Review Article

An update on pharmacotherapy for type 2 diabetes

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Abstract

Glucose lowering drugs have been available for clinical use for over the past 60 years or so with the last 2 decades seeing a significant number of new agents being developed making treatment increasingly complex and also somewhat controversial. This stems from the fact that while it is now known that patients with diabetes have an increased risk for cardiovascular disease and mortality there are mounting concerns with regards to the cardiovascular effects of certain antihyperglycemic agents leading to uncertainties when it comes to drug prescription. This has left many clinicians perplexed with respect to optimal strategies for management for management of such patients leading to many regulatory bodies to issue recommendations for antihyperglicimic therapy in adults with type 2 diabetes. These all uniformly advocate an individualised approach, keeping in mind each patients' unique health profile (such as age and weight) and their cardiovascular risk factors vis-a-vie the specific attributes, side effects and adverse effects of each antihyperglycemic agent. This article will focus on the ten major categories of diabetic therapies looking specifically at their mode of action, safety profile as well as key trial data and where possible the long-term outcome studies for each class.

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Introduction

The last few decades have seen a considerable increase in the therapeutic armamentarium for the management of patients with type 2 diabetes (T2 DM). As the incidence and prevalence of diabetes continues to increase worldwide so has been the struggle to find the ideal antihyperglycemic agent which is cost-effective at achieving and maintaining near-normal blood glucose levels, but also has a favourable safety profile, has good tolerability with limited side effects and possibly also exerting positive effects on surrogate markers of cardiovascular risk[1-3] This stems from the fact that patients with T2 DM have an increased risk of cardiovascular morbidity and mortality and while data from recent key trials have shown that tight glycaemic control results in sustained reductions on microvascular event rates (including nephropathy, neuropathy and retinopathy), strict and aggressive blood glucose control does not necessarily exert beneficial effects on macrovascular events and may actually increase mortality.[2-9] Thus, keeping in mind that the ultimate aim for diabetic patients would be to reduce this excess cardiovascular risk one should look at other characteristics of anithyperglycemic agents independent of glycemic control which may influence cardiovascular outcomes in such patients.[2] In fact over the past few years, many questions have arisen regarding the cardiovascular safety or otherwise of drugs used to treat diabetes. This occurred following the results of a highly publicized meta-analysis in 2007 concerning the thiazolidinedione rosiglitazone. Here the authors demonstrated a significant increase in risk of myocardial infarction (odds ratio 1.43) and death from cardiovascular (CV) causes (odds ratio 1.46) with rosiglitazone use fuelling a lot of controversial issues with respect to prescribing this drug as well as stimulating the debate on whether diabetes drugs should have long-term trials showing cardiovascular safety [10-11]). This eventually led the U.S. Food and Drug Administration (FDA) to issue a 'boxed warning in the drug's labelling about potential increased risk for heart attacks'. Furthermore in 2008 it also issued new recommendations with respect to evaluation of cardiovascular risk in the premarketing and postmarketing assessment of novel antidiabetic therapy defined as the upper bound of the 95% Confidence Interval for major adverse cardiovascular events

(MACE) of < 1.3 leading to profound changes to the way new antidiabetic drugs are developed.[6,12-15] Keeping all this in mind, this article will focus on the ten major classes of drugs used to treat T2DM focussing on their mode of action, their safety profile as well as key trial data and where possible the long-term outcome studies for each class.

Sulphonylureas

Sulphonylureas (SU) have been in use for the past 50 odd years making them the oldest class of oral antihyperglycemic agents. They are the major insulin secretagogues and their mode of action is well understood. These exert their effect by binding to the adenosine triphosphate (ATP)-sensitive potassium channels situated on the Beta (β)-cells inhibiting potassium efflux leading to subsequent depolarization of the β-cell, which ultimately results in insulin secretion.[16-19] Interestingly these ion channels are also present in cardiac myocytes and have been implicated for the adverse effects of SU on the heart.[2] There are a number of agents available in this class with the major difference between them being in their side-effect profile and their duration of action. SU reduce HbA1c by around -0.9 to -2.5% and have thus been advocated for use as monotherapy and first line agents in non-obese individuals or in combination with other antihyperglycemic drugs.[1,16-18] The well-known side-effects of these drugs include the risk of hypoglycaemia and weight gain. Much of our knowledge on SU comes from the United Kingdom Prospective Diabetes Study (UKPDS). This landmark multicentre study which was carried out over 20 years between 1997 and 1999 in the UK randomised more than 4000 newly diagnosed type 2 diabetic patients to either intensive treatment with insulin or SU (with a small subset of overweight patients being given metformin instead) or to conventional therapy consisting of dietary and lifestyle modification. Patients randomised to intensive treatment with SU/insulin showed a lower risk of microvascular complications (25%) then conventional therapy as well as a non-significant (16%) reduced risk of myocardial infarction (*p*=0.052), however, this was at the expense of significantly greater weight gain which however was less than in those treated with insulin. Hypoglycaemic episodes were more frequent in the intensively treated group however patients assigned to SU treatment exhibited lower rates of both minor and major hypoglycaemia when compared to those on insulin therapy.[18-22] On the other hand, the specific effects of SU therapy on CV outcomes is still conflicting. Previous studies (including the University Group Diabetes Program [UGDP] which used the older generation SU tolbutamide) have implied that SU treatment may be associated with adverse CV effects.[23] Conversely in the UKPDS, this suggestion was not reproducible as none of

the SU used showed an increased rate of adverse CV outcomes.[22, 24] Furthermore, in the 10-year post trial follow-up of the UKPDS, the sulphonylurea-insulin group continued to have significant risk reductions for any diabetes-related end point, microvascular disease, all-cause mortality as well as significantly reduced risk for myocardial infarction despite convergence in glucose control between the different treatment arms after one year.[21, 22] This implies a legacy-effect and that early aggressive glycaemic control led to sustained benefits after 10 years of follow-up with respect to microvascular disease with the added benefit of reduced macrovascular events which were not seen during the interventional phase of the trial.[19,21-22,24] Recently meta-analysis looking at cohort and case-control studies showed that SU monotherapy or in combination treatment was associated with higher all-cause and cardiovascular mortality risks when compared to patients receiving non-SU treatment. The authors explain that the potential causes for this could be due to four specific effects of SU therapy namely hypoglycaemia, weight gain, increased proinsulin release and activation of SU receptors on myocardial muscle cells. However they caution that these results should be interpreted carefully not only because data from randomised controlled trials was missing but also because the data had high treatment group heterogeneity.[25] Interestingly these findings were also echoed in another meta-analysis by an Italian group of authors published in the same year.[26] Another important issue that emerges from the UKPDS is the effect of SU on β-cell function. The widely held view that SU are associated with loss of β-cell function is not reproducible in this study as it was found that the percentage mean β-cell function decreased in all groups irrespective of the treatment modality used[19] Thus while treatment with SU has been established over the last 5 decades or so, they should be used judiciously within a multi-factorial risk reduction strategy and treatment tailored according to the patients characteristics (such as age and weight), presence of co-morbidities and other risk factors.[25]

Biguanides

The widely available drug in this class is metformin and its use has been around for the past five decades or so, thus establishing itself as a safe and cost-effective glucose lowering agent such that most guidelines now uniformly advocate its use as a first line agent in the management of overweight or obese type 2 diabetics[1]). Metformin has been classified as an insulin sensitizer but its mode of action has only recently been understood. This involves activation of an adenosine monophosphate (AMP)- kinase enzyme which plays an important part in carbohydrate and lipid metabolism as well as inhibition of mitochondrial respiration leading to inhibition of hepatic glucose production, increased

glucose uptake in contracting muscle, increased fatty-acid oxidation, decreased lipolyisis and enhanced insulin sensitivity without the undesirable side effects of weight gain or hypoglycaemia.[17, 1, 27-29] Metformin, when used as monotherapy has been associated with a reduction in glycated haemoglobin (HbA1c) of between -1.1% to -3% [18](). Two important clinical trials using metformin are the Diabetes Prevention Program (DPP) and the UKPDS. In the DPP, metformin showed a 31% reduction in diabetes incidence over approximately 3 years and this effect was sustained in the ten-year follow up of the DPP suggesting that metformin is a good long-term strategy for diabetes prevention.[27,29-30] In the UKPDS trial, patients randomised to treatment with metformin achieved similar FPG and HbA1c levels to those randomised to treatment with insulin or sulfonylurea however with the added benefit of no weight gain and reduced risk of hypoglycaemia[31]). With respect to complications, in the UKPDS metformin was associated with a 32% lower risk of developing any diabetes related end-point, a 36% lower risk of all-cause mortality, a 42% risk reduction for diabetes-related death and 39% lower risk of myocardial infarction then in the conventionally treated group.[27-31] Moreover, these results were sustained in the 10 year follow-up study albeit differences in glycemic control were blunted after the first year of follow-u [21, 28] This study thus implies that metformin has numerous advantages notably amelioration of macrovascular risk that make it the ideal first choice treatment in obese diabetics [27,30]). Metformin has also been associated with a reduced incidence of the metabolic syndrome (by 17% when compared with placebo) in the DPP.[29] Moreover several meta-analysis have also shown that metformin exerts favourable effects on surrogate markers of CV risk with reduction in fasting and postprandial plasma triglycerides, low density lipoprotein (LDL)-cholesterol, and free fatty acids.[18, 28] Another important landmark of metformin is its effects on heart failure. It has been shown that metformin monotherapy is associated with reduced mortality rates as well as lower hospitalization rates in subjects with heart failure when compared with other anti diabetic drugs.[28, 32] Another important feature of metformin is its role in fertility in women with Polycystic Ovary Syndrome (PCOS) with recent studies showing that therapy with metformin significantly improves pregnancy rates as well as live-birth rates.[28] Metformin has also been associated with anti-neoplastic properties due to its action on AMPK which leads to inhibition of the mammalian Target Of Rapamycin (mTOR) causing inhibition of the cell cycle.[28] Metformin's anti-neoplastic effects range from solid to haematological malignancy, however further research is required in this field. The main documented side effects of metformin include gastrointestinal adverse effects, notably bloating, diarrhoea, flatulence, and abdominal

cramps.[1,27-28] These are usually off-set by introducing metformin at a low dose and increasing it gradually over a few days to weeks. The risk of lactic acidosis is actually very rare with studies showing that this event may occur in situations associated with a tendency for hypoxia or acidosis – such as sepsis or acute heart failure.[27,29] Metformin has also been associated with vitamin B deficiency, however, this too is a rare event but should be sought in patients with macrocytic anaemia, peripheral neuropathy or cognitive impairment.[27,29] With respect to long-term outcome studies on metformin, the UKPDS trial and its 10-year follow up show convincing evidence that metformin is as good as sulfonylureas or insulin on glycemic control and it was the only drug to show a reduction in myocardial infarction rates which persisted in the 10-year post trial follow-up. Meta-analyses have shown that the benefits of metformin on cardiovascular risk were observed in those trials compared with placebo or no therapy (CI 0.64-0.98, p=0.031) but disappeared when compared to active comparator trials suggesting that the cardiovascular protection is due to the improved glycemic control.[22, 33] Taking all this into account metformin is still considered a safe drug and given its low cost is an ideal agent for first line treatment in type 2 diabetes.

Thiazolidinediones

Thiazolidinediones (TZDs) are insulin sensitizing agents and work primarily by activating the peroxisome proliferator-activated receptor (PPAR)-γ leading to increased transcription of genes involved in glucose and lipid metabolism as well as energy balance. One of these is the glucose transporter GLUT-4 which in the presence of insulin is associated with increased glucose uptake. PPAR-γ is also expressed in adipocytes and endocrine signalling from adipocytes results in enhanced adipognensis and decreased fat breakdown (mediated by signalling factors such as free fatty acids and TNF-α) leading to a reduction in liver fat and improvement in insulin sensitivity in liver and muscle.[1, 18, 22] The two available TZDs are rosiglitazone and pioglitazone however, concerns associating rosiglitazone with increased risk of ischemic cardiac events (as already mentioned in the introduction of this article) led to the withdrawal from marketing authorisation of this drug within the EU in 2010 by the European Medicines Agency (EMA) and highly restricted access within the States by the FDA.[1, 10, 12, 18, 34] Over the last few years TZDs have been studied in a number of trials, mostly to assess efficacy and durability of these drugs as well as their long-term outcomes and safety profile. TZDs are comparable to metformin and SU when it comes to glucose lowering, with an approximate HbA1c reduction of between -1.2% to -2.3% over a period of 3 to 12 months.[18, 22] They are not associated with increased risk

of hypoglycaemia and the A Diabetes Outcome Progression Trial (ADOPT), showed that rosiglitazone was associated with a lower cumulative incidence to monotherapy failure at 5 years then did metformin or glyburide suggesting that it had greater glycemic durability over the other drugs.[22, 35] The most common side-effects of these drugs include weight gain, fluid retention leading to peripheral oedema as well as contributing to heart failure, effects on lipid profile as well as an associated increased risk of bone fractures in women in the long term.[1, 22, 34] Weight gain is dose-dependent and more pronounced when TZDs are used with insulin. With respect to their effect on lipid profile and other biochemical parameters, several studies have shown that TZDs are associated with an overall improved lipid profile with respect to HDL-C and TG, however in one study rosiglitazone was associated with significant increases in LDL-C. Other improved cardiovascular parameters include a lowering of highly sensitive (hs)-CRP (anti-inflammatory effect) improved endothelial function and a reduction in procoagulatory state.[18] The side effect of fluid retention with TZDs is widely recognised as is the associated consequence of heart failure, however, their effect on other cardiovascular end-points have been of much debate over the last few years. When looking at individual clinical trials as well as meta-analyses of RCT and observational studies with respect to cardiovascular events, studies on rosiglitazone seem to show an increased risk while studies on pioglitazone show a possible cardiovascular benefit.[10, 36-40] Although the meta-analysis by Nissen and Wolski in 2007 showed that there was a significant increased risk of myocardial infarction, angina and cardiovascular mortality in patients taking rosiglitazone when compared with metformin, SU or placebo, this meta-analysis was heavily criticised for excluding studies with no relevant events and that some trials were too short to assess cardiovascular outcomes.[10, 41] On the other hand the RECORD (rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes) study (which was a multicentre, randomised, open-label non-inferiority trial) showed that rosiglitazone did not increase the risk of a composite end point of MACE when compared with SU or metformin, but it did not rule out an elevated risk of myocardial infarction.[37, 42] The results of this study were also questioned partly in view of the open-label, unblinded design as well as concerns regarding data integrity which led to the FDA to ask for readjudication of the data. Following this, the results which emerged were reassuring that rosiglitazone was not associated with excess cardiovascular risk which eventually led the FDA in 2013 to remove some of the prescribing and dispensing restrictions on rosiglitazone.[15, 43] With respect to pioglitazone, several leading studies have shown a

benefit of this drug on cardiovascular end-points. The notable PROactive (PROspective pioglitazone Clinical Trial In macrovascular Events) randomised controlled study found that in patients with prior evidence of macrovascular disease, pioglitazone was associated with reduced risk of all-cause mortality, myocardial infarction (MI) and stroke.[39] These differences on cardiovascular risk between pioglitazone and rosiglitazone are thought to be brought about by their differences on blood lipid profile – with pioglitazone having better effects on TG and HDL-C.[6] However, the PROactive study did show an increase risk of oedema and congestive heart failure (CHF) in the pioglitazone treated groups when compared with placebo. An important feature not to be missed but is seen in most of the studies mentioned above is the fact that TZDs all have a decreased incidence of stroke.[22] With respect to fracture risk the ADOPT study showed an increased risk of distal bone fractures in women above the age of 60 with more fractures of the upper-limb and foot rather than femoral neck or vertebrae thus stating that care should be taken when prescribing TZDs to female patients with regards to fracture risk.[6] The fact that pioglitazone is both a PPAR-γ and α agonist, it has been linked to possibility of bladder cancer. A recent cohort study showed that short term use of pioglitazone was not associated with increased bladder cancer incidence, however increased risk is seen if treatment is given for more than 2 years.[44] In light of all this one may wonder what is the place of these drugs in treatment strategies for patients with type 2 diabetes. Judicious use on an individualised basis should be the way forward with the hope that ongoing studies may shed more light and provide definitive answers.

'Glinides' (Meglitinides)

This class of antihyperglycaemic agents is also classified as insulin secretagogues, however they have a more rapid onset and shorter duration of action when compared to SU. Their mode of action is similar to SU in that they also bind to the ATP-dependent K^+-channel on cell membranes of pancreatic β-cells, however they exert their actions via a different binding site.[45] The fact that glinides have a short metabolic half-life (< 1 hour) with a fast onset of action makes them suitable as a prandial glucose regulators and hence ideal agents to cover the glucose load associated with meals. Thus, repaglinide allows for flexibility of dosing such that if a meal is missed then so is the corresponding dose and this will in turn lead to a reduced risk of hypoglycaemia. One study on repaglinide assessed glycemic control after patients were randomised to treatment with either this drug or placebo. Use of repaglinide was associated with significantly lower values of HbA1c, fasting and postprandial glucose (FPG, PPG) then placebo and at the end of the study there was a mean group difference in HbA1c of -1.7%. The commonest adverse event

encountered in both treatment groups was mild-to – moderate hypoglycaemia with most of the events in the repaglinide treated group occurring during the dose-adjustment period.[45] In another study, repaglinide was administered to patients uncontrolled on metformin monotherapy. This led to significant reductions in HbA1C and FPG then when repaglinide or metformin were given on their own suggesting synergism when metformin is combined to repaglinide however, there was a significant increase in body weight with repaglinide use.[46] Thus this agent appears to be an ideal component in managing type 2 diabetes as it has desirable characteristics which make it advantageous for use in certain patients such as the elderly (due to decreased risk of hypoglycaemia) or in patients with renal impairment due to its preferential metabolism in the liver.[45]

α-glucosidase inhibitors

This class of drugs suppresses glucose levels by preventing the digestion and absorption of complex gut carbohydrates (starch and sucrose) secondary to inhibition of intestinal α-glucosidase, thus lowering the post- prandial blood glucose level. These agents are used more infrequently nowadays, globally, mostly due to their renowned gastrointestinal side effects of flatulence and diarrhoea.[1, 18, 22] They commonly reduce HbA1c by around -0.6 to -1.3% and are approved for use both as monotherapy and in combination with other anti hyperglycaemic drugs.[18] With respect to weight, a Cochrane review stated that treatment with acarbose (the most commonly used α-glucosidase inhibitor) is associated with around -1.2kg weight loss in patients with prediabetes compared to placebo treatment. Furthermore there were nonsignificant ameliorations in serum lipid levels as well as BP.[18] A commonly cited meta-analysis on acarbose (which included 7 placebo-controlled RCTs) found that this drug was associated with reduced risk of 'any cardiovascular event' and also MI.[47] Another RCT called the STOP-NIDDM assessed the effects of acarbose on development of frank diabetes in patients with impaired glucose tolerance. Here the authors found that decreasing the post-prandial hyperglycaemia was associated with a 49% risk reduction in developing any cardiovascular event with the major reduction occurring in the risk of MI. There was also a statistically significant reduction in BP, even though it must be acknowledged that there were a significant number of patients who discontinued treatment due to side-effects.[48] However in a substudy of the UKPDS, patients randomised to acarbose did not have any significant differences on the risk of major clinical events.[49] Thus, although there is no doubt about the benefits of acarbose on blood glucose lowering, data with respect to cardiovascular risk is still conflicting.

Amylin analogues

Amylin is a peptide hormone which is co-secreted with insulin from pancreatic β-cells following ingestion of nutrients of which secretion is either absent or diminished in diabetic patients. Pramlintide, which is an amylin - receptor agonist is an equipotent synthetic analogue to amylin and has been approved for treatment of both type 1 and type 2 diabetes since 2005. It is thought to exert its glucose lowering effects by suppression of endogenous postprandial glucagon production leading to suppression of postprandial hepatic glucose production, by reducing gastric emptying time as well as induction of satiety through centrally mediated mechanisms leading to a reduction in postprandial glucose levels.[1, 18, 50-51] Treatment with Pramlintide has proven to be efficacious in both type 1 and 2 diabetes with beneficial effects on various metabolic parameters including HbA1c, weight and lipid levels. Since pramlintide is a peptide, it must be administered via the subcutaneous route (like insulin) to avoid degradation by gastrointestinal acids. In type 2 diabetes, it has been approved for use as adjunctive treatment to mealtime insulin in patients with or without concurrent use of SU and/or metformin in patients not achieving adequate glucose control. The observed reductions in HbA1c were around -0.6% and this was not accompanied by any increases in hypoglycaemia as well as proportionately lower total daily insulin doses in type 2 diabetics.[50] With respect to weight, pramlintide was associated with significant reductions in weight (of around -0.5 to 1.4kg) despite reductions in HbA1c, with more pronounced weight loss occurring when baseline BMI > 40kg/m².[8, 50] When it comes to its effect on biomarkers of cardiovascular disease further studies are need to elucidate the effect of pramlintide on the complications of diabetes. However, a study in type 2 diabetics showed significant reductions in total and LDL-cholesterol compared with placebo, with the greatest reductions seen when pramlintide was used at the highest dose.[18, 51] The side-effect profile of pramlintide includes nausea as well as vomiting and anorexia, however all these occur most frequently during initiation of therapy and tend to ease off with continued use. There is also an increased risk of severe postprandial hypoglycaemia occurring within 3 hours of administration of pramlintide, and thus it is advisable for patients to increase the frequency of monitoring in order to detect hypoglycaemia.[51]

Incretin based therapies

The incretin system consists of gut hormones notably glucose-dependent insulinotropic polypeptide (GIP) and glucagon like peptide-1 (GLP-1). GIP is synthesised in the enteroendocrine K cells of the proximal ileum whereas GLP-1 is released from the enteroendocrine L cells of the distal ileum and is rapidly inactivated by the enzyme didpeptidyl peptidase IV

within the circulation. However administration of a dipeptidyl peptidase IV inhibitor prevents degradation of this peptide hormone allowing it to have a more prolonged action. It is thought that these hormones are responsible for the enhanced insulin secretion seen in the postprandial phase. However, in patients with type 2 diabetes this incretin effect is either lost or blunted, with a more pronounced impairment in GLP-1 secretion.[1-2, 16-17, 52-53] Consequently the two available drugs in this category are thus the GLP-1 agonists and the DPP IV inhibitors. Some studies have shown that the insulinotropic effects of GLP-1 are preserved, such that infusion of GLP-1 may completely normalize beta and alpha cell sensitivity to glucose leading to potential novel pharmacotherapy in patients with type 2 diabete.[53]

Glucagon like peptide-1 receptor agonists (GLP-1 RA)

The most commonly available agents in this class are exenatide (twice daily), exenatide extended-release (once weekly) and liraglutide. These agents are peptide hormones and thus need to be injected via the subcutaneous route. As already stated, GLP-1 analogues are responsible for the stimulation of insulin secretion which is regulated by the intracellular glucose level as well and also reduce glucagon secretion from the alpha-cells leading to a robust HbA1c lowering of around 0.8-2.0%. However GLP-1 RA are associated with other beneficial effects including a delay in gastric emptying as well as early satiety resulting in decreased oral intake which may explain the modest weight loss seen with this treatment. GLP-1 RA also exerts positive effects on β-cells, namely it enhances β-cell proliferation and is also capable of inhibiting β-cell apoptosis.[2, 52, 54] Looking at the cardiovascular effects of these drugs it is thought that GLP-1 RA exert beneficial effects on the cardiovascular system due to the presence of GLP-1 receptors in the heart and this happens independent of glucose control. Studies have shown that administration of GLP-1 resulted in improvement in the ejection fraction and both global and regional wall indices in patients who had had an acute myocardial infarct with associated low left ventricular ejection fraction, and that exenatide treatment was associated with lower rates of CV disease event rates when compared with other agents.[2, 52-53] It is also well known that GLP-1 RA have a beneficial effect on the metabolic profile in type 2 diabetics. Exenatide therapy led to reductions in total cholesterol and triglycerides as well as reductions in systolic and diastolic blood pressure after 16 weeks of therapy.[2, 18, 52] With respect to weight loss all studies report a positive effect of GLP-1RA on weight with a reduction in BMI by around – 0.44kg/m² when compared to placebo or insulin therapy.[54-55] With respect to adverse effects, GLP-1R analogues have been associated with lower risk for hypoglycaemia when administered as monotherapy or when compared to insulin.[52, 55-56] Other adverse side effects include an increased incidence of gastrointestinal effects including nausea, vomiting and diarrhoea when compared to placebo or insulin therapy.[52, 54-55] Regarding long term cardiovascular outcome studies, one meta- analysis did not find any evidence to suggest an increase in cardiovascular morbidity when compared to placebo or other drugs.[57] There have been reports of short-term risk of acute pancreatitis as well as potential for long-term risk of chronic pancreatitis in patients taking this class of drugs, however, patients had other potential causes for this and the data available to date does not convincingly prove this risk. Even so, the FDA asks for vigilance when prescribing these drugs to patients and to report any such cases.[58] Concerns have also been raised on GLP-1R analogues with regards to their propensity to cause proliferative changes in rodent thyroid C cells including C-cell hyperplasia, adenomas, and medullary thyroid carcinomas although data in human subjects did not show any elevations in serum calcitonin levels and there have been no case reports describing medullary thyroid carcinomas in patients receiving GLP-1R agonist treatment. However more long term trials need to be available concerning the above issues as till now the data is not robust enough.[52] Finally there is limited data with respect to mortality with GLP-1 analogues, however studies to date suggests that there is no increased risk during treatment with such drugs.[59]

Dipeptidyl peptidase-4 (DPP-4) Inhibitors

This class of drugs are also part of the incretin system of gut hormones. These work by preventing breakdown of endogenous GLP-1 and GIP leading to enhanced circulating concentrations of these hormones which in turn lead to glucose dependent insulin secretion as well as inhibition of glucagon secretion. The four widely available agents are all orally active and include sitagliptin, vildagliptin, saxagliptin and linagliptin.[1-2, 18, 22, 52, 60] Studies have shown that these drugs are generally well tolerated, reduce HbA1c by around -0.8% are weight neutral and by themselves are not associated with hypoglycaemia, thus the FDA has approved them for both monotherapy as well as in combination with other anti-hyperglycaemic drugs in the treatment of type 2 diabetic patients.[1, 18, 52, 58, 60] Their pharmacodynamic and pharmacokinetic properties are what make DPP-4 inhibitors attractive for use especially in certain groups of people. The fact that they cause glucose dependent insulin secretion and thus decreased risk of hypoglycaemia when compared to SU, as well as the fact that saxagliptin and vildagliptin are metabolised by the liver implies that they may be used in elderly patients or patients with renal failure. They also enjoy good overall tolerability (when compared with metformin they are associated with lower

gastrointestinal adverse effects) and are not associated with the weight gain seen with SU and TZD use.[18, 22, 59, 61] Moreover they are also associated with positive effects on surrogate parameters of cardiovascular risk. Studies have shown a favourable trend with regard to triglyceride, HDL-C and LDL-C levels[52-53] and emerging data from recent studies and meta-analysis also show that DPP-4 inhibitors have a positive effect on the cardiovascular system. One study has shown that administration of sitagliptin to patients with coronary artery disease led to increased ejection fraction and improved contractile function of the ischemic areas.[62] Also, it has been shown that DPP-4 inhibitors reduce blood pressure in a number of studies and in animal studies gliptins seem to exert a positive effect on the evolution of heart failure which was independent of blood glucose control.[63] When looking at the effects of DPP-4 inhibitors on cardiovascular events two recent meta-analyses state that DPP-4 inhibitor reduce the risk of major adverse cardiovascular events – in particular myocardial infarction as well as decreased all-cause mortality and are thus reported as having a safe profile from a cardiovascular standpoint which is not seen with certain other anti-hyperglycaemic agents.[64-66] Several other large-scale trials are in the making specifically designed to assess the cardiovascular effects of each gliptin. One such study, the SAVOR-TIMI 53, has recently published data which states that saxagliptin found no excess or reduction in rates of ischemic events. It was noted, however that patients randomised to the saxagliptin arm had increased rates of hospitalisation for heart failure, which warrants further investigation.[67] With respect to the association of DPP-4 inhibitors with the risk of pancreatitis, pancreatic cancer and C-cell proliferation, data is very minimal and not uniformly reproducible in human studies thus further data is required in this area.[59] Thus the literature available implies that these novel drugs are proving to be pivotal in the treatment of type 2 diabetes, and that the benefits of DPP-4 inhibitor therapy by far outweigh the risks, making them key agents in the therapeutic armamentarium for type 2 diabetes.

Insulins

Insulin is the mainstay of treatment in type 1 diabetes and is an option in type 2 diabetes when other hypoglycaemic agents fail to maintain adequate blood glucose levels.[16-17, 34, 52, 58] With respect to other antihyperglycemic agents, insulin delivers superior glucose reductions and this is consolidated by the fact that it offers up to 4.9% reductions in HbA1c levels.[18] There are various different types of insulins available depending either on the source (animal, human or analogue insulins) or their action profile (short-, intermediate- and long-acting insulins).[17] Short acting insulins include those with a rapid onset and short duration of action such as soluble insulin (Humulin S®) or the newer analogues (such as aspart or gluisine) and notably these are used to cover prandial glucose excursions.[16-17, 52] Intermediate acting insulin such as isophane insulin (neutral protamine Hagerdon [NPH] has an onset of action within 1-2 hours and lasts for around 8-14 hours whereas long acting insulins (notably the analogues glargine or detemir) have a longer duration of action of around 22-24 hours and provides a consistent release of insulin during the day reminiscent of natural basal insulin release without any peaks of activity.[68-69] Insulin therapy in type 2 diabetes can be administered in different ways. Usually, insulin initiation takes the form of bedtime insulin using either isophane insulin or a once daily long-acting insulin analogue (such as glargine) and step-up treatment with either bi-daily injection of premixed biphasic insulin or short-acting insulin before meals (in a basal –bolus fashion) occurring if adequate glucose control is still not achieved.[34, 52] In the United Kingdom Prospective Diabetes Study (UKPDS) tight glycemic control with a combination of insulin and oral hypoglycaemic agents was associated with lower HbA1c values then those in the conventionally treated group and also had significantly decreased risk of microvascular complications, and furthermore, in the 10 year post trial follow up there was also a significant reduction in myocardial infarctions thus implying that insulin use is indispensable in type 2 diabetes and is also effective at preventing onset of complications. However, these results came at the expense of an increase in the rate of both hypoglycaemia and weight gain.[20-21, 69-70] With the development of long acting insulin analogues there is an improvement the insulin profile such that when injected subcutaneously there is a constant release of insulin into the bloodstream and without any peaks in insulin concentration over 24 hours (as opposed to isophane insulin) thus providing the basal component in the basal-bolus regime with the added benefit of once daily dosing.[69, 71] Thus, these inherent pharmacokinetic and pharmacodynamic properties of insulin analogues have been thought to be responsible for the decreased risk of hypoglycaemia especially nocturnal hypoglycaemia.[69, 71] Several studies have shown that long-acting insulin analogues achieve comparable glucose control to NPH insulin with lower rates of symptomatic and nocturnal hypoglycaemia with detemir also showing significantly less weight gain.[34, 68-69, 72-73] With respect to long term outcome trials, in the 10-year post-trial follow-up of the UKPDS, patients subjected to an intensive treatment regime continued to show a reduction in microvascular risk by 15% as well as reductions for any diabetes-related end point and death from any cause (9% and 13% respectively) even though the differences in HbA1c levels attained were lost after the first year. This 'legacy-effect' implies that early aggressive glycemic

control is associated with a sustained reduction in microvascular risk and in any diabetes-related end point. Furthermore, there was also a significant reduction in risk of either myocardial infarction or death from any cause which was not seen during the interventional phase of the trial.[18, 21] Finally, the UKPDS also investigated the concerns that exogenous insulin may potentially be harmful by enhancing atheroma formation due to the high insulin concentrations. This was unproven in the study since patients assigned to intensive insulin treatment did not have an increase in myocardial infarctions suggesting that inherent treatment with insulin did not pose a cardiovascular risk.[20] There have also been insinuations that high concentrations of insulin and thus increased binding of insulin to IGF-1 receptors may promote tumorigenesis. Insulin glargine has increased potency at the IGF-1 receptor then regular human insulin, however studies in rats and mice as well as a recent review of glargine-treated patients did not support an increased risk of carcinogenicity.[69-70]

Conclusion

Thus as one can see the clinician has at his disposal a number of antihyperglycemic agents available for the management of hyperglycemia. As with all chronic medical conditions an individualised approach within a comprehensive care framework should be the way forward with many regulatory bodies advocating pharmacotherapy to be used as an adjunct to lifestyle modification. It is now universally acknowledged that management of diabetes does not only involve lowering of blood glucose but also the management of other cardiometabolic parameters such as serum lipid levels, blood pressure and platelet aggregation which have all been associated with adverse cardiovascular events. It is understood that most patients will eventually require more than one antihyperglycemic agent for optimum control of their diabetes, and thus the risks and benefits of each drug should be considered when prescribing a treatment regime as should the individual patient characteristics (such as age, weight, presence of comorbidities, risk of hypoglycaemia and so forth) in order to be successful at achieving optimum glycemic control without the occurrence of undesirable effects.

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