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Pharmacological management of type 2 diabetes : what's new in 2017 ?

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Abstract

Introduction

Novelties in the management of type 2 diabetes are dominated by the commercialisation of new glucose-lowering agents, which offer alternatives to older antidiabetic medications, and by the publication of several prospective placebo-controlled outcome trials, which demonstrated not only cardiovascular safety but also cardiovascular and renal protection with some new medications.

Areas covered

Updates regarding the use of glucose-lowering agents are discussed from a clinical point of view. Some new viewpoints concern older antidiabetic agents such as metformin, sulfonylureas and glitazones whose benefit-risk balance has been revisited, especially in high risk patients. The recent data regarding DPP-4 inhibitors (gliptins) focused on the safety profile of this pharmacological class, including in patients with impaired renal function. The highlight concerns the cardiovascular (and renal) protection by some GLP-1 receptor agonists (liraglutide, semaglutide) and SGLT2 inhibitors (empagliflozin, canagliflozin) in patients with high cardiovascular risk. Finally, efficacy and safety of new combinations and advances in insulin therapy will be briefly discussed.

Expert Opinion/commentary

The recent data from randomized controlled trials, meta-analyses and observational real-life studies should trigger a revision of the algorithm for the treatment of hyperglycemia in type 2 diabetes, especially in patients with high cardiovascular and/or renal risk.

Keywords : Cardiovascular – DPP-4 inhibitor – SGLT2 inhibitor – GLP-1 receptor agonist – Kidney – Metformin – New insulin

1. Introduction

Since the publication in 2015 of the last version of the position statement on the management of hyperglycemia of type 2 diabetes (T2D), jointly by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), [1] an update has been recently published by the ADA in "the Standards of medical care in diabetes - 2017". [2] The latter is almost a copy-paste of the 2015 version, [1] except the addition of a specific comment that recommends agents that have proven a cardiovascular (CV) protection in T2D patients at high CV risk. [2] Simultaneously, the American Association of Clinical Endocrinologists (ACCE) and American College of Endocrinology (ACE) also published a 2017 updated consensus statement on the comprehensive T2D management algorithm, which proposed a more detailed hierarchy in the choice of second-line and third-line therapies after failure of metformin initial monotherapy. [3]

CV disease represents a high burden in patients with T2D, even if a progressive and sustained decline in major cardiovascular events (MACE) has been reported during the last two decades, both in the US [4] and in Sweden. [5] Nevertheless, fatal outcomes declined less among patients with T2D than among controls [5] and the excess risk in patients with T2D remains high compared to nondiabetic subjects. [4] In this context, confirming the CV safety and potentially demonstrating the CV efficacy of glucose-lowering agents are of major interest [6] so that further treatment differentiation among available antihyperglycemic drugs may be made on the basis of this evidence. [7]

Because an increasing number of patients with T2D become older, a large proportion of them are progressing to moderate-severe chronic kidney disease (CKD). Thus, the safe use of glucose-lowering agents in this population deserves specific studies as well as the demonstration of a potential to prevent or retard the progression to end-stage renal disease (ESRD), even beyond improved glucose control. [8]

Despite the emergence of a large variety of new antidiabetic agents, the management of T2D remains challenging [2, 3] and so-called "treatment resistant T2D" leading to poor glucose control is a common phenomenon in clinical practice for many reasons. [9] The use of glucose-lowering medications should be optimized according to a patient-centred approach, and the emergence of precision medicine may help to have a better strategy for the management of T2D in the future, although the road might be long and difficult. [10]

The aim of the present narrative review is to discuss the most important recent findings concerning the different glucose-lowering agents currently used for the management of T2D. Glinides and alpha-glucosidase inhibitors will not be considered in this article, because they are no novelties recently published with these two classes of oral antidiabetic medications; the results of the Acarbose Cardiovascular Evaluation (ACE) trial investigating the effects of the alpha-glucosidase inhibitor acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance should be available soon. Furthermore, glinides and alpha-glucosidase inhibitors are not mentioned in the position statement jointly published by the American and European Diabetes Societies (1). Other aspects of diabetes management, such as lifestyle measures, progresses in glucose monitoring, advances in detection and treatment of diabetic complications, will not be considered in this article.

2. Novelties regarding metformin

2.1 Use in at risk patients

Metformin is considered a first-line glucose-lowering agent in most international guidelines [1-3] although its use was limited for many decades because of numerous contraindications that could potentially lead to an increased risk of lactic acidosis (though the risk is much lower with metformin than with phenformin that was withdrawn from the market because of this severe potentially fatal complication). Of major interest, recent observational data have suggested that T2D patients considered at risk because of the presence of traditional contraindications may still derive benefit from metformin therapy with reductions in morbidity and mortality compared with other glucose-lowering agents, especially sulfonylureas (though a properly-designed head to head CV outcome trial is lacking), and without increased risk of lactic acidosis. [11, 12]. This concerns patients with CV disease, including stable heart failure (HF), [11, 12], but also T2D patients with mild to moderate CKD. [13] These observations led the US Food and Drug Administration (FDA ; April 8, 2016) and the European Medications Agency (EMA ; October 13, 2016) to allow the prescription of metformin in patients with an estimated glomerular filtration rate (eGFR) between 30 and 59 ml/min/1.73 m², provided that some rules of good practice are respected. In particular, the daily dosage of metformin should be reduced by half, the renal function should be regularly monitored and metformin should be stopped when eGFR drops below 30 ml/min/1.73 m². [2]

These recent changes will increase the use of metformin in T2D patients with historical contraindications or precautions, especially in the elderly. [12]

2.2 Mode of action revisited

Gastrointestinal intolerance of metformin is commonly observed in clinical practice. [14] This adverse effect may suggest a possible mechanism of action of the drug in the gastrointestinal tract. [15] Classically, the main mode of action of metformin has been considered to be located in the liver, via an inhibition of gluconeogenesis, an effect that contributes to reduce hepatic glucose production. [16] However, an increasing number of studies have emphasized the role of the intestine in the mechanism of action of the biguanide. [15, 16] Metformin increases intestinal glucose uptake and lactate production, increases glucagon-like peptide-1 (GLP-1) concentrations and the bile acid pool within the intestine, and alters the microbiome. [15, 16] An elegant recent study showed that the changes in the gut microbiome induced by metformin in individuals with treatment-naive T2D contributes to the therapeutic effects of the drug. [17] A novel delayed-release preparation of metformin has been shown to improve glycemic control to a similar extent to immediate-release metformin, but with less systemic exposure. [18, 19]. However, whether delayed release metformin will provide better management of T2D remains an open question. [20]

3. Concern about the cardiovascular safety of sulfonylureas

Despite a widespread use of sulfonylureas for the management of T2D worldwide, their CV safety is still contentious. [21] Direct comparative randomized clinical trials (RCTs) with other antidiabetic agents are scarce and do not provide conclusive results. [21] In a recent methodological meta-regression analysis of available observational studies, sulfonylureas were associated with an increased risk of CV events and mortality in the majority of studies with no major design-related biases (relative risks 1.16-1.55). [22] A potential role of hypoglycemia is increasingly recognized. Indeed, hypoglycemia, often asymptomatic, is a frequent finding in well-controlled sulfonylurea-treated T2D, and hypoglycemia can be associated with increased QT dynamicity and QTc prolongation in some individuals and thus have detrimental CV sequelae. [23]

4. Renewed interest for glitazones

After the failure to demonstrate a significant reduction in the primary composite CV outcome in the PROactive trial with pioglitazone [24] and the results from a meta-analysis of phase 2-3 RCTs with rosiglitazone, [25] the use of thiazolidinediones in the management of T2D has dramatically decreased. In some countries, pioglitazone has been withdrawn from the market because of a concern about bladder cancer, although the available recent evidence

from RCTs and epidemiological studies is low and controversial. [26] Nevertheless, this pharmacological class has still a place in the various algorithms proposed for the management of hyperglycemia in T2D. [1-3] With the benefit of hindsight, the results of the PROactive trial [primary composite endpoint (hazard ratio or HR, 0.90, 95% confidence interval – CI - 0.80-1.02, p=0.095; main secondary endpoint - composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke - (HR 0.84, 0.72-0.98, p=0.027)] should be viewed more positively, [27] especially when compared with the more recent RCTs having reported similar CV outcomes with dipeptidyl peptidase-4 (DPP-4) inhibitors versus placebo (non-inferiority without superiority : see below section 5). Furthermore, the recent IRIS trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or transient ischemic attack, the risk of stroke or myocardial infarction was significantly lower among patients who received pioglitazone than among those who received placebo (HR, 0.48; 95% CI 0.33-0.69; P<0.001). [28] In a secondary analysis of the IRIS trial, pioglitazone has been shown to reduce the risk for acute coronary syndromes after a recent cerebrovascular event (HR, 0.71; 95% CI, 0.54-0.94; P=0.02). [29] These favourable data were confirmed in two meta-analyses. [30-31]. However, thiazolidinediones are associated with bone fractures, weight gain and fluid retention. It has been proposed that pioglitazone might be an ideal agent to combine with a sodium glucose cotransporter type 2 inhibitor (SGLT2i) to further reduce CV events in high risk diabetic individuals. Indeed, SGLT2i promote salt/water loss (see below section 7) so that one may hypothesize that they could minimize the risk of fluid retention associated with pioglitazone therapy, though this remains to be better evidenced. [32, 33]. Because pioglitazone, SGLT2is (see below section 7) and GLP-1 receptor agonists (GLP-1RAs) (see below section 6) appear to reduce CV risk by different mechanisms, it has been recently suggested that, if used in combination, the effects of these antidiabetes agents may be additive with regard to CV benefit. [34]

5. Cardiovascular safety of DPP-4 inhibitors

DPP-4is occupy an increasing place in the management of T2D, progressively replacing sulfonylureas in numerous countries. The reasons for this trend are that DPP-4is are not associated with hypoglycemia or weight gain, have a good safety profile and are very easy to use. [35, 36] They can be prescribed in patients with moderate to severe CKD, provided that the daily dose is adjusted to the eGFR (except linagliptin that has a predominant biliary excretion). [37] The results of three CV outcome trials have been published during recent years : SAVOR-TIMI 53 with saxagliptin, [38] EXAMINE with alogliptin [39] and TECOS

with sitagliptin [40] (Table 1). All three studies showed non-inferiority of the DPP-4i versus placebo regarding the primary composite endpoint (triple MACE : CV mortality, nonfatal myocardial infarction and nonfatal stroke). These results proved the CV safety of DPP-4is in a population at high CV risk (secondary prevention). [35, 36] However, these results may appear somewhat disappointing in regard of the CV protection reported afterwards with GLP-1RAs and SGLT2is (see below sections 6 and 7). One intriguing result was the significant increase in the rate of hospitalisation for HF in SAVOR-TIMI 53 with saxagliptin, [41] an effect not retrieved at all with sitagliptin in TECOS [40] (only a non-significant trend was reported in EXAMINE with alogliptin) [39] (Table 1). In 2017, four years after the original publication, [38] no explanation could be proposed for this finding, which might be due to bad chance.

The effects of DPP-4is on renal outcomes were not well studied. A recent extensive review of the literature showed discrepancies between animal and human studies. [42] Indeed, despite promising results in preclinical experiments, the data obtained in clinical trials only showed a reduction in albuminuria, with no significant effect on renal function. [42] This was particularly the case in further analyses of SAVOR-TIMI 53 with saxagliptin [43] and TECOS with sitagliptin. [44]

A concern about a possible higher risk of acute pancreatitis associated with the use of DPP-4is was raised soon after the commercialisation of this pharmacological class. [45] In 2017, all available data, especially those from the three large prospective placebo-controlled CV outcome trials, confirms a slight increase of the incidence of acute pancreatitis with DPP-4is, but the overall risk remains low (5.5 extra cases/10,000 patients/year and a number needed to harm of 1940/year). [46] No increased risk of pancreatic cancer was noticed in any CV outcome trial. [38-40] However, these trials were not necessarily long enough and not specifically designed or powered to confirm or refute such a risk.

6. Cardiovascular and renal protection with GLP-1 receptor agonists

All GLP-1RAs share the same mechanism of action by mimicking the effects of the natural intestinal incretin hormone GLP-1. However, they belong to an heterogeneous pharmacological class with important differences regarding the nature of the compound [exendin-4 derivatives (exenatide, lixisenatide) versus human GLP-1 analogs (liraglutide, albiglutide, dulaglutide, semaglutide)], the duration of the glucose-lowering efficacy [short-

acting (exenatide, lixisenatide) versus long-acting (exenatide LAR, liraglutide, albiglutide, dulaglutide)] and the injection regimen [daily injections (exenatide, lixisenatide, liraglutide) versus weekly injections (exenatide LAR, albiglutide, dulaglutide, semaglutide)]. [47] A new form of continuous subcutaneous administration of exenatide is currently in development (ITCA 650). [48] Although concern about a possible risk of acute pancreatitis and pancreatic cancer was raised a few years ago, more recent data are reassuring and only a higher risk of cholelithiasis has been evidence in RCTs. [49]

A recent comprehensive meta-analysis of 117 RCTs with any type of GLP-1RA showed that the agents of this class appear to reduce all-cause mortality, CV mortality, and the incidence of myocardial infarction, without effect on stroke or HF. [50] Although phase2/3 RCTs showed generally favourable results for all GLP-1RAs, heterogeneity was observed when comparing the large prospective CV outcome studies, even if overall results with GLP-1RAs were better than those reported with DPP-4is. [51]

The first CV outcome trial published with GLP-1RAs confirmed the safety of lixisenatide in T2D patients after an acute coronary syndrome. [52] However, if the non-inferiority versus placebo was proven, no superiority could be evidenced (Table 2). Apparently, similar results were observed in two other CV outcome trials, EXSCEL with exenatide LAR and FREEDOM-CVO with exenatide continuous subcutaneous infusion (ITCA 650). However, this information was only given in two press releases and the publication of the final results is still pending.

In contrast, in the landmark LEADER trial, significant reductions in the primary outcome (triple MACE), CV mortality and all-cause mortality were observed in patients receiving liraglutide (titrated up to 1.8 mg once daily) compared with those receiving a placebo after a median follow-up of 3.8 years (Table 2). [53] The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for HF were numerically but non significantly lower in the liraglutide group than in the placebo group. A significant reduction in the composite renal outcome was also noticed in the liraglutide group versus the placebo group (Table 2). [53] These favourable results were partially confirmed in a smaller and shorter CV outcome trial with the once-weekly GLP-1RA semaglutide in SUSTAIN-6 [54] (Table 2). Again a significant reduction in the primary outcome (triple MACE) was noticed. However, some differences were apparent when compared to LEADER. Indeed, no reduction in CV mortality and all-cause mortality was observed in SUSTAIN-6, but a significant reduction in the incidence of stroke was reported in the semaglutide group compared to the placebo group

(Table 2). The underlying protective mechanisms of GLP-1RAs remain largely unknown, even if pleiotropic anti-atherogenic/anti-inflammatory effects are generally proposed. [55]

All these trials were performed in T2D patients at high CV risk, mainly in secondary prevention. The reasons for the between-trial differences remain unknown and it is not possible to decide whether they could be attributed to differences in pharmacological activities of the various compounds or to differences in studied populations or slight variations in the protocol design. It should be noted, however, that all three trials using exendin-4 derivatives (ELIXA, EXSCEL, FREEDOM-CVO) reported non-inferiority but no superiority versus placebo whereas both trials using human GLP-1 analogs (LEADER, SUSTAIN-6) reported superiority as far as the primary CV composite outcome is concerned. The ongoing CV outcome trials with albiglutide (HARMONY OUTCOME) and dulaglutide (REWIND), two other GLP-1 analogs, will provide further information in this respect. [56] Currently, only reassuring results regarding CV safety were reported from meta-analyses of phase 2-3 RCTs. [57]

No increased risk of hospitalization for HF has been reported with GLP-1RAs in meta-analyses of phase 2-3 trials and in the three large prospective CV outcome trials whose results have been already published. [58] However, in all these studies, almost no or only a minority of T2D patients had diagnosed HF at inclusion. Two recent studies investigated the effect of liraglutide in patients with HF. In the FIGHT study among patients recently hospitalized with HF and reduced left ventricular ejection fraction, the use of liraglutide was associated with a trend for more rehospitalizations for HF (HR, 1.30, 95% CI, 0.89-1.88; P = 0.17). [59] In the LIVE study carried out in patients with clinically stable and on optimal HF treatment, liraglutide treatment did not affect left ventricular systolic function compared with placebo, but was associated with an increase in heart rate and more serious cardiac adverse events. [60] These two studies raise some concern with respect to the use of liraglutide in patients with chronic HF and reduced left ventricular function. Thus, more data on the safety of liraglutide and other GLP-1RAs in different subgroups of HF patients are needed.

7. Cardiovascular and renal protection with SGLT2 inhibitors

7.1 Multiple effects of SGLT2is

SGLT2is exert a glucose-lowering effect via a renal action by enhancing glucosuria, independently of insulin. As a consequence, they do not induce hypoglycemia and can be

used in all stages of the natural history of T2D, except in presence of moderate (stage 3b) to severe (stages 4-5) CKD. [61] Overall, this new pharmacological class is characterized by a good efficacy/risk balance. [62] Beyond improved glucose control, they exert multiple effects among which a weight reduction (calorie loss due to glucosuria), a drop in arterial blood pressure (mainly due to natriuresis and a diuretic effect) and a reduction in serum uric acid levels (enhanced urinary excretion). [63]

7.2 EMPA-REG OUTCOME trial

The most impressive results were reported in the EMPA-REG OUTCOME trial. [64] Empagliflozin (10 or 25 mg once daily) was associated with a clinically relevant and statistically significant reduction not only in the primary CV composite outcome (triple MACE), but also in CV mortality and all-cause mortality in T2D patients with established CV disease (secondary prevention) [64] (Table 3). Furthermore, a significant reduction in hospitalisation for HF [65] and in a composite renal outcome [66] was noticed in patients treated with empagliflozin compared with those receiving placebo (Table 3). Although the mechanisms explaining the effects on HF and renal outcomes are somewhat better understood, [67] those responsible for the marked reduction in mortality remain highly debated. [68, 69]. It is unlikely, however, that they could be explained either by the modest reduction in glycated haemoglobin (HbA1c, though equipoise glucose control in both arms was not achieved), or by the slight reduction in arterial blood pressure in already well-controlled T2D patients, [70] or by a common diuretic effect. [71] Even a combination of all these mechanisms appears insufficient to explain the drastic reduction in mortality so that other hemodynamic [67] or metabolic [72] mechanistic alternatives have been proposed, which are not mutually exclusive but still remain to be confirmed.

An intriguing finding of EMPA-REG OUTCOME was the trend for an increased risk of stroke in the empagliflozin group compared with the placebo group, despite the reduction in various risk factors. [64] This was a surprising observation for a drug that reduces arterial blood pressure as hypertension is a well-known risk factor for stroke. [70] However, these data regarding stroke events in EMPA-REG-OUTCOME were specifically reanalysed recently, with quite reassuring results reported in various sensitivity analyses. [73] Furthermore, according to this specific analysis, patients with the largest increases in hematocrit or largest decreases in systolic blood pressure did not have an increased risk of stroke. [73]

7.3 CANVAS program

The results of the recently published CANVAS program partially confirmed those previously reported in EMPA-REG OUTCOME. [74] The SGLT2i canagliflozin (100-300 mg) reduced the primary CV composite outcome (triple MACE), the rate of hospitalisation for HF and the composite renal outcome in a similar extend as that reported with empagliflozin in comparison with placebo (Table 3). Nevertheless, important differences may be detected when comparing the two trials. Indeed, in contrast to the marked reduction in CV and all-cause mortality reported in EMPA-REG OUTCOME, [64] no such significant reduction was noticed in CANVAS. [74] This difference may be at least partially explained by the characteristics of the T2D patients : in CANVAS, almost 35 % of the population were in primary prevention whereas in EMPA-REG OUTCOME, nearly all patients were in secondary prevention. A subgroup analysis of the CANVAS results showed that the primary composite CV outcome was significantly reduced in patients with antecedents of CV disease (although to a smaller extent than the reduction reported in EMPA-REG OUTCOME trial), while it was not the case in absence of such CV complications at inclusion. Nevertheless, the interaction test did not reach statistical significance (P=0.18), so that no firm conclusion could be drawn.

Another interesting result of CANVAS was the trend to a reduction in stroke in T2D patients treated with canagliflozin, [74] which contrasts with the trend to a moderate increase with empagliflozin in EMPA-REG OUTCOME. [64, 73]. As discussed in the publication of CANVAS, [74] apparent differences for secondary and exploratory outcomes between trials may be attributable to chance, since precision in the effect estimates of each is limited. The issue of stroke with SGLT2is likely won't be settled before the results of the next SGLT2i CV outcome trial, DECLARE (with dapagliflozin), are available.

7.4 Perspectives in cardiorenal protection

In 2016, ESC (European Society of Cardiology) Guidelines for the diagnosis and treatment of acute and chronic HF recommended that empagliflozin should be considered in patients with T2D to prevent or delay the onset of HF and prolong life (Class IIa, level B). [75] Considering the recent data of CANVAS, [74] with a similar reduction in hospitalisation for HF as in EMPA-REG-OUTCOME [64] (Table 3), it may be reasonable to extend this recommendation to canagliflozin too.

The FDA recently added a new indication for empagliflozin, to reduce the risk of CV death in adults with T2D and CV disease. [2] Whether other SGLT2is will have the same effect in high-risk patients and whether empagliflozin or other SGLT2is will have a similar effect in T2D patients at lower risk remain unknown. [2] However, recent results of the CANVAS program [74], of the CV-REAL study [76] and of a meta-analysis of RCTs with dapagliflozin [77] tended to support this hypothesis.

In a large multinational study (CVD-REAL), treatment with SGLT2is (most T2D patients treated with canagliflozin in the US, but with dapagliflozin in European countries) versus other glucose-lowering agents was associated with a lower risk of hospitalization for HF and death, suggesting that the benefits seen with empagliflozin and canagliflozin in RCTs may be a class effect applicable to a broad population of T2D patients in real-world practice. [76] A pre-specified meta-analysis of CV events from 21 phase 2b/3 RCTs with dapagliflozin suggested the potential for a beneficial CV effect in any of the populations investigated, which is consistent with the multifactorial benefits on CV risk factors seen with SGLT2is. [77] The results of the ongoing DECLARE trial with dapagliflozin, which has recruited a large proportion of T2D patients in primary CV prevention will answer the question whether the cardiorenal protection by SGLT2is could be extended to all patients at risk of CV disease (both in primary and secondary prevention). [78]

6.5 Adverse effects of SGLT2 inhibitors

The most common adverse events reported with SGLT2is are explained by the specific renal mechanism of action of this pharmacological class. [62, 79] Mycotic genital infections occurred 4-6 times more frequently with SGLT2is than with placebo or other antidiabetic agents, more frequently in women than in men and generally not severe. Urinary tract infections are rare and not significantly increased when compared with comparators in most studies. Nevertheless, rare cases of urosepsis have been reported. Side effects related to dehydration are more frequent with SGLT2is (mostly hypotension), but rather rare in published RCTs. Nevertheless, caution is required in the elderly more frailty population, especially in patients receiving loop-diuretics. [62, 79]

In 2015, regulatory agencies warned that SGLT2is may favour diabetic ketoacidosis (DKA), in absence of severe hyperglycemia. Reduction in insulin dose, stimulation of the release of glucagon and enhanced ketone re-absorption in the renal tubuli could contribute to the increase in the concentration of ketone bodies, whereas enhanced glucosuria limits the

amplitude of hyperglycemia. [80, 81] In a meta-analysis of RCTs, no signal of increased risk for DKA was observed for SGLT2is as a class (MH-OR, 1.14, 95% IC 0.45-2.88, p=0.78) or as individual molecule. These results showed that, when the drug is properly prescribed, the risk of DKA is negligible. [82] However, a large claims database of commercially insured patients in the United States showed that shortly after initiation, SGLT2is were associated with approximately twice the risk of DKA compared to that reported with DPP-4is, although cases leading to hospitalization were infrequent. [83] A recent paper provides a detailed analysis of DKA reports in which an SGLT2i was listed among suspect or concomitant drugs in the US FDA Adverse Event Reporting System. [84] The proportional reporting ratio of DKA in reports including versus those not including an SGLT2i was 7.9 (95% CI 7.5-8.4) and was higher for type 1 diabetes than for T2D. Based on the profile of these reports, SGLT2i-associated DKA may not be limited to any particular demographic or comorbid subpopulation and can occur at any duration of SGLT2i use. [84] Thus, the increased risk of DKA with SGLT2is should be considered at the time of prescribing and throughout therapy if patients present with symptoms suggestive of DKA, essentially nausea and vomiting.

During the last year, other additional warnings were made by the FDA concerning a potential risk of fractures and lower limb amputations with canagliflozin. Indeed, a higher risk of such complications has been reported with the use of canagliflozin in the CANVAS program. [74] However, the underlying mechanisms remain quite obscure and whether these adverse effects are specific to canagliflozin or might be a class effect remains an open question.

8. New combinations

T2D is a complex disease with several pathophysiologic defects targeting different organs. [85] Consequently, it is elusive that one single glucose-lowering agent would be able to tackle all these defects, an observation that paves the road for combination therapies. Each new glucose-lowering class has its own safety profile, but combining different compounds does not increase the risk of adverse events, including hypoglycaemia, at least based on currently available data (Table 4).

Classically, a stepwise approach is recommended starting with metformin and moving progressively towards a dual therapy first, followed by a triple therapy. [1-3] However, this stepwise approach driven by failure of therapy and exposing to clinical inertia commonly observed in T2D management in real life has been recently challenged. [86] For instance, an

exploratory study showed that combination therapy with metformin/pioglitazone/exenatide in patients with newly diagnosed T2D is more effective and results in fewer hypoglycemic events than sequential add-on therapy with metformin, sulfonylurea and then basal insulin. [86] It is conceivable that combined therapies will be proposed at an earlier stage for the treatment of T2D in the near future, especially because an increasing number of options is available, with a low risk of hypoglycemia and weight gain. [3, 87]. Furthermore, as already discussed, an additional benefit in preventing the risk of CV or renal complications may be expected from some drug combinations. [33, 34]. However, among incretin-based glucose-lowering therapies, a recent trial showed that sitagliptin, in patients already treated with a GLP-1RA (liraglutide), increased intact GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) concentrations, but with marginal, non-significant effects on glycaemic control, thus suggesting that such a combination is useless. [88]

8.1 DPP-4 inhibitor plus SGLT2 inhibitor

There is a strong rationale for combining a DPP-4i and a SGLT2i in patients with T2D because the two drugs exert different and complementary glucose-lowering effects. [89, 90] Dual therapy (initial combination or stepwise approach) is more effective than either monotherapy in patients treated with diet and exercise or already treated with metformin. Combining the two pharmacological options is safe and does not induce hypoglycemia. Two fixed-dose combinations (FDCs) are already available (saxagliptin-dapagliflozin and linagliptin-empagliflozin) and others are in current development. [89, 90]

8.2 GLP-1 receptor agonist plus SGLT2 inhibitor

SGLT2i and GLP-1RAs effectively reduce HbA1c, body weight and arterial blood pressure, but via very different mechanisms, making them an effective duet for combination therapy. [91] This concept has been proven in the DUAL-8 study where co-initiation of exenatide and dapagliflozin improved various glycemic measures and CV risk factors in patients with T2D inadequately controlled by metformin monotherapy. [92] Furthermore, both antidiabetic classes have been shown to reduce CV events, most probably by different mechanisms as previously mentioned, thus raising the possibility that combined therapy with these two classes may produce additive CV benefits. [34] Similarly, both SGLT2is and GLP-1RAs reduce albuminuria, decrease the time for doubling of serum creatinine, and slow the time to end-stage renal disease, which may also suggest a possible additive effect on renal

outcome. [91] Further combination studies should confirm these hypotheses of enhanced cardiorenal protection.

8.3. GLP-1 receptor agonist plus basal insulin

GLP-1RAs represent a good alternative to basal insulin after failure of oral therapy. However, GLP-1RAs may also be combined with insulin therapy, prandial insulin [93] but more frequently basal insulin. [94, 95] Two fixed-dose combinations of a GLP-1RA and basal insulin are currently available, lixisenatide plus glargine and liraglutide plus degludec. [96] A recent systematic review and meta-analysis of RCTs showed that the switch from basal insulin to fixed ratio combinations with a GLP-1RA is associated with a reduction in HbA1c (-0.72%; 95% CI -1.03 to -0.41) and body weight (-2.35 kg; 95% CI -3.52 to -1.19), reducing also the risk for hypoglycemia [odds ratio 0.70; 95% CI 0.57 to 0.86), but increasing the incidence of nausea. [95]

9. Improved formulations of insulin

The two major aims of insulin therapy are to control blood glucose both in the fasting (postabsorptive, essentially during the nocturnal period) and in the postprandial states (after each meal, usually three times a day), without exposing the patient to a too high risk of hypoglycemia.

9.1 Basal insulin

Manufacturers of insulin products have long sought ways to modify the absorption rate of exogenously administered insulin in order to mimic basal insulin secretion. [97] Newer basal insulin analogs have used multihexamer formation in addition to albumin binding (insulin degludec) or up-concentration in addition to precipitation (insulin glargine U300). These new formulations share a longer duration of action (> 24 hours) and a lower day-to-day variability of the glucose-lowering profile. [97] The most clinically relevant advantage of these recent analogues is a reduction in hypoglycemia, especially at night) with similar HbA1c control when compared with earlier long-acting insulin products, especially NPH insulin. [97] A recent head-to-head comparative trial (DEVOTE) reported a significantly lower risk of severe hypoglycemia with insulin degludec than with insulin glargine in T2D patients (rate ratio, 0.60; $P<0.001$). In this trial, degludec was noninferior to glargine with respect to the incidence of MACE. [98] As already mentioned, basal insulin formulations may

also be optimised by using a fixed-dose combination with a GLP-1RA, [96] which could also reduce the risk of hypoglycemia [95] and the rate of MACE in high CV risk patients. [53, 54]

9.2 Fast-acting insulin

Another challenge in the management of diabetes with subcutaneous insulin injections is to control early postprandial hyperglycemia without inducing late hypoglycemia. Short-acting insulin analogues offer advantages in this matter compared to regular human insulin, but do not completely solve the problem. Fast-acting insulin aspart ("faster aspart") is the insulin analog aspart in a new formulation in which two additional excipients have been added, L-arginine (a stabilizing agent) and niacinamide (responsible for accelerated initial insulin absorption after subcutaneous injection). Faster-acting insulin aspart has proven its potential to better mimic the physiologic meal-induced insulin secretion and thereby to improve postprandial glucose control compared with classical insulin aspart. This advantage is important for the management of type 1 diabetes but may also be of potential interest in T2D. [99]

10. Anti-obesity agents and bariatric/metabolic surgery

Most patients with T2D are overweight or obese and attempts to control hyperglycemia with several antidiabetic agents may promote weight excess. [100] The pharmacotherapy of obesity gave rather disappointing results until now, even if some new opportunities are emerging. [101] Several anti-obesity agents were recently commercialized in the US (lorcaserin, phentermine plus topiramate, naltrexone plus bupropion), but few are available in Europe, among which liraglutide at the dosage of 3.0 mg once daily. Here also, there is a potential for combination therapies, for instance GLP-1RA plus SGLT2i, in obese patients with T2D. [101]

Given its role in metabolic regulation, the gastrointestinal tract constitutes a meaningful target to manage T2D. [102] Although additional studies are needed to further demonstrate long-term benefits, there is sufficient clinical and mechanistic evidence to support inclusion of metabolic surgery among antidiabetes interventions for people with T2D and obesity, including patients with body mass index 30.0-34.9 kg/m² if hyperglycemia is inadequately controlled despite optimal treatment with either oral or injectable medications. [103]

11. Conclusion

The field of T2D is becoming very exciting during recent years with the commercialization of new glucose-lowering agents, the validation of several efficacious and safe combined therapies, the proposal of different treatment algorithms and, last but not least, the publication of prospective placebo-controlled trials that demonstrated the possibility to prevent CV and renal outcomes in T2D patients at high risk of CV disease. Nevertheless, challenges still remain in 2017 and many questions should be solved during the coming years, especially to optimize a personalized approach in patients with T2D (head-to-head comparison studies would be helpful in the respect) and further reduce the risk of diabetic complications.

Expert commentary

The commercialization of new glucose-lowering agents markedly increases the number of choices as monotherapy if lifestyle does not succeed to maintain adequate glucose control. Nevertheless, metformin still keeps its first place and its use will continue to increase because some contraindications have been abandoned during the last year. In contrast, the use of sulfonylureas is progressively decreasing in many countries as they are replaced by new oral drugs that offer the advantages of no hypoglycemia and no weight gain.

The availability of new glucose-lowering agents offers to the clinician a series of innovative combined therapies, which appear to be both efficacious and safe. However, an earlier place of combined therapy in the management of T2D is still debated, especially because it remains to demonstrate which combination has the best capacity to limit the progression of the disease by protecting the beta-cell, or to prevent diabetic complications.

Several new compounds from the pharmacological classes of GLP-1RAs and SGLT2is have proven their potential to reduce CV and renal outcomes, which is a major breakthrough in the management of T2D. However, which patient will better respond to one or another agent remains largely unknown. Furthermore, because the underlying mechanisms of action responsible for the protection most probably differ between the various glucose-lowering agents, there is hope that combining different medications will enhance the cardiorenal protection in high risk T2D patients. However, this remains to be proven.

Some adverse events have been reported for several new glucose-lowering agents even if overall the benefit/risk balance remains excellent. The risk of acute pancreatitis and pancreatic cancer with incretin-based therapies, which was considered as alarming a few years

ago by some people, appears to be a rare event in RCTs, though long-term post-marketing surveillance in real life conditions is still recommended. Beyond their expected side effects related to the increased glucosuria (genital mycotic infections, urinary tract infections, adverse events related to dehydration), unexpected adverse events have been reported with SGLT2is, essentially euglycemic ketoacidosis. This specific adverse effect is more frequently observed in type 1 diabetes than in T2D, although caution is also required in certain circumstances in T2D patients. This is particularly the case after surgery, a condition that may contribute to limit carbohydrate intake, reduce insulin supply and increase glucagon and other stress hormones, all factors that favor the production of ketone bodies). Bone fractures and lower limb (mainly toe and metatarsial) amputations have been also reported, with data mainly derived from the CANVAS program with canagliflozin. These adverse effects raised warnings from the regulatory agencies, which may limit the use of this new pharmacological class in clinical practice. The identification of T2D patients at higher risk for such events would be of major interest to help the clinician in choosing the best treatment option.

The recent demonstration that GLP-1RAs (liraglutide in LEADER) and SGLT2is (empagliflozin in EMPA-REG OUTCOME) are able to significantly reduce the incidence of CV and renal outcomes in T2D patients at high risk of CV disease has already triggered some adjustments in the recommendations for the management of such patients, including those with or at risk of heart failure. However, two important questions remain to be answered. First, it should be proven that these favorable effects may be considered as a class effect. In this regard, data with SGLT2is (EMPA-REG OUTCOME, CANVAS) seems more homogeneous than those reported with GLP-1RAs, a pharmacological class that seems more heterogeneous, even if the results of SUTAIN-6 with semaglutide partially confirmed those previously reported in LEADER with liraglutide. Second, it is not known whether these favorable effects that were obtained in high CV risk patients (mainly secondary prevention) may be extended to the common T2D population without CV disease but with several CV risk factors (primary prevention, which represents the large majority of the T2D cohort). The results of several ongoing protective outcome studies (DECLARE with dapagliflozin, REWIND with dulaglutide, HARMONY-OUTCOME with albiglutide) are awaited with interest as they should help to answer these two questions.

Finally, several guidelines or position statements have been published during the last two years. All emphasized the importance of a patient-centered approach. However, some discrepancies are present between them, which may increase confusion among clinicians,

especially first-line healthcare providers. Considering the increasing complexity of the management of T2D, it is of major importance that advice to be given to the physician is based on a consensus, which can be supported by the ADA/EASD, the ACCE/ACE and most of the national diabetes societies.

5 Year View

It is doubtful that new classes of oral glucose-lowering agents will be commercialized during the next 5 years, even if some are currently in phase I-II clinical investigation such as new insulin secretagogues or glucagon receptor antagonists. Thus, GLP-1RAs and SGLT2is will probably provide the most interesting new findings during this period of time as it was already the case for the last two years. New cardiovascular outcomes RCTs are awaited with interest, especially the DECLARE trial with dapagliflozin and several others with once-weekly GLP-1RAs. Besides supporting a class effect of SGLT2is, DECLARE should answer the question whether the benefit reported in EMPA-REG OUTCOME and CANVAS may be extended from secondary to primary CV prevention. Another key question is whether once-weekly GLP-1RAs would be able to reproduce the CV protection reported with once-daily liraglutide in LEADER. Besides CV outcomes, more information will also be available regarding the renal protection by SGLT2is and GLP-1RAs as well as their safety profile in long-term observational studies. Currently a step-wise approach is proposed for the management of hyperglycemia in T2D. However, this strategy is increasingly challenged and initial or at least earlier pharmacological combinations are more and more recommended in order to better protect the beta-cell and thus avoid the progression of T2D and to more efficiently prevent diabetic (including CV) complications. In 5 years from now, it is possible that the management of T2D will be profoundly different from the current classical strategy. However, despite recent progress in genotyping, it would be too early for a valuable help of precision medicine in the selection of the pharmacological option that will guarantee the best efficacy/safety profile for an individual T2D patient.

Key issues

- Incretin-based therapies (DPP-4is and GLP-1RAs) and SGLT2is have broadened the spectrum of glucose-lowering agents for the management of T2D
- These new agents may be used as add-on therapies to older agents such as

metformin, sulfonylureas and glitazones, but may also represent valuable alternatives to these medications

- New combinations emerge for the management of T2D, especially DPP-4i-SGLT2i, GLP-1RA-SGLT2i and GLP-1RA plus basal insulin
- Recent prospective CV outcome trials demonstrated the CV safety of all new agents, but interestingly also showed superiority versus placebo for some of them (liraglutide, semaglutide, empagliflozin, canagliflozin)
- Similarly, composite renal outcomes were also favourably influenced by GLP-1RAs (liraglutide, semaglutide) and SGLT2is (empagliflozin, canagliflozin)
- Unexpected adverse effects with some new glucose-lowering agents raised warnings from regulatory agencies, which should be confirmed in further studies
- Insulin therapy in T2D patients may be optimized by using different approaches in order to improve glucose control while minimizing the risk of hypoglycemia.

Conflict of interest statement : A.J. Scheen has received lecturer/advisor/investigator fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, NovoNordisk and Sanofi.

He worked as clinical investigator in the PROactive, TECOS, LEADER, EMPA-REG OUTCOME, CANVAS-R and DECLARE trials.

Table 1 : Cardiovascular outcome trials comparing a DPP-4 inhibitor with a placebo. Results are expressed by hazard ratio (with 95% confidence intervals).

Clinical trial	DPP-4 inhibitor	Primary cardiovascular composite outcome (*)	Myocardial infarction (fatal or nonfatal)	Stroke (fatal or nonfatal)	Cardiovascular mortality	All-cause mortality	Hospitalisation for heart failure
SAVOR-TIMI 53 [38]	Saxagliptin	1.00 (0.89 – 1.12)	0.95 (0.80 – 1.12)	1.11 (0.88 – 1.39)	1.03 (0.87 – 1.22)	1.11 (0.96 – 1.27)	1.27 (1.07 – 1.51) P=0,007
EXAMINE [39]	Alogliptin	0.96 (≤1.16) **	1.08 (0.88 – 1.33)	0.95 (≤1.14) **	0.85 (0.66 – 1.10)	0.88 (0.71 – 1.09)	1.07 (0.79 – 1.46)
TECOS [40]	Sitagliptin	0.98 (0.89-1.08)	0.95 (0.81 – 1.11)	0.97 (0.79 – 1.19)	1.03 (0.89 – 1.19)	1.01 (0.90 – 1.14)	1.00 (0.83 – 1.20)

(*) Cardiovascular death, nonfatal myocardial infarction or nonfatal stroke. (**) Upper boundary of the one-sided reported confidence interval.

Table 2 : Cardiovascular outcome trials with GLP-1 receptor agonists. Results are expressed by hazard ratio (with 95% confidence intervals).

Clinical trials	GLP-1 receptor agonist	Primary cardiovascular composite outcome (*)	Myocardial infarction	Stroke	Cardiovascular mortality	All-cause mortality	Hospitalisation for heart failure	Composite renal outcome
ELIXA [52]	Lixisenatide	1.02 (0.89–1.17) P=0.81	Fatal and nonfatal 1.03 (0.87–1.22) P=0.71	Fatal and nonfatal 1.12 (0.79–1.58) P=0.54	0.98 (0.78–1.22) P=0.85	0.94 (0.78–1.13) P=0.50	0.96 (0.75–1.23) P=0.75	NA (**)
LEADER [53]	Liraglutide	0.87 (0.78–0.97) P=0.01	Nonfatal 0.88 (0.75–1.03)	Nonfatal 0.89 (0.72–1.11)	0.78 (0.66–0.93) P=0.007	0.85 (0.74–0.97) P=0.02	0.87 (0.73–1.05) P=0.14	0.78 (***) (0.67–0.92) P=0.003

			P=0.11	P=0.30				
SUSTAIN-6 [54]	Semaglutide	0.74; 95% confidence interval [CI], 0.58 to 0.95	Nonfatal 0.74 (0.51-1.08) P=0.12	Nonfatal 0.61 (0.38-0.99) P=0.04	0.98 (0.65-1.48) P=0.92	1.05 (0.74-1.50) P=0.79	1.11 (0.77-1.61) P=0.57	0.64 (****) (0.46-0.88) P=0.005

(*) Cardiovascular death, nonfatal myocardial infarction or nonfatal stroke.

(**) NA : not available. Only a slight reduction in the urinary albumin/creatinine ratio has been reported with lixisenatide in the ELIXA trial.

(***) New onset of macroalbuminuria or a doubling of the serum creatinine level and an eGFR of 45 ml/min/1.73 m^2, need for continuous renal-replacement therapy, or death from renal disease

(****) New or worsening nephropathy : persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of less than 45 ml/min/1.73 m^2 (MDRD criteria), or need for continuous renal-replacement therapy

Table 3 : Cardiovascular outcome trials with SGLT2 inhibitors. Results are expressed by hazard ratio (with 95% confidence intervals).

Clinical trials	SGLT2 inhibitor	Primary cardiovascular composite outcome (*)	Myocardial infarction (fatal or nonfatal)	Stroke (fatal or nonfatal)	Cardiovascular mortality	All-cause mortality	Hospitalisation for heart failure	Composite renal outcome
EMPA-REG OUTCOME [64, 66]	Empagliflozin	0.86 (0.74–0.99)	0.87 (0.70–1.09) P=0.23	1.18 (0.89–1.56) P=0.26	0.62 (0.49–0.77) P<0.001	0.68 (0.57–0.82) P<0.001	0.65 (0.50–0.85) P=0.002	0.61 (**) (0.53–0.70) P<0.001
CANVAS [74]	Canagliflozin	0.86 (0.75–0.97) P= 0.02	0.85 (0.69–1.05) NS	0.90 (0.71–1.15) NS	0.87 (0.72–1.06) NS	0.87 (0.74–1.01) NS	0.67 (0.52–0.87) P<0.001	0.60 (***) (0.47–0.77) P<0.001

NS : non significant.

(*) Cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke

(**) Progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease

(***) Sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes

Table 4 : Adverse events reported with new glucose-lowering agents

Glucose-lowering agents	Class adverse events	Molecules	Adverse event related to a specific molecule (*)
DPP-4 inhibitors	Acute pancreatitis	Alogliptin	
		Linagliptin	
		Saxagliptin	Hospitalisation for heart failure [38]
		Sitagliptin	
		Vildagliptin (**)	
GLP-1 receptor agonists	Nausea, vomiting, diarrhoea Acute pancreatitis Cholelithiasis	Exenatide	
		Lixisenatide	
		Liraglutide	
		Albiglutide	
		Dulaglutide	
		Semaglutide	Retinopathy [54]
SGLT2 inhibitors	Genital infections Dehydration Diabetic ketoacidosis	Canagliflozin	Bone fractures, amputations [74]
		Dapagliflozin	Bone fractures and bladder cancer currently unresolved issues
		Empagliflozin	

(*) To be confirmed in further studies

(**) Vildagliptin is not available in the United States

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