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Review

Pharmacotherapy of type 2 diabetes: An update

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Abbreviations: T2DM, type 2 diabetes; IR, insulin resistance; HbA1c, glycated hemoglobin A1c; GLUT-4, glucose transporter4; GLP-1, glucagon-like peptide-1; DPP4, dipeptidyl peptidase; eGFR, estimated glomerular filtration rate; HF, heart failure; UKPDS, United Kingdom Prospective Diabetes Study; DR, delayed-release; MI, myocardial infarction; SU, sulfonylureas; SUR, sulfonylurea receptor; AMPK, adenosine monophosphate-activated protein kinase; ACCORD, Action to Control Cardiovascular Risk in Diabetes Trial; ADOPT, A Diabetes Outcome Progression Trial; VADT, Veteran Affairs Diabetes Trial; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; RECORD, rosiglitazone evaluated cardiovascular outcomes in oral agent combination therapy for type 2 diabetes; AGS, American Geriatrics Society; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; IGT, impaired glucose tolerance; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; NYHA, New York Heart Association; NASH, nonalcoholic steatohepatitis; CRP, C-reactive protein; PROACTIVE, Prospective Pioglitazone Clinical Trial In Macrovascular Events; ACS, acute coronary syndrome; CVD, cardiovascular disease; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; NPH, protamine Hagedorn; EASD, European Association for the Study of Diabetes; ORIGIN, Outcome Reduction with Initial Glargine Intervention; NPL, protamine lispro; LVEF, left ventricular effective fraction; GLP-1RA, GLP-1 receptor agonists; FDG PET, fluorodeoxyglucose positron emission tomography; fMRI, functional magnetic resonance imaging; PP, pancreatic polypeptide; ACE, angiotensin converting enzyme; HOMA, homeostatic model of assessment; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus –Thrombolysis in Myocardial Infarction; EXAMINE, The Examination of CV Outcomes with Alogliptin vs. Standard of Care; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; CAROLINA, Cardiovascular Outcome Study of Linagliptin vs. Glimepiride in Patients with T2DM; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with T2DM; SGLT-2, sodium glucose co-transporter 2; ADA, American Diabetes Association; EMA, European Medicine Agency; RCT, randomized controlled trials; AACE, American Association of Clinical Endocrinologists; LEAD, Liraglutide Effect and Action in Diabetes; AWARD-2, Assessment of Weekly Administration of LY2189265 [dulaglutide] in Diabetes-2; ELIXA, The Evaluation of Lixisenatide in Acute Coronary Syndrome; LEADER, The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; LYDIA, Effects of Liraglutide in Young Adults With Type 2 DIAbetes; EXSCEL, The EXenatide Study of Cardiovascular Event Lowering; MACE, major adverse cardiovascular events; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; CANVAS, CANagliflozin cardioVascular Assessment Study; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial; (DECLARE TIMI-58, Dapagliflozin Effect on CardiovascuLAR Events; PTP-1B, Protein Tyrosine Phosphatase inhibitors.

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ABSTRACT

Type 2 diabetes (T2DM) is a leading cause of morbidity and mortality worldwide and a major economic burden. The prevalence of T2DM is rising, suggesting more effective prevention and treatment strategies are necessary. The aim of this narrative review is to summarize the pharmacologic treatment options available for patients with T2DM. Each therapeutic class is presented in detail, outlining medication effects, side effects, glycemic control, effect on weight, indications and contraindications, and use in selected populations (heart failure, renal insufficiency, obesity and the elderly). We also present representative cost for each antidiabetic category. Then, we provide an individualized guide for initiation and intensification of treatment and discuss the considerations and rationale for an individualized glycemic goal.

Contents

1. Introduction

Type 2 diabetes (T2DM) is a leading cause of morbidity and mortality worldwide and its prevalence is rising, rendering prevention and treatment of paramount importance. By 2040, the total number of diabetics worldwide is projected to increase to $642 million resulting in an increased economic burden [1]. In 2012, the total cost related to T2DM in United States of America (USA) was $245 billion with direct health care costs of $176 billion and reduced productivity of $69 billion [2]. After adjusting for population age and sex differences, average medical expenditures in individuals with T2DM were 2.3 times higher than those without diabetes, highlighting the need for more cost-effective strategies to prevent and treat diabetes [2].

T2DM is primarily characterized by insulin resistance (IR) and a defect in insulin secretion, the latter regarded as an early abnormality. The interplay between defective insulin secretion and IR initially leads to hyperglycemia, due to increased hepatic glucose production and decreased peripheral uptake of glucose. At a later stage, persistent hyperglycemia causes glucotoxity, increased oxidative stress and lipotoxicity, which causes further [3] reduction in insulin secretion due to progressive beta-cell failure [4]. Death risk in diabetes is about twice compared with non-diabetic individuals of similar age [5]. This proportion is even higher for women and younger individuals, although there is consideration about estimating mortality in T2DM [6]. The target for T2DM aims to reduce the risk of long-term complications and mortality [7–9]. Decrease in glycated hemoglobin A1C (HbA1c), an index for

diabetes regulation and follow-up, lead to risk reduction for vascular complications and diabetes-related mortality (37% and 21%, respectively) [10]. Tight control of glycaemia (HbA1c <7%, as shown in UKPDS study) can reduce some of diabetic complications. On the other hand, glycemic targets should be more flexible in older individuals, particularly those with comorbidities, because hypoglycemia may result in higher mortality in these patients [11,12]. Therefore, an individualized approach is recommended by recent clinical guidelines [13,14].

The aim of this narrative review is to summarize the available pharmacologic treatment options for patients with T2DM. We also provide an individualized guide for initiation and intensification of treatment regimens and discuss the considerations and rationale for individualized HbA1c goal.

2. Medications

2.1. *Older Medications*

2.1.1. *Biguanides*

2.1.1.1. *Mechanism of Action.* The first biguanides, metformin and phenformin, were introduced in 1957. Phenformin was withdrawn in most countries because of increased risk of lactic acidosis [15]. In the USA, metformin was approved in 1994. Metformin primarily decreases hepatic glucose production by inhibiting gluconeogenesis. Secondarily, it enhances peripheral insulin sensitivity in the skeletal muscle by increasing insulin receptor tyrosine kinase activity and glucose transporter (GLUT)-4 translocation to the cell membrane [16]. Metformin also improves beta-cell responsiveness to a glucose load through correction of glucose toxicity [17]. Furthermore, metformin increases endogenous glucagon-like peptide (GLP)-1 level by two- to three-fold, acting through a distinct mechanism to that of dipeptidyl peptidase (DPP)-4 inhibition, thus resulting in additive effects, when co-administered with DDP-4 inhibitors [18–20]. A recent study on delayed-release (DR) metformin has demonstrated a 50% in bioavailability and 40% increase in potency of the drug as compared to metformin extended-release and immediate-release; by dissociating the glycemic effect from plasma exposure with gut-restricted metformin DR, this study provided evidence of predominantly lower gut-mediated mechanism of metformin action [21]. Despite its multiple physiologic targets, metformin modestly reduce postprandial glucose excursions, because it does not induce insulin secretion. Metformin regulates primarily fasting glucose levels [22] with the maximum lowering effect at 12 months. An effective response to metformin may be maintained for several years [23].

2.1.1.2. *Dose and Position in Treatment Armamentarium.* Metformin is initiated at a dose of 500 mg once or twice/d with breakfast and dinner and increased to 850 or 1000 mg twice/d after a week, if no gastrointestinal side effects occur. A clear dose-response glycemic control is demonstrated up to a total dose of 2000 mg/d, whereas higher dose has minimal effect on glucose control, but increases the side effects [24]. Metformin is contraindicated in patients prone to develop metabolic acidosis, including chronic kidney disease (stage 4 and 5), liver failure, congestive heart failure (HF), major surgery, sepsis, alcoholism and intravenous contrast iodine administration (for 24 h) [17,22]. Because hospitalized patients are at risk to develop acidosis, metformin discontinuation may be considered during hospitalization. Nonetheless, there is evidence supporting safety and usefulness of metformin in T2DM patients with stable HF. A few observational studies suggest that metformin reduces the incidence of HF and mortality in patients with T2DM, while improving survival rates in those with HF [25,26]. The use of metformin in patients without severe chronic kidney disease is generally accepted; it can be administered in patients with estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m^2 without dose adjustment, and in those with eGFR 45–60 ml/min/1.73 m^2, requiring however frequent monitoring (3–6 months) of kidney function. Dose adjustment is required in patients with eGFR 30–45 ml/min/1.73 m^2 [13]. Metformin is contraindicated in patients with eGFR <30 ml/min/1.73 m^2. Main side effects are gastrointestinal (nausea, anorexia and diarrhea) and tend to subside with continuing treatment over a few weeks. Of importance, however, 8% of patients exhibit persistent metformin intolerance (mostly diarrhea), thus the medication is discontinued. Metformin can interfere with vitamin B12 absorption, thus reducing B12 levels, but rarely causes anemia [17].

Metformin can be used as monotherapy and is the first-line agent in the treatment of T2DM, as proposed by all guidelines [13,14]. It can also be used in combination with other antidiabetic medications and/or insulin. Metformin decreases HbA1c by 1.5% as monotherapy and causes mild weight loss, mainly due to a reduction in energy intake [13,27]. In the Diabetes Prevention Program cohort, metformin reduced the risk of progression from prediabetes to T2DM by 31% as compared to placebo [28]. Thus, treatment with metformin might be useful in individuals with prediabetes that failed to modify lifestyle [13].

2.1.1.3. *Outcomes.* In the United Kingdom Prospective Diabetes Study (UKPDS), patients assigned to metformin, compared with the conventional group (assigned to no pharmacologic treatment), showed a 10-year risk reduction of 32% in diabetes-related endpoints, 42% in diabetes-related death and 36% in all-cause mortality. This was primarily achieved by a reduction in cardiovascular (CV) events [e.g. myocardial infarction (MI), stroke] [9,29]. Metformin was superior to sulfonylureas (SUs) and insulin in reducing mortality, despite a comparable glycemic control [9]. Metformin also resulted in lower rates of hypoglycemia and had a more favorable effect on weight than insulin or SUs. When metformin was added on insulin therapy, the risk for macrovascular disease, including MI, heart failure, stroke, peripheral artery disease and sudden death, was reduced [30]. On the contrary, there was no decrease in the risk of microvascular complications, partly owing to the relatively short follow-up (4.3 years) [30].

Some studies have also shown lower risk of cancer and lower cancer-specific mortality in T2DM patients on metformin compared with other antidiabetic agents [31,32]. A recent meta-analysis of 24 studies showed that metformin was

associated with reduced risk of cancer in both cohort and case-control studies [33]. This possible anti-carcinogenic effect of metformin may be achieved by inhibiting growth of cancer cells via 5' adenosine monophosphate-activated protein kinase (AMPK) pathway. However, data on the anti-cancer effect of metformin are currently conflicting; the presence of important confounders, including duration of T2DM and switching to other oral therapies, renders it a difficult task in clinical setting [34].

Cost: Very Low ($10 per month)

2.1.2. *Sulfonylureas*

2.1.2.1. *Mechanism of Action.* SUs, the first oral antidiabetic medications used, were approved by the Food and Drug Administration (FDA) in 1958. In the USA, currently available SUs include the first-generation chlorpropamide, the second-generation glyburide (or glibenclamide) and glipizide, and the third-generation drugs, glimepiride and gliclazide. Of these, glyburide and glipizide are the most commonly used in the USA. SUs are insulin secretagogues. They bind to the SU receptor (SUR)1 on the pancreatic beta-cell membrane, thus closing the associated ATP-sensitive K^+ channel [35]. Inhibition of these channels leads to depolarization of the cell membrane, opening of voltage-gated calcium channels, fusing of insulin granules with the cell membrane, thus releasing insulin into the blood [35]. This effect is independent of plasma glucose concentrations, leading to increased risk of hypoglycemia. The glucose lowering effect is maximal at 4 months and glycemic control is shown to be maintained at least for 33 months [36,37].

2.1.2.2. *Dose and Position in Treatment Armamentarium.* Efficacy of SUs plateaus above half-maximum doses and further titration is not recommended, because it only increases its side effects. Glyburide's dosage starts at 2.5 to 5 mg/d and can be increased by 2.5 mg/wk to a maximum of 20 mg/d; doses over 10 mg/d should be divided into two. Glipizide is available both in an immediate and an extended release formulation. The immediate release starts at 5 mg/d and can be titrated by 2.5–5 mg every few days to a maximum of 40 mg/d. Doses over 15 mg/d should be divided. Extended release glipizide starts at 5 mg/d and can be increased to a maximum dose of 20 mg/d. Glimepiride starts at 1–2 mg/d and can be increased by 1–2 mg every 14 days to a maximum of 8 mg/d (6 mg/d in Europe). Gliclazide extended release starts at 30–60 mg/d and can be increased to a maximum dose of 120 mg/d. Chlorpropamide is not commonly used due to high rates of hypoglycemia. Glyburide and glimepiride are longer-acting than glipizide [38–40].

SUs have been approved for use as monotherapy, but are most commonly used as second-line agent in combination with metformin [41]. The HbA1c-lowering effect of monotherapy ranges between 1–1.5% and it is achieved faster than other second-line agents, such as thiazolidinediones [42–44] or DPP-4 inhibitors [45]. Glimepiride is the only SU approved for use with insulin [45] and it is one of the most cost-effective agents for the treatment of T2DM [13,46]. SUs are category C drugs for pregnancy, being inferior to metformin and insulin for gestational diabetes mellitus [47].

2.1.2.3. *Outcomes.* Concerns exist regarding increased CV risk in patients on SUs. Mechanistically, SUs are known to bind to SURs outside the pancreas, including to SUR2 on cardiac myocytes, which may affect ischemic preconditioning [48]. Different SUs have varying affinity and function after binding with extra-pancreatic SUR receptors, with glyburide appearing to be the strongest [49–51]. By blocking SUR2, SUs may theoretically influence the adaptive response to ischemia, thus worsening the outcomes in ischemic heart disease. However, this has not been clinically proved yet [48]. Regarding their effect on CV risk factors (e.g., blood pressure, lipids), there are conflicting results [52–56]. The first observation towards a potential negative association between SUs and CV outcomes arose in the University Group Diabetes Program (UGDP) trial in the 1960s, in which increased mortality in patients on tolbutamide was reported [57]. Subsequent studies have pointed out that this study was not powered for CV outcomes and its results were not corrected for the higher CV risk present at baseline [58]. Subsequently, the UKPDS found no increase in CV outcomes in patients on SUs [9]. Other large-scale trials, including Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial, A Diabetes Outcome Progression Trial (ADOPT), Veteran Affairs Diabetes Trial (VADT), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and Rosiglitazone evaluated cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD) have confirmed this observation [11,12,23,59,60].

The most common side effects of SUs are hypoglycemia and weight gain. It is estimated that 1% of patients on SUs experience severe hypoglycemia requiring treatment compared with 0.05% of those on metformin and 10% on insulin [40]. Although the hypoglycemia of SUs is rarer than insulin, it is reported to be more severe and more prolonged than that of insulin. Hypoglycemias are often more pronounced in older patients, partly due to impaired renal function. It varies in severity dependent on the half-life of each SU. For example, glipizide causes fewer hypoglycemias than glyburide that has longer half-life than glipizide. Glyburide has been added to the Beers List for potentially inappropriate medications for older adults (AGS 2012 Beers Criteria; American Geriatrics Society). The mean weight gain from SU therapy is about 1.6 kg per year, but tends to lessen over time, as found in the ADOPT study [23,39].

Apart from side effects, consideration arises from the primary treatment failure to SUs and decreased efficacy over time (up to 34% cumulative incidence of failure over five years of monotherapy), potentially due to beta-cell apoptosis [23]. In conclusion, SUs remain a cost-effective therapy for T2DM, although the risks of weight gain and hypoglycemia have limited their use. Special consideration should be taken in older patients and in patients with renal insufficiency, owing to higher risk of hypoglycemia.

Cost: Low ($4–20 per month)

2.1.3. *Meglitinides or Glinides*

2.1.3.1. *Mechanism of Action.* Available meglitinides include repaglinide, mitiglinide and nateglinide. Repaglinide was approved in 1997 and nateglinide in 2000. There is also a

combination of repaglinide/metformin. Meglitinides act similarly to SUs by binding SUR1 (at a different site than SUs). Inhibition of ATP-dependent K^+ channels leads to depolarization of cell membrane, opening of calcium channels, thus insulin releasing. Meglitinides have a shorter onset and duration of action compared with SUs, due to their weaker binding affinity and faster dissociation from the SUR1 (half-life 1–2 h) [61]. Nateglinide has a slightly different site of action than repaglinide, resulting in shorter onset and duration of action [62]. Although a study showed inhibition of DPP-4 [63] by nateglinide that can potentially affect the incretin system, another study has not confirmed this finding [64].

2.1.3.2. *Dose and Position in Treatment Armamentarium.* Starting doses are 0.5 mg and 60 mg before each meal for repaglinide and nateglinide, respectively. Maximum doses are 4 mg and 120 mg, respectively. The dose can be increased weekly, driven mainly from postprandial glucose monitoring. Because of their short action, meglitinides should be administered three times per day with meals and be omitted if a meal is omitted. Therefore, they are a useful option for patients with irregular meal schedule [65,66]. They primarily affect postprandial rather than fasting glucose. Similar to the SUs, meglitinides can cause hypoglycemia and weight gain, although they have shorter half-life and thus lower risk of hypoglycemia and weight gain than SUs [65,66]. Meglitinides can be used in renal impairment. For repaglinide, no dose adjustment is necessary for eGFR >40 ml/min/1.73 m^2. For GFR <40 ml/min/1.73 m^2, careful titration is recommended. No studies exist for eGFR <20 ml/min/1.73 m^2, so its use is not justified in this case. More caution is required in hepatic impairment, in which longer intervals between doses should be considered. For nateglinide, no dose adjustment is necessary in mild to severe renal disease (stages 1–4). However, in severe renal impairment, patients are more susceptible to hypoglycemia, due to lower binding of nateglinide to protein carriers. No dosage adjustment is needed in mild hepatic impairment, but no studies exists for nateglinide in moderate to severe hepatic impairment, in which its use is not justified [66].

Meglitinides are generally well tolerated. They can be used in combination with other oral antidiabetic medications (second-line) or as monotherapy (e.g., in metformin intolerance). As monotherapy, expected improvement in HbA1c is 0.5–1.5% [67]. Either as monotherapy or in combination with metformin, repaglinide has greater effect on HbA1c compared with nateglinide [68]. Apart from hypoglycemia and weight gain, headache and upper respiratory infections may occur [69,70]. The glucose lowering effect was maximal at 12 months and was maintained for at least 57 months [23].

2.1.3.3. *Outcomes.* Repaglinide is reported to be associated with similar CV outcomes with metformin and gliclazide, but better outcomes compared to other SUs [71,72]. Repaglinide was also reported to slow the progression of carotid intima media thickness compared with SUs [73]. However, repaglinide does not improve triglycerides, low-density lipoprotein cholesterol (LDL-C) or high-density lipoprotein cholesterol (HDL-C) [74]. Moreover, the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial did not show any beneficial effects on the progression of impaired glucose tolerance (IGT) to T2DM or CV events [75]. Limitations of meglitinides include cost, which is more than four times higher than metformin or SUs [76], and the need for frequent dosing, which may result in poor compliance. Similarly to SUs, meglitinides have a theoretically increased CV risk, but this is clinically uncertain [77]. Owing to their metabolism in CYP2C8 and CYP3A4, certain drug interactions should be considered (e.g. gemfibrozil).

Cost: Medium ($30–60 per month)

2.1.4. α-Glucosidase Inhibitors

Acarbose, the main α-glucosidase inhibitor, slows the digestion of carbohydrates, thus delaying glucose absorption and reducing postprandial glucose levels. Due to their mechanism of action, they do not cause hypoglycemia [78]. Therapy can be started at 25 mg orally twice/d with meals, for 4–8 weeks and then can be increased at 50 mg twice/d, to maximum 100 mg twice/d. If the patient weighs <60 kg, 50 mg twice/d dosing is recommended. The major side effects, which lead to a high rate of discontinuation, are abdominal pain, bloating, diarrhea and flatulence, due to increased delivery of carbohydrates to the distal intestine. Thus, gastrointestinal disorders are their main contraindications. Contraindications also include liver cirrhosis and renal insufficiency (creatinine >2 mg/dl) [79]. They can be used as monotherapy or in combination (acarbose) with SUs or metformin or insulin. They can lower HbA1c by 0.8%; dosages >50 mg twice/d offer no additional effect on HbA1c, whereas worsen side effects [80]. A large trial, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), in patients with IGT showed that acarbose reduced the progression to T2DM by 25%, CV events by 49% [81] and carotid-intima-media thickening by 50%. However, discontinuation of acarbose abated the benefit [82]. Compared to placebo, acarbose reduced the relative risk of CV events by 35% [78]. These findings are of clinical implication, as postprandial hyperglycemia increase both atherogenesis and CV events [82,83].

Miglitol is another α-glucosidase inhibitor. In contrast to acarbose, miglitol is systemically absorbed and is excreted by the kidneys. Miglitol was recently shown to decrease subclinical hypoglycemia and decrease glucose fluctuations in T2DM patients with recent ACS in Miglitol on Glucose Metabolism in Acute Coronary Syndrome (MACS) Study [84]. A third member of the same class is voglibose [85], which decreased post-prandial hyperglycemia and produced adverse events similar to acarbose (in dose of 0.3 vs. 50 mg, respectively) [86]. However, it is noteworthy the high interindividual variations on hyperglycemia, which may largely be affected by the adverse effects (mainly gastrointestinal). In a small comparative study of acarbose (300 mg/d) vs. miglitol (150 mg/d) vs. voglibose (0.9 mg/d), the three medications had similar effect on HbA1c, but only miglitol reduced HbA1c significantly more than controls (no medication) [87]. The differences in HbA1c, however, were minimal in all groups.

In the current algorithms for the treatment of T2DM, α-glucosidase inhibitors do not have a clear position, mainly due to the inconclusive benefit-side effects ratio [13].

Cost: Medium ($30–50 per month)

2.1.5. *Thiazolidinediones*

2.1.5.1. *Mechanism of Action.* Thiazolidinediones (TZD) were first discovered in the 1980s, when Japanese researchers observed hypoglycemic effect on mice treated with a novel, considered hypolipidemic agent. Troglitazone, the first TZD, was approved in 1997, but was subsequently withdrawn due to hepatic side effects. Rosiglitazone (Avandia®) and pioglitazone (Actos®) were approved in 1999 [88]. TZDs act primarily in the skeletal muscle and adipose tissue by activating the nuclear transcription factor peroxisome-proliferator-activated receptor (PPAR)γ, thus enhancing glucose uptake by the skeletal muscle, beta-cell function, and IR in the adipose tissue, skeletal muscle and liver [89,90]. TZDs also activate sodium channels in the distal nephron, leading to their common side effect, water retention [91].

2.1.5.2. *Dose and Position in Treatment Armamentarium.* Rosiglitazone dosing starts at 4 mg/d and can be titrated to a maximum of 8 mg/d (single or divided doses) after two to three months. Pioglitazone dosing starts at 15–30 mg/d and can be titrated to a maximum of 45 mg/d. TZDs are second-line agents, also approved for use as monotherapy, if needed (e.g., metformin intolerance) [92,93]. Apart from treating T2DM, TZDs may also delay the progression to T2DM in patients with glucose intolerance by possibly preserving beta-cell function [5]. In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study the risk of progression to T2DM with rosiglitazone was reduced by 32% and 63% compared with metformin and glyburide, respectively [44]. TZDs can be used in patients with renal failure up to stage IV (GFR <30 ml/min/1.73 m^2). On the contrary, they are contraindicated in patients with heart failure (New York Heart Association [NYHA] Classes III-IV). TZDs should also be used with caution in patients with peripheral vascular disease [13].

2.1.5.3. *Outcomes.* TZDs improve HbA1c by 1.0–1.5% as monotherapy [94–96], similarly to SUs [97]. Targeting the level of gene expression, they are slower in onset (maximum effect reached after 2–4 weeks), but appear to have more durable effects than SUs [97]. Hypoglycemia after TZDs is comparable to that of metformin and milder than SUs [13,98]. Except for improving glycemic control, TZDs appear to have beneficial effects on dyslipidemia and hypertension, commonly seen in T2DM patients. Pioglitazone reduces triglyceride levels by 16%, and raises HDL-C by 12-19%, while rosiglitazone increases both HDL-C and LDL-C [99,100]. Systolic and diastolic blood pressure is also lowered when compared to other antidiabetic agents or placebo [101,102]. TZDs also decrease microalbuminuria, though they are not clearly linked to improvement in renal end-points [103]. Moreover, TZDs are associated with improvement in anti-inflammatory markers, including high-sensitive C-reactive protein (CRP) and adiponectin [13,99,104]. Partly due to increasing adiponectin, TZDs improve nonalcoholic steatohepatitis (NASH), a condition highly related with T2DM [105–107]. Furthermore, a recent expert panel statement recommends the use of pioglitazone in patients with NASH [108]. Finally, TZDs are reported to decrease carotid and coronary artery thickening [109] and prevent restenosis after percutaneous coronary angioplasty [110].

Despite their pleiotropic effects, TZD use has been limited because of their side effects. TZDs cause comparable weight gain to SUs [111]. Weight gain is mainly attributed to water retention [91]; fat stores are redistributed, since TZDs increase subcutaneous and decrease visceral fat, the latter being more actively involved in the pathogenesis of the metabolic syndrome [112,113]. Peripheral edema is more profound when TZDs are co-administered with insulin [114]. Due to their water retaining effect, TZDs have been linked with increased rate of hospitalization for heart failure, without however increasing the heart failure-related mortality [60,115]. Macular edema has been reported with TZD use, with the greatest risk in predisposed to peripheral edema [116]. TZDs have also been associated with reduced bone mineralization and an increased risk of fracture, especially in women. In the Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROACTIVE) trial, the rate of fracture in women was 5.1% in the TZD group vs. 2.5% in the placebo group. Higher risk of fractures in patients on TZDs was also observed in the ADOPT (A Diabetes Outcome Progression Trial) compared with oral antidiabetic medications [117,118]. PROACTIVE trial has also raised concern regarding the risk of bladder cancer in patients on pioglitazone [101]. A subsequent meta-analysis showed a relative risk of 1.2 in patients on pioglitazone, which appears to increase as cumulative dose and duration of therapy increase [119]. These data prompted the FDA to include cautions against the use of pioglitazone in patients with either a history of bladder cancer or active disease. Nevertheless, more recent analyses on large cohorts did not confirm the association of pioglitazone with bladder cancer [120].

Most importantly, there is a concern regarding CV outcomes in patients on TZDs, which refers most to rosiglitazone than pioglitazone. The PROACTIVE trial showed a significant 16% relative risk reduction of the secondary end-point (total mortality and non-fatal MI and non-fatal stroke). A *post-hoc* analysis of the PROACTIVE study showed a significant 50% relative risk reduction in stroke, in the subgroup of patients having experienced a previous cerebrovascular event. [101,121], a finding that is in accordance with the recently published IRIS (Insulin Resistance Intervention after Stroke) trial in non-diabetic, insulin resistant individuals [122]. Other studies also demonstrated improvement in surrogate markers of cardiovascular disease (CVD) (i.e., intima media thickness or atheroma volume) [123–126]. Subsequent meta-analyses showed either no effect or a protective effect of pioglitazone on CV outcomes [127,128]. On the other hand, two meta-analyses showed a 40% increase in the risk of MI in patients on rosiglitazone [129,130]. Nevertheless, large-scale clinical trials, including the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, DREAM, ADOPT, ACCORD, VADT and RECORD, did not show increased CV risk and a *post-hoc* analysis of VADT suggested a potential reduction in CV events and mortality in the subgroup of patients receiving rosiglitazone [11,23,44,59,60,131]. A follow-up meta-analysis found no increase in CV mortality, but a 28-39% increase in the risk of MI [132]. Based on these data, the FDA initially severely limited rosiglitazone use, although later (2013) voted to ease some of these restrictions after re-adjudication of the results of RECORD study, showing no difference in CV outcomes or mortality in patients on rosiglitazone compared with other antidiabetic medications [133].

Cost: Low ($12–$20 per month)

2.1.6. *Insulin*

Insulin secretion physiologically includes basal secretion regulating mainly hepatic glucose production and bursts of insulin at mealtimes promoting glucose disposal and inhibiting postprandial hepatic glucose production.

Insulin was classically regarded as the last choice in the treatment of T2DM, when beta-cell function is severely limited. However, it seems to be beneficial in newly diagnosed patients with T2DM [134]. Insulin could be considered at first-line in patients presenting with HbA1c >9%, severe symptoms, evidence of ketoacidosis, in pregnancy (or when a woman with T2DM is planning pregnancy), when oral antidiabetic medications are contraindicated (e.g., renal or hepatic insufficiency, heart failure, MI, etc.) or when glycemic goal is not achieved by combination of antidiabetic medications.

According to their pattern of action, the available preparations of insulin are classified into basal, prandial or combination (premixed) [13]. At the molecular level, insulin preparations are classified into human insulin and insulin analogs, in which human insulin structure has been slightly modified to achieve better pharmacokinetics. Insulin is the preferred pharmacotherapy during pregnancy. Most insulin preparations are category B for pregnancy; however glargine, glulisine, and degludec are category C, thus not recommended during pregnancy.

2.1.6.1. Basal Insulin. Available human preparation is the protamine Hagedorn (NPH) insulin (Humulin N, Novolin N or Insuman). Insulin analogs include detemir, glargine and degludec. NPH is intermediate-acting insulin with onset of action at 2–4 h, peak at 4–10 h and duration of 12–18 h, due to which twice daily administration is typically required. High individual variability to NPH is within its limitations [135]. Insulin detemir binds to albumin and provides stable levels of free insulin. Its onset of action is at 1–1.5 h, peak at 4–7 h (peak is not pronounced) and duration of 20 h, hence it may be administered once or twice daily. Insulin glargine forms micro precipitates in subcutaneous tissue at the site of injection, thus delaying its systemic absorption. Its onset of action is at 1–1.5 h, peak at 8–12 h and duration of 24 h. It has a gradual and relatively constant release pattern over 24 h, reaching a plateau at 4–6 h, without a pronounced peak, thereby being usually administered once daily. Recently approved Toujeo (Glargine U300), is a three times more concentrated form of glargine with onset of action at 2–12 h, peak at 4–6 h and duration of 36 h, thus administered once daily [136]. The higher concentration of this formulation renders the insulin precipitates more tightly packed in the subcutaneous depot, thereby leading to a more constant release [137,138]. Both detemir and glargine have more stable profile, prolonged action, less pharmacokinetic variability and lower rates of hypoglycemia compared with NPH, despite similar HbA1c reduction [68,137,139–141].

Insulin degludec is a newer basal insulin analog with possibly more stable profile [142]. Owing to its longer half-life (24 h), its duration of action is 42 h [143], without peak. Degludec has a four-fold lower variability in lowering glucose compared to glargine [144]. A meta-analysis of 5 trials from Phase 3a showed that degludec decreased overall (21%) and nocturnal (52%) hypoglycemic events compared with glargine [145].

A few years ago, consideration was raised on the possible association between glargine and increased cancer risk. Glargine, through increasing IGF-1, was hypothesized to stimulate the proliferation of cancer cells, as was shown *in vitro* [146]. Initially, a German cohort study with a relatively low follow-up (1.6 years) reported a dose-dependent increase in cancer risk in patients on glargine compared with human insulin [147]. This report led the European Association for the Study of Diabetes (EASD) to ask for validation cohorts across the European countries. In the Swedish cohort, an association between glargine and breast cancer only was observed over a 2-year follow-up [148]. In the Scottish cohort, glargine was not associated with increased risk of all cancers over a period of 4 years [149]. In the British cohort, insulin analogs vs. human insulin were not associated with higher cancer risk. Importantly, patients on insulin or insulin secretagogues (e.g., SUs) were more likely to develop solid cancers than those on metformin; this risk was mostly attenuated by concurrent use of insulin with metformin [150]. Similarly, another 5-year study reported similar cancer risk in patients on glargine or NPH [151]. Subsequently, Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial, a large, randomized, controlled, double-blinded, internationally designed study, showed similar cancer risk and related mortality in patients on glargine and standard care after a follow-up of 6.2 years [152]. Taken together, available clinical evidence does not support a carcinogenic effect of glargine.

2.1.6.2. Prandial Insulin. Available human preparations include regular insulin and insulin analogs, including lispro, insulin aspart and insulin glulisin. Regular insulin peaks at 2–4 h and has duration of 4–6 h. Molecular modifications of insulin analogs (lispro, aspart and glulisine) lead to shorter time to peak (30 min–2 h) and duration of action (3–5 h), which more closely mimics physiologic postprandial insulin action. Insulin analogs are considered to regulate early postprandial hyperglycemia and late postprandial hypoglycemia better compared with regular insulin [153].

Inhaled insulin, another formulation of prandial insulin, was approved by the FDA in 2006, but was withdrawn by the manufacturer in 2007, due to concerns about possible lung-related side effects. Another, inhaled insulin (Affreza) was approved by the FDA in 2014. The onset of action of Affreza is at 15 min, which is faster than prandial insulin analogs, and duration of 2–3 h, which is similar to prandial insulin analogs. Safety, tolerability and non-inferiority of Affreza were evaluated in T2DM patients, who experienced less weight gain and fewer hypoglycemic events compared with insulin aspart, when combined with basal insulin. Affreza holds a black box warning for bronchospasms in patients with asthma or chronic obstructive pulmonary disease, which are its main contraindications [154].

2.1.6.3. Premixed Insulin Combinations. Available human preparations include 70/30 Humulin® or Novolin® (70% NPH and 30% regular) and 50/50 Humulin® (50% NPH and 50% regular). Available insulin analogs include 75/25 Humalog® (75% protamine lispro [NPL] and 25% lispro), 50/50 Humalog® (50% NPL and 50% lispro), 70/30 Novolog Neutral® (70%

protamine aspart, 30% aspart) and Ryzodeg® 70/30 (70% degludec and 30% aspart). These premixed insulin formulations containing both basal and prandial insulin are considered to provide more flexibility and convenience by eliminating the need for self-mixing, simplifying the insulin regimen and reducing the number of daily injections. On the other hand, the dose of their basal and prandial component cannot be separately adjusted, which limits the flexibility of eating and exercise. Premixed insulin is usually administered twice daily. A 3-year study comparing basal, prandial and premixed insulin showed comparable reduction in HbA1c, but less hypoglycemias and weight gain with basal insulin [155].

Cost: High and variable depending on type of insulin ($145–365 per month)

2.1.7. *Amylin Analogs*

Amylin is released together with insulin by pancreatic beta-cells. Beta-cell dysfunction results in both insulin and amylin deficiency [156]. Amylin decreases gastric emptying, thus slowing the rate of food absorption, a mechanism possibly centrally mediated [157]. It is also possibly increases satiety and decreases caloric intake [158,159]. Pramlintide is an amylin analog, whose starting dose (for T2DM) is 60 mg injected subcutaneously and can be increased to 120 mg after 3–7 days [156]. Current recommendations suggest decreasing prandial insulin by 30–50% when initiating pramlintide to decrease the risk of hypoglycemia [160].

The most commonly reported side effects include nausea (16-31%), vomiting, anorexia and decreased appetite. These effects are common within the first four weeks of treatment and can be minimized with slow dose titration. Hypoglycemia may also occur, though it is less common with pramlintide (55%) than insulin [161]. Because of the risk of hypoglycemia, patients should self-monitor glucose levels; pramlintide must not be prescribed in those unable to self-monitor glucose or those with a history of hypoglycemic unawareness. There is currently no data regarding the safety and efficacy of pramlintide for the management of hospitalized patients with hyperglycemia [162]. Contraindication for pramlintide includes gastroparesis, given the slowing gastric emptying effect of pramlintide. Pramlintide is approved for use in patients with eGFR >20 ml/min/1.73 m^2 without dose adjustment. Pramlintide is not approved for use in pregnancy or lactation.

Addition of pramlintide on glargine improves postprandial glucose and HbA1c more than placebo (0.4–0.6%) [163–165]. The greater benefit of pramlintide is observed when baseline HbA1c >8.5% [164]. Postprandial glucose levels decrease 43–90 mg/dl at 2 h, when used in combination with prandial insulin. HbA1c was also reduced significantly by 0.56% from baseline [166]. Of note, the insulin group increased weight by 4.7 kg, whereas the addition of pramlintide resulted in no weight gain [161].

Pramlintide has also been evaluated for weight loss in T2DM patients [163,164,166–168]. Dosing in these studies was quite variable, ranging from 30 mg/d to 150 mg thrice/day, with the most common dosing being 120 mg twice/d. Weight loss was also variable, being 0.5–2.8 kg within a period 6–12 months; higher doses were associated with increased weight loss. Worsening of nausea was not linked to weight loss, possibly implying that nausea is not the mechanism for weight loss [163,168]. Short-term drug administration (4 weeks) showed no difference in weight loss between those on pramlintide or placebo [169], implying that long-term administration is necessary for weight loss, although its long-term safety and efficacy remain unknown. Of note, the higher weight loss was observed in patients with higher BMI at baseline [168,170]. However, these results should be cautiously interpreted, since weight loss was not their primary target: pramlintide is not currently approved as a weight loss medication. Limitations of pramlintide include the high cost and the need for frequent injections. Because of these limitations, pramlintide has not gained popularity. For now, amylin analogs do not have a clear position in the current algorithms and they are typically reserved for T2DM patients treated with intensive insulin therapy [13]. However, given the growing evidence suggesting its role in weight loss, a resurgence of pramlintide may be seen when its patent expires.

Cost: Very High ($500–800 per month)

2.2. *Newer Medications*

2.2.1. *The Incretin System*

In healthy individuals, oral ingestion of glucose promotes a greater insulin response than parenteral infusion of an equivalent glucose load [171]. This response, known as the incretin effect, is largely mediated by two incretin hormones: GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) [172]. GIP is mostly secreted from K-cells in the duodenum and proximal jejunum, and GLP-1 from the L-cells in the distal ileum and proximal colon [173–175]. The main stimulus for GIP and GLP-1 secretion is nutrients in the gut lumen, especially carbohydrates and lipids [173,176,177]. Other stimuli are neural vegetative efferent. GIP and GLP-1 are released within 5-10 min of ingestion of a meal [178] and are broken down by DPP-4 at a half-life of a few minutes [179]. G-protein coupled receptors for GLP-1 are expressed on pancreatic islets, thus binding GLP-1 stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner. It also slows gastric emptying and reduces appetite and food intake [176] in normal-weight and obese individuals [180–182], and T2DM patients [183]. In T2DM, the incretin effect is found to be reduced due to decreased responsiveness of beta-cells to GIP [184]. GLP-1 remains effective, but only at supraphysiologic doses [185]. Experiments in rodent models and human cell cultures have shown that GLP-1 promotes beta-cell survival, increases beta-cell proliferation and leads to differentiation of beta-cells. GLP-1 infusion normalizes beta-cell responsiveness to glucose and restores first and second phase of insulin secretion regardless of the severity of T2DM [186–190]. Exogenous infusion of GLP-1 also inhibits gastric emptying, increases satiety, decreases hunger and food intake [180,191–194]. GLP-1 infusion has also shown cardio-protective effects, such as improvement in left ventricular effective fraction (LVEF) in patients with MI and severe left ventricular dysfunction [195].

Besides gastric distension and peripheral vagal nerve activation, GLP-1 receptor agonists (GLP-1RA) induce satiety by influencing brain regions involved in the regulation of feeding..Animal studies have shown that GLP-1 can cross the blood brain barrier and act on receptors identified in the central nervous system, such as the hypothalamus and nucleus tractus solitari, which regulate energy balance, increase satiety and suppress food intake [196,197]. Administration of GLP-1 into the lateral ventricle resulted in powerful

inhibition of feeding during refeeding of fasted male rats [197]. This effect was dose dependent and blocked by administration of exendin [9–39], a highly selective antagonist of the GLP-1 receptor [198]. Human neuroimaging studies demonstrate that peripherally administered GLP-1 affects brain activity in areas involved in the regulation of feeding. For example, in one study using ^{18}fluorodeoxyglucose positron emission tomography (^{18}FDG PET), exogenous GLP-1 infusion in lean individuals was associated with altered cerebral glucose metabolism [198]. In another study, the effect of intravenous exenatide vs. saline infusion on hypothalamic connectivity was studied using functional magnetic resonance imaging (fMRI) in obese males: increased hypothalamic connectivity was observed in the "responders" (i.e., those who showed reduction in *ad libitum* food intake after exenatide infusion) while rating food images compared with "non-responders" [199]. Most importantly, administration of a GLP-1RA (liraglutide) in patients with T2DM altered brain activity in response to highly desirable food cues in non-hypothalamic areas involved in reward system (e.g. parietal cortex, insula, putamen) [200,201]. Taken together, these studies indicate that peripherally administered GLP-1 affects brain activity in areas involved in the regulation of feeding. These effects could contribute to the appetite-suppressing effect of GLP-1 and weight loss seen during GLP-1RA treatment. The benefits of incretin-based therapies include improved glycemic control with low rates of hypoglycemia and weight loss, which are more favorable in overweight/obese patients with T2DM, especially when hypoglycemia may be life-threatening. There is also some evidence for beneficial effects of incretin-based therapies on other metabolic disorders related to T2DM, including NASH, but further large trials are needed to establish this association [202].

2.2.1.1. DPP-4 Inhibitors

2.2.1.1.1 Mechanism of Action. DPP-4 is a plasma membrane enzyme (T-cell Ag CD26) widely expressed throughout the body, including circulating T-lymphocytes, exocrine pancreas, gastrointestinal tract and brain [174,203–205]. DPP-4 affects not only GIP and GLP-1, but also other molecules, including pancreatic polypeptide (PP), chemokines and substance P [203,204]. A wide range of effects, such as impaired immunosurveillance and decreased nociception have been associated with abnormal DPP-4 levels [203,206–208]. DPP-4 inhibitors inhibit the enzymatic degradation of incretins, including GLP-1 and GIP, thus increasing the endogenous bioactive GLP-1 level by 2-3 folds. This increases insulin secretion in a glucose-dependent fashion, unlike SUs, which act in a glucose-independent manner, and decreases glucagon secretion [209].

2.2.1.1.2 Dose and Position in Treatment Armamentarium. There are four available agents approved in the USA including sitagliptin, saxagliptin, alogliptin and linagliptin approved in 2006, 2009, 2011 and 2013, respectively. They are approved for use as monotherapy, if needed, or in combination with other antidiabetic medications. Vildagliptin has been approved in more than 100 other countries, but not in the USA yet. Sitagliptin, alogliptin, linagliptin, saxagliptin and vildagliptin are available in a fixed-dose combination with metformin. Alogliptin is also available in combination with pioglitazone. DPP-4 inhibitors are administered as a single oral dose of 100 mg for sitagliptin, 5 mg for saxagliptin and linagliptin and 25 mg for alogliptin. Vildagliptin is administered divided into two doses of 50 mg in the European Union. For sitagliptin, dose adjustment is required for moderate and severe renal insufficiency: half the full dose, if creatinine clearance <50 ml/min/1.73 m^2, and one-fourth the full dose, if creatinine clearance <30 ml/min/1.73 m^2. For alogliptin, half the full dose, if creatinine clearance <60 ml/min/1.73 m^2, and one-fourth the full dose, if creatinine clearance <30 ml/min/1.73 m^2. For saxagliptin, half the full dose, if creatinine clearance ≤50 ml/min, whereas it is not approved for end-stage renal disease. For vildagliptin, half the full dose, if creatinine clearance <60 ml/min/1.73 m^2, and the same, if creatinine clearance <30 ml/min/1.73 m^2. No dose adjustment is required for linagliptin in renal or hepatic impairment. Main contraindication is hypersensitivity reaction. DPP-4 inhibition may interfere with degradation of substance P, which is implicated in angiotensin converting enzyme (ACE) inhibitor-associated angioedema. An increased risk of angioedema, though small in absolute terms, was found among patient taking DPP-4 and ACE inhibitors [210].

2.2.1.1.3 Safety and Outcomes. Early clinical studies with DPP-4 inhibitors had shown a slightly increased risk of infections, including nasopharyngitis, bronchitis, urinary tract infections and headache, with an overall excellent safety and tolerability profile [211,212]. Increased risk of infections with DPP-4 inhibitors was not confirmed in the subsequent surveys [213]. The risk of upper respiratory tract infections is 2.9–8.8% with sitagliptin and 4.4–8.3% for saxagliptin. The risk for urinary tract infections is 2.0–5.4% for sitagliptin [214–216] and 5.2-10.7% for saxaglitpin [217,218]. Eighty-eight post-marketing cases of acute pancreatitis, including 2 of hemorrhagic or necrotizing pancreatitis, were also reported to the FDA. However, data from large CV safety trials have not showed statistically higher rates of any type of pancreatic disease [219,220]. Furthermore, a meta-analysis of both randomized and non-randomized controlled trials, cohort and case-control studies with GLP-1RAs or DPP-4 inhibitors in adults with T2DM provided evidence that the incretin based drugs do not increase the risk of pancreatitis [221]. Limited case reports of Stevens-Johnson syndrome have also been reported after DPP-4 inhibitors [222].

DPP-4 inhibitors reduce HbA1c by 0.4–0.8% in monotherapy and by 0.9 ± 0.1% as add-on to pioglitazone [215,223–226]. They also have positive effects on pancreatic beta-cell function, evaluated by homeostatic model of assessment (HOMA)-β and proinsulin-to-insulin ratio [215–217,227]. The durability of efficacy of DPP-4 inhibitors can be sustained for at least 2 years [228]. Most clinical trials did not find significant changes in blood pressure, although one study with sitagliptin reported a 2 mmHg reduction in systolic and diastolic blood pressure and another study with saxagliptin reported 3.2–3.9 mmHg reduction in systolic and 1.8–3.3 mmHg in diastolic blood pressure [229]. However, these reductions may be clinically insignificant.

DPP-4 inhibitors have been evaluated in CV safety trials. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) study examined 16,492 patients with T2DM who had a history or were at risk of CV events to receive saxagliptin or placebo, and followed them for a median of 2.1 years [221]. The Examination of CV Outcomes with Alogliptin vs. Standard of Care (EXAMINE) trial followed T2DM patients with either an acute MI or unstable angina requiring hospitalization within the previous 15–90 days to receive alogliptin or placebo in

addition to existing antidiabetic medications and CV drug therapy for a median of 18 months [220,230]. Both studies showed CV safety, but no CV benefit, on the primary composite end point of CV death, non-fatal MI or non-fatal ischemic stroke [221,230]. The rate of hospitalization for heart failure was increased in those with high baseline brain natriuretic peptide (BNP), but the effect of saxagliptin was similar across all strata of BNP in the SAVOR-TIMI-53 study [221]. \booklink="CM" A recently published study assessed the rates of hospital admission for heart failure in the patients of the EXAMINE trial. The rates of patients with a first event of heart failure did not differ between the alogliptin (3.1%) and placebo (2.9%) group. Furthermore, no difference in CV death rate was found in a *post hoc* analysis [231]. Nevertheless, the FDA added warnings of increased risk of heart failure in the labels of both saxagliptin and alogliptin. Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study showed CV safety for patients treated with sitagliptin for a median follow-up of 3 years, but no CV benefit [232]. Cardiovascular Outcome Study of Linagliptin vs. Glimepiride in Patients with T2DM (CAROLINA) and Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with T2DM (CARMELINA) are ongoing studies for linagliptin and the results are to be reported by 2018.

Based on comparisons of both glycemic and non-glycemic effects, such as risk of hypoglycemia, weight gain, durability and route of administration, DPP-4 inhibitors is a considerable second-line option after metformin [233]. Compared to SUs as add-on metformin, all DPP-4 inhibitors have demonstrated equal glycemic efficacy, plus lower rates of hypoglycemia and no weight gain [234–236]. A disadvantage of DPP-4 inhibitors compared with SUs is their higher cost. Novel once-weekly DPP-4 inhibitors are now under development (Omarigliptin, SYR-472) and the results from the first clinical trials have shown significant improvement in glycemic control along with improved tolerance [237].

Cost: High ($380 per month)

2.2.1.2. GLP-1 Receptor Agonists. Short-acting GLP-1RA is more effective in lowering postprandial hyperglycemia, while long-acting GLP-1RA improve basal hyperglycemia [238]. This differentiation resembles the action of prandial and basal insulin preparations, respectively. Exenatide and lixisenatide are short acting formulations, whereas modified exenatide, liraglutide, dulaglutide and albiglutide are long acting formulations. GLP-1RAs are not used during pregnancy or lactation.

2.2.1.2.1 Exenatide.

2.2.1.2.1.1 Mechanism of Action. Exenatide was the first GLP-1 RA developed and approved by the FDA in 2005. It is a synthetic form of exendin-4, originally identified in the saliva of a lizard, Gila monster, sharing about 50% sequence homology to the endogenous GLP-1, whereas having a longer half-life, due to greater resistance to DPP-4 degradation and greater effective receptor affinity [239,240].

2.2.1.2.1.2 Dose and Position in Treatment Armamentarium. Exenatide is administered as a subcutaneous injection at a starting dose of 5 mg twice/d, 60 min before the morning and evening meals and can be titrated up to 10 mg twice/d after 1 month (adaptation period to subside gastrointestinal side effects). The median peak concentration is reached in 2 h and exenatide, as aforementioned, primarily targets postprandial glucose.

Exenatide LAR is a long-acting form of 2 mg exenatide, which is administered subcutaneously once weekly and target primarily basal glucose. In this formulation, exenatide is encapsulated in Poly-(d,l-Lactide-Co-Glycolide) microspheres, allowing a long and constant release of exenatide from the subcutaneous depot, as the microspheres degrade slowly [241]. Exenatide LAR is released in three phases: the initial phase, the diffusion phase and the erosion phase. The initial phase, occurring 2–5 h of administration, results in an immediate release of drug and a rise in exenatide serum concentration. During the diffusion phase, the drug is released into the circulation at a constant rate. During the erosion phase, the microspheres are disintegrated and the remainder of the drug is released [241]. Clinically, it is important to note that full activity of exenatide LAR is only achieved after 6–8 weeks of therapy.

Exenatide is approved for use with one or two of the following antidiabetic medications: metformin, SUs, thiazolidinediones, basal insulin and sodium glucose co-transporter 2 (SGLT2) inhibitors, or monotherapy, if necessary [242,243]. According to American Diabetes Association (ADA)/EASD consensus, exenatide may be added to metformin, especially in patients with obesity and/or high risk of hypoglycemia [13]. Patients on SUs may require a decrease in SU dose to reduce the risk of hypoglycemia, but no adjustment of metformin or thiazolidinedione is necessary. Adding exenatide to basal insulin improves glycemic control without significantly increasing hypoglycemia risk, whereas mitigating the weight gain effect of insulin [244].

2.2.1.2.1.3 Safety and Outcomes. Exenatide should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min/1.73 m^2) or severe gastrointestinal disease, since its use is commonly associated with gastrointestinal side effects, such as nausea (3–51%), vomiting (4–19%) and diarrhea (up to 17%). However, gastrointestinal side effects, which are dose-dependent, may subside within 4–8 weeks of treatment and are the main reason to start treatment on lower dose [245–248]. Acute pancreatitis is also a consideration for exenatide, based on a report of 36 cases. As 27 of these 36 patients had at least one more risk factor for acute pancreatitis (gallstones, severe hypertriglyceridemia, alcohol intake), pancreatitis could not be definitely attributed to exenatide [249,250]. Therefore, the FDA and the European Medicine Agency (EMA) have issued a statement that there is currently no definite evidence for pancreatitis risk imposed by GLP-1RAs, but initiated long-term observation [251]. Other reported side effects include injection-site reactions, dysgeusia, somnolence, allergic reaction and increase in creatinine levels. There have been 78 reported cases of renal insufficiency or acute renal failure in patients on exenatide [252], hence its contraindicated in patients with eGFR <30 ml/min/1.73 m^2. Mild to moderate dose dependent hypoglycemia was reported in 14% (5 mg) and 36% (10 mg) when combined with SUs, but not with metformin [245,246]. Patients on exenatide may develop anti-exenatide antibodies that may reduce the efficacy of exenatide. Thus observation for hypersensitivity reactions is required. Benign thyroid C-cell hyperplasia was observed in female rats, but not in mice or humans [251].

A meta-analysis of randomized controlled trials (RCT) with exenatide twice/d or once/week showed reduction of 1.1% in HbA1c [253]. Exenatide LAR yielded greater reduction in HbA1c (1.9%) than exenatide twice/d (1.5%) [254], similar weight reduction and less gastrointestinal side effects (nausea and vomiting) [255]. When exenatide and metformin were combined with SUs,

the additional HbA1c reduction was 0.8% [245–247], and slightly higher when combined with TZD (1.0%) [256]. In a 2-year study of exenatide in patients on metformin and SUs, HbA1c was reduced by 1.1% and weight was reduced by 4.7 kg [257]. This glycemic improvement maintained after 3 years of treatment [258]. Clinical trials comparing exenatide with basal or biphasic insulin demonstrated similar improvement in HbA1c (0.8–1.4%); however, exenatide was associated with dose-dependent weight loss (2.2–3.6 kg), whereas insulin with weight gain (1.0–2.9 kg) [259–262]. In extension trials, weight loss was not associated with nausea, thus supporting the hypothesis that weight loss was not owing to gastrointestinal adverse events [257,258]. Exenatide seems also to improve HDL-C, LDL-C, triglycerides, apolipoprotein B, systolic and diastolic blood pressure [246,260–265]. However, it is not clear whether these changes are clinically significant. As expected, improvement in proinsulin-to-insulin ratio and HOMA-β, indices of beta-cell function, was also reported [260–265].

When compared to sitagliptin as add-on to metformin, although both similarly reduced fasting glucose, exenatide showed greater reduction in 2 h and 4 h postprandial glucose and caloric intake. Patients switched from sitagliptin to exenatide experienced a decrease, whereas those switched from sitagliptin to exenatide an increase in 2 h postprandial glucose [266]. This superiority of exenatide on postprandial glucose may be due to a greater concentration of GLP-1RA achieved compared with the concentrations of endogenous GLP-1 achieved by DPP-4 inhibitor. Interestingly, in the recently published Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8) trial, a 28-week co-administration of exenatide once/week and dapagliflozin (a SGLT2 inhibitor) led to greater reduction in HbA1c, weight, fasting and postprandial plasma glucose and systolic blood pressure compared with either monotherapy in patients inadequately controlled by metformin [267].

2.2.1.2.2 Liraglutide

2.2.1.2.2.1 Mechanism of Action. Liraglutide is a long-acting GLP-1RA with 97% amino acid homology to the human endogenous GLP-1 [268]. Liraglutide is linked to a fatty acid molecule that binds albumin, thus prolonging the half-life to 13 h compared with 1.5–5 min of endogenous GLP-1 [268,269]. Liraglutide stimulates glucose-dependent insulin secretion and inhibits glucagon secretion [270].

2.2.1.2.2.2 Dose and Position in Treatment Armamentarium. Liraglutide is administered subcutaneously, once daily, independent of meals. Recommended initiation dose is 0.6 mg/d for 1 week and then increase to 1.2 mg/d. Maximum dose is 1.8 mg/d, if needed, based mainly only basal glucose levels [13]. Similarly to other GLP-1RA it is a second-line treatment.

2.2.1.2.2.3 Safety and Outcomes. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with type 2 multiple endocrine neoplasia, based on rodent studies, in which higher rates of thyroid C-cell carcinomas were reported. Unlike humans, rats have a high density of GLP-1 receptor in C-cells, thus predisposing to C-cell hyperplasia [271]. However, no cases of medullary thyroid carcinoma have been reported in clinical trials to-date, and calcitonin levels remained low after treatment with liraglutide [270]. In nonhuman primates, liraglutide dose up to 60 times higher than the maximum recommended in human did not lead to C-cell hyperplasia [272]. Thus the American Association of Clinical Endocrinologists (AACE) made a statement recommending no special surveillance (calcitonin levels or performing thyroid imaging) in liraglutide treated individuals.

Major hypoglycemia is rare with liraglutide, reported in seven of 2026 (0.35%) patients in a 26- week trial. Notably, six of these patients were also taking a SU. No major hypoglycemic events occurred when liraglutide was used as monotherapy or in combination with metformin [273,274]. Minor hypoglycemia was reported in 9.7% of patients on liraglutide compared with 24.2% of patients on glimepiride. Moreover, liraglutide may cause gastrointestinal side effects: nausea (5–40%), vomiting (4–17%) and diarrhea (8–19%), especial at the initiation of treatment, which usually subsides within 4 weeks of treatment [273–278]. Non-inactivating anti-liraglutide antibody formations have also been reported [279], but their clinical relevance remains to be shown.

T2DM itself is associated with a 3-fold higher risk of developing acute pancreatitis and liraglutide does not seem to increase it [254,273–276,278]. Although acute pancreatitis is still listed under warnings and precautions with liraglutide, a recent claim reports no excess risk of acute pancreatitis or pancreatic cancer with liraglutide [280]. However, the low incidence of these events suggests that continuous surveillance is required before a causal link is eliminated. Large-scale clinical trials investigating the long-term CV safety of GLP-1RA are ongoing and may also provide important insights into pancreatic and thyroid safety.

Liraglutide has been studied in phase 3 trials (the Liraglutide Effect and Action in Diabetes [LEAD] program; >4000 patients; duration 26–52 weeks). As monotherapy, liraglutide reduces HbA1c by 1.0–1.7% [269,270]. In combination with metformin, liraglutide further reduces HbA1c by 1.0–1.5% (1.8 mg/d), 1.0–1.2% (1.2 mg/d) and 0.7% (0.6 mg/d) [274]. In combination with SU, the decrease in HbA1c was similar: 1.1% (both 1.2 and 1.8 mg/d) and 0.6% (0.6 mg/d). In combination with metformin and rosiglitazone, HbA1c decreased by 1.5% (both 1.2 and 1.8 mg/d) [277]. Compared with insulin glargine, in patients on metformin and/or SU, liraglutide (1.8 mg/d) reduced HbA1c more significantly (1.1 vs. 1.3%, respectively) [278]. Liraglutide also improves beta-cell function indices, including proinsulin-to-insulin ratio, HOMA-IR and increases HOMA-β [273,274,277,278]. The efficacy and safety of liraglutide (1.8 mg and 1.2 mg) vs. sitagliptin (100 mg) were also compared in patients inadequately controlled with metformin. Both doses of liraglutide resulted in greater reduction in HbA1c compared with sitagliptin (1.5%, 1.2% and 0.9%, respectively). Patients treated with liraglutide lost more weight (3.4 kg [1.8 mg] and 2.9 kg [1.2 mg]) compared with sitagliptin (1.0 kg). Both doses of liraglutide improved more than sitagliptin the markers of pancreatic beta-cell function, including HOMA-β, C-peptide, and proinsulin-to-insulin ratio, although there was no difference in HOMA-IR or fasting insulin levels. Changes in calcitonin levels were similar in both groups. No case of pancreatitis was observed [281].

Compared with exenatide LAR in patients on metformin and/or SU, liraglutide reduced HbA1c more significantly (0.8% vs. 1.1%, respectively), while both reduced body weight similarly (2.9 vs. 3.2 kg, respectively). Liraglutide reduced fasting glucose more

than exenatide LAR, whereas exenatide LAR reduced postprandial glucose more than liraglutide [248]. In the extension of this trial, switching from exenatide to liraglutide significantly reduced HbA1c by 0.3%, weight by 0.9 kg and systolic blood pressure by 4 mmHg, whereas continuing liraglutide further decreased weight (0.4 kg) and systolic blood pressure (2 mmHg), but not HbA1c [248]. The mechanism of reduction in systolic blood pressure is largely unknown, although it may be partly attributed to natriuresis [282]. Systolic blood pressure reduces before substantial weight loss, implying that it may not be related to weight loss [278]. No improvement in diastolic blood pressure was reported by liraglutide. Given, significant reductions in weight with this medication, higher dosages of liraglutide were studied and liraglutide 3 mg has now been approved for the treatment of obesity in the first year of the SCALE Obesity and Prediabetes study [283]. It should be noted that higher rate of acute pancreatitis was observed in the liraglutide (0,4%) than the control group (<0.1%) in this study [283].

2.2.1.2.3 Other GLP-1RA. Other approved GLP-1RAs include the long-acting albiglutide and dulaglutide (once weekly), and the short-acting lixisenatide (once daily). Semaglutide, another long-acting GLP-1RA, has also successfully completed phase 3a and is now under evaluation for FDA approval. Semaglutide reduced HbA1c by 1.1% and weight by 3.6 kg in a dose of 0.5 mg/week, and by 1.4% and 4.9 kg, respectively in a dose of 1 mg/week [284]. An oral formulation of semaglutide is being studied and may probably be available in the next few years (clinicaltrials.gov identifiers: NCT02607865, NCT02692716, NCT02863328).

Dulaglutide is injected subcutaneously at a dose of 0.75 mg once weekly and can be increased to 1.5 mg. The dulaglutide molecule consists of a GLP-1 moiety fused to an immunoglobulin fragment rendering the molecule both resistant to DPP-4 degradation and long-acting through reduced renal excretion. HbA1c reduction, weight loss and safety profile of dulaglutide are similar to those of liraglutide. Compared with insulin glargine in patients on metformin and glimepiride in AWARD-2 (Assessment of Weekly Administration of LY2189265 [dulaglutide] in Diabetes-2), dulaglutide showed greater HbA1c and weight reduction and lower risk of hypoglycemia, albeit higher rates of gastrointestinal side effects [285,286]. Compared with insulin glargine in patients on prandial insulin lispro (AWARD-4), dulaglutide showed greater HbA1c reduction, but higher rates of gastrointestinal side effects [286].

Albiglutide contains albumin allowing weekly administration. Albiglutide has been studied in the HARMONY 1–8 trials for efficacy and safety as monotherapy and as an add-on to metformin, glimepiride, pioglitazone or sitagliptin, liraglutide or sitagliptin, and as an add-on to insulin glargine vs. insulin lispro. These trials have shown superior efficacy or non-inferiority in HbA1c, but consistently smaller weight-reducing effect compared with other GLP-1RAs, which is possibly owing to the big molecular weight of the albiglutide, rendering it less able to cross the blood-brain barrier [287].

Lixisenatide is administered once daily, although its half-life is similar to that of exenatide. It has a 4-fold higher affinity for the GLP-1 receptor than endogenous GLP-1 [288]. Lixisenatide was previously available only in Europe, but has been approved for the USA in 2016. Its CV trial ELIXA (The Evaluation of Lixisenatide in Acute Coronary Syndrome) data demonstrated a neutral effect on CV outcomes [289].

Extended-release formulations of GLP-1 RAs (exenatide once monthly and once yearly and efpeglenatide once monthly are now under investigation. These longer acting GLP-1RAs offer the convenience of longer dosing intervals, but further studies are required to determine whether they provide the same glycemic control and weight loss as the established GLP-1RAs.

2.2.1.2.3.1 Combinations of GLP-1RAs With Insulin. Most studies have shown that the combination of GLP-1RA with basal insulin is equal or more effective than the combination of basal insulin with prandial insulin [244,290,291]. In the current algorithm for the treatment of T2DM patients, this combination is proposed before the addition of prandial insulin, especially in obese patients, those highly endangered from hypoglycemia or those do not desire multiple injections [13].

2.2.1.2.3.2 Cardiovascular Outcomes. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial investigated the effect of liraglutide in T2DM patient at high risk of CVD. After a 3.8-year follow-up, primary composite outcome (CV-related death, nonfatal MI and nonfatal stroke) occurred in fewer patients on liraglutide (13.0%) than placebo (14.9%; $p < 0.001$). All-cause mortality (8.2% in liraglutide vs. 9.6% in placebo) and CV mortality (4.7% in liraglutide vs. 6.0% in placebo) were also significantly lower in the liraglutide group. However, nonfatal stroke, nonfatal MI and hospitalization for heart failure were non-significantly lower in the liraglutide group [292]. It is noteworthy that GLP-1R have been associated with minimal but significant increase in heart rate. In a meta-analysis, this effect was more evident for liraglutide and exenatide LAR than exenatide twice daily [293]. Moreover, LEADER 7 trial showed some baseline differences between the USA and European population, possibly due to variations in targets for CV risk management [294]. Moreover, liraglutide did not improve left ventricular ejection fraction at rest, at low stress, peak stress or recovery in patients with T2DM and stable coronary artery disease compared with placebo [295]. A few trials on different GLP-1RA are still ongoing and are expected to provide further data. Effects of Liraglutide in Young Adults With Type 2 DIAbetes (LYDIA) is an ongoing study comparing the effects of liraglutide and sitagliptin on diastolic function of the heart. The EXenatide Study of Cardiovascular Event Lowering (EXSCEL) compares the impact of adding exenatide once-weekly to usual care vs. usual care alone on major CV outcomes [296]. However, previous study on exenatide vs. placebo in patients with acute MI undergoing percutaneous intervention did not show any difference in infarct size between groups [297].

A large cohort study using the UK-based Clinical Practice Research Datalink looked at 338,233 patients on metformin who were added a second-line antidiabetic medication and reported as rates of major CV events (MACE): 15.9/1000 person-years for GLP1-RA, 19.1/1000 person-years for DPP-4 inhibitors and 33.1/1000 person-years for SUs. As a second-line therapy, DPP-4 inhibitors were associated with a 42% relative risk reduction in all-cause mortality and 36% reduction in MACE vs. SUs [298]. However, a meta-analysis of 100 RCTs of incretin-based therapies showed that exenatide was associated with an increased risk of arrhythmia, saxagliptin with an increased risk of heart failure and sitagliptin with a decreased risk of all cause death [299]. Semaglutide also provided promising CV results, reducing the primary outcome, composed by CV death, nonfatal MI or

nonfatal stroke vs. placebo, although CV mortality was similar between groups. In the recently published trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN)-6, semaglutide significantly reduced the composite endpoint (cardiovascular death, non-fatal MI and non-fatal stroke), as well as the rates of new or worsening diabetic nephropathy compared with placebo in T2DM patients. Semaglutide also decreased body weight. As expected, semaglutide group had higher rates of gastrointestinal side effects. Of note, retinopathy increased more in the semaglutide group [300]. Notably, semaglutide had a beneficial effect on nephropathy, but increased the rate of retinopathy [301]. Ongoing trials including the ongoing Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) for dulaglutide and HARMONY (albiglutide) are expected to report their CV outcomes in 2019.

Cost: High ($720 per month)

2.2.2. *Sodium-glucose Cotransporters 2 Inhibitors*

2.2.2.1. Mechanism of Action. Glucose is freely filtered by the kidneys and is reabsorbed in the proximal convoluted tubule. The quantity of glucose filtered increases linearly with increasing circulating glucose concentration until the glucose transport maximum (Tm_G) is reached. Glucose reabsorption occurs via SGLT2, which are high-capacity, low affinity, membrane-bound carrier proteins. SGLT2 are responsible for up to 90% of glucose reabsorption and act independently of insulin. Through complete reabsorption, there is no glycosuria, as under normal conditions. Glycosuria occurs when the renal threshold for reabsorption (180–200 mg/dl in terms of circulating glucose) is reached [302,303]. Apart from SGLT2, mainly expressed in the luminal surface of epithelial cells lining the S1 segment of the proximal convoluted tubule of the kidneys, several SGLTs are expressed in different organs. SGLT1 are mainly expressed in the intestine, but also in the kidneys, where are responsible for the remaining 10% of glucose reabsorption [304,305]. SGLT2 are upregulated in T2DM patients resulting in a 20% increase in the mean Tm_G, thus enhancing glucose reabsorption [306,307]. SGLT2 inhibitors are drugs that block SGLT2, resulting in lowering of the renal threshold for glycosuria and glucose Tm_G, thus decreasing renal glucose reabsorption. SGLT2 provide a novel target to address hyperglycemia through urinary glucose excretion [308]. Canagliflozin is currently the only SGLT-2 inhibitor that also inhibits SGLT1 [309].

2.2.2.2. Dose and Position in Treatment Armamentarium. There are several SGLT2 inhibitors currently approved, including canagliflozin, dapagliflozin and empagliflozin [310]. Canagliflozin (100 or 300 mg), dapagliflozin (5 or 10 mg) and empagliflozin (10 or 25 mg) are administered orally once/d, independently of meals, but preferably before the first meal of the day; they reduce postprandial glucose excursions due to the delayed intestinal glucose absorption through blocking SGLT1, an effect shown for canagliflozin. SGLT2 inhibitors are included in the recent algorithm recommended by ADA, AACE and EASD [311]. They are approved as monotherapy, but mainly proposed as second-line treatment in addition to metformin or other agents, except for GLP-1RA, although there are emerging data for the latter combination. A recent retrospective observational study showed greater reduction in HbA1c and weight when SGLT2 and GLP-1RA are combined vs. GLP-1RA monotherapy [312]. The GLP-1RA may attenuate the increase in glucagon observed with SGLT2 inhibitors. The combination of SGLT2 inhibitors with insulin is recommended and may be very favorable in patients requiring many units of insulin, as highly insulin-resistant individuals [13]. Combinations with metformin or DPP-4 inhibitors are also available. Other drugs of this category that are in the horizon include luseogliflozin or TS-071, tofogliflozin or CSG452, ipragliflozin or ASP1941, ertugliflozin or PF04971729, LX4211, EGT0001442, remogliflozin, AVE2268 [310].

2.2.2.3. Safety. Genital mycotic infections were more common in canagliflozin groups (2.5%–25.0%) vs. placebo (0–4.3%). The observed infections were mild to moderate, occurred more frequently in women than men, were managed mostly with standard topical treatments and infrequently led to study discontinuation [308,313–318]. Among men, uncircumcised ones or those with history of balanitis/balanoposthitis are at higher risk [315]. The frequency of severe hypoglycemic events of canagliflozin (0–6.8%) was similar to placebo (0–4.1%) [313,318,319], but the rates were higher when canagliflozin was combined with insulin or SUs [315,318]. Adverse events indicative of osmotic diuresis (including dry mouth, nocturia, polyuria, thirst and increase in urine output) or reduced intravascular volume (postural dizziness, hypotension and syncope) were higher in canagliflozin (0–7.0%) than placebo (0–1.9%), although these symptoms were not accompanied by increase in heart rate [313–319]. A dose of 100 mg of canagliflozin is recommended in patients on a loop diuretic, with moderate renal impairment (eGFR 45–60 ml/min/1.73 m^2) or with age ≥75 years, because of a dose-related increase in adverse events related to reduced intravascular volume. It is also recommended canagliflozin be avoided, if eGFR <45 ml/min/1.73 m^2, and be contraindicated in severe renal impairment (eGFR <30 ml/min/1.73 m^2), end stage renal disease, patients on dialysis or severe hepatic impairment. Furthermore, the use of canagliflozin is not permitted during pregnancy and lactation as it is rated as category C drug. During therapy, monitoring of potassium levels is required in patients with impaired renal function and those predisposed to hyperkalemia. Monitoring intravascular volume and correcting hypovolemia may be needed in patients with renal impairment, the elderly, patients with low systolic blood pressure, or on diuretics, ACE inhibitors or angiotensin II receptor blockers. Canagliflozin is metabolized via *O*-glucuronidation to two inactive *O*-glucuronide metabolites. It is mainly excreted in the feces and urine; enterohepatic circulation of canagliflozin is negligible. During canagliflozin therapy, slight decrease in alanine aminotransferase, gamma-glutamyltransferase and serum uric acid, and modest increase in hemoglobin, bilirubin and urea may be observed, which are consistent with the decrease in intravascular volume [314–320]. Canagliflozin may decrease eGFR at 4–6 weeks, but eGFR remains stable from week 12 to 52 [316,318–320]. The safety and side effects of dapagliflozin and empagliflozin are generally comparable to that of canagliflozin. Notably, there is a FDA warning for diabetic ketoacidosis for patients on SGLT2, even with mild hyperglycemia, but the mechanism remains unclear. However, in most cases with

"euglycemic ketoacidosis" induced by SGLT2 inhibitors, certain triggering factors for ketoacidosis have been suggested, including decrease in insulin dose, reduced food and fluid intake, and major illnesses (https://www.fda.gov/Drugs/DrugSafety/ucm446845.htm). There were also patients misdiagnosed as having T2DM instead of T1DM. Recently (February 2017), the EMA required the inclusion of this warning to all SGLT2 inhibitors. Previously (May 2016), the FDA had issued a safety alert about a two-fold risk of leg and foot amputations in patients on canagliflozin. However, further evidence is needed to establish this association. The results of the CANagliflozin cardioVascular Assessment Study (CANVAS) will provide more data on the potential link between canagliflozin and amputations. Furthermore, a higher risk of bone fractures was reported in canagliflozin-treated patients compared with placebo in a separate analysis of the CANVAS trial, whereas no such association has been observed in other studies with canagliflozin [321]. The fractures occurred as early as 12 weeks of therapy initiation and were mainly located in the distal parts of the upper and lower limbs [322,323]. Bone density may also be decreased by canagliflozin [324]. Based on these findings, the FDA revised the safety label of canagliflozin to include data on bone fracture risk and reduced bone mineral density. Nevertheless, there is a need for more evidence in order to elucidate the bone effects of canagliflozin. Of note, dapagliflozin did not change bone markers and bone density in one trial [325]. No bone-related data exist for empagliflozin. Recent results from CANVAS study show that safety and efficacy of canagliflozin were consistent in subgroups of patients with CVD and T2DM [326].

2.2.2.4. *Outcomes*. Canagliflozin has been studied as monotherapy [313] or combination therapy with metformin, SUs, DPP-4 inhibitor, α-glucosidase inhibitor, GLP-1RA, pioglitazone or insulin [314–320] and has shown to reduce fasting glucose and HbA1c. A meta-analysis of 8 studies with canagliflozin showed a HbA1c reduction of 0.8%. Canagliflozin also improves body weight, blood pressure, waist circumference, triglycerides and HDL-C [327,328]. Results of the CANagliflozin cardioVascular Assessment Study (CANVAS) Program were presented at American Diabetes Association, 77th Scientific session. A 14% reduction in the composite endpoint of CV mortality, nonfatal stroke or non-fatal MI was shown with canagliflozin as compared to placebo. Canagliflozin also achieved a 33% reduction in the risk of hospitalization for heart failure (HF) compared with placebo. Potential renal protective effects were also observed with canagliflozin. There was an increased risk of fractures and amputation with canagliflozin observed in CANVAS studies which needs further investigation and follow up studies [329]. Dapagliflozin also reduces fasting plasma glucose, HbA1c, body weight and systolic blood pressure. A meta-analysis of 10 RCTs showed that dapagliflozin reduced HbA1c by 0.5% [330]. Furthermore, a meta-analysis investigating the effect of dapagliflozin as an add-on to conventional antidiabetic treatment showed improved glycemic control without weight gain [331]. Long-term efficacy, safety and tolerability of dapagliflozin vs. placebo were evaluated in a pooled analysis from two phase 3 studies in T2DM patients with CVD receiving dapagliflozin 10 mg/d vs. placebo. Patients on dapagliflozin maintained better glycemic control, body weight and systolic blood pressure, but also experienced higher rates of genital and urinary tract infections. Similar rates of hypoglycemia, renal impairment and volume depletion were observed in dapagliflozin and placebo groups [332]. Improvement in HbA1c and blood pressure were reported in another study, in which systolic blood pressure reduced by 4.3 mm Hg and HbA1c by 0.6% with dapagliflozin compared with the placebo [333]. Similarly, empagliflozin improved glycemic control, blood pressure and body weight. A systematic review and meta-analysis of 10 RCTs showed that it reduced HbA1c by 0.6% (10 mg/d) and 0.7% (25 mg/d) and was also associated with weight loss and a favorable effect on systolic blood pressure. In the same meta-analysis, the glucose lowering efficacy of empagliflozin (25 mg/d) was similar to metformin or sitagliptin [334]. Overall, weight reduction ranged from 1.8–2.5 kg in patients on empagliflozin [334,335]. SGLT2 inhibitors may also reduce uric acid levels and improve glomerular hyperfiltration and albuminuria [336,337]. These effects may lead to preservation of renal function in T2DM patients.

Regarding CV outcomes, news is promising for SGLT2 inhibitors. Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study that involved 7020 T2DM patients with established CVD. The study showed that empagliflozin (10 mg or 25 mg/d), when added to standard care, significantly lowered CV mortality, all-cause mortality and hospitalization for heart failure. There were no significant differences in the rates of nonfatal MI or nonfatal stroke in the empagliflozin group as compared to placebo [338]. This trial demonstrated for the first time that a newer antidiabetic medication, empagliflozin, is able to reduce CV mortality in T2DM patients. Based on these findings, the FDA approved an additional indication for empagliflozin to reduce CV mortality in T2DM patients with established CVD. Furthermore, based on the EMA, the marketing authorization for empagliflozin was changed, recommending its use not just for improving glycemic control, but also for the treatment of adults with uncontrolled T2DM, thus highlighting the clinical significance of treating the patient and not the biomarker (i.e. glucose or HbA1c). Furthermore, in the current ADA guidelines [339], a new statement was added to support the use of empagliflozin or liraglutide in patients with long-standing suboptimally controlled T2DM and established CVD, based on the results of the EMPA-REG OUTCOME and LEADER trials.

A meta-analysis of data from eight randomized trials with T2DM patients on empagliflozin showed a reduced risk of MACE (i.e. non-fatal MI, non-fatal stroke, hospitalization for heart failure and/or CV death) with empagliflozin compared with placebo [340]. Another meta-analysis including six regulatory submissions (37,525 participants) and 57 published trials (33,385 participants) and analyzing data on CV outcomes for seven different SGLT2 inhibitors, showed a reduced risk of MACE, heart failure CV and all-cause mortality. No clear effect was observed for non-fatal MI or angina, whereas a marginally significant increase in the risk of non-fatal stroke was observed. Increased risk of genital infections was also confirmed. The results of the meta-analysis were driven from empagliflozin, the only to-date SGLT2 inhibitor with favorable CV outcomes [341]. Furthermore, a recent meta-analysis suggested a potential CV

benefit of dapagliflozin in T2DM patients at different CV risk categories [342]. In the EMPA-REG OUTCOME trial, empagliflozin showed favorable outcomes on diabetic nephropathy [343]. Several mechanisms have been suggested to explain these cardio- and reno-protective effects of empagliflozin including improvement in cardio-metabolic and renal parameters, hemodynamic changes, natriuresis and shift of fuel metabolism towards ketones bodies [344,345]. Recently published CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors) study that has analyzed a total of 309,056 patients newly initiated either on SGLT-2 inhibitors or any other oral glucose lowering medication showed that use of a SGLT-2 inhibitor (canagliflozin, dapagliflozin or empagliflozin) vs. other glucose-lowering drugs was associated with lower rates of death and hospitalization for heart failure [346].

There are several ongoing trials with CV outcomes of SGLT2, including the CANVAS and the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R), Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial (CREDENCE), Dapagliflozin Effect on CardiovascuLAR Events (DECLARE TIMI-58), Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease, (The VERTIS CV Study), which are going to provide further information in the next few years [347]. The multi-faceted pathogenesis of atherosclerosis in T2DM, affected not only from abnormal glucose metabolism, but also other important CV factors, such as hypertension and obesity, which can be modified by SGLT2 inhibitors, gives promise for the future outcomes [347].

Cost: High ($400.00 per month)

2.3. *Medications on the Horizon*

There are many agents under investigation for the treatment of T2DM, which include:

2.3.1. *Currently Available*

2.3.1.1. *Bromocriptine*. This dopamine agonist was approved for the treatment of T2DM in 2010. The mechanism of action is not clear. A quick release form was studied for one year, reducing HbA1c by 0.6% as monotherapy and 1.2% in combination with SUs and insulin. Bromocriptine also decreased triglyceride and free fatty acid levels by 30% [348].

2.3.1.2. *Ranolazine*. It is used for angina and thought to inhibit potassium-sodium channels and cause calcium release. It reduces HbA1c by 0.6% in patients with T2DM and acute coronary syndrome, and fasting glucose in non-diabetic patients, without causing hypoglycemias [349]. Ranolazine was FDA approved for used in T2DM patients in 2013. Since, concomitant use of ranolazine 1000 mg twice daily and metformin resulted in increased levels of metformin, the maximum dose of metformin that was recommended in combination with ranolazine was 1700 mg/d.

2.3.1.3. *Salsalate*. This known anti-inflammatory agent reduces fasting glucose and glycemic response after an oral glucose challenge in T2DM patients by 13% and 20%, respectively. It also decreases glycated albumin by 17%. Although there was no change in insulin levels, c-peptide levels increased after salsalate. An increase in adiponectin levels by 57% was observed as compared to placebo [350], which may partly explain its anti-diabetic effect. FDA approved dosage of salsalate is 3 g/d.

2.3.2. *In the Pipeline*

2.3.2.1. *INT131*. This is a potent non-TZD, selective PPAR-γ modulator. In preclinical studies and phase 2 clinical trials, INT131 reduced hyperglycemia and improved insulin sensitivity without the undesirable side effects of TZDs, including weight gain and peripheral edema. Some phase 2 studies have shown an early glucose lowering effect (week 1) and upregulation of adiponectin levels [351]. Due to its mechanism of action, INT131 is a useful candidate for the treatment of NASH, which usually coexists with T2DM [107].

Protein Tyrosine Phosphatase (PTP)-1B inhibitors: PTP-1B (e.g., TTP814) has been implicated in the negative regulation of insulin signaling pathway, so inhibition of this system might improve insulin increase [352].

Ultra-fast acting insulin analogs are considered to provide earlier, greater and faster absorption as compared to rapid acting insulin analogs [353]. They have been approved for treatment of T2DM and T1DM in Europe. However, much research is needed before their unrestricted use in clinical practice.

3. Personalized Treatment Approach

3.1. *Algorithm*

Although lifestyle interventions with diet and exercise are the cornerstone of T2DM therapy, they are difficult to achieve and even more difficult to maintain. Thus many patients eventually require pharmacologic therapy, because they fail to achieve the goals through lifestyle interventions. The updated consensus statement from the ADA and EASD (2017) suggests metformin as the first-line pharmacologic therapy, based on its demonstrated efficacy, weight-neutral profile, general tolerability and low cost [13]. Metformin must be initiated at diagnosis of T2DM (unless contraindicated) along with lifestyle intervention and its discontinuation may be considered, if the lifestyle interventions meet their goals (i.e., weight loss and desirable HbA1c).

If HbA1c remains over the individualized target after 3 months, then a second-line agent should be added. One of the following six treatment options should be considered: SU, TZD, DPP-4 inhibitor, GLP-1RA, SGLT2 inhibitor or basal insulin. These medications are also alternative options for monotherapy, if metformin is contraindicated or not well tolerated. Second-line agent choice should be based on various patients', disease and drug characteristics. The other classes of medications are less validated, but could be administered in specific patients under specific conditions. For example, meglitinides could be used instead of SUs in patients who do not follow a regular schedule of meals. The main characteristics of the antidiabetic agents are presented in Table 1. An easy approach in the clinical practice could

be the use of the ABCDE algorithm by ADA and EASD, which includes (A)ge, (B)ody weight, (C)omplications and co-morbidities, Diabetes (D)uration and (E)xpense. Moreover, patient's preference and patient's response with special consideration on differences in T2DM pathogenesis among different races should be always taken into account [354,355].

If HbA1c at diagnosis is higher than 9%, dual combination therapy is recommended from the start.

If the target for HbA1c is not achieved after 3 months of dual therapy, then a third agent should be added. Again the options include SU, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1RA or basal insulin, depending on which the second agent was. The combinations of GLP-1RA with DPP-4 inhibitor must be avoided, because they target to the same mechanism of action. The combination of GLP-1RA or DPP-4 inhibitor with SGLT2 inhibitor has been recently approved by FDA and may prove to be beneficial given complementary mechanism of action [13].

Insulin has the advantage of the highest effectiveness on glycemic control and should be highly considered when random blood glucose >300 mg/dl or HbA1c >10% or catabolic and/or insulinopenic symptoms and signs are present. For initiation of insulin therapy, the simplest way is a single injection of basal insulin (such as glargine, detemir or degludec) to reduce fasting glucose levels. Starting dose can be 10 units or 0.1–0.2 units/kg. Fasting glucose should be monitored to titrate basal insulin by 2 units every 2–3 days, until the target is achieved (usually <120 mg/dl) without provoking nocturnal hypoglycemia. The dose can be increased by 4 units, if fasting glucose >180 mg/dl. Oral and non-insulin injectable agents are usually continued when basal insulin is started [356]. Once the target of fasting glucose is achieved, prandial and bedtime glucose levels should be monitored, if HbA1c levels are not desirable. If prandial or bedtime glucose levels are consistently higher than the goal, despite a reasonable meal plan, combination injectable therapy should be considered. The options include prandial insulin therapy before the meal(s) (one to three injections per day) or a GLP-1RA. Regarding prandial insulin therapy, the initial dose can be 4 units adjusted by 2 units every 23 days, until glucose levels are at the target. Another alternative is the use of premixed insulin formulations, which may be more convenient, since less injection are required, but dose adjustment is less flexible, thereby a more standard plan of meals is required. While prevailing advice is to discontinue SUs, DPP-4 inhibitors and GLP-1RAs when combined insulin therapy (more than basal) is started, recent case reports suggest utility with continuation of GLP-1RAs in obese, insulin-resistant patients who initiate combined insulin therapy. Therapy with metformin, pioglitazone or SGLT2 inhibitors can be helpful especially for patients who need large insulin quantity [13,354,355]. The algorithm steps for the treatment of T2DM are presented in Table 2.

3.2. *Goals*

HbA1c represents the average blood glucose levels over the past two to three months. The usual HbA1c therapeutic goal is 7%. However, therapeutic targets should be personalized, varying from patient to patient and modifying over time even in the same patient. Therapeutic targets are determined by patients' and disease features (disease duration, life expectancy, complications and co-morbidities, personality and attitude, resources and support system) and then individualized targets determine the type and the duration of treatment [355].

In the UKPDS, intensive glucose control with SUs or insulin achieving a HbA1c of 7.0% greatly reduced the risk of microvascular complications compared with diet alone, achieving a HbA1c of 7.9% [9]. Furthermore, intensive treatment with metformin achieving a HbA1c of 7.4% resulted in risk reduction in macrovascular complications and diabetes-related all-cause mortality compared with diet alone, achieving a HbA1c of 8.9% [29]. A 10-year post-trial follow-up of the UKPDS showed that relative risk reduction for microvascular disease persisted and risk reductions for MI and all-cause mortality emerged over time (owing to the occurrence of more events) for SU and insulin groups, although the HbA1c converged for both the groups after one year. Furthermore, risk reduction for MI, diabetes-related and all-cause mortality persisted for the metformin group [357]. Based on these trials and other smaller RCTs, the ADA and EASD consensus guidelines generally recommend a HbA1c target of <7% [13].

On the other hand, large RCTs on tight glycemic control provided conflicting results on CV outcomes and have questioned the usefulness of a generalized HbA1c target. In the ACCORD trial, the intensive group, which reached a HbA1c of 6.4%, had high rates of CV-related and all-cause mortality. Due to these findings, the trial was discontinued after a 3.5 years of follow-up [11]. In contrast, the ADVANCE trial showed that the intensive group, which reached the HbA1c goal of 6.5%, did not have higher rates of macrovascular events or all-cause mortality, but a reduction in microvascular events, mainly nephropathy [12]. The VADT also did not show higher rates of MACE or mortality with intensive glucose control [59]. The Australian Diabetes Society has proposed that a key difference between the UKPDS and ACCORD, ADVANCE and the VADT trials is the population with the UKPDS having recruited newly diagnosed patients, whereas the other three older patients at higher risk of CVD at baseline [358].

In agreement with ADA and EASD [13], a general HbA1c target of 7.0% can be proposed, but therapeutic targets should be further personalized and modified over time following the added comorbidity of an individual patient. In general, newly diagnosed and young patients need tight control to prevent complications, while older patients with shorter life expectancy need to avoid hypoglycemias. Therefore, for patients with T2DM of short duration and no CVD, the HbA1c target should be ≤6.0% for those on lifestyle modifications with or without metformin, ≤6.5% for those on any antidiabetic medication other than metformin and insulin and ≤7.0% for those on insulin. For those with T2DM of duration >10–20 years or CVD, the target should be ≤7.5%. For those with recurrent severe hypoglycemia or hypoglycemia unawareness, the target could be ≤8.0% [358].

4. Conclusions

Pharmacologic treatment options available for patients with T2DM were summarized in this review. Mechanism(s) of

Table 1 – Main characteristics of the antidiabetic classes of medications.

Medication	HbA1c reduction (monotherapy; %)	Durability of action	Weight	Hypoglycemia	Gastro-intestinal side effects	Use in renal failure	Use in heart failure	Effect on cardiovascular outcomes [a]	Approximate cost $$/month
Metformin	1.0–1.5	High	Slight loss	Neutral	Severe	Contraindicated if GFR <30	Contra-indicated in NYHA Class IV	Risk reduction (UKPDS)	10
Sulfonylureas	1.0–1.5	Low	Gain	Moderate to severe	Neutral	Higher hypoglycemia risk should be considered	Contra-indicated	Risk increase (observational trials, meta-analyses)	4
Meglitinides	0.5–1.5	Low	Gain	Mild to moderate	Neutral	Higher hypoglycemia risk should be considered	Contra-indicated	Unknown	31
α-glucosidase inhibitors	0.5–0.8	High	Neutral	Neutral	Moderate	Neutral (not recommended in patients with creatinine >2.0 mg/dl)	?	Unknown (STOP-NIDDM)	28
Thiazolidinediones	1.0–1.5	High	Gain	Neutral	Neutral	Higher fluid retention should be considered	Contra-indicated in NYHA Classes III or IV	Risk Reduction (pioglitazone; PROactive)	14
Insulin	>1.5	High	Gain	Moderate to severe	Neutral	Higher hypoglycemia risk should be considered	Caution with hypoglycemia	Neutral (glargin; ORIGIN)	365 (glargine)
Amylin analogs	0.4–0.8	?	Loss	Neutral	Moderate	Neutral	?	Unknown	
DPP-4 inhibitors	0.4–0.8	?	Neutral	Neutral	Mild	Dose adjustment except for linagliptin	Not contra-indicated (caution with saxagiptin)	Neutral (sitagliptin; TECOS, saxagliptin; SAVOR-TIMI, alogliptin; EXAMINE)	380
GLP-1 analogs	0.5–1.5	?	Loss	Neutral	Mild	Contra-indicated if GFR <30 ml/min/1.7 m^2	Not contra-indicated	Reduction/neutral (liraglutide; LEADER, semaglutide; SUSTAIN 6; ELIXA)	720
SGLT-2 inhibitors	0.5–0.8	High	Loss	Neutral	Neutral	Caution with urinary tract and genital infections; effective in lower dose when GFR 45–60 ml/min/1.7 m^2	Not contra-indicated	Reduction (empagliflozin; EMPA-REG-OUTCOME)	400

?: no clear evidence.

[a] Specific effects on multiple cardiovascular risk factors are presented within the text.

Table 2 – Algorithm steps for the management of patients with T2DM.

Step	Metformin	Sulfonylureas	Thiazolidinedione	DPP-4 inhibitors	GLP-1RA	SGLT2 inhibitors	Insulin
1. Diet and exercise	±	–	–	–	–	–	–
2. Monotherapy	+	If metformin contraindicated or not well tolerated	If metformin contraindicated or not well tolerated	If metformin contraindicated or not well tolerated	If metformin contraindicated or not well tolerated	If metformin contraindicated or not well tolerated	–
3. Dual therapy [a]	+	±	±	±	±	±	± (basal insulin)
4. Triple therapy [a]	+	With metformin and any other agent	With metformin and any other agent	With metformin and any other agent except for GLP-1RA	With metformin and any other agent except for DPP-4-inhibitors	With metformin and any other agent	Basal insulin with metformin and any other agent
5. Combination therapy	+	–	–	–	With metformin and basal insulin	–	Basal insulin with: a) metformin and/or GLP-1RA, or b) prandial insulin

[a] In order to make the best personalized selection for each patient, think of the different antidiabetic agents characteristics (Table 1) and the *ABCDE rule*: (A)ge, (B)ody weight, (C)omplications and co-morbidities, Diabetes (D)uration, (E)xpense.

action, proposed dose and position in treatment armamentarium, expected outcomes, safety issues and estimation of monthly cost are presented for each class of medication. Subsequently, a critical appraisal of current guidelines is provided aiming to an individualized consideration of glycemic targets. Having multiple choices in the armamentarium, therapeutic options should be tailored to the individual patient, combining efficacy, safety and the lower possible cost.

Disclosure statement

The authors have no conflict of interest.

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