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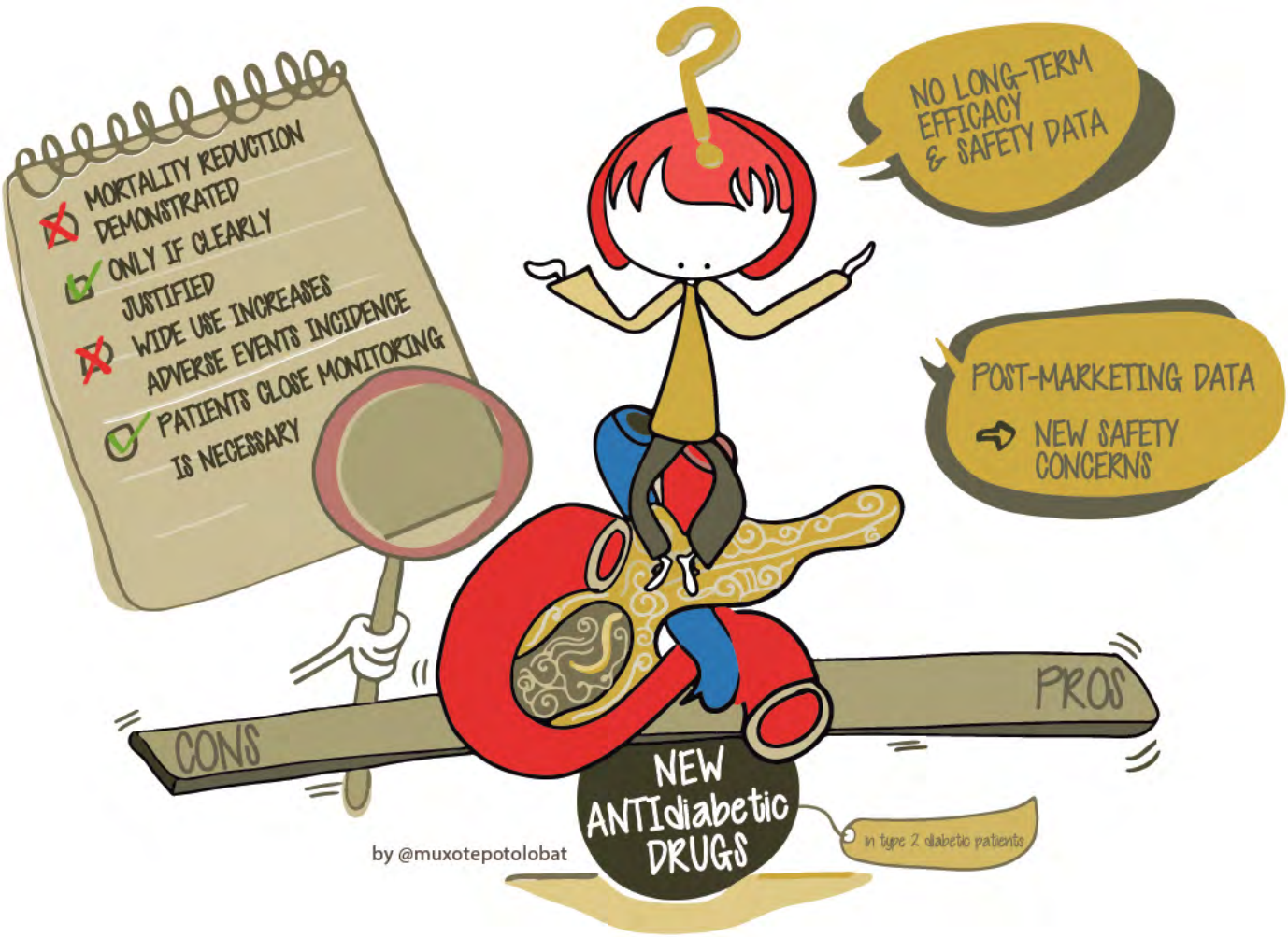

abstract

Objective: To analyze the potential place of new oral antidiabetic drugs in therapeutics based on their effectiveness and safety. **Methods:** A literature search including clinical trials, meta-analyses, EMA's summaries of product characteristics, and safety warnings concerning oral antidiabetics was carried out in Pubmed as of 15/12/2016. **Results and conclusions:** The long-term effectiveness and safety profile of new antidiabetics is still to be established due to the short duration of the trials performed so far. No evidence has been published to demonstrate that new antidiabetics improve the incidence of cardiovascular complications and/or mortality. Metformin is the oral antidiabetic of choice in patients with diabetes mellitus type 2 whose blood glucose levels are not satisfactorily controlled on diet and exercise alone. **Keywords:** safety, diabetes mellitus type 2, oral antidiabetics, GLP-1 analogues.

NEW ANTIDIABETIC DRUGS: WHAT PLACE SHOULD THEY HAVE IN THERAPEUTICS?

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Introduction

Type 2 diabetes mellitus (DM2) is a common chronic disease associated with high rates of morbidity and mortality. In 2014, the prevalence in Spain was 10.6%.[1] However, the true rate is likely to be higher, since it is estimated that 6% of cases are not diagnosed. DM2 is characterized by high glucose levels induced by a deficit in the production of insulin, and/or development of insulin resistance.

DM2 is frequently associated with excessive body weight, hypertension and high lipid levels. People with this condition have a higher cardiovascular risk and an increased risk for macrovascular (ischemic heart disease, cerebrovascular disease, and peripheral vascular disease) and microvascular (retinopathy, nephropathy and diabetic neuropathy) complications. For those whose blood glucose is not sufficiently controlled with diet and exercise, the next step involves the addition of an oral antidiabetic drug. In the recent years, the type of oral antidiabetic prescribed has changed worldwide.[1,2,3]

In Spain between 2000 and 2014, the use of oral antidiabetics and insulin (measured as defined daily doses/1,000 persons/day or DHD) increased by 54% (from 44.6 DHD to 69.9 DHD), and the use of oral antidiabetics has experienced a 56.1% increase. The ratio of insulin to oral antidiabetics use is approximately 1:3 and has remained stable over recent years.[1] The pattern of use of oral antidiabetics has changed over time. In 2000, the most widely used oral antidiabetic drugs were sulfonylureas, whereas from 2010, the use of oral antidiabetics was distributed more evenly among different subgroups. According to the literature, the use of biguanides has increased since 2000, and the most widely used oral antidiabetic drug in Spain in 2014 was metformin (in monotherapy), accounting for 40% of the total oral antidiabetics prescribed.

In the last decade, new therapeutic groups with innovative mechanisms of action have emerged, such as incretin regulators (dipeptidyl peptidase-4 inhibitors or DPP4-I) and glucagon-like peptide 1 (GLP-1) analogues or agonists. Sodium-glucose co-transporter type 2 (SGLT-2) inhibitors have recently been approved on the basis of their effect on glycosylated hemoglobin (HbA1c) levels, rather than on their impact on diabetes-associated mortality and/or morbidity.

Newer antidiabetic drugs are replacing other long-used drugs such as sulfonylureas, glitazones, fast-acting secretagogues or ß-glucosidase inhibitors (figure 1). In Navarre, Spain, the most common antidiabetic drugs after metformin are DPP-4 inhibitors (figure 2). Since their approval in 2014, SGLT-2 inhibitors are gaining popularity over other classes of drugs. The increase in use of the new antidiabetics may be as a result of by their claimed safety, low risk of hypoglycemia, and neutral or beneficial effects on weight. Also, many of these drugs are available as combination products with metformin, which facilitates treatment adherence.

However, some concerns have arisen about the safety of SGLT-2 inhibitors. Such concerns are based on the potential occurrence of adverse events such as pancreatitis and pancreatic cancer (DPP-4 inhibitors and GLP-1 analogues), an increased risk for heart failure (DPP-4 inhibitors), and several safety warnings issued by regulatory authorities about an increased risk for diabetic ketoacidosis or acute renal failure. These facts should lead us to reconsider the place of SGLT-2 in therapeutics.

Newer therapeutic groups

Incretin regulators

These drugs increase the levels of active incretins or stimulates their action. The two main incretin hormones are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are secreted from endocrine cells of the small intestine in response to the presence of glucose. Both hormones undergo rapid degradation —in 1-2 minutes— by the dipeptidyl peptidase-4 enzyme. Incretins stimulate postprandial insulin secretion, slow gastric emptying and reduce glucose-dependent glucagon secretion. This phenomenon is called "incretin effect". Based on this effect, two mechanisms of action are being used to design new medicines: inhibiting the enzyme that degrades incretins (DPP-4 inhibitors) or identifying GLP-1 analogues or agonists.

Figure 1. Changes in use of oral antidiabetics in Navarre from 2007-2016 (data in DDD).

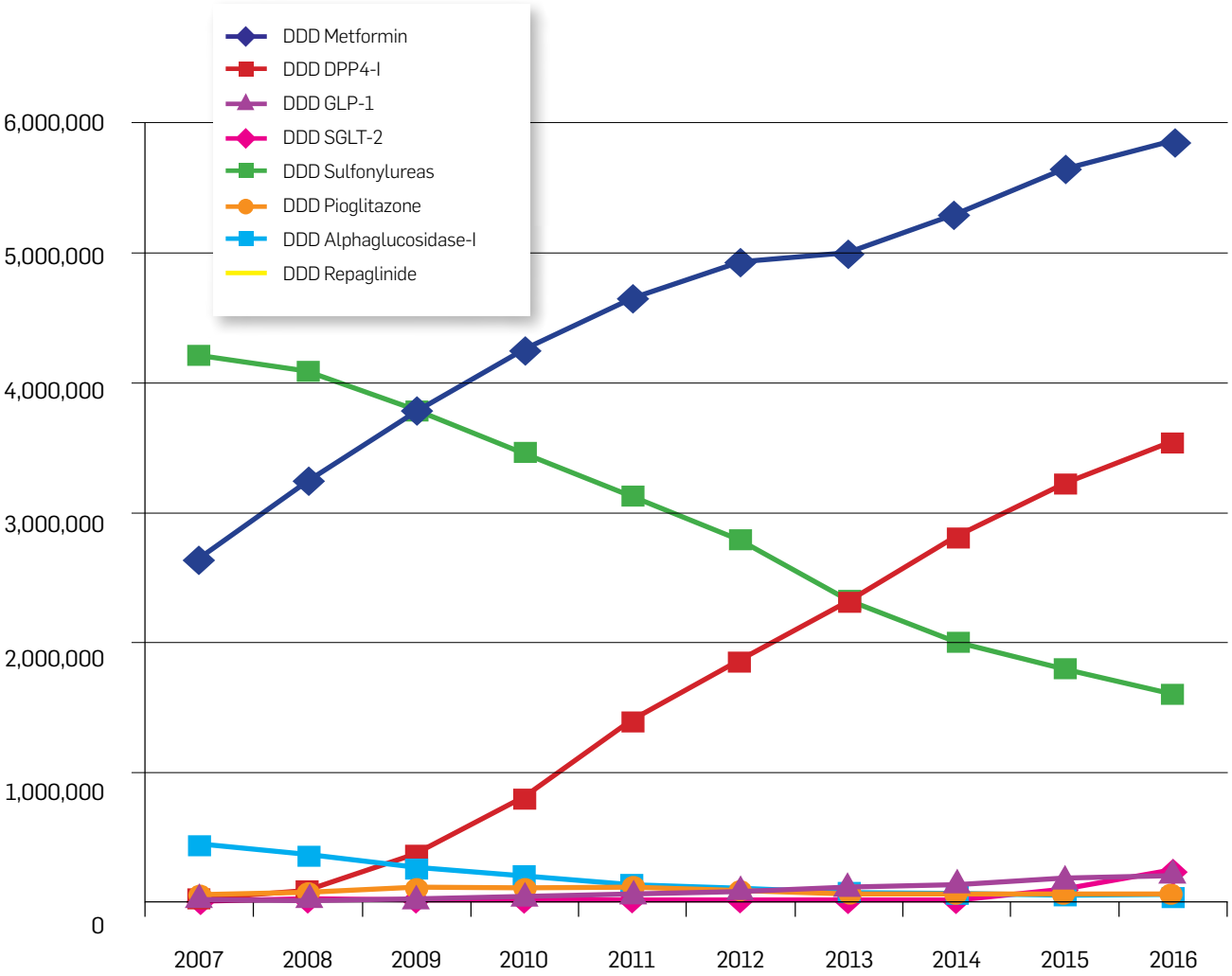
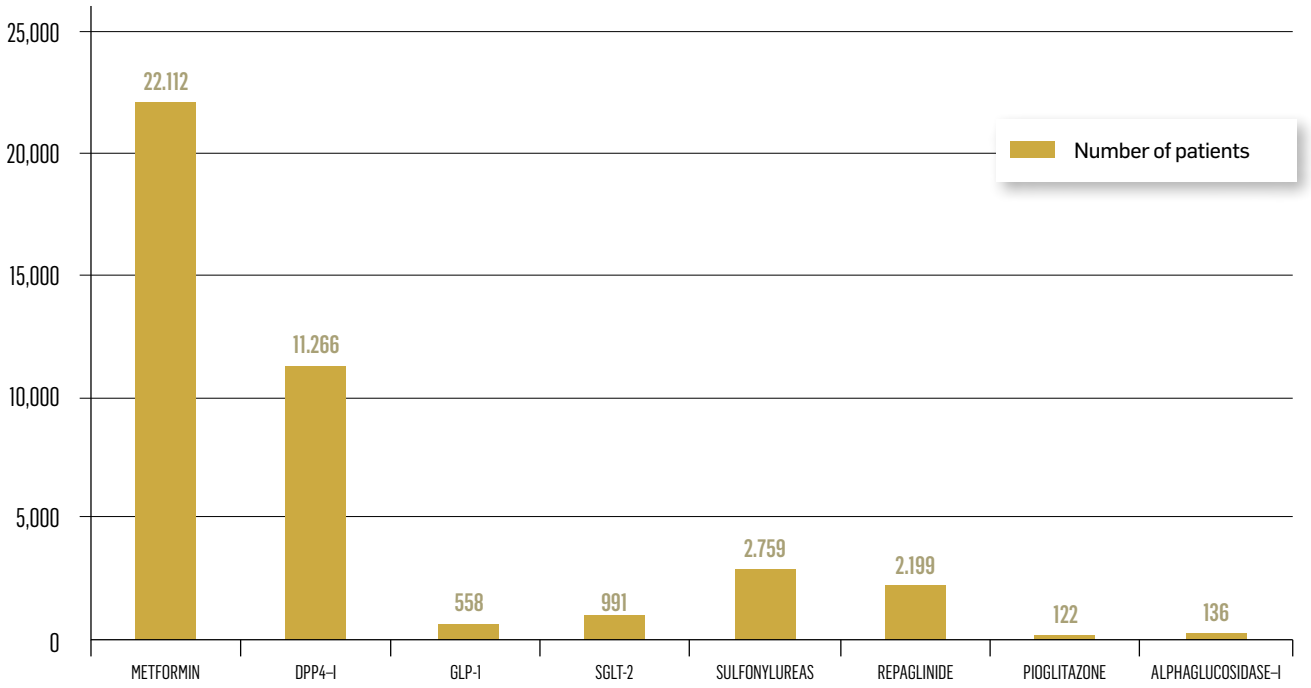


Figure 2. Number of patients treated with antidiabetics in Navarre, Spain. August-October 2016.



1- DPP-4 inhibitors

At present, five DPP-4 inhibitors are marketed in Spain: sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin (table 1).

Safety

Since these drugs were granted authorization by regulatory authorities, reports of acute pancreatitis have increased, and the risk of hospitalization for heart failure associated with saxagliptin has been reported.[4]

Adverse Drug Reactions (ADRs)

ADRs reported to be frequent (1-10%) or very frequent (>10%) in EMA's Summary of Product Characteristics include[5] respiratory tract infections, urinary tract infections, musculoskeletal disorders (myalgias and arthralgias), and headache. After their approval, severe reactions of hypersensitivity have been reported, including: anaphylaxis, angioedema and exfoliative skin diseases such as Stevens-Johnson's syndrome.[5,6]

Cardiovascular Safety

Oral antidiabetics improve glucose control, which is supposed to reduce the incidence of cardiovascular events. However, several cardiovascular safety warnings have been issued on antidiabetic drugs such as tolbutamide, rosiglitazone or pioglitazone.

In the light of this paradoxical finding, the USA Food and Drug Administration (FDA) modified the terms of approval for antidiabetic drugs. The FDA requires that a study (or meta-analysis of phase II-III trials) is performed to compare the incidence of major cardiovascular events associated with the new drug vs. controls. For a new antidiabetic drug to be approved, evidence has to be provided that the upper limit of the 95% confidence interval of the estimated relative risk (RR) is < 1.8 compared with the control intervention. Once the drug is approved, a post-authorization study is required to demonstrate that the 95% confidence interval of the relative risk is < 1.3. In other words, approval is currently granted to antidiabetic drugs that are associated with an increase in cardiovascular events by up to 30% with respect to controls.[7]

As a result, an increasing number of studies are being conducted to assess the cardiovascular effects of DPP-4 inhibitors. Although many of these studies have provided encouraging safety data regarding short-term therapies, concerns persist about the increased cardiovascular risk of certain drugs such as saxagliptin.

Three large studies have been performed so far on the cardiovascular safety of gliptins. The SAVOR[4] study compared saxagliptin vs. placebo in patients with a history of cardiovascular disease or multiple risk factors for cardiovascular disease. The non-inferiority study EXAMINE[8] compared alogliptin vs. placebo in patients with recent acute coronary syndrome. Finally, the non-inferiority TECOS[9] study compared sitagliptin vs. placebo in patients with established cardiovascular disease. No significant differences were found in the primary endpoint in any of the three studies. The primary endpoint of the TECOS and EXAMINE studies was a composite of cardiovascular death, nonfatal stroke, nonfatal MI and unstable angina. The primary endpoint of the EXAMINE study included the same endpoints plus hospitalization for heart failure.

There are no data on the long-term effectiveness and safety of new antidiabetics

The SAVOR study reported that the number hospitalizations for heart failure was higher among patients receiving saxagliptin (3.5% vs. 2.8%), HR=1.25 (95%CI, 1.07-1.51). The absolute risk reduction was 0.75, with a NNH=139 (95%CI, 77-500).

In a *post hoc* analysis of the EXAMINE study, it was observed that patients with high cardiovascular risk receiving alogliptin were more likely to be hospitalized for heart failure. However, differences did not reach statistical significance: 3.1% vs. 2.9% (ARR = 0.02%), HR 1.07 (95%CI, 0.79-1.46). These results should be taken with caution, given that it was a *post hoc* analysis.

In the TECOS study, no differences were observed in the rates of hospitalization for heart failure (3.1% for all groups), HR=1.00 (95%CI, 0.83-1.20).

In contrast, inconsistent results have been obtained in different meta-analyses concerning the cardiovascular safety of new antidiabetics.[10,11,12] The FDA issued a public safety warning that saxagliptin and alogliptins can increase the risk for heart failure, especially in patients with a established cardiovascular or renal disease.[13] This information has been incorporated into the Special Warnings and Precautions for Use section of their respective "Summary of Product Characteristics" document.

In any case, no evidence has been provided to support the initial claims that DPP-4 inhibitors reduce cardiovascular risk. The reason is that all studies were performed in patients with high cardiovascular risk and scant data is available about the cardiovascular effects of these medicines in patients with low cardiovascular risk.[14]

Acute pancreatitis

The use of DPP-4 inhibitors has been associated with a risk of acute pancreatitis. Patients should be informed that severe and persistent pain may be a sign of acute pancreatitis, and those with a history of pancreatitis need to be closely monitored. This recommendation is included in the labels of the five gliptins marketed in Spain.[5]

Tkáč et al have recently performed a pooled analysis of data from the three studies assessing the long-term cardiovascular safety of gliptins[15] (SAVOR,[4] TECOS[8] and EXAMINE[9] trials).The analysis showed that the incidence of acute pancreatitis was significantly higher in the group of patients receiving gliptins vs. placebo (OR=1.79 [95%CI 1.13-2.82]). The absolute risk difference was 0.13% (NNH=844 [95%CI 475-3825]).

Liver failure and vildagliptin

Vildagliptin should not be used in patients with liver failure or high ALT or AST test levels (threefold higher than the upper normal limit). Cases of hepatic dysfunction (including hepatitis) are rare.

Liver function should be monitored in patients receiving vildagliptin at three-month intervals during the first year and regularly thereafter. The liver function of patients with transaminase elevations should be re-examined to confirm the finding and close monitoring should be performed until transaminase levels are normal again. Vildagliptin therapy should be discontinued if AST or ALT levels remain greater than 3 times the upper limit of the normal range.

Vildagliptin therapy should also be interrupted if patients develop jaundice or other signs of hepatic dysfunction. Treatment should not be resumed even when laboratory test results show a normal hepatic function.[5]

Risk Management Plan

Signs or symptoms suggestive of safety problems may appear during the development of new drugs. Upon approval of a new drug, regulatory authorities usually design a risk management plan. A post-marketing risk management plan can also be required later.

Although a drug has been approved by national regulatory authorities, any relevant EU national authority can request the development of a risk management plan on the basis of justified concerns related to the risk-benefit balance of the new drug.

The purpose of a risk management plan is to identify all known risks, potential risks, and unknown data about the safety of a specific drug. A risk management plan includes all pharmacovigilance actions to be undertaken to monitor the safety profile of a medicine, which occasionally includes the performance of phase IV trials. This plan can include a series of guidelines or recommendations for physicians and patients to minimize the risks associated with the use of these drugs.

The following potential risks are included in the risk management plan for DPP-4 inhibitors.

- Infections: infection of the upper respiratory tract, nasopharyngitis and other related diseases (bronchitis, acute bronchitis, pharyngitis, sinusitis and rhinitis).
- Neurotoxicity: tremor, ataxia and balance disorders.
- Renal impairment, including acute renal failure (sometimes requiring dialysis).
- Rhabdomyolysis

Place in the management of type 2 diabetes

The role of these new drugs still remains uncertain. Few long-term studies have been conducted on the glucose-lowering action, major health improvements (cardiovascular effects and/or mortality) or safety profile of these drugs. Therefore, DPP-4 inhibitors should not be the treatment of choice in most patients. Metformin is the antidiabetic drug of choice in monotherapy.[16,17] Gliptins should only be used in monotherapy in patients who cannot take metformin due to intolerance or contraindication, with a high risk of hypoglycemia.

When glucose levels are not satisfactorily controlled, gliptins can be used as an alternative to sulfonylureas or repaglinide in combination with metformin. Gliptins can also be used as add-on therapy to pioglitazone, although the potential damages and restrictions of use of pioglitazone should be previously considered.[5,18,19] Nevertheless, gliptins only have a modest glucose-lowering effect and their experience of use is limited. Therefore, there is no solid evidence supporting DDP-4 inhibitors as the first choice as add-on therapy to metformin.

Finally, DDP-4 inhibitors are indicated in triple therapy with metformin + sulfonylureas or metformin + pioglitazone as an alternative to insulin + metformin therapy.[14]

2-GLP-1 analogues and ag onists

There are some differences among the GLP-1 analogues and agonists currently available on the market. All are administered via subcutaneous injection, although dosage differs according to the formulation. Some of these medicines are administered intravenously twice a day (exenatide), once daily (liraglutide, lixisenatide) or once weekly (prolonged-release exenatide, dulaglutide and albiglutide) (Table 2).

This class of drugs improves glucose control and weight loss (except for albiglutide, which has no effects on body weight).[20] However, few studies have been conducted to assess clinically relevant outcomes such as cardiovascular events or mortality, duration of weight loss, or other safety aspects.[21]

Safety: Adverse drug reactions (ADRs)

The most frequent ADRs (10-15% incidence) associated with GLP-1 agonists are essentially gastrointestinal: nausea, vomiting and diarrhea.[22] These side effects can be reduced using a stepped therapy (e.g. starting with the minimum effective dose and increasing the dose progressively).

Acute pancreatitis and pancreatic cancer

According to EMA's Summary of Product Characteristics for all GLP-1 inhibitors (exenatide, extended-release exenatide, liraglutide, albiglutide, dulaglutide and lixisenatide), their use is associated with a higher risk for acute pancreatitis. However, although some observational studies[23,24] and meta-analyses[25,26] report an increased risk for acute pancreatitis, its incidence is, in general terms, low and it is not clear that a causal relationship exists.

The general recommendation is that treatment should be discontinued on suspicion of pancreatitis. If acute pancreatitis is confirmed, treatment should not be resumed later. Patients with a history of pancreatitis need to be closely monitored.

Cases of pancreatic cancer have been reported in patients treated with exenatide, which has raised doubts about these drugs.[27] Both, the FDA[28] and the EMA[29] agree that there is insufficient evidence proving the relationship between the use of GLP-1 and an increased risk for pancreatic cancer. Subsequent studies concluded that these drugs do not seem to increase the risk for pancreatic cancer, although long-term observational studies are needed to confirm or not a causal relationship.[30,31]

In the light of the severity of this side effect, the EMA has included the study of a potential increase in the incidence of neoplasms in the risk management plan of this group of drugs.

Thyroid cancer

Studies in rodents with liraglutide, extended-release exenatide, and dulaglutide revealed an increased risk for thyroid C-cell tumors. Whether these drugs have the same effects on humans is unknown, since humans require longer follow-up than animals.

Until more reliable data become available, these drugs are contraindicated in patients with a personal or family history of thyroid cancer or with multiple endocrine neoplasia type (MEN2). This type of patients was excluded from clinical trials due to a higher risk of developing thyroid cancer.[32,33,34]

New severe adverse effects have been reported in post-marketing pharmacovigilance

Thyroid-related adverse events are reported in the EMA's Summary of Product Characteristics of liraglutide including increased blood levels of calcitonin, goiter, and thyroid neoplasm —especially in patients with pre-existing thyroid disease—. Therefore, liraglutide should be administered with caution.[5]

Cardiovascular safety

The cardiovascular safety of liraglutide[35] and lixisenatide[36] has been tested in two clinical trials. Both were non-inferiority vs. placebo studies in patients either with high cardiovascular risk (liraglutide) or who had experienced a cardiovascular event (infarction or hospitalization for unstable angina) in the six months prior to the start of lixisenatide therapy.

The trial with liraglutide showed that patients treated with liraglutide were less likely to experience the primary endpoint of a cardiovascular event (cardiovascular death, nonfatal infarction, or nonfatal stroke), HR=0.87 (95%CI, 0.78-0.97). No differences were observed between groups regarding the incidence of nonfatal infarction, nonfatal ictus or hospitalization for heart failure.

In the trial with lixisenatide, no differences were found between the two groups in the primary composite endpoint (cardiovascular death, nonfatal infarction, nonfatal stroke or hospitalization for unstable angina), HR=1.02 (95%CI, 0.89-1.17). No differences were found either in individual endpoints.

Place in the management of people with type 2 diabetes

GLP-1 agonists cannot be employed as first choice for monotherapy or dual therapy for diabetes mellitus.

The NICE guideline[16] recommended GLP-1 in triple therapy regimes plus metformin plus sulfonylureas only if: (I) other triple therapies are not effective, (II) one of the components is contraindicated or not tolerated, (III) the patient has a BMI ≥35, (IV) the patient has a BMI < 35 and needs to lose weight, and (V) the patient is not a candidate for insulin therapy.

Sodium-glucose co-transporter 2 inhibitors (SGLT-2)

These drugs selectively inhibit the sodium-glucose co-transporter in a reversible way, which reduces glucose reabsorption in the kidney thereby increasing glucose excretion. This process causes osmotic diuresis and subsequent glucose reduction, as well as weight loss. This mechanism of action is not insulin-dependent. Currently, there are three drugs of this class on the market: canagliflozine, dapagliflozin and empagliflozin (Table 2).

Safety: Adverse drug reactions (ADRs)

The most frequent ADRs include urinary tract infections (4-6%) and genital candidiasis such as vulvovaginitis and balanitis (5-11%).[5] Cases of sepsis of urinary origin and pyelonephritis requiring hospitalization have also been reported.[37]

Blood pressure

The use of SGLT-2 inhibitors has been associated with a reduction of blood pressure. Although in some cases such reduction can be beneficial,[5] it can cause episodes of symptomatic hypotension in older adults or patients receiving hypotensive treatment.[38]

Cardiovascular safety

In the EMPA-REG OUTCOME trial, empagliflozin was proven to be "non-inferior" to placebo in the primary composite endpoint (cardiovascular mortality, nonfatal stroke and nonfatal ictus). A subsequent analysis revealed that the incidence of episodes of the primary composite endpoint was lower in the empagliflozin group, close to the limit of statistical significance, HR=0.86 (95%CI, 0.74-0.99).

There is no compelling evidence supporting the superiority of empagliflozin over placebo for the prevention of macrovascular complications in diabetic patients with established cardiovascular disease.[39]

Renal effects

The effect of these drugs depends on renal function, and their use should be interrupted in patients with glomerular filtration < 45ml/min. Cases of severe acute renal failure have been reported (some requiring hospitalization and dialysis) in patients receiving canagliflozin or dapagliflozin.[40] Consequently, the FDA recommends that the renal function of all patients receiving treatment with SGLT-2 inhibitors is closely monitored. Concomitant use of loop diuretics is not recommended.

Risk for fractures

Another potential secondary effect is the increased risk for fractures in patients receiving canagliflozin.[41] A randomized phase 3 trial revealed a higher incidence of fractures in patients on treatment with canagliflozin (1.4 to 1.5 fractures/100 patients-year (at doses of 100 and 300 mg/d, respectively) vs. 1.1 fractures/100 patients-year in the placebo group).[42]

The mechanism that causes this effect is unclear, although the development of orthostatic hypotension and the subsequent increased risk for falls might be involved. Another hypothesis is that SGLT 2 inhibitors affect bone mineral density.[43] It is not well understood whether other drugs of the same class have the same effect. No significant increases in the risk for fractures were observed in a meta-analysis performed in patients receiving canagliflozin and dapagliflozin.[44] However, the risk for bone fractures is included in the risk management plan of all drugs of this class.

Diabetic ketoacidosis

Cases of diabetic ketoacidosis without hyperglycemia have been reported. A study was conducted to screen for cases of diabetic ketoacidosis in patients on treatment with SGLT-2 inhibitors. The study revealed that 7 of the 13 cases were patients with DM1, for whom SGLT-2 inhibitors are not indicated.[45] Based on this finding, the regulatory authorities issued a safety communication regarding the risk for ketoacidosis in patients treated with SGLT-2 inhibitors.[46,47]

Finally, an ongoing clinical trial to assess the cardiovascular safety of canagliflocin (CANVAS)[48] has revealed an increase in the number of non-traumatic lower-limb amputations (primarily, toes). Although there is no sufficient data to demonstrate the relationship between the use of SGLT-2 and amputations, the regulatory authorities issued a communication to inform on this potential severe side effect.[49,50,51]

Potential risks included in the Risk Management Plan

Neoplasms:

In the case of dapagliflozin, no signs of carcinogenicity or mutagenicity have been observed in animals. Therefore, the EMA considers it unlikely that a causal relationship exists between dapagliflozin and an increased risk for tumors. Nevertheless, given that the incidence of bladder, prostatic and breast cancer was higher in number in clinical trials with dapagliflozin, warnings have been issued regarding this potential risk. Consequently, the risk for bladder, prostatic and breast cancer has been included in the Risk Management Plan and in EMA's Pharmacovigilance programme.

In the case of empagliflozin, a study in mice revealed an increase in the risk for renal cancer. Given that empagliflozin may pose the same risk to humans, patients on long-term empagliflozin therapy should be closely monitored.

Off-label use:

The Risk Management Plan includes off-label use of canagliflozin, dapagliflozin and empagliflozin to support weight loss. The Risk Management Plan warns that SGLT-2 inhibitors should not be administered to:
- patients aged ≥ 75 years;
- patients with a severe renal disease;
- patients taking loop diuretics such as furosemide;
- patients on pioglitazone therapy.

Other potential risks included in the Risk Management Plan for all glyphlozines:

- Renal failure
- Altered laboratory test results: increased hematocrit linked to depletion of plasma volume, a factor that could have clinical effects;
- Hepatic damage;
- Hypersensitivity reactions (intolerance, allergy).

Place in the management of people with type 2 diabetes

SGLT-2 inhibitors should not be considered as treatment of choice for type 2 diabetes. The routine use of SGLT-2 inhibitors as the second drug in dual antidiabetic treatments is not recommended.[16,41]

Acknowledgements

We are grateful to David Phizackerley, Deputy Editor of the Drug and Therapeutics Bulletin (UK) for reviewing the text.

Table 1. Summary of the clinical effects of the main classes of antidiabetic drugs.

MEDICINE CLASS	METABOLIC ACTION	EFFECTS ON MORBIDITY OR MORTALITY	INDICATIONS	SIDE EFFECTS	SAFETY WARNINGS
Biguanides Metformin	-1.5-2 %	Yes. Reduction of diabetes-related morbidity and mortality in overweight or obese patients (UKPDS 34).[52]	Monotherapy. Double therapy with any drug. Triple therapy with any drug. As add-on therapy to insulin.	No hypoglycemia when alone. Diarrhoea. Lactic acidosis (rare). Reduced vitamin B_{12} absorption.	No
Sulfonylureas Glibenclamide Glycazide Glipentide Glipizide Gliquidone Glimepiride	-1.5-2%	Yes. Reduces microvascular but not macrovascular complications in diabetic patients.[53]	Monotherapy. Double therapy (except for glinides). Triple therapy (except for glinides). As add-on therapy to insulin.	Hypoglycemia (less frequent with glycazide and glimepiride).	No
Rapid-acting secretagogues (Glinides) Repaglinide	-1.5-2 %	No long-term studies.	Monotherapy. Double therapy with metformin.	Few hypoglycemias (do not combine repaglinide with gemfibrozil, it increases the risk for hypoglycemia).	No
Inhibitors a-glucosidase Acarbose Miglitol	-0.5-1 %	No long-term studies.	Monotherapy. Double therapy with metformin or sulfonylureas. As add-on therapy to insulin.	No hypoglycemia when alone, hypoglycemia when combined. Flatulence, diarrhoea.	No
Glitazones (require authorization) Pioglitazone	-1-1.5 %	PROactive trial. No differences in the primary endpoint.[54]	Monotherapy. Double therapy with metformin or sulfonylureas or DPP4-I. Triple therapy with metformin plus sulfonylureas, metformin plus DPP4-I, metformin plus GLP-1 agonist. As add-on therapy to insulin.	No hypoglycemia when used alone. Water retention. Edema. Hepatotoxicity. Increased cardiovascular risk.	Bladder cancer. Congestive heart failure.
IDPP-4 Sitagliptine Vildagliptine Saxagliptine Linagliptine Alogliptine	-0.5-1%	Insufficient data. Little experience of use.	Monotherapy. Double therapy plus metformin or sulfonylureas or pioglitazone. Triple therapy with metformin plus sulfonylureas or metformin plus pioglitazone or metformin plus SGLT-2. As add-on therapy to insulin.	Low risk of hypoglycemia if not combined with secretagogues or insulin. Neutral with respect to weight. Upper respiratory tract processes. Pancreatitis. Hepatitis (vildagliptine).	Heart failure (saxagliptine and alogliptine).
GLP-1 analogues (require authorization) Exenatide Liraglutide Lixisenatide Dulaglutide Albiglutide	-1-1.5%	Insufficient data. Do not seem to increase cardiovascular risk. Little experience of use.	Monotherapy. Double therapy with metformin or sulfonylureas. Triple therapy with metformin plus sulfonylureas or metformin plus pioglitazone . As add-on therapy to insulin.	Low risk of hypoglycemia if not combined with secretagogues or insulin. Weight loss. Nausea, vomiting and diarrhea. Acute pancreatitis.	Thyroid cancer. Pancreatic cancer.
SGLT-2 inhibitors Dapagliflozin Canagliflozin Empagliflozin	-0.5-1%	Insufficient data. Do not seem to increase cardiovascular risk. Little experience of use.	Monotherapy. Double therapy with metformin or sulfonylureas. Triple therapy with metformin plus sulfonylureas or IDPP-4. As add-on therapy to insulin.	Genital infections (candidiasis). Urinary infections. Low blood pressure.	Diabetic ketoacidosis. Risk for bone fracture (canagliflozin). Non-traumatic lower-limb amputations (canagliflozin).[40]

Conclusions

Metformin is the oral antidiabetic drug of choice in patients with type 2 diabetes whose blood glucose levels are not satisfactorily controlled on diet and exercise alone.

New antidiabetics have not been proven so far to reduce mortality and/or the incidence of cardiovascular complications.

The latest studies published cast doubts on the safety of these medicines.

Given the questionable benefit-risk profile of these medicines, they should only be administered when no other options are feasible. Generalized exposure can increase the incidence of potentially severe ADRs without providing clear clinical benefits.

When its use is justified, patients should be closely monitored.

It should be recalled that triple therapy is a temporary alternative to insulin therapy.

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