Short Communication

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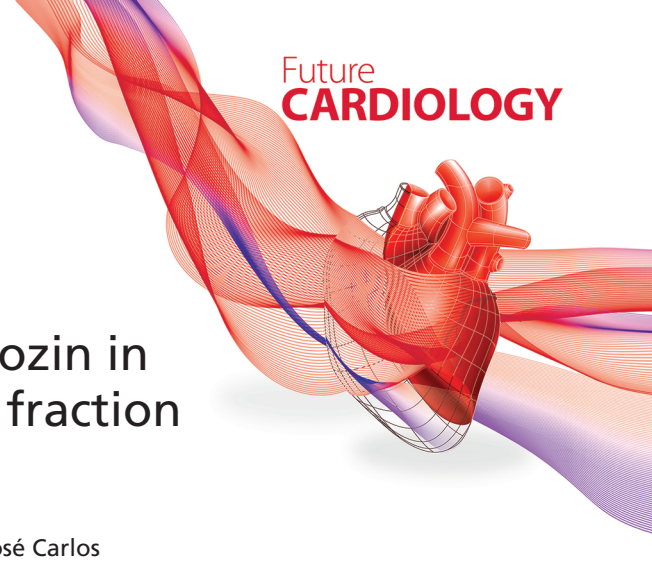

Projected effectiveness of dapagliflozin in heart failure with reduced ejection fraction in clinical practice

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Aim: To estimate the projected effectiveness of dapagliflozin in subjects with heart failure (HF) with reduced ejection fraction in clinical practice in Spain. **Materials & methods:** This multicenter cohort study included subjects aged 50 years or older consecutively hospitalized for HF in internal medicine departments in Spain. The projected clinical benefits of dapagliflozin were estimated based on results from the DAPA-HF trial. **Results:** A total of 1595 patients were enrolled, of whom 1199 (75.2%) were eligible for dapagliflozin. Within 1 year after discharge, 21.6% of patients eligible for dapagliflozin were rehospitalized for HF and 20.5% died. Full implementation of dapagliflozin led to an absolute risk reduction of 3.5% for mortality (number needed to treat = 28) and 6.5% (number needed to treat = 15) for HF readmission. **Conclusion:** Treatment with dapagliflozin in clinical practice may markedly reduce mortality and readmissions for HF.

Plain language summary: Heart failure with reduced ejection fraction is a severe disease with a high risk of hospitalization and mortality. With this condition, the heart muscle cannot pump properly. This means that not enough blood is pumped from the heart, reducing the amount of oxygen to the body. Fortunately, there are treatments that reduce this risk, in patients with heart failure. SGLT2 inhibitors, including dapagliflozin, are among the first therapies given to patients with heart failure. In this study, we investigated the potential benefits of adding dapagliflozin to the treatment of patients admitted to the hospital in Spain for heart failure with reduced ejection fraction. Our data showed that dapagliflozin was able to reduce the risk of further events (e.g., heart attack) in these patients.

Tweetable abstract: The implementation of dapagliflozin may translate into substantial reductions in mortality and heart failure readmissions.

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Keywords: dapagliflozin • death • heart failure with reduced ejection fraction • hospitalization • SGLT2 inhibitors

Future Medicine

It has been estimated that approximately 2% of adults suffer from heart failure (HF) [1], but this proportion will increase in coming years because of aging of the population [2]. HF is associated with great morbidity and mortality. In the Olmsted County study, up to 20% of patients with HF died within the first year after diagnosis, with a hospitalization rate of 1.3 per person-year [3]. Remarkably, HF is the main reason for hospital admission in elderly people in Western countries [1].

Hospitalization represents an inflection point in the evolution of patients with HF. In fact, survival and quality of life of patients markedly decrease with each hospitalization. In addition, the risk of rehospitalization increases following an acute HF event [4]. This is more important during the so-called vulnerable period of HF, in which patients are at high risk of adverse outcomes, including death and rehospitalization, mainly during the first months following an HF hospitalization [5]. As a result, this period actually represents an excellent opportunity to implement the HF therapies recommended by guidelines [6].

Recent clinical trials have shown that some SGLT2 inhibitors added to standard therapy are able to significantly reduce the risk of cardiovascular mortality or HF hospitalization in patients with HF with reduced ejection fraction (HFrEF) regardless of history of diabetes [7–10]. In fact, current guidelines recommend the use of SGLT2 inhibitors as baseline therapy for this population [6]. However, although some studies have analyzed the projected clinical benefits of implementation of SGLT2 inhibitors in real-life patients with HFrEF [11], no data are available in patients from internal medicine settings.

This study is part of a series of three (HF regardless of ejection fraction, HFrEF and HF with mildly reduced/preserved ejection fraction) carried out with the objective of estimating the effect the initiation of dapagliflozin would have on HF patients based on the results of clinical trials in the Registro Nacional de Insuficiencia Cardíaca (RICA) registry [12,13]. In this study, we assessed the HFrEF subtype eligible for the use of dapagliflozin and analyzed the projected impact of treatment with dapagliflozin on outcomes based on results from the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial.

Materials & methods

Patients were those from the RICA cohort study. This registry is supported by the HF and Atrial Fibrillation Working Group of the Spanish Society of Internal Medicine. The design of this registry has been previously described [14,15]. The RICA registry is a multicenter cohort study with a prospective follow-up of 1 year, enrolling individuals aged 50 years or older consecutively admitted with HF to internal medicine departments at 52 public or private Spanish hospitals. Patients with pulmonary hypertension, those who died during the index event, those who declined to participate in the study and those who did not complete the follow-up period were excluded. The registry was approved by the ethics committee of the University Hospital Reina Sofia (Córdoba, Spain). All subjects signed informed consent before inclusion.

Variables were taken from the medical history of patients and recorded in a specific electronic case report form (eCRF). At baseline, biodemographic data, Charlson Comorbidity Index, Barthel index, Pfeiffer index, physical examination, HF data based on New York Heart Association (NYHA) functional class and left ventricular ejection fraction (LVEF), cardiovascular risk factors, vascular disease (coronary artery disease, cerebrovascular disease, peripheral arterial disease), other comorbidities (atrial fibrillation, chronic kidney disease, COPD, cancer, dementia), laboratory parameters determined within the first 48 h during hospitalization and treatment at discharge were collected. HF was defined according to European Society of Cardiology guidelines, and LVEF $\leq$40 was considered to indicate HFrEF [16]. LVEF was determined by 2D echocardiography. Renal function was defined by estimated glomerular filtration rate based on the MDRD equation [17].

During index hospitalization, length of stay and medical complications were determined. Patients were followed up for 1 year ($\pm$ 1 month) after the index event. The proportion of patients rehospitalized for HF and the proportion of patients who died during this period were recorded.

A specific analysis was performed in subjects who met the eligibility criteria for dapagliflozin use as per the summary of product characteristics approved by the EMA [18]. This group included symptomatic patients with HFrEF regardless of the presence of Type 2 diabetes and estimated glomerular filtration rate $\geq$25 ml/min/1.73 m^2. Patients on dialysis, asymptomatic patients (NYHA functional class I) and patients with Type 1 diabetes were excluded. Baseline clinical characteristics, all-cause mortality, all-cause rehospitalizations and HF rehospitalizations

over a 1-year period were evaluated and compared with those of the overall HFrEF population. In addition, the projected benefits of treating this population with dapagliflozin were calculated based on DAPA-HF trial results.

Statistical analysis

Qualitative variables were described by their absolute and relative (percentage) frequency distributions. Quantitative variables were defined by measures of central tendency (mean) and dispersion (standard deviation). The Student's *t* test was used to compare continuous variables between groups. Qualitative variables were compared using the χ^2 test. Projected 1-year cumulative event curves if dapagliflozin had been fully implemented in the RICA cohort were calculated by applying relative treatment effects observed in the DAPA-HF trial [7]. To compute point estimates, the mathematical relationship between the hazard ratio (HR) of a proportional hazard model and the survival functions in two groups was used: survival in the treatment-eligible cohort = (survival in control group, HR), for all-cause mortality (HR: 0.83; 95% CI: 0.71–0.97) and for HF hospitalization (HR: 0.70; 95% CI: 0.59–0.83). Absolute risk reduction (ARR) was calculated as the difference between observed and projected (i.e., implementation of dapagliflozin) reduction in risk at 1 year, and the number needed to treat (NNT) to prevent either HF readmission or all-cause mortality was calculated as 1/ARR. Finally, in generalizing these findings to the RICA registry population, the number of deaths and HF readmissions averted with full implementation of dapagliflozin after hospitalization for HFrEF was estimated [7,19,20]. The level of statistical significance was defined as $p < 0.05$. Statistical analyses were performed using SPSS Statistics 22.0 (IBM Corporation, NY, USA) for Macintosh (Apple Inc., CA, USA).

Results

Overall, 5644 patients were included in the RICA registry. Of these, 1595 (28.3%) had HFrEF, 1199 (75.2%) of whom were eligible for dapagliflozin treatment as per the EMA summary of product characteristics. Mean age was 77.6 years (9.8), 63.9% were men, most were NYHA functional class II (50.5%) or III (39.4%) and LVEF was 30.9 (7.3%). Regarding other conditions, 81.8% of patients had hypertension, 47.1% had diabetes, 40.4% had chronic kidney disease and 37.0% had ischemic heart disease. With respect to HF treatments, 71.6% of patients were taking renin–angiotensin system inhibitors (7.3% of which were angiotensin receptor–neprilysin inhibitors), 80.8% were taking beta-blockers and 34.4% were taking mineralocorticoid receptor antagonists (Table 1). The clinical profile of patients eligible for dapagliflozin use as per the EMA summary of product characteristics was very close to that of the overall HFrEF population. However, patients eligible for dapagliflozin were more frequently NYHA functional class II (51.1%) or III (42.2%), as NYHA functional class I was excluded, and had higher levels of CA-125 (100.6 [142.0] vs 90.20 [128.6] U/ml; p = 0.04) and estimated glomerular filtration rate (61.6 [25.9] vs 59.0 [25.6] ml/min/1.73 m^2; p = 0.008). Additionally, more patients were taking mineralocorticoid receptor antagonists (38.3 vs 34.4%; p = 0.04), without significant differences in the prescription of other HF drugs. Among patients eligible for dapagliflozin, 25.4% were taking renin–angiotensin system inhibitors, beta-blockers and mineralocorticoid receptor antagonists simultaneously. Baseline treatments for diabetes in the overall diabetic HFrEF population are included in Supplementary Table 1.

Outcomes during the study period in the overall HFrEF population and in subjects eligible for dapagliflozin are presented in Table 2. Mean length of stay was 9.9 days (8.5), and 23.3% of patients presented a complication during admission. After 1 year, 22.1% of patients were readmitted for HF and 27.3% died. Length of stay was similar between groups, but more complications (20.9 vs 23.3%; $p < 0.01$) and higher mortality rates during follow-up (20.5 vs 27.3%; $p < 0.01$) were observed in the overall HFrEF population compared with patients eligible for dapagliflozin.

Applying the observed relative risk reductions observed in the dapagliflozin arm of the DAPA-HF trial, the projected 1-year numbers for mortality and HF rehospitalizations were 17.0% and 15.1%, respectively, and in the placebo group of DAPA-HF trial, 11.7% and 18.8%, respectively. The reduction in mortality yielded an estimated ARR of 3.5% (NNT to prevent one death = 28). The projected incidence of readmission for HF with the use of dapagliflozin was 15.1%, yielding an estimated ARR of 6.5% (NNT to prevent one readmission for HF = 15) (Figures 1 & 2).

Discussion

Patients with HFrEF treated in internal medicine departments are elderly and have many other conditions and a high risk of death and readmission after HF hospitalization. Although there is still room for traditional HF

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Table 1. Baseline demographic and clinical characteristics of the overall heart failure with reduced ejection fraction population and heart failure with reduced ejection fraction patients eligible for dapagliflozin treatment as per EMA summary of product characteristics.

	HFrEF (n = 1595)	HFrEF Dapa (n = 1199)	p-value
Biodemographic data			
Age, years (SD)	77.6 (9.8)	77.4 (9.9)	0.60
Sex, female (%)	36.1	36.4	0.89
Charlson Comorbidity Index, points (SD)	3.4 (2.7)	3.3 (2.5)	0.32
Barthel index, points (SD)	86.1 (20.5)	86.5 (19.7)	0.60
Pfeiffer index, points (SD)	1.7 (2.0)	1.4 (2.0)	<0.01
Physical examination			
BMI, kg/m^2 (SD)	27.7 (7.2)	28.0 (7.8)	0.29
Systolic blood pressure, mm Hg (SD)	132.0 (25.6)	132.2 (25.2)	0.84
Diastolic blood pressure, mm Hg (SD)	75.3 (15.5)	75.3 (15.0)	0.99
Heart rate, bpm (SD)	88.1 (22.9)	87.3 (22.7)	0.36
HF data			
HF etiology, ischemic (%)	45.6	46.4	0.68
NYHA functional class (%) I II III IV	 6.9 50.5 39.4 3.2	 0 51.1 42.2 2.7	 <0.01
LVEF, % (SD)	30.9 (7.3)	30.9 (7.2)	0.99
Cardiovascular risk factors			
Hypertension (%)	81.8	82.8	0.49
Dyslipidemia (%)	53.9	54.7	0.68
Diabetes mellitus (%)	47.1	48.0	0.62
Obesity (%)	26.6	28.1	0.39
Smoking (%)	10.0	8.7	0.23
Vascular disease			
Coronary artery disease (%)	37.0	37.5	0.77
Cerebrovascular disease (%)	13.6	14.0	0.76
Peripheral arterial disease (%)	14.2	13.8	0.76
Other comorbidities			
Atrial fibrillation (%)	42.4	42.6	0.90
Chronic kidney disease (%)	59.4	52.9	<0.01
COPD (%)	25.5	26.7	0.49
Cancer (%)	12.2	12.5	0.82
Dementia (%)	5.8	5.7	0.86
Laboratory parameters			
Hemoglobin, mg/dl (SD)	12.5 (2.0)	12.5 (2.0)	0.99
Glucose, mg/dl (SD)	140.7 (69.4)	138.5 (68.1)	0.40
HbA1c, % (SD)	7.0 (2.3)	7.2 (2.6)	0.03
Creatinine, mg/dl (SD)	1.34 (0.6)	1.2 (0.4)	<0.01
Urea, mg/dl (SD)	69.4 (36.9)	65.7 (30.6)	0.005
eGFR, ml/min/1.73 m^2 (SD)	59.0 (25.6)	61.6 (25.9)	0.008
Sodium, mmol/l (SD)	138.4 (0.6)	138.4 (5.6)	0.95
Potassium, mmol/l (SD)	4.3 (0.6)	4.3 (0.6)	0.99
Uric acid, mg/dl (SD)	8.0 (2.5)	8.0 (2.4)	0.95
Total cholesterol, mg/dl (SD)	149.1 (41.0)	144.7 (34.4)	0.003
Troponin I, ng/ml (SD)	1.41 (0.6)	1.36 (0.6)	0.03

ACE: Angiotensin-converting enzyme; ACEi: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor–neprilysin inhibitor; BB: Beta-blocker; COPD: Chronic obstructive pulmonary disease; Dapa: Dapagliflozin; eGFR: Estimated glomerular filtration rate; HbA1c: Hemoglobin A1c; HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; LVEF: Left ventricular ejection fraction; MRA: Mineralocorticoid receptor antagonist; NYHA: New York Heart Association; SD: Standard deviation.

Table 1. Baseline demographic and clinical characteristics of the overall heart failure with reduced ejection fraction population and heart failure with reduced ejection fraction patients eligible for dapagliflozin treatment as per EMA summary of product characteristics (cont.).

	HFrEF (n = 1595)	HFrEF Dapa (n = 1199)	p-value
BNP, pg/ml (SD)	1959 (3597)	2043 (3946)	0.56
NT-proBNP, pg/ml (SD)	9106 (10747)	8916 (9908)	0.63
CA-125, U/ml (SD)	90.20 (128.6)	100.6 (142.0)	0.04
Outpatient treatment			
ARNI (%)	7.3	8.0	0.47
ACEi or ARB (%)	64.3	66.5	0.24
BB (%)	80.8	81.9	0.47
MRA (%)	34.4	38.3	0.04
BB + ACEI or ARB or ARNI (%)		59.0	
BB + ACEi or ARB or ARNI + MRA (%)		25.4	

ACE: Angiotensin-converting enzyme; ACEi: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor–neprilysin inhibitor; BB: Beta-blocker; COPD: Chronic obstructive pulmonary disease; Dapa: Dapagliflozin; eGFR: Estimated glomerular filtration rate; HbA1c: Hemoglobin A1c; HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; LVEF: Left ventricular ejection fraction; MRA: Mineralocorticoid receptor antagonist; NYHA: New York Heart Association; SD: Standard deviation.

Table 2. Outcomes during follow-up in the overall heart failure with reduced ejection fraction population and heart failure with reduced ejection fraction patients eligible for dapagliflozin treatment as per EMA summary of product characteristics.

	HFrEF (n = 1595)	HFrEF Dapa (n = 1199)	p-value
In-hospital outcomes			
Length of stay, days (SD)	9.9 (8.5)	9.9 (8.6)	0.99
Complications during hospitalization (%)	23.3[†]	20.9	<0.01
1-year follow-up period			
Mortality (%)	27.3	20.5	<0.01
Readmission (%)	35.1	34.5	0.72
Readmission for HF (%)	22.1	21.6	0.61

[†] One patient could have more than one complication: acute renal insufficiency (creatinine >2 mg/dl): 37.1%; need for antihypertensive medication: 35.0%; transfusion of blood cells: 20.4%; acute confusional syndrome: 19.6%; mechanical ventilation: 16.2%; need for morphine derivatives: 15.9%; nosocomial urinary tract infection: 15.3%; hyperkalemia (>5.5 meq/l): 13.6%; need for inotropic drugs: 10.5%; intensive care unit admission: 8.3%; malnutrition: 6.0%; nosocomial pneumonia: 5.8%; catheter infection: 3.4%; orotracheal intubation: 2.2%; venous thromboembolic disease: 2.1%; need for hemofiltration: 1.1%.
Dapa: Dapagliflozin; HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; SD: Standard deviation.

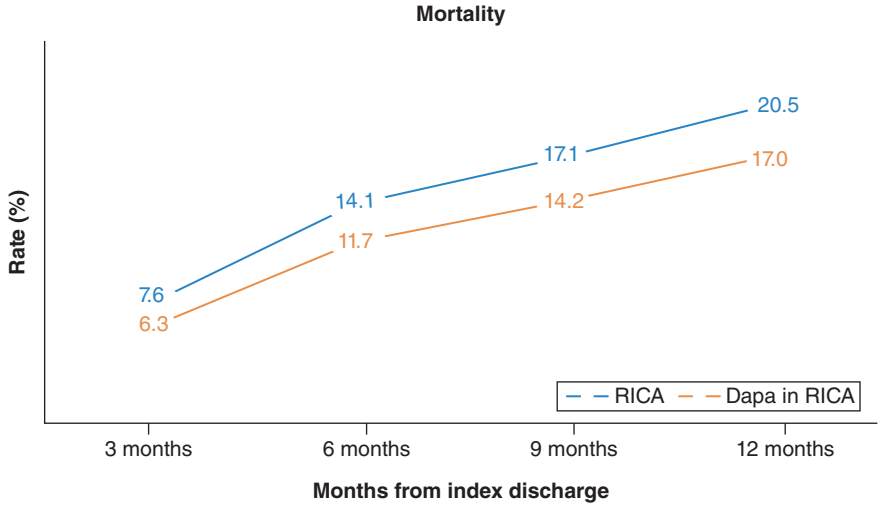

Figure 1. Simulated mortality benefits of dapagliflozin implementation in heart failure with reduced ejection fraction patients.
Dapa: Dapagliflozin; RICA: Registro Nacional de Insuficiencia Cardíaca.

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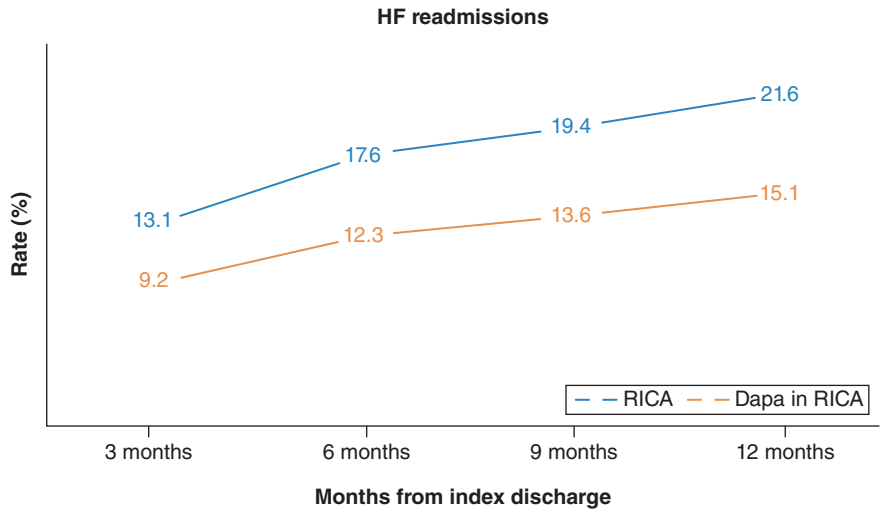

Figure 2. Simulated heart failure rehospitalization benefits of dapagliflozin implementation in heart failure with reduced ejection fraction patients.
Dapa: Dapagliflozin; HF: Heart failure; RICA: Registro Nacional de Insuficiencia Cardíaca.

therapies, the use of dapagliflozin in many eligible HFrEF patients of the RICA cohort would markedly reduce the possibility of death and HF readmissions.

Considering that there are relevant differences in the results of HF registries depending on the inclusion criteria in real-life studies [21], the RICA registry offered relevant information about patients who were admitted to internal medicine departments as a result of HF hospitalization. Our study showed that patients with HFrEF were elderly and mostly functional class II/III and had many comorbidities. This implies that the management of this population is challenging and requires a comprehensive approach. This is even more important considering that 22% of patients were rehospitalized for HF and 27% died within the first year after the acute event. These numbers are greater than those reported in previous studies [3,4,22], reflecting a more complex population. Optimization of the management of these patients through the use of disease-modifying therapies, even during hospitalization, is mandatory to reduce HF complications [6]. In our study, around 71% of patients were taking renin–angiotensin system inhibitors (7% sacubitril–valsartan), 81% were taking beta-blockers and around one-third were taking mineralocorticoid receptor antagonists. Low use of HF drugs has also been described in other registries, even in younger patients with fewer comorbidities [23,24]. This is very important, as this underuse of HF drugs has been associated with a higher use of healthcare resources, mostly in the form of first and recurrent hospitalizations [25]. Considering that the main determinant of HF costs is hospitalizations, the use of recommended HF therapies would reduce not only morbidity and mortality but also healthcare-related costs [22].

Of note, as the results of clinical trials with SGLT2 inhibitors in patients with HFrEF [7–9] were published after patient enrollment, the use of these drugs in this population could not be determined. In this context, we performed a specific analysis in HFrEF patients eligible for the use of dapagliflozin to determine the impact of its implementation on outcomes. In this context, a high proportion of patients with HFrEF included in the RICA registry were candidates for the use of dapagliflozin, even considering that this was an elderly and fragile population with many comorbidities. This is in line with previous studies that have also shown great eligibility for dapagliflozin in real-life patients with HFrEF [26–28]. The DAPA-HF trial showed that the benefits of dapagliflozin could be seen in both elderly and frail patients [29,30]. A recent study that included Medicare beneficiaries with HFrEF showed that complete implementation of dapagliflozin in treatment-eligible patients would translate into an ARR of 5% for mortality (NNT = 19) and 9% for HF readmission (NNT = 12) by 1 year [11]. In our study, these numbers were 3.5% for mortality (NNT = 28) and 6.5% for HF readmission (NNT = 15). Although disparities in the numbers may be related to the different clinical profiles of the patients, the fact is that the benefits of treating patients with HFrEF with dapagliflozin are substantial. Remarkably, based on an estimated 62,943 patients admitted to Spanish internal medicine departments for HF each year, it would be expected that approximately 14,500 of them would be eligible for treatment with dapagliflozin at hospital discharge [15,22]. Applying the NNTs observed in our analysis, 518 deaths and approximately 1000 readmissions for HF could potentially be avoided in Spanish internal medicine

departments with the full implementation of dapagliflozin for 1 year. In addition, the DAPA-HF trial showed that dapagliflozin could be safely used in patients with HFrEF with a low risk of hypoglycemia (in contrast to other antidiabetic drugs, such as sulfonylureas) regardless of diabetes status, facilitating its use in clinical practice [7,31].

Our study has several limitations. Since this was an observational cohort study that started recruiting patients in 2008, during this period recommended HF therapies have changed over time. In addition, only those patients who survived during the index event were included in the study. As only patients with HF admitted to internal medicine departments were included in this study, this could limit the generalizability of the results. Moreover, although the information provided by our study is relevant, a prospective trial would provide more information about the real impact of dapagliflozin in this population in clinical practice.

Conclusion

Patients with HFrEF admitted to internal medicine departments are elderly and have many other conditions. These patients have a high risk of readmission or death within the first year after HF hospitalization. This may be partially due to an underuse of HF therapies, which is often attributable to the patient's comorbidities. Therefore, these patients' prescriptions should be enhanced during hospitalization or at early discharge to reduce HF burden. The use of effective and safe drugs like dapagliflozin in HFrEF candidates may translate into substantial reductions in mortality and HF readmissions.

Summary points

- Patients with heart failure (HF) with reduced ejection fraction admitted to internal medicine departments are elderly and have many other conditions.
- These patients have a high risk of death and readmission within the first year after HF hospitalization, partially due to an underuse of HF therapies.
- The use of effective and safe drugs like dapagliflozin in candidates with HF with reduced ejection fraction may translate into marked reductions in mortality and HF readmissions.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fca-2023-0016

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Financial & competing interests disclosure

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AstraZeneca Farmacéutica Spain provided writing assistance.

Ethical conduct of research

The registry was approved by the ethics committee of the University Hospital Reina Sofia (Córdoba, Spain). All patients provided written informed consent before being included in the registry.

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