dtbn

DRUG AND THERAPEUTICS BULLETIN OF NAVARRE, SPAIN

YEAR 2020
VOL 28, Issue 4
www.dtb.navarra.es
@DTB_Navarre.es

GLUCOSE-LOWERING THERAPY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND HEART FAILURE

OBJECTIVE The approach to patients with type 2 diabetes mellitus (DM2) and heart failure is a challenge in primary care. The purpose of this issue is to review the evidence available on glucose-lowering therapy for patients with heart failure and DM2 and determine the optimal treatment for this subgroup of patients. METHODS A PubMed search was performed including clinical guidelines, systematic reviews, clinical trials and observational studies involving patients with heart failure who were receiving treatment for DM2. The pharmacologic approaches of glycemic treatment in clinical guidelines and cardiovascular outcome trials were reviewed. RESULTS AND CONCLUSIONS It is important to consider the cardiovascular safety and effectiveness in cardiovascular events when an antidiabetic therapy is started. Meformin is the first-line treatment for patients with DM2 and heart failure. Sodium–glucose cotransporter 2 inhibitors (SGLT2i) are safe in the presence of cardiovascular disease and reduce hospital admission for episodes of heart failure. Glucagon-like peptide receptor agonists (arGLP-1) emerge as an alternative to these patients, as they do not increase cardiovascular events or all-cause mortality. Caution should be taken with dipeptidyl peptidase-4 inhibitors (DPP4i) in patients with heart failure, and saxagliptin is contraindicated. There is no conclusive evidence on cardiovascular safety in patients treated with sulfonylureas, glinides and acarbose. Insulin therapy can be considered a late alternative, due to the higher risk for complications in this subgroup of patients. Pioglitazone is contraindicated in patients with heart failure.

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INTRODUCTION

Diabetes mellitus is a frequent comorbidity in patients with heart failure.[1]

Patients with type 2 Diabetes mellitus (DM2) are at a significantly higher risk of developing heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF) or stroke patients with DM2 are at a higher risk of developing cardiovascular events, with a poorer prognosis, and are more likely to require hospitalization. Despite advances in the prevention and treatment of cardiovascular diseases, which starting therapy includes lifestyle modifications, DM2 continues to have a significant impact on cardiovascular disease outcomes.[2]

The evidence available indicates that the risk for macrovascular complications increases with the severity of hyperglycemia.[2]

When antidiabetic therapy is started or maintained in patients with heart failure, the regimen must be tailored to the individual patient. Priority must be given to antidiabetics with a higher cardiovascular safety profile and ability to prevent major cardiovascular events.[2]

In the recent years, clinical guidelines for the management of diabetes have included specific algorithms for patients with heart failure.[3,4]

The purpose of this issue is to review the evidence in the literature about antidiabetic agents, including the level of evidence of recommendations provided in clinical guidelines and determine the most appropriate treatment of patients with DM2 and heart failure.[5]

Clinical guidelines were used as an evidence-based source of information and to describe the current framework for treatment.

Methods

A search was performed on PubMed for clinical guidelines, systematic reviews, clinical trials and observational studies involving patients with heart failure who were receiving treatment for DM2. In relation to the drugs recommended in clinical guidelines, a review was performed of their position in guidelines, studies in patients with concomitant heart failure and cardiovascular outcome trials. With regard to new antidiabetic drugs, information was mostly obtained from cardiovascular outcome trials required by the Food and Drug Administration (FDA).

Glucose-lowering therapy is a challenge in patients with heart failure

One of the most widely studied endpoints in clinical trials is the so-called MACE, a composite endpoint used in research to assess cardiovascular events. Based on the number of events, it is called MACE-3P (includes cardiovascular death, non-fatal infarction and non-fatal stroke) or MACE-4P (when it also includes unstable angina).

THERAPEUTIC GROUPS

Sodium–glucose cotransporter 2 inhibitors (SGLT2i)

Apart from reducing major cardiovascular events in patients with established cardiovascular disease or diabetic kidney disease,[6] the sodium-glucose cotransporter-2 inhibitors (SGLT2i) was the first class of hypoglycemic drugs to demonstrate that they reduce the risk for heart failure in patients with DM2.[2,7]

How did SGLT2i attain such a high positioning?

A number of non-inferiority trials were performed to meet FDA's mid-term cardiovascular safety requirements. The promising results obtained prompted the performance of different clinical trials to assess their potential benefits in patients with heart failure.[2]

The first agent to be proven to reduce cardiovascular mortality and heart failure-related hospitalization was empagliflozin, in the EMPA-REG OUTCOME study. In 2016, DTB Navarre published a comprehensive review of the EMPA-REG OUTCOME trial. In that review, an analysis of some methodological flaws of the study was performed, including the doubtless presence of conflicts of interest in the main publications of the trials, and access of laboratory staff to confidential data, including some modifications to the protocol with a high impact on results, and changes to the statistical plan.[8]

Figure 1. Studies assessing the cardiovascular safety of SGLT2i.

2015	2016	2017		2018	2019	2020
		CANVAS	CANVAS-R			
EMPA-REG OUTCOME		CANVAS PROGRAM			DECLARE-TIMI 58	VERTIS-CV
					CREDENCE	EMPEROR-REDUCED
					DAPA-HF	SOLOIST-WHF

It should be taken into account that 100% of the patients included in the DAPA-HF, EMPEROR-REDUCED and SOLOIST-WHF have a previous history of heart failure. This means that study samples were composed of patients at a higher risk for heart failure-related hospitalization and cardiovascular death, as compared to the samples of other studies.

Some clinical trials such as CANVAS-R and CREDENCE were aimed at assessing kidney safety. These data can be found in the published results of clinical trials and will not be detailed in this issue.

Meta-analysis

A recent meta-analysis reviewed data from EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, CREDENCE and VERTIS-CV, with a total of 46,969 patients. As shown in Table 1, inconsistent percentages of patients with a history of cardiovascular events and chronic kidney disease were obtained in the different trials, whereas the percentage of patients with a diagnosis of heart failure was similar across studies, except for VERTIS-CV, with a higher percentage. In total, 13.8% of the patients included in the meta-analysis had a previous history of heart failure. In the meta-analysis, it is estimated that SGLT2i are associated with a reduction in the composite endpoint MACE-3P HR (95%CI)=0.90 (0.85-0.95) I^2=23.4% and in the endpoint of heart failure-related hospitalization and cardiovascular death HR=0.78 (0.73-0.84) I^2=50.6%. Statistical significance persists when these two endpoints are analyzed separately.[18]

Another previous meta-analysis[19] not including VERTIS-CV data showed the following results: MACE-3P HR=0.88 (0.82-0.94) I^2=0% and heart failure-related hospitalizations HR=0.68 (0.60-0.76) I^2=0%.

Table 1. Main characteristics and profile of the patients included in the cardiovascular outcome trials.

Type of clinical trial	Clinical trial	Patients included	Groups	Age (mean± SD) / % female	n / follow-up time	Duration of diabetes (mean) baseline HbA1c	% HF	% previous CV events	HFH per 1.000 patients (year placebo group)	Annual CV/HFH mortality per 1.000 patients-(year placebo group)	Comments
SAFETY Non-inferiority	EMPA-REG OUTCOME (2015)[16,17]	DM2 CVD GFR≥ 30mL/min/1.73m²	Empagliflozin 10mg Empagliflozin 25 mg Placebo	63.1 (±8.7) 28.5%	7,020 3.1 years	7-10% (7-9% in naïve) (mean: 8.1%)	10.1%[3]	>99%	14.5	30.1 (fatal stroke excluded)	Although the estimated duration was 6-8 years to record a minimum of 681 events, the goal was attained much earlier.
	CANVAS PROGRAM (CANVAS and CANVAS-R) (2017)[11]	DM2 CVD/risk factors GFR> 30mL/min/1.73m² NYHA IV excluded	Canagliflozin 100 mg Canagliflozin 300 mg Placebo	63.3(±8.3) 35.8%	10,142 2.4 years	13.5 years 7-10.5% (mean: 8.2%)	14.40%	65.6%	8.7	20.8	In 71.4% of patients, treatment was intensified with canagliflozin 300 mg.
	DECLARE-TIMI 58 (2019)[12]	DM2 CVD/risk factors NYHA IV excluded	Dapagliflozin 10mg Placebo	63.9(±6.8) 37.4%	17,160 4.2 years	11 years 6.5-11.9% (mean: 8.2%)	10% 3.9% HF-rEF (EF<45%)	40.6%	8.5	14.7	The clinical trial was initially designed with MACE-3P safety as the primary objective. Once the results of the EMPA-REG OUTCOME trial were published, the endpoints "effectiveness for MACE-3P" and CV death+ HF hospitalization were later included as primary objectives.
	VERTIS-CV (2020)[13]	DM2 CVD GFR≥30ml/min/1.73m² NYHA IV excluded GFR≥20mL/min 1.73m²	Ertugliflozin 5mg Ertugliflozin 15mg Placebo	64.4(±8)	8,246 3.5 years	13 years 7-10.5% (mean: 8.2%)	23.7%	100%	11	27	Event-driven trial.
EFFECTIVENESS Superiority	CREDENCE (2019)[14]	DM2 CKD with albuminuria GFR>30mL/min/1.73m² NYHA IV excluded	Canagliflozin 100mg Placebo	63(±9.2) 33.9%	4,401 2.6 years	15.8 years 6.5-12% (mean: 8.3%)	14.80%	50.4%	25.3	45.4	Only the 100 mg dose was administered, although 300mg/day can be administered with GFR>60 mL/min/1.73m².
	DAPA-HF (2019)[15]	With and without DM2 HFrEF (EF<40%) NYHA-II-IV	Dapagliflozin 10mg (reduction to 5mg in some cases) Placebo	66.2 (±11) 23.4%	4,744 1.8 years	42% had DM2+ 3% new-onset de DM2	100%	-	In total: 98.3 patients-year Diabetic: 122.5 Non-diabetic: 79.7	In total:153 Diabetic:190.9 Non-diabetic: 124	Most patients included had NYHA-II (67.7% with dapagliflozin). NYHA IV only 0.8% with dapagliflozin. Patients with decompensated HF in the previous 4 weeks, among others.
	EMPEROR-REDUCED (2020)[20]	With and without DM2 HFall with EF≤40%	Empagliflozin 10mg Placebo	Empagliflozin: 67.2 (±10.8) Placebo: 66.5 (±11.2)	3,730 1.3 years	Diabetes 49.8%	100% 73% FEVI≤30%	-	155	210	Event-driven trial.
	SOLOIST-WHF (2020)[21]	DM2 GFR≥30ml/min/1.73m²	Sotagliflozin 200 mg (o 400mg) Placebo	Mean: 70 años 33.7%	1,222 9.2 months	Median HbA1c: 7.1%	100%	-	-	-	Specific trial in patients with DM2 with recent heart failure-related hospitalization. The trial was terminated early and the primary objective was modified due to lack of funding.

CKD Chronic kidney disease. **CVD** Cardiovascular disease. **DM2** Type 2 Diabetes Mellitus. **EF** Ejection fraction. **GFR** Glomerular filtrate rate. **HbA1c** Glycated hemoglobin. **HF** Heart failure. **HF-rEFr** Heart failure with reduced ejection fraction. **HFH** Heart failure-related hospitalization. **MACE-3P** Composite endpoint of cardiovascular death, non-fatal infarction and non-fatal stroke. **SD** Standard deviation.

Table 2. SGLT2i clinical trial results.

	MACE-3P HR (IC95%)	CV death+HF hospitalization HR (95%CI)	HF hospitalization HR (95%CI)	CV death HR (95%CI)	All-cause mortality HR (95%CI)	Other results of interest HR (95%CI)	Comments
EMPAREG-OUTCOME[10]	0.86 (0.74-0.99)	0.66(0.55-0.79) (Fatal stroke excluded)	0.65 (0.50-0.85)	0.62 (0.49-0.77)	0.68 (0.57-0.82)	MACE+hospitalization for unstable angina: 0.89 (0.78-1.01)	The benefits of the primary endpoint result from a reduction in cardiovascular death. The two doses were combined to reach statistical significance in the secondary analysis of superiority, silent MI was excluded from the primary endpoint, and deaths of unknown causes were considered CV death. With 692 events, statistical significance in superiority was not attained, so events were increased to 772. No statistically significant differences in stroke or non-fatal infarction (1 clinical trial, n=36282).
CANVAS PROGRAM[11]	0.86 (0.75-0.97)	0.78 (0.67-0.91)	0.67 (0.52-0.87)	0.87 (0.72-1.06)	0.87 (0.74-1.01)	HF hospitalization of fatal HF: 0.70 (0.55-0.89)	None of the composite primary endpoint reached statistical significance separately. Statistical significance was not attained separately in the composite endpoint in CANVAS and CANVAS-R.
DECLARE-TIMI 58 (2019)[12]	0.93 (0.84-1.03)	0.83 (0.73-0.95)	0.73 (0.61-0.88)	0.98 (0.82-1.17)	0.93 (0.82-1.04)		The main benefit is the reduction in the rate of HF hospitalizations.
VERTIS-CV[13]	0.97 (0.85–1.11)	0.88 (0.75–1.03)	0.70 (0.54-0.90)	0.92 (0.77–1.11)	0.93 (0.80-1.08)		Primary endpoint: non-inferiority; secondary endpoint: superiority. Hierarchical test, second primary endpoint not statistically significant (CV death+HF hospitalization).
CREDENCE (2019)[14]	0.80 (0.67-0.95)	0.69 (0.57-0.83)	0.61 (0.47-0.80)	0.83 (0.68-1.02)	0.78 (0.61-1.00)	CV death, MI, stroke, HF hospitalization or unstable angina 0.74 (0.63-0.86)	The clinical trial was finished early because the criteria of effectiveness established for termination of the study were met early.
DAPA-HF (2019)[15]		0.75 (0.65-0.85)	0.70 (0.59-0.83)	0.82 (0.69-0.98)	0.83 (0.71-0.97)	HF exacerbation + CV death: 0.74 (0.65-0.85)	In total, 67.7% of patients in the dapagliflozin group and 67.4% in the placebo group had NYHA-II, and only 0.8 and 1%, respectively, had NYHA-IV. Subgroup analysis was only performed for patients with DM2 included in the primary endpoint, with a HR (95%CI)=0.75(0.63-0.90) for diabetic patients.
WORSENING-REDUCTION[16]		0.75 (0.65-0.86)	0.70 (0.58-0.85)	0.92 (0.75-1.12)	0.92 (0.77-1.10)	To first HF hospitalization 0.69 (0.59-0.81)	Data for all patients (with and without DM2). Subgroup analysis was only performed for patients with DM2 included in the primary endpoint, with a HR (95%CI)=0.72(0.60-0.87) for diabetic patients.
SOLOIST-WHF (2020)[17]		0.67 (0.52-0.85)*	0.64 (0.49-0.83)*	0.84 (0.58-1.22)			*HF hospitalization also includes admissions to the emergency department for HF that did not require hospitalization.

Primary endpoint of the study. Secondary endpoint of the study. **MACE-3P** Composite endpoint of cardiovascular death, non-fatal infarction and non-fatal stroke. **DM2** Diabetes Mellitus 2. **CV** Cardiovascular. **MI** Myocardial infarction. **HF** Heart failure.

Does reduction of heart failure-related events occur also in patients with a history of heart failure?

The results of the clinical trials DAPA-HF[15] and EMPEROR-Reduced[16] are the ones that best demonstrate the benefits of SGLT2i in patients with a history of heart failure.

In contrast, no interaction was observed in the remainder of clinical trials and the two meta-analyses reviewed, when previous history of heart failure (yes/no) was analyzed as a different subgroup of patients. Therefore, it seems that the benefit is obtained for the two groups of patients.

To determine whether statistically significance is attained according to the presence or not of heart failure, we used the subgroup-effect calculator of Joaquin Primo.[20]

Of note, in the VERTIS-CV study, although no interaction was observed in the subgroup-analysis, considering that the primary endpoint was studied as non-inferiority by accepting the upper limit of 95%CI of HR was 1.3 in the group of patients with heart failure, non-inferiority of ertugliflozin with respect to placebo would not be met.[13]

When are they more beneficial, in heart failure with preserved ejection fraction (HFpEF) or in heart failure with reduced ejection fraction (HFrEF)?

In the DECLARE-TIMI58 clinical trial, ejection fraction was measured prior to randomization. When patients with HFpEF and HFrEF were analyzed as pre-specified subgroups, with HFrEF defined as left ventricular ejection fraction (LVEF)<45%, interaction was observed. Thus, a higher benefit was documented for patients with HFrEF, in terms of cardiovascular death, all-cause mortality and composite endpoint of cardiovascular death and heart failure-related hospitalization.[22]

In contrast, in the CANVAS program, ejection fraction was identified as preserved or reduced (LVEF<50%) at occurrence of heart failure, and no significant differences were observed between the two groups.[23]

There were no differences in the EMPAREG-OUTCOME trial. In VERTIS-CV and EMPEROR-Reduced, only patients with an ejection fraction equal to or less than 40% were included, and in the DAPA-HF study, all patients had an ejection fraction less than 40%. There are ongoing studies such as EMPEROR-Preserved and DELIVER, involving patients with preserved ejection fraction.

Table 3. Results of the clinical trials by subgroups of patients (history of heart failure).

	Endpoint	With HF HR (95%CI)	Without HF HR (95%CI)	Significant difference
CANVAS PROGRAM[11]	n	1,461	8,681	
	MACE-3P	0.80 (0.61-1.05)	0.87 (0.76-1.01)	No
DECLARE-TIMI 58[12]	n	1,724	15,436	
	MACE-3P	1.01 (0.81-1.27)	0.92 (0.82-1.02)	No
	CV death+ HFH	0.79(0.63-0.99)	0.84 (0.72-0.99)	No
EMPAREG-OUTCOME[21]	n	709	6,311	
	CV death or HFH	0.72 (0.50-1.04)	0.63 (0.51-0.78)	No
	HFH	0.75 (0.48-1.19)	0.59 (0.43-0.82)	No
	CV death	0.71 (0.43-1.16)	0.60 (0.47-0.77)	No
VERTIS-CV[13]	n	1,958	6,288	
	MACE -3P	1.05 (0.82-1.35)	0.95 (0.81-1.11)	No
	CV death+HFH	0.85 (0.66-1.09)	0.91 (0.75-1.11)	No

Table 4. Meta-analysis results by subgroups of patients (history of heart failure).

	HF history	MACE -3P HR (95%CI)	HFH+CV death HR (95%CI)
McGuire et al[18]	Yes	0.95 (0.83-1.08)	0.75 (0.66-0.86)
	No	0.90 (0.84-0.96)	0.82 (0.74-0.90)
	Significant difference?	No	No
Arnott et al[19]	Yes	0.92 (0.79-1.08)	0.73 (0.63-0.84)
	No	0.88 (0.81-0.95)	0.76 (0.69-0.84)
	Significant difference?	No	No

HF Heart failure.
CV Cardiovascular.
HFH Heart failure-related hospitalization.
MACE-3P Composite endpoint of cardiovascular death, non-fatal infarction and non-fatal stroke.

Are these data applicable to all NYHA grades?

In the DAPA-HF study, it was observed that the difference between dapagliflozine and placebo in the primary composite endpoint (heart failure exacerbation and cardiovascular death) was statistically significant for NYHA-II HR=0.63 (0.52-0.75) but not for NYHA III-IV HR=0.90 (0.74-1.09). It should be taken into account that 67.7% of patients in the dapagliflozin group and 67.4% in the placebo group had NYHA-II and only 0.8 and 1% had NYHA-IV, respectively.[15]

What are the most remarkable aspects of SGLT2i safety?

It should be noted that SGLT2i are associated with a higher risk of intravascular volume depletion. This is especially relevant for patients with heart failure, as they frequently use diuretic therapy. Monitoring of potential diabetic ketoacidosis[24] and infections should be performed. There are post-commercialization reports of necrotizing fasciitis of the perineum (Fournier's gangrene) which are very rare by potentially fatal.[25]

By March 1st, 2021, eight, six and four cases had been recorded in the Spanish Pharmacovigilance Database (FEDRA), of Fournier's gangrene associated with

canagliflozin, dapagliflozin, and empagliflozin, respectively. Of note, no cases have been reported of Fournier's gangrene secondary to the use of ertugliflozin.

The FDA recently (08/2020) decided to remove Boxed Warning about the risk of amputation for canagliflozin, as they concluded that the risk of amputation is lower than previously described, particularly when appropriately monitored.[26] Nevertheless, healthcare professionals should provide information to patients about routine preventative foot care and monitoring.[25] In Europe, the only active substance that continues to require additional monitoring is ertugliflozin.

SGLT2i are safe in cardiovascular terms and reduce the risk of heart failure-related hospitalization

What about patients with concomitant chronic kidney disease?

In most clinical trials, patients with estimated glomerular filtration rates (GFR) < 30 mL/min/1.73 m^2 were excluded. Starting therapy with creatinine clearance < 60 mL/min/1.73 m^2 is not recommended in the labels of empagliflozin, dapagliflozin and ertugliflozin. Once initiated, treatment should be discontinued if GFR decreases below 45 mL/min/1.73 m^2 due to a reduced glucose-lowering effect in these cases, and the risk of volume depletion. In the case of canagliflozin, it is recommended to adjust the dose in mild-moderate renal impairment and not to start treatment with GFR <30 mL/min/1.73 m^2.

The results of the latest meta-analysis[18] do not confirm their beneficial effects in patients with renal impairment.

Conclusions

The main benefit of SGLT2i in diabetic patients with heart failure is that it reduces heart failure-related hospitalization rates. However, in the remainder of endpoints, statistical significance was only reached in the analysis of composite endpoints.

In most clinical trials, patients with advanced heart failure (NYHA IV), who generally had chronic kidney disease, were excluded.

The main benefit obtained from this therapy is in terms of heart failure-related hospitalization.

Weight loss

Adverse effects:

Severe infections, amputations, diabetic ketoacidosis.

Volume-interaction depletion with loop diuretics.

Table 5. Results by patient subgroup according to the glomerular filtration rates in the most recent meta-analysis.[18]

	MACE-3P HR (95%CI)	**HFH+CV death** HR (95%CI)
GFR≥90mL/min/1,73m^2	0.94 (0.86-1.05)	1.02 (0.84-1.24)
GFR=60-89 mL/min/1,73m^2	0.92 (0.85-1.00)	0.82 (0.71-0.95)
GFR<60mL/min/1,73m^2	0.89 (0.78-1.01)	0.77 (0.62-0.95)

GFR Glomerular filtration rate.
CV Cardiovascular.
HFH Heart failure-related hospitalization.
MACE-3P Composite endpoint of cardiovascular death, non-fatal infarction and non-fatal stroke.

Metformin

What is its position in guidelines?

In patients with DM2 and stable heart failure, metformin is used to reduce glycemia if the estimated glomerular filtration rate is > 30 mL/min/1.73 m^2, although it should not be administered to unstable patients or hospitalized patients with heart failure. Grade of evidence B[27] (level of evidence based on cohort studies, prospective cohort studies, meta-analyses of cohort and case-control studies).

Metformin is the most commonly used antidiabetic agent and continues being the first-line treatment for DM2. It can be used in monotherapy or in combination therapy with other antidiabetics. However, a recent Cochrane's revision concluded that there is not conclusive evidence supporting that metformin alone, as compared with any intervention, placebo, diet, or other antidiabetic agents (sulfonylureas in most cases) exerts more benefits in term of all-cause mortality, severe adverse events, health-related quality of life or macrovascular or microvascular complications. Severe hypoglycemia was less frequent in patients treated with metformin compared to sulfonylureas.[28]

In patients with heart failure, metformin was contraindicated mainly due to the associated risk of lactic acidosis.[7]

Is metformin associated with a higher risk for lactic acidosis?

The most severe adverse effect, although rare, is lactic acidosis, characterized by dyspnea, abdominal pain, cramps, asthenia and hypothermia, followed by coma.[29]

The incidence of lactic acidosis in patients treated with metformin changes across studies from three to 10 in 100,000 patients/year at 10 years.[30] Nevertheless, a Cochrane review concluded that there is no evidence that metformin is associated with a higher risk for lactic acidosis or with higher levels of lactate, as compared to other glucose-lowering therapies.[31] Patients with cardiovascular diseases were excluded in this review.

This adverse effect is more frequent in patients with kidney disease, cardiorespiratory disease or septicemia.[32,33]

What is the evidence available on heart failure?

Subsequent observational studies involving patients with DM2 and heart failure showed that patients treated with metformin had better outcomes than those treated with other antidiabetic agents.[7,34–36]

A meta-analysis of nine cohort studies in 34,000 patients with heart failure and DM2 analyzed the morbidity and mortality of patients treated with metformin, as compared to controls (most of the patients in this group were treated with sulfonylureas).[34] Metformin was found to be associated with lower mortality rates in 23% vs. 37% [adjusted relative risk (RR)=0.80 (0.74–0.87)]. This agent was also associated with a 35% reduction of hospitalizations for any cause vs. 64% [adjusted RR=0.93 (0.89–0.98)] in patients treated with metformin, as compared to controls. Metformin exerts cardioprotective effects but its mechanism is unknown.[2] No differences were observed in terms of mortality or ejection fraction.[34]

Metformin is the first-line treatment

A systematic review published in 2017 based on 17 observational studies assessing the use of metformin vs. sulfonylureas (in most cases) in patients with DM2 and chronic moderate-severe kidney disease, congestive heart failure or chronic liver disease with liver failure, demonstrated that the use of metformin was associated with a reduction of all-cause mortality in patients with congestive heart failure HR=0.78 (0.71-0.87). The use of metformin did not increase cardiovascular disease and was associated with a reduction of readmission of patients with heart failure [HR= 0.87 (0.78-0.97)].[37]

According to these findings, the FDA removed the restriction on the use of metformine use from the label in 2006.[38] In Spain, in accordance with the recommendations included in the label, the use of metformin is contraindicated in acute metabolic acidosis (lactic acidosis, diabetic ketoacidosis), diabetic precoma, severe kidney failure and diseases causing tissue hypoxia, especially acute disease or exacerbation of a chronic disease such as heart or respiratory failure, recent myocardial infarction, and shock.[33]

Conclusions

Meformin is the first-line treatment for patients with DM2 and heart failure.

It can be used in patients with stable heart failure.

Metformin should be stopped in episodes of heart failure exacerbation, unstable heart failure, and metabolic alterations.

Kidney function have to be monitored.

Avoid in case of glomerular filtration rate <30 mL/min/1.73m^2.

Thiazolidinediones or glitazones

What is its position in guidelines?

In Spain, pioglitazone is the only thiazolidinedione available in the market due to withdrawal of rosiglitazone in 2010, as it was found to be associated with increased risk for acute myocardial infarction.[39]

In patients with DM2 and known heart failure, do not use pioglitazone, as it is associated with a higher risk for heart failure and profile of adverse effects. It can be used at low doses, as the last therapeutic option in patients with DM2 and other cardiovascular diseases.[27]

What is the evidence available?

The PROactive trial compared pioglitazone vs. placebo in patients with DM2 and previous cardiovascular disease, excluding heart failure. No significant differences were found concerning the primary composite endpoint (all-cause death, non-fatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle).[40] However, the authors conclude that pioglitazone reduces macrovascular complications, based on the significant differences observed in a secondary composite endpoint (death, non-fatal infarction, and stroke) HR=0.84 (0.72-0.98) that had not been described in the study design.[41] In relation to adverse events, there was a significant increase in the incidence of heart failure, edema and weight gain in the group treated with pioglitazone.

Other clinical trials have been conducted in an attempt to shed light on the association of pioglitazone and cardiovascular risk. The IRIS and TOSCA.IT trials are examples.

The IRIS trial[42] compared pioglitazone vs. placebo in patients with insulin resistance but without DM2 who had an ischemic stroke or a recent transient ischemic attack. The study demonstrated that pioglitazone reduced the risk for the cardiovascular events included in the primary composite endpoint (stroke, acute myocardial infarction, heart failure-related hospitalization) HR=0.78 (0.65-0.93) as compared to placebo. In contrast, no differences were documented in the risk for heart failure or heart failure-related hospitalization.

The TOSCA.IT trial[43] compared pioglitazone vs. sulfonylureas in patients with DM2 treated with metformin. In this study, only 11% of patients had a previous cardiovascular event, excluding heart failure. This study was stopped early because the analysis at 57.3 months did not show any significant differences in the primary composite endpoint (all-cause death, non-fatal myocardial infarction, non-fatal stroke or urgent coronary revascularization). No significant differences were found either in the risk for heart failure.

Conclusions

Differences in the baseline characteristics of patients, study designs, primary endpoints, and the duration of the trials hinder that conclusive evidence is obtained from comparative analysis.

No specific studies have been published on the use of pioglitazone in patients with DM2 and heart failure.

Pioglitazone is contraindicated in patients with DM2 and heart failure of all NYHA grades.

Contraindicated in heart failure. Contraindicated in bladder cancer, uninvestigated macroscopic hematuria, hepatic impairment and diabetic ketoacidosis.

Important adverse effects: edemas, weight gain, fractures.

Dipeptidil peptidase-4 inhibitors (DPP4i)

What is its position in guidelines?

Currently, DPP4i are positioned as the third-line therapy for DM2 in patients with established atherosclerotic cardiovascular disease or heart failure due to there are other therapies with better risk/benefit balance for these types of patients. Therefore, DPP4i is only used after failure of previous recommended therapies (SGLT2i and arGLP-1), if intensification of antidiabetic therapy is needed, or patients do not tolerate these treatments anymore.[27,44]

What is the evidence available?

Five cardiovascular outcome trials have been conducted to compare DPP4i vs. placebo in terms of incidence of major cardiovascular events in patients with DM2 and a high cardiovascular risk, as regulatory agencies require. In four of these trials, the primary endpoint is the MACE composite endpoint, which includes cardiovascular death, non-fatal infarction and non-fatal stroke, but does not include the rate of heart failure-related hospitalization.

Although the results of the SAVOR-TIMI 35[45], EXAMINE[46], TECOS[47] and CARMELINA[48] trials were consistent in relation to the primary endpoint MACE, the rate of heart failure-related hospitalization were different among the DPP4i. Post-hoc cardiovascular outcome trials were conducted to determine whether DPP4i increased the

Table 6. DPP4i cardiovascular outcome trials: patient characteristics and results of primary outcomes.

Drug Trial (year)	Comparator	Population	N	Patients with history of CVD (%)	Follow-up (mean or median)	Primary endpoint	Impact on the primary endpoint HR (95%CI)	Impact on HF hospitalization HR (95%CI)	Comments
Saxagliptin SAVOR-TIMI53 (2013)	Placebo	CVD or high risk of CV	16,492	13	2.1 years	MACE-3P	Non inferior 1.00 (0.89-1.12)	↑ risk 1.27 (1.07-1.51)	↑ risk of HF hospitalization in patients with HF, CKD and elevated levels of PNB
Alogliptin EXAMINE (2013)	Placebo	Recent acute coronary syndrome	5,380	28	1.5 years	MACE-3P	Non inferior 0.96 (*-1.16)	No differences 1.07 (0.79-1.46)	
Sitagliptin TECOS (2015)	Placebo	History of cerebrovascular disease	14,724	18	3.0 years	MACE-4P	Non inferior 0.98 (0.89-1.08)	No differences 1.00 (0.83-1.20)	
Linagliptin CARMELINA (2018)	Placebo	Previous CV events and different CKD grades	6,979	27	2.2 years	MACE-3P	Non inferior 1.02 (0.89-1.17)	No differences 0.90 (0.74-1.08)	
Linagliptin CAROLINE (2019)	Glimepiride	Cerebrovascular disease or high risk of CV	6,033	42	6.3 years	MACE-3P	Non inferior 0.98 (0.84-1.14)	No differences 1.21 (0.92-1.59)	
Vildagliptin VIVIDD (2012)	Placebo	HFrEF	254	-	1.0 years	Changes in LVEF	Non inferior 0.62 (2.21-3.44)	Not assessable	

HF Heart failure. **CVD** Cardiovascular disease. **CV** Cardiovascular. **CKD** Chronic kidney disease. **HFrEF** Heart failure with reduced ejection fraction. **LVEF** Left ventricular ejection fraction. **MACE-3P** Composite endpoint of cardiovascular death, non-fatal infarction and non-fatal stroke. **MACE-4P** Composite endpoint of cardiovascular death, non-fatal infarction, non-fatal stroke and unstable angina. **MI** Myocardial infarction. (*) Not specified in the study. **PNB** B-type natriuretic peptide.

risk of heart failure-related hospitalization in general or exhibit within-class differences, but no conclusive results were obtained.

In the SAVOR-TIMI 53 trial with saxagliptin, a statistically significant increase in the incidence of heart failure-related hospitalization was observed in respect to placebo (3.5% vs. 2.8%) HR=1.27(1.07-1.51).[45] In a post-hoc analysis of this trial, it was documented that this risk of heart failure-related hospitalization was highest among patients with previous heart failure, chronic kidney disease (estimated glomerular filtration rate ≤60 mL/min/1.73m^2), or elevated levels of B-type natriuretic peptide.[49]

The EXAMINE trial with alogliptin, TECOS with sitagliptin and CARMELINA with linagliptin did not show significant differences in the rate of heart failure-related hospitalization as compared to placebo.

In the VIVIDD trial[50], vildagliptin had no significant effect on left ventricular ejection fraction (LVEF) in patients with heart failure and reduced ejection fraction with respect to placebo. The rate of heart failure-related hospitalization was not directly evaluated, and conclusions about the secondary endpoints could not be drawn due to the low statistical power and short duration of the study.

The cardiovascular outcome trial CAROLINE[51] demonstrated no difference in the MACE primary endpoint and no increase in the rate of heart failure-related hospitalization between linagliptin and glimepiride.

Conclusion

The safety of DPP4i has been demonstrated, since they do not increase the risk of major cardiovascular events, although they do not provide cardiovascular benefit.

The systematic review of the literature demonstrates a slight increase in absolute and relative terms in the risk of heart failure-related hospitalization in patients with heart failure who receive these drugs.[52] However, these results may be associated with the higher risk of hospitalization for heart failure linked to the use of saxagliptin. With the evidence available, it cannot be determined whether it is a class effect or not of DPP4i.[53]

Further studies are needed to identify the cause of inconsistencies in the estimated risk of heart failure-related hospitalization associated with DPP4i. The currently ongoing MEASURE-HF trial is evaluating the effects of saxagliptin, sitagliptin, and placebo in patients with DM2 and heart failure, which includes a detailed assessment of left ventricular size and function using imaging techniques.

According to these data, there is no conclusive evidence that DPP4i can be recommended for patients with heart failure. Indeed, evidence shows more risk than benefit, and these drugs should be used in these patients with caution.

The European Society of Cardiology in a position paper[54] also recommends that these drugs should be used with caution in patients with heart failure and not use saxaglipitin.

Not increase the risk of major cardiovascular events vs. placebo.

Saxagliptin increase the risk of heart failure-related hospitalization.

There is not enough evidence to determine whether it is an effect class or not.

Table 7. Effects of DPP4i on major cardiovascular events assessed in cardiovascular outcome trials.

	MACE-3P	CV death	MI	STROKE	HFH
DPP4i	↔	↔	↔	↔	↑ **RISK** Saxagliptin
Saxagliptin Alogliptin Sitagliptin Linagliptin Vildagliptin	↔	↔	↔	↔	↔ Alogliptin Sitagliptin Linagliptin Vildagliptin

MACE-3P Composite endpoint of cardiovascular death, non-fatal infarction and non-fatal stroke.
CV Cardiovascular.
MI Myocardial infarction.
HFH Heart failure-related hospitalization.

Sulfonylureas (glibenclamide, glipizide, and glimepiride)

Sulfonylureas can cause hypoglycemia (prevailingly nocturnal) and weight gain.

What is its position in guidelines?

Sulfonylureas are considered a third-choice therapy in the presence of high cardiovascular risk, chronic kidney failure or heart failure. More specifically, glimepiride is recommended due to its associated lower risk of hypoglycemia and a similar cardiovascular safety profile as DPP4i drugs.[23] Drugs sulfonylureas are also the last option if a patient is at risk of hypoglycemia or they want to lose weight. Sulfonylureas are only considered when glycosylated hemoglobin (HbAc1) exceeds the target (1.5 to 2% times higher), and there is no risk of cardiovascular risk, chronic kidney failure or heart failure.[1]

Severe hypoglycemia can cause arrhythmias, ischemic events or cerebrovascular accidents, and it is associated with increased mortality rates.[55] The risk of sulfonylurea-induced hypoglycemia increases as kidney function worsens,[56] and they are not recommended in patients with GFR<30 ml/min/1.73 m^2.

What is the evidence available?

In 2016, a systematic review analyzed the association between sulfonylurea-based treatments and all-cause and cardiovascular mortality. This study included clinical trials of at least 52 weeks duration where sulfonylureas were compared to placebo or an active comparator. The study concluded that sulfonylureas were not associated with all-cause mortality or cardiovascular mortality. An association with either an increased risk of acute myocardial infarction or stroke was not found.[57]

In 2017, a systematic review of 23 randomized clinical trials with different antidiabetics vs. placebo in patients with DM2 revealed contradictory results for the role of sulfonylureas in improving cardiovascular outcomes.[58]

In 2020, a systematic review of 232 meta-analyses was conducted to assess 10 groups of different antidiabetics. Six drugs were associated with an increased risk of cardiovascular disease; glimepiride was associated, with a higher risk of acute myocardial infarction RR= 2.01 (1.02-3.98).[59]

Placebo-controlled trials

In a trial, 11,140 patients were randomized to receive either intensive glycemic control with glycoside if HbA1c ≤ 6.5% vs. conservative glycemic control with diet and a follow-up of five years. No significant differences were observed in the MACE-3P endpoint, albeit there was a significant decrease in the risk for microvascular complications, especially of kidney disease.[55]

Another trial studied 3,867 patients who were randomized to either intensive glycemic control with a sulfonylurea (chlorpropamide, glibenclamide, or glipizide) or standard glycemic control with diet during a 10-year follow-up. The study did not reveal any significant differences in MACE-4P endpoint. In contrast, the risk of microvascular complications decreased by 25%.[60]

Comparative studies with metformin

Observational studies suggest that treatment with sulfonylureas is associated with an increased risk of heart failure as compared to metformin.[61,62,63,29] There is evidence of an increased risk of death of patients treated with sulfonylureas as compared to patients who received metformin.[64,36,29]

Comparative studies with DPP4i

A retrospective cohort study involving 127,555 patients revealed that DPP4i drugs reduce the risk of heart failure-related hospitalization, as compared to sulfonylureas HR=0.78 (0.62-0.97).[65]

In a cohort study, cardiovascular effects were assessed in 10,089 diabetic patients treated with DPP4i drugs or sulfonylureas as add-on therapy to metformin. Patients treated with DPP4i drugs exhibited a lower risk of all-cause mortality HR=0.63 (0.55-0.72) and a lower risk of major cardiovascular effects HR=0.68 (0.55-0.83) as compared to patients treated with sulfonylureas and metformin.[66]

However, another retrospective study of 2017 showed no differences in terms of safety between these two treatment groups. The authors concluded that the use of DPP4i drugs does not increase the risk of heart failure, as compared to sulfonylureas.[67]

In 2019, the CAROLINE trial assessed the cardiovascular safety of linagliptin vs. glimepiride. The study did not find significant differences in the primary endpoint MACE-3P or an increase rate of heart failure-related hospitalization.[51]

Conclusion

To date, the risk of cardiovascular disease in patients treated with sulfonylureas has not been adequately assessed. Data available on the use of sulfonylureas in patients with DM2 and heart failure are limited, and cannot be generalized to all drugs included in this group.

None of the three labels for the sulfonylureas available in the Spanish market includes a warning about their use in patients with cardiovascular disease.

There is no evidence demonstrating an increased cardiovascular risk in patients with DM2.

The risk of hypoglycemia is the limiting factor for the use of this group of drugs.

Glinides or meglitinides (repaglinide and nateglinide)

These drugs are similar to sulfonylureas as they share a similar mechanism of action. These agents allow a better control of postprandial glycemia and are useful for patients with regular meal timings due to their short half-life and rapid action.

The risk for hypoglycemia is similar to that of sulfonylureas. However, for patients with an advanced age, treatment switch from sulfonylureas to repaglinide has been observed to have positive effects on reducing the fluctuations of blood glucose levels.[40]

Repaglinide can be used at all stages of kidney failure. In contrast, it cannot be used in the presence of severe liver disease.

What is its position in guidelines?

Guidelines do not include this pharmaceutical group in the algorithm for the treatment of DM2 in patients with cardiovascular disease.

What is the evidence available?

The goal of the NAVIGATOR trial was to determine whether the combination of nateglinide and valsartan could prevent or delay the development of DM2 and cardiovascular complications in patients with glucose intolerance and either established cardiovascular disease or cardiovascular risk factors. No evidence was obtained about the effectiveness of nateglinide in reducing the risk of mixed cardiovascular events or heart failure-related hospitalization rates.[68]

In 2015, the results of a cohort study involving 36,118 patients with DM2 were published. This study assessed cardiovascular risks related to the use of second-line metformin therapy. No differences were observed in the risk of any cardiovascular event between the different combined treatment groups. However the risk of acute myocardial infarction was significantly lower in the group of glinides HR=0.39 (0.20-0.75) and alpha glucosidase inhibitors, as compared to the other groups HR=0.54 (0.31-0.95).[69]

Another 8-year cohort study published in 2019 assessed all-cause mortality and the combined risk of acute myocardial infarction and stroke as primary endpoint in a group of patients treated with different sulfonylureas vs. another treated with repaglinide. Glimepiride was the drug that showed the best outcomes, with a lower risk of mortality and cardiovascular risk, as compared to other drugs. Using the glimepiride group as a reference, the HRs of the two endpoints for repaglinide were HR=1.88 (1.45-2.43) and HR=1.69 (1.25-2.59), respectively.[70]

Conclusion

There is no evidence available about the effects of glinides on cardiovascular outcomes in patients with DM2 or heart failure.

There is no evidence demonstrating an increased cardiovascular risk in patients with DM2.

It can be used in patients with kidney failure.

The risk of hypoglycemia is the limiting factor for the use of this group of drugs.

Alpha-glucosidase inhibitors (acarbose)

Acarbose causes weight loss when administered either alone or in combination with metformin, sulfonylureas or insulin.[71] The advantages of acarbose include weight control, an absence of hypoglycemia risk, and a better control of postprandial glycemia.[72]

What is its position in guidelines?

Guidelines do not include this pharmaceutical group in the algorithm for the treatment of DM2 in patients with cardiovascular disease.

What is the evidence available?

Cochrane's review of 2018 includes eight randomized, placebo-controlled, clinical trials assessing the effectiveness of acarbose vs. placebo in preventing DM2. Acarbose was not found to have any effects on the risk of all-cause mortality, death from heart disease, severe side effects, stroke or heart failure. Treatment with acarbose did reduce the risk of heart attack, as compared to placebo RR=0.10 (0.02-0.53).[73] However, the quality of evidence was considered to be low, since the patients included in these studies did not have DM2 or heart failure.

A meta-analysis of seven randomized controlled trials in 2,180 patients diagnosed with DM2 revealed a significant 64% decrease in the risk for acute myocardial infarction HR=0.36 (0.16-0.80) and a 35% reduction in the risk for any cardiovascular event HR= 0.65 (0.48-0.88) of acarbose vs. placebo.[74]

The ACE trial was a randomized, double-blind, placebo-controlled study in 6522 patients with known heart disease and intolerance to glucose. The follow-up mean was five years. The authors assessed the outcomes associated with acarbose in patients with diabetes or heart disease and concluded that this agent did not reduce the risk of cardiovascular events.[75]

Conclusion

There is no solid evidence that alpha glucosidase inhibitors increase or reduce cardiovascular risk in diabetic patients.

Alpha-glucosidase inhibitors are not considered as an option for patients with DM2, since they act mainly on postprandial glycemia.

Weight loss.

They act mainly on postprandial glycemia.

Adverse gastrointestinal effects.

Glucagon-like peptide receptor agonists (arGLP-1)

Some considerations

There are five glucagon-like peptide receptor agonists (arGLP-1) authorized in Spain: dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide.

Oral semaglutide was not available in Spain at the moment of this review.

Apart from their glucose-lowering effect, these drugs reduce weight (2-4 Kg) and may improve lipid profile. Their adverse effects include gastrointestinal events (nauseas, vomits, diarrhea) and seem to increase heart rate.[7]

They are administered subcutaneously and can be used alone or in combination with other antidiabetic drugs and insulin. However, in Spain, these drugs are only financed as combination therapy with other antidiabetics for DM2 in obese patients with a body mass index (BMI) ≥ 30 Kg/m^2.[7]

What is its position in guidelines?

In patients with DM2 and cardiovascular disease, arGLP-1 have demonstrated to be effective in reducing the risk of cardiovascular events. Therefore, these analogs are recommended for combined treatment, according to 2020 ADA guidelines[27] (Grade of evidence: A (recommendations based on well-designed randomized

Table 8. Pivotal trials about GLP-1 receptor agonists.

Clinical trial	Drug	Duration (years)	Sex (% women)/Age M(SD)	BMI (Kg/m²)	% HF	% Known CV disease	Primary endpoint	MACE HR (95%CI)	Impact on hospitalization for HF HR (95%CI)	All-cause mortality HR (95%CI)	CV death HR (95%CI)
ELIXA (2015) (n=6,068)	Lixisenatide 20 mcg/day sc	2.1	31% 60 (10)	30.1 (5.6)	22	100	MACE-4P	1.02 (0.89-1.17)	0.96 (0.75-1.23)	0.94 (0.78-1.13)	0.98 (0.78-1.22)
LEADER (2016) (n=9,340)	Liraglutid 1.8 mg/day sc	3.8	36% 64 (7)	32.5 (6.3)	18	81	MACE-3P	0.87 (0.78-0.97)	0.87 (0.73-1.05)	0.85 (0.74-0.97)	0.78 (0.66-0.93)
SUSTAIN-6 (2017) (n=3,297)	Semaglutide 0.5 mg/day or 1 mg/day sc	2.1	39% 65 (7)	32.8 (6.2)	24	83	MACE-3P	0.84 (0.58-0.95)	1.11 (0.77-1.61)	1.05 (0.74-1.50)	0.98 (0.65-1.48)
EXSCEL (2017) (n=14,752)	Exenatide 2 mg/week sc	3.2	38% 62 (9)	32.7 (6.4)	16	73	MACE-3P	0.91 (0.83-1.00)	0.94 (0.78-1.13)	0.86 (0.77-0.97)	0.88 (0.76-1.02)
HARMONY* (2018) (n=3,183)	Albiglutide 30 or 50 mg/week sc	1.6	31% 64 (7)	32.3 (5.9)	20	100	MACE-3P	0.78 (0.68-0.90)	0.85 (0.70-1.04)	0.95 (0.79-1.16)	0.93 (0.73-1.19)
REWIND (2019) (n=9,901)	Dulaglutide 1.5 mg/week sc	5.4	46% 66 (7)	32.3 (5.7)	9	31	MACE-3P	0.88 (0.79-0.99)	0.93 (0.77-1.12)	0.90 (0.80-1.01)	0.91 (0.78-1.06)
PIONEER (2019) (n=3,183)	Semaglutide 14 mg/day oral	1.3	31% 66 (7)	32.3 (6.5)	12	85	MACE-3P	0.79 (0.57-1.11)	0.86 (0.48-1.55)	0.51 (0.31-0.84)	0.49 (0.27-0.92)

(*) Albiglutide is not available in the spanish market. Primary endpoint of the study. Secondary endpoints of the study. **MACE-3P** Composite endpoint of cardiovascular death, non-fatal infarction and non-fatal stroke. **MACE-4P** Composite endpoint of cardiovascular death, non-fatal infarction, non-fatal stroke and unstable angina.

clinical trials (ACE) and high-quality meta-analyse).

The redGDPS 2020 algorithm determines that an arGLP-1 can be added in patients with cardiovascular disease who do not get glycemic targets, since these analogs have been proven to reduce the risk of cardiovascular mortality and all-cause mortality.[4]

How did arGLP-1 reach their position?

A number of studies have been conducted to assess their cardiovascular safety. In general, consistent evidence has been obtained of the beneficial cardiovascular effects of these drugs.

The first drug that demonstrated to reduce cardiovascular mortality was lixisenatide in the ELIXA trial. It was a non-inferiority, randomized, double-blind trial. Lixisenatide did not reveal statistically significant differences in MACE, heart failure-related hospitalization or all-cause mortality.[76]

The following study was LEADER, which assessed the cardiovascular safety of liraglutide. The sample was composed of patients with type 2 diabetes with a high cardiovascular risk. Subjects were randomized into two arms: liraglutide 1.8 mg/day or placebo. Statistically significant differences were observed in the primary endpoint in the group of liraglutide vs. placebo 13.0% vs. 14.9%, HR= 0.87 (0.78-0.97). Liraglutide was also found to be associated with lower cardiovascular mortality rates 4.7% vs. 6.0%, HR=0.78 (0.66-0.93) and all-cause mortality 8.2% vs. 9.6%, HR=0.85 (0.74-0.97). This study was performed at the highest recommended doses of the drug. Therefore, the beneficial effects observed could be obtained at high doses, but the dose most commonly used in clinical practice is 1.2 mg/day.[77] In contrast, there were no differences with respect to the placebo group in the secondary endpoints non-fatal/fatal acute myocardial infarction, or heart failure-related hospitalization.[78]

The SUSTAIN trial assessed the cardiovascular safety of semaglutide at weekly doses of 0.5 or 1 mg vs. placebo.[79] The MACE-3P endpoint decreased in the group treated with semaglutide 6.6% vs. 8.9%,HR=0.74 (0.58-0.95), explained by a 39% reduction in the incidence of non-fatal stroke 1.6% vs. 2.7% for placebo, HR=0.61 (0.38-0.99). However, no differences were found in cardiovascular mortality, non-fatal acute myocardial infarction, heart failure-related hospitalization and all-cause mortality. However, a review carried out by the NHS concluded that this study does not provide conclusive evidence about the cardiovascular benefits of semaglutide.[77]

The EXSCEL study compared the effects of 2mg of exenatide weekly vs. placebo. The primary endpoint MACE-3P was similar in the two groups 11.4% vs. 12.2%; HR=0.91 (0.83-1.00), the same occurred in relation to the other endpoints. Of note, a reduction in all-cause mortality was observed in the exenatide group HR=0.86 (0.77-0.97).[80]

In the REWIND Trial evaluating dulaglutide, significant differences were documented for MACE-3P 12.0% vs. 13.4%; HR=0.88 (0.79-0.99) and non-fatal stroke HR=0.86 (0.77-0.97). There were no differences in cardiovascular or all-cause mortality.[81]

The PIONEER trial investigated the use of oral semaglu-

tide vs. placebo and did not show statistically significant differences in MACE-3P, but did in cardiovascular death HR=0.49 (0.27-0.92) and all-cause mortality, HR=0.51 (0.31-0.84).[82]

A systematic review published in 2019 comparing cardiovascular outcomes associated with these drugs revealed a 12% reduction in MACE, HR=0.88 (0.82–0.94). Cardiovascular mortality also decreased HR=0.88 (0.81–0.96) as did non-fatal stroke HR=0.84 (0.76–0.93) and non-fatal infarction HR=0.91 (0.84–1.00). GLP-1 receptor agonists reduced all-cause mortality by 12%; HR=0.88 (0.83–0.95).[83]

What is the evidence available for patients with HFrEF?

There are two studies assessing the benefits of these drugs on patients with HFrEF. In the FIGHT study (Functional impact of arGLP-1 for the treatment of heart failure), 300 patients with HFrEF and recent heart failure-related hospitalization were randomized to receive either liraglutide (1.8 mg/day) or placebo for six months. No effects were observed in post-hospitalization clinical stability or no statistically significant differences were observed in readmission rates.[84] Similar results were obtained in the LIVE study in 241 patients with stable HFrEF. The 122 patients were treated with liraglutide (1.8 mg/day) and 119 patients with placebo. There were no effects on systolic ventricular function at 24 weeks. In the liraglutide group, an increase of cardiac adverse effects was noted [12 patients (10%) vs. three patients (3%) in the placebo group, p<0.04]. There was a mean increase (95%CI) of seven beats (5-9) per minute in heart failure in the group of liraglutide vs. placebo (p<0.0001).[85]

Therefore, the two studies concluded that the use of arGLP-1 in patients with HFrEF could involve a higher risk of adverse effects related to heart failure.

Can they be used in all NYHA classes of heart failure?

There is no experience with patients with NYHA class IV congestive heart failure. The patients included in this group were generally excluded from the clinical trials commented above. Hence, the use of these drugs is not recommended for this group of patients.[82]

What is the evidence available about patients with concomitant kidney failure?

GLP-1 receptor agonists increase natriuresis and reduce albuminuria, which is suggestive of a potential benefit on renal function.[7] In a systematic review,[83] renal outcomes were assessed using a compound renal endpoint composed of: development of macroalbuminuria, renal failure (increase in serum creatinine> 40%), end-stage renal disease and death from renal disease. The incidence of this endpoint decreased by 17% HR=0.83 (0.78-0.89) in patients treated with arGLP-1 as compared to placebo. These findings were mainly due to the reduction of albumin clearance. The secondary endpoints studied were incidence of macroalbuminuria and worsening of renal function. A significant 24% decrease was also observed in the incidence of macroalbuminuria in these patients HR=0.76 (0.68-0.86). No differences were found in the incidence of kidney failure in patients treated with arGLP-1. Data are shown in table 9.

It is worth mentioning that the ELIXA, LEADER, SUSTAIN-6, EXSCEL and REWIND trials[76,77,79,80,81] included patients with GFR<30 mL/min/1.73 m^2. All these studies excluded patients with GFR <15 mL/min/1.73 m^2, whereas the HARMONY and PIONEER trials excluded patients with GFR <30 mL/min/1.73 m^2.[82,86]

The ELIXA and EXSCEL trials did not show statistically significant difference in the compound renal endpoint or in kidney failure, as it can be observed in Table 9.[76,80]

Table 9. Summary of clinical trials assessing renal risk.

	ELIXA HR (95% CI)	**LEADER** HR (95% CI)	**SUSTAIN-6** HR (95% CI)	**EXSCEL** HR (95% CI)	**REWIND** HR (95% CI)
Composite renal endpoint*	0.84 (0.68–1.02)	0.78 (0.67–0.92)	0.64 (0.46–0.88)	0.88 (0.73–1.01)	0.87 (0.77–0.95)
Worsening of renal function	1.16 (0.75–1.83)	0.89 (0.67-1.19)	1.28 (0.64-2.58)	0.88 (0.74-1.05)	0.70 (0.57-0.85)
Incidence of macroalbuminuria	0.81 (0.66-0.99)	0.74 (0.60-0.91)	0.54 (0.37-0.77)	0.79 (0.64-0.97)	0.77 (0.68-0.87)

Composite renal endpoint*: Development of macroalbuminuria, renal failure (increase in serum creatinine> 40%), end-stage renal disease and death from renal disease.

In the LEADER trial, liraglutide was associated with a 22% reduction of kidney disease. The risk of macroalbuminuria decreased significantly, HR=0.74 (0.60-0.91), however, no statistically significant differences were observed in kidney failure or end-stage renal disease.[78]

In the SUSTAIN-6 trial, semaglutide was associated with a 36% reduction in the risk of development of exacerbation of kidney disease, HR=0.64 (0.46-0.88). The risk of macroalbuminuria decreased significantly, HR=0.54 (0.37–0.77), however, no statistically significant differences were observed in kidney failure or end-stage renal disease.[79]

The REWIND trial associated dulagutide with a 13% reduction of kidney disease. The risk of macroalbuminuria and the worsening of renal function also decreased significantly, as shown in table 9.[81]

The AWARD-7 trial involving patients with moderate-to-severe chronic kidney failure demonstrated the non-inferiority of the reduction of HbA1c in patients treated with dulaglutide (doses 1.5 and 0.75 mg weekly) as compared to glargine at 26 weeks, with this effect persisting until week 52.[7,87]

This drugs seems to have nephroprotective effects, however, the mechanism is unknown.

GLP-1 receptor agonists seem to reduce the risk of microalbuminuria. However, their effects on renal outcomes are unclear.[88,89]

Therefore, at this moment, these agents are not recommended for patients with glomerular filtration rate <15 mL/min/1.73 m^2.[7]

Which are the most remarkable aspects of the safety of arGLP-1?

The FDA alerted about the increased risk of developing non-fatal thyroid C-cell tumors in patients treated with oral semaglutide. At present, the FDA contraindicates their use in patients with a history of medullary thyroid carcinoma or endocrine neoplasms.[90,91] However, the European Medicines Agency (EMA) considers that the risk is low and does not contraindicate their use in these cases.[92]

Conclusions

Based on the available evidence, arGLP-1 emerge as an alternative treatment for patients with DM2 and cardiovascular disease, since they can reduce the risk of adverse cardiovascular events and mortality in diabetic patients. However, they do not seem to have a significant impact on heart failure-related hospitalization. GLP-1 receptor agonists have not been proven to exert beneficial effects in patients with HFrEF. Furthermore, they are only financed when administered to obese patients as part of a combination therapy (BMI ≥ 30 Kg/m^2).

They reduce weight (2-4 Kg) and may improve the lipid profile.

In Spain, they are only financed when they are administered in combination with other antidiabetics to patients with a BMI ≥ 30 Kg/m^2.

They do not increase cardiovascular events or all-cause mortality.

In patients with HFrEF, arGLP-1 should be administered with caution.

They are not recommended in congestive heart failure NYHA class IV.

Insulin therapy

What is its position in guidelines?

Insulin therapy is positioned was first-line treatment for patients with DM2 when glucose targets are not attained with lifestyle and oral glucose-lowering drugs. In patientswith heart failure, insulin can be considered as second orthird option due to an increased risk for weight gain andsafety concerns.

For most patients with heart failure, HbA1c target should be less demanding (<8%) due to their age, comorbidities and medication load.[93]

External supply of insulin and severe hypoglycemia have been associated with increased all-cause mortality and cardiovascular mortality.[94]

In addition to its glucose-lowering function, insulin is an anabolic hormone with effects on lipid and protein metabolism, which results in weight gain, recurrent hypoglycemia and other potential adverse effects, including iatrogenic hyperinsulinemia that predisposing patients to inflammation, atherosclerosis, hypertension, dyslipidemia, heart failure and arrhythmia.[95]

What is the evidence available?

Only a few prospective studies assessing the relationship between insulin and heart failure have been conducted. Results obtained on the effects of exogenous insulin on cardiovascular outcomes are heterogeneous and contradictory.[96]

The prospective study about diabetes in the United Kingdom, the UK prospective diabetes study (UKPDS), was one of the first large studies in DM2 to demonstrate that control of glucose in blood with sulfonylureas or insulin reduce significantly the risk of microvascular complications. Although no macrovascular benefits were documented in the initial 5-year follow-up, a decrease of 15% was observed in the incidence of myocardial infarction at 10 years.[97]

However, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial suggested that an intensive glucose control to reach post HbA1c <6% was associated with an increased rate of all-cause mortality, without a reduction in cardiovascular events. There is no conclusive evidence available on such increase in mortality, although hypoglycemic episodes, which were more frequent in the group receiving intensive treatment, are associated with a higher risk of cardiovascular mortality in patients at high risk.[96]

The study about the results of the intervention of initial insulin therapy (ORIGIN) is a randomized trial of cardiovascular safety to apply the hypothesis that replacement sufficient amounts of baseline insulin to normalize the glucose levels may reduce the risk of cardiovascular events in patients with glucose metabolism alterations. This study included a subgroup of non-diabetic patients with cardiovascular risk factors, including altered glucose levels, without differences in glycosylated hemoglobin (HbA1c ≥ 6.4%) with the subgroup of patients with DM2. Among other results, no significant differences were found in both subgroups with respect to hospitalizations related to cardiovascular events.[98] There were no differences in mortality rate and microvascular disease between insulin glargine and the recommended treatment (mainly oral antidiabetics). However, by the end of the study, 11% of non-diabetic group of patients were treated with a treatment regimen that included insulin. The ORIGIN study could not demonstrate any cardiovascular benefit of early treatment with insulin in DM2.[96]

Observational studies found an increased cardiovascular and mortality risks HR=1.27 (1.16-1.38), as well as an increase of incidence of heart failure-related hospitalization HR=1.23 (1.13-1.3) in patients with DM and HFrEF treated with insulin.[99] Also, it was observed an increased of composite endpoint (death and heart failure-related hospitalization) HR=1.41 (1.23-1.63) and sudden death HR=1.67 (1.20-2.32), in patients with DM and HFpEF who received insulin.[100]

In patients with heart failure, insulin therapy can be considered a later alternative treatment

Retrospective observational studies have several limitations: the difficulty in measuring all differences between participants and adjusting for all potential confounding factors. Another limitation is that treatment outcomes may not be attributable to the medication.[96]

Conclusion

Insulin should be considered an essential medication in those patients who have not achieved glycemic control targets with other glucose-lowering drugs. In patients with heart failure, insulin therapy can be delayed due to the risk of weight gain and increase risk of complications.

Glucose-lowering drugs.

Higher risk of weight gain and complications.

Acknowledgment

We would like to thank to Anisa Rowhani-Farid and Peter Doshi for their translation support.

SUMMARY

The approach to patients with type 2 diabetes mellitus (DM2) and heart failure continues to be a challenge in primary care. When an antidiabetic therapy is started, it is important that its cardiovascular safety and effectiveness in preventing cardiovascular events are considered.

Metformin is the first-line treatment for patients with DM2 and heart failure. It cannot be used in patients with severe kidney failure (GFR<30 mL/min/1.73 m^2) and metabolic acidosis.

SGLT2i are safe in cardiovascular terms and reduce hospital admissions for heart failure.

GLP-1 receptor agonists do not increase cardiovascular events or all-cause mortality. They can be an alternative for patients with heart failure and DM2. In Spain, arGLP-1 are only financed in patients with a BMI ≥30 Kg/m^2.

DPP4i do not increase the risk of major cardiovascular events vs. placebo. These drugs should be administered with caution in patients with heart failure and saxagliptin is contraindicated in these patients.

With regard to sulfonylureas, glinides and acabose, there are no randomized clinical trials that provide conclusive evidence about their cardiovascular safety in patients with DM2 and heart failure.

Insulin therapy can be considered a later alternative treatment, because of the higher risk of complications in these patients.

Pioglitazone is contraindicated in patients with heart failure.

ASPECTS TO BE CONSIDERED IN THE MEDICATION REVIEW

Table 10a. Type 2 Diabetes Mellitus treatment. Aspects to be considered in the medication review of patients with heart failure and DM2.

Therapeutic group / Drug	Indication	Monitoring	Contraindication
SGLT2i	Second-line therapy of DM2 with heart failure.	Renal function Volume depletion Fungal infections Ketoacidosis	End-stage kidney failure or dialysis
Metformin	First-line treatment of DM2	Renal function HbA1c Interactions (iodine contrasts)	Severe kidney failure (GFR < 30 mL/min/1.73m^2) Metabolic acidosis
Glitazones	Contraindicated for the treatment of DM2 with concomitant heart failure.	Liver function Weight control and occurrence of edema Visual acuity Interactions (gemfibrozil, rifampicin ...)	Heart failure, liver failure, diabetic ketoacidosis, bladder cancer, macroscopic hematuria of unknown etiology
DPP4i	Third-line treatment for DM2 with concomitant heart failure.	Liver and renal function Acute pancreatitis Skin manifestations	Saxagliptine is contraindicated in the presence of heart failure
Sulfonylureas	Alternative	Glucose-lowering drugs Liver function HbA1c Hematologic control Weight	Severe kidney failure (GFR < 30 mL/min/1.73m^2)
Glinides	Alternative	Glucose-lowering drugs	Severe liver failure Diabetic ketoacidosis Concomitant use with gemfibrozil
Alpha-glucosidase inhibitors	They are not considered a treatment option		
GLP-1 receptor agonists	Possible alternative in patients with DM2 and heart failure with BMI >30 Kg/m^2	Renal function weight, BMI, HbA1c	Severe kidney failure (GFR < 15 mL/min/1.73m^2)
Insulin	Delay as long as possible in patients with DM2 and heart failure	Renal function HbA1c	Obesity

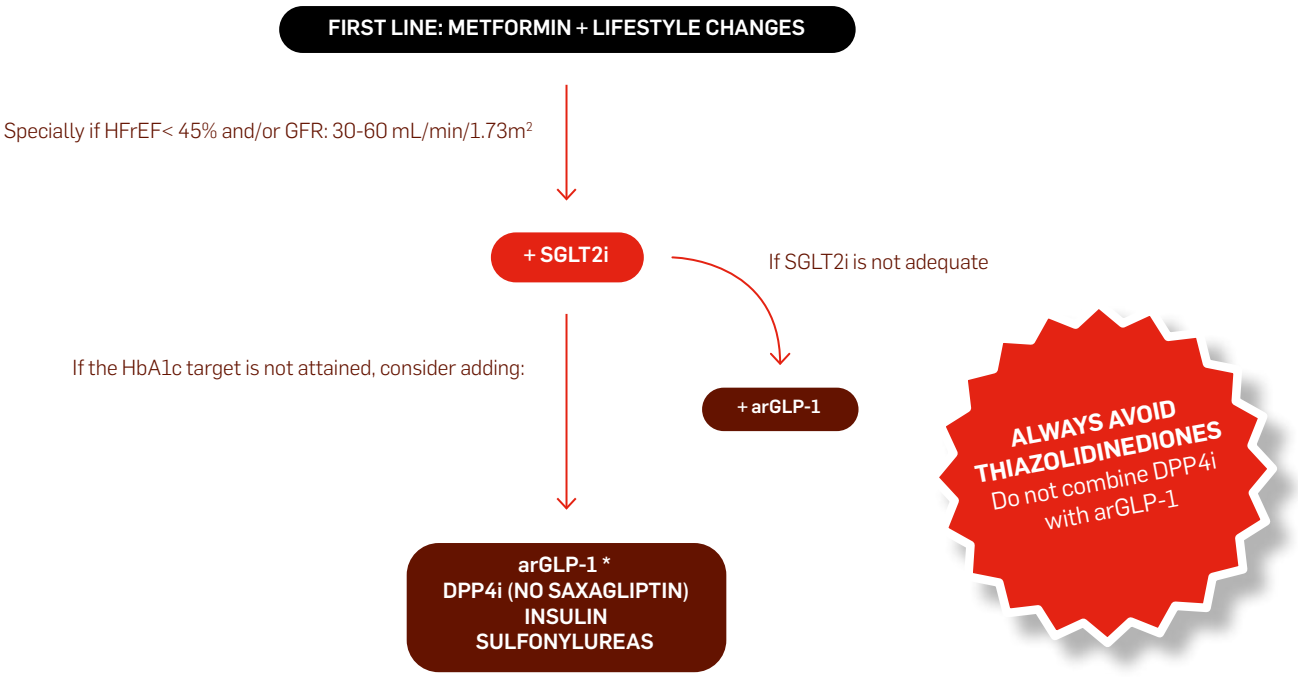
The aspects to be considered for the treatment of heart failure are the same as in patients with or without DM2.

Table 10b. Heart failure treatment. Aspects to be considered in the medication review of patients with heart failure and DM2.

Therapeutic group / Drug	Indication	Monitoring	Contraindication
ACE inhibitors	First-line treatment in the presence of HF (NYHA II-IV).	Renal function. Ionogram.	Angioedema. Bilateral renal stenosis.
ARB	First-line treatment in the presence of HF (NYHA II-IV).	Renal function. Ionogram.	Angioedema. Estenosis renal bilateral.
Beta-blockers	First-line treatment in the presence of HF (NYHA II-IV). HFrEF.	BP. Heart rate. Interactions (verapamil, amiodarone ...).	Asthma. Atriventricular block. Caution in the presence of NYHA IV HF.
Mineralocorticoid Receptor Antagonists	Persistent HF (NYHA II-IV). Symptomatic HFrEF desoute treatment with ACE inhibitors (or ARB) and beta-blockers.	Renal function. Ionogram. Interactions (NSAIDs, CYP3A4 inhibitors...).	
Diuretics	HFpEF and HFrEF with signs/symptoms of congestion.	BP, congestive symptoms, weight, diuresis, renal functions and ionogram (including magnesium).	Thiazide diuretics are not effective with GFR <30mL/min/1.73m^2
Sacubitril/Valsartan	HFrEF with LVEF <35% despite optimal treatment with ACE inhibitors or ARB, beta-blockers and anti-aldosteronics with concomitant elevated levels of BNP or NT-proBNP.	BP. Ionogram. Renal function. BNP.	Not combined with ACE inhibitors/ ARB. Angioedema.
Digoxin	Symptomatic HFrEF and AF. Symtomatic HFrEF in sinus rhythm despite treatment with beta-blockers, ACE inhibitors (or ARB) and aldosterone antagonists.	Renal function. Ionogram (potasium, calcium) Interactions (verapamil, amiodarone ...).	Intermittent heart block or second-grade atrioventricular block. Supraventricular arrhythmias.
Hydralazine / Isosorbide dinitrate	Alternative in patients with HFrEF, NYHA II-IV who do not tolerate ACE inhibitors or ARB (due to severe kidney failure or hyperkalemia).	Renal function. BP. Interactions (isosorbide contraindicated with phosphodiesterase 5 inhibitors).	Coronary/arterial disease. Cardiogenic shock.
Ivabradine	HFrEF in sinus rhythm with heart rate at rest ≥70bpm who remain asymptomatic despite treatment with beta-blockers, ACE inhibitors/ARB and aldosterone antagonists.	Renal function and BP. Interactions (verapamil, diltiazem, amiodarone ...).	Acute coronary syndrome. Transient ischemic attack. Severe hypotension.

ACE Inhibitors: angiotensin converting enzyme 2 inhibitors.
ARB Angiotensin II receptor blockers.
HF Heart failure.
HFrEF Heart failure with reduced ejection fraction.
HFpEF Heart failure with preserved ejection fraction.
LVEF Left-ventricular ejection fraction.
BP Blood pressure.
GFR Glomerular filtrate rate.
BNP Natriuretic peptide type B.
NT-ProBNP N-terminal ProB-type natriuretic peptide.
bpm Beats per minute.
HbA1c Glycated hemoglobin.
BMI Body mass index.

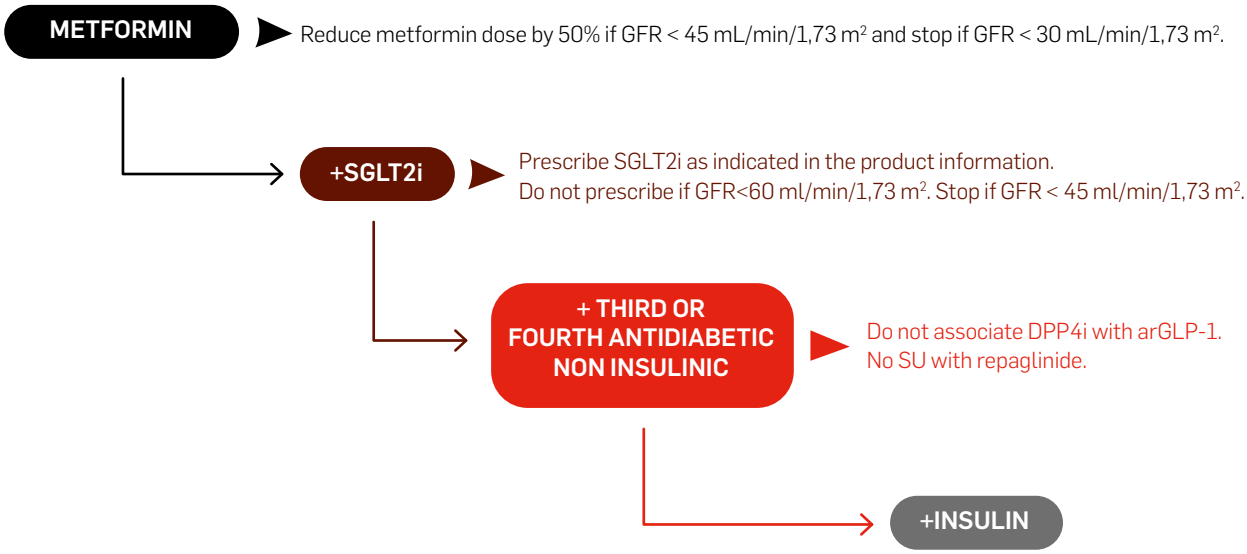
Figure 2. Algorithm of antidiabetic therapy in patients with DM2 and heart failure (adapted from redGDPS 2020).



(*) arGLP-1 are only financed in Spain for patients with BMI>30 Kg/m²
HFrEF Heart failure with reduced ejection fraction.
GFR Glomerular filtration rate.
HbA1c Glycated hemoglobin.
BMI Body mass index.

Figure 3. Algorithm of antidiabetic therapy in patients with DM2, heart failure and kidney disease (adapted from redGDPS 2020).

Glomerular filtration rate: 30-59 mL/min/1.73m^2



Glomerular filtration rate: <30 mL/min/1.73m^2

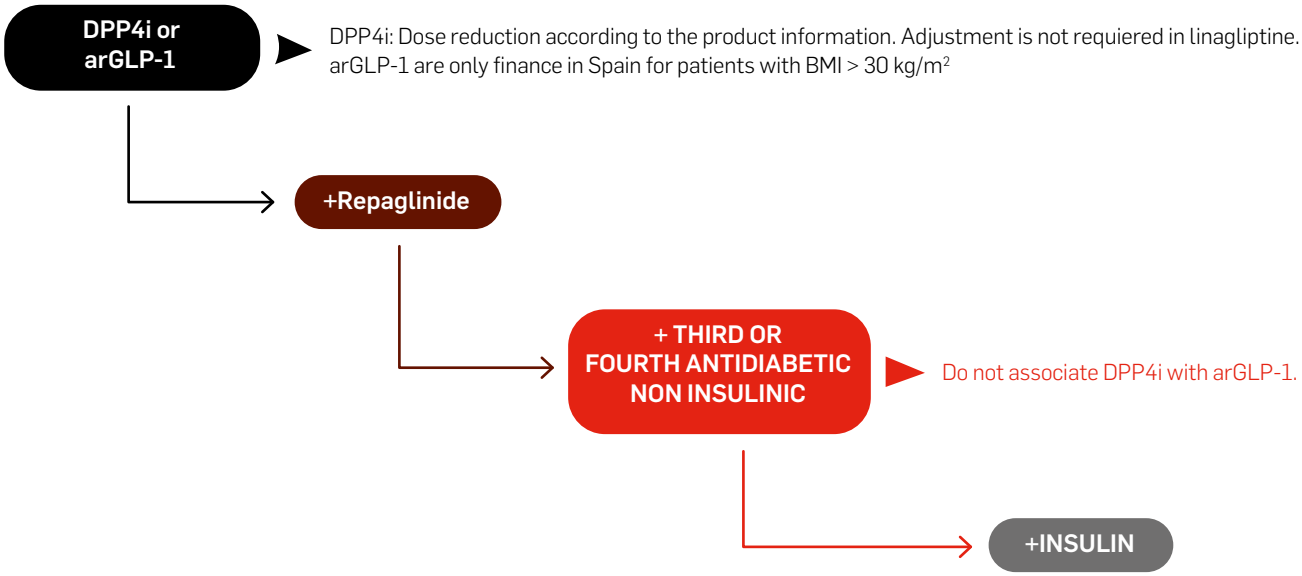
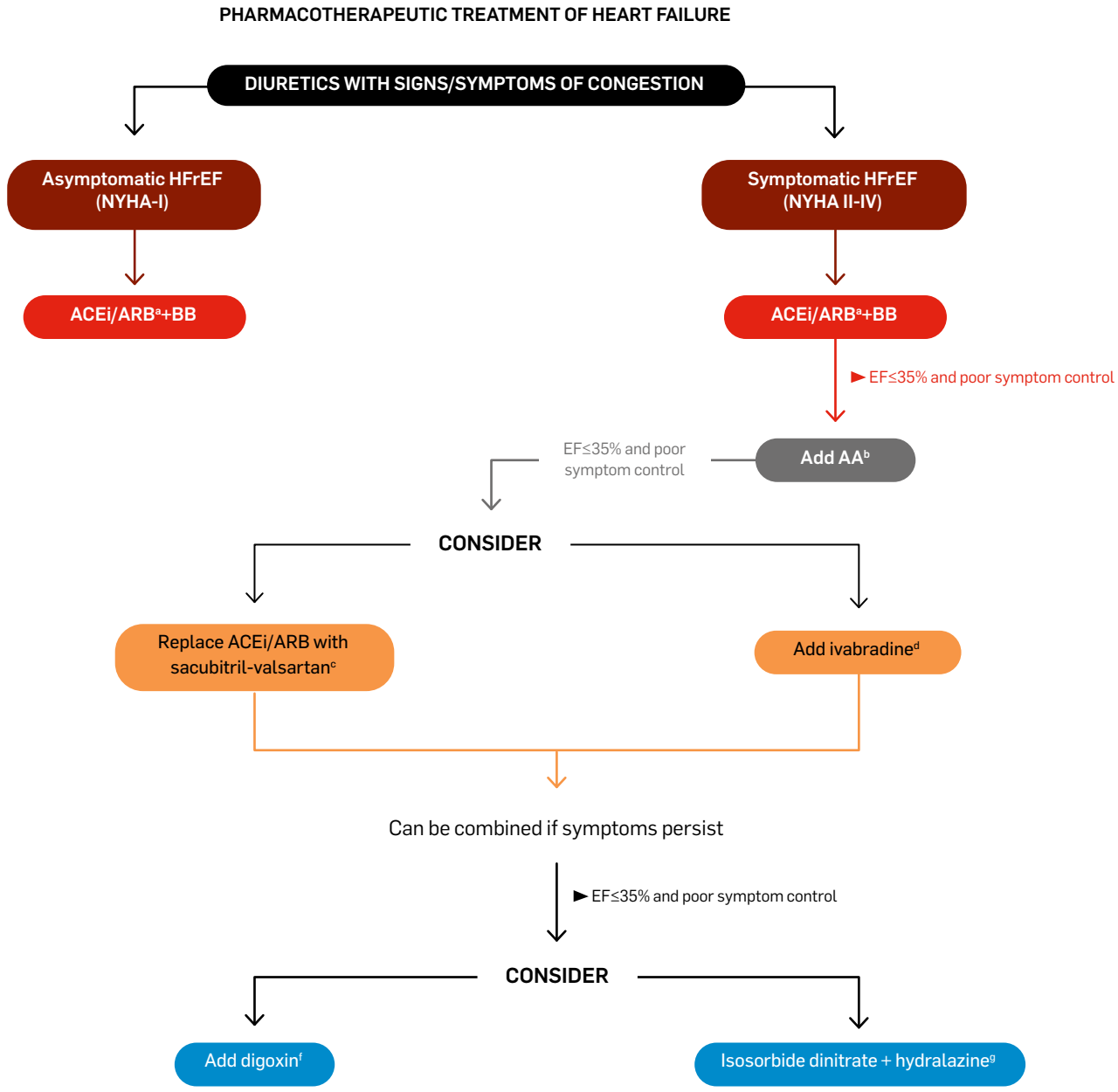


Figure 4. Algorithm for the treatment of heart failure.



(a) **ARB** if ACE inhibitors are contraindicated/not tolerated.
(b) If AA is contraindicated or not tolerated, consider combining ACEi+ARB+BB under close monitoring.
(c) NYHA II-III and elevated levels of natriuretic peptides, ACEi/ARB not contraindicated/tolerated; no history of angioedema, hypotension, kidney failure.
(d) NYHA II-IV heart rate ≥ 70bpm, sinus rhythm, hospitalization in the previous 12 months.
(f) Severe HFrEF, sinus rhythm, poorly controlled rapid atrial fibrillation.
(g) If ACEi/ARB are contraindicated/not tolerated.
HFrEF Heart failure with reduced ejection fraction.
NYHA New York Heart Association.
ACEi Angiotensin converting enzyme 2 inhibitors.
ARB Angiotensin II receptor blockers.
BB Beta-blockers.
AA Aldosterone antagonists.
HR Heart rate.
EF Ejection fraction (left ventricular).

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ISSN
1138-1043

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