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Recommendations and management of non-insulin hypoglycemic agents in patients with heart failure or cardiovascular events

Esther Álvarez-Rodríguez[1]✉, MD, PhD; Marina Povar Echevarría[2], MD; y F. Javier Martín Sánchez[3], MD, PhD

[1] Emergency Department, Hospital Universitario Severo Ochoa. Leganés, Madrid, Spain.
[2] Department of Internal Medicine, Hospital Miguel Servet. Zaragoza, Spain.
[3] Emergency Department, Hospital Universitario Clínico San Carlos. Madrid, Spain.

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ARTICLE INFORMATION

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Acronyms
DM: diabetes mellitus
DPP-4: dipeptidyl peptidase-4 inhibitors
GLP-1: glucagon like peptide-1 receptor agonist
HbA1c: glycated hemoglobin
HF: heart failure
SGLT-2: sodium-glucose cotransporter-2 inhibitors

ABSTRACT
Both diabetes mellitus and heart failure often go hand in hand. The results of recent studies on decreased mortality, heart failure hospitalization and the occurrence of cardiovascular events, which have shown certain non-insulin hypoglycemic agents, have brought about changes in the diabetes treatment recommendations. The classic goal of diabetes treatment, focused on reducing glycated hemoglobin to reduce microvascular damage, although still important, may have faded into the background, since we have drugs that could also reduce macrovascular damage.
Keywords: Diabetes mellitus, Heart failure, Cardiovascular diseases, Drug therapy

Recomendaciones y uso de los hipoglucemiantes no insulínicos en los pacientes con insuficiencia cardíaca o eventos cardiovasculares

RESUMEN
Tanto la diabetes mellitus como la insuficiencia cardíaca son dos enfermedades que frecuentemente van de la mano. Los resultados de recientes estudios sobre disminución de mortalidad, hospitalización por insuficiencia cardíaca y aparición de eventos cardiovasculares, que han demostrado ciertos hipoglucemiantes no insulínicos, han hecho que cambien las recomendaciones en cuanto al tratamiento de la diabetes mellitus. El objetivo clásico del tratamiento de la diabetes, centrado en la reducción de la hemoglobina glicada para reducir el daño microvascular, aunque siga siendo importante, puede que haya pasado a un segundo plano, ahora que disponemos de fármacos que podrían disminuir también el daño macrovascular.
Palabras clave: Diabetes mellitus, Insuficiencia cardíaca, Enfermedades cardiovasculares, Tratamiento farmacológico

✉ *E Álvarez-Rodríguez*
Hospital Severo Ochoa
Av. de Orellana s/n
28911 Leganés. Madrid, España.
E-mail address:
docenciaurgen.hsvo@salud.madrid.org

INTRODUCTION

Heart failure (HF) and diabetes mellitus (DM) are two common diseases in the general population and they often coexist. A prevalence of DM is estimated in patients with HF between 30-50%[1-4]. The DM has been described

as an independent mortality factor in patients with acute or chronic HF[5,6], and it is associated with a higher risk of hospitalization for HF and mortality due to cardiovascular causes[7]. Log data of the HF registry of the European Society of Cardiology (ESC-HF Long-Term Registry)[8] showed that the presence of DM was associated with a substantial increase in hospital mortality and for any reason, after a year, and to the increase of risk of readmission due to HF. In addition, the DM in the HF has been associated with worse results in the walking test, quality of life and functional class in the scale of the New York Heart Association (NYHA) with respect to non-diabetic patients[7].

The main causes of HF in patients with DM are high blood pressure and coronary artery disease, but also direct damage caused by the DM in the myocardium (diabetic cardiomyopathy)[7,9].

In the 2016 clinical guidelines of the Spanish Society of Cardiology for the treatment of HF, there are no special considerations for patients with DM, hence, the pharmacological treatment and the one with devices is similar[10]; although the treatment with sacubitrile/valsartan was associated with greater reduction of the glycated hemoglobin (HbA1c) with respect to the enalapril[11]. On the other hand, it is necessary to take into account a series of considerations in the treatment of DM of patients with HF, since some anti-diabetic drugs have shown to modify the natural history of the disease.

The aim of this work is to review the scientific evidence available so far and to propose some indications in the treatment of diabetic patients with HF at the emergency department.

Is there any current evidence that can modify the history of the disease?

In the decision-making for the DM treatment, the re-

Table 1. Clinical trials on cardiovascular safety with anti-diabetic drugs[18-27].

Family	Drug	Clinical trial	Year of publication	Bibliographical reference
DPP-4	Alogliptin	EXAMINE	2013	White WB, *et al.*[19] N Engl J Med 2013;369:1327-35.
	Saxagliptin	SAVOR	2013	Scirica B, *et al.*[18] N Engl J Med 2013;369:1317-26.
	Sitagliptin	TECOS	2015	Green JB, *et al.*[20] N Engl J Med 2015;373:232-42.
	Linagliptin	CAROLINA CARMELINA	On going	Publicación de resultados: 2018 y 2019
GLP-1	Lixisenatide	ELIXA	2015	Bentley-Lewis R, *et al.*[21] Am Heart J 2015;169:631-638.
	Liraglutide	LEADER	2016	Marso SP, *et al.*[23] N Engl J Med 2016;375:311-22.
	Semaglutide	SUSTAIN-6	2016	Marso SP, *et al.*[24] N Engl J Med 2016; 375:1834-44.
	Exenatide	EXSCEL	2017	Holman R, *et al.*[22] N Engl J Med 2017; 377:1228-39.
	Dulaglutide	REWIND	On going	Resultados preliminares: 2018 Publicación de resultados:2019
SGLT-2	Empaglifozin	EMPAREG	2015	Zinman B, *et al.*[25] N Engl J Med 2015;373:2117-28.
	Canaglifozin	CANVAS	2017	Neal B, *et al.*[26] N Engl J Med 2017;377:644-57.
	Dapaglifozin	DECLARE DAPA-HF, DAPA-CKD	2018	Wiviott SD, *et al.*[27] DOI: 10.1056/NEJMoa1812389

DPP-4, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon like peptide-1 receptor antagonists; SGLT-2, sodium-glucose cotransporter-2 inhibitors.

duction of HbA1c has traditionally been pursued, since it has been shown that glycemic control reduces microvascular complications. However, the effectiveness in preventing macrovascular complications because of anti-diabetic drugs was not entirely clear, and although it could be partly explained by the reduction of glycemia, based on published studies, there would have to be other mechanisms[12-15].

It was also found that drugs such as rosiglitazone, in addition to lowering blood glucose, had a positive profile against dyslipidemia; nevertheless, they demonstrated a harmful profile in terms of risk of myocardial infarction, death for a cardiovascular cause and appearance of HF[16-17], thus, its commercialization was withdrawn. From that moment, and in order to prevent similar cases, the Food and Drug Administration (FDA) of the United States and the European Medicines Agency (EMA) have demanded conducting clinical trial that assess the cardiovascular safety of new anti-diabetic drugs.

These trials compare each drug with a placebo in a "non-inferiority" design, in populations at high cardiovascular risk, and they evaluate primarily cardiovascular events such as myocardial infarction or stroke, death from cardiovascular causes or any cause, as well as the hospitalizations for HF; they have provided evidence on the possibility of different anti-diabetic drugs to modify the prognosis of the disease. The clinical trial associated with each drug is displayed in **table 1**.

In this regard, the dipeptidyl peptidase-4 inhibitors (DPP-4) that have proven cardiovascular safety are: saxagliptin, alogliptin and sitagliptin, although the first two could favor hospitalization for HF[18-20].

Among the glucagon like peptide-1 receptor antagonists (GLP-1), which have also shown cardiovascular safety, are the weekly lixisenatide[21] and exenatide[22]. However, within this group of drugs there are others that have not only demonstrated "non-inferiority" but also superiority in certain aspects. It is the case of liraglutide, a GLP-1, which decreases 22% of death from cardiovascular causes and 15% of death from any cause; it is neutral regard-

Box 1. Evaluation and treatment of glycemia at the emergency department and hospitalization in patients with heart failure or cardiovascular risk.

Diabetic patient or with hyperglycemia without previously known diabetes
Monitoring of capillary glycemia: before breakfast, lunch and dinner, or every 6 hours if not oral feeding.
To request HbA1c (unless a recent one)
To remove non-insulin anti-diabetic drugs
To start subcutaneous basal-bolus insulin regimen, except for critical patients, in which it will be used in perfusion with serotherapy, according to recommendations[32]
To design a therapeutic plan at discharge, according to results and evolution (**Box 2**)

Box 2. Therapeutic plan at discharge of the diabetic patient with heart failure or cardiovascular risk.

Patient with hyperglycemia without previously known diabetes	
At discharge, to begin anti-diabetic treatment as recommended[33]. If choosing non-insulin anti-diabetic drugs, to consider possible contraindications, risks and benefits of different therapeutic options in patients with heart failure or cardiovascular risk	
To reevaluate treatment in the diabetic patient, at discharge	
According to previous and current monitoring, to consider possible contraindications and risks of previous drugs, and potential benefits of a change in terms of HF and CV risk	
If accurate monitoring, absence of contraindications in prior treatment and possible lack of benefit with the change	To continue with the same treatment
If poor monitoring, existence of contraindications for prior treatment and/or possible benefits with the change	To consider a change of treatment

CV, Cardiovascular; HF, heart failure

ing the hospitalization for HF[23], and it provides a positive profile in terms of renal failure, when reducing its risk based on the decrease of the macroalbuminuria. Also, the semaglutide, which seems to reduce especially the risk of stroke24. This did not happen with the weekly lixisenatide or exenatide, thus, it did not seem then a class effect of the GLP-1.

Among the sodium-glucose cotransporter-2 inhibitors (SGLT-2), the EMPAREG trial, carried out with empaglifozin, is the one that has obtained, so far, the strongest results[25]. The empaglifozin reduces 38% of death for cardiovascular cause, 32% of death from any cause and in 35% the hospitalization for HF, which places this anti-diabetic drug in a preferential position with respect to the others in this case. In addition, it reduces the albuminuria, which makes it especially indicated if there is diabetic nephropathy, although it should not be used in cases of moderate or advanced renal failure[28].

Pending publication of the results with other SGLT-2, in cross-sectional studies on population databases, it did seem that the canaglifozin and dapagliflozin could get similar results to empaglifozin[26,29,30], which led to a possible class effect. However, although canaglifozin also seems especially indicated in patients with renal failure[26], it has not obtained such positive results, as empaglifozin, in the reduction of cardiovascular events and, in addition, it carries an increased risk of amputation in the lower limbs.

Summing up, from the studies of cardiovascular safety with not insulin anti-diabetic drugs recently published, in patients with cardiovascular risk or with HF, events and mortality can be reduced with empaglifozin and liraglutide, already on the market, and the sulfonylureas, glitazones, saxagliptin and alogliptin must be avoided.

Then, in the clinical praxis at the emergency department or hospitalization, or both, what guidelines should be followed in diabetic patients with HF or cardiovascular risk?

Based on what has been previously mentioned, in all patients diagnosed with HF or a cardiovascular event, the blood glucose level and the possible history of diabetes should be checked, since the adequacy of their treatment for discharge could reduce short-term adverse events[31]. In all diabetic patients and in those suffering glycemia above 180 mg/dl, without known diabetes, all usual measures for treatment during the hospitalization must be applied: blood glucose monitoring, HbA1c determination, to remove non-insulin anti-diabetic drugs and treatment with a basal-bolus insulin regimen[32] (**Box 1**). Depending on the evolution, a plan must be developed considering the discharge from the emergency department or hospitalization, both, in the patient with hyperglycemia and without known diabetes, in which the need to start an anti-diabetic treatment should be considered at discharge, as in the known diabetic patient, in which the usual treatment must be reconsidered, taking into consideration the HF and cardiovascular risk[33] (**Box 2**).

The development of anti-diabetic drugs has evolved in a way that, in addition to reducing the HbA1c, it can provide other qualities such as a low risk of hypoglycemia, a reduction in weight instead of a gain, or a decrease in cardiovascular events or the risk of HF (**Table 2**)[16-25,34-36].

For This reason, it is necessary to prescribe the anti-diabetic treatment depending on comorbidities and the patient's clinical profile. Thus, for example, in patients in which there is a weight loss, the GLP-1 could be the option; or in order to prevent the progression of diabetic nephropathy, the empaglifozin can be used. In addition, a range of possibilities opens up for the fragile patient where hypoglycemia need to be avoided and in which, perhaps, the diabetes appropriate behavior that insulin needs is very difficult.

After an event of HF or a cardiovascular event, a scheme treatment for the type 2 diabetes is recommended, in which three measures are valued: a) withdrawal of anti-diabetic drugs that may favor HF (pioglitazone, alogliptin, saxagliptin), b) treatment with metformin, if not already followed, and if there are no contraindications to its use, and c) addition, if necessary, of empaglifozin or liraglutide, or both, due to the current evidence of their benefits (**Table 3**).

As for the combinations of the different families of non-insulin anti-diabetic drugs, physiologically, the association of drugs with the same incretin effect, i.e., DPP-4 with GLP-1[33], would not be indicated, but both, metformin and SGLT-2 can be combined with GLP-1 or DPP-4.

If you want to add DPP-4, the sitagliptin is preferred, because it does not favor the HF; while the linagliptin would be the chosen one in the renal failure (waiting for the results of its study of cardiovascular safety).

With very high HbA1c or large insulinopenia with

Table 2. Therapeutic options for the treatment of type 2 diabetes.

Parameter	Insulin	Metformin	SU/GLI	Glitazones	DPP-4	SGLT-2	GLP-1
HbA1c reduction (%)	Variable	1.5-2	1.5-2	1.5	0.6-0.9	0.5-0.7	0.5-1
Hypoglycemia risk	Moderate/ high, according to compound	Low	Moderate/ high Glylicazide	Low	Low	Low	Low
Weight	Gain	Light loss	Gain	Gain	Neutral or Slight loss	Loss	Loss
HF	-	-	-	Rosiglitazone Pioglitazone	Alogliptin Saxagliptin Sitagliptin	Empaglifozin Canaglifozin	Neutral
CV safety and effectiveness	Glargine	Yes	SU Glycazide Repaglinide	Rosiglitazone Pioglitazone	Neutral	Empaglifozin Canaglifozin	Liraglutide Semaglutide Lixisenatide
On CRF	Yes	Up to GFR 30-45 ml/min	Repaglinide up to GFR 45 ml/min	Up to GFR 60 ml/min	Linagliptin Up to GFR 30-45 ml/min	Up to GFR 30-45 ml/min	Up to GFR 30-45 ml/min
Contra-indications	-	GFR <30 ml/min, hypoxemia	Liver failure	Liver failure, HF	-	UTI	Medullary thyroid carcinoma, MEN

CRF, chronic renal failure; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4 inhibitors; GFR, glomerular filtration rate; GLP-1, glucagon like peptide-1 receptor antagonists; HbA1c, glycated hemoglobin; HF, heart failure; MEN, multiple endocrine neoplasia; UTI, urinary tract infection; SGLT-2, sodium-glucose cotransporter-2 inhibitors; SU/GLIN, sulfonylureas/ glinides.
A "traffic light" color code has been used according to the existing evidence:
Black: Neutral effect, non-inferiority
Green: Advantage or superiority
Orange: Inferiority in several aspects or disadvantage
Red: Disadvantage or inferiority

Table 3. Treatment at discharge of type 2 diabetes mellitus after an event of heart failure.

Measure	Description
1st Measure	Withdrawal of anti-diabetic drugs that may favor HF (pioglitazone, alogliptin, saxagliptin)
2nd Measure	Metformin except GFR <30 ml/min or other contraindication
3rd Measure	SGLT-2: Empaglifozin, Canaglifozin. Contraindicated in advanced CRF
	GLP-1: Liraglutide, semaglutide. Particularly suitable if obesity and contraindicated on advanced CRF
Metformin and SGLT-2 can be combined with GLP-1 or DPP-4	
If for the sake of the glycemic monitoring, the DPP-4 is wanted to be added, it is preferable to use sitagliptin, which does not favor the HF or linagliptin in the CRF	
In patients with cardinal symptoms, great insulinopenia or HbA1c >10%, it is recommended to add insulin in the case of not having it previously oriented	
Any non-insulin anti-diabetic drug can be combined with insulin considering the risk of hypoglycemia	

CRF, chronic renal failure; DPP-4, dipeptidyl peptidase-4 inhibitors; GFR, glomerular filtration rate; GLP-1, glucagon like peptide-1 receptor antagonists; HbA1c, glycated hemoglobin; HF, heart failure;SGLT-2, sodium-glucose cotransporter-2 inhibitors;

cardinal symptoms, insulin should be administered, although it can be combined with the anti-diabetic drug that provide these benefits at the level of mortality in patients with heart disease or at high cardiovascular risk. In patients treated with insulin, if one of these anti-diabetic drugs is decided to be used, the risk of hypoglycemia should be considered, and in some cases, even a reduction of the insulin dose may be needed in order to avoid it.

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