Diabetes and Treatments

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Milan Obradovic, Emina Sudar-Milovanovic, Zoran Gluvic, Takashi Gojobori, Magbubah Essack, and Esma R. Isenovic

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M. Obradovic · E. Sudar-Milovanovic · E. R. Isenovic (✉)
Department of Radiobiology and Molecular Genetics, VINČA Institute of Nuclear Sciences - National Institute of the Republic of Serbia, Belgrade, Serbia
e-mail: isenovic@yahoo.com

Z. Gluvic
Clinic for Internal Medicine, Department of Endocrinology and Diabetes, Zemun Clinical Hospital, School of Medicine, University of Belgrade, Belgrade, Serbia

T. Gojobori · M. Essack
Computer, Electrical and Mathematical Sciences and Engineering Division (CEMSE), Computational Bioscience Research Center, Computer (CBRC), King Abdullah University of Science and Technology (KAUST), Thuwal, Kingdom of Saudi Arabia

Biological and Environmental Sciences and Engineering Division (BESE), King Abdullah University of Science and Technology (KAUST), Thuwal, Kingdom of Saudi Arabia

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Abstract

The diabetes pandemic demands solutions for proper glycemic control and prevention of future chronic complications that could result in organ failure or comorbidities. In this regard, we now know that patients diagnosed with diabetes require individual management plans. Thus, new treatment management strategies have been designed to allow clinicians to tailor the most appropriate therapy for diabetes patients individually. These treatment management plans extend beyond defining the appropriate medications for patients; they provide a directive toward some acute and chronic complications that should be screened for, as they are historically known to occur with diabetes. Observing any of the complications or comorbidities requires the patient medication regimen to be adapted accordingly. This chapter describes such modern treatment plans for the two primary forms of diabetes, type 1 and type 2, based on both basic and clinical studies, later incorporated in various diabetes management guidelines and outlines expected future trends.

Keywords

Diabetes · Delivery of insulin · Islet transplantation · Stem cells therapy · Hyperbaric oxygen therapy · Pharmacotherapy of diabetes

Introduction

Diabetes mellitus (DM) is an endocrine disease, characterized by hyperglycemia and multiple metabolic disorders that cause serious local and systemic effects (Nair 2007; Forbes and Cooper 2013; Katsarou et al. 2017). Nowadays, DM is one of the biggest health problems and has reached pandemic proportions (Forouhi and Wareham 2014). According to the International Diabetes Federation, 425 million people worldwide have DM, with a tendency to be 629 million in 2045 (Cho et al. 2018). There are at least five types of DM, while the two primary forms are DM type 1 (DMT1) and DM type 2 (DMT2) (ADA 2010; Katsarou et al. 2017; Cho et al. 2018). Autoimmunity is a significant factor in the development of DMT1, while genetic predisposition and obesity are leading risk factors for the development of DMT2 (Al-Goblan et al. 2014; Nair 2007).

Long-term anti-diabetic pharmacotherapy and lifestyle adaptations are necessary to achieve glycemic control and decline multisystem disorders in DM patients (Rai et al. 2016; Katsarou et al. 2017).

History

Nearly one century ago, exogenous insulin became available (Banting and Best 1990; Maclean 1926). In the meantime, plenty of oral hypoglycemics were designed, and they achieve desirable results in patients with DMT2 (Butterfield et al. 1957; Krall et al. 1958). However, exogenous insulin is irreplaceable in the treatment of people with DMT1, being required in abundant cases of DMT2 as well (Handelsman et al. 2015). Despite constant progress in terms of the new therapeutic approaches, a comprehensive and efficacious cure for DM is still not accomplished. Current therapies for patients with DM have several shortfalls, including efficacy, timings, and glycemic control (Shah et al. 2016; Castle et al. 2017; Evans et al. 2011; Pathak et al.

2019). Also, these therapies produce numerous side effects like gastric irritation, injection phobia, diarrhea, and loss of appetite (Pathak et al. 2019; Rai et al. 2016; Zaric et al. 2019).

Etiology and Pathophysiology of DMT1 and DMT2

Diabetes mellitus (DM) is a metabolic disorder characterized by alterations and impairment in insulin and glucagon secretion and/or action that lead to hyperglycemia (ADA 2009; Girard 2017). Besides the increased blood glucose level, DM is also characterized by other biochemical disorders arising as a consequence of inadequate regulation of insulin synthesis/actions, in association with long-term injury, dysfunction, and failure of different organs, especially blood vessels and heart (Jovanovic et al. 2017; Obradovic et al. 2017; Sudar-Milovanovic et al. 2015, 2017; Obradovic et al. 2015; Soskic et al. 2011), however also nerves, kidneys, and eyes (ADA 2009).

The overall prevalence of DM among adults over 18 years of age is steadily growing, and it has been increasing more rapidly in countries with low- and middle-income economies. The growth in DM prevalence reflects the rise in overweight and obesity, which are a consequence of physical inactivity and unhealthy diets (Roglic 2016). The World Health Organization (WHO) shows DM prevalence grew from 4.7% (1980) to 8.5% (2014), being the seventh leading cause of death worldwide in 2016 (WHO 2018). Furthermore, it is one of the leading causes of stroke, heart and kidney failure, blindness, as well as lower limb amputation.

Type 1 Diabetes

DMT1 is a multifactorial autoimmune disease that develops under the influence of environmental or/and genetic factors (Atkinson et al. 2014; Ikegami et al. 2011). DMT1 mostly develops in patients at a young age, before the age of 30. The main characteristic of DMT1 is lack of insulin production, and DMT1 patients are dependent on exogenous insulin application.

DMT1 is an immune-mediated type of DM, and typically an autoimmune demolition of the insulin-secreting beta cells is based on DMT1 development. Factors involved in its pathogenesis trigger lymphocyte infiltration in pancreatic beta cells, and the consequent production of different proinflammatory cytokines responsible for the pancreatic beta cells destruction (Fatima et al. 2016).

Increased risk for DMT1 is generally recognized in patients by serological confirmation of an autoimmune process occurring in pancreatic islets/beta cells, considering that this is one of the first pathological alterations, and additionally by genetic marker determination (ADA 2009). Some patients with DMT1 can exhibit detectable insulin secretion, indicating some surviving beta cells, or an ongoing cycle of destruction and regeneration of such cells (Meier et al. 2005).

Type 2 Diabetes

It represents the vast majority (85–90%) of DM cases. DMT2 is a heterogeneous, progressive metabolic and endocrine illness, and it occurs as an interplay of various genetic as well as environmental factors. The underlying origins are insulin resistance in combination with deficient compensatory beta-cell reaction and adequate insulin secretion (ADA 2009). The impairment of insulin-secreting pancreatic beta cells shows progression over time.

When DMT2 patients with normal fasting plasma glucose, however with postprandial hyperglycemia, exhibit impaired insulin action, usually it is caused by a reduction of total insulin receptor numbers (Belfiore et al. 2009; Obradovic et al. 2019).

Delivery of Insulin, Islet Transplantation, and Stem Cells

The management of DM aims to recover glycemic control and reduced micro- and

macro-vascular complications, by administrating pharmacological therapy and modifications of lifestyle. Insulin replacement represents the first-line option for insulin-dependent DM patients (Pathak et al. 2019). One of the significant challenges in the treatment of patients with DM is the efficacy of exogenous insulin in achieving long-term normal ranging glycemia (Yeh et al. 2012). One alternative is the use of continuous insulin infusion pumps (Yeh et al. 2012; Heller et al. 2017). Also, the creation of insulin analogs with different times of action, from rapid and short-acting to ultra-long acting, contributed to improvements in therapy (Shah et al. 2016; Pathak et al. 2019). Implementation of these technological advances does not prevent long-term insulin dependence, and adverse effects like invasiveness (Shah et al. 2016).

Noninvasive Insulin Administration

To avoid such complications, researchers proposed new routes for insulin administration beyond the standard subcutaneous route (Rys et al. 2018; Atkinson et al. 2014), such as nasal (Kullmann et al. 2018; Schmid et al. 2018), oral (Fonte et al. 2013), pulmonary (Mastrandrea 2010; Ledet et al. 2015), and transdermal delivery systems (Zaric et al. 2019).

Drug delivery carrier systems protect antidiabetic drugs from enzymatic degradation at the absorption site, and ensure delivery at the optimal and effective concentration for a more extended period at the target site (Rai et al. 2016). The encapsulation of insulin in particles increases its potential and allows its appropriate transport to the specific site to better control of DM (Rai et al. 2016; Zaric et al. 2019). These particles are usually microsized or nanosized. The microparticle system adjusts the pattern of drug release and improves the hypoglycemic effect of oral delivery of insulin (Wong et al. 2018). The main limiting factors of microparticle systems are the size of particles and their hydrophilic/hydrophobic nature that makes difficult their transport through biological membranes (Wong et al. 2018).

The use of nanocarriers reduces these obstacles (Bahman et al. 2019). The small size and structural diversity of nanoparticles increase the potential of insulin through better absorption and distribution, site specificity, and protection from enzymatic degradation (Bahman et al. 2019). Also, this form of application extends the release pattern of insulin and decreases the frequency of dosage, facilitating normoglycemia for a more extended period, up to 22 days (Peng et al. 2012). Other approaches considered for delivery of insulin and antidiabetics include encapsulation in liposomes, vesicular systems, and other nanoparticles (Souto et al. 2019).

The Artificial Pancreas

The use of continuous insulin infusion pumps and glucose monitoring has enabled a constant movement toward artificial pancreas development (Boughton and Hovorka 2019). Pancreas or islet transplantation seems to be the best choice to prevent dependence on insulin; however, donor shortages limit this option. Although islet transplantation was substantially enhanced in the past 2 decades, there are still limitations like instant blood-mediated inflammatory reaction, ischemia-induced loss of islet, harmful effects of immunosuppressive drugs, and apoptosis of transplanted cells (Bottino et al. 2018).

Stem cells generating new beta cells represent a promising approach for long-term treatment of DM (Stanekzai et al. 2012; Cierpka-Kmiec et al. 2019; Aguayo-Mazzucato and Bonner-Weir 2010). Many studies show that human embryonic stem cells can be used for beta cell generation and transplantation in patients with DMT1 (Cierpka-Kmiec et al. 2019; Kalra et al. 2018). Challenges are generation of genetically stable cells, survival rate of the cell, potential of transplanted cells, and ethical issues considering utilization of embryo-derived stem cells (Kalra et al. 2018). Some of these issues are overcome using induced pluripotent stem cells generated from somatic cells of patients with DMT1 to produced functional beta cells (Kalra et al. 2018; Kunisada et al. 2012).

Transplantation of insulin-producing human embryonic stem cells into streptozotocin-induced diabetic mice resulted in long-term normalization of blood glucose levels (Vegas et al. 2016). Yet loss of novel beta cells immediately after portal vein transplantation is in the range of 5–47% (Potter et al. 2014; Naziruddin et al. 2014). A current suggestion is co-transplantation of islets with different cell types, such as mesenchymal stem cells (MSC), bone marrow-derived MSC, endothelial colony-forming cells, and others (Kerby et al. 2013; de Souza et al. 2017; Borg et al. 2014; Corradi-Perini et al. 2017; Jung et al. 2014), to reduce losses of beta cells and increase their potential. This approach was shown to increase islet survival and function, and promote angiogenesis and better glycemic control due to the anti-apoptotic and pro-angiogenic effects of MSC (de Souza et al. 2017; Pathak et al. 2019).

Drugs

Non-insulin agents or those who sensitize insulin action enable the opening of new chapters in diabetes management (Grant and Kirkman 2015; Rowley et al. 2017; Leon and Maddox 2015). Some of the innovations also concern insulin treatment, namely insulin analogs with improved control of glycemia and lowered hypoglycemia risk, as well as the development of non-parenteral route/s of insulin administration (Biester et al. 2017; Fink et al. 2018). Such innovations are placed into clinical practice through precisely defined recommendations, such as those of the American Diabetes Association (ADA) (ADA 2018), American Association of Clinical Endocrinologists (AACE) (Garber et al. 2019), European Association for the Study of Diabetes (EASD) (Davies et al. 2018), and the National Institute for Health and Care Excellence (NICE) (McGuire et al. 2016). Even though these recommendations have subtle differences, they are oriented toward a patient-centered approach, and direct clinicians toward better and more uniform management of the patients (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016). Well-controlled diabetes apparently slows down the atherosclerotic process, which is the base of associated micro- and macrovascular diabetes complications and major cardiovascular events, including ones with fatal outcomes (Zoungas et al. 2014).

Pharmacotherapy of DMT1

Current recommendations are focused on individually tailored management of DMT1, consisting of appropriate dietary habits and physical activities, along with administration of insulin. It is strongly advised to adapt insulin treatment to carbohydrate intake, pre-prandial glycaemia, and anticipated physical activity (ADA 2018; Handelsman et al. 2015; National Clinical Guideline Centre 2015).

The mainstay of DMT1 management is insulin, administered by pen device or continuous subcutaneous insulin infusion (CSII). The amount and number of divided insulin doses in children or adults immediately after DMT1 diagnosis are often small (1–2 divided doses), however often increases in time (Biester et al. 2017; Fink et al. 2018; Pickup 2019). In the last decades, there was a tendency to opt for insulin analogs with improved pharmacokinetics, pharmacodynamics, and safety compared to human insulin (Biester et al. 2017; Fink et al. 2018; Heinemann et al. 2017).

Rapid insulin analogs are active immediately after administration, with short-lived effects. Basal analogs have more prolonged effects than classic neutral protamine Hagedorn (NPH) human insulin regarding glycemia control, with lower hypoglycemic risk. The usual dose is 0.5 IU/kg of body weight. During puberty and in exceptional circumstances, insulin requirements are higher. Overall, CSII is widely recommended, and it can be used in patients older than 65 years (ADA 2018; Handelsman et al. 2015; National Clinical Guideline Centre 2015; REPOSE Study Group 2017; Beck et al. 2017).

In addition, pre-prandial inhaled insulin has been shown to be efficient in the form of rapid insulin analogs (B28 aspart-insulin); however, its use in DMT1 patients is not widespread as it was

expected (ADA 2018; Heinemann and Parkin 2018).

Non-insulin Pharmacological Agents

Metformin, dipeptidyl peptidase 4 inhibitors (DPP-4i), glucagon-like peptide 1 receptor agonists (GLP-1 RA), and sodium-glucose cotransporter-2 inhibitors (SGLT-2i) are not Food and Drug Administration (FDA)-approved, despite showing beneficial effects in obese DMT1 patients (ADA 2018; Handelsman et al. 2015; Livingstone et al. 2017).

Pramlintide, an analog of the hormone amylin also secreted by pancreatic beta cells, is approved for use of DMT1 adults; however, it exhibits higher risk for hypoglycemia and obliged reduction of prandial insulin (Hieronymus and Griffin 2015). For patients with ineffective glycemic regulation or diabetics referred to renal transplantation, pancreas and islet transplantation could be the better treatment option (Gruessner 2011; Nakamura et al. 2019).

Pharmacotherapy of DMT2

Non-pharmacological measures are usually the preferred initial treatment for DMT2 patients. Apart from lifestyle changes (nutrition and physical activity) and eventual pharmacotherapy, an integral part of DMT2 management is the screening for cardiovascular disease (CVD) risk factors as well as the detection of chronic micro- and macro-vascular complications (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016).

DMT2 management aims to achieve clinical and biochemical goals (actual profile and retrograde glycemic regulation), avoiding hypoglycemic episodes and gain in body weight in obese patients, as well as controlling the risk of atherosclerotic CVD (ASCVD) (ADA 2018).

Therapeutic Aims

HbA1c, morning glycemia, and 5-point daily glycemic profile should be adjusted to age, duration of DM, risk of hypoglycemia, and the presence of comorbidities and chronic vascular complications. The level of HbA1c is an essential marker for the assessment of retrograde glycemic control. In DM patients with no comorbidities and low hypoglycemia risk, HbA1c level $\leq$7% (ADA 2018) indicates reasonable retrograde DM control for the previous 90–120 days. On the other hand, in DM patients with severe comorbidities and considerable risk of hypoglycemia, the acceptable level of HbA1c is $<$8% (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016). A more stringent HbA1c goal of $<$6.5% is set in some special populations of individuals suffering from DM (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016).

Pharmacotherapy of DMT2 is conducted as mono- or combination-therapy. The therapy chosen depends on biochemical and clinical factors, existing comorbidities, as well as side effects of administered drugs.

Monotherapy of DMT2

For patients with newly diagnosed DMT2 and HbA1c $<$9% (6) or $>$6.5% (9), metformin is the initial therapy, with a daily dose of 1.5–2.0 g. Metformin contributes to decrease in body weight, and reduces the risk of hypoglycemia. Gastrointestinal side effects are often transitional and dose-dependent. It is contraindicated if glomerular filtration rate (eGFR) is $<$30 ml/min. (Livingstone et al. 2017; Sanchez-Rangel and Inzucchi 2017).

In metformin-intolerant patients, acceptable alternatives are GLP1-RA, DPP-4i, alpha glucosidase inhibitors (AGi), and SGLT-2i. With the administration of such agents, the risk of

hypoglycemia is lower, and there is no weight gain. Other alternatives are thiazolidinediones (TZD) and sulphonylureas (SFU) or glinides, however with more risk of hypoglycemia and weight gain (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016).

Combination Therapy for DMT2

In DMT2 patients with HbA1c >9% (ADA 2018) or ≥7.5% (Garber et al. 2019; McGuire et al. 2016), as well as in those for whom metformin is not enough to achieve adequate glycemic regulation, another agent is added to the treatment regime (management intensification). Metformin-intolerant patients are administered two or more agents, with a complementary mechanism of action. There are fixed combinations that include metformin + DPP-4i/TZD/SFU on the market. Additionally, metformin with modified-release could be a suitable alternative for some of the metformin-intolerant. The acceptable level of HBA1c after management intensification should be <7%.

Insulin Introduction

If despite the use of non-pharmacological measures and dual pharmacotherapy, HbA1c is ≥7.5%, basal insulinization should be the solution. Insulin treatment starts with a plan of its administration, and continued use of metformin is recommended in suitable and tolerant patients (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016).

Dose tapering or need for administration of other non-insulin glucose-lowering agents are relevant concerns (McGuire et al. 2016). If HbA1c >9%, indicating poor control, the patient should be conducted to dual oral treatment. Furthermore, if the patient initially presented with HbA1c ≥10% or with glycemia >16.7 mmol/L or is clinically symptomatic, combined treatment of insulin and oral antihyperglycemic therapy, or even multiple insulin injections, should be considered (ADA 2018). If an insulinization process of basal insulin introduction along with metformin and/or other non-insulin glucose-lowering agents fails to control DMT2, the addition of one or more doses of rapid-acting insulin or GLP-1RA is a possible alternative (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016). Also, if a DMT2 patient is suffering from ASCVD, the addition of a CVD-beneficial agent such as empagliflozin, canagliflozin, dapagliflozin, or liraglutide is worth considering (Arnett et al. 2019; Zelniker et al. 2019; Wiviott et al. 2019; Furtado et al. 2019).

Exenatide, Liraglutide, Lixisenatide and Semaglutide

These are GLP-1RA peptides, structurally homologous to the natural incretin glucagon-like peptide-1 (GLP-1), and currently available for subcutaneous administration. Semaglutide has been approved by FDA in 2019 for oral use. GLP-1RA stimulate glucose-dependent pancreatic insulin secretion as well as reduce glucagon secretion, slowing down gastric emptying. They also significantly reduce body weight and lower HbA1c levels. They are devoid of negative effects on bone metabolism, the appearance of diabetic ketoacidosis (DKA), and congestive heart failure (CHF) deterioration. Some gastrointestinal side effects could be encountered (nausea, vomiting, bloating, gastroesophageal reflux disease, and gastroparesis); however, they often improve with time. The risk of hypoglycemia is low.

In studies on rodents, exenatide intake lead to hyperplasia of C cells and medullary thyroid cancer, while all GLP-1RA were associated with pancreatitis. Exenatide is not indicated in patients with eGFR < 30 ml/min. (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016; Deacon 2019).

Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, and Alogliptin

These represent the family of DPP-4i, blocking the DPP4 enzyme involved in the degradation of incretins such as GLP-1 and gastric inhibitory peptide (GIP). As a result, more elevated incretin levels act on a simultaneous increase in glucose-dependent insulin secretion, and decrease in glucagon secretion. There is no convincing evidence regarding the higher risk of pancreatitis or pancreatic cancer with the use of DPP-4i. DPP-4i exhibit neutral effects regarding hypoglycemia risk and body weight change, and gastrointestinal side effects are not frequent. DPP-4i effectively reduce albuminuria and do not have negative effects on the bones and the appearance of DKA. Saxagliptin is not recommended for CHF patients. Also, renal dose adjustment is required when using all DPP-4i except for linagliptin (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016; Deacon 2019; McGuire et al. 2019; Scirica et al. 2013).

Acarbose, Miglitol, and Voglibose

These AGi block the alpha-glucosidase enzyme involved in carbohydrate reabsorption in the gastrointestinal system. Digestive side effects can be frequent, including bloating, diarrhea, abdominal cramps, and mild elevation of liver enzymes. They are neutral regarding hypoglycemia risk, body weight change, bone disease, CHF deterioration, and the appearance of DKA. Renal dose adjustment is not required (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016; Liu and Ma 2017).

Pioglitazone

This TZD activates the PPARγ receptors and, through determined signal pathways, decreases insulin resistance in various tissues, predominantly in skeletal muscles (Yki-Jarvinen 2004). The clinicians are under pressure to precisely select the patients for their use because of some associated side effects, such as body weight gain, fluid retention, higher risk of bone fractures, and bladder cancer (Wang et al. 2017; Mehtala et al. 2019). Hypoglycemia risk and body weight change are not common with moderate doses, and there are no associated gastrointestinal side effects. They occasionally exhibit mild negative effects on the bones, CHF deterioration, and the appearance of DKA. Renal dose adjustment is not required; however, TZDs are generally not recommended in any stage of renal failure due to fluid retention (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016; Yki-Jarvinen 2004; Wang et al. 2017; Mehtala et al. 2019).

Sulphonylureas and Glinides (Gliclazide, Glipizide, Glimepiride, Repaglinide)

Such drugs mediate insulin secretion after binding to SUR Ki6.2 receptor, the sodium channel (Kalra and Gupta 2015). Significant effects are to be expected regarding hypoglycemia and weight gain. Mild negative effects on CHF deterioration are likely, however not on bones and DKA. Renal dose adjustment is required (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016; Wang et al. 2018; Harsch et al. 2018).

Dapagliflozin, Canagliflozin, and Empagliflozin

SGLT-2i reduce proximal tubule glucose reabsorption by binding to the SGLT-2 receptors. Ascending urinary infections, chronic and treatment-resistant urinary and vaginal candidiasis, elevation of LDL-cholesterol, dehydration, and hypotension, as well as DKA have been registered (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016; Wanner and Marx 2018; Lupsa and Inzucchi 2018). They are usually safe regarding hypoglycemia risk and contribute to bodyweight reduction. There are no associated gastrointestinal side effects.

SGLT-2i use is not indicated in patients with eGFR < 45 (60) ml/min. Empagliflozin use requires special attention regarding potential negative effects on the bones, as well as the use of all SGLT-2i regarding DKA appearance (ADA 2018; Garber et al. 2019; Davies et al. 2018; McGuire et al. 2016; Singh and Kumar 2018). Some studies point out to positive effects of empagliflozin and dapagliflozin in cases with the occurrence of major CVD, ASCVD, and CHF deterioration (Arnett et al. 2019; Zelniker et al. 2019; Wiviott et al. 2019; Furtado et al. 2019).

In exceptional circumstances, when it is impossible to control DMT2 with the usual mono/dual/combined therapy, colesevelam (Ooi and Loke 2014) and quick-release bromocriptine (Lopez Vicchi et al. 2016) could be used. Their mechanism in blood sugar lowering is not known; however, the risk of hypoglycemia is low.

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