New Drugs or Established Regimens for the Management of Type 2 Diabetes – Are the Choices and Decisions Facing Consultants and Their Patients Straightforward?

a report by

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Type 2 diabetes is a chronic progressive condition leading to significant morbidity and premature mortality from its microvascular and macrovascular complications. The evolving epidemic of type 2 diabetes, which was estimated to affect 53 million people in Europe in 2007, and the recognition that control of hyperglycaemia can prevent or delay complications make effective treatment a priority.

For decades only insulin, sulphonylureas and metformin were available, but in the last 10 years new classes of drugs have been approved for diabetes management. These include alpha glucosidase inhibitors, thiazolidinediones, glinides, incretin-based treatments such as glucagon-like peptide-1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors. Insulin analogues have been developed, enabling easier and more physiological insulin replacement regimens. Although metabolic control has been improved in an increasing proportion of patients, leading to a reduced risk of developing nephropathy and retinopathy, the effects on cardiovascular morbidity and mortality and the long-term side effects associated with many of these agents remain poorly characterised, rendering it difficult to make informed treatment choices. Whether used alone or in combination with other therapies, the availability of the new agents has increased the number of choices for doctors and patients and created new uncertainty about the most appropriate approach.

A consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) on the approach to the management of hyperglycaemia in individuals with type 2 diabetes was published in 2006[1] and updated twice in the last year after consideration of new adverse events data and new therapies.[2,3] The recommendations for treatment are generally broad and allow individual clinicians considerable flexibility in their treatment choices. In summary, the guidelines advise early intervention with metformin in combination with lifestyle changes. Timely augmentation of therapy with additional agents, including early initiation of insulin therapy, is recommended as a means of achieving and maintaining glycaemic targets (glycated haemoglobin [HbA_{1c}] <7% for most patients and <6% for selected patients) without inducing significant hypoglycaemia. Although three oral agents can be used, the initiation and intensification of insulin treatment may be preferred based on effectiveness and expense.

In this article we will discuss the therapeutic choices that face clinicians, including the new incretin-based treatments, and explain why these are not straightforward, taking into account glucose-lowering potency, non-glycaemic effects and the side effects of available therapies. This commentary is based on the evidence from the previous detailed reviews of treatments of type 2 diabetes and also includes the most recent findings of the long-term outcomes of interventions in type 2 diabetes and trial results of new drugs, as well as our own clinical experience. We recognise that control of non-glycaemic abnormalities in type 2 diabetes to prevent cardiovascular morbidity is particularly important. However, the treatment options and goals of therapy for hypertension and hyperlipidaemia are beyond the scope of this review and are not discussed.

Lifestyle and Weight Loss Interventions

Lifestyle intervention programmes to promote weight loss and increase physical activity levels should be an early and sustained part of diabetes management. The beneficial effects are seen rapidly, and weight reduction of as little as 4kg will often ameliorate hyperglycaemia. These programmes are safe and will also have additional benefits for the reduction of cardiovascular disease. The most effective component of lifestyle programmes is weight loss. Studies of non-pharmacological weight-reducing interventions consistently show improvements in HbA_{1c}. Pharmacological treatment of the overweight and obese is also associated with improved glycaemic control. Pooled data of orlistat and sibutramine studies in patients with type 2 diabetes and high body mass indices consistently show significant weight reduction and improvement in HbA_{1c} of around 0.3%.[4,5] The XENDOS trial (Xenical in the prevention of diabetes in obese subjects) showed a significant 37.3% reduction in the incidence of type 2 diabetes in patients with impaired glucose tolerance treated with orlistat compared with placebo.[6] The benefits of sustained weight loss are shown most dramatically by the effect of bariatric surgery, which is associated with a marked improvement in glycaemic control: 76.8% (95% confidence interval [CI] 70.7–82.9%) of patients achieve full remission of diabetes after surgery, and 85.4% (95% CI 78.4–93.7%) achieve improvement in glycaemic control. The main limitations of lifestyle interventions are that they rarely achieve the 20–30% weight loss seen with surgery and the weight loss is seldom maintained long-term. As the interventions are generally unsustainable in the long term, and because

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diabetes is a progressive disease, the large majority of patients will require pharmacological therapy. This may include the drugs described above to treat the obesity or specific antihyperglycaemic agents described below.

Pharmacological Treatment

The choice of a specific antihyperglycaemic agent is based on the balance between effectiveness and safety. Although effectiveness is judged in the short term by the effect on glucose lowering, additional long-term effects, including the reduction of long-term microvascular and macrovascular complications, weight change and β-cell preservation, should also be considered. Safety is assessed by tolerability and adverse events, particularly the rates of hypoglycaemia. Finally, the cost of treatment cannot be ignored. Although controlled clinical trials have established the glycaemic goals of therapy, few good-quality clinical trials have directly compared different diabetes treatment regimens.

Established Regimens

Effectiveness of Lowering Glycaemia

The effect of hypoglycaemic therapy on long-term complications is predicted from the achieved level of glycaemic control and not the drug's mechanism of action. The three classes of oral hypoglycaemic drug (sulphonylurea, metformin and insulin) compared in the UK Prospective Diabetes Study (UKPDS)[8,9] all had a similar effect on microvascular complications despite differences in their mode of action to lower and maintain blood glucose levels. A meta-analysis of large numbers of placebo-controlled trials showed a mean lowering HbA_{1c} of 1% with pioglitazone, 1.2% with rosiglitazone, 1.1% with metformin, 1.5% with sulphonylureas, 0.5% with nateglinide and 0.8% with acarbose,[10] suggesting that the potency of the newer agents is not superior to that of established treatments. The glucose-lowering effectiveness is predicted not only by the choice of drug but also by the baseline glycaemia, duration of diabetes, previous therapy and other factors. The higher the baseline HbA_{1c}, the greater the expected fall with treatment. Although most oral hypoglycaemic agents will reduce HbA_{1c} by about 1% on average, this effect wanes in the long term. The UKPDS showed that none of the three agents was able to maintain patients at goal, emphasising the progressive nature of diabetes. There has been discussion as to whether some of the newer agents may preserve β-cell function and affect the natural history of diabetes.

ADOPT (A Diabetes Outcome Progression Trial) was undertaken to assess whether there was a difference between rosiglitazone, metformin and glibenclamide in the time to monotherapy treatment failure based on fasting glucose concentrations.[11] Rosiglitazone maintained glycaemia for longest, while the effect of sulphonylurea action was least sustained. The difference in HbA_{1c} lowering at four years was smaller between rosiglitazone and metformin (0.13%) than between rosiglitazone and glibenclamide (0.42%). Similarly, the proportion of patients achieving HbA_{1c} <7% at four years was similar between metformin and rosiglitazone (36 versus 40%). The glycaemic advantage of rosiglitazone was achieved at the expense of more weight gain than with either glibenclamide (2.5kg more) or metformin (6.9kg more) and fluid retention. In addition, the initial improvement in insulin secretion seen at one year was not sustained and was comparatively similar to the effect of metformin. Given the modest glycaemic benefit of rosiglitazone, the risk of fluid retention and weight gain, metformin remains the logical choice to achieve glycaemic control when initiating therapy for type 2 diabetes.

Non-glycaemic Effects

Cardiac Effects

In addition to the variable effects on glycaemia, specific effects of individual therapies on cardiovascular disease should be considered. Most of the available data come from studies of surrogate end-points, such as hypertension or dyslipidaemia, but there are important clinical studies that include cardiovascular events as end-points.

Dyslipidaemia and hypertension: Thiazolidinediones have a beneficial effect on high-density lipoprotein (HDL) cholesterol (mean relative increase 0.08–0.13mmol/l) but a harmful effect on low-density lipoprotein (LDL) cholesterol (mean relative increase 0.26mmol/l) compared with other oral agents. Overall, however, compared with other oral agents the net effect appears to be beneficial as the total to HDL cholesterol ratio is improved with time. In addition, pioglitazone reduces triglyceride level by a mean of 0.29mmol/l. The effects on blood pressure are very small and similar between all three major groups of antidiabetic agents.[10]

Cardiovascular event studies: The UKPDS (metformin) study showed that newly diagnosed, overweight, type 2 diabetes patients primarily treated with metformin achieved a significant 39% reduction in the risk of myocardial infarction compared with controls.[9] This was maintained for at least 10 years after the discontinuation of the study (relative risk [RR] reduction of 33%).[12] Intensive treatment with insulin or sulphonylurea lowered the risk by 16% but did not reach clinical significance. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) recruited patients with type 2 diabetes and evidence of macrovascular disease. The results suggested a benefit for pioglitazone treatment, but these did not reach statistical significance in the pre-specified primary end-point. However, there was a significant benefit for pioglitazone for the primary secondary end-point of all-cause mortality, non-fatal myocardial infarction and stroke in high-risk patients.[13] This was further investigated in the recent meta-analysis of pioglitazone trials,[14] which confirmed a significantly lower risk of death, myocardial infarction or stroke (hazard ratio 0.82) among a diverse population of patients with type 2 diabetes. However, this meta-analysis was dominated by the PROACTIVE study.

This does not appear to be the case with rosiglitazone. An interim analysis of the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) study showed no significant benefit on myocardial infarction (hazard ratio [HR] 1.17), but confirmed the risk of heart failure (HR 2.15).[15]

Although the evidence suggests a modest cardiovascular benefit from thiazolidinediones, over the last year there has been concern about the cardiovascular safety of this class of drug. Both rosiglitazone and pioglitazone are associated with a two-fold increased risk of heart failure[14,16] as a result of fluid retention. These drugs are contraindicated in people with, or at risk of, heart failure. Specific concerns about the effect of rosiglitazone were raised following the publication of a meta-analysis of cardiovascular events in trials involving rosiglitazone, which showed a 43% increased risk of myocardial ischaemia with rosiglitazone.[17,18] Although this analysis has received considerable criticism and the findings have not been confirmed in subsequent randomised controlled trials,[15] it is apparent that the thiazolidinediones are not as effective at reducing cardiovascular events as may have been expected from the earlier animal and surrogate end-point trials.

Fatty Liver Disease

Thiazolidinediones are the only agents that inhibit lipolysis and are effective in reducing levels of inflammatory cytokines. There have been several trials of metformin, pioglitazone and rosiglitazone that have shown that these agents may benefit patients with non-alcoholic steatohepatitis.[19]

Bone Disease

A recent and worrying observation is the effect of thiazolidinediones on bone. Peroxisome proliferator-activated receptor (PPAR)-γ receptors regulate the fate of pluripotent mesenchymal cells, leading to increased adipogenesis at the expense of bone formation. Thiazolidinedione treatment has been shown to reduce bone formation and bone mass in animal studies and, more recently, several clinical studies have demonstrated that thiazolidinediones also decrease bone formation and accelerate bone loss in healthy and insulin-resistant humans and increase the risk of distal fractures in women with type 2 diabetes.[20]

Monotherapy Choice

Metformin remains the overall first choice to be initiated on diagnosis of type 2 diabetes together with lifestyle measures. It typically lowers HbA_{1c} by 1% and is both well tolerated and inexpensive. It does not generally cause hypoglycaemia and has a less adverse effect on weight than other treatments. The UKPDS reported the beneficial effects of metformin on cardiovascular disease outcomes. Most patients with type 2 diabetes should receive metformin treatment as first-line therapy unless limited by gastrointestinal side effects or co-morbidities predisposing to lactic acidosis.

Combination Therapy

Progressive loss of β-cell function over time requires the initiation of combination therapy.[21] The combination of drugs, which may include insulin, should also be considered from the outset when the initial levels of glycaemia are high (e.g. HbA_{1c} >8.5%). Logically, drugs acting on different pathophysiological pathways should be combined.

There are very few studies directly comparing different combination regimens. A recent systematic review of clinical trials of diabetes therapies[10] noted that data on long-term outcomes were not available in most clinical trials. There is some evidence that combination therapy works, and triple therapy is also effective when rosiglitazone or insulin is added to the combination of metformin and sulphonylurea,[22] although with greater benefit for insulin at higher HbA_{1c} levels. Various studies have examined the effect of combining insulin with either metformin or sulphonylurea, or both. Pooled results of those studies[23] established that the mean final dose of insulin was 32% lower when metformin was continued, 42% lower when sulphonylurea was continued and 62% lower when both oral agents were continued. This benefit is shown more clearly when insulin titration is more aggressive.[24,25] These combination regimens allow the use of fewer insulin injections, making dose titration simpler and improving compliance, as well as preventing excessive weight gain and reducing hypoglycaemia.

There has been considerable interest over the last year about the choices of combination therapy and the effects of lowering glycaemic targets on cardiovascular disease. Preliminary data from a small study suggest that combining metformin with insulin reduces macrovascular end-points (HR 39%)[26] compared with insulin alone. This is in contrast to the negative vascular outcomes observed with the combination of metformin and sulphonylurea therapy in the UKPDS. A recent meta-analysis of observational studies of combination therapy with sulphonylureas and metformin reported a significantly increased relative risk (1:43) of the composite end-point of hospitalisation for cardiovascular events or mortality irrespective of the reference group.[29] The cause of this finding is unclear; it is possible that patients requiring combination therapy had a more aggressive form of diabetes or higher risk of hypoglycaemia and therefore represent a different patient group. As such, it is still justified to use this combination of treatment in appropriately selected patients because of the beneficial effect of improved glycaemic control on the risk of microvascular complications along with low cost.

The aim of the ACCORD[29] and ADVANCE[30] studies was to assess whether lowering HbA_{1c} to levels that are below currently accepted standards in high-risk patients with type 2 diabetes reduced cardiovascular events. The rate of use of glitazones and insulin was particularly high in the ACCORD study: 90% of patients in the treatment group and 58% of patients in the control group used rosiglitazone. Neither study showed a beneficial effect on cardiovascular disease in the short term (five years) and, interestingly, the ACCORD study reported increased all-cause mortality in the intensive therapy group. These results were unexpected and there has been debate about the reason for this. In the ACCORD study, there was significant weight gain of 3.5kg and more than 10kg in more than 27% of patients. Consequently, a beneficial effective of lower glucose may have been offset by the increased obesity rates. The rate of glucose lowering was very fast, with a 1.4% reduction in HbA_{1c} within four months. One consequence of improved control may have been an increased risk of hypoglycaemia. There is evidence that hypoglycaemia adversely affects cardiac function, suggesting that the reduction in myocardial ischaemia may have been balanced by an increase in sudden cardiac death from arrhythmia. The current evidence suggests that we should not be adopting particularly aggressive glucose lowering with the currently available treatments in high-risk patients.

The glucose targets may need to be adjusted according to the duration of diabetes, as aggressive blood glucose control in the early stages of diabetes seems to be advantageous. Recently published 30-year follow-up data from the UKPDS clearly demonstrated that newly diagnosed patients with type 2 diabetes who received intensive glucose-lowering therapy at the outset had persistent reductions in the risk of microvascular complications despite loss of glycaemic differences 10 years after the discontinuation of the study. A reduction in risk of myocardial infarction (15%) and death from any cause (13%) was also observed. This suggests that early and aggressive blood glucose control from the time of diagnosis of diabetes establishes a legacy effect and improves outcomes despite subsequent deterioration in glycaemic control.[12]

A different approach is needed in people with long-standing diabetes, those with established complications, in the presence of co-morbidities and in elderly patients. In these instances, lowering HbA_{1c} to <7% with the associated increased risk of hypoglycaemia might be detrimental and does not seem to improve cardiovascular outcome.[30] Although triple oral therapy is not more effective than addition of insulin, and is more expensive, it may be considered when HbA_{1c} is close to target (<8%).[31] Glycaemic effects appear to be additive when oral drugs are used in combination.[32] Patients generally prefer not to choose insulin because of its route of administration, the need for blood glucose monitoring, the driving restrictions and increased frequency of hypoglycaemia and weight gain.

In clinical practice, and in most clinical studies, despite a rigorous protocol-driven approach, the majority of patients do not achieve target HbA_{1c} with monotherapy or the combination of two or more oral hypoglycaemic agents. Combining insulin with metformin and sulphonylurea should, theoretically, bring everybody to target as there is no dose limitation, but this achieved only a 30–40% success rate because of the limitations of hypoglycaemia and weight increase.[33]

It seems that new and better treatment approaches are needed to deliver optimum diabetes care. Weight-neutral or weight-reducing therapies are needed with a lower risk of hypoglycaemia, which will improve patient compliance and improve cardiovascular outcome.

New Treatment Options

GLP-1 is an incretin hormone produced by the L cells in the ileum in response to the presence of nutrients in the intestinal lumen. It stimulates glucose-dependent insulin secretion, reduces glucagon production, slows gastric emptying and centrally suppresses appetite. People with type 2 diabetes have partial GLP-1 deficiency[34] but remain sensitive to its administration. When given systemically, GLP-1 reduces glucose concentration, particularly post-prandial peaks. The use of native GLP-1 is limited by its short half-life as the enzyme dipeptidyl peptidase-4 (DPP-4), which is expressed in many tissues, rapidly degrades it.

Two groups of therapies have been developed based on this system, the first being analogues of GLP-1 and the second inhibitors of DPP-4.

GLP-1 Analogues

Exenatide, the first licensed drug from this group, is a synthetic exendin-4 and shares partial homology with human GLP-1. It is administered subcutaneously as a twice-daily injection at a dose of 5 or 10mcg. A once-weekly preparation is now in development.[35] Exenatide increases insulin secretion in people with type 2 diabetes in a dose-related and glucose-sensitive fashion. It is as effective as insulin at lowering blood glucose[36,37] in combination with metformin. It also reduces HbA_{1c} by 1.2%, with a sustained effect over at least three years. There is a progressive weight loss with treatment. Observed weight loss was 1.6–2.8kg at 30 weeks and 5.3kg at three years. Even patients who did not lose weight achieved an HbA_{1c} reduction of around 0.7%, while those who lost weight achieved a 1.7% decrease in HbA_{1c}.[38–40] Initial clinical trials suggest that exenatide LAR, a long-acting depot formulation, administered once weekly is more effective in lowering HbA_{1c} levels than twice-daily injections (1.9 versus 1.5%), leading to a greater proportion of patients achieving HbA_{1c} <7% (77 versus 61%), with no increased risk of hypoglycaemia and a similar reduction in bodyweight.[42] Reduced dosing frequency is also likely to be more acceptable to patients.

In vitro exenatide induces β-cell proliferation, although whether this has any clinical relevance is not yet clear.[41] Exenatide is approved for use in combination with other oral agents. Although it can be used as monotherapy, in view of its route of administration and cost it is more practically used as a second-line treatment in overweight or obese patients, particularly if insulin use is contemplated.

The main side effects are gastrointestinal and include nausea (57% of patients within the first eight weeks) and vomiting. They tend to improve with time, with 5–10% reporting nausea by week 24. There have been rare reports of pancreatitis, although most patients had at least one other risk factor for this condition.

Liraglutide is in clinical development and differs from exenatide in that it is a true analogue of GLP-1 and not simply a mimetic. It is structurally similar to physiological GLP-1 but contains a C16-fatty-acid chain attached to Lys26, which presumably orientates to mask the DPP-4 cleavage site. Liraglutide at the highest dose reduces HbA_{1c} by 1.74% on average compared with placebo, from a baseline of 8.5%. In addition, a dose-dependent decrease in bodyweight is maintained.[43]

There are no reports of adverse cardiac effects from GLP-1 analogues. They do not cause lactic acidosis, oedema or hypoglycaemia unless used in combination with sulphonylurea, and may therefore be a useful in patients with ischaemic heart disease or heart failure.

DPP-4 Inhibitors

Several drugs have been developed that inhibit the breakdown of endogeneous GLP-1 and therefore enhance meal-related endogeneous GLP-1 concentrations. They are administered orally but appear less effective than exenatide and have a less diverse range of action. For example, sitagliptin treatment is associated with a 0.6–0.7% HbA_{1c} reduction as monotherapy and 0.9% reduction in combination with metformin and pioglitazone.[44–46] While the results showed better effects in newly diagnosed patients, only 45% of patients attained an HbA_{1c} <7%. Vildagliptin 50mg daily has been tried in drug-naïve patients and in combination with metformin, glimepiride, thiazolidinediones and insulin[47–50] with similar efficacy to sitagliptin (HbA_{1c} reduction of 0.9, 0.6 and 0.5%, respectively).[40] If added to metformin, it is as effective as pioglitazone without the 1.6kg weight gain over six months seen in the pioglitazone group.[51] Higher doses of vildagliptin cause de-arrangement of liver function tests (LFTs) and are contraindicated in those with liver disease. Even at lower doses, LFTs should be checked at initiation of treatment and monitored periodically.

Unlike GLP-1 analogues, DPP-4 inhibitors do not delay gastric emptying or suppress appetite, but are weight-neutral. As they are less effective than metformin and cost significantly more, they will not replace this as a first-line choice of drug. They may be used as an addition to metformin, sulphonylureas or glitazones. One recent study of the combination of vildagliptin with insulin suggested a small benefit on HbA_{1c} with reduced hypoglycaemic risk.[52]

There are concerns about the role the inhibitors play in suppressing DPP in other tissues, including haematological and immune cells. Currently available preparations seem to be highly DPP-4-selective, and significant side effects have not been reported so far from clinical trials.[44–46] Post-marketing surveillance of sitagliptin has reported a number of hypersensitivity reactions, including Steven-Johnson syndrome within the first three months of treatment and sometimes after the first dose. There have also been reports of increases in urinary tract infections, headaches and nasopharyngitis.[38] Close patient monitoring is therefore recommended.

DPP-4 inhibitors are licensed for use in combination therapy. They should be considered as a second- or third-line therapy in overweight or obese patients with contraindications or an intolerance of other oral hypoglycaemic agents. DPP-4 inhibitors are less potent and, considering their cost and concern regarding potential side effects, should be used

with caution. In comparison, GLP-1 analogues are more promising for the maintenance of long-term glycaemia in obese patients, although their parenteral mode of administration is less appealing. They should be considered when insulin treatment is contemplated. New long-acting preparations (once-weekly injection) might be more useful.

Summary

The ever-expanding repertoire of antihyperglycaemic drugs leaves clinicians with a large number of choices to apply to individual patients, many of whom have complicated medical problems. Metformin remains the first-line pharmacological agent and the ADA/EASD algorithm is helpful as a guide for further choices. The treatment should be individually tailored to aim for as close to physiological blood glucose levels as possible without causing significant adverse effects, particularly hypoglycaemia. The non-glycaemic effects, in particular cardiovascular risk and β-cell preservation, as well as cost of therapy, should also be considered. This requires a high level of specialist input to make the best choice of intervention and the patient's involvement to avoid non-compliance. ■

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