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DIABETES MELLITUS [EASA.2022.C20]

D1.2 Review of Treatment Options

An Agency of the European Union

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SUMMARY

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by high blood sugar levels. Diabetes as well as its treatment modalities might be associated with unstable blood glucose levels (hyper and hypoglycaemia) which both are associated with significant impact in the cognitive abilities.

Their effects can bring about incapacitation, which erodes safety margins and might disrupt normal operations. On a more critical level, they can lead to errors and affect decision making.

"PILOT AND ATCO AEROMEDICAL FITNESS - DIABETES MELLITUS" is a research project implemented by the European Union Aviation Safety Agency (EASA) and funded under the framework of the European Union's Horizon Europe research and innovation program. The project aims to provide evidence-based recommendations for practice standards as well as new medical developments regarding the diagnosis, treatment and complication of diabetes and its treatment modalities.

The findings will be applied to better understand issues which could pose a safety risk for aviation. This would consequently cause pilots and air traffic control officers (ATCOs) to be deemed unfit for license privileges due to safety purposes.

DESCRIPTION OF WORK

The following report provides an overview of the existing evidence in regard to the management and treatment measures for DM.

To compile the report, a thorough literature search was performed in major databases (Scopus, Embase, Web of Science, Google Scholar, MedLine/PubMed). The grey literature was also thoroughly reviewed.

The experts refuted the idea of a Cochrane-type systematic review and decided that the most robust and up-to-date evidence is already present in the most recent consensus from the two biggest diabetes societies: the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD). These were updated recently on type 1 and type 2 diabetes mellitus in the two consensus reports "The Management of Type 1 Diabetes in Adults"[1] and "Management of hyperglycaemia in type 2 diabetes, 2022"[2], produced jointly by the ADA and EASD. The recommendations for topics that are not included in the consensus are based on the "Standards of Care in Diabetes—2023" produced by ADA[3].

The evidence is presented and applied with a specific focus on pilots and ATCOs.

1. MANAGEMENT OF TYPE 1 DIABETES

1.1 Immediate Aims[1,4,5]:

(a) Address symptoms (thirst, polyuria, infection)
(b) Avert hyper- and hypoglycaemic comas
Meeting these goals is generally manageable, making individuals with type 1 diabetes (T1D) feel symptom-free. Nonetheless, long-term complications may arise from chronic hyperglycaemia if only partial metabolic balance is achieved.

1.2 Long-term Aims:

(a) Prevent complications (micro- and macroangiopathy, neuropathy)

(b) Enhance self-care and disease acceptance, promoting normal social integration. To deter serious vascular complications, tight glycaemic control is necessary, provided it is technically and psychologically feasible. A normal HbA1c level may help protect against all diabetes-related complications. Current treatments involve intensive insulin therapy alongside patient education, aiming for the lowest achievable HbA1c based on individual capacity. Ideally, HbA1c should be below 7%1,6–9.

However, T1D management requires balancing between optimal biochemical outcomes and psychological sustainability. This balance may change over time, becoming more stringent as individuals mature. Early initiation of intensive insulin therapy and good glycaemic control is crucial, as the initial years significantly impact the risk of complications (metabolic memory). Nonetheless, maintaining the individual's quality of life remains a priority. Optimal glycaemic control relies on coordinating insulin therapy, diet, and exercise1,6–9.

RESOURCES

Insulin reimbursement, education, and monitoring technique reimbursement policies differ among European countries10.

2. INSULIN REPLACEMENT THERAPY IN TYPE 1 DIABETES

Pilots with type 1 diabetes mellitus are currently deemed unfit to fly under the existing regulations set by the European Union Aviation Safety Agency (EASA). This stipulation is in place as a safety measure, and it's one of the criteria that can disqualify an individual from obtaining or maintaining a pilot's license within the jurisdiction of EASA.

Pilots with diabetes mellitus who are treated with insulin might be allowed to fly if they apply, commit, and follow the procedures under ARA.MED.330 protocol as established by EASA in countries such as the UK, Austria, and Ireland, with some limitations and restrictions. Canada was the first country to permit carefully selected pilots with insulin-treated diabetes to fly commercial aircraft, starting in

2002. The UK joined in 2010 when the Civil Aviation Authority (CAA) assembled a team of experts to evaluate the scientific understanding of the issue. Subsequently, they formulated guidelines to ensure the safe flight of pilots on insulin therapy, culminating in the ARA.MED.330 protocol in 2012.

This protocol, based on capillary blood glucose measurements, necessitates meticulous monitoring, comprehensive record-keeping, and systematic data gathering. It's important to note that current European Union regulations do not allow the issuance of Class 1 medical certificates (needed to validate a commercial pilot's license) or Class 2 medical certificates (required for a private pilot's license) to individuals with insulin-treated diabetes. However, these regulations do include provisions that allow for the consideration of emerging medical technologies, drugs, or methodologies to assess a pilot's fitness to fly.

2.1 Insulins

Most insulin formulations have a concentration of 100 units per ml (U100). However, recent years have seen the development of more concentrated insulin forms (lispro U200, degludec U200, and glargine U300). Glargine U300's higher concentration results in a distinct effect profile compared to the U100 version (slower and longer lasting). As a result, they are marketed under separate brand names: Lantus® for glargine U100 and Toujeo® for the U300 form. *[11–14]*

2.1.1 Biosynthetic Human Insulin:

- Short-acting insulin: ("regular", clear solution) begins glucose-lowering action within 20 minutes and lasts for approximately 4-6 hours. Examples include Humulin Regular® and Actrapid®.[15,16]
- Long-acting insulin: ("retard", cloudy solution) is protamine-buffered and has a duration of action of around 8-16 hours. Examples include Insulatard® and NPH®.[17,18]

2.1.2 Insulin Analogues:

- Ultra-rapid-acting insulin: (clear) includes faster-acting insulin aspart (FIASP®) and ultra-rapid-acting insulin lispro (Lyumjev® U100 and U200). It initiates action within 5 minutes and lasts for approximately 2-3 hours.[12,19–21]
- Rapid-acting insulin: (clear) examples are Humalog® U100 and U200 (lispro), Novorapid® (aspart), and Apidra® (glulisine). It begins action within 10 minutes and lasts for around 3-4 hours.(18,19)
- Long-acting insulin: (clear) such as Lantus® (glargine), Levemir® (detemir), and Toujeo® (glargine U300) with a duration of action of approximately 24 hours.[24,25]
- Ultra-long-acting insulin: (clear) includes Tresiba® (degludec), which lasts for about 42 hours.(11,23)

2.1.3 Premixed Insulins:

(Primarily used for type 2 diabetes (T2D)) These are commercial combinations of slow-acting human insulin with rapid-acting human insulin or ultra-rapid-acting insulin analogues. Examples include Humulin 30/70® (30% regular insulin and 70% retard insulin) and Novomix 30® (30% aspart and 70% long-acting insulin). They come in various rapid-acting/slow-acting insulin percentage combinations. However, these are infrequently used for individuals with T1D and are not considered part of modern T1D treatment (ref consensus).[27,28]

2.2 Pharmacokinetic properties of different insulins

Insulin and its analogues are usually administered to patients with insulin-dependent diabetes subcutaneously to meet physiological needs. Injections can be self-administered by individuals using a "pen" delivery device or, in the case of ultra-rapid-acting or rapid-acting analogues, by insulin pumps. Ideally, injection sites should be rotated frequently to prevent subcutaneous tissue transformation (e.g. lipodystrophy) associated with repeated adipose tissue injury, which can lead to inconsistent insulin absorption[29–31]

Insulin absorption variability is a significant challenge, particularly with rapid-acting human insulin, though less so with analogues. Intra-patient variability is estimated at about 10% for rapid-acting analogues and 30% for rapid-acting human insulin[30,32,33]. Intra-patient variability for long-acting insulin analogues also differs between analogues, with up to 30% for detemir and degludec whereas it is 45% for glargine.

However, dedicated studies date back to some 20 years ago, and the injection technique errors mentioned above involved in lipodystrophy may strongly contribute to intra-individual insulin absorption variability Therefore, lower percentages are expected nowadays with newer insulin analogues, especially in well-trained and motivated patients.[34,35]

Achieving optimal glycaemic control is challenging when attempting to mimic physiological insulin secretion. In individuals without diabetes, insulin is continuously secreted into the portal vein, directly reaching the liver. This secretion consists of basal secretion (approximately 50% of daily production or 0.7 iU/h) and a bolus with each meal (making up remaining 50% of daily production)[36].

Human short-acting insulin is identical to insulin produced by the pancreas' beta-cells but requires dissociation into monomers for bloodstream entry when injected subcutaneously. This insulin's absorption rate can be further slowed by binding it to an anchor substance at the injection site, typically a protein like protamine, resulting in long-acting human insulins. In Europe, human insulins are rarely used for in T1D due to the short-acting form's inadequacies in managing meal-induced glucose fluctuations and the basal insulin metabolic needs as well as the significant variability in protamine-delayed insulins' profile[37].

Insulin analogues, designed for faster (rapid and ultra-rapid acting) or longer (long and ultra-long acting) effectiveness, have replaced human insulins in intensive insulin therapy for T1D patients. These synthetic analogues facilitate a closer approximation of the physiological insulin profile in individuals with T1D, who are entirely dependent on exogenous insulins.

Rapid-acting insulin analogues are monomeric, featuring amino acid chain modifications that create charge differences, preventing hexamerization and allowing faster migration from the subcutaneous tissue to the bloodstream. Ultra-rapid-acting insulin analogues, such as FIASP® and Lyumjev®, have refined solvents that accelerate the onset and offset of insulin aspart/lispro by approximately 5 minutes. This provides greater flexibility for mealtime and insulin administration for individuals with T1D.[21,38]

Long-acting insulin analogues have distinct mechanisms of action. Glargine has a lower isoelectric point than human insulin, achieved through amino acid chain modifications. This change causes glargine to be soluble for injection at acidic pH (pH 4 in the vial) which then crystallizes within subcutaneous depots as pH neutralizes. Insulin is gradually absorbed from this depot, with glargine U100 lasting up to 24 hours. The higher concentration of glargine in Toujeo® extends its duration of action beyond 24 hours, providing a stable profile and reduced hypoglycaemia risk, particularly nocturnal[24,38].

Detemir (Levemir®) has a different mechanism, involving a minor amino acid chain alteration (threonine deletion) and the addition of a fatty acid to the B-chain. This creates di-hexamers of insulin and enables binding to albumin via the fatty acid chain. Detemir is soluble in the vial (clear insulin

solution) and forms di-hexamers upon subcutaneous injection, binding to albumin in the bloodstream and target organ proteins, resulting in a stable, long-acting insulin[25,38].

The ultra-long-acting insulin degludec (Tresiba®) attaches a fatty acid to human insulin via a linker molecule, forming multi-hexamers upon subcutaneous injection and leading to even slower absorption. Degludec has a 25-hour half-life and a 42-hour duration of action. This stable, long profile allows greater flexibility in injection timing for T1D individuals and reduces the risk of nocturnal hypoglycemia[13,14,38].

2.3 Insulin replacement therapy schemes:

The properties mentioned above can be exploited and adapted to any specific lifestyle and clinical conditions by different T1DM patients to achieve the most adequate glycaemic control. Therefore, to achieve optimal glycaemic control in people with T1D, an individualized insulin replacement regimen is designed collaboratively by the diabetes care team and the patient, considering personal preferences, life situations, and evidence on the efficacy and safety of specific insulins[1].

Popular insulin schemes include[1]:

2.3.1 Multiple Daily Insulin Injections (MDI - basal-bolus system):

- Rapid-acting insulin is administered with each meal to control post-prandial hyperglycaemia.
- One dose of long-acting or ultra-long-acting insulin, typically given before bedtime (or at other times with Toujeo® or Tresiba®), is used to maintain basal insulin requirement.

In Europe, insulin is commonly delivered using insulin pens (reusable or disposable). The MDI regimen enables dose adjustments for rapid-acting insulin according to current glycemia, anticipated activity, and nutrition (see carbohydrate counting). Periodically, the dosing scheme is adjusted based on previous glucose measurements, HbA1c levels, and occurrences of hypoglycaemia. Target fasting glycemia is 80-100 mg/dl (4.4-5.6 mmol/L), and post-meal is 130-140 mg/dl (7.2-7.8 mmol/L). Successful intensive insulin therapy requires adequate patient engagement and education. This is supported by glucose monitoring methods such as self-blood glucose monitoring (SBGM), intermittently scanned Continuous Glucose Monitoring (isCGM), and real-time Continuous Glucose Monitoring (rtCGM)[1].

2.3.2 Continuous Subcutaneous Insulin Infusion (CSII)

CSII is increasingly popular among patients with T1D. This method involves continuous subcutaneous infusion of rapid-acting insulin at a variable rate (basal rate) with the option to administer mealtime insulin boluses. Both basal and bolus CSII systems are connected to the body via a catheter and tubeless systems (e.g. patch pumps) are also available. The pump programming ("open loop") is carried out collaboratively by the medical team and the patient, based on glycaemic measurements and planned meals or exercise[39,40].

Most CSII systems are now compatible with CGM systems and utilize algorithms to suspend insulin infusion when hypoglycaemic values are detected (Low Glucose Suspend) or anticipated (Predictive Low Glucose Suspend) by the sensor. With the implementation of advanced machine learning, these systems have progressed to (Advanced) Hybrid Closed Loop (HCL) systems, which not only halt insulin infusion during hypoglycaemic episodes but also adjust the rate based on current sensor readings, glucose level trends, and carbohydrate input. HCL systems are quickly becoming the preferred therapeutic option for many people with T1D[41–43].

3. PATIENT EDUCATION AND SELF-MONITORING IN TYPE 1 DIABETES

Patients with T1D play a central role in managing their daily treatment, necessitating comprehensive education and motivation. Effective management requires good understanding of insulin administration, impact of exercise and effect of food on glucose levels, importance carbohydrate counting, hypoglycaemia management, and more. Supported by a diabetes care team, patients with T1D are empowered to take responsibility for their treatment. Diabetes educators, including specialist nurses and dietitians, provide essential training and guidance and serve as the primary contact when difficulties arise. [1,9,44,45]

Self-monitoring is a critical aspect of treatment management for patients with T1D in their daily lives[1,9,44,45]:

- Bloodless monitoring methods such as rtCGM and isCGM has largely replaced finger-prick capillary glucose monitoring for most patients with T1D.
- The advent of isCGM and rtCGM systems has led to the introduction of new metrics for interpreting glucose readings. One such metric is the "Time in Range (TIR)", which refers to the percentage of time a person's glucose levels remain within the target range of 70 to 180 mg/dl (3.9-10 mmol/L). The desired TIR for most patients with T1D is >70% on average. This metric not only reflects the average glucose level but also its stability. Additionally, isCGM and rtCGM systems provide information on Time Above Range (TAR) and Time Below Range (TBR).
- Achieving optimal glycaemic control without an excessive risk of hypoglycaemia is crucial. The consensus is to maintain TBR (<70mg/dl; <3.9 mmol/L) below 4% and specifically less than 1% for severe hypoglycaemia (<54mg/dl; 3 mmol/L). For individuals who need to avoid hypoglycaemia (e.g., frail elderly people) or require heightened vigilance (e.g., during pregnancy), these targets can be adjusted according to their needs.

4. DIET AND PHYSICAL ACTIVITY IN TYPE 1 DIABETES

The nutritional requirement for patients with T1D is fundamentally similar to individuals without diabetes. In those without diabetes, insulin secretion adapts to dietary intake, physical activity, and other factors influencing energy regulation. Through insulin analogues and understanding of food composition, particularly carbohydrate content, dietary variety can be preserved for patients with T1D. Diabetes educators, including nurses and dieticians, can utilize tools to help educate patients on carbohydrate counting. Otherwise, the actual diet composition is largely consistent with general healthy eating guidelines. The introduction of insulin analogues and CSII further supports mealtime flexibility for these patients.

The total caloric intake is flexible, provided that the patients with T1D maintain a normal body mass index (BMI). For some individuals, slight calorie restriction may be necessary if weight increases during treatment due to the anabolic effects of insulin or compensatory eating habits to prevent hypoglycaemia. Caloric distribution by energy source does not differ from typical nutrition and the consumption of healthy fats is recommended to prevent cardiovascular risks. Ensuring adequate insulin therapy remains a priority to prevent diabetic complications.

Engaging in adequate physical activity is also essential for patients with T1D, as it is for any individual. Physical activity contributes to glycaemic reduction without the need for insulin intervention. Furthermore, an active lifestyle helps to prevent cardiovascular diseases (e.g., through effects on HDL

cholesterol). However, patients with T1D must integrate physical activity into their treatment plan, which may necessitate adjustments in diet and/or insulin dosage. [46–49]

5. ADJUNCT THERAPY IN T1D

The demographic of patients with T1Ds is evolving, with an increasing prevalence of overweight and obese. This mirrors trends observed in the general population and is exacerbated by intensive insulin therapy and the avoidance or compensatory behaviours of hypoglycaemia, leading to weight gain. Consequently, a vicious cycle emerges, where increased insulin resistance necessitates higher insulin doses and contributes to an elevated cardiovascular risk (overlap of metabolic syndrome and T1D)[50].

As a result, many overweight or obese patients with T1D may benefit from the incorporation of treatments typically used for individuals with T2D. Agents that enhance insulin sensitivity (e.g., metformin), affect the incretin system (e.g., GLP1RA), or induce glucosuria (e.g., SGLT2 inhibitors) have been investigated as adjunct therapies in T1D. Currently, no adjunct treatments for T1D are approved in Europe. However, metformin, GLP1 receptor agonists, and SGLT2 inhibitors are occasionally used off-label. SGLT2 inhibitors' side effects, observed in T2D (including genital fungal infections), are also experienced by patients with T1D.

The primary concern with SGLT2 inhibitors in patients with T1D is the risk of diabetic ketoacidosis. Insulin dosage reduction, required to prevent hypoglycaemia in the presence of an SGLT2 inhibitor, results in decreased lipolysis suppression, increased ketone production, and potential progression to acidosis. Diabetic ketoacidosis in patients with T1D treated with SGLT2 inhibitors is particularly dangerous, as it can occur without typical hyperglycaemia.

Education for patients with T1D and healthcare professionals on preventing this complication is crucial (e.g. measuring ketones when unwell, avoiding prolonged fasting, abstaining from ketogenic diets, and being cautious with alcohol). [51–53]

6. PREVENTION OF TYPE 1 DIABETES

Efforts have been made over the years to halt the decline in beta-cell function and mass in individuals newly diagnosed with T1D, primarily through immunotherapy. In the 1980s, it was demonstrated that chronic treatment with cyclosporine could temporarily preserve C-peptide levels, an indicator of beta-cell function and mass, in individuals who had recently developed clinical T1D. However, the side effects associated with this type of chronic immune suppression render this approach unsuitable for a condition that primarily affects younger individuals[54,55].

More recent studies have shown that short-term immunotherapy at diagnosis (stage 3) can stabilize beta-cell functional mass for several months. Additionally, it has been demonstrated that a 14-day treatment with an antibody (Teplizumab or Tzield®) targeting T lymphocytes that express CD3 on their surface at an earlier stage (stage 2: presence of antibodies and dysglycemia) can delay clinical diagnosis by 2 to 3 years.[56–58] This treatment has since been approved by Food and Drug Administration of the US.

7. AIM OF THERAPY IN TYPE 2 DIABETES

7.1 Objectives

The primary aim of therapy for individuals with T2D is to optimize quality of life, which is closely linked to the development of acute and chronic complications. The main focus in people living with T2D is thus the delay and prevention of microvascular and macrovascular disease[2].

7.2 DIETARY AND LIFESTYLE MODIFICATIONS IN T2D

Adjusting the "energy balance" is crucial in managing T2D given the associations between obesity and insulin resistance. Specifically, limiting caloric intake, optimizing food composition (relative distribution of carbohydrates, proteins, and fats as discussed in T1D), and, if possible, increasing energy expenditure (through regular physical exercise) form the foundation of any therapy for T2D[2,46].

7.3 Diet and weight reduction strategies

A caloric deficit of approximately 300 calories per day can result in a weight loss of 1 kg per month and is initially achievable for most patients with T2D. The target is a normal BMI (<25 kg/m^2), although it is often unattainable. Therefore, losing weight to an individually achievable level is the primary goal, as it reduces insulin resistance and enhances the remaining insulin secretion, ultimately correcting glycaemic and lipid abnormalities. The diet should primarily involve reducing overall caloric intake, increasing fiber intake, consuming less saturated fats, eliminating refined sugars and avoiding alcohol (reducing "empty" calories)[46,59,60].

Even modest reductions in body weight, such as 5 to 10%, significantly improve insulin resistance. Intensive guidance is a valuable tool as, for instance, involving a dietician can often yield substantial results[61].

When selecting glucose-lowering agents, their effect on body weight should be considered[2]. In select individuals (BMI > 35 kg/m^2), bariatric surgery may be considered.

7.4 Lifestyle

Exercise and smoking cessation alongside dietary measures is essential, especially considering the patient's age and cardiovascular health. Physical activity often improves lipid profiles such as elevating HDL levels and help reduce cardiovascular risks. The type and intensity of exercise should be tailored to the patient, and significant improvements in insulin resistance can be achieved with minor efforts (such as 30 minutes of walking per day)[46].

Considering the importance of cardiovascular disease as a cause of death in patients with T2D, all cardiovascular risk factors should be managed and avoided as much as possible. A strict no-smoking policy is recommended.[62,63]

8. GENERAL CONSIDERATIONS ON THE MANAGEMENT OF T2D

Glucose-lowering therapy for T2D necessitates a different approach compared to T1D. New consensus has been established by experts from ADA and EASD, in 2018 and 2022, respectively.[2]

The illustrating figures from the ***Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) on the Management of Hyperglycaemia in Type 2 Diabetes, 2022,*** can be found on the Annex section of this document.

The primary message is that management of T2D should be integrated into a comprehensive treatment plan, with the patient at the center and as part of the decision-making process. A multifactorial approach should form the basis of therapy, including focusing on risk factors beyond glucose, promoting healthy lifestyles, and avoiding clinical inertia[2].

There is a general recommendation to initiate a biguanide (e.g., metformin) as the first line therapy, along with a tailored diet and lifestyle changes for every patient with T2D upon diagnosis. If glycaemic levels do not sufficiently normalize, further medications or combination therapy is indicated. Besides individualized glycaemic control targets, personalized weight targets should be set for patients with T2D. When managing weight, bariatric surgery and the choice of glucose-lowering therapy should also be considered.[2]

Insufficient glycaemic control can typically be defined as fasting glycemia >100 mg/dl (5.6 mmol/L) and/or HbA1c >7%. Higher HbA1c values may be acceptable in frail patients with T2D or those with limited life expectancy. The selection of subsequent glucose-lowering products will be guided by comorbidities, side effects, and the cost/accessibility of therapy[2,9].

The presence of atherosclerotic heart disease, heart failure, or chronic renal disease primarily directs the choice of glucose-lowering therapy in T2D. In patients with T2D and cardiovascular disease, GLP-1 receptor agonists or SGLT2 inhibitors with demonstrated cardiovascular protective effects should be included in therapy. If heart failure or kidney disease (albuminuria) is the primary concern, SGLT2 inhibitors are preferred. Direct renal protection is seen in both patients with normal (eGFR>60 mg/min) and impaired renal function (eGFR<60 ml/min). It is crucial that GLP-1 receptor agonists or SGLT2 inhibitors that demonstrate direct cardio-renal protective effects are recommended for people with cardiovascular or chronic kidney disease, irrespective of HbA1c levels or metformin-use as these drugs are recommended in these patient populations[2,64].

In the absence of specific contraindications, the selection of glucose-lowering agents for clinicians should be determined by additional factors, importance of managing hypoglycaemia risk (favouring DPP4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, or low-dose pioglitazone) and mitigating weight gain (opting for SGLT2 inhibitors or GLP-1 receptor agonists). The consensus document categorizes glucose-lowering medications based on their efficacy in reducing glucose levels and their impact on weight[2].

A progressive escalation of treatment is the conventional approach, however, in cases where HbA1c exceeds the target value by more than 1.5%, the immediate initiation of combination therapy alongside lifestyle modifications is a viable option. Recent evidence supports the utilization of combination therapy for the majority of patients with T2D from the outset[2].

Furthermore, the consensus favours GLP-1 receptor agonists over insulin-only therapy when initiating injectable therapy for patients with T2D. Where insulin is required, basal insulin regimen is the recommended choice[2].

9. NON-INSULIN PHARMACOLOGICAL AGENTS FOR THE TREATMENT OF TYPE 2 DIABETES

9.1 Biguanides

According to the guidelines for managing T2D, initiating metformin therapy, alongside exercise and a balanced diet, is recommended for all patients with T2D. Metformin, an oral biguanide, effectively lowers blood glucose levels without a significant risk of hypoglycaemia. Its mechanism of action is multifaceted, primarily involving decreased hepatic glucose production, increased peripheral insulin sensitivity, and delayed intestinal glucose absorption. Adverse effects commonly include gastrointestinal disturbances and can result in rare, but potentially fatal, lactic acidosis. Compared to sulphonylureas or insulin, biguanides often result in modest weight loss and improved insulin resistance. It is crucial to observe contraindications, such as renal dysfunction (creatinine >1.5mg/dl), hepatic dysfunction, severe cardiopulmonary insufficiency, or uncontrolled hypertension. Biguanides should be discontinued before surgery, or in anticipation of potential tissue hypoxemia or shock, due to the risk of lactic acidosis. A prior history of lactic acidosis is also a contraindication.[2,65]

9.2 Dipeptidyl peptidase-4 (DPP-4)

Dipeptidyl peptidase-4 (DPP-4) inhibitors, administered orally, impede the enzyme responsible for degrading GLP-1 and other incretins. Consequently, endogenous incretins circulate at elevated levels and demonstrate increased efficacy. These agents can reduce HbA1c levels by up to 1%. As DPP-4 inhibitors lead to moderately elevated incretin levels compared to mimetics, they do not induce nausea or weight loss. Similarly to mimetics, they stimulate glucose-dependent insulin secretion and suppress α-cell glucagon secretion, predominantly affecting postprandial glycaemic control. Cardiovascular outcome trials have established the safety of DPP-4 inhibitors.[2,66,67]

9.3 α-Glucosidase inhibitors

α-Glucosidase inhibitors impede glucose absorption in the intestine by selectively inhibiting disaccharide digestion. When taken orally with meals, acarbose effectively reduces blood glucose levels (20-40 mg/dl; 1.1-2.2 mmol/L). Adverse effects primarily stem from carbohydrate digestion in the large intestine, such as flatulence, cramps, and diarrhea.[2,68]

9.4 Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are administered subcutaneously or orally. These agents are analogues or homologues of human GLP-1, but their duration of action is extended to hours or days, in contrast to the short-acting native GLP-1. Molecular modifications render these products resistant to degradation by human enzymes (e.g., DPP4) or slow the rate of renal excretion (e.g., liraglutide, exenatide, lixisenatide). Additional alterations in metabolism or molecular structure can prolong their duration of action further (e.g. exenatide LAR, dulaglutide, semaglutide).[69,70]

Generally, GLP-1 RAs cannot be administered enterally, apart from oral semaglutide (Rybelsus®). The inclusion of an absorption enhancer, salcaprozate sodium (SNAC), enables semaglutide to enter the bloodstream via the stomach, albeit with low bioavailability. This necessitates a logarithmically higher dose administered daily rather than weekly. Rybelsus® should be taken on an empty stomach with half a glass of water, and patients should wait at least 30 minutes before consuming other oral medications or food to avoid affecting absorption[71].

GLP-1 RAs reduce HbA1c levels by approximately 1 to 2% without hypoglycaemia risk, as β-cell insulin secretion is glucose-dependent. Side effects mainly involve gastrointestinal symptoms, such as nausea, vomiting, and potentially desirable weight loss. Several GLP-1 RA products have demonstrated

protection in patients with T2D against major adverse cardiovascular events, such as myocardial infarction, stroke, and cardiovascular death. Additionally, its protective effect on kidney function (e.g. reduction in macroalbuminuria) and beneficial cognitive effects have been reported[2,72].

The ADA/EASD international consensus and various guidelines recommend incorporating a GLP-1 RA with established cardiovascular benefits into the glucose-lowering therapy for all patients with T2D with high cardiovascular risk, irrespective of HbA1c levels. The choice between a subcutaneous (daily or weekly) or oral product depends on the preference of both the clinician and patient. Numerous large cardiovascular outcome studies reveal that several GLP-1 RAs exhibit cardiovascular and renal protective effects, with risk reductions in MACE, stroke, cardiovascular mortality, and renal endpoints documented.[2,72]

9.5 Sodium-glucose cotransporter-2 (SGLT2) inhibitors

SGLT2 inhibitors, such as canagliflozin, dapagliflozin, empagliflozin, prevent the glucose reabsorption by inhibiting glucose cotransporter-2 in the renal proximal tubule of nephrons. Consequently, hyperglycaemia leads to glycosuria which subsequently reduces the glucose in the blood. This glucose-lowering mechanism offers several advantages: it complements all other glucose-lowering medications (allowing additive combination therapy), does not rely on β-cell function (theoretically applicable to all diabetes forms), does not lead to hypoglycaemia, and induces calorie loss and weight reduction due to glucose loss. SGLT2 inhibitors' side effects include a slightly elevated risk of urinary infections and a thrice higher risk of fungal genital infections, particularly in women. These agents can decrease HbA1c levels by up to 1% but are ineffective in severe renal impairment.[2,73,74]

Within the SGLT2 inhibitor class, several products have demonstrated protection against major cardiovascular adverse events in patients with T2D and pre-existing cardiovascular disease or high cardiovascular risk. Additionally, a significant renal protective effect has been described, halving the risk of progression to dialysis/transplantation, doubling of serum creatinine, renal failure, and mortality. These effects are largely independent of their glucose-lowering action, as heart and kidney protection persists at low eGFRs (<60ml/min; where glucose-lowering effect is negligible) and in individuals without T2D. [2,73,74]

9.6 Sulphonylureas

Sulphonylureas, when orally administered, stimulate insulin secretion by activating sulphonyl urea receptors, leading to cell membrane depolarization, increased intracellular calcium concentration, and ultimately insulin granule exocytosis. All sulphonylureas share the same mechanism of action but differ in intrinsic activity (reflected in the average daily dose) and pharmacological properties (e.g., duration of action, metabolism). Sulphonylureas are contraindicated in severe diabetic dysregulation (acidosis), insulinopenia (T1D), or kidney or liver disease. Preparations with shorter or longer durations of action are available (see table). Among oral antidiabetic drugs, sulphonylureas are the most potent in lowering blood glucose levels, with hypoglycaemia and weight gain as the main side effects.

Additional adverse effects include overdose (causing prolonged hypoglycaemia), gastrointestinal discomfort, skin rash, and rare haematological abnormalities or ion disturbances[75,76]. Sulphonylureas are the agents most associated with hypoglycaemia risk together with insulin and should be avoided in the treatment of people with type 2 diabetes. In those treated with sulphonylureas, monitoring of glucose levels is indicated.

The risk for pilots and ATCOs treated with sulphonylureas should be placed at the same level at for those treated with insulin.

9.7 Thiazolidinediones

Thiazolidinediones reduce insulin resistance by inhibiting free fatty acid release through nuclear receptor (PPARγ) activation, stimulating glycolysis, and suppressing gluconeogenesis. The improvement in blood glucose levels is slow but sustained. Hypoglycaemia does not occur, but the primary side effects include fluid retention, a significantly increased risk of cardiac decompensation, and weight gain. Liver toxicity is rare but potentially life-threatening, necessitating liver function monitoring. Currently, only pioglitazone (Actos®) is available on the market.

10. INSULIN THERAPY IN PATIENTS WITH TYPE 2 DIABETES

Pilots with insulin-treated type 2 diabetes mellitus are currently deemed unfit to fly under the existing regulations set by the European Union Aviation Safety Agency (EASA). This stipulation is in place as a safety measure, and it's one of the criteria that can disqualify an individual from obtaining or maintaining a pilot's license within the jurisdiction of EASA.

Insulin therapy in patients with T2D differs from that in T1D. The goal for patients with T2D is to lower blood glucose levels in conjunction with oral glucose-lowering agents (supporting β-cell function). Due to the natural progression of T2D (gradual β-cell failure), insulin therapy may eventually be required for many patients with T2D. However, the current ADA/EASD consensus recommends GLP-1 RAs over insulin therapy as the first injectable treatment. Insulin is preferred for patients with very high HbA1c levels or signs of catabolism. Basal insulin is the preferred method for initiating insulin therapy in patients with T2D[2,77,78].

Generally, one injection of basal insulin (0.1 iU/kg or 10 iU) is administered at bedtime. Patients with T2D should be taught self-monitoring of blood glucose levels when starting insulin therapy, either through self-monitoring of blood glucose (SMBG) using finger-prick glucose measurements, Flash glucose monitoring and CGM. The insulin dose is incrementally adjusted based on fasting glucose levels (typical target fasting glucose <100 mg/dl (5.6 mmol/L), tailored to the patients with T2D profile). In cases of pronounced insulin resistance, the insulin requirement often surpasses the normal physiological production/need (approximately ±40 iU/day). Consequently, weight gain may occur if food intake remains constant (similarly with sulphonylureas), emphasizing the importance of adhering to a weight loss diet.[79,80]

As endogenous insulin production diminishes, insulin doses must be increased. If fasting blood glucose is controlled but HbA1c remains above target levels (usually less than 7% for most patients with T2D), intensification of the treatment regimen is needed. This may involve adding an SGLT2 inhibitor, a GLP-1 receptor agonist, or mealtime insulin. Mealtime insulin can be added gradually, beginning with one injection at the largest meal (basal-plus) and eventually progressing to a basal-bolus regimen like that in T1D. Weight control should be monitored, and excessive insulin doses avoided[,76,77,78,79].

As in T1D, hypoglycaemic events must be prevented, as they can be distressing, promote weight gain due to increased food consumption, and occasionally be dangerous, particularly in cases of coronary or cerebrovascular insufficiency or severe eye damage. Targeted diabetes education is essential for patients with T2D, with an even greater emphasis on dietary and lifestyle modifications. Physicians should also ensure the timely identification and management of complications or related conditions (e.g., metabolic syndrome) following the guidelines for T1D follow-up. Diabetes educators play a vital role in this process[2,9].

11. APPROACH TO THE MANAGEMENT OF MODY AND GESTATIONAL DIABETES

11.1 MODY

Maturity-Onset Diabetes of the Young (MODY) encompasses a collection of monogenic diabetes mellitus disorders characterized by early onset, generally prior to the age of 25. Treatment for MODY is contingent upon the specific genetic subtype, as each variant of MODY exhibits a unique aetiology and pathophysiology. Several prevalent MODY subtypes and their respective treatments include[81,82].

MODY 2 (GCK-MODY): This MODY variant arises from mutations in the glucokinase gene and is typically characterized by mild, stable hyperglycaemia, which frequently does not necessitate targeted treatment. Lifestyle modifications, such as adherence to a balanced diet and consistent physical activity, are generally adequate for regulating blood glucose levels[82–84].

MODY 3 (HNF1α-MODY): This subtype originates from mutations in the hepatocyte nuclear factor 1-alpha (HNF1α) gene. HNF1α-MODY treatment typically entails low-dose sulphonylureas, which can effectively manage blood glucose levels in most cases. Nonetheless, some patients may ultimately require insulin therapy as beta-cell function deteriorates[82,85].

MODY 1 and MODY 5 (HNF4α-MODY and HNF1B-MODY, respectively): Both subtypes result from mutations in distinct hepatocyte nuclear factor genes (HNF4α and HNF1β). Treatment for these MODY variants is akin to HNF1α-MODY, with sulphonylureas frequently serving as the initial treatment. Insulin therapy may be necessary if sulphonylureas prove insufficient for glycaemic control[82,86,87].

Other MODY subtypes: Treatment for rarer forms of MODY is typically individualized based on the specific genetic aberration and the severity of hyperglycaemia. In some instances, insulin therapy or alternative oral glucose-lowering agents may be mandated[81,82].

Accurate diagnosis of the MODY subtype is imperative in order to devise the most suitable treatment plan. Genetic testing and consultation with a specialist proficient in monogenic diabetes are vital for proper diagnosis and management[81,82].

11.2 Gestational Diabetes

Managing gestational diabetes mellitus often first involves changes in lifestyle. However, if these changes are not enough to reach blood sugar targets, insulin may be introduced. Insulin is the recommended treatment for high blood sugar levels in gestational diabetes. It's important to note that metformin and glyburide should not be the initial treatments because they can pass to the foetus through the placenta. There is also a lack of long-term safety data on other oral and injectable glucose-reducing medications.[88]

12. GLUCOSE-LOWERING TREATMENT OPTIONS FOR PEOPLE LIVING WITH DIABETES: IMPLICATIONS FOR PILOTS AND ATCO – MAIN CONCLUSIONS

This summary provides guidance for glucose-lowering therapies in pilots and ATCO and refers to the full text for details.

The aim of glucose-lowering in people living with diabetes is to prevent acute and chronic complications of diabetes and provide people with a good quality of life.

Many forms of diabetes exist, with the two most prevalent ones being T1D and T2D. Uncontrolled diabetes, with hyperglycaemia, is to be avoided in all, in particular pilots and ATCO, as hyperglycaemia affects performance, in particular cognitive functions and can result in complications (long-term), such as retinopathy leading to visual impairment, nephropathy, cardiovascular disease and neuropathy.

Treatment of diabetes, in all its forms, has important pillars, including education about the disease, dietary and lifestyle measures as well as pharmacological therapy.

12.1 Type 1 diabetes

T1D is characterized by an autoimmune destruction of the insulin-producing beta-cells leading to insulin-dependence for survival.

To date, in most countries of Europe, pilots and ATCO are considered unfit to function.

Under EASA ARA.MED.330 protocols, in some ~~those~~ countries ~~where~~ pilots and ATCO with T1D are allowed to function (UK, Ireland, Austria), providing that follow the strict protocol with good and stable glucose control is of the utmost importance to avoid hyperglycaemia (see above) but also hypoglycaemia (low blood sugars). Hypoglycaemia will ensue when an excess of administered insulin is present, e.g., due to less food intake or higher level of physical activity. Hypoglycaemia has different stages, with an important impact on cognitive functioning and should thus be avoided in pilots and ATCO.

12.1.1 Education

Education on the disease, on how insulin works and what the impact of physical activity, stress, food intake etc. is on insulin needs is of the utmost importance in pilots and ATCO. They should be followed by specialized teams, providing therapeutic patient education, and carefully assessing the insight of the pilot/ATCO in his/her disease. Particular attention should be given to avoiding hyper- and hypoglycaemia and how to cope with unforeseen circumstances. Pilots/ATCO traveling through time zones should be instructed by the specialized medical teams on how to adapt their therapy.

12.1.2 Dietary and lifestyle measures

Pilots and ATCO should adhere to healthy eating habits and regularly exercise. Using flexible insulin regimens (see below) will allow them to eat irregularly without compromising glucose regulation. A balanced diet, without severe restrictions, can be advised when using modern insulin regimens.

12.1.3 Insulin therapy

At the moment, pilots and ATCO treated with insulin are considered unfit to fly in most countries in Europe.

In a medical context, referring to the best evidence regarding health outcomes, intensive insulin therapy is advised in people with type 1 diabetes, with intensive monitoring of glucose levels, using sensors with alarms, warning on impending hyper- and hypoglycaemia episodes and use of individualized insulin regimens, assisted by specialized medical teams. Multiple daily injections of insulin can be used (combining slow- and rapid-acting insulins), but insulin pumps (CSII), connected to continuous glucose sensors with feedback and low-glucose suspend functions or full hybrid closed loop systems are preferred.

The hybrid closed loop systems, where continuous glucose sensors are connected to the insulin pumps and where algorithms (artificial intelligence) drive insulin administration, have been shown to bring down the risk of hypoglycaemia dramatically.

The safety of this therapeutic approaches concerning the conditions of risk and safety in the cockpit require additional evidence and further research. As of yet, under the EASA regulations, pilots with insulin treated are deemed unfit to fly.

12.2 Type 2 diabetes

T2D is characterized by insulin resistance and a progressive failing of the insulin producing beta-cells.

Treatment consists of oral or injected medications, some of which, including insulin, can provoke hypoglycaemia. However, the array of treatments for people with T2D has expanded dramatically in recent years, making use of insulin rarer in T2D, or at least simpler (limited to a basal insulin supplement).

For pilots and ATCO with T2D, good and stable glucose control is of the utmost importance to avoid hyperglycaemia (see above) but also hypoglycaemia (low blood sugars). In people with T2D two types of glucose-lowering medications can cause hypoglycaemia: insulin (see T1D) or sulphonylurea (promoting insulin secretion by beta-cells). All other medications do not cause hypoglycaemia to a level that impacts on cognitive functioning and can thus safely be used in pilots and ATCO.

12.2.1 Education

Education on T2D in pilots and ATCO is of the utmost importance. Again, they should be accompanied by expert medical teams. Education should span insights into the disease, the importance of healthy lifestyle (e.g., importance of diet, physical activity, cardiovascular protection) and how the medications they are taking for glucose-lowering work (e.g., if insulin is needed in the therapeutic regimen, specific attention on prevention of hypoglycaemia is needed).

12.2.2 Dietary and lifestyle measures

Pilots who have diabetes are advised to adhere to the same guidelines for maintaining a healthy lifestyle as their peers without diabetes. The aim is for them to lead a life that is as normal as possible. There is no specific evidence suggesting that individuals with diabetes who work night shifts or have a busy lifestyle need to follow unique rules.

Pilots and ATCO should adhere to healthy eating habits and regularly exercise. A balanced diet, targeting avoidance (or reversal) of overweight should be advised as well as physical activity. Special attention should be given to cardiovascular protection (e.g., smoking cessation, blood pressure control).

12.2.3 Pharmacological therapy

Most people with T2D can now be treated with agents that are potent glucose lowering, without causing hypoglycaemia and with direct organ-protecting effects (SGLT2 inhibitors and GLP1-receptor agonists). These agents will lower glucose levels effectively and combined with metformin, will be the therapy of choice in pilots and ATCO with T2D.

Other glucose-lowering therapies that can be used safely are the DPP4 inhibitors. These agents are less potent but allow glucose control with a very low risk of hypoglycaemia.

When using lifestyle measures, together with either of the above-mentioned pharmacotherapies, self-monitoring of glucose levels (preferentially using CGM) is optional.

Self-monitoring of glucose levels preferentially using CGM) is mandatory for pilots/ATCO when using insulin or sulphonylurea, as both these agents can cause hypoglycaemic attacks. When insulin is needed, a supplement of a basal insulin analogue, with the lowest risk of hypoglycaemia (degludec or glargine U300) should be preferred on top of metformin, SGLT2 inhibitors and/or GLP1 receptor agonists). Sulphonlyurea should be avoided maximally or used at the lowest possible dose.

A multifactorial approach is needed in T2D, with specific attention to blood pressure control and lipid control, to avoid in particular macrovascular disease (myocardial and cerebral infarction).

13. IMPLICATIONS IN TREATING PILOTS AND ATCOS WITH DIABETES

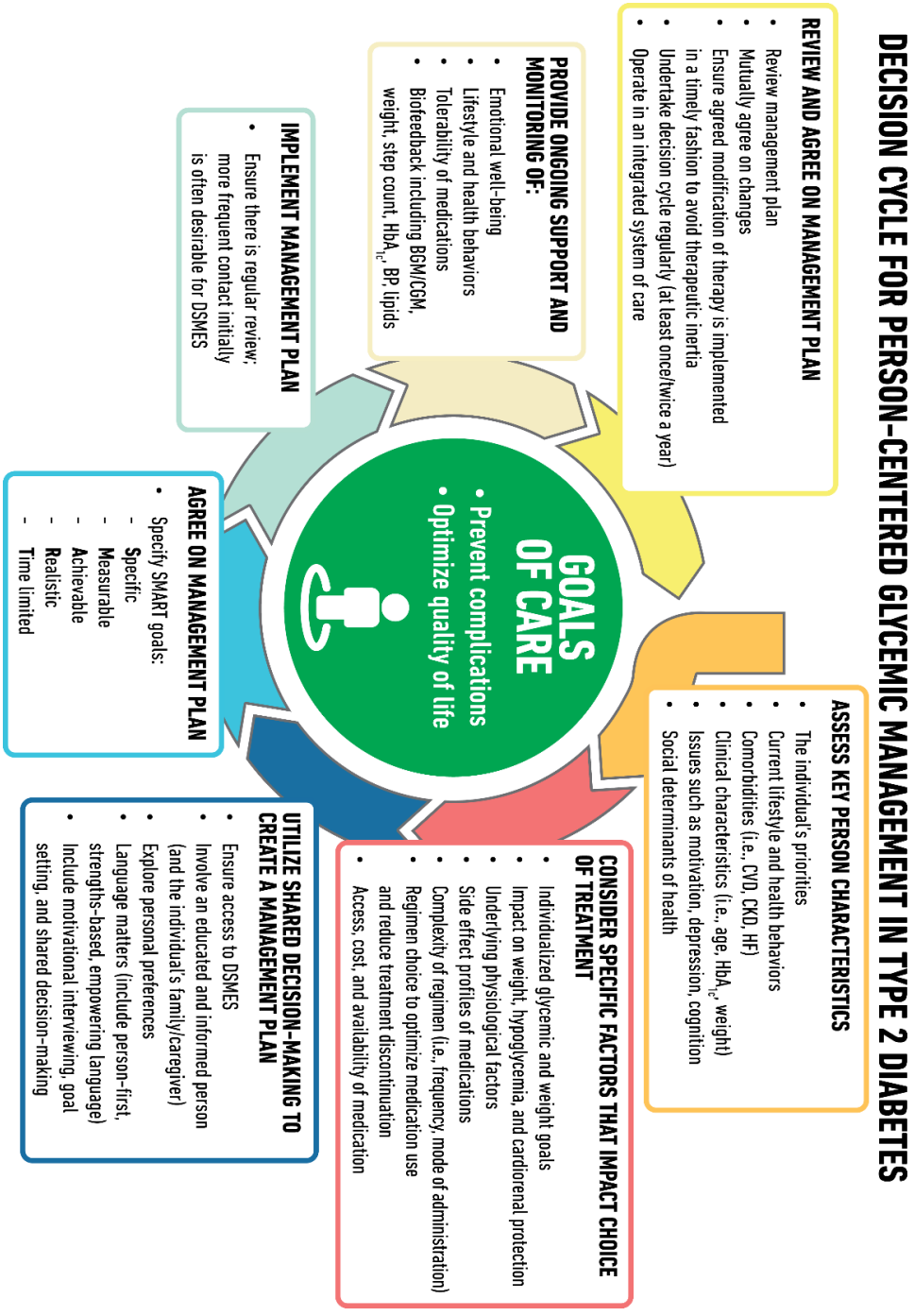
The unique environment that pilots and ATCOs work in provides greater challenges for the management and treatment of diabetes. In addition, safety concerns in general must be taken into consideration. The risk of hypoglycaemia and incapacitation is the most widely quoted reason for a blanket ban policy preventing safety-critical operations being performed by people with diabetes managed with insulin or hypoglycaemic agents that can lower blood glucose below normal. Advances including new insulin analogues which reduce the risk of hypoglycaemia, insulin pumps, and non-invasive CGM and techniques have led to vastly improved glycaemic control in insulin-treated diabetes.

There has been a reduced frequency of severe hypoglycaemia events and a delay in diabetes-related comorbidities and complications. It is thus possible to re-appraise the relative risks and extend the boundaries of what is possible, practical, and safe[89]

14. ANNEXES

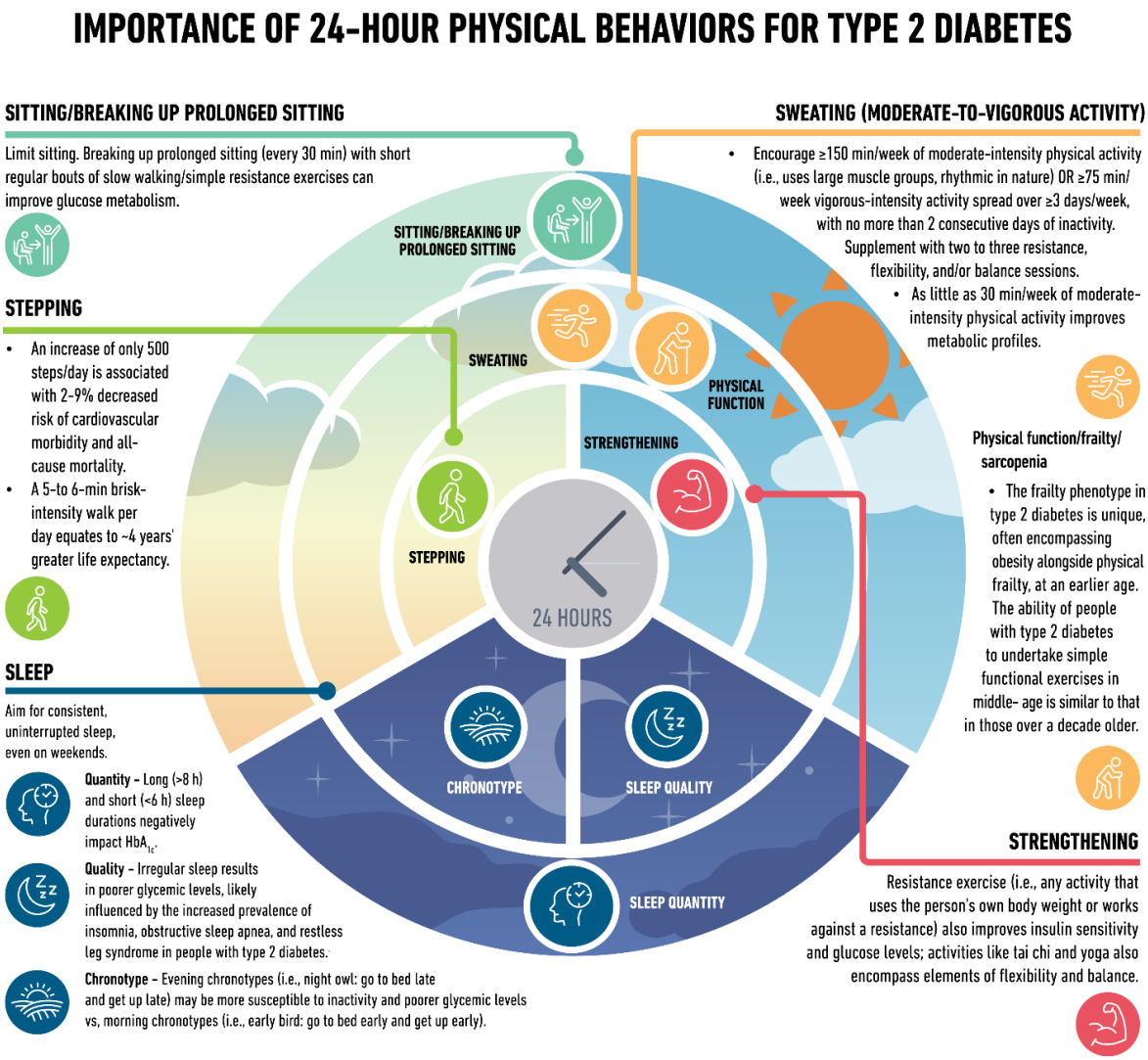
14.1 Figure 1

Decision cycle for person-centred glycaemic management in type 2 diabetes.



14.2 Figure 2

Importance of 24-h physical behaviours for type 2 diabetes.



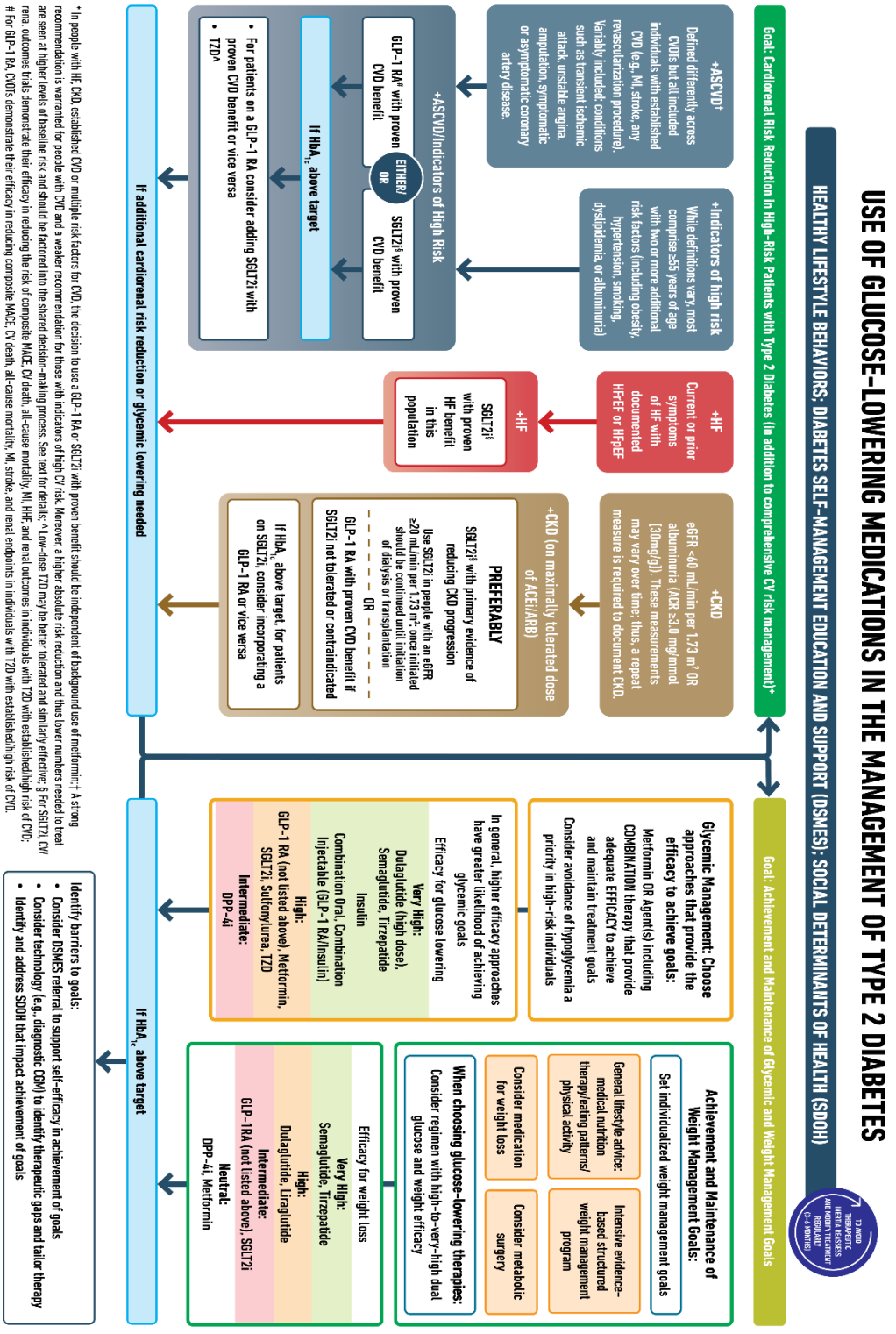
	Glucose/insulin	Blood pressure	HbA_{1c}	Lipids	Physical function	Depression	Quality of life
SITTING/BREAKING UP PROLONGED SITTING	↓	↓	↓	↓	↑	↓	↑
STEPPING	↓	↓	↓	↓	↑	↓	↑
SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)	↓	↓	↓	↓	↑	↓	↑
STRENGTHENING	↓	↓	↓	↓	↑	↓	↑
ADEQUATE SLEEP DURATION	↓	↓	↓	↓	?	↓	↑
GOOD SLEEP QUALITY	↓	↓	↓	↓	?	↓	↑
CHRONOTYPE/CONSISTENT TIMING	↓	?	↓	?	?	↓	?

IMPACT OF PHYSICAL BEHAVIORS ON CARDIOMETABOLIC HEALTH IN PEOPLE WITH TYPE 2 DIABETES

↑ **Higher levels/improvement** (physical function, quality of life); ↓ **Lower levels/improvement** (glucose/insulin, blood pressure, HbA_{1c}, lipids, depression); ? no data available;
↑ Green arrows = **strong evidence**; ↑ Yellow arrows = **medium strength evidence**; ↑ Red arrows = **limited evidence**.

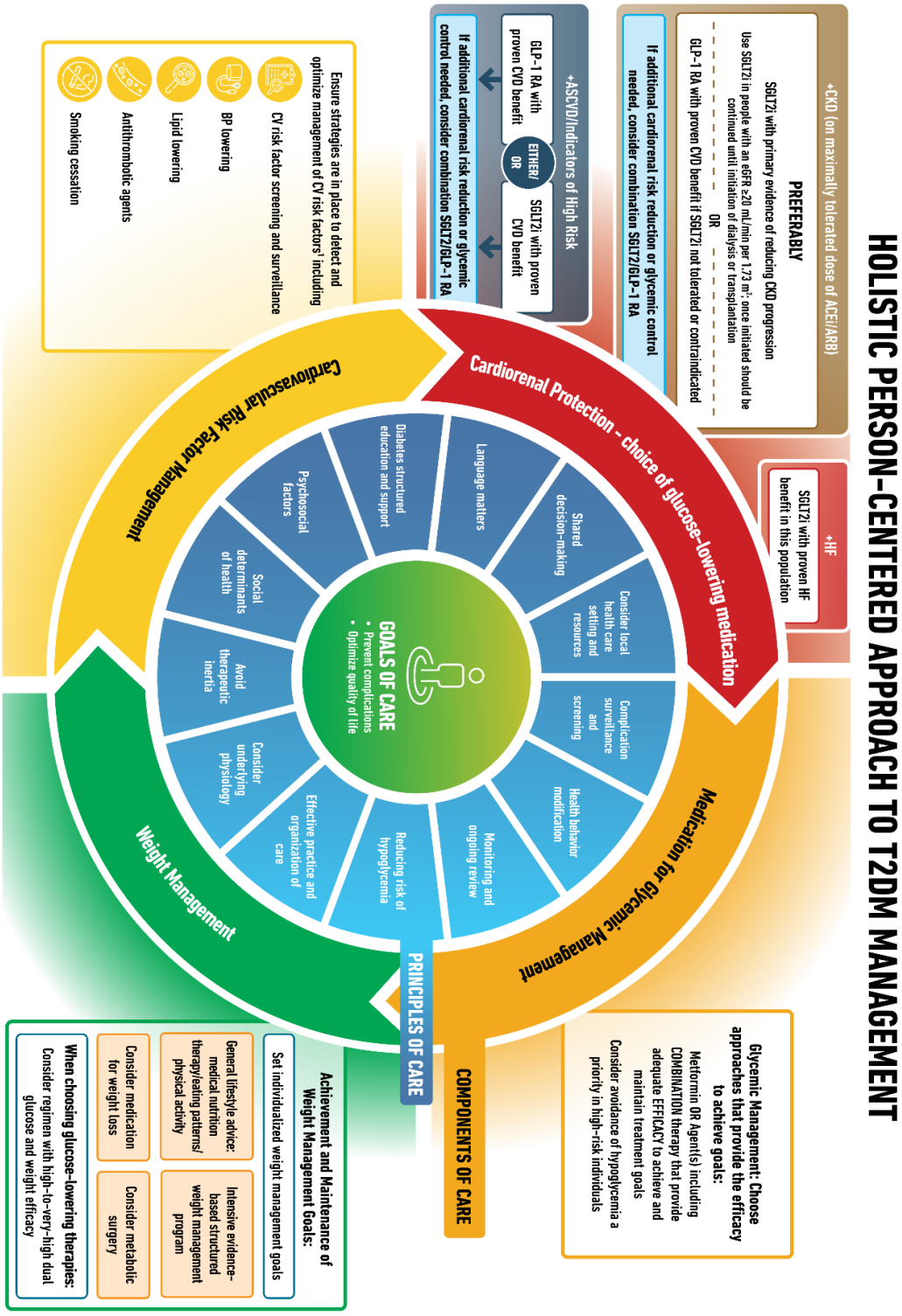
14.3 Figure 3

Use of glucose-lowering medications in the management of type 2 diabetes.



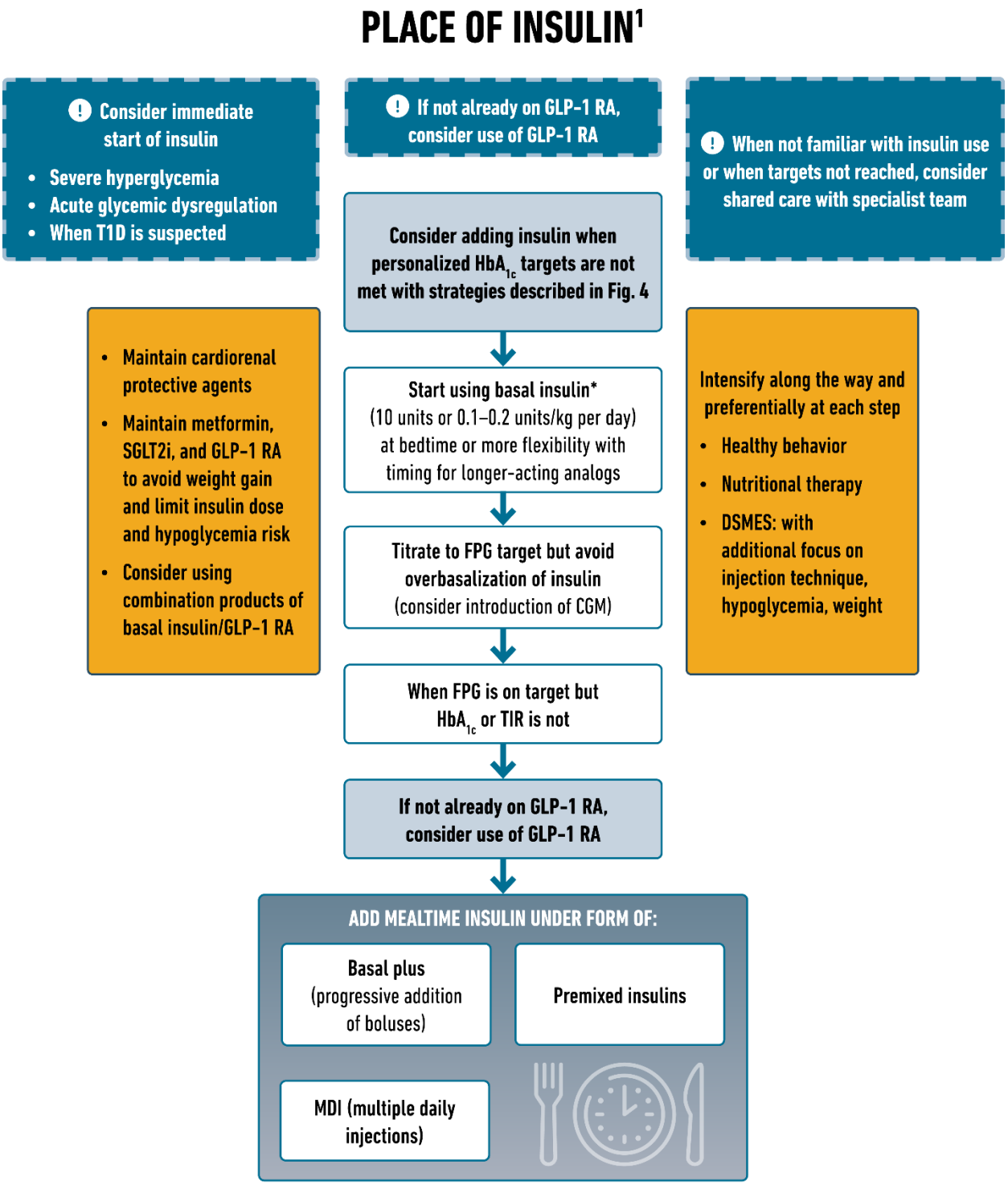
14.4 Figure 4

Holistic person-centered approach to T2DM management.



14.5 Figure 5

Place of insulin.



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