

Update on Pharmacological Management in Type 2 Diabetes

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My AGENDA

- Targets For Glycaemic Control
- Glucose - Lowering Drugs
- Algorithm For Glucose- Lowering In Type2 Diabetes

Targets For Glycaemic Control



**World Health
Organization**

- Diabetes is a chronic disease, which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. This leads to an increased concentration of glucose in the blood (hyperglycaemia).
- Type 1 diabetes (previously known as insulin-dependent or childhood-onset diabetes) is characterized by a lack of insulin production.
- Type 2 diabetes (formerly called non-insulin-dependent or adult-onset diabetes) is caused by the body's ineffective use of insulin. It often results from excess body weight and physical inactivity.

- The immediate purpose of lowering blood glucose is to provide relief from symptoms (thirst, polyuria, nocturia, and blurred vision).
- Thereafter ,the aim is to prevent micro vascular complications (retinopathy , nephropathy , neuropathy) and macro vascular complications (myocardial infraction, stroke, and peripheral arterial disease).
- The effects of glucose – lowering therapies on cardiovascular morbidity and mortality are therefore of major importance and not necessarily related to glucose-lowering unfortunately, the majority of clinical trials to date have focused narrowly on glucose control (as assessed by HbA1c concentrations), and on the risks of weight gain and hypoglycaemia.

- Glucose control deteriorates continually with time in most people with type 2 diabetes-it is **not a chronic stable condition**.
- This is known to be due to **progressive failure of insulin secretion** .
- Accordingly therapy has to **be stepped up** with time, one drug added to another until such as time as only exogenous insulin replacement will suffice.
- Reducing HbA1c levels ranging from 6.4% to 8.0% is associated with a reduction in micro vascular and macro vascular complications in patients with type 2 diabetes .

- The American College of Physicians (ACP) 2008
advise setting hemoglobin A1c (HbA1c) goals around 7%.
- American Family Physician 2006
Recommendations for Adults with Diabetes

Glycemic control
A1C level less than 7 percent*
Blood pressure less than 130/80 mm Hg
Peak postprandial capillary plasma glucose level less than 180 mg per dL (10 mmol per L)
Preprandial capillary plasma glucose level 90 to 130 mg per dL (5.0 to 7.2 mmol per L)

- American Diabetes Association 2006

- The hemoglobin A_{1c} goal for patients in general is less than 7% .
- Also recommends hemoglobin A_{1c} less than 6% may reduce morbidity in patients with severe acute illness, perioperatively , after myocardial infarction ,and in pregnancy

- **Canadian Diabetes Association(2003)**

Be targeted to achieve a hemoglobin A_{1c} level of 7.0% or lower.

- **Institute for clinical Systems Improvement(2004)**

A hemoglobin A_{1c} level less than 7.0% .

- **National Institute for Health and Clinical Excellence(2002)**

A hemoglobin A_{1c} between 6.5% and 7.5%.

- **Scottish Intercollegiate Guidelines Network(2001)**

The target should be around 7.0%

- **Veterans Health Administration(2003)**

The hemoglobin A_{1c} target should be 7%

- **American Geriatrics Society (2003)**

The hemoglobin A_{1c} status is 7% or lower

- Several studies have assessed the benefit of intensive glycaemic control on cardiovascular risk and other outcomes , in particular by achievement of predefined HbA1c targets ranging from 6.4% to 8.0% .
- Studies that were not primarily designed to compare intensive glycaemic control versus a less intensive strategy were not considered to contribute to the evidence base informing optimal glycaemic targets.

The United kingdom prospective diabetes study 33 (UKPDS 33)

examined the effects of sulphonylureas , metformin and insulin over a median 10 year period in people with newly diagnosed diabetes . Mean HbA1c was lowered to 7.0 % in the intensive arm compared to 7.9 % in the conventional treatment group . In UKPDS 34, HbA1c was lowered to 7.4% in a subgroup of overweight people who were randomised to metformin compared with 8.0% in the conventional therapy group .

The Action in Diabetes and Vascular Disease : Preterax and Diamicron MR controlled

Evaluation (ADVANCE) study used modified release gliclazide (MR) then increased metformin , thiazolidinedione , acarbose and insulin (initial basal with prandial added as required) to reduce HbA1c to a mean of 6.5% compared with a mean of 7.3% from a baseline of 7.5% by aiming for a target of <6.5% as compared with standard care. Mean duration of Diabetes in this trial was 7.9 years .

The Action to control Cardiovascular Risk in Diabetes (ACCORD) study used the standard range of presently available therapy (including sulphonylureas, metformin , thiazolidinediones , insulin , DPP-4 inhibitors and exenatide) to reduce HbA1c rapidly to a mean of 6.4% compared with a mean of 7.5% from a baseline of 8.3% by aiming for a target of 6.0% as compared with a target of 7.0% to 7.9%. Mean duration of diabetes in this trial was 10 years .

The Veterans Affairs diabetes trial

(VADT) compared an intensive treatment strategy (maximal doses of metformin and rosiglitazone for people with BMI > 27 kg/ m² ; maximal doses of glimepiride and rosiglitazone for people with BMI <27 kg/ m² ; insulin added in if HbA1c>6% with standard treatment strategy (half maximal doses of same agents ; insulin added in if HbA1c > 9%. Achieved HbA1c levels were 6.9% and 8.4% respectively.

Mortality:-

- Reducing blood glucose to specific mean HbA1c targets did **not significantly reduce mortality** during follow up in most RCTs .
- In the study ACCORD with the lowest mean HbA1c attained in the intensive treatment group 6.4% treatment was **stopped** early as mortality in this group was **significantly higher** than in the usual care group .
- Ten year post-randomization follow up of UKPDS 33 and 34 suggested long term beneficial effect of more intensive glycaemic control in the early years after diagnosis of diabetes despite similar control in intensive and conventional groups after study close-out.
- **Reduction in all-cause mortality** were reported for people treated with sulphonylurea or insulin and for people treated with metformin

Cardiovascular Risk:-

UKPDS study reported that intensive glycaemic control reduced the risk for cardiovascular disease but did not reduce the risk for all-cause mortality .

Microvascular Morbidity:-

Reduction of HbA1c to a mean level of 6.4 to 8% reduces microvascular disease morbidity (ADVANCE – VADT – UKPDS 33)

Hypoglycaemia:-

Treatment to glycaemic targets increases incidence of hypoglycaemia. Significantly more episodes were reported in intensive versus conventional therapy groups in most studies.

Weight Gain:-

Patients who were allocated to intensive control groups gained more weight or were heavier at follow up than conventional treatment groups in most studies.

Glucose - Lowering Drugs

Glucose - Lowering Drugs

- Metformin
- Sulphonylureas
- Thiazolidinediones
- Dipeptidyl Peptidase-4 Inhibitors
- Alpha-glucosidase inhibitors
- Meglitinides
- Glucagon like peptide-1 agonists
- Insulin

Metformin

- Metformin decreases hepatic glucose production
- Improve peripheral glucose disposal while suppressing appetite and promoting weight reduction .
- Activation of the energy – regulating enzyme AMP- kinase in liver and muscle is a principal mode of action.
- Metformin should be considered as the first line oral treatment option for overweight patients with type 2 diabetes.

- **Checklist For Provision Of Information:**

- Metformin should be taken with or immediately after a meal.
- It should be introduced in low dose, with gradual escalation (e.g. 500mg once daily for one week, 500mg twice daily in week two, 500mg thrice daily in week three, and 1g twice daily in week four) .
- Some individuals may not tolerate higher doses, in which case dose reduction is appropriate .
- Nausea, diarrhoea, and abdominal pain are the most common adverse effects.
People should be informed that these side effects often improve after a few days of continued therapy, or with a small dose reduction.

- A modified release preparation (metformin MR) is also available suitable for once daily dosing; some individuals otherwise intolerant of metformin may find this more acceptable , or may in some cases be able to taken higher doses.
- Metformin should usually be discontinued during a severe illness (e.g. myocardial infraction, pneumonia, severe infection and/ or dehydration) as it may aggravate tissue hypoxia and accumulate when renal function is impaired . In these circumstances, it may be appropriate to use insulin.
- As iodine-containing contrast media may cause acute deterioration of renal function, discontinuation of metformin prior to radiological investigations using >100ml of contrast or where serum creatinine is raised .

Sulphonylureas

- Sulphonylureas increase endogenous release of insulin from pancreatic β -cells.
- The drugs available are classed according to their date of release :
 - First generation (acetohexamide, chlorpropamide, tolbutamide, tolazamide)
 - Second generation (glipizide , gliclazide, glibenclamide(glyburide), gliquidone, glyclopyramide, glimepiride).
- Sulphonylureas should be considered as first line oral agents in patients who are not overweight , who are intolerant of , or have contraindications to, metformin.

- **Checklist For Provision Of Information:**

- These agents should ideally be taken 30 minutes before food.
- The main risk is hypoglycaemia. This risk is increased in older age groups, and in those with renal impairment and/or liver disease .
Glibenclamide is particularly prone to causing hypoglycaemia and should not be used in the elderly. The warning signs of hypoglycaemia, which should be outlined to people taking these agents, include (early signs) tremor, sweating, shaking, irritability, and (later signs) lack of concentration.

- Gliclazide is available in modified release (MR) preparation. This permits once daily dosing even when higher doses are required .
- Prescribers should be aware that gliclazide MR 30mg is therapeutically equivalent to standard gliclazide 80mg (maximum dose therefore 120mg once daily rather than 160mg twice daily).
- People taking sulphonylureas should also be advised of their propensity to cause weight gain (avoid excess calorie).

Thiazolidinediones

- Thiazolidinediones (TZDs) increase whole-body insulin sensitivity by activating nuclear receptors and promoting esterification and storage of circulating free fatty acids in subcutaneous adipose tissue .
- Two Thiazolidinediones are available for use: pioglitazone and rosiglitazone .

- **Checklist For Provision Of Information:**

- People prescribed TZDs should be advised that they may cause ankle oedema. Where this occurs, discontinuation is usually appropriate.
- People taking TZDs should also be advised of the likelihood of weight gain and increased risk of fracture, although these are not necessarily reasons for discontinuing.

Pioglitazone:-

- Pioglitazone can be added to metformin and sulphonylurea therapy , or substituted for either in cases of intolerance.
- Pioglitazone should not be used in patients with heart failure .
- The risk of fracture should be considered in the long term use (care of female patients treated with pioglitazone).

Rosiglitazone:-

- o One meta-analysis study^(12th may 2007) concluded that rosiglitazone was associated with significant increase in the risk of MI and a borderline significant finding for death from CV causes.
- o Rosiglitazone can be added to metformin and sulphonylurea combination therapy, or substituted for either in cases of intolerance.
- o Rosiglitazone should not be used in patients with heart failure.

- Rosiglitazone should not be used in patients with acute coronary syndrome or a history of myocardial infraction.
- The risk of fracture should be considered.
- Patients prescribed rosiglitazone should be made aware of the increased risk of peripheral oedema.

Dipeptidyl Peptidase-4 Inhibitors

- Dipeptidyl peptidase -4 inhibitors are oral agents which inhibit activity of the enzyme DPP-4 and hence prolong the actions of endogenous glucagon like peptide 1 (GLP-1) .
- There are three DPP-4 inhibitors currently available:

Sitagliptin , Vildagliptin and Saxagliptin.

- These newer agents are generally well tolerated.
- However, questions remain about the possibility that they may predispose either to more frequent (usually minor) **infections**, or even **acute pancreatitis** .
- People prescribed these agents should therefore be encouraged to report potentially serious symptoms , particularly severe abdominal pain.

Alpha-glucosidase inhibitors (acarbose)

- Alpha-glucosidase inhibitors are **oral glucose-lowering** agents that specifically inhibit alpha-glucosidases in the brush border of the small intestine. These enzymes are essential for the release of glucose from more complex carbohydrates .
- Alpha-glucosidase inhibitors can be used as monotherapy for the treatment of patients with type 2 diabetes if tolerated.

- When acarbose is prescribed, patients should be advised of the likelihood of gastrointestinal symptoms, particularly abdominal pain, diarrhoea and wind. These symptoms mainly arise from the fermentation of undigested carbohydrates by colonic bacteria.

Meglitinides

(repaglinide ,nateglinide)

- Meglitinides act on the same β -cell receptor as sulphonylureas but have a different chemical structure.
- The systematic review included three trials that compared repaglinide with metformin and reported similar improvements in glycaemic control.
- One study compared nateglinide with gliclazide as add-on therapy to metformin in patients inadequately controlled on the latter. There were no significant differences in glycaemic control.

- Meglitinides have not been assessed for their long term effectiveness in decreasing microvascular or macrovascular risk and are more expensive than other glucose-lowering agents.
- Weight gain was more common (up to 3 kg in three months) and hypoglycaemia was more frequent in those treated with meglitinides compared with metformin .

Glucagon like peptide-1 agonists

- Glucagon like peptide (GLP)-1 is one of the key 'incretin' hormones
- A group of rapidly metabolised peptides secreted from the gut in response to food which amplify secretion of insulin from pancreatic β -cells and inhibit inappropriate glucagon secretion .
- They also slow gastric emptying, resulting in slower absorption of glucose following meals , and reduce appetite .
- GLP-1 agonists mimic endogenous GLP-1 activity but are resistant to breakdown by the DPP-4 enzyme, resulting in more prolonged action.

- Hence , weight loss is a possible advantage of GLP-1 agonist therapy compared to insulin therapy and some oral glucose-lowering drugs, e.g. sulphonylureas and thiazolidinediones
- These newer agents require to be **injected subcutaneously**, like insulin.
- In keeping with the appetite-suppressant effect of these agents (exenatide,liraglutide) the most common adverse effects are nausea, vomiting and diarrhoea.
- Increased contact with the diabetes team is required particularly in the first weeks of use, usually with monitoring of therapeutic response-weight and HbA1c.

- Hypoglycaemia is much less frequent than with insulin , but may occur with GLP-1 agonist, particularly when administered in combination with a sulphonylurea . When a GLP-1 agonist is added to a sulphonylurea , a reduction in sulphonylurea dose should be considered .
- As there is a small risk of acute pancreatitis with these agents, people receiving these agents should be encouraged to report any unexpected or severe symptoms

- As for oral agents , people taking exenatide or liraglutide may hold a regular driving licence without restriction.
- GLP-1 agonists (exenatide or liraglutide) may be used to improve glycaemic control in obese adults ($\text{BMI} > 30\text{kg/m}^2$) with type 2 diabetes who are already prescribed metformin and/ or sulphonylureas .
- AGLP-1 agonist will usually be added as a third line agent in those who do not reach target glycaemia on dual therapy with metformin and sulphonylurea (as an alternative to adding insulin therapy).

Insulin

- *Continuing oral agents when initiating basal insulin :-*
 - A systematic review showed that when starting insulin therapy , continuing metformin therapy is associated with lower HbA1c (by up to 0.6%) and less weight gain (by up to 3.7 kg) without an increase in the risk of hypoglycaemia.
 - Continuing sulphonylurea therapy when starting once daily insulin monotherapy is associated with a greater HbA1c reduction (0.3, to 0.6%) than insulin monotherapy alone.
 - Continuing metformin, or sulphonylurea or both, in combination resulted in lower insulin requirements by 46% (range – 5% to 74%) compared with insulin monotherapy alone.
 - Oral metformin and sulphonylurea therapy should be continued when insulin therapy is initiated to maintain or improve glycaemic control.

Initiating basal insulin : Long-Acting insulin analogues versus intermediate-acting human insulin

- When starting insulin therapy as a single injection before bed-time, NPH insulin is as effective in reducing HbA1c as basal insulin analogue therapy. However ,basal insulin analogue therapy is associated with fewer episodes of nocturnal and overall hypoglycaemia .
- No difference was seen for severe hypoglycaemia.
- Collating evidence from six short term trials , it was necessary to treat eight patients with type 2 diabetes (95% CI 6 to 11) with glargine compared with NPH (continuing oral agents) to avoid one episode of nocturnal hypoglycaemia.
- Weight gain was slightly less with detemir than with NPH insulin when added to oral glucose-lowering agents (1 kg, 95%CI-1.69 to -0.23 kg).

- In a UK health technology assessment of newer drugs for blood glucose control in type2 diabetes , the incremental cost per quality adjusted life year (QALY) gained for use of glargine in place of NPH insulin was estimated at £417,625.
- Once daily bedtime NPH insulin should be used when adding insulin to metformin and/or sulphonylurea therapy . Basal insulin analogues should be considered if there are concerns regarding hypoglycaemia risk.

Insulin initiation and intensification: Basal versus pre-mixed insulins

- When commencing insulin therapy , bedtime basal insulin should be initiated and the does titrated against morning (fasting) glucose.
- If the HbA1c level does not reach target then addition of prandial insulin should be considered.

Intensifying insulin therapy: Pre-mixed preparations

- Adding in rapid-acting insulin in a pre-mixed biphasic preparation results in lower HbA1c than with basal analogue therapy alone.
- Aim to optimise insulin dose and regimen to achieve target glycaemia while minimising the risk of hypoglycaemia and weight gain.

Intensifying insulin therapy: Rapid-acting insulin analogues versus human insulin

- No difference in HbA1c reduction has been demonstrated between pre-mixed preparations containing rapid-acting analogues compared with those containing regular insulin.
- Soluble human insulin or rapid-acting insulin analogues can be used when intensifying insulin regimens to improve or maintain glycaemic control
- When intensifying insulin therapy by addition of rapid-acting insulin, sulphonylurea therapy should be stopped.

Algorithm For Glucose-Lowering In Type2 Diabetes

Algorithm for Glucose- lowering in people with Type2 Diabetes

The British National Formulary (www.bnf.org) and the Scottish Medicines Consortium (www.scottishmedicines.org.uk)

Review and Set Glycaemic Target : HBA1C < 7% or Individualised as Agreed

1st Line options in addition to lifestyle measure ; start one of

Metformin (MF)

Sulphonylurea*(SU)

- If intolerant of metformin or
- If weight loss/osmotic symptoms

Review and if
Not reaching
Target move
to 2nd line

2nd Line options in addition to lifestyle measure , adherence to medication and dose optimisation; ADD one of

Sulphonylurea* (su)

Thiazolidinedione*

- If hypos a concern (eg driving , occupational hazards , at risk of falls)
- If no congestive heart failure

DPP-4 inhibitor*

- If hypos a concern
- If weight gain a concern

Review and if
not reaching
Target move to
3rd line

3rd Line options in addition to lifestyle measure, adherence to medication and dose optimisation; ADD or Substitute with one of

Oral (continue MF/SU if tolerated)		Injectable (if willing to self inject; continue MF/SU if tolerated)	
Thiazolidinedione *	DPP4 inhibitor* If weight gain a concern	Insulin * (inject before bed) <ul style="list-style-type: none"> • If osmotic symptoms /rising HbA1c;NPH insulin initially • If hypos a concern , use basal analogue insulin as an alternative • Add prandial insulin with time if required 	GLP-1 agoints * <ul style="list-style-type: none"> • If BMI >30 kg/m² • If a desire to lose weight • Usually < 10 years fom diagnosis

	Usual approach
	Alternative approach. Special considerations
*	Continue medication if EITHER idividuals target achieved or HbA1c falls > 0.5% in 3-6 months



**Glycaemic control compared to placebo
(or diet)**

**Glycaemic control compared with other
glucose – lowering agents**

In non-obese patients metformin monotherapy reduced postprandial glycaemia in similar way to repaglinide and was significantly more effective in reducing postprandial hypercholesterolaemia and hyperinsulinaemia.

Hypoglycaemia/ Weight gain / Adverse effects

There has been some controversy about the impact of tight glycaemic control in patients with type 2 diabetes and heart failure . A recent systematic review found two studies showing a significant improvement in outcome in patients allocated metformin compared with sulphonylureas and concluded that metformin was the only glucose-lowering agent not associated with harm in this group .

Cardiovascular morbidity:-

There were no significant differences between metformin and other comparison arms for other outcomes such as stroke, peripheral arterial disease and microvascular disease.

Despite the benefits of metformin for overweight patients in comparison with a conventional treatment strategy , no benefits were observed for any of the above outcomes for comparisons between intensive treatment with metformin and intensive treatment with chlorpropamide, glibenclamide , or insulin (n=951).

Glycemic control:-

A meta-analysis of six short term studies including 1,364 patients suggested that sulphonylureas can achieve significant improvement in glycaemic control when added to metformin in patients who have inadequate glycaemic control.

- * Hypoglycaemia/ Weight gain/ Adverse effects
- * Cardiovascular Morbidity