Overcoming the barriers to effective glycaemic control for type 2 diabetes

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Introduction

The rising prevalence of type 2 diabetes will impose an increasing burden of diabetic complications on healthcare systems worldwide. The results of the UK Prospective Diabetes Study (UKPDS), and other studies, confirm the potential of effective glycaemic control to improve and extend the lives of people with type 2 diabetes. However, current management algorithms do not achieve sufficient glycaemic control in most patients to realise these improved clinical outcomes. We need a greater readiness to employ intensification of antidiabetic therapy earlier and in a manner that supports good compliance if we aim to maintain effective, long-term control of type 2 diabetes.

Audit of current diabetes management

Current management guidelines for type 2 diabetes in Europe and the USA set out challenging targets for glycaemic control.[1-3] However, most type 2 diabetic patients managed in the community are not meeting these goals, and a survey of 6,544 patients in the UK (figure 1) suggests that during the 1990s only one in seven patients achieved $HbA_{1C} \leq 7.0\%$.[4] Further evidence from Germany shows that in 1998 only 26% of patients achieved $HbA_{1C} < 6.5\%$.[5] Data from the Third National Health and Nutrition Examination Survey (NHANES III) in the USA complement the European experience.[6] The majority of patients with diabetes severe enough to receive pharmacological treatment had HbA_{1C} above the US goal level of $\leq 7\%$, and a substantial minority (20–30%) had $HbA_{1C} > 9\%$ (figure 2).

We will face even greater challenges from type 2 diabetes in the future. The increasing obesity of the US population has driven a marked rise in the prevalence of type 2 diabetes. It is well known that obesity, particularly visceral adiposity, is associated with the development of insulin resistance and glucose intolerance.[7,8] Between 1990 and 1998, the average weight of men and women in the USA increased by 3.4 kg and 3.9 kg, respectively.[9] During the same period, the prevalence of diabetes in the USA increased from 4.9% to 6.5%. The number of states with a prevalence of type 2 diabetes below 4% declined from seventeen to four, and the number of states with more than 6% of citizens with type 2 diabetes increased from two to twenty-five (figure 3).[9]

The global prevalence of type 2 diabetes is increasing and it is estimated that the number of people with diabetes will rise

Figure 1. Patients achieving pre-defined treatment goals in a metropolitan area of the UK[4]

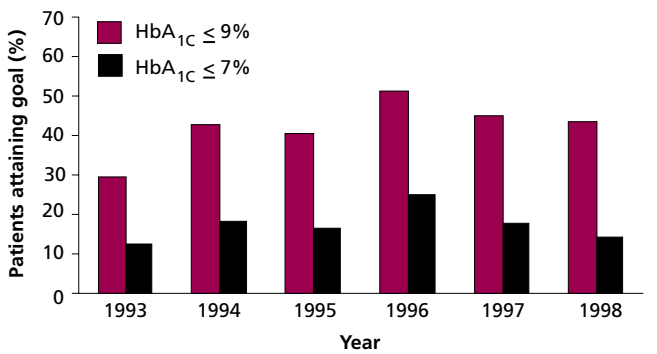

Figure 2. Mean HbA_{1C} in cohorts of patients on different antidiabetic therapies in the USA (1988–1994): data from NHANES III[6]

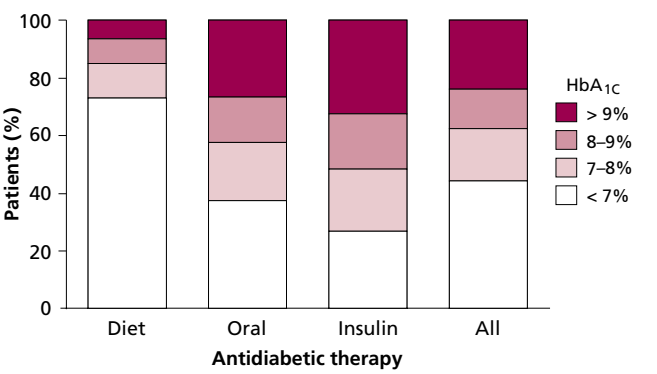

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Figure 3. Obesity and type 2 diabetes in the USA: **a**) mean body weight in American men and women; **b**) changing prevalences of type 2 diabetes[9]

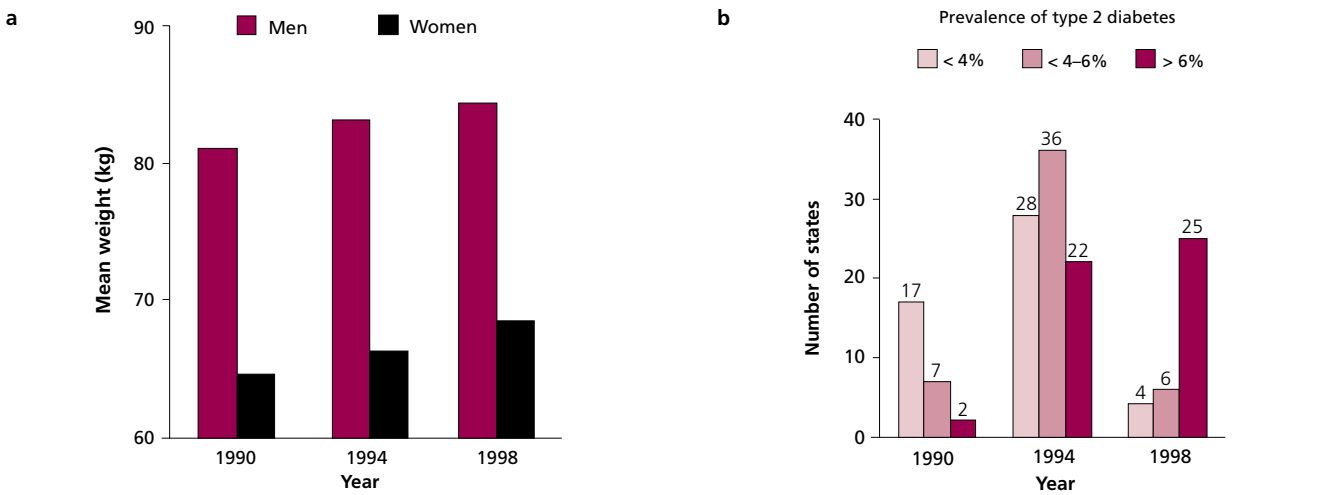
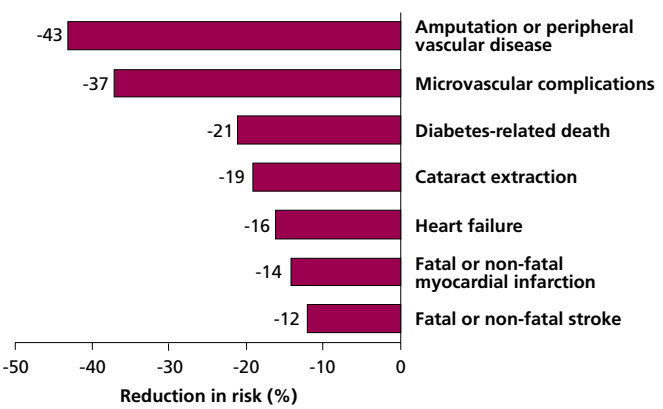


Figure 4. Reduction in risk in diabetic complications associated with each 1% reduction in HbA_{1C} in the UKPDS[16]



from 150 million in the year 2000 to 220 million in 2010.[10] Furthermore, half of all cases of type 2 diabetes are believed to be undiagnosed, and the insidious damage due to long-term hyperglycaemia is often evident even when patients present for diagnosis. Ultimately, some 60% of type 2 diabetic patients will die a cardiovascular death, with only one patient in five achieving a normal life span. The earlier diabetes is diagnosed, the more there is to lose: patients diagnosed in middle age (40–49 years) lose an estimated 7–10 years of life, compared with 5–7 years for patients diagnosed at age 50–59 years and 3–5 years for patients diagnosed at age 60–69 years.[11] This does not bode well for individuals diagnosed with type 2 diabetes at 20–30 years of age, who represent the fastest-growing segment of the type 2 diabetic population.

The cost of treating type 2 diabetes is high, especially managing the complications which reduce both the quality and duration of life.[12,13] More evidence from the CODE-2 study showed that, while diabetic patients without complications were 30% more expensive to manage compared with patients with other conditions, overall management costs for patients with both macrovascular and microvascular complications were more than four-fold greater than those for non-diabetic patients.[5] Worldwide, the cost of managing diabetes alone accounts for as much as 2–3% of total healthcare expenditure in every country.[14] The global pandemic of type 2 diabetes will represent the single greatest challenge to healthcare systems worldwide during the early decades of this century.

Importance of effective glycaemic control

The results of the UKPDS, among other studies, leave us in no doubt that effective control of glycaemia improves and extends the lives of patients with type 2 diabetes. The main analysis of the UKPDS determined the effects of intensive management on glycaemia and clinical outcomes. This was based on treatment with insulin or a sulphonylurea compared with a conventional management policy of diet and exercise in 3,867 patients followed for an average of ten years.[15]

An epidemiological analysis of the UKPDS revealed that a reduction in HbA_{1C} of 1% was associated with reductions in the risk of a range of diabetic complications (figure 4), including diabetes-related death (-21%), myocardial infarction (-14%), microvascular disease (-37%) and peripheral vascular disease (-43%).[16]

The association between HbA_{1C} and risk of complications was continuous and extended downwards into the normal range (HbA_{1C} < 6.0%). Thus, each 1% reduction in HbA_{1C} would be expected to deliver improvements in clinical outcomes.

Part of the UKPDS evaluated the effect of metformin, in comparison with diet-based treatment and intensive glycaemic

management with a sulphonylurea or insulin, in 1,704 overweight patients (defined as being > 120% of ideal body weight).[17] Metformin significantly reduced the risk of any diabetes-related complication (by 32%), diabetes-related death (by 42%) and fatal or non-fatal myocardial infarction (by 39%), while trends towards reduced risk of stroke, peripheral vascular disease or microvascular complications did not achieve statistical significance.

The results of the UKPDS provide a strong base of evidence to underpin the benefits of effective glycaemic control. Identifying and overcoming the barriers to improving our management of type 2 diabetes will allow us to realise the benefits seen within the UKPDS for all of our type 2 diabetic patients.

Overcoming the barriers to effective control of diabetes

The dual metabolic defect of type 2 diabetes

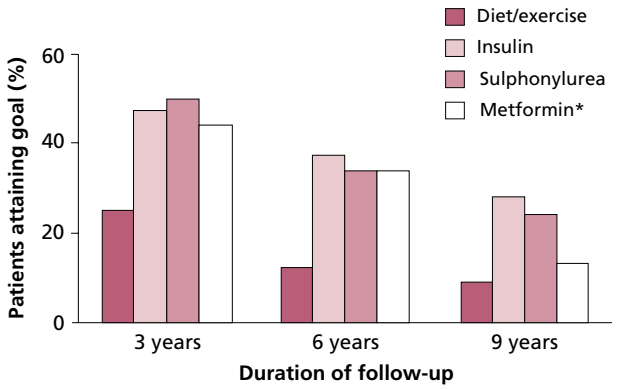
Type 2 diabetes in almost all cases is driven by a dual metabolic defect of insulin resistance and a relative impairment of insulin secretion. Insulin resistance is usually well established by the time that diabetes is diagnosed, and remains at a relatively constant level throughout the remainder of the course of the disease.[18,19] Although the impairment of beta-cell function also begins a number of years before the patient presents for diagnosis,[20] patients may still have sufficient beta-cell capacity to increase insulin secretion in an attempt to compensate for the insulin resistance for some years. As a result, a period of hyperinsulinaemia is often observed during the early years of clinical type 2 diabetes. Eventually, however, beta-cell function declines to the point where glycaemic control degenerates rapidly and treatment with exogenous insulin will be required.

Antidiabetic treatments may induce a short-term improvement in beta-cell function,[20] and some success has been achieved in delaying or preventing the onset of type 2 diabetes in glucose-intolerant individuals using lifestyle modification or metformin treatment.[21] On the other hand, no treatment has yet been demonstrated to slow the decline in beta-cell function durably in patients with established type 2 diabetes. Thus, type 2 diabetes can be considered to represent a 'moving target',[22] in that the underlying pathophysiology is dynamic in nature and unlikely to respond adequately to any single therapy during long-term treatment.

Limitations of diet/exercise and oral antidiabetic monotherapy

Current management algorithms for type 2 diabetes call for initial treatment with lifestyle modification followed by oral antidiabetic monotherapy. Therapy with diet and exercise controlled HbA_{1C} in only about one quarter of patients in the UKPDS after three years of treatment, and in less than 10% of patients after nine years of treatment (figure 5).[23] Data from the UKPDS have confirmed the limited efficacy of monotherapy in controlling glycaemia in the type 2 diabetic patient over the long term. Clearly, the majority of these patients would benefit from intensification of therapy using oral antidiabetic agents.

Figure 5. Patients in the UKPDS achieving HbA_{1C} < 7.0% on different treatment regimens[23]



* Overweight patients

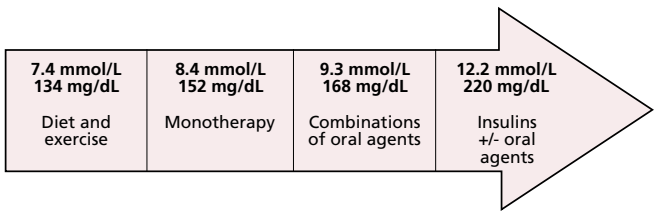
Even then, the dual metabolic defect underlying type 2 diabetes complicates the design of antidiabetic pharmacotherapy. Current oral antidiabetic monotherapy can address only one of the endocrine defects underlying the disease as its primary mechanism of action. Attempts to improve efficacy by increasing the dose of monotherapy may increase the likelihood of side effects[24] that often cause patients to discontinue treatment. For example, insulin secretagogues (sulphonylureas or meglitinides) are associated with hypoglycaemia or weight gain in some patients. The principal side effect of metformin is diarrhoea, though this can be minimised by careful titration of therapy. Metformin has also been associated with lactic acidosis, although the risk of this serious side effect is very low (three cases per 100,000 patient-years of treatment).[25] Thiazolidinediones cause weight gain, along with oedema in some patients, and have a limited indication in Europe. Finally, α-glucosidase inhibitors induce frequent and troublesome gastrointestinal side effects and the need for frequent daily dosing may hinder compliance (see below).

For these reasons, long-term antidiabetic monotherapy will be sufficiently effective for only a minority of patients. For example, in the UKPDS, therapy with a sulphonylurea, metformin or insulin controlled HbA_{1C} to below 7% in less than half of the patient population after three years of treatment, and in only about one quarter of patients or less after nine years of treatment (figure 5).[23] These data emphasise the need to challenge the way that we manage type 2 diabetes, starting from the early stages of the disease, in order to maintain protection from diabetic complications from the point of diagnosis.

Moving away from failure-based glycaemic management

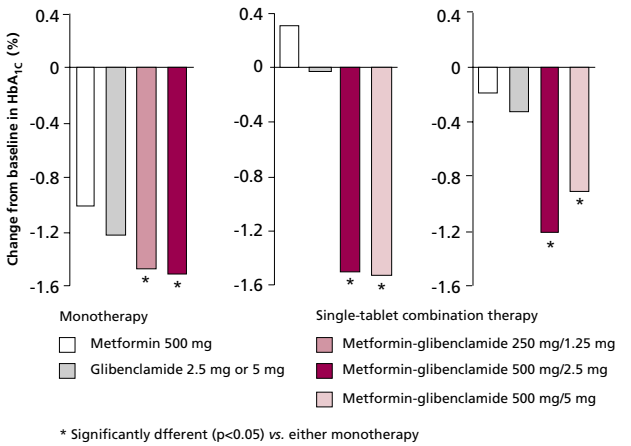
The progressive nature of type 2 diabetes requires regular adjustment of therapy to retain metabolic control. All too often, however, management strategies for type 2 diabetes are 'failure-based', in that there is a tendency to persist with monotherapy

Figure 6. Levels of glycaemia at which US physicians stated their intention to apply intensified antidiabetic therapies



Bristol-Myers Squibb. Data on file.

Figure 7. Glucose-lowering efficacy of single-tablet combination therapy compared with monotherapies in patients previously treated with diet and exercise,[30] at least half-maximal doses of a sulphonylurea[35] or metformin[34]



* Significantly different ($p<0.05$) *vs.* either monotherapy

until glycaemic control has been lost, perhaps irretrievably. The maximum efficacy of an oral antidiabetic treatment is achieved within 2–3 months,[26,27] so that intensification of therapy will be required if glycaemic control is not achieved. Furthermore, increasing the dose of an insulinotropic agent beyond half of the maximally recommended dosage usually produces little additional efficacy.[27-29]

An early switch to antidiabetic combination treatment that addresses the dual endocrine defects of insulin resistance and beta-cell dysfunction, would deliver a markedly greater reduction in HbA_{1C} for such patients and would provide a prompt and clinically important reduction in the risk of diabetic complications, as described above.[16] Furthermore, there is evidence that physicians may tolerate higher levels of hyperglycaemia in patients who receive more complex antidiabetic regimens, compared with those receiving diet and exercise or oral antidiabetic monotherapy. A survey of primary care physicians in the USA found that, on average, diet and exercise therapy would commence when fasting plasma glucose (FPG) reached 7.4 mmol/L (134 mg/dL) (figure 6). The same survey showed that patients would not receive an oral antidiabetic combination, or oral therapy plus insulin, until further marked deteriorations in glycaemia had been observed (figure 6). These data imply that patients requiring more intensive therapy are being exposed unnecessarily to hyperglycaemia.

A new approach to diabetes management is needed which recognises the urgent need to control glycaemia as a central part of the therapeutic strategy. This requires a greater readiness on the part of physicians to intensify antidiabetic therapy earlier and more frequently, using rational combinations of antidiabetic treatments with complementary mechanisms of action. For example, the combination of metformin, which addresses insulin resistance as its primary mechanism, with an insulinotropic agent such as a sulphonylurea or meglitinide, which enhance beta-cell function, addresses both components of the dual endocrine defects of type 2 diabetes.

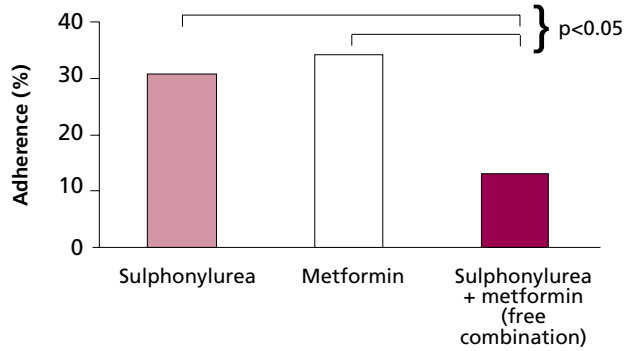
Well-designed clinical studies support the use of such combinations to deliver better glycaemic control than oral monotherapy in patients previously treated with diet[27,30] or oral antidiabetic monotherapy.[31-35] Figure 7 shows improved efficacy with metformin and glibenclamide (glyburide in the USA), as a single tablet (Glucovance®), compared with either agent given as monotherapy in patients previously treated with diet, metformin or a sulphonylurea. The incidence of hypoglycaemic symptoms with the lower dosage strength of the single combination tablet (which could be used to initiate combination therapy) was either lower than[30] or similar to glibenclamide alone.[34,35] While there is clinical evidence supporting the use of metformin and a sulphonylurea in combination, combinations of other oral antidiabetic agents may also be of benefit.

The use of such single-tablet combinations differs from the conventional use of free combinations. With a free combination, the first component is usually titrated to the maximum efficacy, tolerability or permitted dose. The second component is then added at a low dose and the titration process repeated. With a single-tablet combination, treatment can commence with both components at a relatively low dose and then titrated in parallel. This approach uses potential synergy between the components to enhance glucose-lowering efficacy with relatively low doses of both components.

Poor compliance with therapy

Type 2 diabetic patients bear a burden of polypharmacy[36] which is a barrier to compliance.[37,38] Indeed, many patients need to take as many as ten different medications every day for their diabetes and concurrent conditions. Given the need to take different medications, with different dosage frequencies and different numbers of tablets at different times of the day, it is hardly surprising that many patients are unable to follow treatment regimens closely. The Diabetes Audit and Research in Tayside, Scotland (DARTS) study provides a quantitative evaluation of the impact of regimen complexity on compliance with antidiabetic therapy.[39,40] The medication details of 2,920 patients were

Figure 8. Impact of polypharmacy on adherence to an antidiabetic regimen in the DARTS study[39]



Key messages

- Effective glycaemic control improves and extends the lives of people with type 2 diabetes
- Poor glycaemic control remains widespread in community practice
- We need to overcome barriers to effective glycaemic control
- Earlier use of combination therapy, in a manner that supports patient compliance, is required

followed retrospectively for 12 months, and information on prescriptions issued were used in the calculation of an 'Adherence Index', an estimate of the extent of actual therapeutic coverage from the antidiabetic treatment. Patients with an Adherence Index > 90% were considered to have complied adequately with therapy.

Only about 30% of patients met this goal while receiving monotherapy with either a sulphonylurea or metformin but adherence to therapy worsened by 13% when a free combination of these agents was used (figure 8). Furthermore, annual drug coverage was greater ($p<0.01$) in patients receiving monotherapy with a sulphonylurea (300 days) or metformin (302 days) than in patients receiving a free combination of these antidiabetic agents (266 days).

The DARTS study confirms the adverse impact of complex treatment regimens on routine adherence to therapy. Even the most effective treatment cannot benefit patients if it is not taken as prescribed. It is important that intensification of treatment regimens do not reduce patient compliance. The use of novel formulations, including single-tablet combinations, provides an avenue for further evaluation.

Looking ahead

The challenging glycaemic targets in current management guidelines provide a useful framework for improving patient outcomes in type 2 diabetes. We know that intensive oral antidiabetic regimens are effective, and reduce the risk of diabetic complications[15,17] without impairing patients' quality of life.[41] A greater readiness to treat to target and to intensify therapy earlier will form a key element in future diabetes management strategies. Single-tablet combinations offer the potential to maximise antidiabetic efficacy without reducing patient compliance and single-tablet combinations are already accepted in other fields of medicine.[42,43]

Current treatment algorithms need updating to include the use of single-tablet combinations in the management of type 2 diabetes. Indeed, a recent review of target-driven care concluded that the development of single-tablet combination therapies 'seems of the utmost priority for the prevention of complications of type 2 diabetes'.[44]

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