Review Article

Anti-diabetic medications: How to make a choice?

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ABSTRACT

Diabetes is the third commonest chronic illness in children following asthma and epilepsy. More recently the overall prevalence of diabetes in children and adults continued to increase dramatically. In children, this has partially been contributed to by the pandemic of obesity. Understandably, this posed an economic burden on health authorities and countries dealing with significant morbidity of the disease with potentially serious complications. In parallel to this, more therapeutic discoveries expanded the list of choice for available medications. We hypothesize that specialist clinicians are requested by an authority to submit a report of prioritization for anti-diabetic drugs. The authority new policy is to purchase for only three of anti-diabetic medications among a long list of old and new drugs. We gave a recommendation here in response to this request based on different properties of these medications and also based on the largest known clinical trials in the field. Some may have a different choice for a third medication besides insulin and metformin and physicians in many clinical settings may have a choice of more than three at a time. However, we, at least, provide here a thorough review of these drugs, their mechanistic of action, benefits and side effects to facilitate a better choice for individual patients according to underlying pathophysiological cause, other medical needs and tolerance to different medications. Paediatricians are increasingly managing adolescents with type 2 diabetes these days. Hence, we wrote this review as a quick reference guide to anti-diabetic medications to which they might be less familiar.

Keywords:

Classes, diabetes, glucose, hyperglycaemia, incretin, insulin, medications, metformin.

INTRODUCTION

The International Diabetes Foundation (IDF) estimates a prevalence of 366 million adults with diabetes worldwide in 2011 that was estimated to rise, by 2030, to 552 million [1]. However, a sharper jump has occurred to 395 million in 2014 with a rate of rise of 93% in Africa and 85% in the Middle East and North Africa, which increased the prevalence to already 425 million in 2017. Understandably, the cost of treatment of the disease and its complications has also increased significantly putting an economic

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burden on healthcare systems. Since Type 2 diabetes (T2D) remains a leading cause of cardiovascular disorders (CVD), severe eye, neurological and renal complications and also hospitalisations, hence, effective planning of management is of a paramount importance [2]. There are many medication classes and treatment regimens for T2D. For example, in the United States, 11 classes of medications are approved for this purpose; 9 of these classes are available since 1995 [3]. Most patients with T2D will require 2 classes of diabetes medications simultaneously to achieve and maintain reasonable glycaemic control (GC) [4]. The main goals of Anti diabetes therapy are to reduce symptoms of hyperglycaemia and to reduce the risk of long-term complications of diabetes. GC, using glycosylated haemoglobin (HbA1c) as a marker, is known to reduce the risk for microvascular complications, including retinopathy and neuropathy [5-7]. Patients with T2D have a higher risk of mortality from CVD [8]; however, intensive GC may not reduce that risk in all age groups, and at all stages of T2D [9,10]. Type 1 diabetes (T1D) is due to autoimmune destruction of beta cells of the pancreas in most of the cases requiring exogenous insulin [1]. Thorough information about medical and cost effectiveness and safety of different anti diabetic medications is crucial to help well-informed clinical decision making between choices [11].

We put a hypothetical scenario of a health authority requesting us as dialectologists to write a report providing conclusions on different anti-diabetic medications to guide a policy of limited purchase for three of these medications. The authors admit that a choice between incretin based therapy and sulphonylureas could be so difficult in terms of the wide range of use of each of these medications and from cost effectiveness point of view. A choice could also be difficult in different patients with variable age groups and individual needs. However, our report only focused on the scientific aspect of prioritization using a generic approach to the task and the authority would consider further reporting on medications costs in order to make a final selection of a temporary policy that would be re-evaluated in few years time. We thought such a scenario would make us more critical and comparing between wide ranges of different families of anti-diabetic medications; namely for type 2 diabetes.

This report (review) is meant to provide some reference guidance to physicians, especially paediatricians who are increasingly treating children with type 2 diabetes nowadays, to facilitate better selection of medications, to which paediatricians are less familiar, according to individual patients needs.

Report outlining conclusions about individual anti-diabetes medications (10 classes)

Nowadays, the management of T2D has become increasingly complex and, to some extent, controversial, with the wide range of available anti-diabetes medication [2]. Although the ideal therapy to achieve targeted GC for patients with diabetes is lifestyle modification, this usually requires supplementation with anti-diabetic drugs [12].

A multi factorial risk reduction framework for diabetic patients is required. This arises from the fact that T2D patients are at higher risk of CVD; therefore, more greater benefits are expected from intensive management of cardiovascular risk factors, such as blood pressure, lipid therapy and anti-platelet treatment [2].

This report has been written incorporating the best available evidence about 10 classes of anti-diabetic medications, and it includes:

- A brief overview of the pathogenesis of diabetes and where target therapies are directed.
- A review of the classes (Table 1) [2].
- A summary of data from the key trials.
- Summary and recommendation.

Overview of the pathogenesis [2]

- Hyperglycaemia is the net result of glucose influx exceeding glucose outflow from the plasma compartment.
- Increased hepatic glucose production is the direct cause of hyperglycaemia in the fasting state.
- In the postprandial state: the cause is either or combination of insufficient suppression of this glucose output and defective insulin stimulation of glucose disposal in target tissues, mainly skeletal muscle.
- Abnormal islet cell function is a key feature of T2D. Insulin kinetics, such as the ability of the pancreatic beta cell to release adequate insulin hormone parallel

to rising glycaemia, are profoundly compromised. This functional islet incompetence is the main quantitative determinant of hyperglycaemia [13] and progresses over time.
- In addition, pancreatic alpha cells, in T2D, hyper secrete glucagon, which further enhances hepatic glucose production [14].
- Islet cell dysfunction can be reversible if the burden from beta cells is relieved [15].
- Abnormalities in the incretin system. Though it is unclear whether this is a cause or effect [16].
- Insulin resistance is a prominent feature in most T2D patients, especially the obese.

Anti-hyperglycaemic agents are directed at one or more of the pathophysiological defects of T2D, or modify physiological processes relating to appetite or to nutrient absorption or excretion [2].

Ultimately, T2D is a disease that is heterogeneous in its pathogenesis, which should be considered when making a choice of treatment.

KEY CLINICAL TRIALS

HbA1c remains a major focus of therapy because the risk of microvascular and macrovascular complications is directly related to GC [17]. Prospective RCTs have documented reduced rates of microvascular complications in T2D patients treated to lower glycaemic targets (Table 2) [2,12].

UK Prospective Diabetes Study (UKPDS) [2,18,19]

Patients with newly diagnosed T2D were randomised to two treatment arms. In the conventional group, the mainstay of treatment was the lifestyle intervention with the addition of pharmacological therapy only if hyperglycaemia became severe. In the more intensive treatment arm, patients were randomly assigned to either a sulfonylurea or insulin, with a subset of overweight patients randomised to metformin. The overall HbA1c achieved was 0.9% lower in the intensive treatment group compared with the conventional treatment arm (7.0 vs 7.9% [53 vs 63 mmol/mol]). There was a reduction in the risk of microvascular complications with intensive therapy in association with this difference in GC. There was a trend towards reduced rates of myocardial infarction (MI) in this group but was not statistically significant [18]. However, a statistically significant fewer metformin-treated patients experienced MI, diabetes-related and all-cause mortality [20], despite only 0.6% lower difference in a mean HbA1c from the conventional policy group.

In the UKPDS 10 year follow-up, There statistically significant benefits for those been on the intensive policy including: the CVD endpoints and total mortality in those initially assigned to sulfonylurea/insulin, and persistence of CVD benefits in the metformin-treated patients [21], in spite of the fact that the mean HbA1c levels between the groups returned to become statistically non different after the conclusion of the trial.

Similar short and long term benefits of intensive GC were noted in type 1 diabetes patients in the **Diabetes Control and Complications Trial (DCCT)** and **the Epidemiology of Diabetes Interventions and Complications (EDIC)** study [22, 23].

In 2008, three shorter-term studies reported the effects of two levels of glycaemic control on cardiovascular endpoints in middle and old-aged patients with T2D who were at high risk for CVD. These are:

- Action to Control Cardiovascular Risk in Diabetes [ACCORD] [24].
- Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation [ADVANCE] [25].
- Veterans Affairs Diabetes Trial [VADT] [26].

ACCORD and VADT aimed for an HbA1c <6.0% (<42 mmol/mol) using combinations of oral agents and insulin. ADVANCE aimed for an HbA1c ≤6.5% (≤48 mmol/mol) using a less intensive approach based on the sulfonylurea gliclazide.

None of the trials demonstrated a statistically significant reduction in the primary combined cardiovascular endpoints. In fact, a 22% increase in all cause mortality with intensive therapy was observed in ACCORD, mainly driven by CVD. The cause of these findings remains uncertain, although hypoglycaemia may be responsible for the adverse outcomes since the rates of hypoglycaemia were threefold higher with the intensive policy. However, the adverse event could also be as a result of other factors such as more weight gain, or simply the greater complexity of therapy.

Table 1- A review of the 10 different classes of anti-diabetic medications.

Class	Compounds	Mechanistic	Benefits	Side effects/ Disadvantages
Insulins	• Human NPH • Human • Regular • Lispro • Aspart • Glulsine • Glargine • Detemir • Pre mixed • Several types	• Activates insulin receptors. • ↓glucose disposal • ↑hepatic glucose production	• Universally effective • Theoretically unlimited efficacy • ↓microvascular risk.(UKPDS) • Variable cost	• Hypoglycaemia • Weight gain • Mitogenetic effect • Injectable • Training requirements • Stigma (for patients)
GLP-1 agonists (e. exenatide (BYETTA) Liraglutive (VICTOSA)	• Exenatide • Exenatide extended release • Liraglutide	• Activates GLP-1 receptors • ↑ Insulin secretion (glucose-dependent) • ↓ Glucagon secretion (glucose-dependent) • Slows gastric emptying • ↑ Satiety	• No hypoglycaemia • Weight reduction • ? Potential for improved beta cell mass/function • ? Cardiovascular protective actions	• Gastrointestinal side effects • (nausea/vomiting) • ? Acute pancreatitis • C cell hyperplasia/ medullary thyroid tumours in animals • Injectable • Training requirements • High cost
Biguanides	Metformin	• Activates AMP-Kinase • ↓hepatic glucose production	• Extensive experience • No weight gain • No hypoglycaemia • Likely ↓CVD events (UKPDS) • Low cost	• Gastrointestinal side effects (diarrhoea, abdominal cramping) • Lactic acidosis risk (rare) • Vit B12 deficiency Multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc.
Sulphonylureas	2nd generation: • Glibenclamide/ glyburide • Glipizide • Gliclazide • Glimepiride	• Closes KATP channels on beta cell plasma membranes • ↑Insulin secretion	• Extensive experience • ↓Microvascular risk (UKPDS) • Low cost	• Hypoglycaemia • Weight gain • ? Blunts myocardial ischaemic preconditioning • Low durability
'Glinides' (Meglitinides)	• Repaglinide • Nateglinide	• Closes KATP channels on beta cell plasma membranes • ↑Insulin secretion	• Postprandial glucose excursions • Dosing flexibility	• Hypoglycaemia • Weight gain • ? Blunts myocardial ischaemic preconditioning • High cost
Thiazolidinediones	• Pioglitazone • Rosiglitazone	• Activates the nuclear transcription factor PPAR-γ • ↑Insulin sensitivity	• No hypoglycaemia • Durability • HDL-C • ↓Triacylglycerols (pioglitazone) • ? ↓CVD events (ProACTIVE, pioglitazone)	• Weight gain • Oedema/heart failure • Bone fractures • ↑LDL-C (rosiglitazone) • ? ↑MI (meta-analyses, rosiglitazone) • ? ↑Bladder cancer (pioglitazone) • High cost
'Gliptins' (DPP4 inhibitors)	• Sitagliptin • Vildagliptina • Saxagliptin • Linagliptin • Alogliptin	• Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations • ↑Insulin secretion (glucose-dependent) • ↓Glucagon secretion (glucose-dependent)	• No hypoglycaemia • Well tolerated • No weight gain	• Generally modest HbA1c efficacy • Urticaria/angioedema • ? Pancreatitis • High cost
α-glucosidase inhibitors	• Acarbose • Miglitol • Vogliboseb,d	• Inhibits intestinal α-glucosidase • Slows intestinal carbohydrate digestion/ absorption	• No hypoglycaemia • ↓Postprandial glucose efficacy Excursions • ? ↓CVD events (STOP-NIDDM) • Non-systemic	• Generally modest HbA1c Gastrointestinal side effects (flatulence, diarrhoea) • Frequent dosing schedule • Modest cost

Amylin analogues	• Pramlintide	• Activates amyline receptors • Reduces glucagon secretion • Slows gastric emptying • Increase satiety	• Decrease postprandial glucose excursions • Weight reduction	• Generally modest HbA1c efficacy • Gastrointestinal side effects • Hypoglycaemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule • High cost
SGLT2 inhibitor	• Gliflozins • Canagliflozin, • Dapagliflozin • Empagliflozin	• Block sodium/glucose cotransporter 2 (SGLT2) in renal tubules • Reduces glucose reabsorption in the kidney • Decease in serum blood glucose level	• Decrease weight • Improve A1c • Lower BP • Can have good impact on decreasing CVS events in patients with established cardiovascular diseases • Low risk of hypoglycemia	• Should monitor renal function while on SGL2 inhibitor • Generally well tolerated • May increase risk of genital fungal infection and UTI • May increase risk of euglycemic DKA

The collective evidence from these trials as well as UKPDS suggests that patients without overt CVD, with shorter duration of disease, and lower baseline HbA1c, benefited from the more intensive strategies. Though, modest improvements in some microvascular endpoints in the 3 short-term trials were also demonstrated. This clearly suggests that although the practice of treating to a reasonable target of HbA1C (<7%) should continue, one should carefully focus on avoiding hypoglycaemic episodes, i.e not to treat to the lowest possible GC, in those with risk factors of CVD, with longer duration of illness and with considerably high baseline HbA1c.

Last but not least, although no benefits shown in stroke or total mortality a meta-analysis of cardiovascular outcomes of these trials suggested that every reduction of approximately 1% in HbA1c may be associated with a 15% relative risk reduction of 15% in non-fatal MI [26].

Table 2- Summary of major clinical trials.

Study	Microvascular	Macrovascular	Mortality
UKPDS (Type 2)	Decreased *	Decreased *	Decreased *
DCCT/EDIC (Type 1)	Decreased *	Decreased *	Equivocal *
ACCORD (Type 2)	Unclear	-	Increased
ADVANCE (Type 2)	Decreased	-	-
VADT (Type 2)	Decreased	-	-

*= Long-term outcome.

Subsequently, other key trials have also been reported including:

- **ADOPT (A Diabetes Outcome Progression Trial)**: a large, double-blind RCT involving 4360 patients followed for a median of 4 years, in which patients were randomly assigned to receive metformin, rosiglitazone, or glyburide (27). Time to monotherapy failure was assigned as the primary outcome of the trial. The same rates of all-cause mortality, CVD mortality and morbidity, and stroke in the 3 study groups were reported. Compared with the trial data, observational studies had conflicting results showing that Metformin was associated with a lower risk for all-cause mortality and CVD disease mortality and morbidity than the sulfonylureas [28].
- **RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes)**: the only study with cardiovascular mortality as its primary outcome, reported that the combined groups of rosiglitazone plus metformin and rosiglitazone plus sulfonylurea were non inferior to metformin plus a sulfonylurea for the primary end point of hospitalization or death from CVD (hazard ratio, 1.08 [CI, 0.89 to 1.31]) over a mean follow-up of 5.5 years [29].
- However, Rosiglitazone has been subsequently

removed from the US and EU markets because of its CV serious side effects. After that, there are 3 cohort studies presented conflicting results, but no RCTs directly compared rosiglitazone with pioglitazone for CVD outcomes [28].

- **The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) [30]**: assessed the effect of pioglitazone, with anti-inflammatory and vascular properties, on the secondary prevention of macrovascular events in T2D. It was a double-blind randomized study in patients with T2D who had macrovascular disease; Patients on pioglitazone were randomized with those on placebo in addition to existing therapy. The primary end point was the time from randomization to occurrence of a new macrovascular event or death. Follow-up was estimated to span 4 years. Patients taking pioglitazone had a 10% relative risk reduction in the primary composite end point of all-cause death, MI, cardiac interventions, stroke, major leg amputation, or leg revascularization [30]. A setback, however, for pioglitazone, was a higher rate of bladder malignancies diagnosed in the patients taking pioglitazone [30]. Though in a longer follow up (six-year results) of the PROactive study, no more likely cases of bladder cancer or any other malignancy has been noted and the macrovascular events are neither higher nor lower among patients taking pioglitazone [31,32].
- **Other trials**: As we write this report, the number of ongoing clinical trials, at our institution and others in Saudi Arabia are recruiting some patients in them, to explore the efficacy and safety of different combinations of the above medications, such as Inceretin based therapy and SGLT2 in children with type 2 and also type 1 treatment. These are very likely to provide soon new evidence and perspectives in the field.

Summary & recommendations to the Healthcare commissioners

In summary:

- In general, glucose-lowering medications have a favourable risk/benefit profile in patients with type 2 diabetes.
- The glucose lowering effect and ability to lower HbA1c is not much different between these different medications. Therefore, to make a good choice: Less side effects, other side benefits, favourable mechanism of action which can hopefully lead to better long term outcome as well as cost effectiveness should be carefully considered.
- Hypoglycaemia is the most common associated adverse event with the use of these medications, and it may be associated with increased mortality in high risk group. It is more common among patients receiving sulfonylureas or insulin therapy.
- The side effects of lactic acidosis (Metformin), pancreatitis (Incretin based medications), and hypersensitivity reactions (Sitagliptin), appear to be rare.
- Increased risks of massive oedema, congestive heart failure and bone fractures in thiazolidinedione (Pioglitazone) treated patients are of concern and should limit a free use of these medications.

Recommendation

From the above discussion and summary, and as there is an intention to limit the diabetes treatment prescriptions to 3 classes of drugs, we will recommend the following 3 classes:

- Insulins (different brands).
- Beguanides (Metformin).
- Incretin based therapy – Both work through incretin receptor signalling. These are "Gliptins" (DPP4 inhibitors) and "incretin mimetics" (GLP-1 agonists).

Though, in an era of a patient centred care, one would expect a limited availability and supply of other choices should they be to be suggested by individual scenarios in special circumstances.

Reasons for supporting the continued prescription of the 3 above agents

Insulin is the only, so far, treatment available for pure T1D. Metformin is considered, even at international levels, as the initial drug of choice for treating T2D, as shown in the above data from key clinical trials, in terms of efficacy and safety and the favourable long-term outcome. In addition to that:

Metformin

The Diabetes Prevention Program, a 2.8-year randomized clinical trial, found a reduction of incidence of diabetes by 58% with intensive lifestyle modification and by 31% with Metformin therapy for adults with high-risk [33]. In addition to insulin, many patients with progressive T1D may be using dimethylbiguanide and other oral ant diabetic medications traditionally used for the treatment of T2D due to the associated high BMI and insulin resistance, which is nowadays known as "double diabetes" [34].

Most monotherapies reduce haemoglobin A1c levels by similar amounts and metformin causes more diarrhoea than thiazolidinediones [11]. But, metformin therapy [11]:

- Reduces body weight compared with thiazolidinediones and sulfonylureas
- Decreases low-density lipoprotein and cholesterol levels compared with pioglitazone, sulfonylureas, and DPP-4.
- Causes less hypoglycaemia than sulfonylureas.
- Has shown positive long term outcome, and most of the trials used it as alone or in combination therapy (so a lot of efficacy and safety as well as long term data are available).

Insulin

T1D is caused by autoimmune destruction of beta cells of the pancreas and results in the reduction or elimination of biological insulin production requiring exogenous insulin [1]. Patients with T2D may require insulins if hyperglycemia cannot be controlled with diet or oral medications, especially after longer standing T2D [1].

Reasons in favour of using incretin based therapy

We think insulin and metformin are not debatable choices. The debatable choice will, as expected, be the in third one between incretin based therapy (DDP-4 inhibitors or GLP-1 agonist) and Sulphonylurea. The latter is less expensive and has longer history with T2D and both achieve near similar GC. Therefore in a quick glance, one would choose sulphonylurea. However, on critical analysis and applying a multifactorial risk reduction framework in the management of patients with T2D aiming at an ultimate goal of reducing mortality rate, I will recommend the use of incretin based therapy, namely DPP-4 inhibitors, which is less costly than GLP-1 agonists, with less side effects and may be more tolerable being in oral form.

For all newly approved drugs there is a lag period of several years before results from longer-term studies become available. Even for the traditional antidiabetic medications (e.g., sulphonylureas), this level of evidence has not been provided despite being in the market since the 1970s (e.g. glibenclamide) [35].

From cost point of view, one should look at the overall cost in a cost/benefit assessment.

Both DPP-4 inhibitors and incretin mimetics (that work through incretin receptor signalling) [35]:

- Have shown efficacy in terms of reducing fasting and postprandial glucose concentrations and glycated haemoglobin [36].
- They are not inferior in lowering HbA1c and fasting glucose concentrations when compared to sulphonylurea (Glipizide) in combination with metformin [37].
- Not associated with hypoglycaemias like sulphonylureas.
- "No weight gain" benefit [36]. Incretin based drugs are the only classes of insulinotropic drugs that do not promote weight gain.
- From analyses of phase 3 studies and post-marketing surveillance over 1–2 years after receiving approval, both classes overall have to be considered safe. Absence of potentially severe side effects and life threatening adverse events.
- Potential cardiovascular benefits [38, 39].
- Treatment with DPP-4 inhibitors has improved b-cell numbers and function in animal models, and also seen in human studies of T2D [40, 41].

Moreover, a very recent review that highlights the advantages of the above medications supporting our prioritization has been published this year [42].

Last but not least, this report is meant to guide a policy of prioritization between different classes of antidiabetic medications. Yet, each of these medications is a useful compound that might be required for use

in individual patients with special needs. We suggest that, in a controlled way, practising physicians should always have access to "Non- formulary" as well as "Out of policy" medications for selected cases.

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