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FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database

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Aims Oral glucose-lowering medications are associated with excess risk of heart failure (HF). Given the absence of comparative data among drug classes, we performed a retrospective study in 32 Health Services of 16 Italian regions accounting for a population of 18 million individuals, to assess the association between HF risk and use of sulphonylureas, DPP-4i, and glitazones.

Methods and results We extracted data on patients with type 2 diabetes who initiated treatment with DPP-4i, thiazolidinediones, or sulphonylureas alone or in combination with metformin during an accrual time of 2 years. The endpoint was hospitalization for HF (HHF) occurring after the first 6 months of therapy, and the observation was extended for up to 4 years. A total of 127 555 patients were included, of whom 14.3% were on DPP-4i, 72.5% on sulphonylurea, 13.2% on thiazolidinediones, with average 70.7% being on metformin as combination therapy. Patients in the three groups differed significantly for baseline characteristics: age, sex, Charlson index, concurrent medications, and previous cardiovascular events. During an average 2.6-year follow-up, after adjusting for measured confounders, use of DPP-4i was associated with a reduced risk of HHF compared with sulphonylureas [hazard ratio (HR) 0.78; 95% confidence interval (CI) 0.62–0.97; $P = 0.026$]. After propensity matching, the analysis was restricted to 39 465 patients, and the use of DPP-4i was still associated with a lower risk of HHF (HR 0.70; 95% CI 0.52–0.94; $P = 0.018$).

Conclusion In a very large observational study, the use of DPP-4i was associated with a reduced risk of HHF when compared with sulphonylureas.

Keywords Diabetes • Heart failure • Incretin • Epidemiology • Medications

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Introduction

Type 2 diabetes (T2D) is associated with excess cardiovascular disease, including a marked increase in the risk of heart failure (HF).[1] Interest in the cardiovascular effects of glucose-lowering medications is extremely high, and the number of drug categories for the treatment of T2D is rapidly expanding. According to the joint EASD/ADA position statement on the management of hyperglycaemia in T2D, 'comprehensive cardiovascular risk reduction must be a focus of therapy'.[2] Unfortunately, availability of robust data on solid cardiovascular endpoints in patients treated with different glucose-lowering regimens is limited. Incretin-based therapies, including GLP-1 receptor agonists and DPP-4 inhibitors (DPP-4i), have pleiotropic cardiovascular effects, demonstrated experimentally and clinically, which may translate into protection from vascular events.[3] However, recent data have raised concerns about the risk of HF associated with the use of DPP-4i. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) study, therapy with the DPP-4i saxagliptin vs. placebo over a median of 2.1 years was associated with a 27% excess hospitalization for HF (HHF).[4] In contrast, the EXAMINE trial, conducted in patients with recent acute coronary syndrome, showed that the DPP-4i alogliptin did not significantly increase the risk of HHF compared with placebo.[5] Subsequently, results from observational studies on DPP-4i therapy reported a neutral effect on HHF,[6,7] or excess risk of HHF,[8] or excess HHF risk only in patients with a previous HF history.[9] Results from meta-analyses of randomized trials also suggested that DPP-4i is associated with an increased HF risk,[10–12] although most of this conclusion is driven by the SAVOR trial.

In this study, making use of a registry including about 30% of the Italian population, we performed a retrospective analysis to assess the association between use of oral glucose-lowering medications and subsequent HHF. We specifically assessed the risk conferred by DPP-4i compared with sulphonylureas, as still being the most widely used oral medications for T2D in Italy, and with thiazolidinediones (glitazone), as they have been previously associated with excess HF risk.

Methods

Data retrieval

This retrospective study used data from the Nationwide OsMed Health-DB Database. This database, participated by 35 Italian Local Health Units (LHUs), includes about 18 million subjects (30% of the Italian population), with a uniform distribution in North (28.7%), Center (33.7%), and South (29.8%) of Italy and a historical series from 2009. The mean age (43.5 years) and the percentage of males (48.5%) in individuals included in the database are in accordance with national data.

The Italian Medicines Agency (AIFA—Agenzia Italiana del Farmaco) is the national competent authority responsible for regulation of medicine's use in Italy. Inside AIFA, the OsMed monitors nationwide the use of medicines in Italy, and it performs analyses on patients' level data prospectively by the technical support of CliCon. Clicon was delegated by AIFA for data warehousing and data mining activities of information voluntarily provided by LHUs and stored in their own local administrative databases. To comply with privacy legislation, patient ID code was anonymized by LHUs. Using this database, OsMed reports on medication use in Italy are published yearly by AIFA with the following objectives: (i) to describe drug consumption nationwide, (ii) to examine changes in drug use over time, (iii) to benchmark drug consumption across different Italian regions, and (iv) to evaluate appropriate use of drugs and adherence with treatment.

For this study, anonymous patient records were retrieved from multiple administrative health service databases, including peripheral and centralized pharmaceutical services, hospital discharge charts, disease-specific economic exemption, and health services provided by LHUs and hospitals. For each individual, such data were integrated to yield a chronologic and analytic profile. Accrual time was set between 1 January 2010 and 31 December 2012. We included all patients with T2D who were prescribed for the first time and at least once a DPP-4i (ATC classes A10BH/A10BD07/A10BD08), a sulphonylurea (ATC classes A10BB/A10BD01/A10BD02), or a glitazone (ATC classes A10BB/A10BD01/A10BD02), alone or in combination with metformin. No other combinations were allowed, but patients could have been previously treated with different oral glucose-lowering drugs in the 12 months preceding the index date. The date of first prescription was set as the index date, from which the observation of each patient started. The endpoint was defined as a hospital discharge event with a primary diagnosis of HF, with an ICD-9 code 428, up to the end of the observation period, at 31 December 2013 or the death, whichever occurred earlier. This information was retrieved only from hospital discharge charts, which are uniformly coded and standardized in all Italian LHUs and hospitals, are compiled by the physician(s) directly in charge of the patients, and are individually validated by hospitals against detailed clinical-instrumental data, as they determine reimbursement from the National Health System. In addition, to limit the chance of misclassification in the primary analysis, the endpoint was met only when HF was the primary diagnosis in discharge charts, and not when it was a concomitant diagnosis (e.g. HF in patients with a primary diagnosis of acute kidney disease or acute respiratory failure), because the interplay between glucose-lowering medications and secondary HF may be indirect and more difficult to infer. Exposure time was calculated from prescriptions and access to the pharmaceutical services to indicate total treatment duration, whereas time to event was the time elapsed from index data and date of the event (coded date of the hospital discharge).

Exclusion criteria for the primary analysis were: a previous HHF (hospital discharge ICD-9 code 428) during the 12 months before the index date; use of insulin during the 12 months before the index date or during the observation period; and observation time shorter than 6 months after the index date, to ensure a minimum interval for adherence assessment (the use of short intervals to assess adherence does not reflect long-term behaviours)[13] and to avoid reverse causality. Several subsequent sensitivity analyses were then performed including: patients with a previous HHF episode; patients censored in the first 6 months; and patients with HHF episodes in secondary diagnosis. For all patients, we collected the following data, recorded in the 12 months before the index date: age, sex, Charlson index, previous hospitalization for cardiovascular causes (ICD-9 codes 410–414 for myocardial infarction, ICD-9 430–438 for stroke, ICD-9 440–442 for peripheral arterial disease, and ICD-9 401–405 for other cardiovascular diseases), previous glucose-lowering medications use, ongoing medications for hypertension (ATC classes C02, C03, C07–09), dyslipidaemia (ATC class C10), chronic obstructive pulmonary disease (ATC class R03), and anti-inflammatory (ATC class M10) and anti-platelet medications (ATC class B01). Adherence to glucose-lowering medications was defined using the medication possession ratio (MPR), a method used in prior studies to quantify medication adherence.[14,15] The MPR was estimated by calculating the proportion of pill-days available from filled prescriptions of the oral glucose-lowering medications during the interval from the index date until a first HHF, death, or 31 December 2013, whichever occurred

first. In the case of combination with metformin, the average of the MPRs for each class of drugs was calculated. Days when patients were in an institutionalized care setting, such as hospitals, were excluded from the MPR calculation. We defined 'non-adherence' as an MPR $<$ 80%.[16,17]

Statistical analysis

Data are expressed as mean ± standard deviation or as percentage where appropriate. Comparisons among groups were performed using analysis of variance (ANOVA) and Pearson's χ^2 test for continuous and categorical data, respectively. The *post hoc* Bonferroni correction was used to account for multiple testing. The Cox proportional hazard regression analysis was used to describe the associations between glucose-lowering medication regimen and the endpoint. The other covariates in the model were: age, sex, the use of certain medications (yes/no) (drugs for hypertension, dyslipidaemia, chronic obstructive pulmonary disease, non-steroidal anti-inflammatory drugs, and anti-platelet medications), the presence of previous hospitalizations (yes/no), the Charlson index level grouped into three categories (index score = 1; between 2 and 3; and ≥4), previous oral glucose-lowering medications (yes/no), the presence of a co-treatment with metformin (yes/no), and adherence level categorized on the basis of the MPR and grouped into two categories, i.e. MPR $<$ 80 and MPR ≥ 80%. Patients without study outcomes were considered as censored. The proportional hazards assumption was not violated.

In addition to the main analysis, as in the observational studies, treatment selection is often influenced by subject characteristics; in order to address the issues of confounding by indication, we used a propensity score-matching analysis to balance the different glucose-lowering treatment groups on the possible baseline confounders (1 : 1 : 1 match).[18] A multinomial logistic model was performed, and the probability of receiving each treatment category given the observed covariates was estimated. All the variables listed in *Table 1* were included in the model, regardless of statistical significance.[19] After fitting the model, patients were ranked by their estimated propensity score and grouped within quintiles.[20] Quintiles are commonly used for adjustment, as they are expected to remove 90% of the confounding. However, the smaller the strata are, the better they will balance the covariates and the more confounding they will remove.[21] Thus, also deciles of the propensity score were created. The balance of the confounders was assessed using the standardized difference.[21] Next, a pairwise random sampling approach was used. Within each stratum, first, equal sample sizes in the DPP-4i and glitazone groups were selected; then, equal sample sizes were randomly chosen among the DPP-4 sample previously selected and the sulphonylurea group, obtaining the same sample size among the three groups.[22] We used Kaplan–Meier curve techniques to calculate cumulative survival probability of HHF among the three propensity score-matched samples.[23] Unadjusted survival group comparisons were made with a log-rank test. An additional Cox proportional hazard regression analysis was performed to describe the associations among glucose-lowering medication regimen, adherence level, and the endpoint. Statistical significance was accepted at $P < 0.05$, and Stata software version 12.1 (StataCorp LP, College Station, TX, USA) was used.

Results

Baseline characteristics

A total of 127 555 patients were included in the analysis. During the observation period, 14.3% were treated with a DPP-4i, 72.5% with a

Table 1 Clinical characteristics of the entire study cohort

Characteristics	All	DPP-4i	Sulphonylureas	TZD	*P*-value
Number (%)	127 555 (100.0)	18 294 (14.3)	92 463 (72.5)	16 798 (13.2)	
Age, mean ± SD	67.0 ± 13.4	62.3 ± 11.6*	68.5 ± 13.5	63.5 ± 13.2***	<0.001
Sex, % male	51.9	56.3*	50.5**	54.6***	<0.001
Charlson index					
1	72.6	58.4*	76.8**	64.7***	<0.001
2–3	24.1	37.7*	20.1**	31.6***	
≥4	3.3	3.9*	3.1**	3.7***	
Previous cardiovascular event (%)	4.5	5.3*	4.4	4.6***	<0.001
Previous glucose-lowering medications (%)	35.9	77.8*	24.1**	54.8***	<0.001
Other medications					
Diuretics (%)	1.1	0.7*	1.3**	0.9	<0.001
Beta-blockers (%)	2.2	3.0*	2.1	2.3***	<0.001
Calcium channel blockers (%)	1.5	1.3*	1.6**	1.3	<0.001
RAS blockers (%)	15.3	19.9*	13.8**	18.5***	<0.001
Combination of blood-pressure-lowering drugs (%)	31.8	37.3*	30.6**	32.2***	<0.001
Lipid lowering (%)	26.3	44.2*	21.5**	33.2***	<0.001
Anti-inflammatory (%)	20.0	19.5*	19.7**	22.1***	<0.001
Anti-chronic obstructive pulmonary disease (%)	7.5	6.9*	7.6	7.5	0.004
Anti-platelet (%)	26.2	34.0*	24.3**	27.9***	<0.001

ANOVA *P*-values are shown: after *post hoc* Bonferroni correction.
*$P < 0.05$ in the comparison between DPP-4i and sulphonylureas.
**$P < 0.05$ in the comparison between sulphonylureas and glitazones (TZD).
***$P < 0.05$ in the comparison between DPP-4i and TZD.

Table 2 Incidences of the endpoint (events of hospitalization discharge with a diagnosis of HF) in patients before (whole cohort) and after propensity matching

Before propensity matching	DPP-4i	Sulphonylureas	TZD
Patient number	18 294	92 463	16 798
Patients with events, *n* (%)	96 (0.5)	1085 (1.2)	138 (0.8)
Total events, *n*	131	1465	182
Patients with fatal events, *n* (%)	27 (0.2)	176 (0.2)	25 (0.1)
Mean exposure time ± SD	2.2 ± 0.8	2.6 ± 0.8	2.6 ± 0.8
Crude event rate (per 1000 person-years)	2.4	4.5	3.1
After propensity matching			
Patient number	13 155	13 155	13 155
Patients with events, *n* (%)	71 (0.5)	128 (1.0)	103 (0.8)
Total events, *n*	93	183	127
Patients with fatal events, *n* (%)	19 (0.1)	22 (0.2)	19 (0.1)
Mean exposure time ± SD	2.2 ± 0.8	2.6 ± 0.8	2.6 ± 0.8
Crude event rate (per 1000 person-years)	2.4	3.8	3.0

sulphonylurea, and 13.2% with a glitazone (which was pioglitazone in 98.2% of the cases). Overall, 70.7% of the patients were co-treated with metformin (86.4% for DPP-4i, 79.5% for glitazones, and 65.9% for sulphonylureas). Upon ANOVA or Pearson's χ^2 test, all clinical characteristics differed according to the ongoing glucose-lowering regimen (*Table 1*).

Hospitalization for heart failure risk

During the observation period (mean follow-up of 2.6 years), a total of 1778 HF hospital discharge events were recorded, occurring in 1319 patients (equal to an average 1.35 episodes/patient). Incidences of the outcome in patients divided according to the ongoing glucose-lowering regimen are reported in *Table 2*.

In a Cox proportional hazard regression model adjusted for all clinical variables collected at baseline, the HHF risk was significantly lower in patients treated with a DPP-4i [hazard ratio (HR) 0.78 (0.62–0.97); $P = 0.026$] and lower, but not significantly, in patients treated with a glitazone [HR 0.89 (0.74–1.06); $P = 0.188$] than that in patients treated with a sulphonylurea (*Table 3*). With DPP-4i as reference, the HRs were 1.29 (1.03–1.61) for sulphonylureas ($P = 0.026$) and 1.14 (0.88–1.48) for glitazones ($P = 0.334$), respectively. Overall, the HHF resulted in death in 17.3% of the patients. There were no differences in the incidence of fatal HHF among patients treated with DPP-4i, sulphonylureas, and glitazones (*Table 2*).

Given the multiple statistically significant and clinically relevant differences among the groups of patients treated with DPP-4i, glitazones, and sulphonylureas (*Table 1*), a propensity score matching was performed. Once the logistic model was fitted, patients were ranked, divided into quintiles, and the balance of confounders was checked, but it was not good enough. The data were then divided into deciles of the propensity score, and the balance of confounders was re-checked (*Figure 1*). We obtained a better balance using 10 strata rather than 5, and the differences were much smaller than before (all <0.1 SD). After performing the random selection within strata, the number of patients included in the analysis was reduced to 39 465 (Supplementary material online, *Table S1*). In this matched cohort, DPP-4i, glitazones, and sulphonylureas were associated with metformin on average on 80.6% (83.4% for DPP-4i, 83.3% for glitazones, and 75.0%, for sulphonylureas). Incidences of the outcome in this subcohort divided according to the ongoing glucose-lowering regimen are reported in *Table 2* (lower part). *Figure 2* shows the Kaplan–Meier curves of HHF-free survival among the propensity score-matched groups. The crude HHF incidence was lowest in patients treated with DPP-4i and highest in patients treated with sulphonylureas ($P = 0.014$). In the Cox proportional hazard regression analysis, the risk of HF remained significantly lower in patients treated with a DPP-4i [HR 0.70 (0.52–0.94); $P = 0.018$] than that in patients treated with a sulphonylurea, even after propensity matching (*Table 3*). Using DPP-4i as reference, the HRs were 1.42 (1.06–1.91) for sulphonylureas ($P = 0.018$) and 1.16 (0.86–1.58) for glitazones ($P = 0.331$), respectively. Still, no differences among groups in fatal HHF were detected (*Table 2*).

Sensitivity analysis

Among the 2609 patients excluded from the primary analysis for having less than 6 months of follow-up, 508 (19.5%) experienced a HHF. Using sulphonylureas as reference, the HRs for HHF were 1.46 [95% confidence interval (CI) 1.09–1.96; $P = 0.011$] for DPP-4i and 0.89 (95% CI 0.65–1.22; $P = 0.457$) for glitazones. When these subjects were included in the primary analysis, for a total of 130 164 patients, the HRs for HHF were 0.92 (95% CI 0.77–1.09; $P = 0.318$) for DPP-4i and 0.86 (95% CI 0.74–1.01; $P = 0.062$) for glitazones. Violation of proportional hazard assumption in this model lends support to the exclusion of patients with <6 months of follow-up.

Including patients who had experienced a HF episode during the 12 months before the index date, using the sulphonylurea as

Table 3 Results of the Cox proportional hazard multiple regression analysis in the whole study population

Variable	Before propensity matching		After propensity matching	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.066 (1.060–1.072)	<0.001	–	–
Sex male	1.301 (1.165–1.454)	<0.001	–	–
Charlson index				
1 (reference)	1.000			
2–3	1.301 (1.132–1.495)	<0.001		
≥4	1.580 (1.250–1.998)	<0.001	–	–
Previous cardiovascular event	1.950 (1.651–2.304)	<0.001	–	–
Previous glucose-lowering medications	1.235 (1.061–1.437)	0.007		
Glucose-lowering medications				
Sulphonylureas (reference)	1.000		1.000	
Glitazones	0.885 (0.738–1.061)	0.188	0.816 (0.629–1.059)	0.126
DPP-4 inhibitors	0.777 (0.623–0.970)	0.026	0.702 (0.524–0.940)	0.018
Combination with metformin	1.025 (0.902–1.165)	0.705	–	–
Adherence to therapy	0.492 (0.437–0.555)	<0.001	0.458 (0.364–0.576)	<0.001
Other medications				
Diuretics	1.706 (1.215–2.395)	0.002	–	–
Beta-blocking agents	0.690 (0.410–1.160)	0.162		
Calcium channel blockers	1.252 (0.850–1.844)	0.256		
Agents acting on the renin–angiotensin system	0.770 (0.624–0.950)	0.015		
Combination of blood-pressure-lowering drugs	1.519 (1.311–1.761)	<0.001		
Lipid-lowering	0.907 (0.796–1.034)	0.144	–	–
Anti-inflammatory	0.716 (0.621–0.827)	<0.001	–	–
Anti-chronic obstructive pulmonary disease	1.259 (1.074–1.477)	0.005	–	–
Anti-platelet	1.667 (1.461–1.902)	<0.001	–	–

reference, the HRs for HHF were 0.63 (95% CI 0.34–1.16; $P = 0.140$) for DPP-4i and 1.31 (95% CI 0.80–2.16; $P = 0.282$) for glitazones.

When considering hospitalizations with both primary and secondary HF diagnoses, a total of 3229 HF hospital discharge events were recorded, occurring in 2210 of the 127 555 patients, 60% of whom had already been included in the primary analysis. Using sulphonylureas as reference, the HRs for HHF were 0.75 (95% CI 0.63–0.89; $P = 0.001$) for DPP-4i and 0.93 (95% CI 0.81–1.06; $P = 0.277$) for glitazones (*Table 4*). After the propensity score matching, using sulphonylureas as reference, the HRs for HHF were 0.64 (95% CI 0.51–0.81; $P < 0.001$) for DPP-4i and 0.78 (95% CI 0.63–0.95; $P = 0.014$) for glitazones.

Discussion

In this retrospective analysis of 127 555 unmatched patients with T2D, extracted from a population of 18 million individuals, we show that the risk of HHF in patients with T2D taking DPP-4i over a period of 2.6 years was significantly lower than that in patients taking sulphonylureas. The finding was confirmed when the analysis was restricted to 39 465 propensity-matched patients with T2D. This resulted from a decrease of non-fatal HHF in DPP-4i-treated patients, as the rate of fatal HHF was not different among treatment groups.

Almost all oral glucose-lowering medications may increase the risk of HF.[24] The excess cardiovascular risk of glitazones prompted regulatory agencies to require post-approval safety studies for all new products approved for the treatment of T2D.[25] Given that this guideline has been implemented only recently, observational studies can bridge this gap of information, while awaiting results of cardiovascular safety studies.

Incretin-based therapies have pleiotropic effects that may reduce cardiovascular risk.[26] However, there are several reasons whereby pre-clinical findings and clinical studies on surrogate endpoints may not translate into a protection from hard endpoints. DPP-4i can affect vascular function via GLP-1-dependent and -independent actions.[3] Although GLP-1-dependent effects are common to GLP-1 receptor agonists, the DPP-4 enzyme inactivates several substrates different from incretin hormones (including cytokines, chemokines, and neurohormones),[27] many of which can exert favourable, but unpredictable, vascular effects in the clinical setting and in the long run.

Unexpectedly, in the SAVOR trial, conducted on 16 492 patients with T2D and a history of, or at risk for, cardiovascular events, who were randomized to saxagliptin or placebo, an excess 27% HHF was detected in the saxagliptin group over a mean follow-up of 2.1 years.[4] A subsequent re-analysis of this study reported that excess

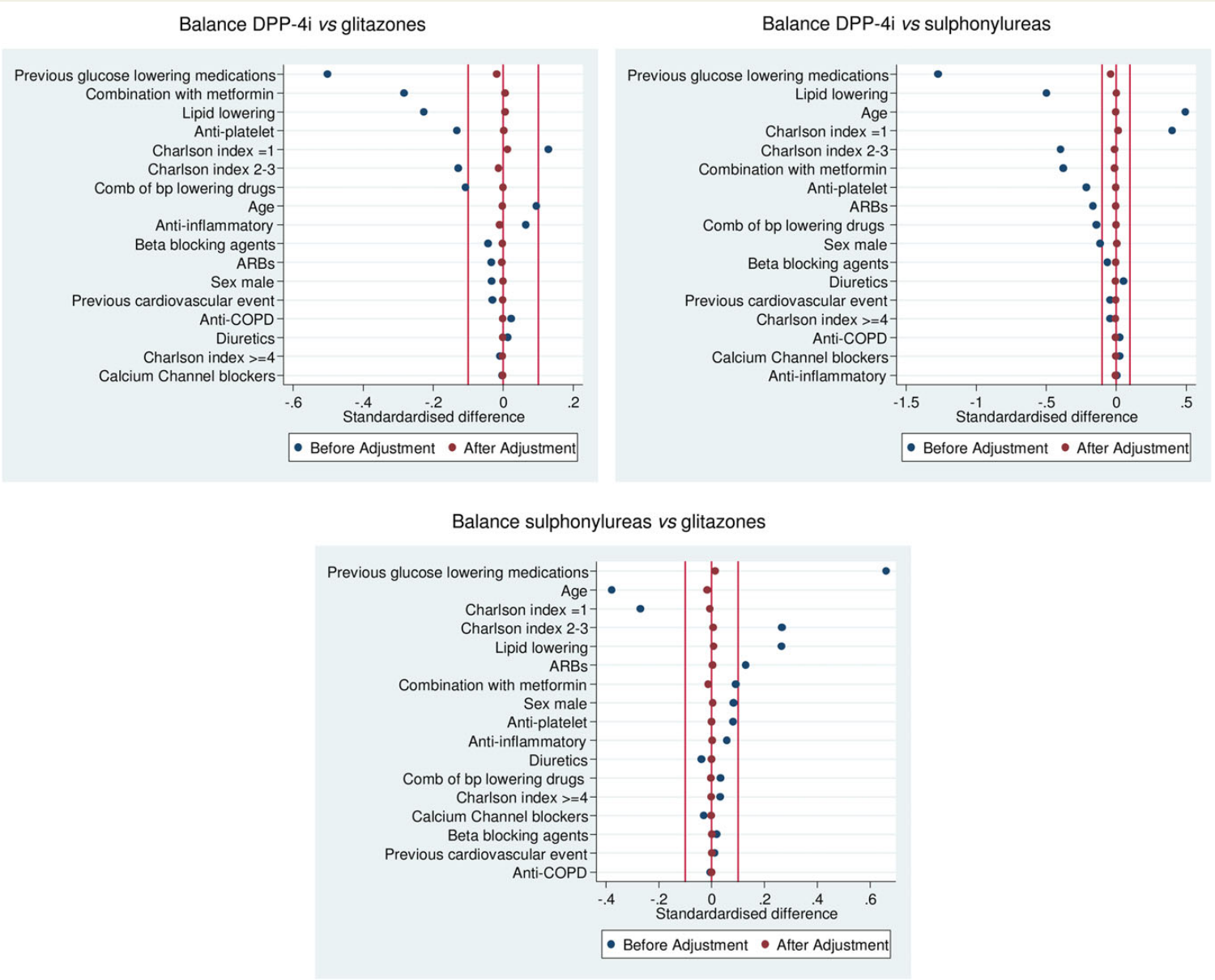

Figure 1 Balance of confounders after stratifying into deciles in the propensity matching procedure. The standardized differences are shown in Love plots.

HHF risk decreased after the first 6 months of randomization and was highest among patients with elevated levels of natriuretic peptides, previous HF, or chronic kidney disease.[28]

Primed by these data, several observational studies reported conflicting results on the association between DPP-4i and HF. In a population-based study in Taiwan, including 8288 matched pairs of patients, treatment with sitagliptin was associated with a significant 21% increase in HHF, with no change in all-cause mortality.[8] In a nested case–control study conducted on 10 073 Danish patients with T2D, DPP-4i had a neutral effect on all cardiovascular outcomes, including HF.[7] In a population-based retrospective cohort study including 7620 patients with T2D and incident HF in Canada, sitagliptin use was associated with an increased risk of HHF only among patients with pre-existing HF.[9] Finally, Velez *et al.*[29] reported that, among 4224 patients with T2D treated with an incretin- or non-incretin-based regimen (1 : 2 ratio), the use of DPP-4i was associated with a significantly lower risk of HHF, all-cause hospitalization, and mortality.

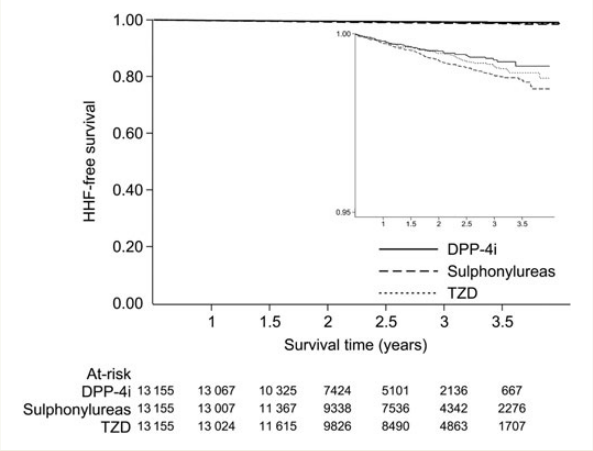

Figure 2 Kaplan–Meier curves showing HHF-free survival in the three groups of patients on DPP-4 inhibitors (DPP-4i), glitazones, or sulphonylureas in matched samples. Owing to the low absolute rate of HHF, curves are indistinguishable when the *Y*-axis is set from 0 to 1. The plot has been therefore exploded in the insert graph with *Y*-axis set from 0.95 to 1.00.

In addition to these observational data, three meta-analyses of phase III–IV randomized-controlled trials, including 55 141–85 224 patients, reported an increased risk of HHF from 16 to 19% associated with the use of DPP-4i.[10–12] However, the increased risk of HHF was mainly driven by the SAVOR trial, which was the largest and longest study included in the aforementioned meta-analyses.

Uncertainty remains on the concerns raised by the SAVOR study regarding the risk of HF associated with DPP-4i therapy vs. placebo, but the question raises on the comparative effect of DPP-4i vs. other second-line oral agents for T2D. In this very large observational study, we specifically focused on the comparison between DPP-4i and sulphonylureas, which are still the most used oral medications for the treatment of T2D in Italy. In order to limit selection bias, we purportedly excluded patients on diet alone or on metformin monotherapy, as they would be predicted to be healthier, with shorter disease duration and lower HbA1c than patients who received treatment intensification with a second-line oral agent (sulphonylurea, TZD, or DPP-4i). The 28–30% lower risk of HHF detected in the DPP-4i group may thus derive from a beneficial protective effect of DPP-4i or from a detrimental effect of sulphonylureas on HF. In fact, sulphonylureas have been associated with an increased risk of HF compared with metformin.[30–32] In any case, our findings may have implications for the care of T2D in routine clinical practice and may favour a shift in prescription trends towards oral medications, with a more favourable cardiovascular risk profile. We also show that use of glitazones was not associated with excess HHF, likely because clinicians aware of the potential HF-precipitating effect of glitazones do not prescribe such drugs to patients deemed at risk.

Our study has limitations inherent to its observational and retrospective nature. The typical bias is that differences in the outcomes according to ongoing therapies may not be attributable to specific effects of the drugs, but rather to the reasons whereby different patients receive different drugs. This is clearly demonstrated by the statistically significant and clinically meaningful differences in baseline characteristics, according to the glucose-lowering medication regimen (*Table 1*). Despite multivariable adjusting, residual bias is typically generated from unmeasured confounders. For instance, we have no data on body mass index, glucose control, disease duration, microvascular complications, and asymptomatic left ventricular dysfunction, all of which may affect the risk of HF. In addition, prescription of DPP-4i is subjected to a registry-based appropriateness evaluation and monitoring in Italy, thereby increasing the

Table 4 Results of the Cox proportional hazard multiple regression analysis in the whole study population including hospitalization episodes with a primary or secondary HF diagnosis

Variable	Before propensity matching		After propensity matching	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Glucose-lowering medications				
Sulphonylureas (reference)	1.000		1.000	
Glitazones	0.926 (0.807–1.063)	0.277	0.777 (0.635–0.950)	0.014
DPP-4 inhibitors	0.751 (0.630–0.895)	0.001	0.642 (0.510–0.808)	<0.001

likelihood that patients on DPP-4i were prescribed the drugs more appropriately and followed-up more regularly in a specialty settings than those prescribed other medications. To improve reliability and cope with selection and prescription biases, the propensity score matching provides a means of reducing the differences among patient groups by accounting for the covariates that predict receiving the treatment.[33] After matching, the study cohort was reduced to 39 465 patients, and use of DPP-4i was still associated with a significantly lower risk of HHF. These results strongly reinforce what was shown in the total population using multivariate adjustment. In addition, use of DPP-4i was associated with a lower HR risk than use of sulphonylureas, even when including hospitalization with both primary and secondary diagnoses of HF.

In the sensitivity analysis, the use of DPP-4i was associated with an increased risk of HHF compared with sulphonylureas in patients with less than 6 months of follow-up. This analysis does not allow proper adjustment for adherence to medications, which is critical when exposure is determined by prescription records, thereby generating uncertainties on whether the patients actually took the drugs. The results may be also explained by reverse causality, i.e. a higher likelihood of being prescribed a DPP-4i than a sulphonylurea in patients deemed at risk for HHF in the short term. In fact, when the analysis included patients with a previous history of HF, those in which the risk of subsequent HF is highest, the use of DPP-4i still showed trend protection against HHF.

In conclusion, this large observational study shows lower HHF risk in DPP-4i- vs. sulphonylurea-treated patients. These data do not confirm, nor contrast with what was shown by the SAVOR trial, which only compared saxagliptin with placebo. While waiting for the forthcoming phase IV randomized comparator-controlled trials on cardiovascular outcomes of DPP-4i, this reassuring finding may provide a basis for guiding the clinical care of patients with T2D.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

All authors contributed substantially to study conception and design, acquisition of data, analysis and interpretation of data, drafting the article, or revising it critically. All authors approved the final version to be published. The views presented in this article are those of the authors and should not be understood or quoted as being made on behalf of the Italian Medicines Agency (AIFA) and/or the European Medicines Agency (EMA) and/or their scientific committees.

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