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Review

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What to add in with metformin in type 2 diabetes?

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Summary

This review considers the therapeutic choices currently faced by people with type 2 diabetes and those caring for them when glucose levels initially controlled with lifestyle management and metformin start to rise. While sulphonylureas are familiar agents and cheaper than other alternatives, they cause hypoglycaemia and modest weight gain, and robust outcome data are still lacking. Dipeptidyl peptidase 4 inhibitors ('gliptins') have an attractive pharmacological and adverse effect profile, but their effects on the cardiovascular system are also uncertain. Thiazolidinediones ('glitazones') are effective glucose-lowering agents, but cause weight gain and increase the risk of fracture, while the cardiovascular benefits hoped for in association with 'insulin-sensitization' have not been as expected. Glucagon-like peptide-1 agonists will not be acceptable as initial second-line agents for many people as they are injectable rather than oral. Well-powered 'head-to-head' clinical trials of adequate duration are therefore required to allow evidence-based decisions on second-line therapy.

Introduction

Hyperglycaemia is the defining characteristic of type 2 diabetes mellitus (T2DM). Although, it is not always symptomatic at diagnosis, good glucose control is important in preventing complications and should be established as soon as possible. In accordance with current guidelines,[1–4] this can be achieved in most cases in the first instance by lifestyle modification (healthy eating, exercise) with or without a single oral pharmacological agent—usually metformin—as 'monotherapy'. However, as T2DM is a progressive condition, higher dose metformin may be required within a year or two, and subsequently addition of a second (and then third) oral—or injectable—agent. This article focuses on the evidence base informing choice of therapy at this more complex stage of management.

Metformin

The ascendancy of this biguanide agent 'first line' in pharmacological glucose lowering in T2DM is now almost unchallenged. However, before proceeding to consider the relative merits and demerits of 'second-line' options, it is helpful briefly to consider those of metformin.

Metformin is a remarkable drug, which has been available on the UK market for >50 years, although for only 15 years in the USA. Its mechanism of

action is complex but involves activation of AMP-kinase, a key enzyme regulating cellular energy metabolism.[5] Important effects at the physiological level are to decrease hepatic glucose production, and enhance peripheral glucose disposal.[6] In its early years, metformin was much less frequently used than at present in the UK (and was not used at all in the USA) mainly because of concerns about safety centring around lactic acidosis. However, these are now considered negligible for metformin[8] and instead attributable to the earlier agent phenformin.

Results published in 1998 from the UK Prospective Diabetes Study (UKPDS) were responsible for securing metformin's position first-line.[9] These highlighted reduced rates of diabetes-related deaths, all-cause mortality and myocardial infarction with metformin monotherapy in obese people with T2DM-effects recently shown to persist even 10 years after randomization was discontinued.[10] Metformin, therefore, has many of the qualities desirable of an 'ideal' pharmacological agent for glucose lowering in T2DM: promoting weight stabilization, carrying a low risk of hypoglycaemia and being available at low cost.

Despite these attractive properties, and the strength of the clinical trial data, the evidence for metformin should not be accepted entirely uncritically. It can cause significant gastrointestinal adverse effects, particularly during initiation and when dose escalation is too rapid. There appear to be 'responders' and 'non-responders', but no established means of *a priori* prediction. Despite increasing use in non-obese individuals, there is a lack of outcome-based evidence in this group (it was reserved in UKPDS for those with body weight >120% 'ideal'—approximating to BMI >31.4 kg/m^2). The reductions shown in diabetes-related death and myocardial infarction with metformin in UKPDS were in comparison with a mainly dietary strategy (342 individuals randomized to metformin, target fasting plasma glucose 6 mmol/l vs. 411 individuals treated mainly with diet, target fasting plasma glucose 15 mmol/l) rather than in comparison with intensive therapy with other agents.[9] Moreover, in UKPDS, sulphonylurea (SU)–metformin combination therapy resulted in a near doubling of diabetes-related death: although this finding should be treated with caution (based on only 40 deaths), the investigators considered it worthy of further study.[9] Finally, of those participants who entered UKPKDS post-trial monitoring, full data for non-fatal events at the end of the study were only available for 65% of surviving participants.[10] Thus, despite metformin's strengths, its case for first-line use rests mainly on stronger evidence for positive long-term cardiovascular outcomes when used as monotherapy than any of the other options—a situation which is not unassailable. For these reasons, a better first-line oral glucose-lowering agent could still emerge—or may even already be available.

What next?

In contrast to the situation at the time of publication of the UKPDS, a variety of agents are now available for adding in 'second line' with metformin when glycaemic control slips from target. Although glucose-lowering efficacy varies to some extent between the available classes in terms of time of onset, maximum effect and sustainability over time, these differences are generally smaller than unpredictable differences in response to the same drug between individuals. Moreover, it is increasingly recognized that glucose-lowering agents may have divergent metabolic and cardiovascular effects (whether acting via their main target or an 'off target' effect), so that glucose-lowering *per se* is not a guarantee of long-term benefit in terms of outcome. Indeed, cardiovascular 'safety' has been highlighted in the last 3 years by concerns initially raised by Nissen and Wolski[11] regarding the thiazolidinedione (TZD) agent rosiglitazone. The ensuing debate has reshaped the therapeutic landscape, prompting both renewed scrutiny of older agents (including SUs) and closer attention to the long-term effects of other more recently introduced classes [DPP4 inhibitors and glucagon-like peptide-1 (GLP1) agonists].

The key factors guiding drug choice are therefore:

(i) adverse effects associated with main pharmacological action (e.g. hypoglycaemia, weight gain);
(ii) agent-specific less predictable (or idiosyncratic) adverse effects [e.g. oedema, fluid retention, fractures (TZDs); pancreatitis (GLP-1 agonists); risk of infection (DPP-4 inhibitors)];
(iii) host factors (e.g. duration of disease/pre-existing congestive heart failure/renal impairment);
(iv) cost;
(v) years of patient exposure (as a crude indicator of safety).

The latter two are of course closely associated (Table 1).

It is important to recall that the effects of any particular agent in combination with metformin may not be the same as when that agent is used as monotherapy—although this is often assumed to be the case in clinical practice.

Table 1 Summary of evidence (2010) for glucose-lowering agents in T2DM

	Metformin	SUs	Pioglitazone	Rosiglitazone	DPP-4 inhibitors	GLP-1 analogues
Better cardiovascular outcome than other agents	Probable	No	Possible	No	Not known	Not known
Weight	Stabilization or loss	Initial gain	Ongoing gain	Ongoing gain	Neutral	Loss
Risk of hypoglycaemia	Negligible	High	Negligible	Negligible	Mostly when prescribed with SUs	Mostly when prescribed with SUs
Favoured for specific subgroups		BMI <25 kg/m				Obese willing and able to self-inject
Main contraindications	eGFR <30–50 ml/min		CHF	CHF, Previous MI		
Adverse effects	Gastrointestinal	Hypoglycaemia, weight gain	Oedema, weight gain, fractures	Oedema, weight gain, fractures		Nausea
Cost	Low	Generally low	High—may fall if generics are produced after patent expiry in 2011	High	High	Highest
Pharmaco-vigilance experience (years)	50	50	10	10	3	3

SUs

As these agents (SUs) were the mainstays of pharmacological glucose lowering in the decades prior to the publication of UKPDS, they are very familiar to prescribers. Given that they are widely available in generic form, SUs are also low in cost to health services.

The onset of action of SUs to lower blood glucose is more rapid than with other agents. As they increase the amount of insulin secreted by pancreatic β-cells at any given ambient glucose concentration, there is a dose-dependent risk of weight gain and hypoglycaemia.[12] In terms of quantifying these risks, participants treated with glibenclamide monotherapy in A Diabetes Outcome Progression Trial (ADOPT) gained 1.6 kg—all of which occurred over the first year.[13] Severe hypoglycaemia (requiring ambulance and/or hospital treatment) occurs in approximately one in every 100 people treated with a SU each year vs. one in every 2000 with metformin and one in every 10 with insulin.[14] The effect of SUs on glycaemia appeared in ADOPT to be less sustained over time than with either metformin or TZDs (all as monotherapy),[13] a phenomenon attributed to 'β-cell exhaustion'.

Second-generation SUs (e.g. glibencamide, gliclazide and glimepiride) are associated with very low rates of other adverse events, but evidence for their cardiovascular safety is surprisingly sparse, particularly as their mechanism of action depends on opening potassium–ATP (K_{ATP}) channels and some agents (e.g. glibenclamide) bind to both β-cell (SUR1) and cardiac (SUR2A) subtypes of the adjacent SU receptor.[15] The only comparison between SUs and placebo which attempted to assess rates of cardiovascular disease was the University Group Diabetes Programme, published in 1970, which reported 26 cardiovascular deaths in participants randomized to tolbutamide vs. 10 allocated to placebo ($n = 205$).[16] However, this finding cannot be relied on as evidence in that significantly more patients allocated to tolbutamide had cardiovascular disease at baseline.[17]

The UKPDS comparisons between individual intensive treatments and conventional treatment can be taken as partial reassurance on this account in that the confidence intervals (CIs) for relative risk of diabetes-related death (although wide) spanned unity for both chlorpropamide and glibenclamide vs. a mainly dietary approach.[18] Indeed, in ADOPT, there was a trend for fewer serious cardiovascular events with SUs than with metformin— although the trial was not powered to study cardiovascular endpoints.[13] However, a number of contemporary epidemiological

investigations—albeit by definition potentially affected by unmeasured confounding variables—suggest higher cardiovascular disease event rates in patients on SUs in comparison with metformin;[20,21] biological plausibility is provided by higher rates in those who started SUs first and had metformin added in compared with vice versa.[20]

Thus, while SUs are inexpensive, familiar to prescribers and provide rapid relief of osmotic symptoms in those with severe hyperglycaemia, they have significant short- and medium-term adverse effects which are combined with an ongoing lack of robust cardiovascular outcome data.

TZDs

In the late 1990s, this new class of 'insulin-sensitizing' agents (TZDs) gradually gained ground in preference to SUs for second-line treatment in combination with metformin, despite considerably higher costs. The two available agents, pioglitazone and rosiglitazone, act on the gamma subtype of nuclear peroxisome proliferator activated receptors (PPARγ), abundantly expressed in adipose tissue.[22] Their action to promote glucose disposal in muscle is complex but associated with subtle redistribution of adipose tissue between visceral and subcutaneous depots, with an associated reduction in circulating concentrations of non-esterified fatty acids.[22] In contrast to the mechanism of action of SUs, lowering of blood glucose with TZDs is associated with 'decreased' circulating insulin concentrations—or 'sensitization' to insulin action. With mounting evidence in the 1990s that the cardiovascular complications of T2DM were causally related to insulin resistance—and not just hyperglycaemia—this property was considered likely to be associated with a favourable cardiovascular profile on theoretical grounds. However, as insulin has complex actions on different target tissues, including the vasculature,[23] this view has proven somewhat simplistic.

TZDs have a slower onset of action than SUs, taking up to 3 months to achieve their full glucose-lowering effect. ADOPT suggested that glycaemic control (as measured by requirement for addition of a second agent) can be maintained for longer with TZD monotherapy—in this case rosiglitazone—than with metformin and SUs.[13] Rates of therapy-induced hypoglycaemia are negligible (similar to metformin), but the propensity to cause weight gain is greater and more sustained than with SUs—nearly a kilogram every year for 5 years with rosiglitazone in ADOPT.[13] Recent data suggest that TZD–metformin combination therapy is associated with less weight gain than TZD monotherapy.[24] An additional clinically relevant adverse effect in a small proportion of individuals is fluid retention resulting in ankle oedema, which may be a result of renal tubular salt and water retention, but which may in some cases reflect unmasking of pre-existing left ventricular dysfunction: TZDs are therefore contraindicated in heart failure.[4]

As already mentioned, the hoped-for cardiovascular benefits of TZDs have not been fully supported by the trial evidence. Most promising was the PRO active study ($n = 5238$) which indicated a significant reduction in major adverse cardiovascular events as a secondary endpoint, but reported a negative primary cardiovascular endpoint—probably as a feature of an idiosyncratic choice of individual endpoints in the composite.[25] Numerous *post hoc* analyses examining various endpoints in subgroups with pre-existing cardiovascular disease[26,27] and subgroups with different background therapies[28] have provided some reassurance, but are far from conclusive. A systematic review (2008) which excluded PROactive reported a reduction of all-cause mortality with pioglitazone [odds ratio (OR) 0.30; 95% CI 0.14–0.63; $P < 0.05$), but no significant effect on non-fatal coronary events.[29] In the case of rosiglitazone, the argument moved from cardiovascular benefit to cardiovascular 'safety' in 2007 following a provocative independent meta-analysis which pooled adverse events occurring in small Phase 2 studies designed to examine the more immediate endpoint of glucose lowering.[11] Although data from the subsequent large Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Combination Therapy for Type 2 Diabetes study provided a degree of reassurance on the cardiovascular effects of rosiglitazone[30] in 2009, further clinical research data reporting an increased risk of myocardial infarction, stroke and all-cause mortality,[31,32] resulted (by September 2010) in the US Food and Drug Administration (FDA) restricting the use of rosiglitazone to fully-informed individuals already established on treatment.[33] The European Medicines Agency (EMA) went further, withdrawing its marketing authorization.[34]

The 'rosiglitazone controversy' has therefore resulted in a drawing back in prescribing habits from TZDs towards cheaper and more established SUs for second-line therapy. This has been reinforced by small but statistically significant increases in rates of fracture with both rosiglitazone and pioglitazone.[35]

Dipeptidyl peptidase IV inhibitors

These agents ('DPP-4 inhibitors' or 'gliptins') are the new challengers to SUs for second-line therapy. Acting by prolonging the duration of action of gut hormones—including glucagon-like peptide 1 (GLP-1)—which amplify insulin secretion as a physiological response to feeding ('incretin response'), they have glucose-lowering efficacy which is comparable with SUs and TZDs (depending on interpretation of clinical trial evidence).[36] They have an attractive pharmacological profile in that they are not associated with weight gain, and risk of hypoglycaemia with monotherapy is negligible. During medium-term use, reported adverse event rates are similar to placebo.[36] Concerns that effects on kinin metabolism might result in a clinically relevant excess risk of infection have diminished over the 3 years since the 'first in class' sitagliptin was launched (now accompanied by vildagliptin and saxagliptin—and soon alogliptin).

DPP-4 inhibitors were launched into a changed marketplace following the rosiglitazone controversy, with a new and rigorous regulatory environment requiring cardiovascular safety to be demonstrably 'non-inferior' to other available therapy [with specific FDA guidance at both pre-marketing (licensing) and post-marketing stages)].[37] Thus, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin study is currently randomizing 14 000 patients to sitagliptin or placebo in combination with a variety of other therapies in order to examine cardiovascular outcomes over 3 years, with the aim of reporting in 2015.[38] In the meantime, DPP-4 inhibitors are gaining ground as second-line therapy in primary care, while in secondary care they are particularly being used in patients who are intolerant of other agents. As all remain on patent at present they are more expensive than SUs.

At present, there are no published studies of duration longer than 12 months comparing SUs and DPP-4 inhibitors as second-line therapy added in with metformin and examining any outcome.[39,40] However, a meta-analysis of small trials designed to demonstrate glucose-lowering efficacy has suggested a potentially beneficial signal for their cardiovascular safety (albeit not statistically significant).[41]

Other oral agents

Intestinal disaccharidase inhibitors are effective glucose-lowering agents, with some evidence of potential cardiovascular benefit,[42] but are poorly tolerated by many people with T2DM.[43] Meglitinides are similar to SUs, albeit with a shorter duration of action, and as such have yet to find a significant niche in the therapeutic armamentarium. The recent NAVIGATOR trial demonstrated that nateglinide did not reduce rates of cardiovascular outcomes in 9306 people with impaired glucose tolerance at high cardiovascular risk.[44] Nonetheless, metformin/repaglinide combination therapy is associated with a greater likelihood of achieving target glycaemic control (defined as HbA1c < 7.1%) than either drug alone [(59% (combination therapy) vs. 20% (metformin or repaglinide monotherapy)].[45] Comparing metformin/repaglinide with metformin/glyburide combination therapy, the former therapeutic strategy was associated with fewer episodes of biochemical hypoglycaemia.[46]

Non-insulin injectable agents

All the agents discussed above are administered orally. Few people with T2DM would consider moving on to injectable therapy after a trial of only a single oral agent. However, one exception to this rule may be in the very obese. Two glucagon-like peptide-1 (GLP-1) agonists have been launched in the UK in the last 2 years: exenatide (2007) and liraglutide (2009). Their use is associated with significant weight reduction, as well as substantial glucose-lowering efficacy and low risk of hypoglycaemia (except where given in combination with SUs).[47] Weight reduction may be associated with other beneficial cardiometabolic effects including reduction of LDL cholesterol and blood pressure[48]—indeed, clinical trials are in progress examining the potential of these agents for weight reduction even in non-diabetic individuals. Their mechanism of action is to act as incretin agonists, replacing the physiological response with a pharmacological one. Although GLP-1 agonists are licensed for use as second-line therapy (with metformin and/or a SU), they are currently recommended by most guidelines for initiation as third agents in individuals with frank obesity—and for continuation in those who demonstrate a definite glucose-lowering response in the initial months of therapy.[49] However, a number of 'once weekly' injectable GLP-1 agonists are on the immediate horizon: with falling costs, these agents could become realistic candidates for second-line treatment provided cardiovascular safety, and other safety,[50] can be demonstrated in ongoing trials designed to meet FDA specifications which have now been initiated.

Insulin

There has been recent interest in early insulin therapy in T2DM, with the hypothesis that this approach may preserve endogenous β-cell function for longer in T2DM.[51] However, most of the studies to date can be criticized for comparing metabolic function in individuals intensively treated with insulin vs. those receiving only 'usual care'. It seems likely for the present that insulin will not be an acceptable option for most people with T2DM until they have tried at least two oral agents in combination.

Summary and conclusions

While metformin is not ideal, it is the best drug we have for pharmacological treatment of T2DM and its current 'first-line' position seems unassailable at least over the next 5 years. None of the other available agents can be regarded at present as clear favourite for second-line 'add-in' treatment with metformin. As experience with the TZDs, and to a greater extent DPP-IVs and GLP-1 agonists, is very much less than for SUs, assessing the evidence to date can only give a provisional answer and the evidence may yield further surprises.

When will we have the evidence we require to be sure whether SUs, TZDs or gliptins are the best second-line choice for oral therapy in T2DM? A clinical trial with adequate statistical power for cardiovascular endpoints comparing these options 'head-to-head' as add-in therapy with metformin in unselected patients could cost around £50 million. Such funding is unlikely to be forthcoming from any public body or charity. The pharmaceutical industry 'spend' on research and development could cover such a sum if pooled, but the pressures of competition between companies make a continued focus on individual products (vs. placebo) more likely. Perhaps it is more likely in the foreseeable future that greater understanding of disease causation/mechanisms of drug action will more reliably identify subgroups of people with T2DM who can be predicted to respond well (or poorly) to particular drug classes. Further major changes in prescribing practices could result from currently unpredicted drug safety developments: more reliable mechanisms of pharmacovigilance are urgently required.

As things stand, SUs, TZDs and gliptins all have advantages and disadvantages for use as second-line therapy in T2DM, on the background of a fast-moving situation. In most health-care systems, including the UK, cheaper and more established agents will continue to be favoured until newer and more expensive agents are proven definitely superior, not just in terms of glucose lowering, but also in their effects on cardiovascular and other complications.

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