Glitazones: Evidence to inform daily practice

Michael Kirby, Anthony Barnett

Achieving and sustaining glycaemic control after diagnosis of type 2 diabetes is central to its management and a constant challenge owing to the progressive nature of the condition. When control declines, an appropriate stepwise care for managing glycaemia and cardiovascular risk is needed *(Figure 1)*. Guidelines providing evidence-based recommendations for the management of type 2 diabetes must constantly evolve with the advent of new clinical trial data. Inevitably, the process of reviewing such guidelines in the light of new evidence is slow, during which time there can be a widening of the gap between common clinical practice and formal guidance. The glitazones are a relatively new class of oral anti-diabetes agents. In this article, we focus on the place of the glitazones in the treatment pathway in view of recently reported large-scale clinical studies and product licence extensions.

Article points

1. Achieving and sustaining glycaemic control in type 2 diabetes is central to its successful management.
2. In this article, we focus on the place of the glitazones in the treatment pathway in view of recently reported large-scale clinical studies and product licence changes.

Key words

- Glitazones
- Guidelines
- Metformin
- Sulphonylureas
- Combination therapy

The glitazones are oral anti-diabetes agents that have been available for 7 years in the UK. In September 2002, NICE published guidelines on managing blood glucose levels in type 2 diabetes and looked at the role of glycaemic control in limiting or preventing the associated complications (NICE, 2002). Within this guidance, NICE recommended the glitazones to be prescribed in combination with either metformin or a sulphonylurea as an alternative to a metformin/sulphonylurea combination in people unable to tolerate, or contraindicated against taking, either metformin or a sulphonylurea. They were also recommended for people when HbA_{1c} remains unsatisfactory despite adequate trial of metformin with insulin secretagogues. In addition, the 2002 NICE guidelines stated that glitazones are contraindicated in combination therapy with insulin. A review of the 2002 NICE guidance is currently in progress and the revised guidelines are expected to be issued in March 2008. In August 2003, NICE published new guidance on the use of the glitazones for the treatment of type 2 diabetes (NICE, 2003). This guidance was published at a time when the UK licence for rosiglitazone and pioglitazone did not include triple combination therapy (with other oral anti-diabetes agents), monotherapy or use in combination with insulin. However, a few days after this guidance was issued, a change in licence for the glitazones indicating use as monotherapy in people (particularly overweight individuals) not able to tolerate metformin was granted. In 2004, in response to these licence extensions and additional published evidence, the Association of British Clinical Diabetologists (ABCD) published a position statement on the use of glitazones in the UK to provide clear and pragmatic guidance

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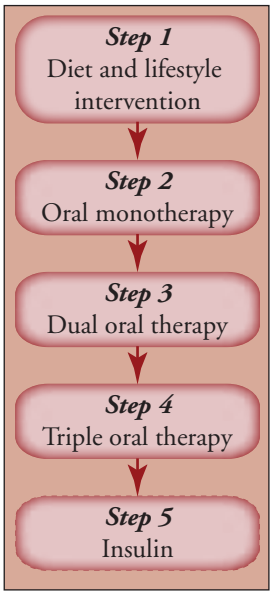

Figure 1. Stepwise treatment of type 2 diabetes.

to the multidisciplinary diabetes team (Higgs and Krentz, 2004). The authors expect that the revised NICE guidance on the management of type 2 diabetes, due in 2008, will take into account more recent extensions to the licence for the glitazones and will encompass new and evolving practices in the management of type 2 diabetes.

The Scottish Intercollegiate Guidelines Network (SIGN) developed national clinical guidance on the management of diabetes (types 1 and 2) in November 2001, the aim being to provide an evidence-based approach to influence current practise in order to reduce the burden of long-term complications. The 2001 SIGN guidance covers seven aspects of care: lifestyle, visual impairment, pregnancy, children and young people, renal disease, foot disease and cardiovascular disease. It does not, however, focus on the management of hyperglycaemia per se and no guidance is given on the place of the glitazones in the treatment pathway (SIGN, 2001). However, after a consultation in 2005, it was recommended that the SIGN guidance should be reviewed in light of new evidence.

In February 2007, SIGN published some national clinical guidance on risk estimation and the prevention of cardiovascular disease (SIGN, 2007). Within this report, the guidance states that insulin-sensitising drugs (such as metformin and glitazones) are known to be effective in centrally obese people with overt diabetes, and suggests that these agents may also be useful in people with metabolic syndrome at high cardiovascular risk.

The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines describe a consensus algorithm for the management of hyperglycaemia in type 2 diabetes, providing the most recent direction on best practice treatment in type 2 diabetes (Nathan et al, 2006). These guidelines put emphasis on a stepwise approach to the management of hyperglycaemia by rapidly adding in new agents and transitioning to new regimens when people fail to achieve adequate glycaemic control *(Figure 2)*.

We have used the ABCD position statement from 2004 on the place of the glitazones to provide a useful framework for reviewing the impact of more recent evidence on the role of the glitazones and their position within a diabetes treatment algorithm that is based on stepwise control of deteriorating glycaemia. *Table 1* shows the current indications for the glitazones.

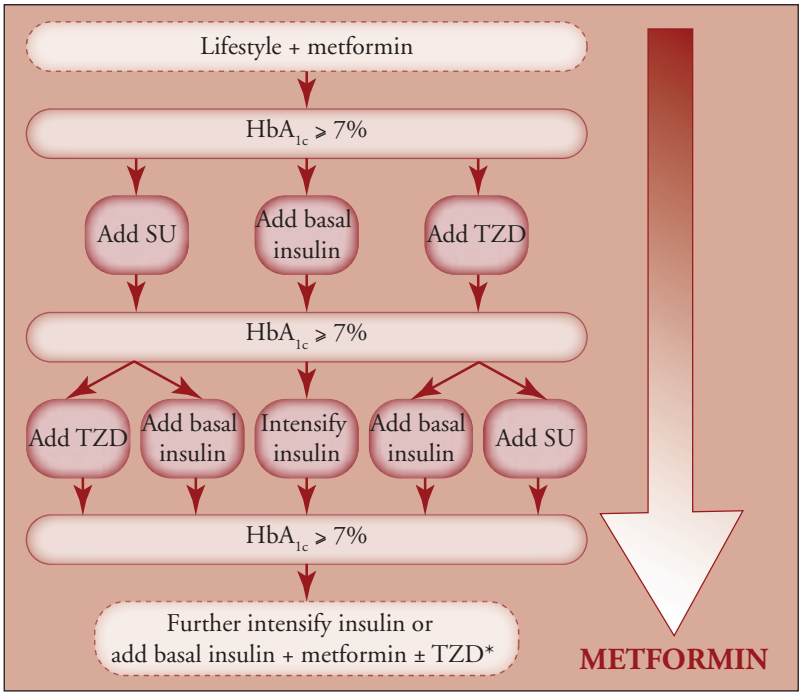

Figure 2. Simplified ADA/EASD consensus algorithm for type 2 diabetes (Nathan et al, 2006).
**Pioglitazone is only indicated for combination with insulin in people with insufficient glycaemic control on insulin for whom metformin is inappropriate owing to contraindications or intolerance. SU: Sulphonylurea; TZD: Thiazolidinedione.*

First-line monotherapy

Glitazones should be considered as monotherapy for people whose diabetes is inadequately controlled by diet and exercise, and for whom metformin is inappropriate owing to contraindications or intolerance. This is particularly the case for overweight individuals (Electronic Medicines Compendium [EMC], 2007a; EMC, 2007b). Higgs and Krentz (2004) add that they should be considered in place of metformin in renal impairment.

A Diabetes Outcome Progression Trial (ADOPT) showed that glitazone monotherapy could achieve more durable glycaemic control over a 5-year period than metformin or

Table 1. Glitazone licensed indications (EMC, 2007a; EMC, 2007b).

Glitazone	Monotherapy	Licenced indication
Pioglitazone	√	- in patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance
Rosiglitazone	√	- in patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance
	Dual oral therapy	**In combination with:**
Pioglitazone	√	- metformin, in patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin - a sulphonylurea, only in patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulphonylurea
Rosiglitazone	√	- metformin, in patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin - a sulphonylurea, only in patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite monotherapy with a sulphonylurea
	Triple oral therapy	**In combination with:**
Pioglitazone	√	- metformin and a sulphonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy
Rosiglitazone	√	- metformin and a sulphonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy
	In combination with insulin	
Pioglitazone	√	- pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance
Rosiglitazone	X	

Page points

1. Addition of a glitazone to metformin has been recommended as the preferred second-line agent in obese people with type 2 diabetes.
2. ADA/EASD guidelines highlight the synergy of a metformin/glitazone combination as both agents effectively increase sensitivity to insulin through complementary modes of action via different target organs.

sulphonylurea monotherapy (Kahn et al, 2006). In addition, the Diabetes REduction Assessment with ramipril and rosiglitazone Monotherapy (DREAM) study showed that glitazone therapy delayed the progression to diabetes and substantially increased the likelihood of regression to normoglycaemia over a 3-year treatment period in adults with impaired glucose tolerance or impaired fasting glucose (Gerstein et al, 2006). The durability of glucose lowering observed in these individuals supports the use of glitazone monotherapy where metformin is not tolerated or contraindicated; however, prescribers need to be aware of a potential increase in the risk of weight gain, oedema and heart failure with these agents.

There is insufficient evidence to support the substitution of metformin with a glitazone unless metformin is contraindicated or there is intolerance. Metformin remains the preferred first-line treatment in terms of cost, safety, efficacy, longstanding use and evidence for cardiological protection (UKPDS Group, 1998).

Dual therapy

Addition of a glitazone to metformin has been recommended as the preferred second-line agent in obese people with type 2 diabetes (Higgs and Krentz, 2004).

This approach has theoretical advantages since obese individuals are often insulin resistant and should benefit from the insulin-sensitising actions of the glitazones. The recent SIGN guidelines for managing cardiovascular risk also state that insulin-sensitising agents such as the glitazones and metformin are effective in people with central obesity (SIGN, 2007). Furthermore, the ADA/EASD guidelines highlight the synergy of a metformin/glitazone combination as both agents effectively increase sensitivity to insulin through complementary modes of action (Nathan et al, 2006).

Dual therapy is made simpler by the availability of fixed-dose twice-daily combination products combining the glitazone with metformin, indicated for use in people unable to achieve glycaemic control with maximally tolerated

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1. It is well accepted that triple oral therapy is a useful strategy for those who are uncontrolled on dual therapy or who would rather delay the need for insulin therapy owing to the perceived disadvantageous effects on lifestyle and injection aversion.
2. The incorporation of a glitazone into a triple therapy regimen enhances the effects of endogenous insulin.
3. People should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin.
4. Caution is needed to monitor for fluid retention and heart failure, particularly in people with renal disease and those receiving insulin.

doses of metformin alone. The use of fixed-dose combinations as a route to better concordance to multiple drug therapy has been endorsed; for example, in hypertension, by the British Hypertension Society (Brown et al, 2003). A recent study of a glitazone/metformin fixed-dose combination showed that after 12 months, the single-tablet combination product was associated with adherence in 83% of people compared with 67% taking the components as two separate tablets (Vanderpoel et al, 2004).

Triple therapy

Triple oral therapy may be considered in very obese individuals, as well as those unwilling to consider insulin therapy (Higgs and Krentz, 2004).

It is well accepted that triple oral therapy is a useful strategy for those who are uncontrolled on dual therapy or who would rather delay the need for insulin therapy owing to the perceived disadvantageous effects on lifestyle and injection aversion. The incorporation of a glitazone into a triple therapy regimen enhances the effects of endogenous insulin. This insulin-sensitising effect was demonstrated by the addition of pioglitazone to dual therapy with metformin and a sulphonylurea, and resulted in more people having either metformin or sulphonylurea dropped from their regimen (16%) compared with placebo-treated individuals (8%), and fewer (16%) than placebo (31%) having insulin added to their regimen (Charbonnel et al, 2006). In a separate study, 42% of individuals achieved HbA_{1c} <7% with rosiglitazone in combination with metformin and a sulphonylurea, compared with 14% taking add-on placebo (Dailey GE III et al, 2004).

At the time of preparation of the NICE guidance for the use of glitazones in type 2 diabetes, the UK licence did not include the use of glitazones in triple oral combination therapy (NICE, 2003). The Committee did acknowledge that the off-licence use of glitazones as part of triple therapy was practised widely in the UK at the time for people in whom switching to insulin therapy was unacceptable. However, the committee did not put forward a recommendation for the use of glitazones in triple therapy. Both pioglitazone and rosiglitazone are now licensed for use in triple oral therapy, reflecting both the evidence-base provided for the efficacy of glitazones in triple therapy and the evolution of medical practice (EMC, 2007b).

Use with insulin

Glitazones should not be a substitute for insulin in people with poor glycaemic control on maximum-tolerated doses of sulphonylurea and metformin. Used in combination with insulin, it is essential to screen for oedema, heart failure and significant left ventricular dysfunction (Higgs and Krentz, 2004).

Unlike the US, where glitazone–insulin co-prescription has been licensed for several years, it is only since early 2007 in Europe that the contraindication for use of pioglitazone with insulin has been removed (the fixed-dose combination of rosiglitazone with metformin has also had the contraindication for use in combination with insulin removed; this has not yet been approved for rosiglitazone alone). In addition, pioglitazone now has a specific licensed indication for use in combination with insulin for those individuals on insulin for whom metformin is inappropriate (EMC, 2007b). This will include individuals who experience intolerable gastrointestinal symptoms with metformin and those with deteriorating renal function for whom metformin is contraindicated. The appropriate precautions that have evolved since the ABCD guidance provided in 2004 should be considered: people should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin (EMC, 2007b).

In the PROspective pioglitAzone Clinical Trial in macroVascular Events (PROactive) study, pioglitazone was shown to reduce the insulin requirements of those who were already taking insulin at baseline (daily insulin dose decreased by 5U in the pioglitazone group compared with an increase of 8U in the placebo group; Scheen et al, 2006). In addition, insulin was discontinued in 9% of individuals in the pioglitazone group compared with 2% in the placebo group (Scheen et al, 2006). A 6-month study of pioglitazone 30mg added to insulin monotherapy showed that

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1. The use of the glitazones is contraindicated in people with heart failure or a history of heart failure.
2. In those people in whom a glitazone is used in combination with insulin, it is essential to screen for oedema, heart failure and significant left ventricular dysfunction during initiation of insulin treatment.
3. The product label for pioglitazone has recently been revised and now includes details of the PROactive study stating that 'the results suggest that there are no long-term cardiovascular concerns regarding use of pioglitazone'.
4. A meta-analysis of 42 trials has recently reported a significant increase in the risk of MI associated with rosiglitazone treatment; a finding that has subsequently sparked much debate and controversy.
5. Although these data do raise a signal of concern, caution should be taken not to over-interpret the findings of the meta-analysis, as the results were based on a very small number of events.

18% of people achieved HbA_{1c} <7.0% compared with 7% taking placebo (Mattoo et al, 2005).

Safety and tolerability

Since the publication of the 2003 NICE guidance on the use of glitazones in type 2 diabetes, both agents have had licence extensions and are now indicated for use in monotherapy and in triple oral therapy.

Cardiovascular risk:benefit ratio

Fluid retention

Caution is needed to monitor for fluid retention and heart failure, particularly in people with renal disease and those receiving insulin (Higgs and Krentz, 2004).

The glitazones can cause fluid retention that may exacerbate or precipitate signs or symptoms of congestive heart failure. In each of the three large-scale studies mentioned, oedema was reported significantly more than placebo. Fluid retention needs to be managed correctly and individuals should be observed for signs and symptoms of heart failure, weight gain or oedema, particularly those with reduced cardiac reserve. Glitazone therapy should be discontinued if any deterioration in cardiac status occurs (EMC, 2007a; EMC, 2007b).

Heart failure

The use of the glitazones is contraindicated in people with heart failure or a history of heart failure (New York Heart Association class I to IV) in Europe. An increased incidence of heart failure has been observed with glitazone treatment in several clinical trials (Kahn et al, 2006; Gerstein et al, 2006; Ryden et al, 2007).

Since insulin and glitazones are associated with fluid retention, concomitant administration may increase the risk of oedema. Therefore, in those people in whom a glitazone is used in combination with insulin, it is essential to screen for oedema, heart failure and significant left ventricular dysfunction during initiation of insulin treatment.

Cardiovascular disease

While the ABCD guidelines did not consider the effects of the glitazones on cardiovascular outcomes, there are data from the first prospective cardiovascular outcome study of the glitazones that provide important information. In the PROactive study, treatment with pioglitazone, in addition to optimised standard of care, significantly reduced the principal secondary composite end point of death, stroke or myocardial infarction (MI) by 16% (P=0.027). The primary composite end point (all-cause mortality, non-fatal MI [including silent MI], stroke, acute coronary syndrome, leg amputation, coronary revascularisation or revascularisation of the leg) was reduced by 10% but did not reach statistical significance (Dormandy et al, 2005).

The product label for pioglitazone has recently been revised and now includes details of the PROactive study stating that 'the results suggest that there are no long-term cardiovascular concerns regarding use of pioglitazone' (EMC, 2007b). Indeed, further pre-specified analyses from the PROactive study have demonstrated that in high-risk people with type 2 diabetes, pioglitazone was associated with decreases in the risk of recurrent MI by 28% (P=0.045; Erdmann et al, 2007), recurrent stroke by 47% (P=0.008; Wilcox et al, 2007) and major adverse cardiovascular events (cardiovascular mortality, MI and stroke) by 18% (P=0.02; Wilcox and Kupfer, 2006).

The favourable cardiovascular outcomes associated with pioglitazone treatment may relate to its beneficial effects on a number of risk factors for cardiovascular disease. In PROactive, pioglitazone treatment had a beneficial effect on the lipid profile producing increases in high-density lipoprotein cholesterol (HDL-c) of 0.2 mmol/l, decreases in triglycerides of 0.2 mmol/l and a reduction in the low-density lipoprotein cholesterol (LDL-c):HDL-c ratio from 2.6 to 2.3 (Dormandy et al, 2005). Systolic and diastolic blood pressure were also reduced in the PROactive study by a median of 3 mmHg and 2 mmHg, respectively (Dormandy et al, 2005).

The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) study (results expected 2009) is investigating the long-term impact of rosiglitazone on cardiovascular outcomes in people with type 2 diabetes (Home et al,

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1. It is advised that weight should be closely monitored in people taking glitazones.
2. Treatment with a glitazone is associated with weight gain of between 2 and 5 kg.
3. Further studies are required to establish whether or not 2-monthly monitoring of liver function is clinically justified during any glitazone therapy.
4. Analysis from ADOPT has revealed that rosiglitazone was associated with a higher risk for upper arm, hand or foot fractures in women taking rosiglitazone compared with metformin and glyburide.

2005). A meta-analysis of 42 trials has recently reported a significant increase in the risk of MI associated with rosiglitazone treatment; a finding that has subsequently sparked much debate and controversy (Nissen and Wolski, 2007; Psaty and Furberg, 2007). Although these data do raise a signal of concern, caution should be taken not to over-interpret the findings of the meta-analysis, as the results were based on a very small number of events (The Lancet Editorial, 2007; Krall, 2007). Both the Lancet and the European Medicines Agency (EMEA) have called for a responsible approach to these findings, suggesting we await the results of the RECORD study that will provide the definitive answer by looking specifically at cardiovascular outcomes with rosiglitazone treatment (The Lancet Editorial, 2007; European Medicines Agency Press Office, 2007).

An interim analysis of the RECORD study was inconclusive in determining whether or not rosiglitazone treatment is associated with an increased risk of MI owing to limited statistical power (Home et al, 2007). It would be unwise to throw the baby out with the bath water until we have further information with enough statistical power to clarify the situation.

The overall findings of RECORD when it reports in 2009 will determine whether or not the cardiovascular benefits of pioglitazone seen in the PROactive study are specific to that particular agent or a class effect of the glitazones, since neither ADOPT nor DREAM had cardiovascular end points.

Weight gain

It is advised that weight should be closely monitored in people taking glitazones (EMC, 2007a; EMC, 2007b). The findings of PROactive, DREAM and ADOPT consistently show, in line with previous experience, that treatment with a glitazone is associated with weight gain of between 2 and 5 kg. Such weight gain correlates with a redistribution of body fat from visceral to subcutaneous fat and, in ADOPT, was associated with a reduction in waist-to-hip ratio since hip circumference increased in the absence of waist expansion (Miyazaki et al, 2002; Kahn et al, 2006). This suggests that weight gain experienced with glitazone treatment should not add to the burden of cardiovascular risk in these people (Melanson et al, 2001), although further work in this area is required.

Liver function

Further studies are required to establish whether or not 2-monthly monitoring of liver function is clinically justified during any glitazone therapy (Higgs and Krentz, 2004).

After initial serious hepatic safety concerns leading to the withdrawal of the first-in-class agent troglitazone 10 years ago, and a requirement for strict hepatic function testing of pioglitazone and rosiglitazone, the last 2 years have seen a relaxation in the requirement for frequent liver enzyme testing. Now, only periodic monitoring of liver enzymes is done after initial pre-treatment testing (EMC, 2007a). Liver enzymes should be checked prior to the initiation of therapy in all individuals and monitored periodically thereafter based on clinical judgement (EMC, 2007b). Rigorous liver function analysis in clinical studies has shown that both pioglitazone and rosiglitazone improve some parameters of liver function (Gerstein et al, 2006; Heine et al, 2006; Kahn et al, 2006; Spanheimer et al, 2006). However, glitazones should not be initiated in people with increased baseline liver enzyme levels (alanine aminotransferase >2.5 × the upper limit of normal) or with any other evidence of liver disease (EMC, 2007a; EMC, 2007b).

Fractures

Analysis from ADOPT has revealed that rosiglitazone was associated with a higher risk for upper arm, hand or foot fractures in women taking rosiglitazone (9.3%) compared with metformin (5.1%) and glyburide (3.5%) over the 5-year period (Kahn et al, 2006). This equates to a fracture incidence of 2.74 fractures per 100 patient years in the rosiglitazone group compared with 1.54 for metformin and 1.29 for glyburide. The fractures reported were not thought to be related to osteoporosis and the mechanism remains unclear and is subject to further analysis. In response to these findings, some wording has recently been added to the rosiglitazone label in the 'special warnings and precautions for use' section of the

summary of product characteristics to highlight the increased incidence of bone fractures observed in females taking rosiglitazone as monotherapy (EMC, 2007a). The same addition to the product licence is expected for pioglitazone later this year.

Subsequent to the findings of the ADOPT study, both GlaxoSmithKline (rosiglitazone) and Takeda UK Ltd (pioglitazone) have reviewed their ongoing clinical trial data and previous clinical trial safety databases, reporting consistent findings with those initially highlighted in ADOPT with respect to an increased risk of fractures in women (MHRA, 2007a; MHRA, 2007b). The results of the interim analysis of the ongoing RECORD study with rosiglitazone were also reported as being consistent with the observations from ADOPT.

Moving forward

While metformin remains the first pharmacological treatment choice for people with type 2 diabetes, it is clear that clinical evidence combined with broadening of licensed indications are supporting a wider role for the glitazones, alongside the sulphonylureas, from early to later stages of the condition. Current recommendations, supported by new international guidelines, state that glitazones are indeed a suitable second-line treatment option for the management of type 2 diabetes and take their place as such alongside sulphonylureas in people failing on metformin monotherapy. Safety concerns remain regarding fluid retention and heart failure; however, there is now much clearer guidance on how to manage these risks and which groups are not suitable for glitazone treatment. Any potential differences between the glitazones in terms of effects on cardiovascular risk factors and early disease progression will be clarified by the outcome of forthcoming trials expected to report in the next 3 years; for example, ACTos now for the prevention of diabetes (ACTnow; Texas Diabetes Institute, 2005) and RECORD (Home et al, 2005).

Summary and conclusion

Current NICE guidelines for the management of type 2 diabetes are now 5 years out of date. Within this time period, the evidence base supporting the use of glitazones has expanded with corresponding licence extensions leading to these agents becoming established within the treatment pathway for type 2 diabetes. These changes, however, are not currently reflected in any formal guidance in the UK. While guideline revision is a lengthy process, clinical practice and strategies for managing type 2 diabetes continue to evolve. The glitazones offer the potential for additional and durable glycaemic control at whatever stage they are at in their journey with diabetes.

We await the revised NICE guidelines, due in March 2008, and expect them to reflect the modern management of type 2 diabetes and to endorse the updated place of the glitazones. ■

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2. Safety concerns remain regarding fluid retention and heart failure; however, there is now much clearer guidance on how to manage these risks and which groups are not suitable for glitazone treatment.
3. We await the revised NICE guidelines, due in February 2008, and expect them to reflect the modern management of type 2 diabetes and to endorse the updated place of the glitazones.

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