutide is given once daily. In addition to their glucose-lowering effect, the GLP-1 agonists are associated with weight loss and this effect may be greater when compared with insulin.\textsuperscript{29} They are not licensed for use with insulin. GLP-1 agonists are associated with low risk of hypoglycaemia, but hypoglycaemia has been reported in combination
with sulfonylurea. Modest reductions in blood pressure have also been noted with these agents, although the mechanism of this is unclear. Despite the fact that they are injectable, the preference for these drugs has been reported to be greater than for insulin perhaps due to the ease of titration and the expectation of weight loss. Nausea and vomiting are reported in up to a third of patients treated with GLP-1 agonists and slightly less frequently with DPP4 inhibitors. Tolerance to these side effects, however, develops with continued use. Both DPP4 inhibitors and GLP-1 agonists must be used with caution in patients with renal impairment. Pancreatitis is a rare but serious adverse event reported with incretin therapy.

Achieving tight glycaemic control without causing weight gain and hypoglycaemia has been a challenge for a long time. Some of the newer therapies appear to fulfil these unmet needs and therefore are attractive therapies to consider in patients with diabetes. Ease of administration, weight neutrality and low risk of hypoglycaemia may make them more appealing for use in the elderly. It is important, however, to note that the long-term safety and cardiovascular effects of these agents is not yet known and the decision to prescribe these agents must be carefully weighed against these limitations.

### Glycaemic control and cardiovascular risk

The relationship between hyperglycaemia and cardiovascular disease is intriguing. While there appears to be a clear epidemiological link between hyperglycaemia and cardiovascular disease, intensive glycaemic control has failed to demonstrate reduction in cardiovascular risk. Results of the ACCORD trial suggest that intensive glycaemic control may in fact be associated with increased risk of cardiovascular disease and two other trials—ADVANCE and VADT trials—showed no benefits with intensive glycaemic control. Despite these uncertainties, glycaemic control remains central to the management of diabetes. A more holistic approach that aims to achieve tight control of other cardiovascular risk factors besides glycaemic control is therefore necessary. Such an approach is clearly required in elderly individuals who have higher risk of cardiovascular disease compared with younger individuals.

Management of diabetes in elderly individuals can present additional challenges. Absence of clear guidelines for the elderly and the fact that most of the clinical trial evidence is restricted to those aged less than 75 years add to the difficulties in making the right treatment decisions. In the absence of robust evidence, the choice of therapy must be made based on individual needs. Presence of other comorbidities, functional status and convenience of drug administration may all need to be considered whilst making the choice of treatment.

### Conclusion

As new therapies become available, healthcare professionals will not only have to make difficult clinical decisions but also cope with the demands from patients for these treatments. Managing these expectations within the available resources and at a time when major reforms to the healthcare system are in progress can be very daunting. As a part of the changes proposed in the NHS White Paper, it is envisaged that the existing structure of PCTs will be replaced by General Practice consortia. This new system is expected to give more autonomy to them and will allow them to commission services based on the needs of the population they serve. The extent to which these changes will affect the care of people with diabetes is difficult to predict. While the GPs will have greater freedom to make treatment choices, it is inevitable that the pressures to deliver a cost effective service may force many GPs to adopt a cautious approach towards new and expensive treatments. Whether the preference will be for the familiarity of the old or the promise of the new will largely depend on the evidence that supports the long-term effectiveness and safety of the newer treatments.

**References**


23. DeFronzo RA, Hissa MN, Garber AJ, Luiz GJ, Yuyan DR, Ravichandran S et al. The efficacy and safety of saxagliptin when added to metformin therapy
Type-2 diabetes


32. Black N. "Liberating the NHS"—another attempt to implement market forces in English health care. N