UPDATE ON THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS

INTRODUCTION
Diabetes mellitus (DM) is a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action, or a combination of both. Over 90% of adults with diabetes have type 2 DM (T2DM). It affects approximately 5% of Irish adults, however the true prevalence is probably underestimated. In many countries, the prevalence of T2DM is rising steadily, due to the ageing population and increased rates of obesity. In Ireland its prevalence is predicted to increase by 37% over the 10-year period from 2005-2015. T2DM is usually diagnosed in people >40 years, with a peak age of onset 60 - 70 years, however it is increasingly being diagnosed in younger people including children. The prolonged exposure to hyperglycaemia associated with DM results in microvascular (retinopathy, nephropathy and neuropathy), and macrovascular complications (cardiovascular, cerebrovascular and peripheral artery disease). Therefore, in addition to being an important public health issue, T2DM is a huge financial burden to health services.

This bulletin will provide an update on the therapeutic options which are currently available to treat T2DM.

PATHOPHYSIOLOGY
T2DM is a progressive disease; the hyperglycaemia occurs due to a combination of genetic predisposition, unhealthy diet, physical inactivity, and increasing weight. T2DM results from a combination of decreased insulin secretion and a progressive development of insulin resistance, with the subsequent dysfunction of pancreatic beta cells. There is a clear association between T2DM and obesity (in particular abdominal obesity); abdominal fat leads to the release of excessive amounts of free fatty acids which causes insulin resistance in the liver and muscle cells. This leads to increased gluconeogenesis in the liver and inhibition of insulin-mediated glucose uptake by muscle cells, resulting in increased levels of circulating glucose. Initially the pancreas releases increasing amounts of insulin in response to the insulin resistance and increased glucose. This cannot be maintained, and pancreatic beta cell function deteriorates over time, leading to a reduction in insulin and consequent hyperglycaemia. It is estimated that at the time of diagnosis, those with T2DM often have lost about 50% of their beta cell function.

DIAGNOSIS
T2DM is characterised by a long pre-clinical phase; usually patients experience impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) in the initial phases of the disease process. Many patients are asymptomatic until well after long term, microvascular and macrovascular complications have occurred. Early detection requires clinical suspicion combined with systematic and opportunistic case-finding. Screening for T2DM should be considered in all at risk individuals who are ≥ 45 years and if normal should be repeated at 3-year intervals. Screening should be considered at a younger age or carried out more frequently in individuals who are overweight (BMI ≥25kg/m²) and who have additional risk factors for T2DM.

For decades the diagnosis of diabetes has been based on plasma glucose criteria, either the fasting plasma glucose or the 75-gram oral glucose tolerance test. More recently, an international expert committee has recommended that DM can also be diagnosed by demonstrating increased haemoglobin A₁c (HbA₁c) of ≥ 48mmol/mol (note the change in units; equivalent to ≥ 6.5%). which has also been endorsed by the WHO. Traditionally HbA₁c was reported as percentage of total haemoglobin, however the International Federation of Clinical Chemistry and Laboratory Medicine has established a new reference measurement system for the worldwide standardisation of HbA₁c, levels in mmol/mol. HbA₁c reflects average plasma glucose levels over a 2-3 month period and is widely used as the standard biomarker for glycaemic control. A normal HbA₁c cannot exclude the presence of diabetes or IGT as the HbA₁c may be affected by a variety of genetic, haematological and illness-related factors including certain forms of anaemia and haemoglobinopathies. The diagnosis of diabetes in an asymptomatic person should not be made on the basis of a single abnormal plasma glucose or HbA₁c level; at least one additional HbA₁c or fasting plasma glucose should be repeated to confirm the diagnosis.

Table 1: Criteria for diagnosis of diabetes mellitus

<table>
<thead>
<tr>
<th>Any one of the following criteria is diagnostic:</th>
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<tbody>
<tr>
<td>1. HbA₁c ≥ 48mmol/mol (equivalent to ≥ 6.5%)*</td>
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<tr>
<td>or</td>
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<tr>
<td>2. Fasting plasma glucose ≥7 mmol/L*</td>
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<td>or</td>
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<tr>
<td>3. Two hour plasma glucose ≥11.1 mmol/L during an oral glucose tolerance test*</td>
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<td>or</td>
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<td>4. Symptoms of hyperglycaemia and random plasma glucose ≥11.1 mmol/L</td>
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* in the absence of unequivocal hyperglycaemia, results should be confirmed by repeat testing

THERAPEUTIC OPTIONS
Lowering of plasma glucose with diet and/or medication reduces long-term complication rates and is central to the overall management of diabetes. The main modalities of hyperglycaemia management are lifestyle interventions and pharmacotherapy.
**LIFESTYLE INTERVENTIONS**

Lifestyle intervention, in particular the promotion of weight loss and exercise, is very important in the management of T2DM and has been shown to reduce the HbA1c by up to 2%.\(^2,17,18\)

**Weight loss** has positive effects on metabolic control\(^19\) and cardiovascular (CV) risk factors in T2DM.\(^20\) Options for healthy eating include simple calorie restriction, reducing fat intake, consumption of carbohydrates with low glycaemic index and restricting the total amount of dietary carbohydrate.\(^21\)** Patients should be advised to maintain a healthy weight in order to maintain a BMI of 20-25kg/m\(^2\).** The benefits of weight loss have been demonstrated in morbidly obese patients with T2DM who have undergone bariatric surgery; with some patients experiencing remission of the disease.\(^20,22\)** However for the majority of patients, bariatric surgery is not an option.\(^20\)** Some of the most successful programmes for long-term weight control have involved combinations of diet, exercise and behaviour modification.\(^2\)** Exercise** improves glycaemic control even without weight loss and results in reduced body fat content and increased insulin response.\(^23\)** Studies have shown that regular physical activity is associated with reduced cardiovascular disease (CVD) and total mortality in diabetic patients; the reduction in CVD risk associated with physical activity may be comparable with that of pharmacological treatment prescribed to patients with T2DM.\(^1\)** Guidelines recommend 30 minutes of physical activity at least 5 times per week.\(^2\)**

**PHARMACOLOGICAL MANAGEMENT**

Due to the progressive nature of T2DM, the majority of people eventually require hypoglycaemic drugs and many will require combination hypoglycaemic drugs including insulin.\(^6,17\)** The choice of the hypoglycaemic drug needs to be individualised to the patient. While the efficacy of the various therapies at lowering glucose is similar, hypoglycaemic drugs have different side effect profiles and may have the potential advantage of modifying CV risk factors such as lipid profiles.\(^17\)** Prescribers should refer to the Summary of Product Characteristics (SmPC) for full prescribing information for the individual medicinal products.

### Oral therapies

Table 2 summarises the oral therapeutic agents currently authorised.

**Table 2: Summary of oral glucose-lowering therapeutic interventions**\(^{13,17,24-37}\)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mode of Action</th>
<th>Expected ↓ in HbA1c %*</th>
<th>Comments</th>
<th>Adverse effects</th>
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</thead>
<tbody>
<tr>
<td><strong>Biguanides</strong></td>
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<tr>
<td>Metformin</td>
<td>Inhibits gluconeogenesis</td>
<td>1.0-2.0</td>
<td>Weight neutral</td>
<td>GI side effects, rarely lactic acidosis</td>
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<tr>
<td><strong>Sulfonylureas</strong></td>
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<tr>
<td>Glibenclamide, glimepiride, glipizide</td>
<td>Enhances insulin secretion (secretagogue)</td>
<td>1.0-2.0</td>
<td>Rapidly effective</td>
<td>Weight gain, hypoglycaemia (especially with glibenclamide)</td>
</tr>
<tr>
<td><strong>Thiazolidinediones</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>Pioglitazone</td>
<td>Increase the sensitivity of muscle, fat and liver to insulin</td>
<td>0.5-1.4</td>
<td>Improved lipid profile</td>
<td>Fluid retention, CHF,** weight gain, bone fractures, possible association with bladder cancer</td>
</tr>
<tr>
<td><strong>Glinides</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide, nateglinide</td>
<td>Enhances insulin secretion (secretagogue)</td>
<td>0.5-1.5***</td>
<td>Reduce post-prandial hyperglycaemia</td>
<td>Three times daily dosing</td>
</tr>
<tr>
<td><strong>Dipeptidyl peptidase-4 inhibitors</strong> (DPP-4)</td>
<td>Prolongs duration of incretin hormones</td>
<td>0.5-0.8</td>
<td>Weight neutral</td>
<td>Long-term safety not established Association with pancreatitis</td>
</tr>
<tr>
<td>Vildaglaptin, sitagliptin, saxagliptin, linagliptin</td>
<td></td>
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<td></td>
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<tr>
<td><strong>Alpha-glucosidase inhibitors</strong></td>
<td>Reduces the digestion of polysaccharides in the intestine</td>
<td>0.5-0.8</td>
<td>Weight neutral</td>
<td>Frequent GI side-effects, including flatulence, diarrhoea and abdominal pain</td>
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<tr>
<td>Acarbose</td>
<td></td>
<td></td>
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* based on monotherapy, ** congestive heart failure, *** repaglinide is more effective than nateglinide at lowering blood glucose \(^17\)

**Biguanides:** Metformin is recognised as the first line pharmacological treatment of T2DM\(^18,19\)** and is also used in combination with other hypoglycaemic agents. **Metformin has been shown to have a significant beneficial effect on cardiovascular morbidity.**\(^12,24\)** It is not usually associated with hypoglycaemia. Gastrointestinal adverse effects can be minimised by slowly increasing the dose over several weeks.\(^44\)** Renal dysfunction is considered a contraindication to its use as it may increase the risk of lactic acidosis.\(^17,24\)**

**Sulfonylureas** have similar efficacy to metformin in lowering blood glucose. They are used as monotherapy if there are contraindications to using metformin or in combination with other hypoglycaemic drugs.\(^23,35-38\)** Hypoglycaemia which can be prolonged and life threatening (occurring relatively more frequently in the elderly)\(^17\)** is more common with glibenclamide than with the newer second generation sulfonylureas.\(^17\)**

**Thiazolidinediones (TZDs)** (also known as glitazones) have similar efficacy to metformin and sulfonylureas in lowering blood glucose. Pioglitazone is indicated as second or third line treatment for T2DM and is used as combination therapy with other hypoglycaemic drugs, or as monotherapy if the patient is overweight and there are contraindications to metformin.\(^30\)** Pioglitazone is contraindicated in heart failure.\(^26\)**

**Glinides** have a shorter half-life than sulfonylureas and must be administered more frequently.\(^17\)** They are used in combination therapy with metformin\(^31,32\)** and repaglinide can be used as monotherapy, if metformin is contraindicated.\(^31\)** Hypoglycaemia may be less frequent with nateglinide than with some sulfonylureas.\(^17\)**

**Dipeptidyl peptidase-4 inhibitors (DPP-4)** The incretin hormones (glucagon-like peptide [GLP-1] and glucose-dependent insulinitropic peptide [GIP]) are secreted at low basal levels in the fasting state, which increase rapidly and transiently following food ingestion. DPP-4 inhibitors (also known as gliptins) act by prolonging the duration of incretin hormones,\(^41\)** resulting in increased glucose mediated insulin secretion and reduced glucagon.\(^37\)** **DPP-4 inhibitors are not generally associated with hypoglycaemia**\(^17\)** and are **weight neutral.**\(^42\)** They are used as combination therapy with other antidiabetic agents.\(^35,36\)** Sitagliptin, linagliptin and vildagliptin are also indicated for monotherapy if there are contraindications to metformin.\(^33,34,36\)** Dosage of some of the DPP-4 inhibitors may need to be reduced in renal impairment; the individual SmPC...
should be reviewed. \(^{33-35}\) There is concern that DPP-4 inhibitors may interfere with immune function;\(^ {41}\) an increase in upper respiratory infections has been reported.\(^ {17}\) There is also an association of pancreatitis with DPP-4 inhibitors,\(^ {33-35,61}\) and an increased risk of serious hypersensitivity reactions with use of saxagliptin.\(^ {43}\) Alpha-glucosidase inhibitors such as acarbose, lower post-prandial glucose levels but do not cause hypoglycaemia.\(^ {17}\) Acarbose can be used as monotherapy or in combination with other antidiabetic agents.\(^ {37}\) In clinical trials up to 45% of patients discontinued use due to GI effects.\(^ {17}\)

**Parenteral therapies**

Table 3 summarises the parenteral therapeutic agents currently available.

Table 3: Summary of parenteral glucose-lowering interventions\(^ {17,44-53}\)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mode of Action</th>
<th>Expected % in HbA(_1c)</th>
<th>Comments</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 agonist</td>
<td>Mimics the action of the incretin hormone GLP-1</td>
<td>0.5-1.0</td>
<td>Associated with weight loss</td>
<td>GI side-effects (diminish with time)</td>
</tr>
<tr>
<td>Insulin</td>
<td>Mimics normal insulin response</td>
<td>1.5-3.5</td>
<td>Rapidly effective, improves lipid profile</td>
<td>Weight gain (2-4kg), risk of hypoglycaemia</td>
</tr>
</tbody>
</table>

* based on monotherapy

**Insulin** is the most effective therapy for lowering glycaemia.\(^ {2,17,54}\) Insulin initiation is usually carried out in a diabetes day care centre,\(^ {2}\) and as part of a structured programme.\(^ {40}\) It can also take place in primary care where expertise exists.\(^ {12,55,56}\) Insulins include human insulin and recombinant insulin analogues.\(^ {57}\) The insulin analogues currently available include insulin aspart, glargine, detemir, lispro and glulisine.\(^ {49-53}\) There are 3 main types of insulin with regard to speed and duration of action: short, intermediate and long-acting; in addition pre-mixed combinations are available.\(^ {57}\) Initial therapy is aimed at increasing basal insulin supply, usually with intermediate or long-acting insulins, however patients may also require prandial therapy with short or rapid-acting insulins.\(^ {17}\) The very rapid-acting and long-acting analogues have not been shown to lower Hb\(_{1c}\) more effectively than the older, rapid acting or intermediate acting insulin formulations.\(^ {17}\) however they are associated with less hypoglycaemia.\(^ {6,17,57}\)

A recent Irish study has shown that the prescribing of human insulin is decreasing and that of the insulin analogues is increasing.\(^ {58}\) Insulin therapy is indicated for those not tolerating oral hypoglycaemic therapy, not achieving appropriate glycaemic control, being pregnant or planning pregnancy (note that not all analogues are suitable for use in pregnancy)\(^ {59}\) and those with painful neuropathy.\(^ {57,60}\) In addition to lowering glucose, insulin also has beneficial effects on lipids.\(^ {17}\) The patient is the key player in insulin therapy and it is essential that he/she is trained and empowered to treat hypoglycaemia; all patients on insulin should be supplied with a glucagon kit and be familiar with its use.\(^ {2}\)

**MANAGEMENT OF TYPE 2 DIABETES MELLITUS IN PRACTICE**

The HSE Diabetes National Clinical Programme will be published updated guidelines on the management of type 2 diabetes mellitus in the near future.\(^ {12}\) A practical guide to integrated T2DM care was published jointly by the ICGP, the Irish Endocrine Society, the HSE and the Department of Health in 2008.\(^ {2}\) This guide, and other expert groups, recommend that the management of patients with T2DM should be provided by an integrated multi-disciplinary team including, the patient with diabetes, the GP, pharmacist, practice nurse, endocrinologist, diabetes specialist nurse, dietician, ophthalmologist and podiatrist.\(^ {2,17,60}\) In addition patients should have access to specialist services including vascular, cardiology, nephrology and psychology when required.\(^ {2}\) All patients require a comprehensive initial assessment and the inclusion on a practice register and a regular review.\(^ {2}\) Education is a key component in the prevention and management of diabetes; in particular self-management education training is important as the Cv risk factors and long-term complications of T2DM.\(^ {2,21,60}\)

**Lowering hyperglycaemia:** Evidence has shown that intensive glucose lowering therapy using hypoglycaemic drugs significantly reduces microvascular complications in patients with T2DM.\(^ {61-63}\) There is controversy as to whether intensive therapy is associated with reduced macrovascular complications.\(^ {64-68}\)

The measurement of Hb\(_{1c}\) plays a critical role in the management of a patient with diabetes, since it correlates well with both microvascular and to a lesser extent macrovascular complications.\(^ {1,2}\) Most consensus groups recommend that the Hb\(_{1c}\) target level should be in the region of 53mmol/mol (or 7%), however it needs to be individualised to the patient.\(^ {1,2,12,21,60,69}\) Hb\(_{1c}\) should be tested at least twice yearly in patients who are meeting their target level and every 3-4 months in patients whose therapy has changed or who are not meeting targets.\(^ {2}\) For selected individuals, more stringent Hb\(_{1c}\) targets could be suggested, provided that the level can be achieved without substantial hypoglycaemia or other adverse effects of treatment; these patients may include those with a short duration of diabetes, a long life expectancy and no significant cardiovascular disease.\(^ {14,68}\) Conversely, higher Hb\(_{1c}\) goals should be considered for patients with a history of severe hypoglycaemia, a limited life expectancy, advanced microvascular or macrovascular complications or extensive co-morbid conditions.\(^ {14,68}\) Self-monitoring of blood glucose (SMBG) is recommended for all insulin-treated patients with diabetes, however the role of SMBG in patients with T2DM treated with diet and other anti-diabetic agents is controversial.\(^ {14,70}\) Table 4 outlines the current approach to glucose lowering therapy.\(^ {2,21}\)
**Macrovascular complications:** Patients with diabetes have a two- to four-fold increased risk of CVD compared to non-diabetic patients. Numerous studies have shown the efficacy of controlling individuals’ CV risk factors in preventing or slowing CV in people with diabetes. In 2010, the National Cardiovascular Health Policy recommended that a protocol for the early detection and structured CV care of patients with diabetes should be agreed in order to manage this high-risk group. Hypertension is up to three times more common in patients with diabetes than non-diabetics. Blood pressure should be measured at every routine diabetes visit. In patients with diabetes and hypertension, the recommended target for blood pressure is <130/80 mmHg. Further information on the treatment of hypertension is available in the recent NMIC bulletin [NMIC Vol 17 (5), 2011]. Dyslipidaemia is common in T2DM and the prevalence is more pronounced in women than men. Lifestyle modifications focusing on diet, weight loss (if indicated) and increased physical activity should be recommended to improve the lipid profile in patients with diabetes. Statin therapy should be added to lifestyle therapy regardless of the baseline lipid levels for diabetic patients with overt CVD, those without CVD who are >40 years and have ≥1 CVD risk factor and those <40 years with poor CV risk factor profile. Fibrates may be required for those with high triglycerides. The recommended targets for patients with T2DM are lower than for non-diabetic patients; the most recent European Society of Cardiology and European Atherosclerosis Society guidelines recommends a target LDL cholesterol <1.8mmol/l or a ≥50% reduction from baseline. Thrombosis: Aspirin therapy has been shown to decrease the risk of major CV events occurring in patients with diabetes without CVD, however there is a trend toward higher rates of bleeding and gastrointestinal complications. Low dose aspirin is generally recommended for patients with T2DM ≥50 years at increased CV risk, however it is not recommended for CVD prevention in patients at low CV risk due to the potential adverse effects from bleeding. Lifestyle: In addition to advice on diet and exercise, all patients with T2DM who smoke, should be counselled on smoking cessation and treated with pharmacological agents for smoking cessation if appropriate.

**Microvascular complications** occur in many patients with diabetes. Up to 40% of patients with T2DM have diabetic retinopathy at the time of diagnosis. Diabetes duration, glycaemic control and blood pressure are the strongest risk factors for the development and progression of retinopathy. All patients should have a comprehensive assessment by an ophthalmologist shortly after diagnosis and annually thereafter. Diabetic nephropathy arises from the combination of hyperglycaemia and hypertension driving glomerular damage, which occurs in up to 40% of patients within 25 years. Aggressive blood pressure reduction and glycaemic control are of vital importance in managing diabetic nephropathy. In patients with diabetes, serum creatinine and urine albumin/creatinine ratio should be measured at diagnosis and at least annually thereafter. Diabetic neuropathy refers to a spectrum of various neurological disorders associated with diabetes; the most common form is a distal, symmetrical sensorimotor neuropathy which may be asymptomatic in up to 50%, however focal (entrapment syndromes, cranial nerve palsies, diabetic amyotrophy) and autonomic (postural hypotension, erectile dysfunction) neuropathy also occur. All patients should be screened to assess their risk of developing a foot ulcer and patients should be educated on the importance of regular foot review. The management of neuropathy is mainly supportive, although good glycaemic control can reduce the progression. Once neuropathy has been established, glycaemic control has little influence in controlling pain which is the main symptom. A holistic approach is required in the management of painful neuropathy; simple analgesics may be of benefit, however other agents including antidepressants and anti-epileptics are often required.

**SUMMARY**

The prevalence of T2DM is increasing in Ireland due to the ageing population and increase in obesity. A multi-disciplinary approach to the management of diabetes which includes the patient is recommended. Successful treatment of T2DM is often complicated by the inevitably progressive nature of the disease and the need to balance target blood glucose levels against an increased risk of treatment-related adverse effects such as hypoglycaemia and weight gain. All patients require a full initial assessment and regular review to ensure that they are meeting their target HbA1c, and are being monitored for CV risk factors and microvascular complications. A lifestyle intervention programme to promote weight loss and increase activity levels should be included as part of diabetes management. Adherence of patients to treatment is often compromised by the fear of hypoglycaemia and weight gain, as well as complex therapeutic regimens, therefore patient education is a vital aspect of management. Most patients require combination anti-diabetic therapy and many patients will require insulin. In addition to glucose lowering therapy, management of the patient’s CV risk factors and microvascular complications is an essential aspect of diabetes management.
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