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Advances in Pharmacologic Therapies for Type 2 Diabetes

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Abstract Type 2 diabetes (T2DM) is a multi-causal, heterogeneous and progressive cardiometabolic condition, with an increasing prevalence worldwide. T2DM is associated with multiple comorbidities that may impact patients' quality of life. Treatment is multifactorial, but pharmacologic treatment of hyperglycemia is still regarded as the mainstay of diabetes management. Current established therapies include metformin, sulfonylurea agents and insulin, the long-term use of which was associated with reduced micro- and macrovascular events in the United Kingdom Prospective Diabetes Study. Despite major recent advances in diabetes care, a large proportion of patients remain in poor glycemic control, necessitating the development of new therapeutic options. The recently published position statement of the American Diabetes Association and European Association for the Study of Diabetes for the management of hyperglycemia in T2DM has accommodated this wider range of therapy choices, as it is less prescriptive and advocates an individualized treatment approach, taking into account many relevant patient- and disease-related factors. This review summarizes the updates on various established agents as well as the recent developments with regard to incretin-based therapies, inhibitors of the renal tubular sodium-glucose-linked-transporter-2 and ultra-long acting basal insulin formulations.

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Introduction

Worldwide, the prevalence of type 2 diabetes (T2DM) has reached alarming proportions, strongly related to the obesity pandemic. Since T2DM is a leading cause of blindness, chronic kidney disease, cardiovascular disease and mortality [1], its pandemic occurrence will impose a major burden on societies and health-care resources.

T2DM is a multi-causal, heterogeneous and progressive cardiometabolic condition, commonly associated with obesity, dyslipidemia, hypertension, inflammation and endothelial dysfunction. The mechanisms underlying its development are only partly unveiled and both genetic and environmental factors are implicated [2]. Abnormal islet cell function and insulin resistance are key features.

Although the treatment of T2DM is multifactorial [3], achieving euglycemia is the major initial treatment target. Recently, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published the novel conjoined position statement regarding the management of hyperglycemia in T2DM [4•]. This time, the guidelines are less prescriptive than previous versions and recommend a patient-centered approach with respect to treatment targets and medication choices. Among others, based on the outcomes of the so-called mega-trials, i.e. the Action in Diabetes and Vascular disease: preterAx and diamicroN mr Controlled Evaluation (ADVANCE), the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Veterans Affairs Diabetes Trial (VADT) trials [5–7], the position statement proposes to consider specific patient- and

disease-related factors when setting a glycemic target and making drug choices for the individual patient. Consequently, strict glycemic control may not be recommendable in all patients. In order to make optimal treatment choices for the individual patient and ensure compliance, health-care providers are advised to make these decisions in close alignment with their patients.

When initiating pharmacologic treatment, metformin remains the drug of choice, unless it is not tolerated. After metformin, however, there is little evidence to guide physicians [8]. In contrast to the previous version, the new ADA/EASD statement allows a greater role for newer agents, including dipeptidyl peptidase-4 inhibitors (DPP-4i) and glucagon-like peptide-1 receptor agonists (GLP-1RA), by positioning them equivalently to the established sulfonylureas, thiazolidinediones and insulin as a second add-on medication when metformin monotherapy fails [4•]. However, to date, it has been estimated that approximately 25 % of T2DM patients do not respond sufficiently to the available therapies. Conversely, intensified treatment schedules with current agents are associated with increased risk of side effects, such as weight gain and risk of hypoglycemia [9]. Thus, in order to achieve successful personalized treatment for all, development of novel agents is still mandatory. Therefore, the search for novel molecular targets associated with the key defects of the T2DM phenotype is ongoing and has to date yielded several potentially interesting agents that are currently in early or more advanced (clinical) development [10, 11••]. In the current review we summarize the recent advances in pharmacologic therapy for T2DM, focusing on agents that recently have been approved and those for which approval is pending.

Overview of and Updates on Established Non-Insulin Drug Classes

Metformin

This biguanide, which is derived from extracts of the French Lilac [12], remains the first choice agent for treatment of T2DM worldwide, because of its efficacy, low cost, weight neutrality, no increased risk of hypoglycemia, and most importantly, its proven long-term efficacy on outcome [13, 14]. Metformin improves glycemic control to a similar or greater extent than most other agents, including sulfonylurea, thiazolidinediones and α-glucosidase inhibitors [15], as well as the newer DPP-4i [16]. Metformin, when tolerated, can be used at all stages of T2DM, whether as monotherapy or in combination with any of the available agents, including insulin. Its use is associated with gastrointestinal side effects, most notably diarrhea, reported in up to 15 % of patients, while lactic acidosis is a rare event, occurring in elderly patients and those with renal dysfunction [17]. Although metformin was introduced to the market as early as the 1950s (UK: 1958, USA: 1995), it was not until the beginning of this century that its mechanism of action has been (partly) uncovered [18]. Indeed, metformin mainly improves hepatic insulin sensitivity by stimulating AMP-activated kinase (AMPK), among others, via inhibition of components of the mitochondrial respiratory chain [19]. Recent evidence has even implicated metformin as an adjuvant agent in cancer therapy [20].

Sulfonylureas

The sulfonylureas were introduced in the 1940s and, therefore, may be regarded as the oldest available oral antihyperglycemic drugs. Sulfonylurea stimulate insulin secretion by closing the ATP-dependent potassium (K_{ATP})-channels on the beta-cell surface [21], in a glucose-independent manner. Sulfonylureas effectively lower blood glucose, as monotherapy (e.g. when metformin is contra-indicated or not tolerated) or in combination with other agents [15, 22], but their use is associated with an increased risk of hypoglycemia and weight gain. Also, sulfonylureas have a beta-cell depleting effect, occurring rapidly after an initial blood-glucose lowering response, leading to secondary failure [23]. Furthermore, the proposed interaction of sulfonylureas with cardiac K_{ATP}–channels, potentially interfering with the beneficial hibernation process of the ischemic myocardium during myocardial infarction, has raised safety concerns [24]. In spite of these concerns, the United Kingdom Prospective Diabetes Study (UKPDS) has shown no harm with sulfonylurea use in newly diagnosed T2DM at 10 years after randomization [25], nor at 10-year follow-up after study cessation [14]. More recently, after the lack of cardiovascular benefit or even the suggested harm of intensified glycemic treatment in the megatrials [5–7] that was associated with an increased hypoglycemia rate in a fragile high-risk population, the debate regarding the wide use of sulfonylurea was revived, encouraged by marketing authority holders of the new incretin-based agents that have low hypoglycemia risk [26].

Today, in spite of these controversies, being cheap and efficacious, worldwide, sulfonylureas are the leading second choice antihyperglycemic agents, although in some countries a decline in prescription rate was noted [27].

Thiazolidinediones

Thiazolidinediones or peroxisome proliferator-activated receptor (PPAR)-γ activators are insulin-sensitizing agents, acting primarily in adipose tissue and the liver [28]. They promote genesis of small-sized, insulin sensitive adipocytes and redirect fat from non-adipose tissues, such as liver fat, back to (subcutaneous) adipose depots. Additional

beneficial actions include reduction in hepatic gluconeogenesis, anti-inflammatory effects, improvement in endothelial functions and, as more recently established, beta-cell preservation [28, 29••]. However, thiazolidinediones are associated with weight gain, fluid retention and an increased incidence of heart failure [28]. Based on the reported association of its use and increased myocardial infarction risk [30], the use of rosiglitazone has been severely restricted in the US and its marketing suspended in the EU [31]. In contrast, in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE), pioglitazone versus placebo effectively reduced major cardiovascular events and death, which were defined as principal secondary endpoints [32]. Also, in the ensuing extensive analyses, prompted by the rosiglitazone affair, pioglitazone was not found associated with an increased cardiovascular disease (CVD) risk [33]. However, in addition to above-listed side effects, pioglitazone use is also associated with increased fracture risk [34] and bladder cancer [35, 36]. Weighing the risks and benefits, pioglitazone may still be beneficial in specific patients, such as young male T2DM patients with central obesity, hepatic steatosis and a pro-inflammatory profile, who have no history of heart disease or bladder cancer.

Bromocriptine

Timed-release bromocriptine is a centrally acting sympathicolytic D2-dopamine agonist that reduces plasma glucose (HbA_{1c}-reduction of 0.6–0.7 %), triglyceride and free fatty acid levels without increasing plasma insulin levels [37]. Bromocriptine, which is only available in the US for the treatment of T2DM, reduced cardiovascular events in a prospective 1-year study [38]. It can be used as mono- and add-on therapy, does not induce weight gain or hypoglycemia and has a mild and often transient side effect profile (nausea, asthenia, constipation and dizziness) [37].

Colesevelam

After approval by the Food and Drug Administration (FDA) in 2000 for the treatment of hyperlipidemia, the bile acid sequestrant colesevelam was shown to improve glycemic control in patients with T2DM, with a mean HbA_{1c}-reduction of 0.5 %. Thus, in 2008 the FDA approved colesevelam as an add-on drug for glycemic control in T2DM patients [39]. The exact mechanism influencing glucose metabolism remains unexplained. A potential receptor involved seems to be the TGR5, a G-protein-coupled receptor expressed in brown adipose tissue and muscle, where it controls the activity of type 2 deiodinase. Its activation by bile acids leads to increased active thyroid hormone levels, thereby increasing energy expenditure [40]. Interestingly, TGR5 is also present in entero-endocrine L cells [41], where its activation might stimulate intestinal GLP-1 release, leading to the observed metabolic effects [40]. Another mechanism might include its effects on the intestinal and hepatic farnesoid X receptor (the bile acid receptor), possibly reducing endogenous glucose production [42].

Colesevelam reduces LDL-, total and non-HDL-cholesterol levels. However, it increases triglyceride levels and the agent is therefore contraindicated in patients with hypertriglyceridemia. Colesevelam is weight neutral and has a low risk of hypoglycemia, especially when combined with metformin. Side effects are often mild and include constipation and dyspepsia [39].

Amylin

Amylin is a peptide co-secreted with insulin by the pancreatic β-cells. It decreases postprandial glucose excursions by suppressing postprandial glucagon secretion, slowing gastric emptying and increasing satiety. Pramlintide acetate is an amylin analogue, which is available in the US for subcutaneous administration immediately before each meal and is indicated in patients treated with intensive insulin therapy, usually T1DM patients. In T2DM patients it reduces HbA_{1c} by a mean 0.6 % and body weight by approximately 1.3 kg. Side effects include hypoglycemia, nausea, vomiting and anorexia, all of which are usually mild and transient [43].

Novel Non-Insulin Drug Classes

Incretin-Based Therapies

The incretin hormones consist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP)-1 and were isolated in the 1970s and 1980s, respectively [44–46]. GLP-1 is secreted after food ingestion by the more distally located intestinal L-cells, whereas GIP is released from the more proximal K-cells. Both incretin hormones enhance glucose-dependent insulin secretion and production, but only GLP-1 additionally suppresses glucagon secretion, slows gastric emptying and promotes weight loss by inducing satiety and reducing food intake [47]. Since GLP-1, but not GIP [48], retains its insulinotropic efficacy in T2DM when administered exogenously, agents rather based on GLP-1 were developed for therapeutic use. As GLP-1 is quickly degraded by the ubiquitous enzyme dipeptidyl peptidase 4 (DPP-4), resulting in a half-life of 2 min [49], two different approaches were followed to enhance GLP-1 receptor signaling without the need of continuous GLP-1 infusion: 1) the development of degradation-resistant GLP-1RA, and 2) oral DPP-4 inhibitors (DPP-4i), enhancing endogenous incretin action.

GLP-1 Receptor Agonists

In 2005 the first GLP-1RA, exenatide, was approved by the FDA for the treatment of T2DM. Exenatide is the synthetic form of exendin-4, which is isolated from the salivary glands of the Gila monster. Its amino acid sequence shows 53 % homology to human GLP-1 [47] and its half-life is approximately 2.5 h. Twice daily subcutaneous injection of 10 μg, before breakfast and dinner, yielded the most advantageous dose-effect relation and tolerance. In the 3 AC2993 Diabetes Management for Improving Glucose Outcomes (AMIGO) phase-III trials (n=1446) exenatide twice daily (ExBID) as add-on agent to metformin and/or sulfonylurea lowered HbA_{1c} by 0.8–0.9 % and reduced weight by 1.6–2.8 kg. Mild or moderate nausea and occasional vomiting were the most frequently reported side effects but appeared usually transient [50–52]. Risk of hypoglycemia was low unless the GLP-1RA was combined with sulfonylurea [50, 52].

Liraglutide for once daily use (QD) is a long-acting GLP-1 analog with 96 % structural resemblance to human GLP-1 [53] that was approved by the FDA in 2010. Liraglutide was evaluated in the phase-III Liraglutide Effect and Action in Diabetes (LEAD) (n=4456) program. Exenatide for once weekly use (ExQW) consists of exenatide incorporated into a matrix of poly(D,L-lactide-co-glycolide) for continuous drug release [54] and received FDA approval in 2012 based on the Diabetes therapy Utilization: Researching changes in A1c, weight and other factors Through Intervention with exenatide ONce weekly (DURATION) (n=3249) phase-III program. Within the LEAD program, study duration was 26 weeks, except for LEAD 3, which was 52 weeks (with another 3-year open-labeled extension), whereas studies in the DURATION program ranged from 24 up to 30 weeks (DURATION-1 was extended to 4 years and DURATION-3 up to 3 years) [55, 56].

Both long-acting GLP-1RA result in more robust HbA_{1c}-lowering than ExBID, i.e. up to 1.5 % for liraglutide (1.8 mg QD) [57] and 1.9 % for ExQW (2 mg QW) [58] as add-on agent in metformin and/or sulfonylurea treated T2DM. In the phase-III trials, weight reduction by liraglutide QD and ExQW ranged between 0.2–3.2 [55] and 2.0–3.7 kg [58, 59], respectively. Studies comparing liraglutide QD and ExQW to basal insulin glargine (IG) added to ongoing metformin and/or sulfonylurea showed a slight but significant difference in HbA_{1c}-reduction of 0.24 % and 0.2 %, in favor of the respective GLP-1RA. Both GLP-1RA resulted in weight loss while IG caused weight gain, resulting in a treatment difference of 3.4 kg and 4.0 kg, respectively. For both agents, hypoglycemia rates were lower in the respective GLP-1RA than IG treated groups. In the LEAD-5, due to concomitant sulfonylurea use in 94–95 % of participants, the overall hypoglycemia rate was higher than in DURATION-3, where only 30 % used sulfonylurea/metformin combination [60, 61]. Direct comparison between ExQW 2 mg and liraglutide 1.8 mg QD in the DURATION-6 trial resulted in a difference of 0.21 % in HbA_{1c} and 0.9 kg in weight reduction in favor of liraglutide. Interestingly, 20 % of patients treated with liraglutide experienced nausea and/or vomiting, compared to only 9 % of patients treated with ExQW [62].

The three available GLP-1RA differentially affect the various components of dysglycemia: long-acting GLP-1RA shift the entire blood-glucose curve downwards, thereby significantly lowering fasting glucose levels but not postprandial glucose excursions, whereas short-acting ExBID, due to its pharmacokinetic profile, has a modest effect on fasting glucose, but it completely prevents postprandial glucose elevations [63]. These differential actions of the long- versus short-acting GLP-1RA may be explained by the observed tachyphylaxis for the gastric decelerating effect that seems to develop with continuous versus intermittent GLP-1 receptor stimulation [63, 64]. The waning effect on gastric emptying over time also results in the more favorable side effect profile of the long-acting GLP-1RA, which show an overall lower incidence and a faster decline of initial nausea.

Structural differences from native GLP-1 have been implicated in the observed immunogenicity of ExBID and ExQW compared to liraglutide QD. After 30 weeks of treatment, 36.7 % of patients in the ExBID and 56.8 % in the ExQW group tested positive for anti-exenatide antibodies, with usually low titers (≤125). Efficacy was not impaired in both patient groups, except for a small subset of patients with high titers (≥625) (5 % ExBID and 12 % ExQW), in which a statistically significant reduction in HbA_{1c}-lowering efficacy was shown for treatment with ExQW [65]. Antibody titers and the percentage of antibody-positive individuals decreased during the course of treatment [66]. No cross-reactivity was noted with native GLP-1 or glucagon. For both ExBID and ExQW, a higher incidence of potentially-immune related treatment-emergent adverse events was observed in antibody-positive versus antibody-negative patients, that was predominantly due to an increase in injection-site reactions, the majority of which were mild and transient [65].

In the LEAD trials, 26-week liraglutide exposure resulted in 8.7 % and 8.3 % antibody-positivity in patients receiving 1.2 mg and 1.8 mg QD, respectively. Mean HbA_{1c}-reduction was 1.1–1.3 % versus 1.2 % in antibody-positive versus -negative patients, indicating no consequences for treatment efficacy. In patients treated with ExBID in the LEAD-6 trial, 61 % tested positive for anti-exenatide antibodies and here high antibody titer was correlated with significantly smaller HbA_{1c}-reductions. A higher incidence of cross-reactivity with native GLP-1 was reported for antibodies against

liraglutide compared to anti-exenatide antibodies, likely due to differences in sequence homology compared to GLP-1 [67]. Cross-reactivity with the sequence-related hormone glucagon, however, was not reported.

Multiple novel GLP-1RAs are currently being evaluated in phase-III clinical trials. Lixisenatide is based on exendin-4(1–39) and modified C-terminally with six additional lysine residues [63]. It has a fourfold increased affinity for the GLP-1 receptor compared to human GLP-1 and an elimination $t_{1/2}$ of ~3 h [68]. Although different dosages were tested for BID and QD use, the optimal balance between efficacy and tolerability was shown for lixisenatide 20 μg QD. In spite of once daily administration of both agents, lixisenatide versus liraglutide showed robust decreases in postprandial glucose but modest reductions in fasting plasma glucose [69]. The extensive phase-III GET GOAL program (n=4686), comparing lixisenatide to established T2DM therapies, has been completed and FDA approval submission is soon expected. In the 24-week Get Goal X trial, head-to-head comparison was made between lixisenatide 20 μg QD and ExBID 10 μg in patients insufficiently controlled on metformin. HbA_{1c} dropped by 0.79 % and 0.96 %, body weight by 2.96 kg and 3.98 kg, respectively. A significantly lower rate of hypoglycemia (2.5 % versus 7.9 %) as well as nausea (24.5 % versus 35.1 %) was reported for lixisenatide QD versus ExBiD. Here, lixisenatide QD met the non-inferiority end point and had a more favorable side effect profile compared to ExBID, with only slightly less weight loss. Because of its effects on postprandial hyperglycemia, lixisenatide may be suitable for combination with basal insulin [70]. Indeed, in T2DM patients using basal insulin ±metformin, addition of lixisenatide QD versus placebo for 24 weeks reduced HbA_{1c} by 0.36 %, 2-h postprandial glucose by 3.8 mmol/l and weight by 1.28 kg. Side effects were mainly those involving the gastrointestinal system, which tended to subside over time [71].

The GLP-1RA albiglutide consists of 2 GLP-1(7–36) molecules connected to recombinant human albumin. A single amino acid substitution (ala→gly) renders the molecule resistant to DPP-4. Albiglutide has a half-life of approximately 5 days, which allows weekly dosing. Because of its size, the molecule does not seem to cross the blood–brain barrier, which may have consequences for GI tolerability and body weight reduction [72]. Albiglutide is being evaluated as mono- and add-on therapy in the phase-III Harmony program (n=approximately 5000), the completion of which is planned for early 2013. In the 26-week Harmony 6 trial (n=563) patients insufficiently controlled with IG, metformin and/or thiazolidinedione were randomized to either albiglutide 50 mg QW or prandial insulin lispro. HbA_{1c} was reduced from baseline by 0.82 % and 0.66 %, respectively, thus meeting the primary non-inferiority endpoint. Weight change from baseline was −0.73 kg versus +0.81 kg (week 26) and −0.96 kg and +1.66 kg, respectively, at 52 weeks. Adverse events more pronounced with albiglutide were nausea (13.0 % versus 2.1 %) and injection site reactions (9.5 % versus 5.3 %). Hypoglycemia was more frequently reported with lispro (49.8 % versus 32.6 %) [73]. The 32-week non-inferiority trial Harmony 7 (n=812) comparing albiglutide 50 mg QW to liraglutide 1.8 mg QD in patients inadequately controlled with metformin, thiazolidinedione and/or sulfonylurea showed a reduction in HbA_{1c} from baseline of 0.78 % and 0.99 %, in weight of 0.64 kg and 2.19 kg and in fasting plasma glucose of 1.22 mmol/l and 1.69 mmol/l, respectively. With albiglutide, fewer patients had gastrointestinal discomfort, whereas injection site reactions were less common in patients treated with liraglutide. Albiglutide did not meet the prespecified criterion of non-inferiority to liraglutide [67]. In the 52-week Harmony 8 trial, albiglutide was compared to sitagliptin in 507 T2DM patients with renal impairment. At the 26-week primary endpoint, albiglutide versus sitagliptin reduced HbA_{1c} from baseline by 0.83 % versus 0.52 %, compatible with superiority. Also, weight loss was significantly greater for albiglutide versus sitagliptin (0.79 kg versus 0.19 kg). At 52 weeks, diarrhea was the most common adverse event for albiglutide, whereas nausea and vomiting rates were comparable across both treatment arms [74].

DPP-4 Inhibitors

In 2006 the first DPP-4i, sitagliptin, was introduced to the market, swiftly followed by several other compounds. Oral DPP-4i enhance endogenous incretin action, leading to improved glycemic control in a glucose-dependent manner [69]. DPP4i lower fasting and more profoundly postprandial glucose, but do not influence gastric emptying. They are weight neutral and well tolerated [75]. Currently, sitagliptin, saxagliptin (2009) and linagliptin (2012) have been approved by the FDA, whereas vildagliptin is additionally available in the EU (European Medicines Agency; EMA 2008) and alogliptin in Japan (2010). Although indications may be country dependent, DPP-4i can be used as monotherapy or as add-on to other oral agents and insulin. At their respective recommended doses, all DPP-4i sufficiently inhibit DPP-4-activity for 24 h after once daily administration [76]; however, vildagliptin requires twice daily administration. In a recent meta-analysis including 14 studies using sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin, DPP-4i treatment on average reduced placebo-corrected HbA_{1c} from baseline by 0.7 %, when added to ongoing metformin in T2DM patients. No significant difference in HbA_{1c}-reduction was found compared to ExBID. Overall hypoglycemia rates were low and comparable between GLP-1RA and DPP-4i [77]. In a second meta-analysis, including 50 studies using the aforementioned DPP-4i,

mean HbA_{1c}-changes from baseline ranged between −1.1 % and −0.6 %. Mean weight loss ranged between 0.2 and 0.6 kg. HbA_{1c}-changes were greatest for vildagliptin (−1.06 %), but otherwise comparable between all compounds (sitagliptin −0.67 %, saxagliptin −0.68 %, linagliptin −0.60 % and alogliptin −0.69 %), Noteworthy is the relatively wide 95 %-confidence interval for vildagliptin, from −1.48 % to −0.64 % [78]. DPP-4i showed similar efficacy in reducing HbA_{1c} as add-on therapy to metformin when compared to glimepiride (sitagliptin) [26] and pioglitazone (vildagliptin) [79].

Elimination of sitagliptin, alogliptin and saxagliptin occurs primarily via renal excretion and involves active tubular secretion, such that ~80 % of the compound appears in the urine unchanged. Therefore, for these DPP4i, dose adjustment is necessary in patients with impaired renal function. Vildagliptin is also mainly eliminated via the kidney, but is also metabolized in the liver via a CYP450-independent mechanism. Twenty-two percent of the dose is excreted unchanged, while 55 % appears in the urine as the major metabolite. Elevated liver enzymes were reported after use of vildagliptin and, therefore, regular liver function testing is recommended. Vildagliptin is only recommended for patients with normal and mildly impaired renal function (creatinine clearance ≥50 ml/min) and should not be prescribed in patients with hepatic insufficiency. Linagliptin is minimally metabolized and 78 % of the dose is excreted unchanged by a hepatobiliary route via the feces. Only 5 % is excreted via the kidney, probably by escaping glomerular filtration because of a high degree of protein binding. Therefore, no dose adjustment is necessary in patients with renal failure and it might be an attractive therapeutic option for T2DM patients with moderate to severe or even end stage renal disease. Because the main route of elimination of linagliptin is the liver, caution is mandatory in prescribing linagliptin to patients suffering from hepatic insufficiency [76, 80].

Safety Profile of Incretin-Based Therapies

Meta-analyses of the phase-II and -III trials, as requested by the 2008 FDA guidance for Industry Evaluating Cardiovascular Risk in New Antidiabetic Therapies [81] have hitherto shown no increase in cardiovascular events or mortality for GLP-1RA and DPP-4i. Although the overall number of events in these trials is limited and the patients included have a relatively low risk to develop cardiovascular disease, the meta-analyses suggest that these compounds may lower cardiovascular risk, possibly by their beneficial effects on bodyweight, blood pressure, postprandial lipids and markers of inflammation and oxidative stress [63, 82–84] (see Fig. 1). However, all GLP-1RA consistently increased resting heart rate, typically by 2–4 beats-per-minute, an effect that in epidemiological studies is known to be associated with cardiovascular and all-cause mortality [85]. Large outcome trials are ongoing for most compounds of both classes, as was recently summarized in this journal [86].

Rare cases of acute pancreatitis (AP) in association with use of both incretin-based classes were first reported to the FDA in 2008 [87, 88]. The large number of ensuing reports showed inconsistent results [87–90]. This was due to the bias that comes with observational studies as well as the varying quality of the data-sources used, which often contained self-reported not adjudicated cases. Also, pre-treatment risk factors for AP, including history of pancreatitis, hyperlipidemia, cholelithiasis and drug and alcohol use were lacking. As T2DM per se carries an increased risk of AP [91, 92], it is challenging to establish a causal association between the use of a drug and AP in these patients. The above-mentioned long-term outcome trials will hopefully settle this hitherto unresolved question as to whether a causal relationship exists between the use of incretin-based agents and AP in T2DM. A recent mechanistic study showed that exenatide reduced cholecystokinin-induced gallbladder emptying in healthy fasting subjects, which could potentially impact on bile composition, cholelithiasis and AP risk [93].

Sporadic cases of acute renal failure were reported for both incretin-based classes [94], but large-scaled database studies, meta-analyses and most animal studies did not confirm these findings [95]. Dehydration due to persistent GLP-1RA-related vomiting in high-risk patients with pre-existent renal compromise using vasoactive medications may have exacerbated renal insufficiency. However, the mechanisms underlying DPP4i-related renal failure are presently incompletely understood.

Liraglutide, but not short-acting exenatide was associated with increased calcitonin secretion, thyroid C-cell hyperplasia and C-cell carcinoma in rodents, probably due to continuous high-dose GLP-1RA exposure [96]. However, after careful and extensive evaluation, these side effects were absent in non-human primates and humans [96]. Also, in over 5000 human subjects treated with liraglutide, plasma calcitonin levels remained low [97]. FDA considers the risk of developing thyroid carcinoma to be low in patients treated with GLP-1RA, but liraglutide is contra-indicated in patients with a history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia type 2 syndrome [98].

Sodium-Glucose-Linked-Transporter-2 (SGLT-2) Inhibitors

The renal sodium-glucose-linked-transporter-2 (SGLT-2) has been identified as potent treatment target in the development of new glucose lowering agents. This is a low affinity, high capacity glucose transporter, predominantly located in the proximal tubule. The remainder of

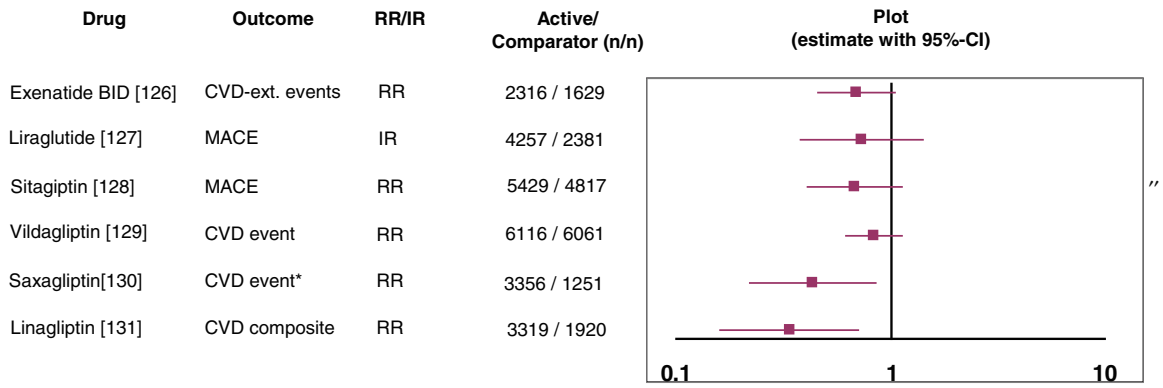

Fig. 1 Cardiovascular safety profile of incretin-based therapies. Forest plot of phase-II and -III trials of current incretin-based therapies [126–131]. Collectively, studies for both incretin classes show no indication of harm with respect to cardiovascular events. Please note the differences in outcome parameters and estimators between studies. CVD=cardiovascular disease, CVD-ext. events=myocardial infarction/ischemia, stroke, cardiac death, arrhythmia, revascularization procedures, heart failure, CVD event=myocardial infarction, ischemic stroke or coronary revascularization procedure, *=adjudicated events by clinical events committee, CVD composite=CV death, nonfatal stroke/myocardial infarction and hospitalization for unstable angina pectoris, IR=incidence ratio, MACE=major adverse cardiovascular events, RR=relative risk

glucose not reabsorbed by SGLT-2 is reabsorbed by SGLT-1, located in the proximal tubule as well as in the intestine [99]. SGLT-2 inhibitors (SGLT-2i), with a greater selectivity for SGLT-2 versus SGLT-1 have been developed, which decrease hyperglycemia and induce calorie loss by inhibiting renal glucose reabsorption in an insulin-independent manner [100]. Dapagliflozin is the first selective SGLT-2i that has finalized its phase-III program. Dapagliflozin has 84 % bioavailability in rats, it binds to albumin and has a half-life of 4.6 h [101]. In a 24-week study (n=546) [102], patients uncontrolled with metformin, received dapagliflozin 2.5, 5, 10 mg QD or placebo. Mean HbA_{1c}-reductions were 0.67, 0.70, 0.84 and 0.30 % and mean changes in weight were −2.2, −3.0, −2.0 and −0.9 kg, respectively. The reductions in body weight began early and continued to progress over the course of the study. This might be explained by an initial diuretic effect of SGLT-2 inhibition, whereas continued weight loss is consistent with the elimination of glucose. The amount of glucosuria observed with dapagliflozin (50–60 g/day) is equivalent to a caloric loss of 200–240 cal/day, which over the course of weeks could explain the 2–3 kg weight loss [103]. The observed osmotic diuresis was accompanied by small increases in blood urea nitrogen and hematocrit and a modest decrease in systolic blood pressure (2.1 to 5.1 mmHg). Hypoglycemia rates were similar to placebo, however, the incidence of mild and transient genitourinary infections was increased [102]. Consistent reductions in HbA_{1c} and weight due to dapagliflozin as add-on therapeutic were shown in patients treated with metformin and insulin in 102- and 104-week randomized trials [104, 105]. Safety concerns were raised due to reports of an increased incidence of bladder and breast cancer associated with dapagliflozin use. Pooled data from 18 trials (n=8165) showed no difference in incidence rates for bladder and breast malignancies between patients treated with dapagliflozin and controls. Hazard ratio for cardiovascular death, myocardial infarction or stroke for dapagliflozin versus control was 0.82 (95 % CI 0.583–1.152) [106]. The FDA declined approval of dapagliflozin because evidence concerning efficacy and safety was insufficient at the time of filing for approval. FDA marketing authorization is shortly expected since the EMA recommended the approval of dapagliflozin in April 2012.

A second SGLT-2i awaiting FDA approval is canagliflozin. Other SGLT-2i currently being investigated are tofogliflozin, luseogliflozin, empagliflozin, ipragliflozin and LX4211. The latter does not only inhibit SGLT-2, but also SGLT-1. The added benefit of inhibiting SGLT-1 is to reduce enteral glucose absorption. When glucose reaches the distal gut, it stimulates the release of GLP-1 and peptide YY, which in turn suppresses appetite, potentially leading to added benefits on weight control [107]. An overview of recent studies conducted on LX4211 did not show an increased rate of diarrhea (by osmosis or bacterial overgrowth) or urinary tract infections [108].

Insulin

Insulin was discovered in the summer of 1921 by Banting and Best [109]. Ever since the first impure extract of bovine insulin was injected into a human being in January 1922, insulin and devices for insulin injection have undergone fascinating developments. Today, many different human insulin formulations, insulin analogs and disposable pens with painless miniature needles are available that help patients to perform optimal self-management and, as much as possible, “mimic” normal insulin physiology (see Table 1,

Table 1 Currently available blood glucose lowering agents

Group	FDA Approved Drugs	Mechanism	% HbA_{1c} reduction	Cost	Advantages	Disadvantages
Biguanides	Metformin Metformin ER[A]	Activates AMP-kinase, ↓hepatic glucose production	1.0–2.0	$	Low cost, extensive experience, no hypoglycemia, improved lipid profile, ↓CVD risk	GI intolerance (diarrhea, abdominal cramping), lactic acidosis (rare)
Sulfonylureas	Glipizide[a] Glimepiride Tolbutamide	Closes K_{ATP} channels on β-cells, thereby ↑insulin secretion	1.0–1.5	$	Low cost, extensive experience, ↓microvascular risk	Hypoglycemia, weight gain, low durability
Meglitinides	Nateglinide Repaglinide	Closes K_{ATP} channels on β-cells, thereby ↑insulin secretion	0.5–1.0	$$$	Short duration of action, less postprandial glucose excursions, dosing flexibility	Hypoglycemia, weight gain, low durability, frequent dosing schedule
Thiazolidinediones	Pioglitazone Rosiglitazone[b]	Activation of PPAR-γ, ↑insulin sensitivity	0.5–1.4	$$$	No hypoglycemia, durability, improved lipid profile	Edema, heart failure, weight gain, bone fractures, bladder cancer, cardiovascular events
α-glucosidase inhibitors	Acarbose Miglitol	Inhibits intestinal α-glucosidase, thereby ↓carbohydrate digestion and uptake	0.5–0.9	$$	↓ postprandial hyperglycemia, hypoglycemia rare	Flatulence and diarrhea, frequent dosing schedule
DPP-4 inhibitors	Sitagliptin Saxagliptin Linagliptin	Inhibits activity of DPP-4, increasing GLP-1 levels, leading to ↑insulin secretion	0.5–0.8	$$$	No hypoglycemia, well tolerated	Urticaria/angio-edema, long term side effects unknown, pancreatitis (?)
GLP-1 receptor agonists	Exenatide BID Exenatide QW Liraglutide	Activates GLP-1 receptor, ↑insulin secretion, ↓glucagon secretion, ↓gastric emptying, ↑ satiety	0.5–1.5	$$$	Hypoglycemia rare, weight loss, possibly cardioprotective, ↑ β-cells mass/function (?)	GI side effects (nausea, vomiting, diarrhea), injectable, requires training, pancreatitis (?), unknown long-term safety, thyroid tumors in animals
Bile acid sequestrants	Colesevelam	Binds intestinal bile acids, increases hepatic production, mechanisms on glucose unclear, possible ↑ incretins	0.5	$$$	No hypoglycemia, ↓ LDL	GI side effects (constipation), hypertriglyceridemia, may reduce absorption of other medication
Dopamine-2 agonists	Bromocriptine[a]	Activation (central) dopaminergic receptors, modulating hypothalamic regulation of metabolism, ↑ Insulin sensitivity	0.5	$$$	No hypoglycemia, ↓ triglyceride- and FFA levels, ↓ CVD events	GI side effects (nausea), dizziness, fatigue, rhinitis
Amylin mimetics	Pramlintide[a]	Activation of amylin receptor, leading to ↓ glucagon secretion, ↓ gastric emptying, ↑ satiety	0.5–1.0	$$$	↓ Postprandial hyperglycemia, weight reduction	GI side effects (nausea, vomiting), hypoglycemia, injectable, frequent dosing schedule, unknown long-term safety
Insulins	Rapid acting (aspart, lispro, glulisine), short acting (Human regular), Intermediate acting (Human NPH), Long acting (glargine, detemir), Premixed	Activates insulin receptor, thereby ↑ glucose uptake and ↓ hepatic glucose production	1.0–2.5	$ to $$$	Effective in all patients, ↓ microvascular risk	Hypoglycemia, weight gain, injectable, requires training

BID twice daily, *CVD* cardiovascular disease, *ER* extended release, *FFA* free fatty acid, *GI* gastrointestinal *QW* once weekly

[a] Not approved in Europe

[b] Prescribing highly restricted in the US; withdrawn in Europe

'Insulins'). The numerous types of insulin allow many possible treatment regimens. Prandial insulins lower the postprandial glycemic excursion, while basal insulins suppress (nocturnal) hepatic glucose production and lower fasting plasma glucose.

In the 4 T study (Treating To Target in Type 2 diabetes), different insulin regimes were compared with respect to several surrogate endpoints but also with respect to their 3-year effects on cardiovascular events and mortality. Subjects were randomized to a biphasic (NovoMix 30 twice daily), prandial (NovoRapid three times daily) or basal (Levemir once or twice daily) scheme. The study design allowed the addition of a second type of insulin when hyperglycemia became unacceptable. After 3 years of treatment, a similar amount of patients in all groups required additional insulin therapy and no difference in HbA_{1c}-reduction existed between groups (1.3 %, 1.4 % and 1.2 %, respectively) [110]. Also, no differences were seen in mortality rate. However, the biphasic and prandial schemes were associated with more weight gain and episodes of hypoglycemia compared with the basal insulin scheme. Moreover, treatment satisfaction was highest with the basal insulin schemes [111]. These data support the recommendations of the recent ADA/EASD position statement [4•], to initiate insulin therapy using a basal insulin regimen.

Insulin Preparations

In spite of large advances ever since its discovery, none of the currently available insulins truly mimics normal insulin physiology. Endogenous insulin is secreted into the hepatic-portal system and consequently exposes the liver to concentrations of insulin which are ~2.5-fold greater than in non-hepatic tissues. In contrast, exogenous insulin administration results in high systemic plasma insulin levels with a low hepatic and high non-hepatic tissue exposure. Therefore, the current developments of oral insulin formulations, which lead to high portal levels [112], as well as liver-preferential injectable insulin formulations, which specifically target the liver [113], seem promising.

In contrast to endogenous insulin, exogenous human regular insulin is slow (time of onset at least 30 min) and long-acting (7–8 h). The prandial insulin analogs insulin lispro (reversed lysine and proline residues on the C-terminal end of the B-chain), insulin aspart (proline at B28 replaced by aspartic acid) and insulin glulisine (asparagine at B3 replaced by lysine and lysine at B29 replaced by glutamic acid) were modified such that they prevent the formation of insulin dimers and hexamers. These modifications allow rapid availability from subcutaneous depots after injection, leading to faster time of onset (±15 min) and shorter time of action (2–5 h) [114]. However, a recent Cochrane review did not show differences between regular human insulin and the various analogs in glycemic control or rate of hypoglycemia [115]. Still, a major benefit of the analogs over regular insulin is that patients can inject the insulin shortly prior, during or even after the meal, instead of 30 min in advance. Novel ultra-fast acting agents are under development, which have even faster and higher insulin (peak) concentrations and reduced late post-meal exposure, potentially flattening postprandial glucose excursions with fewer hypoglycemic events.

Basal insulins should mimic endogenous basal insulin secretion, i.e. having a reproducible, smooth and peakless pharmacokinetic profile with 24-h activity. Currently, worldwide, Neutral Protamine Hagedorn (NPH) insulin is the most widely used basal insulin, in spite of a considerable day-to-day variability, a clear peak-effect at 4–6 h after injection, associated with hypoglycemia risk and mere (dose-dependent) 14–16 h activity. In 2000, the long-acting basal insulin glargine (IG) was introduced, consisting of modifications of the insulin molecule including substitution of glycine for asparagine at A21 and addition of two arginines to the carboxy terminal of B chain, thus rendering the molecule more soluble at low pH. After injection into the neutral subcutaneous space, higher-order aggregates form, resulting in a slow, peakless dissolution and absorption. Since degradation already starts at the injection site, not only IG is absorbed, but also its metabolites M1 and M2, all of which lower blood glucose. IG achieves a peakless level for at least 24 h [114]. The second basal insulin analog insulin detemir (ID) was introduced in the US in 2005 (Europe: 2004). ID has a myristic acid bound to the lysine amino acid at position B29, resulting in fast absorption from the subcutaneous depot, but subsequent strong binding to plasma albumin, from which it slowly dissociates, resulting in a peakless level of approximately 14 h [114]. Despite the peakless profile and low day-to-day variability of both IG and ID versus NPH insulin [116], a recent Cochrane review showed comparable effects of IG, ID and NPH insulin on overall glycemic control [117]. The main advantage of IG and ID is the decrease in (nocturnal) hypoglycemic episodes, while ID use is additionally associated with less weight gain.

Several insulin formulations with ultra-long duration of action are under development. In insulin degludec (IDeg) the amino acid sequence is identical to human insulin except for removal of threonine at B30. At B29, a glutamic acid spacer is attached that bridges to a 16-carbon diacid. The side chain (linker) forms an accurate fit between IDeg hexamers to form multi-hexamers in the subcutaneous depot, which are key to the protraction mechanism [118]. Subsequently, the zinc present in the structure diffuses slowly causing individual hexamers to disassemble, releasing monomers that enter the circulation. These structural adaptations result in a smooth, peakless pharmacokinetic profile

at steady-state and a mean half-life of 25.4 h, in contrast to the 12.5 h of IG [119]. In addition, IDeg has a more stable and reproducible glucose lowering effect at steady-state [120]. IDeg was studied in a large number of trials, in both T1DM and T2DM populations [121, 122]. Indeed, in a recently published 52-week phase-III trial, IDeg was non-inferior to IG with respect to HbA_{1c}-lowering in a basal-bolus regimen with prandial insulin aspart in T2DM patients (1.1 % versus 1.2 %, respectively) [121]. IDeg treatment was associated with lower hypoglycemia rates, both overall and nocturnal. Due to its prolonged action, IDeg was initially proposed for administration three-times per week, but has been filed for approval to FDA and EMA for once-daily use. In the third week of October 2012 IDeg was approved by the EMA.

Safety Profile of Insulin

Although insulin therapy in insulin-deficient type 1 diabetes is clearly a life-saving treatment, the clinical utility and safety of strict glycemic control, particularly when using insulin, in T2DM remains unclear. In the UKPDS, in both the conventional and intensive treatment policy group, new-onset T2DM patients received ultralente or NPH insulin, however, in the latter, regular prandial insulin was added when the daily dose exceeded 14U or premeal or bed-time glucose levels rose above 7 mmol/L [25]. At 10-year follow-up, HbA_{1c} was 7.9 % in the conventional and 7 % in the intensive treatment group; however, this conferred merely benefit regarding microvascular, not macrovascular outcomes. At a median 8.5 years of post-trial follow-up, the between-group differences in HbA_{1c} had disappeared, but now in the intensive-therapy group, consisting of patients initially randomized to either sulfonylurea or insulin treatment, significant risk reductions were noted for any diabetes-related end point, microvascular disease, diabetes-related death, myocardial infarction and death from any cause [14]. Although the UKPDS aimed to compare treatment strategies (conventional versus intensive) rather than single agents, these results showed clear benefit of aggressive glucose control in the early stage of T2DM, irrespective of the drug used, but also, the UKPDS follow-up study showed no harm from insulin use [14].

Apart from the well-known side effects of insulin therapy, i.e. hypoglycemia and weight gain, there have been concerns about the mitogenic potency of high levels of circulating insulin, and particularly IG. The FDA recently issued a communication to inform the public about four published observational studies, three of which suggested an increased risk of cancer associated with the use of IG [123], but due to methodological limitations, the data was considered inconclusive. Additional review of a 5-year randomized clinical trial in which the effects of IG versus NPH insulin on retinopathy progression were compared in T2DM patients [124] showed no difference in cancer incidence. However, this trial was not designed or powered to evaluate cancer outcomes. Subsequently, the Outcome Reduction with Initial Glargine Intervention (ORIGIN) clinical trial was amended to adjudicate all cases of cancer occurring during the trial. The ORIGIN trial, following 12,537 patients for a median 6.2 years, was designed to answer the question as to whether early IG treatment in T2DM would reduce cardiovascular events. IG had a neutral effect on cardiovascular outcomes and no increase in cancer incidence was noted [125]. The post-trial follow-up of participants is still ongoing.

Conclusion

Treatment of T2DM, a disease that has reached epidemic proportions worldwide, may still be considered a challenge despite the availability of an increasing amount of therapeutic tools. Although metformin, sulfonylurea and insulin proved effective in improving outcome in the UKPDS, the heterogeneity and progressive nature of T2DM and the fact that its underlying pathophysiologic mechanisms are only partly unveiled, necessitate the ongoing quest for novel targets and treatment modalities. The recently introduced incretin-based therapies, including GLP-1RA, both short- and longer-acting formulations, and DPP-4i, effectively lower blood glucose, without weight gain and risk of hypoglycemia. For the choice of a second drug after metformin, incretin-based agents now were given a position equivalent to the established drug-classes in the recent ADA/EASD T2DM position statement. For the SGLT-2i, which, by promoting glucosuria, lowers blood glucose and body weight, FDA approval is currently pending. The new ultra-long acting IDeg, which is associated with lower risk of nocturnal hypoglycemia, also awaits FDA approval, but was recently approved by the EMA. Promising agents targeting novel molecular mechanisms are under development. Together, the available and emerging drug classes should provide physicians with a broad range of pharmacologic options to successfully individualize patient treatment, as recommended by the 2012 ADA/EASD position statement. However, long-term pragmatic trials comparing novel to established agents, as well as different drug-combinations and treatment strategies in T2DM patients with and without comorbidities are needed to underpin the recommended patient-centered personalized treatment and to prove the added value of all emerging pharmacologic innovations.

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- • Of importance
- •• Of major importance

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