Need for intensive, early glycaemic control in patients with type 2 diabetes

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Introduction

The management of type 2 diabetes remains a major clinical challenge. This progressive, debilitating condition is associated with a two- to three-fold increase in the incidence of cardiovascular disease[1] and a substantial reduction in life expectancy.[2,3] Furthermore, the number of individuals with type 2 diabetes continues to increase, from some 135 million worldwide in 1995 to 160 million in 2000. By 2015, it is predicted that there will be 300 million sufferers.[4]

The number of individuals diagnosed with type 2 diabetes is increasing for many reasons. Not only is the prevalence of the condition rising due to Westernisation and lifestyle changes, but intensive screening campaigns and the introduction of new diagnostic criteria with lower threshold values have also added to the number of patients identified. For example, whereas patients were formerly classified as having diabetes only when their fasting plasma glucose (FPG) exceeded 7.8 mmol/L, the World Health Organisation has revised the figure downwards to the new value of 7.0 mmol/L.

In response to such updated diagnostic criteria and outcome data from landmark intervention studies such as the United Kingdom Prospective Diabetes Study (UKPDS), guidelines in Europe and the US have been revised to propose new, lower glycaemic targets. In the US, for example, a target HbA_{1c} value of 7.0% has been proposed by the American Diabetes Association. In Europe, guidelines proposed by the European Diabetes Policy Group are even more challenging, with limits for good control stated as FPG ≤ 6 mmol/L and HbA_{1c} ≤ 6.5%.[5]

Healthcare providers are also becoming increasingly aware of both the clinical and financial benefits of prompt diagnosis and therapy as a means of minimising complications. Indeed, epidemiological analysis of the UKPDS study[6] showed that each 1% increase in HbA_{1c} elevated the risk of micro- and macrovascular complications (table 1). Key landmark studies have shown that tight control of blood glucose, combined with early diagnosis, are associated with significant delays in, or can even prevent the development of complications such as retinopathy, neuropathy, myocardial infarction and stroke.[7,8] Physicians, therefore, are being encouraged to identify patients at an earlier stage in the disease and to implement early treatment. This development is driving the need for effective and safe treatment modalities, particularly for glycaemic control after dietary failure.

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Table 1. Increased risk of complications associated with a 1% rise in HbA_{1c} level

Event	Increase in risk of event (%)
Diabetes-related death	21
Myocardial infarction	14
Peripheral vascular disease	43
Microvascular disease	37
Cataract extraction	19

Approaches to treatment

Two general approaches may be used to manage type 2 diabetes: (i) a conservative, stepwise, 'failure orientated' strategy, and (ii) an intensive, 'goal orientated' strategy.

(i) Conservative strategy

It has been traditional to use a stepwise approach when treating type 2 diabetes. This strategy aims primarily to control acute symptoms (figure 1).

Conventional therapy often comprises dietary measures alone but this is sufficient to control glycaemia beyond the first year of therapy after diagnosis in only a small minority of patients. In those with unsatisfactory blood glucose control, oral monotherapy, comprising metformin, sulphonylurea or sometimes acarbose, is usually recommended. If oral monotherapy proves inadequate, then combination therapy with these agents is started. If this also proves insufficient, conversion to insulin is the next step, either alone or in combination with an oral agent such as metformin to allow a reduction in the insulin dosage and to minimise weight gain. The recent introduction of the thiazolidinediones, rosiglitazone and pioglitazone, also offers new options for both monotherapy and combination.

Figure 1. A conservative approach to the management of type 2 diabetes, where regimens are changed only when symptoms become apparent

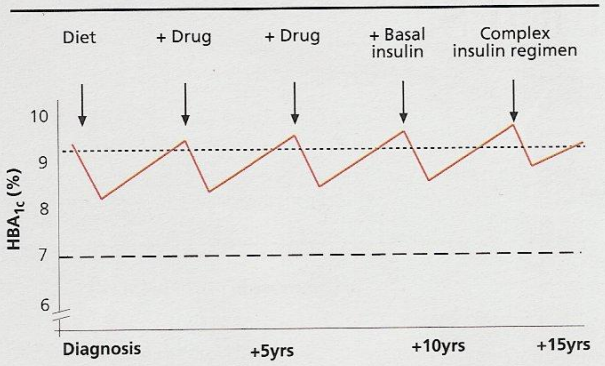
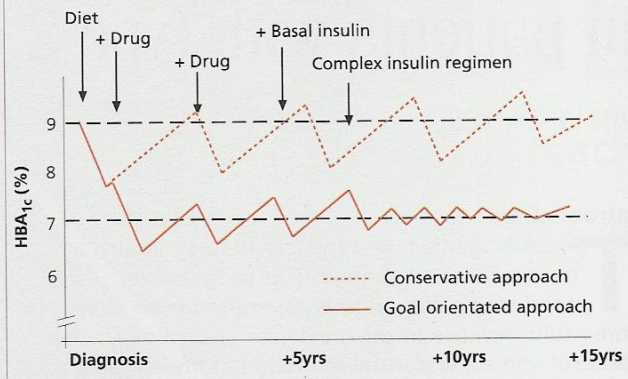


Figure 2. A treatment regimen based on reducing HbA_{1c} levels to <7%



While this conventional strategy may be successful in some cases, it has been increasingly recognised that in the majority it does not lead to sustained glycaemic control.[9] For example, in the UKPDS, diet proved effective in less than 45% of patients at six years[10] and less than 20% of patients by 12 years.[7] Many doctors intensify treatment only when symptoms of poor glycaemic control become apparent, rather than when glycaemic targets fall outside those presented in treatment guidelines.

(ii) Intensive strategy

This approach avoids the considerable risk of early treatment failure inherent to the conservative approach by adopting an intensive, aggressive therapeutic strategy immediately upon diagnosis.[11-13] The aim is to reduce FPG and HbA_{1c} quickly to predefined target levels and thereby minimise the risk of both acute and long-term complications (figure 2).

In adopting an intensive strategy, the likelihood of some monotherapies providing highly effective glycaemic control may be limited by the fact that, in most individuals, type 2 diabetes is the result of a double deficit – impaired insulin secretion due to progressive failure of pancreatic β-cells and insulin resistance. Indeed, at diagnosis, some 90% of patients are thought to be both insulin deficient and insulin resistant. In clinical practice, this manifests as fasting hyperglycaemia and glucose intolerance after meals (post-prandial hyperglycaemia). Monotherapies can, by their very nature, *specifically target* only one of these defects, although a secondary influence over more than one metabolic defect is recognised in accord with the glucose toxicity hypothesis. For example, agents that decrease insulin resistance can also improve insulin secretion indirectly by reducing plasma glucose levels and hence the toxicity of high glucose concentrations to pancreatic β-cells.

In following an intensive strategy from diagnosis, therefore, combinations of agents with complementary modes of action targeting the double deficit underlying type 2 diabetes are most likely to support tight, long-term glycaemic control. Furthermore, introducing a combination of agents at an earlier stage in the treatment regimen should be considered. A key consequence of such an intensive management strategy, of course, is that patients receive long-term polypharmacy. Any combination regimen must therefore not only be effective, but must also be well tolerated and easy for patients to manage, so as to promote good long-term compliance with treatment.

Table 2. Dosing schedule and duration of action of oral monotherapies

Drug	Dose (mg/day)	Dosage schedule (doses/day)	Duration of action (hours)
Biguanide			
– metformin	500–3000	2–3	8–12
Sulphonylurea			
– glibenclamide	2.5–20	1–2	12–24
– gliclazide	40–320	1–2	12–24
– glimepiride	1–6	1	16–24
– glipizide	2.5–30	1–2	12–24
Thiazolidinedione			
– rosiglitazone	2–8	1–2	12–24
– pioglitazone	1 5–45	1	16–24
α-glucosidase inhibitor			
– acarbose	50–300	3	4*
Meglitinide			
– repaglinide	0.5–16	3	3–4

*post-prandial

Current monotherapies

Five classes of oral antidiabetic agent are currently available (table 2):

(i) *Sulphonylureas* are the longest established oral monotherapy for type 2 diabetes, having been used in clinical practice since the early 1950s. Most physicians currently prescribe sulphonylureas as the oral monotherapy of choice to patients with type

Table 3. Key characteristics of oral antidiabetic agents

	Sulphonylureas	Biguanides	Thiazolidinediones	α-glucosidase inhibitors	Meglitinides
Mechanism of action	↑ Insulin secretion	↑ Peripheral glucose uptake ↓↓ Hepatic glucose production	↑↑ Peripheral glucose uptake ↓ Hepatic glucose production	↓ Intestinal glucose absorption	↑ Insulin secretion
Site of action	Pancreas	Liver and muscle	Liver, fat /muscle	Intestine	Pancreas
Decrease in HbA_{1c}	1.5–2.0%	1.5–2.0%	1.0–1.2%	0.7–1.0%	1.5–2.0%
Plasma insulin level	↑	↓	↓	↔	transient ↑
Main adverse events	Hypoglycaemia	GI upset	Oedema, anaemia	Flatulence, diarrhoea	Hypoglycaemia
Effect on body weight	↑	↓↔	↑	↔	↑

HbA_{1c}: glycated haemoglobin

2 diabetes. These agents are used in approximately 70% of European patients receiving oral treatment. This class of drugs helps to control blood glucose levels by stimulating insulin secretion from pancreatic β-cells. Sulphonylureas are generally well tolerated, hypoglycaemia being the most common adverse event. These agents can also increase body weight if used at high doses for prolonged periods and might therefore be less suitable for patients who are already overweight.

(ii) *Metformin*, a member of the biguanide class, increases the sensitivity of the liver and peripheral tissues, skeletal muscle and adipose tissue to insulin, thereby improving glycaemic control.[14] This agent can therefore be used to complement the pro-secretory action of sulphonylureas. Like sulphonylureas, metformin is well established, having been used worldwide for more than four decades.[15] Although metformin is generally well tolerated in clinical practice, gastrointestinal side effects can limit the use of higher doses in some patients. Being an antihyperglycaemic agent that counters insulin resistance, metformin effectively reduces both fasting plasma glucose and HbA_{1c}, and rarely causes hypoglycaemia.[8,16]

Metformin also offers additional benefits which may improve cardiovascular outcome. These include prevention of body weight gain, an improvement in the plasma lipid profile with a reduction in triglyceride concentrations and sometimes a reduction in LDL-cholesterol (LDL-C) in hyperlipidaemic patients. In addition, metformin has been shown to decrease PAI-1 and increase fibrinolysis, which may result in improved vascular function.[17]

(iii) *Alpha-glucosidase inhibitors* such as acarbose delay the absorption of complex carbohydrates from the gastrointestinal tract.[18] They are therefore of value in controlling post-prandial hyperglycaemia. Acarbose as monotherapy is less potent in reducing blood glucose than sulphonylureas or metformin.[13] Its side effects are dose limiting, mainly flatulence and diarrhoea, and the discontinuation rate for all events has been reported to be as high as 61% after three years of treatment.[19]

(iv) *Thiazolidinediones* improve glycaemic control by decreasing the insulin resistance of peripheral tissues, particularly that of adipose tissue, and by decreasing hepatic glucose production. These agents also reduce levels of free fatty acids.[20-22]

Thiazolidinediones are believed to bind to peroxysome proliferator-activated receptors (PPARs) on the nuclear membrane of cells, leading to the stimulation of insulin-sensitive proteins involved in glucose metabolism. Effective control of plasma glucose is thereby achieved.[23-25] The first agent in this class, troglitazone, was withdrawn from clinical use in March 2000, following reports of severe hepatotoxicity. Other agents in this class such as rosiglitazone and pioglitazone appear, so far, to be free of hepatotoxicity. These agents are well tolerated and do not cause hypoglycaemia. They can cause weight gain of 3–4 kg in the first year of use, oedema is seen in 3–4% of subjects, and they are contraindicated in patients with cardiac failure. The longer term effects of thiazolidinediones on plasma lipids have shown inconsistent results and further clinical studies are awaited.

(v) *Meglitinides* such as repaglinide are a relatively new oral treatment option, increasing insulin secretion by binding to the sulphonylurea receptor site.[26] Their rapid on–off action means that they have a short duration of action, limiting hypoglycaemic episodes between meals and at night. Repaglinide monotherapy is associated with decreased post-prandial hyperglycaemia and reductions in HbA_{1c} comparable with sulphonylureas.[23] Like thiazolidinediones and sulphonylureas, repaglinide therapy can be associated with weight gain. Another agent in this class, nateglinide, is presently undergoing clinical trials both as monotherapy and in combination with metformin.[27-29]

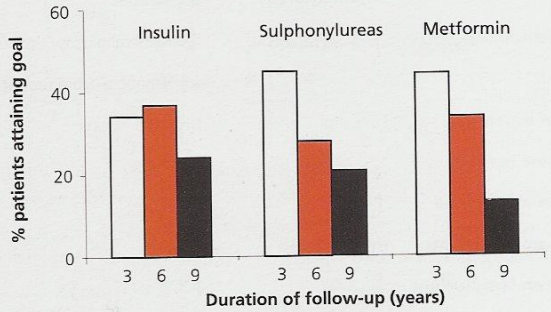
In additional to oral monotherapies, a remaining option is the use of insulin in controlling blood glucose levels effectively.[7,30] The need to self-inject, the potential for hypoglycaemic episodes and the significant weight gain all tend to limit long-term compliance and this, combined with the need for frequent blood glucose monitoring, can compromise long-term efficacy. A large-scale

Table 4. The UKPDS study showed that intensive glycaemic control to reduce HbA_{1c} from 7.9% to 7%, decreased clinical complications

	Change in risk (%)*	p-value
Any diabetes-related endpoint	–12	0.029
Myocardial infarction	–16	0.052
Microvascular endpoints	–25	<0.01
Retinal photocoagulation	–29	0.003
Cataract extraction	–24	0.046
Microalbuminuria at 12 years	–33	<0.001

*versus conventional diet-based treatment policy

Figure 3. Proportion of patients on monotherapy with HbA_{1c} <7.0%[33]



study of insulin therapy in general practice has suggested that insulin is no more effective than sulphonylureas.[31]

The key characteristics of each class of oral antidiabetic agent are shown in table 3.

Efficacy of intensive monotherapy

The clinical value of intensive control of glycaemia using oral monotherapy has been demonstrated by the UKPDS.[7] When used intensively to reduce HbA_{1c} from 7.9%–7%, treatment with glibenclamide or insulin, significantly decreased morbidity in type 2 diabetes (table 4).

In addition, in a group of overweight patients with type 2 diabetes, metformin reduced morbidity and mortality more effectively than other intensive therapies.[8] Of particular note was the 32% reduction in fatal and non-fatal microvascular and macrovascular complications in the metformin treated group compared to other intensive treatments (p=0.0034).

Metformin was shown to improve survival as a primary therapy, reduced the risk of diabetes related deaths by 42% (p=0.017) and reduced all cause mortality by 36% (p=0.011). In a separate substudy, sulphonylurea and metformin combination therapy, after a median of 6.6 years, had a similar morbidity compared with sulphonylurea therapy alone, but there was a higher risk of diabetes related deaths in the combination therapy group (26 deaths) compared with the group assigned sulphonylurea alone (14 deaths).

A further analysis of the UKPDS cohort of patients showed that the expected number of deaths on sulphonylureas alone was 35 deaths. The disparity between the groups was concluded to be due to 'fewer than expected deaths in the sulphonylurea alone group rather than over-representation in the sulphonylurea-metformin combined group'.[32]

Limitations of long-term monotherapy

The UKPDS results indicated that, as type 2 diabetes progresses, it becomes less amenable to monotherapy and, as a result, glycaemic levels begin to fall outside those advocated in treatment guidelines. After three years of monotherapy, for example, less than 50% of patients in UKPDS failed to achieve HbA_{1c} <7% (figure 3).[33]

Combination therapy: targeting the double deficit in type 2 diabetes

Although monotherapies can, at least in theory, improve both metabolic defects underlying most cases of type 2 diabetes, monotherapies of all types gradually fail to correct hyperglycaemia as diabetes progresses. Such progressive treatment failures might be minimised by combining two separate agents, each highly effective in correcting one of the two defects.

Sulphonylurea-based combinations

As more than two-thirds of patients in Europe receiving oral monotherapy receive sulphonylureas (which primarily increase insulin secretion) as their primary oral monotherapy, this drug class in particular has been combined with a number of other types of antidiabetic agent. Bearing in mind the mechanism of sulphonylurea action, the most effective combinations of this class with other drugs might logically be expected to be those involving agents that primarily increase insulin sensitivity (eg. metformin or thiazolidinediones).

(i) *Sulphonylurea plus metformin*

There are a wide range of possible combinations of sulphonylureas (table 2) and metformin. Nevertheless, only glibenclamide and metformin are evidence-based, with several published clinical studies. These have shown that this combination provides enhanced glycaemic control in type 2 diabetes, compared with that offered by either monotherapy. The combination decreased FPG by the order of 3 mmol/L and decreased HbA_{1c} by up to 2.0%.[8, 34-40]

Importantly, sulphonylurea-metformin combinations also compare favourably with insulin. In one study, for example, 24 patients poorly controlled using sulphonylurea monotherapy were randomised to receive six months of twice-daily insulin therapy or a combination of glibenclamide plus metformin. Both these regimens were associated with a 30% improvement in

mean daily blood glucose ($p < 0.001$).[41] Insulin was, however, associated with a 6% weight gain, whereas the oral combination produced no change in mean body weight.

(ii) *Sulphonylurea plus thiazolidinedione*

There has been, to date, limited investigation of the potential benefits of combining sulphonylureas with thiazolidinediones. In one study, in which 574 patients were randomised to receive 26 weeks of treatment using rosiglitazone or placebo, in addition to existing sulphonylurea therapy, the addition of rosiglitazone, 2 or 4 mg daily, significantly decreased HbA_{1c} by 0.6%–1.0% ($p < 0.0001$), and FPG by 1.4–2.4 mmol/L ($p < 0.0001$) compared with sulphonylurea plus placebo.[42] In addition, HDL-cholesterol (HDL-C) and LDL-C increased and free fatty acids decreased, compared with levels in patients receiving the sulphonylurea-placebo combination. Combining a sulphonylurea with another thiazolidinedione, pioglitazone, also decreased FPG (by 2.1–3.2 mmol/L) and HbA_{1c} (by 0.9–1.3%) depending on the choice of daily dosage employed (15–30 mg).[43] In contrast to rosiglitazone, an increase in HDL-C was reported with no change in LDL-C.[44]

(iii) *Sulphonylurea plus α-glucosidase inhibitor*

Several double-blind, placebo-controlled, multicentre studies have shown that adding acarbose to sulphonylurea therapy can lower post-prandial glucose and HbA_{1c}. In one study, 290 patients with FPG ≥ 7.8 mmol/L received acarbose, tolbutamide, a combination of both active agents, or placebo, daily for 24 weeks, followed by six weeks of follow-up.[45] While all active treatments were significantly more effective than placebo in decreasing post-prandial hyperglycaemia and HbA_{1c}, combination therapy was most effective, reducing post-prandial glucose by 4.7 mmol/L, compared with reductions of 3.9 mmol/L for tolbutamide, and 3.1 mmol/L for acarbose. Similar findings have been reported by others.[46-7]

Metformin-based combinations

The UKPDS study confirmed the glycaemic benefits of metformin monotherapy and several other studies of combinations of metformin with other classes of antidiabetic agent have also shown glycaemic advantages.

(iv) *Metformin plus thiazolidinedione*

In a multicentre study of 348 patients, glycaemic control improved significantly in patients receiving metformin plus rosiglitazone, 4 or 8 mg/day, for 26 weeks.[48] Mean levels of HbA_{1c} decreased by 1.0 and 1.2% and mean FPG decreased by 2.2 and 2.9 mmol/L in patients receiving metformin plus rosiglitazone, 4 and 8 mg, respectively, compared with those receiving metformin plus placebo ($p < 0.001$ for all). Mean HDL-C and LDL-C levels were significantly increased (by 0.08–0.10 mmol/L, $p = 0.0002$, and 0.36–0.40 mmol/L, $p < 0.0001$, respectively) in patients receiving metformin plus rosiglitazone, compared with those receiving metformin plus placebo. Free fatty acid levels were also decreased significantly in patients receiving the metformin plus rosiglitazone combination (by 2.62–4.22, $p < 0.001$), compared with those receiving metformin plus placebo, with no significant treatment difference in triglycerides. The proportion of patients with at least one adverse event was similar in all treatment groups, the most common events being URT infection, diarrhoea and headache. Hypoglycaemia was rare in all groups (<5%). Mean body weight decreased by 1.2 kg in patients receiving metformin plus placebo, but increased by 0.7–1.9 kg in those receiving metformin plus rosiglitazone ($p = 0.0001$). In a study of patients inadequately controlled on metformin, the addition of 30 mg pioglitazone once daily for 16 weeks improved FPG and HbA_{1c} by 2.1 mmol/L and 0.8%, respectively.[49] Combined therapy gave rise to a 21% reduction in triglycerides and 8% rise in HDL-C with no significant change in LDL-C.[50]

(v) *Metformin plus meglitinides*

In another multicentre study, 83 patients in whom glycaemic control with metformin monotherapy was poor, were randomised to continue to receive metformin alone, repaglinide monotherapy, or combined metformin plus repaglinide.[51] While no significant differences from baseline in HbA_{1c} or FPG occurred in patients receiving either monotherapy, HbA_{1c} decreased by 1.4% ($p < 0.002$) and FPG by 2.2 mmol/L ($p < 0.001$) in patients receiving the combination. Body weight remained stable in the metformin group but increased by 2.4 and 3.0 kg, respectively, in the repaglinide and combination therapy groups ($p < 0.05$). The potential benefits of combined therapy with nateglinide have been assessed.[27] The coadministration of 120 mg nateglinide, to patients maintained on metformin, led to significant reductions in mealtime glucose, particularly after lunch and the evening meal.

Discussion

The progressive nature of type 2 diabetes means that the most effective treatment should be introduced as early as possible after diagnosis, to provide metabolic stability and to reduce the risk of complications.[52] The stepwise, conservative approach employed by many physicians could conceivably result, however, in the continued use of suboptimal monotherapies in some patients and a delay in the use of possibly more effective polypharmacy.

Although monotherapy provides effective glycaemic control for a considerable time in the majority of patients, glycaemic control becomes progressively more problematic as the condition advances. This leads to a gradual increase in FPG and HbA_{1c}, and the potential development of associated complications.

In assessing the best treatment options, it is useful to remember that the dual defect of insulin resistance and insulin deficiency underlies most cases of type 2 diabetes. Monotherapies can correct both defects to some extent through primary and secondary actions, but combinations of drugs with one component targeting each defect might logically be expected to offer substantial benefit on glycaemic control. Two agents that target insulin resistance might be an alternative approach to diabetes management but in the absence of long-term clinical outcomes data this remains to be proved.

Key messages

- Hyperglycaemia is a significant risk factor for diabetes related complications
- Clinical gain can be expected from measures which intensify glycaemic control to near normal levels
- Meeting today's targets for glycaemic control will demand early intervention with combinations of therapies
- The evidence base supports the use of combined therapies which jointly target insulin resistance and impaired insulin secretion

Indeed, the findings from studies presented in this article have confirmed that many drug combinations are superior to their component monotherapies in providing chronic control of FPG or post-prandial glucose and HbA_{1c}. Combinations of metformin plus a sulphonylurea or a thiazolidinedione provide particularly good control of blood glucose. In particular, a combination of a sulphonylurea to enhance insulin secretion and metformin to improve the action of insulin has been shown to be effective. In addition, it is reassuring that both agents are foundation therapies, and that the effects of their long-term use, in terms of both efficacy and adverse events, are well known.

A direct link between such tight glycaemic control and the delay or prevention of diabetic complications remains a matter for conjecture. However, epidemiological analysis of UKPDS 35 demonstrated that each 1% increase in HbA_{1c} levels elevates the risk of micro- and macrovascular complications.[6]

It is now recognised that the most effective strategies for managing diabetes involve reducing not only blood glucose, but also all other risk factors for complications. A holistic approach should therefore be adopted, targeting lifestyle, hypertension and abnormal lipid profiles, as well as hyperglycaemia. Some studies have suggested that some combination therapies might improve plasma lipid profiles by increasing HDL-C, while lowering LDL-C and triglycerides. This potential additional protective mechanism would, if confirmed by further investigation, tend to contribute to the antiatherogenic effect of tightly controlled blood glucose *per se*.

In selecting an antidiabetic treatment regimen, convenience and the potential for adverse events such as hypoglycaemia and weight gain must be carefully considered, in addition to the associated degree of glycaemic control. The hypoglycaemic risk associated with sulphonylureas and insulin, and the weight gain associated with these agents, as well as with meglitinides and thiazolidinediones, may also render these particular agents unsuitable components of combination therapy in some patients. The treatment regimen must offer the patient the best quality of life whilst on the therapy, and the greatest chance of avoiding complications in the long-term.

Conclusion

The evidence base from controlled intervention studies suggests that complications in type 2 diabetes might be minimised by early implementation of tight glycaemic control. Because combination therapies targeting both insulin resistance and impaired insulin secretion appear to offer tighter control than monotherapies, physicians may wish to consider the early use of such combinations, rather than monotherapies, as main-line therapy in patients recently diagnosed as having type 2 diabetes. In making therapeutic decisions, both the efficacy and tolerability of the agents selected for combination must be considered to optimise the long-term prevention of diabetic complications.

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