



## Impact of Sodium Glucose Cotransporter-2 Inhibitors on Heart Failure Morbidity and Readmission Rates: an observational descriptive study

### Impact des inhibiteurs du Cotransporteur Sodium-Glucose de type 2 sur la morbidité et la réadmission des patients atteints d'Insuffisance cardiaque : une étude descriptive observationnelle

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#### Résumé

**Contexte et objectif.** L'insuffisance cardiaque (IC) est en constante augmentation dans les pays développés, notamment en France, et représente un problème majeur de santé publique en raison de son coût et du taux élevé de réhospitalisations. L'objectif de la présente étude était de déterminer les bénéfices des inhibiteurs du co-transporteur sodium-glucose de type 2 (SGLT-2i) sur la morbidité et les réhospitalisations chez les patients atteints d'IC. **Méthodes.** Une série rétrospective et descriptive des cas d'IC, a été menée du 1er janvier 2020 au 31 décembre 2023 au CH Sud Francilien. L'étude a recueilli des données exhaustives sur des facteurs sociodémographiques, cliniques (l'âge, le sexe, les habitudes de vie, les antécédents médicaux et les spécificités de l'IC), les marqueurs biologiques, les données échocardiographiques et les détails thérapeutiques (les types de médicaments et les effets indésirables des SGLT-2i). **Résultats.** Parmi les 160 patients âgés de  $71 \pm 16$  ans admis pour IC, 95 (59,4 %) n'ont pas reçu d'inhibiteur du SGLT-2, et 67 (70,5 %) d'entre eux ont été hospitalisés. Parmi les 65 patients sous gliflozines, seuls 11 (17 %) ont été réhospitalisés. L'utilisation d'inhibiteurs du SGLT-2 était associée à une réduction du nombre d'hospitalisations. L'absence de prise des SGLT-2 augmente le risque de réhospitalisation de 3,6 (IC 95% : 1,87-6,83,  $p < 0,001$ ); émergeant comme seul unique facteur indépendamment associé à la réhospitalisation pour l'IC. **Conclusion.** Les inhibiteurs du SGLT-2 ont significativement amélioré la prise en charge de l'IC et représente l'unique facteur de risque de réhospitalisation. Des études

#### Summary

**Context and objective.** Heart failure (HF) represents a major and growing public health burden in developed countries, including France, due to its high associated costs and frequent rehospitalizations. This study aimed to evaluate the impact of Sodium Glucose Cotransporter-2 Inhibitors (SGLT-2i) on morbidity and rehospitalization in patients with HF. **Methods.** We conducted a retrospective and descriptive case series study at the Sud Francilien Hospital Center from January 1, 2020, to December 31, 2023. We collected comprehensive data on sociodemographics, clinical characteristics (medical history and HF specifics), laboratory markers, echocardiographic findings, and treatment details to assesses whether SGLT-2i use was associated with a reduction in HF-related hospital readmissions. **Results.** Among the 160 patients (mean age  $71 \pm 16$  years) hospitalized for HF, 95 (59.4%) did not receive SGLT-2i, and 67 (70.5%) of them were readmitted. Out of 65 patients treated with gliflozins, only 11 (17%) were readmitted. The use of SGLT-2i inhibitors was associated with a reduction in hospitalizations. Not receiving SGLT-2 inhibitors increased the risk of readmission by 3.6-fold (95% CI : 1.87-6,83,  $p < 0.001$ ), emerging as the sole independent factor associated to heart failure readmission in this cohort. **Conclusion.** The introduction of SGLT-2i has been associated with improved outcomes and reduced rehospitalizations in HF management at our



complémentaires sont nécessaires pour évaluer la mortalité.

**Mots-clés :** Inhibiteurs du SGLT-2, Insuffisance cardiaque, Morbidité, Réhospitalisation

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## Introduction

The prevalence of heart failure is gradually increasing worldwide, which can be attributed to aging populations, increased risk factors, improved treatment outcomes, and enhanced survival rates. Between 2010 and 2019, there was a 29% increase in the global prevalence of heart failure (1-2). The estimated global prevalence of heart failure was 56.2 million people in 2019, with the highest prevalence observed in East Asia, North America, and Western Europe. (2). In states United, the prevalence of heart failure was estimated at 2,5% among adults, while in Canada it was 3.5% in 2022 (2). Contemporary data from large population-based studies indicate that the incidence of HF in adults in high-income countries ranges from 1 to 5 per 1000 person-years, with prevalence exceeding 1-2% and increasing exponentially with age (1). The prognosis remains serious, with high rates of hospitalization and rehospitalization.

The risk of developing HF increases markedly with age. After an index hospitalization or acutely decompensated HF (ADHF), up to 25% of patients are readmitted within three months, and approximately 45% within one year, highlighting a critical period of vulnerability (4). Applying estimated European incidence rates to the French population suggests between 149 000 and 312 000 new HF cases annually (5). For individuals over 65 years, the prevalence is up to seven times higher than in younger adults (2). This prevalence continues to rise globally, driven

center. Further studies are needed to evaluate their impact on mortality.

**Keywords:** Heart Failure (HF), Morbidity, Rehospitalization, SGLT-2 Inhibitors

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by population aging and improved survival from other cardiovascular conditions. HF is responsible for nearly 70 000 deaths annually in France (6). The management of HF and its frequent comorbidities place a substantial financial strain on healthcare systems.

While the epidemiological transition contributes to a rising burden of non-communicable diseases in sub-Saharan Africa, heart failure retains distinct features in this region. Recent systematic reviews indicate that HF accounts for approximately 10% of all medical admission in African hospitals, with in-hospital mortality rates ranging between 15% and 20% (7). In the Democratic Republic of the Congo (DRC), the clinical profile is dominated by hypertensive heart disease and cardiomyopathies, with reported in-hospital mortality around 14,5% (8). This underscores the critical need for effective therapeutic strategies, such as SGLT-2 inhibitors, which have proven beneficial in diverse populations but whose real-world impact in African and Congolese settings requires further evaluation.

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2i), initially developed for diabetes management, have emerged as cornerstone therapies for HF. Based on robust evidence from major trials such as DAPA-HF, EMPEROR – Reduced, and DELIVER, current European Society of Cardiology (ESC) guidelines give a class I recommendation for SGLT-2i to reduce the risk of HF hospitalization and cardiovascular



death in patients with HF, regardless of ejection fraction or diabetes status (9-11). These agents offer pleiotropic benefits, including diuresis, improved cardiac metabolism, and cardiorenal protection (12).

In alignment with these guidelines, the cardiology department of the Sud Francilien Hospital Center began systematically introducing SGLT-2i into HF treatment protocols in 2023. This study was conducted to evaluate the real-world impact of this therapeutic shift on HF morbidity and rehospitalization rates in our patient population.

## Methods

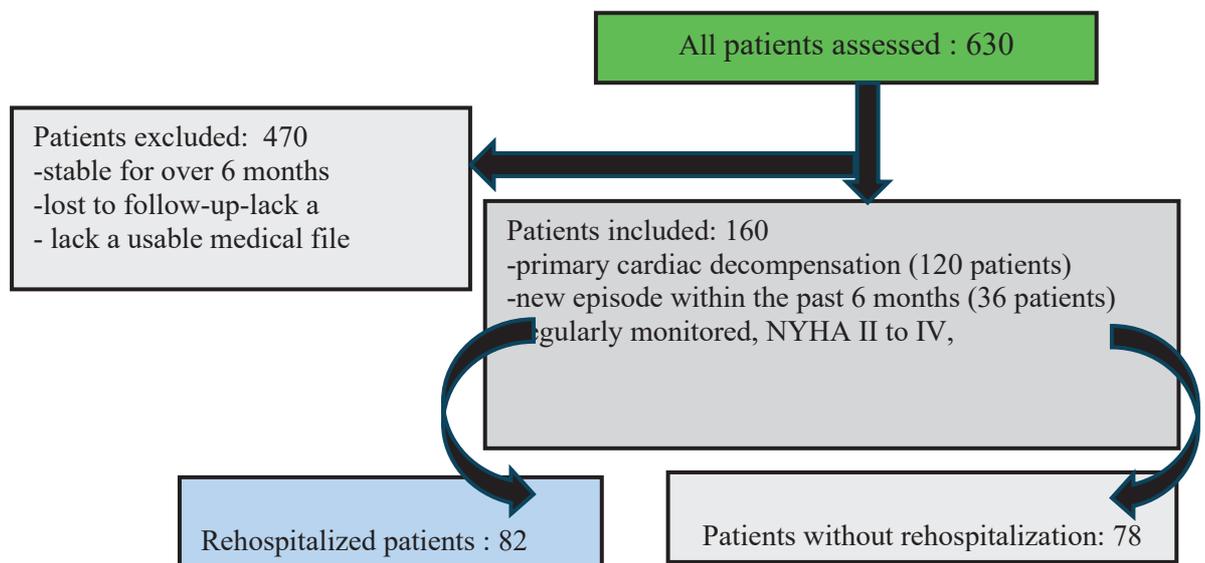
### Study design

A retrospective cohort study was conducted to evaluate the impact of SGLT-2i on readmissions rates patients with heart failure (HF) at the Centre Hospitalier Sud Francilien. This hospital is a

referral center into southern Essonne region of France, serving a population of approximately 600,000 residents. Its cardiology Department includes a dedicated HF treatment unit that provides structured biannual follow-up and maintains a comprehensive clinical database. The study period spanned from January 1, 2020, to December 31, 2023.

### Study Population and Participant flow

The study population consisted of HF patients who were either treated or not treated with gliflozins (SGLT-2i) and followed for at least one year. Figure 1 illustrates the participant flow. To ensure cohort homogeneity regarding disease activity, we initially identified 630 patients under regular following reasons: clinical stability for over six months, loss to follow-up, or incomplete medical records. The remaining 160 patients formed our study cohort.



**Figure 1. Participant flow chart**

### Inclusion and non-inclusion criteria

Inclusion criteria required patients to have HF and to be experiencing either a first episode or a new episode of cardiac decompensation within the past six months. Additionally, they had to be under regular care at the HF unit (NYHA functional class II to IV) and have fully accessible medical record.

Exclusion criteria were: clinical stability for more than six months, current absence from follow-up, or incomplete medical records

### Data collection

We extracted comprehensive data from the HF unit's electronic archives and patient records, including:

- Socio-demographic variables: age, sex, smoking status, and alcohol consumption.
- Clinical variables: symptomatology (NYHA class), blood pressure, body mass index (BMI), cardiovascular risk factors, type of HF, and history of prior hospitalizations.
- Echographic variable : left ventricular ejection (LEVG).



- Therapeutic variables: type of medications (including specific recording of SGLT-2i use, beta-blockers, ACE inhibitors /ARBs/ARNI, aldosterone anatagonists, and iron replacement), treatment duration, and any documented to SGLT-2i

*Definitions of variables and outcomes*

- *Diabetes mellitus* was identified by a fasting serum glucose level exceeding 126 mg/dl, a self-reported diagnosis, or the use of glucose-lowering medications.
- *Dyslipidemia* was defined as total cholesterol above 200 mg/dl, LDL cholesterol at or above 100 mg/dl, and/or HDL cholesterol below 50 mg/dl for women or 40 mg/dl for men.
- *Hypertension* was characterized by blood pressure readings of 140/90 mmHg or higher, or the current use of antihypertensive medications.
- *Obesity* was defined as a BMI  $\geq 30$  kg/m<sup>2</sup>.
- *HF phenotype* was classified based on LVEF: heart failure with preserved ejection (HFpEF) was defined as LVEF  $\geq 50\%$ , HFrEF was defined as LVEF  $\leq 40\%$ , HFmrEF was defined as LVEF 41-49%.
- *Chronic kidney disease (CKD)* was defined as an estimated glomerular filtration rate (eGFR)  $< 60$  ml/min/1,73 m<sup>2</sup>, calculated using the Modification of Diet in Renal Disease (MDRD) equation.
- Additional risk factors extracted from patient records include obstructive sleep apnea-hypopnea syndrome (OSAHS), chronic obstructive pulmonary disease (COPD), cirrhosis, stroke, atrial

fibrillation (Afib), and dilated cardiomyopathy (DCM).

- *Primary Outcome:* The number of hospitalization episodes for HF decompensation over a one-year follow-up period after the index event.
- *Secondary Outcomes:* Changes in clinical (NYHA class, blood pressure, BMI), biological (e GFR, NT-proBNP), and echocardiographic (LEVG) parameters during follow-up.

*Statistical Analysis*

Data were analyzed using Epi Info software version 7.2.6.0. Continuous variables are presented as mean  $\pm$  standard derivation, and categorical variables as absolute numbers and relative frequencies (percentages). Group comparisons were performed using Student's t-test for continuous variables and Pearson's chi-squared or Fisher's exact test for categorical variables, as appropriated. A logistic regression analysis was conducted using SPSS to identify independent factors associated with heart failure (HF) rehospitalization. Results are presented in tables and figures, with a two-sided p-value  $< 0,05$  considered statistically significant.

*Ethical considerations*

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki. This study protocol was reviewed and approved by the Institutional Review Board. Given the anonymous and retrospective nature of the data analysis using archived clinical records.

**Results**

The table 1 presents the association between socio-demographic characteristics and heart failure rehospitalization

The table demonstrates a significant association between age  $\geq 70$  years and heart failure rehospitalization (57.9% vs 35.4% , p=0.002). No significant difference was observed on sex (p=0.144).

**Table 1. Association between socio-demographic characteristics and heart failure rehospitalization**

Characteristics	Rehospitalization		p
	Without (n=82)	With (n=78)	
<b>Age</b> (years old)			
< 70	42 (64.6)	23(35.4)	<b>0.002</b>
$\geq 70$	40 (42.1)	55(57.9)	
<b>Sex</b>			
Male	62(75.6)	53 (67.9)	0.144



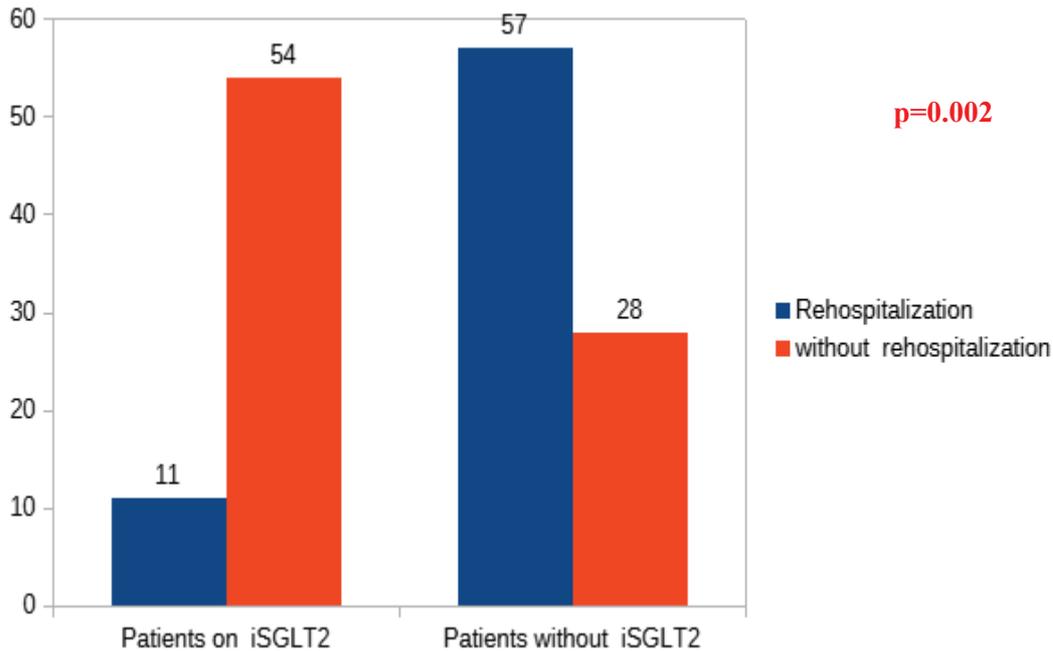
Female

20(24.4)

26(32.1)

The figure 2 illustrates the likelihood of rehospitalization based on SGLT-2 inhibitor use.

As shown, the rate of rehospitalization was significantly higher among patients not taking an SGLT2 inhibitor (62% vs. 17%,  $p= 0.002$ ).



**Fig 2. Rehospitalization depending on the intake of iSGLT2**

Table 2 presents association between cardiovascular risk factors and heart failure rehospitalization.

In this cohort, none of traditional cardiovascular risk factors showed a statistically significant

association with rehospitalization ( $p>0.005$  for all). Hypertension was the most prevalent risk factor among patients.

**Table 2. Association between cardio-vascular risk factors and heart failure rehospitalization**

Cardio-vascular risk factors	Rehospitalization		p
	Without (n=82)	With (n=78)	
HTA	62 (75.6)	59(75.6)	0.498
Type-2 diabetes	29 (35.4)	35 (44.9)	0.132
Dyslipidemia	60(73.2)	50 (64.1)	0.111
Smoking	32(39.0)	32(41.0)	0.399
Inactivity	17 (20.7)	12 (15.4)	0.195
Obesity	18 (22.0)	20 (25.6)	0.295
Ethylism	23(28.0)	11(14.1)	0.09
Heredity	1(1.2)	1(1.3)	0.495

Table 3 outlines the association between comorbidities and heart failure rehospitalization. The analysis identifies chronic obstructive pulmonary disease (COPD), chronic kidney

disease (CKD), and atrial fibrillation (AFib) as comorbidities significantly risk of rehospitalization, with p-values of 0.007, 0 .005 and 0.002, respectively.



**Table 3. Association between comorbidities and heart failure rehospitalization**

Comorbidities	Rehospitalization		p
	Without (n=82)	With (n=78)	
OSAHS	8 (9.8)	11 (14.1)	0.200
COPD	11 (13.4)	23 (29.5)	<b>0.007</b>
Cirrhosis	1 (1.2)	2 (2.6)	0.297
Renal failure	12 (14.6)	25 (32.1)	<b>0.005</b>
Neoplasia	11 (13.4)	20 (25.6)	0.016
Stroke	7 (8.5)	10 (12.8)	0.198
Afib	25 (30.5)	40 (51.3)	<b>0.002</b>

Table 4 presents the results of analysis regarding to association between guideline-directed medical therapy and heart failure rehospitalization.

Among the guideline-directed medical therapies analyzed, only the use of SGLT-2 inhibitors was

significantly associated with a reduced risk of rehospitalization ( $p < 0,001$ ). The absence of SGLT-2i therapy emerged as a strong independent predictor for readmission.

**Table 4. Association between guideline-directed medical therapy and heart failure rehospitalization**

Medication	Rehospitalization		p
	Without (n=82)	With (n=78)	
SGLT-2i	54 (65.9)	11(14.1)	<b>&lt;0.0001</b>
ACE/ARB-ARNI	70 (85.4)	66 (84.6)	0.438
$\beta$ -bloquers	73 (89.0)	62 (79.5)	0.070
Anti-aldosterone	35 (42.7)	32(41.0)	0.350
Iron replacement	15 (18.3)	12 (15.4)	0.230

The table 5 presents the factors associated with heart failure rehospitalisation in both bivariate and multivariate analyses.

In bivariate analysis, several variables showed a significant association with rehospitalization, acting as risk factors :chronic obstructive pulmonary disease COPD (OR 2,698 ,95 % CI [1,21-6,00],  $p=0,015$ ), chronic kidney disease (CKD) (OR 2,75 ,95% CI [1,26-5,97], $p=0,0105$ ), atrial fibrillation (Afib) (OR :2 .66 ,95% CI[1,36-5,19],  $p=0,004$ ) and Age  $\geq$  70 years (2,45,95% CI [1,29-4.66] ,  $p=0.006$  . In contrast, treatment

with SGLT-2 inhibitors emerged as a significant protective factor of rehospitalization (OR=0,85, 95% CI [0,384-0,1865],  $p < 0,001$ ).

However, in the multivariate model adjusted for these covariates, only the absence of SGLT-2 inhibitor therapy remained an independent and significant predictor of rehospitalization. Not receiving SGLT-2i was associated with a 3.6-fold increase in the odds of readmission (adjusted OR 3.6, 95% CI [1,187-6,83],  $p < 0,05$ . The Other variables are considered confounders.



Table 5. Factors Associated with Heart Failure Rehospitalization

Variables	Bivariate analysis		Multivariate analysis	
	p	OR (CI 95%)	p	aOR (CI 95 %)
<b>COPD</b>				
No	<b>0,015</b>	1	0,543	1
Yes		2,698 (1,21-6,01)		0,85 (0,51-1,42)
<b>Renal failure</b>				
Yes	<b>0,0105</b>	1	0,316	1
No		2,75 (1,27-5,97)		0,77 (0,47-1,28)
<b>SGLT-2i treatment</b>				
Yes		0,85 (0,0384-0,1865)		1
No	<b>&lt;0,001</b>	1	<b>&lt;0,001</b>	3,58 (1,187-6,83)
<b>AFib</b>				
No	<b>0,0039</b>	1	0,170	1
Yes		2,66 (1,37-5,17)		0,73 (0,46-1,115)
<b>Age (years)</b>				
<70	<b>0,006</b>	1		1
≥70		2,5103 (1,31-4,82)	0,445	0,82 (0,50-1,36)
<b>Neoplasia</b>				
No	<b>0,032</b>	1	0,3380	1
Yes		2,48 (1,078-5,72)		0,79 (0,46-1,35)

### Discussion

This study investigated the frequency of HF readmissions, identified contributing factors, and evaluated the effect of gliflozin use on readmission rates and clinical-biological improvement. The study revealed that nearly half of the HF patients experienced readmissions. Patients treated with gliflozins showed significant symptomatic improvement in HF, moving from NYHA class III to class II, suggesting substantial cardiovascular benefits. Moreover, the study highlighted that the lack of SGLT-2i use, along with CKD and AFib, were prominent independent risk factors for HF readmissions.

#### *Heart failure readmission rates*

HF readmissions affected nearly half (48%) of the patients in this study, consistent with findings from other studies, such as the 38% rehospitalization rate reported at the Rouen University Hospital (12). This high readmission rate is partly attributable to the aging population, as older adults often accumulate multiple cardiovascular risk factors. In our study, the mean age was  $71 \pm 15$  years; slightly lower than the 81 years reported in other studies. While rehospitalization was statistically significant for

patients over 70 ( $p = 0.002$ ), this association was not maintained in multivariate analysis ( $p = 0.385$ ) (13). These findings align with established medical literature, which indicates that heart failure affects over 23 million individuals globally, with a significant majority (80%) of these patients being 65 years of age or older (14). The prevalence of heart failure demonstrates an exponential increase with advancing age (15), with estimates suggesting it affects 10-15% of individuals over 80 years old (16). Similarly, the annual incidence rate is reported to be between 1% and 5%, also rising markedly with age and reaching as high as 40% in the population segment older than 75 years (17). Despite these general trends, the specific frequency observed in this context fluctuated over the study period, as illustrated in Figure 2. Analysis of the data reveals a substantial decrease in this frequency, from 73% in 2020 to 30% in 2023. This observed reduction can be attributed to two primary factors: firstly, an enhancement in the quality of patient care through reinforced therapeutic education programs. Secondly, and critically, the introduction of gliflozins in 2022 for select



patient groups, particularly individuals with diabetes, played a key role.

The administration of gliflozins was adopted as standard practice at the Centre Hospitalier Sud Francilien in 2023. Symptomatic improvement with gliflozins at admission, 70% of patients presented with NYHA class III HF symptoms. At the final observation, this improved, with 53% exhibiting NYHA class II symptoms. This improvement was significantly more pronounced in patients receiving gliflozins ( $p = 0.001$ ). The reduced symptom burden in patients treated with gliflozins suggests a significant cardiovascular benefit, potentially contributing to lower rehospitalization rates and reduced cardiovascular mortality. While some patients discontinued treatment due to adverse effects such as renal failure and infections, gliflozins remained the most effective option for decreasing rehospitalizations associated with ADHF (18).

#### *Factors Associated with rehospitalization*

Multivariate analysis identified only the lack of SGLT-2i use as an independent factor associated with rehospitalization, increasing the risk of readmission by 3.6-fold ( $p < 0.001$ ). This finding reinforces the rationale for employing this therapy in the management of heart failure. Its beneficial effects to hemodynamic improvements following treatment initiation. Other variables – such as chronic kidney disease (CKD), atrial fibrillation (AFib), age  $\geq 70$  years, and chronic obstructive pulmonary disease (CPOD) as confounding factors in the final model (26).

#### *Study Limitations and Strengths*

This study has limitations. First, its monocentric and retrospective design limits the generalizability of the findings to other healthcare settings or population. Second, the data were collected during routine clinical care rather than within a controlled prospective research protocol. This introduces the potential for selection bias, as the included patients represent those who were available for and adherent to follow-up in a specialized unit, not a systematically recruited population-based sample. Third, the relatively small sample size ( $n=160$ ) may affect the precision of our estimates and the power to detect smaller but potentially meaningful associations, particularly for some secondary outcomes and subgroup analyses. Fourth, the follow-up duration was limited to one year; long-term effects of SGLT-2i on outcomes like mortality or sustained morbidity reduction could not be assessed.

Despite the limitations, the strength of the study lies in its real-world, contemporary setting, providing a "proof-of-concept" for the effectiveness of implementing guideline-recommended SGLT-2i therapy in daily practice. It clearly demonstrates a significant association between SGLT-2i use and reduced HF rehospitalization, reinforcing trial data in routine care context.

#### **Conclusion**

This study evaluated the impact of SGLT-2i on HF rehospitalization. Our findings support the efficacy of SGLT-2i in reducing HF morbidity. However, due to the small, monocentric sample size, larger prospective studies are needed to confirm these results and ensure generalizability. Acknowledgements We thank all the staff of the heart failure treatment unit at the Sud Francilien Hospital Center for the quality of the data and patient monitoring which allowed us to carry out adequate analysis.

#### **Disclosures None**

#### **Author's contribution**

Study design: NBB, APO, CP, FAY, FK

Data collection: APO, FAY, J-PK, FK, AA

Results' interpretation: NBB, APO

Data analyses: NBB, APO

Manuscript penning: APO, NBB, CP, FAY, KK, DB, EMB, CA, TT, AK

Manuscript revision: APO, NBB, CP, FAY, FK, J-RRM, PMB.

Guarantor: NB

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