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Insulin treatment in patients with diabetes mellitus and heart failure in the era of new antidiabetic medications

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ABSTRACT

Background Coexistent heart failure (HF) and diabetes mellitus (DM) are associated with marked morbidity and mortality. Optimizing treatment strategies can reduce the number and severity of events. Insulin is frequently used in these patients, but its benefit/risk ratio is still not clear, particularly since new antidiabetic drugs that reduce major adverse cardiac events (MACEs) and renal failure have recently come into use. Our aim is to compare the clinical effects of insulin in a real-world setting of first-time users, with sodium-glucose cotransporter-2 inhibitor (SGLT-2i), glucagon-like peptide-1 receptor agonist (GLP-1RA) and the other antihyperglycemic agents (other-AHAs).

Methods We used the administrative databases of two Italian regions, during the years 2010–2018. Outcomes in whole and propensity-matched cohorts were examined using Cox models. A meta-analysis was also conducted combining the data from both regions.

Results We identified 34 376 individuals ≥50 years old with DM and HF; 42.0% were aged >80 years and 46.7% were women. SGLT-2i and GLP-1RA significantly reduced MACE compared with insulin and particularly death from any cause (SGLT-2i, hazard ratio (95% CI) 0.29 (0.23 to 0.36); GLP-1RA, 0.482 (0.51 to 0.42)) and first hospitalization for HF (0.57 (0.40 to 0.81) and 0.67 (0.59 to 0.76)).

Conclusions In patients with DM and HF, SGLT-2i and GLP-1RA significantly reduced MACE compared with insulin, and particularly any cause of death and first hospitalization for HF. These groups of medications had high safety profiles compared with other-AHAs and particularly with insulin. The inadequate optimization of HF and DM cotreatment in the insulin cohort is noteworthy.

Significance of this study

What is already known about this subject?

- Around 30% of patients with heart failure (HF) along with diabetes mellitus (DM) are treated with insulin. Results from post hoc analyses of HF trials and epidemiological studies showed that insulin increased the risk of death and HF hospitalizations. No randomized controlled trials have been done to assess the effect of insulin on clinical outcomes, and no data are available on its effects on major acute events when compared with the new antidiabetic medications—sodium glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonist (GLP-1RA). Some SGLT-2i are associated with a risk reduction of all-cause mortality, hospitalization for HF and renal failure in patients with HF with reduced ejection fraction and DM and of the combined endpoint of CV death or hospitalization in HF with preserved ejection fraction; no data from clinical trials in HF are available about GLP-1RA.

What are the new findings?

- The analysis of this population database showed that long-term treatment with either SGLT-2i or GLP1-RA compared to insulin was associated with a significant reduction of risk of death for any cause, first hospitalization for HF and of major cardiovascular events.
- Individuals from the insulin cohort were undertreated with recommended cardiovascular medications and metformin.

How might these results change the focus of research or clinical practice?

- The use of SGLT-2i or GLP-1RA reduces major adverse cardiovascular events when compared with patients treated with insulin and also allow to reduce the insulin daily dose that further may decrease patients' clinical risk. Treatment with insulin should be carefully individualized by a multidisciplinary team which includes cardiologists and diabetologists.

INTRODUCTION

Cardiovascular (CV) disease is the main cause of mortality and morbidity in patients with diabetes mellitus (DM). The risk of heart failure (HF) is more than double compared with that in patients without DM[1] and although the determinants are not completely understood, the most important causes are hypertension, coronary artery disease and independent deleterious biochemical, functional and morphological changes of the myocardium.[2] DM and HF separately are associated with significant mortality and morbidity and their coexistence further

worsens patients' outcomes, quality of life and burden of care.[3 4]

The optimization of treatment strategies can reduce the number and severity of events in these high-risk patients. It is well established that some classes of antidiabetic agents increase the risk of CV events,[3] but this is still not defined for others.

Around 30% of patients with HF along with DM are treated with insulin[5 6] although no randomized controlled trials have been or—could be—done to assess the effect of insulin on clinical outcomes. Therefore, no strong evidence on the effect of insulin in patients with DM and HF is available.

Recent post hoc analyses of clinical trials in patients with HF with reduced and preserved left ventricular ejection fraction found that insulin was associated with higher risk of all-cause mortality and HF hospitalization.[5 6] Cosmi *et al*, using administrative data from an Italian region, Apulia, showed that the risk of these events was even higher in subjects from the real world.[5]

In recent years, new antidiabetic agents—glucagon-like peptide-1 receptor agonist (GLP-1RA) and sodium-glucose cotransporter-2 inhibitor (SGLT-2i)— in patients with diabetes with a high risk of CV events have increased the survival of hospital admission for HF, and renal outcomes independently of a glucose-lowering effect. GLP-1RA treatment was also associated with a significant reduction of non-fatal stroke risk,[7] and SGLT-2i was associated with a risk reduction in all-cause mortality, hospitalization for HF and renal failure (RF) in patients with HF with reduced and preserved ejection fraction (EF) with and without DM.[8–10] Trials with the new antidiabetic drugs also showed a tendency of a lower use of insulin in treated patients compared with controls.[11]

The aim of our analysis was to assess the effects of insulin treatment compared with SGLT-2i, GLP-1RA and other antihyperglycemic agents (other-AHAs) on the risk of death and CV events in two Italian real-world populations with DM and HF. We also tested the safety of study treatments. The administrative databases of two regions, Lombardy and Apulia were used to verify the expected clinical benefits and risks in routine clinical settings and to check for possible North-South differences. Finally, we conducted a meta-analysis combining the data from both regions.

METHODS

Data source

Our study used linkable administrative health databases of two Italian regions, Lombardy and Apulia, which include population registries with demographic data of all residents and detailed information on out-of-hospital medical prescriptions and hospital records.[12]

Healthcare in Italy is publicly funded for all residents, irrespective of social class or employment, and everyone is assigned a personal identification number kept in the National Civil Registration System. All residents are assisted by general practitioners and/or specialists under the National Health System (NHS). The pharmacy prescription database contains the medication name and Anatomic Therapeutic Chemical (ATC) classification code, quantity and date of dispensation of drugs reimbursed by the NHS. Data on hospitalization include date of admission, discharge, death, primary diagnosis and up to five coexisting clinical conditions and procedures received. The diagnoses, uniformly coded according to the Ninth International Code of Diseases (ICD-9-CM) and standardized in all Italian hospitals, are compiled by the hospital specialists directly in charge of the patients and are validated by hospitals against detailed clinical-instrumental data, as they determine the NHS reimbursement. A unique identification code allows linkage of all databases. To ensure privacy, each identification code was automatically converted into an anonymous code before Istituto di Ricerche Farmacologiche Mario Negri (IRFMN) received the dataset.

Study cohorts and follow-up

All subjects 50 years and older with chronic exposure to insulin and/or AHAs (at least two packages in 1 year, ATC code A10*, online supplemental annex 1) from January 1, 2010 through December 31, 2018, from the overall diabetic cohort were included in the analysis, with 44 970 subjects in Apulia and 236 944 in Lombardy. Subjects were split into four groups according to the first exposure (first-time users) as follows: GLP-1RA, SGLT-2i, insulin and other-AHAs including metformin, sulfonylureas, glinides, thiazolidinediones, acarbose and dipeptidyl peptidase-4 inhibitors. First-time users were defined as subjects first exposed to one of the AHAs, in the 5 years before entering the cohort, with no prior exposure to any medications belonging to the same class/group.

Subjects started on GLP-1RA and SGLT-2i were included in the study from 2010 and 2015, depending on the availability of these drugs in the Italian market.

Starting from the overall diabetic cohort, subjects with diabetes and a history of at least one hospitalization for HF were included in the analysis.

Comorbidities for the 5 years before the index date were collected using hospital records. Previous exposure to any AHA class, hospital admissions and Drug Derived Complexity Index (DDCI) were calculated on the previous 5 years, and information on other medications of interest was retrieved for the previous 12 months. Information on duration of diabetes was collected based on the date of the first prescription of an antidiabetic agent or DM hospitalization between years 2000 and 2018 (online supplemental annex 2).

Subjects were followed from starting the drug until the end of follow-up (December 31, 2018); reasons for censoring were migration or admission to a nursing home linked to the type of flow typical of administrative databases since in these two cases we lose the possibility to follow the subjects. The longest period of observation

was 3.5 years depending on the availability of SGLT-2i on the Italian market.

Study outcomes

Outcomes of interest were death from any cause, hospital readmission for HF or kidney failure, stroke (ischemic and hemorrhagic) and myocardial infarction. We also analyzed the results as two different composite outcomes, one defined as death and the first admission for myocardial infarction or stroke (MACE3) and the second as first myocardial infarction, stroke, HF or unstable angina (MACE4).

All clinical events were collected using hospital admission diagnoses according to the ICD-9-CM codes (online supplemental annexes 3 and 4). RF was not considered between the studied outcomes for SGLT-2i to avoid a further bias since these medications were not indicated in patients with RF between 2015 and 2018. Serious adverse events including hospital admission for hypoglycemia, ketoacidosis, diabetes with coma, limb amputation, RF, syncope and fractures, as primary diagnosis were also analyzed.

Sensitivity analyses

Three different preplanned sensitivity analyses of study outcomes were done to reduce confounding due to the imbalance in study covariates and to overcome the gap for missing clinical information: (1) propensity matched cohorts (PMCs), (2) whole cohort and PMC of subjects without a history of renal disease and (3) cumulative incidence of outcome events (Kaplan-Meier curves) in PMC with a similar calendar year of inclusion in the study and duration of follow-up, years 2015–2018 (online supplemental annex 5).

To optimize the interpretation of the results, using data from the Apulia database further analyses were done to assess:

A. Changes in insulin, SGLT-2i, GLP-1RA and other-AHA prescriptions: The exposure to the antidiabetic medications was considered positive when at least one pack was prescribed and dispensed 12 months before entering the cohort study and in the following 12 months, identifying the new prescriptions in the 12 months after the index date.
B. Changes in insulin daily doses in SGLT-2i and GLP-1RA cohorts: The average of the defined daily dose (DDD) of insulin was calculated in 12 months before entering the study cohort and compared with that calculated in the 12 months after the index date.
C. Insulin dose adjustments over 3 years after starting SGLT-2i or GLP-1RA treatment in Apulia: Subjects who reduced, maintained or increased the mean insulin of DDD were identified. In patients from the SGLT-2i or GLP-1RA cohorts whose insulin doses were reduced, the incidence of outcome events was calculated comparing the incidence in 3 years before and after study entry.

Statistical analysis

Frequencies and proportions are presented for categorical variables, and means and SDs for continuous variables. DDCI, previous hospital admission, history of diabetes and follow-up times are expressed as median and quartile 1–quartile 3 (Q1–Q3).

Differences in baseline characteristics among the classes were tested using analysis of variance (for age) or Kruskall-Wallis test (for other numerical values) and χ^2 test for categorical values.

Time-to-first event analysis was conducted using multivariable Cox proportional hazard models; hazard ratios (HRs) and 95% CI for each outcome were estimated, comparing the effects of GLP-1RA, SGLT-2i and other-AHAs versus insulin (outcomes were analyzed by intention to treat, that is, according to first-time drug use). Confounders were chosen if they resulted significantly in the univariate analysis and based on their clinical relevance on outcomes as: age classes (50–59, 60–64, 65–69, 70–74, 75–79, >80), sex, index year, DDCI index and anamnesis of myocardial infarction, ischemic or hemorrhagic stroke, atrial fibrillation, chronic obstructive pulmonary disease (COPD), cancer, renal disease and diabetic history.

In the main and sensitivity analyses, outcomes in studied cohorts were reported as crude incidence rates (IRs) per 100 person-years.

Estimates of the cumulative incidence for death from any cause and first hospitalization for HF are presented as unadjusted Kaplan-Meier curves for each region. The log-rank test was used to compare the survival distribution, and the HR (95% CI) for clinical events was calculated.

Pooled risks from the two regions were presented as a meta-analysis for an overall summary. I^2 was used to calculate heterogeneity between the regions. An I^2 probability ≥50% indicated significant heterogeneity. The fixed effects model was used when there was no significant inter-region heterogeneity; otherwise, the random effects model was used. The log-rank test, stratified by region, was used for comparisons, and HRs with 95% CI for events were calculated.

In all analyses, $p < 0.05$ was considered significant. All analyses were done with SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

From January 1, 2010 to December 31, 2018, 144 970 DM subjects 50 years and older were identified, considered first-time users of antihyperglycemic medications such as SGLT-2i, or GLP-1RA, or insulin or other-AHAs in Apulia and 236 944 in Lombardy; HF coexisted, respectively, in 13 721 (9.5%) and 20 655 subjects (8.7%) (online supplemental figure 1). Baseline

characteristics of subjects from whole studied cohorts are presented in table 1. The most frequent comorbidities in both regions were ischemic heart disease, atrial fibrillation, renal and COPD. At study entry, the median (Q1–Q3) duration of DM was 9 (6–10) years in subjects from Apulia region and 10 (7–10) years in those from Lombardy.

The proportions of subjects with DM and HF treated with SGLT-2i, GLP-1RA, insulin and other-AHAs were similar in Apulia (3.9%, 3.3%, 51.2%, 41.6%) and (3.8%, 3.7%, 53.0%, 39.5%) in Lombardy (table 2).

In both regions, subjects in the insulin and other-AHA cohorts were older and more likely to have concomitant illnesses such as cerebrovascular disease, atrial fibrillation, peripheral artery disease and cancer than the SGLT-2i and GLP-1RA cohorts. COPD was more frequent in subjects from the Apulia region in particular those from the insulin and AHAs cohorts. Renal diseases were frequent in the insulin cohort from both regions, 31.3%in Apulia and 27.1% in Lombardy.

The rates of recommended medications for HF as ACE/angiotensin II receptor agonist blockers were lower in the insulin than in the SGLT-2i and GLP-1RA cohorts in Lombardy. Beta-blockers and lipid-lowering drugs were prescribed less in the insulin and other-AHA cohorts from both regions, while digitalis was prescribed more in the insulin and other-AHAs cohorts, in particular in Lombardy (table 2).

Overall median (Q1–Q3) follow-up time was 2.5 (0.9–5.1) years in Apulia and 2.5 (0.8–5.0) years in Lombardy.

Clinical events

During follow-up, death from any cause and HF were the most frequent events with a higher IRs per 100 person-years in other-AHAs and insulin cohorts in both study regions (figures 1 and 2). A substantial significant reduction in death from any cause, first HF hospitalization and in MACE3 an MACE4 risk, was observed in both the SGLT-2i and GLP-1RA cohorts compared with insulin; a significant reduction in RF risk was also found in the GLP-1RA cohort; risk reduction was similar in both regions.

Kaplan-Meier curves for death from any cause and for first hospitalization for HF show how differences in the cumulative incidence of these events appeared soon when the SGLT-2i and GLP-1RA cohorts were compared with insulin (figure 3A,B); this was not apparent for the comparison with the other-AHAs. The benefit of treatments continued over the 3-year follow-up for the SGLT-2i cohort and 8 years for the GLP-1RA cohort.

Sensitivity analyses and meta-analysis

The three prespecified sensitivity analyses in Apulia and Lombardy of the selected outcomes confirmed the results obtained in the whole population (online supplemental tables 1A, 1B, 2 and 3 and figures 2 and 3).

Meta-analysis of the Lombardy and Apulia cohorts largely confirmed the results from the main analysis of the individual regions (online supplemental figure 4).

Frequency of insulin and other antihyperglycemic prescriptions in the 12 months before and after study entry

The frequency of subjects: (1) treated with insulin before entering the study, (2) those who started in the 12 months following the date of entry, and (3) those who continued insulin for 12 months in both regions are reported in online supplemental figure 5. The highest rate of patients with insulin prescriptions in the 12 months before study entry and in those who continued insulin for 12 months more, was found in the SGLT-2i cohort followed by the GLP-1RA cohort. The frequency of patients who started insulin treatment in the 12 months after study entry resulted much lower.

In the insulin cohort, metformin prescriptions decreased from 71% in Apulia and 65% in Lombardy region in the 12 months before entering in the study to 29.9% and 21.9%, respectively, in the 12 months after entry (online supplemental table 4A, B).

Insulin-defined daily dose and it changes in the SGLT-2i and GLP-1RA cohort

An exploratory analysis of the Apulia cohort (online supplemental methods and table 4) showed that in the 12 months before study entry the average insulin DDD was 257±338 units in SGLT-2i and 160±230 units in GLP-1RA. The rate of subjects who decreased (56%), maintained (9.7%) or increased (34.2%) the mean DDD (mean DDD in the 12 months before vs mean DDD in the 12 months after entry in the study) was significantly different ($p<0.0001$) (online supplemental table 5). The reduction of insulin DDD resulted particularly significant in subjects treated with SGLT-2i ($p<0.001$). In the 244 subjects who reduced the insulin DDD, the incidence rate ratio (95% CI) for HF and myocardial infarction showed a significant reduction at 3-year follow-up (online supplemental table 6).

Safety

The rates of adverse events were similar in both regions. The most frequent serious adverse events were fractures in all cohorts but principally in the insulin (5.5% in Apulia, 5.3% in Lombardy) and the other-AHA cohort (6.9% and 6.6%, respectively). The second more frequent was lower limb amputations (table 3). Hypoglycemia and syncope were more frequent in the insulin and other-AHAs cohorts and absent or rare with SGLT-2i and GLP-1RA.

DISCUSSION

The present study based on a large cohort of diabetic subjects with HF from two Italian regions provides the first consistent evidence that long-term treatment with either SGLT-2i or GLP-1RA compared with insulin is associated with a significant reduction of risk for death from

Table 1 Baseline characteristics of subjects with diabetes and heart failure according to study regions and antihyperglycemic therapy (first-time users from 2010 to 2018)

	Apulia						Lombardy					
Variables	**SGLT-2i (531)**	**GLP-1RA (459)**	**Insulin (7027)**	**Other AHAs (5704)**	**Total (13 721)**	**P-value**	**SGLT-2i (786)**	**GLP-1RA (759)**	**Insulin (10 950)**	**Other AHAs (8160)**	**Total (20 655)**	**P-value***
Age (years), mean±SD§	68.8±7.9	67.7±8.4	78.4±8.7	76.8±8.9	**77.0±9.1**	<0.0001	70.4±8.1	69.5±8.4	79.0±8.5	78.6±8.7	**78.2±8.9**	<0.0001
Age groups (years), n (%)†												
50–59	75 (14.1)	81 (17.7)	216 (3.1)	220 (3.9)	**592 (4.3)**	<0.0001						<0.0001
60–64	82 (15.4)	86 (18.77)	316 (4.5)	355 (6.2)	**839 (6.1)**		80 (10.2)	99 (13.0)	251 (2.3)	228 (2.8)	**658 (3.2)**	
65–69	133 (25.1)	103 (22.4)	575 (8.2)	620 (10.9)	**1431 (10.4)**		95 (12.091)	126 (16.6)	445 (4.1)	359 (4.4)	**1025 (5.0)**	
70–74	107 (20.2)	90 (19.6)	935 (13.3)	898 (15.7)	**2030 (14.8)**		165 (21.0)	146 (19.2)	861 (7.9)	629 (7.7)	**1801 (8.7)**	
75–79	81 (15.3)	60 (17.0)	1487 (21.2)	1210 (21.2)	**2838 (20.7)**		193 (24.6)	160 (21.1)	1423 (13.00	1156 (14.2)	**2932 (14.2)**	
80+	53 (10.0)	39 (8.5)	3498 (49.8)	2401 (42.1)	**5991 (43.7)**		151 (19.2)	129 (17.0)	2261 (20.7)	1669 (20.5)	**4210 (20.4)**	
Female, n (%)†	209 (39.36)	201 (43.79)	3515 (50.02)	2942 (51.58)	**6867 (50.05)**	<0.0001	102 (13.0)	99 (13.0)	5709 (52.1)	4419 (50.5)	**10 209 (48.6)**	<0.0001
Comorbidities, n (%)†												
Cerebrovascular disease	107 (20.15)	68 (14.81)	1634 (23.3)	1409 (24.7)	**3218 (23.45)**	<0.0001	91 (11.6)	80 (10.5)	1939 (17.7)	1403 (17.2)	**3513 (17.1)**	<0.0001
Stroke (all)	22 (4.14)	14 (3.05)	355 (5.1)	260 (4.6)	**651 (4.7)**	0.1545	23 (2.93)	20 (2.64)	470 (4.29)	317 (3.88)	**830 (4.0)**	0.0335
Ischemic heart disease												
Myocardial infarction	153 (28.1)	106 (23.1)	1637 (23.3)	1193 (20.9)	**3089 (22.5)**	<0.0001	208 (26.4)	155 (20.4)	2695 (24.6)	1916 (23.5)	**4974 (24.1)**	0.0335
Other coronary disease	276 (52.0)	195 (42.5)	2896 (41.2)	2468 (43.3)	**5835 (42.5)**	<0.0001	383 (48.7)	340 (44.8)	4247 (38.8)	3213 (39.4)	**8183 (39.6)**	<0.0001
Atrial fibrillation	122 (23.0)	127 (27.7)	2795 (39.8)	2036 (35.7)	**5080 (37.0)**	<0.0001	216 (27.5)	232 (30.6)	4226 (38.6)	3214 (39.4)	**7888 (38.2)**	<0.0001
Peripheral vascular disease	96 (18.1)	114 (24.8)	1271 (18.1)	1072 (18.8)	**2553 (18.6)**	0.0041	106 (13.5)	95 (12.5)	1543 (14.1)	961 (11.8)	**2705 (13.1)**	<0.0001
Lower limb complication	12 (2.3)	23 (5.0)	140 (2.0)	122 (2.1)	**297 (2.2)**	0.0003	28 (3.6)	27 (3.5)	428 (3.9)	263 (3.2)	**746 (3.6)**	0.0968
Pulmonary embolism	3 (0. 6)	4 (0.9)	50 (0.7)	37 (0.7)	**94 (0.7)**	0.9122	3 (0.4)	7 (0.9)	189 (1.7)	132 (1.6)	**331 (1.6)**	0.0133
Renal disease	71 (13.4)	99 (21.6)	2201 (31.3)	1370 (24.0)	**3741 (27.3)**	<0.0001	61 (7.8)	118 (15.5)	2968 (27.1)	1727 (21.1)	**4874 (23.6)**	<0.0001
Neuropathy	26 (4.9)	25 (5.5)	189 (2.7)	242 (4.2)	**482 (3.5)**	<0.0001	39 (4.9)	34 (4.5)	320 (2.9)	307 (3.8)	**700 (3.4)**	0.0002
Diabetic retinopathy	1 (0.19)	0 (0.0)	20 (0.28)	34 (0.6)	**54 (0.4)**	0.0164	5 (0.6)	1 (0.1)	29 (0.3)	24 (0.3)	**59 (0.3)**	0.2399
COPD	137 (25.8)	140 (30.5)	2817 (40.1)	2290 (40.2)	**5384 (39.2)**	<0.0001	144 (18.3)	185 (24.3)	2293 (20.9)	1749 (21.4)	**4371 (21.2)**	0.0273
Cancer	57 (10.7)	50 (10.9)	1294 (18.4)	922 (16.2)	**2323 (16.9)**	<0.0001	71 (9.0)	81 (10.7)	1832 (16.7)	1317 (16.1)	**3301 (16.0)**	<0.0001
Cardiovascular interventions, n (%)†												
Percutaneous coronary intervention/ coronary artery by-pass/other revascularizations	45 (8.5)	47 (10.2)	721 (10.3)	624 (10.9)	**1437 (10.5)**	0.2667	98 (12.5)	122 (16.1)	1425 (13.0)	1133 (13.9)	**2778 (13.4)**	0.0410

Continued

Table 1 Continued

Variables	Apulia						Lombardy					
	SGLT-2i (531)	GLP-1RA (459)	Insulin (7027)	Other AHAs (5704)	Total (13 721)	P-value	SGLT-2i (786)	GLP-1RA (759)	Insulin (10 950)	Other AHAs (8160)	Total (20 655)	P-value*
Valve replacement /annuloplasty /valvuloplasty	15 (2.8)	15 (3.3)	252 (3.6)	173 (3.0)	**455 (3.32)**	0.3302	56 (7.2)	42 (5.6)	542 (4.9)	466 (5.6)	**1106 (5.3)**	0.0148
Device therapy, n (%)†												
Ventricular assist device	1 (0.2)	2 (0.4)	7 (0.1)	1 (0.02)	**11 (0.1)**	0.0110	0 (0.0)	1 (0.1)	5 (0.1)	2 (0.0)	**8 (0.0)**	0.4660
Implantable cardioverter/ defibrillator	69 (13.0)	46 (10.0)	641 (9.1)	508 (8.9)	**1264 (9.2)**	0.0173	60 (7.6)	74 (9.7)	646 (5.9)	472 (5.8)	**1252 (6.1)**	<0.0001
Cardiac resynchronization therapy	20 (3.8)	17 (3.7)	149 (2.1)	112 (2.0)	**298 (2.2)**	0.0054	68 (8.6)	33 (4.3)	438 (4.0)	273 (3.3)	**812 (3.9)**	<0.0001
Pacemaker implantation	32 (6.0)	25 (5.5)	546 (7.8)	481 (8.4)	**1084 (7.9)**	0.0329	42 (5.3)	47 (6.2)	990 (9.0)	844 (9.0)	**1923 (9.3)**	<0.0001
DDCI Index‡, median (Q1–Q3)	8 (7–10)	9 (7–10)	9 (7–10)	9 (7–10)	**9 (7–10)**	<0.0001	8 (7–10)	8 (7–10)	8 (7–10)	8 (6–10)	**8 (7–10)**	<0.0001
No. of hospital admissions‡, median (Q1–Q3)	3 (2–5)	4 (2–6)	4 (2–6)	4 (2–7)	**4 (2–6)**	<0.0001	3 (2–5)	4 (2–6)	4 (2–6)	4 (2–6)	**4 (2–6)**	0.1567
History of diabetes, n (%)†												
0–4 years	3 (0.6)	31 (6.8)	907 (12.9)	1368 (24.0)	**2309 (16.8)**	<0.0001	2 (0.2)	63 (8.3)	1058 (9.6)	1969 (24.1)	**3092 (15.0)**	<0.0001
5–9 years	101 (19.0)	144 (31.4)	2831 (40.3)	2438 (42.7)	**5514 (40.2)**		130 (16.5)	188 (24.7)	2599 (23.7)	1984 (24.3)	**4901 (23.7)**	
10+years	427 (80.4)	284 (61.9)	3289 (46.8)	1898 (33.3)	**5898 (43.0)**		654 (83.3)	508 (67.0)	7293 (66.7)	4207 (51.6)	**12 662 (61.3)**	
Median (Q1–Q3)‡	10 (10–10)	10 (8–10)	9 (7–10)	8(5–10)	**9 (6–10)**		10 (10–10)	10 (8–10)	10 (8–10)	10 (5–10)	**10 (7–10)**	

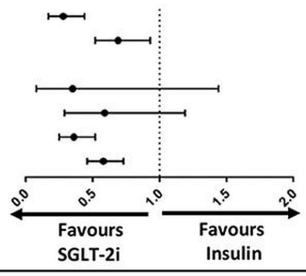
Stroke (all), haemorrhagic and ischemic stroke.
*P value for the comparison between study cohorts.
†χ^2 test for categorical variables.
‡Kruskal-Wallis test for other numerical variables.
§ANOVA was applied for age.
AHA, antihyperglycemic agent; ANOVA, analysis of variance; COPD, chronic obstructive pulmonary disease; DDCI, Drug Derived Complexity Index; GLP-1RA, glucagon-like peptide-1 receptor agonist; Q1–Q3, Quartile 1–Quartile 3; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

Table 2 Concomitant treatments at study entry according to study regions and antihyperglycemic therapy (first-time users from 2010 to 2018)

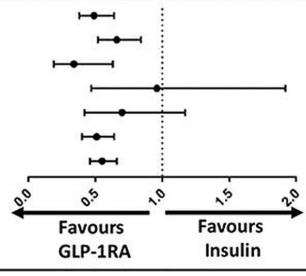
	Apulia					Lombardy				
	SGLT-2i (531)	GLP-1RA (459)	Insulin (7027)	Other AHAs (5704)	Total (13 721)	SGLT-2i (786)	GLP-1RA (759)	Insulin (10 950)	Other AHAs (8160)	Total (20 655)
Variables	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Antihyperglycemic drugs (in the previous 5 years)										
GLP-1RA	5 (0.9)	0 (0.0)	16 (0.2)	22 (0.4)	43 (0.3)	11 (1.4)	0 (0.0)	32 (0.3)	17 (0.2)	60 (0.3)
SGLT-2i	0 (0.0)	0 (0.0)	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other AHAs	506 (95.3)	446 (97.2)	6846 (97.4)	4588 (80.4)	12 386 (90.3)	732 (93.1)	738 (97.2)	10 651 (97.3)	6387 (78.3)	18 508 (89.6)
Insulin	364 (68.6)	250 (54.5)	0 (0.00)	1912 (33.5)	2526 (18.4)	547 (69.6)	396 (52.2)	0 (0.0)	1767 (21.6)	2710 (13.1)
Metformin	483 (90.1)	430 (93.7)	6016 (85.6)	3741 (65.6)	10 670 (77.8)	688 (87.5)	692 (91.2)	9033 (82.5)	4703 (57.6)	15 116 (73.2)
Sulfonylureas	199 (37.5)	207 (45.1)	4621 (65.9)	2732 (47.9)	7759 (56.6)	425 (54.1)	486 (64.0)	8263 (75.4)	4068 (49.8)	13 242 (64.1)
Glinides	186 (35.0)	186 (40.5)	3171 (45.1)	671 (11.8)	4214 (30.7)	124 (15.8)	179 (23.6)	4044 (36.9)	623 (7.6)	4970 (24.1)
Glitazones	77 (14.5)	118 (25.7)	951 (13.5)	379 (6.6)	1525 (11.1)	125 (15.9)	196 (25.8)	1247 (11.4)	274 (3.4)	1842 (8.9)
Acarbose	57 (10.7)	37 (8.06)	517 (7.4)	2 (0.04)	613 (4.5)	72 (9.2)	85 (11.2)	934 (8.5)	5 (0.1)	1096 (5.3)
DDP4 inhibitors	179 (33.7)	154 (33.6)	991 (14.4)	17 (0.3)	1341 (9.8)	213 (27.1)	234 (30.8)	1811 (16.5)	22 (0.3)	2280 (11.0)
None	0 (0.0)	0 (0.0)	181 (2.6)	724 (12.7)	905 (6.6)	7 (0.9)	2 (0.2)	299 (2.7)	1303 (16.0)	1611 (7.8)
Other medications of interest (in the previous 12 months)										
ACE-I/ARBs	435 (81.9)	390 (85.0)	5658 (80.5)	4768 (83.6)	11 251 (82.0)	669 (85.1)	645 (85.0)	8732 (79.7)	6476 (79.3)	16 522 (80.0)
Sacubitril/valsartan	0 (0.0)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	13 (1.6)	5 (0.6)	13 (0.1)	8 (0.1)	39 (0.2)
Beta-blockers	412 (77.6)	319 (69.5)	4028 (57.3)	3200 (56.1)	7959 (58.0)	639 (81.3)	581 (76.6)	7318 (66.8)	5154 (63.1)	13 692 (66.3)
Diuretics	390 (73.5)	368 (80.2)	5770 (82.1)	4576 (80.2)	11 104 (80.9)	644 (81.9)	654 (86.2)	8976 (82.0)	6723 (82.4)	16 997 (82.3)
Mineralocorticoid receptor antagonists	197 (37.1)	163 (35.5)	2646 (37.7)	1842 (32.3)	4848 (35.3)	299 (38.0)	287 (37.8)	3647 (33.3)	2676 (32.8)	6909 (33.4)
Antiarrhythmics	66 (12.4)	63 (13.7)	1276 (18.2)	945 (16.6)	2350 (17.1)	108 (13.7)	120 (15.8)	1886 (17.2)	1464 (17.9)	3578 (17.3)
Digitalis	51 (9.6)	41 (8.9)	1552 (22.1)	1303 (22.8)	1947 (21.5)	61 (7.7)	57 (7.5)	1454 (13.3)	1305 (16.0)	2877 (13.9)
Calcium antagonists	140 (26.4)	128 (27.9)	2335 (33.2)	1909 (33.5)	4512 (32.9)	271 (34.5)	281 (37.0)	4305 (39.3)	3032 (37.1)	7889 (38.2)
Nitrates	64 (12.1)	72 (15.7)	1756 (25.0)	1602 (28.1)	2494 (25.5)	150 (19.1)	178 (23.5)	3552 (32.4)	2838 (34.8)	6718 (32.5)
Ivabradine	65 (12.3)	31 (6.8)	296 (4.2)	196 (3.4)	588 (4.3)	80 (10.2)	55 (7.2)	471 (4.3)	260 (3.2)	866 (4.2)
Lipid-lowering drugs	453 (85.3)	374 (81.5)	4212 (59.9)	3533 (61.9)	8572 (62.5)	633 (80.5)	587 (77.3)	6400 (58.4)	4486 (55.0)	12 106 (58.3)
Antiplatelet drugs	405 (76.3)	321 (69.9)	4767 (67.8)	3978 (69.7)	9471 (69.0)	517 (65.7)	497 (65.2)	6681 (61.0)	4979 (61.0)	12 674 (61.3)
Anticoagulant drugs	135 (25.2)	132 (28.8)	2000 (28.5)	1475 (25.9)	3742 (27.3)	237 (30.1)	250 (32.9)	3606 (32.9)	2813 (34.5)	6906 (33.4)

ACE-I, ACE inhibitors; AHAs, antihyperglycemic agents; ARB, angiotensin II receptor agonist blockers; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

	SGLT-2i (531)		Insulin (7 027)		
	n	IR/100 person year	n	IR/100 person year	HR (CI 95%)
Death from any cause	19	3.1	3808	19.7	0.28 (0.17-0.44)
Heart failure	53	9.2	1854	11.9	0.69 (0.52-0.93)
Renal failure	3	0.5	535	2.9	-
All Stroke	2	0.3	210	1.1	0.35 (0.08-1.44)
Myocardial infarction	9	1.5	362	1.9	0.59 (0.29-1.19)
MACE 3	30	4.9	4028	21.9	0.36 (0.25-0.52)
MACE 4	84	14.9	4716	31.5	0.58 (0.46-0.73)



	GLP-1RA (459)		Insulin (7 027)		
	n	IR/100 person year	n	IR/100 person year	HR (CI 95%)
Death from any cause	63	4.7	3808	19.7	0.49 (0.38-0.64)
Heart failure	78	6.7	1854	11.9	0.66 (0.52-0.84)
Renal failure	11	0.8	535	2.9	0.34 (0.19-0.63)
All Stroke	9	0.7	210	1.1	0.96 (0.47-1.92)
Myocardial infarction	17	1.3	362	1.9)	0.70 (0.42-1.17)
MACE 3	76	5.9	4028	21.9	0.51(0.40-0.64)
MACE 4	128	11.5	4716	31.5	0.55 0.46-0.66)



	Other-AHAs (5704)		Insulin (7 027)		
	n	IR/100 person year	n	IR/100 person year	HR (CI 95%)
Death from any cause	2791	12.7	3808	19.7	0.72 (0.68-0.75)
Heart failure	1623	8.9	1854	11.9	0.88 (0.82-0.94)
Renal failure	425	2.0	535	2.9	0.84 (0.73-0.95)
All Stroke	176	0.8	210	1.1	0.85 (0.69-1.05)
Myocardial infarction	304	1.4	362	1.9	0.85(0.73-1.00)
MACE 3	2999	14.3	4028	21.9	0.73(0.69-0.76)
MACE 4	3632	21.1	4716	31.5	0.75(0.72-0.78)

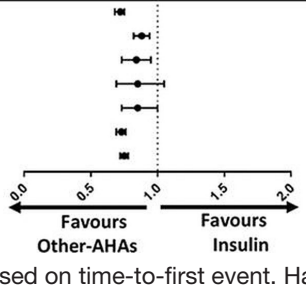


Figure 1 Multivariable Cox proportional hazard regression model based on time-to-first event. Hazard ratios (HRs) and 95% CIs for each outcome, comparing the treatment effects of GLP-1RA, SGLT-2i and other-AHAs versus insulin (reference group) in the Apulia region. Covariates for HR adjustment: age classes (50–59, 60–64, 65–69, 70–74, 75–79, >80 years), sex, index year, myocardial infarction, stroke, atrial fibrillation, chronic obstructive pulmonary disease, cancer, diabetic history and DDCI. AHA, antihyperglycemic agent; DDCI, Drug Derived Complexity Index; GLP-1RA, glucagon-like peptide-1 receptor agonist; IR, incidence rate; MACE, major adverse cardiac event; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

any cause, first hospitalization for HF and the composite MACE3 and MACE4. In the meta-analysis, GLP-1RA treatment was also associated with a reduction in the risk of stroke.

The association with a reduction in risk of death from any cause was markedly high in both regions (72% in Apulia and 71% in Lombardy) in the SGLT-2i cohort compared with the insulin cohort. A substantial risk reduction for death was also observed in the GLP-1RA cohort (51% in Apulia and 53% in Lombardy). The association with a reduction in risk for first hospitalization for HF for the MACE combined events was also significant in both regions. Seeking explanations for this impressive effect, we addressed the following issues.

Overall treatment in the insulin cohort

This study shows that subjects in the insulin cohort were treated differently from those in the cohorts of new antidiabetic drugs. First, beta-blockers, recommended therapy for HF, were less frequently prescribed, while nitrates and digitalis were prescribed more frequently. Second, lipid-lowering medications, associated with a reduction in mortality and disease progression in patients with DM with overt CV disease,[13] were underprescribed to insulin patients.

Insulin dose changed in SGLT-2i and GLP-1RA cohort

Even if insulin appeared as a concomitant treatment in around 65% subjects in the SGLT-2i and GLP-1RA cohorts, a significant decrease was observed in the DDD in particular in the SGLT-2i cohort (online supplemental table 5) with

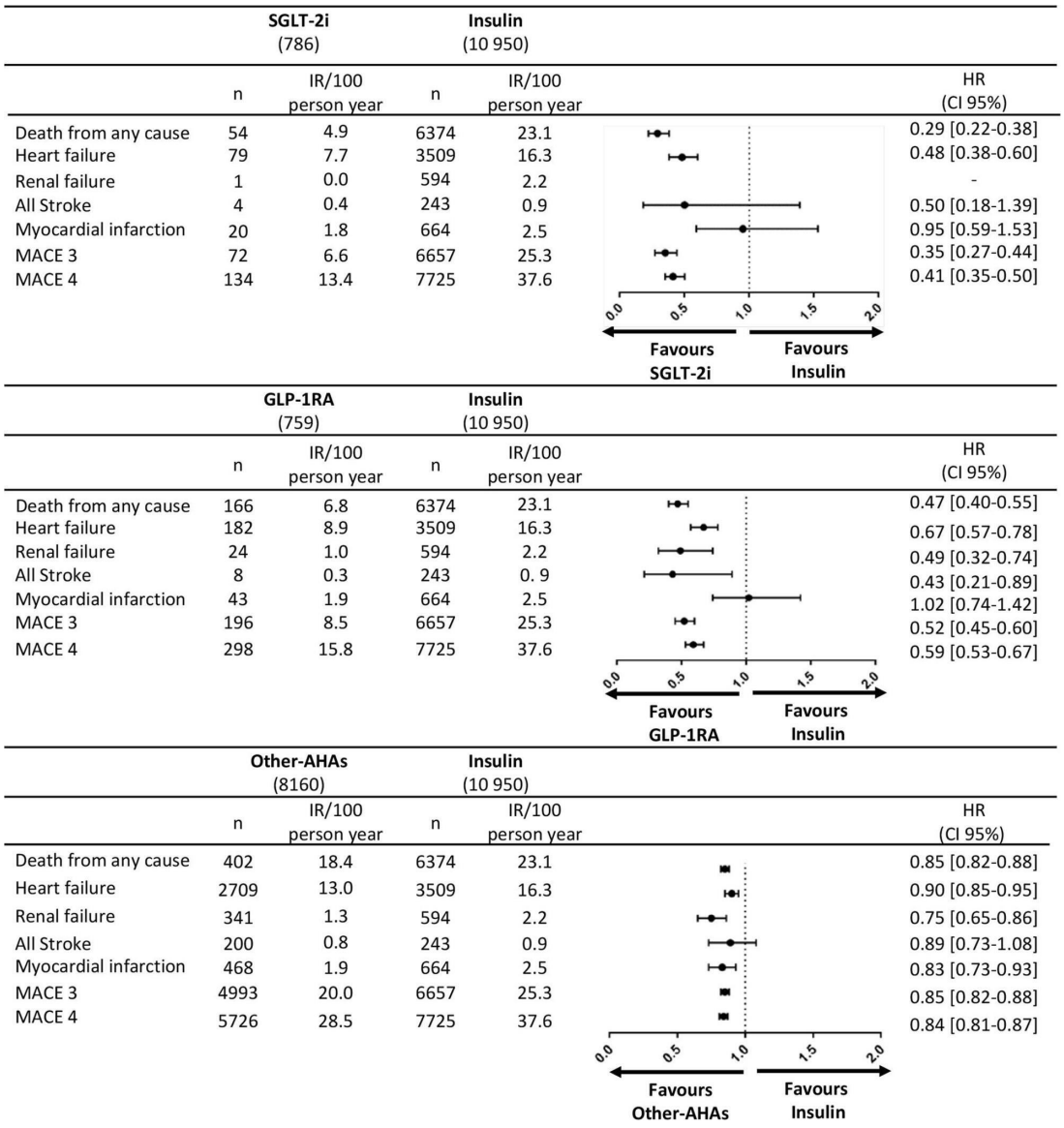


Figure 2 Multivariable Cox proportional hazard regression model based on time-to-first event. Hazard ratios (HRs) and 95% CIs for each outcome, comparing the treatment effects of GLP-1RA, SGLT-2i and other-AHAs versus insulin (reference group) in the Lombardy region. Covariates for HR adjustment: age classes (50–59, 60–64, 65–69, 70–74, 75–79, >80 years), sex, index year, myocardial infarction, stroke, atrial fibrillation, chronic obstructive pulmonary disease, cancer, diabetic history and DDCI. AHA, antihyperglycemic agent; DDCI, Drug Derived Complexity Index; GLP-1RA, glucagon-like peptide-1 receptor agonist; IR, incidence rate; MACE, major adverse cardiac event; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

a significant reduction in 3-year follow-up of hospitalization for HF and for acute myocardial infarction (online supplemental table 6). These results suggest that SGLT-2i and GLP-1RA can be considered for the reduction of insulin DDD, reducing the related adverse effects.[14] Along this line, Cosmi *et al*[11] hypothesized that the reduction in CV events showed by trials that assessed the effect of new antidiabetic drugs was in part due to a reduction in the insulin prescription since the proportion of patients treated with insulin at the study end was lower than at baseline.

Metformin prescription

Another noteworthy finding was the low frequency of metformin prescription in the insulin cohort. Metformin, recommended by international guidelines as standard baseline therapy for patients with DM and HF, was prescribed only in 29% in Apulia and 22% in Lombardy within the 12 months from study entry (online supplemental table 4A). Metformin is not only associated with a reduction of mortality[15] but makes it possible to reduce the insulin DDD and consequently the probability of its adverse effects.[4 16] However, most subjects in the SGTL-2i and GLP-1RA cohorts in our study were treated with metformin similarly to those in clinical trials in patients with DM, which showed the benefit of SGLT-2i and GLP-1RA on CV events.[17] An additive interaction between metformin and the new antidiabetic drugs cannot be excluded.[18]

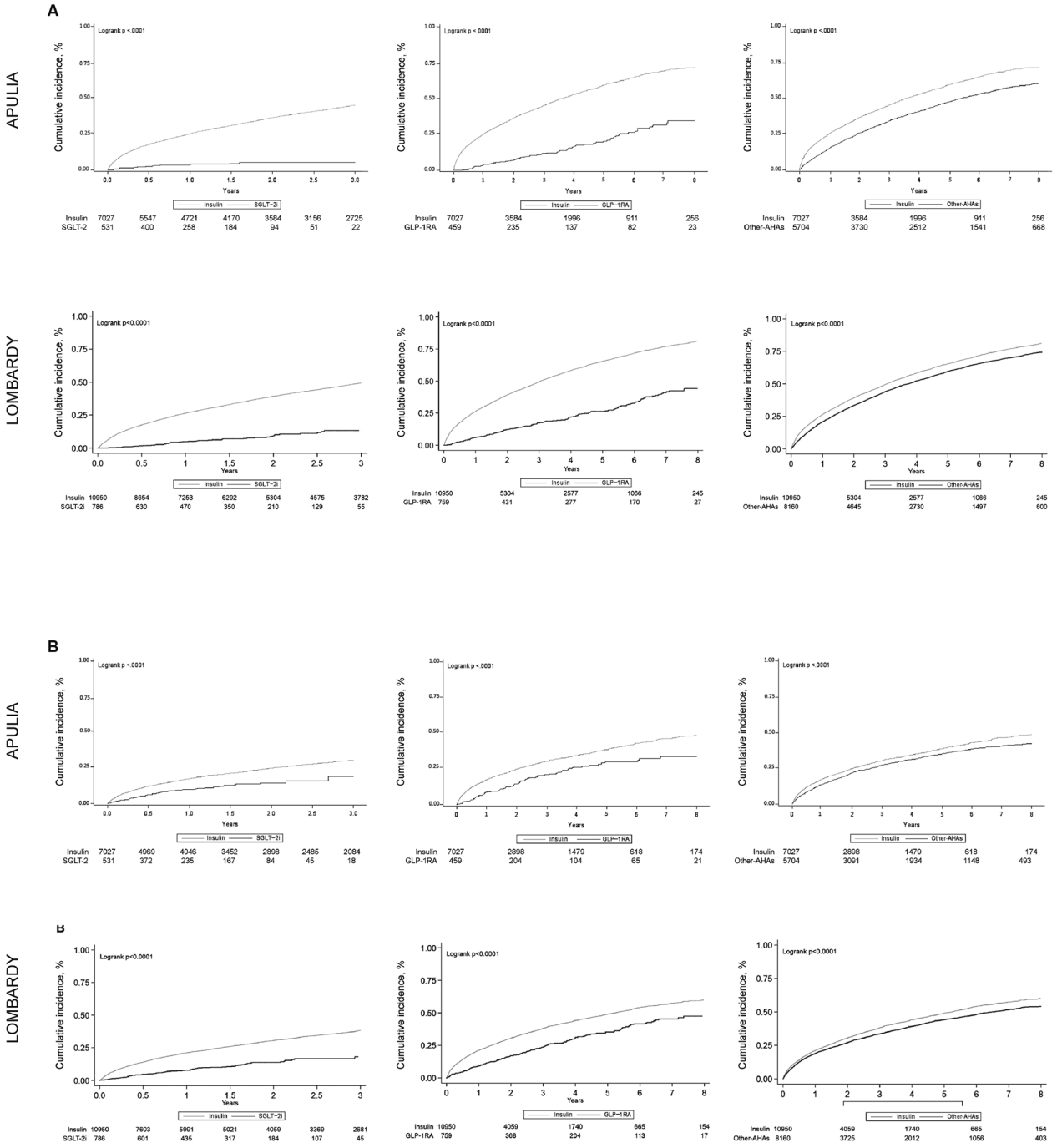


Figure 3 Kaplan-Meier curves of incidence of death from any cause (A) and for first hospitalization for heart failure (B) for the comparison of SGLT-2i, GLP-1 RA and other-AHAs with insulin over all available years of observation in Apulia and Lombardy. AHA, antihyperglycemic agent; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

SGLT-2i and GLP-1RA: patients and clinical effects

The clinical characteristics of subjects from the SGLT-2i cohort show two interesting features in comparison with the other cohorts from both regions: (1) they more frequently had a history of ischemic heart disease and longer duration of DM, both frequent reasons for insulin prescription, suggesting that prescribing preferences of an antidiabetic treatment are changing and (2) patients are more frequently given the recommended treatment for HF and for the prevention of CV events, in particular lipid-lowering drugs.

SGLT-2i were originally designed to treat hyperglycemia in T2DM but as they consistently showed an effect in reducing death, HF hospitalization and RF these agents have been successfully tested in HF. Thanks to DAPA-HF[19] and EMPEROR Reduced-HF trials[20] this class of drugs is now part of the recommended treatment of HF. A meta-analysis on the 8474 patients showed that

Table 3 Serious adverse events in study cohorts according to treatment in Apulia and Lombardy regions from 2010 to 2018

Serious adverse events	Apulia				Lombardy			
	SGLT-2i (531)	GLP-1RA (459)	Insulin (7027)	Other AHAs (5704)	SGLT-2i (786)	GLP-1RA (759)	Insulin (10 950)	Other AHAs (8160)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hypoglycemia	0 (0.0)	0 (0.0)	27 (0.4)	18 (0.3)	0 (0.0)	2 (0.3)	42 (0.4)	42 (0.5)
Ketoacidosis	0 (0.0)	1 (0.2)	7 (0.1)	7 (0.1)	1 (0.1)	1 (0.1)	7 (0.1)	4 (0.1)
Diabetic coma	0 (0.0)	0 (0.0)	9 (0.1)	8 (0.1)	0 (0.0)	0 (0.0)	22 (0.2)	12 (0.2)
Syncope	1 (0.2)	4 (0.9)	79 (1.1)	95 (1.7)	3 (0.4)	6 (0.8)	142 (1.3)	117 (1.4)
Lower limb amputations	6 (1.1)	2 (0.4)	109 (1.6)	84 (1.5)	7 (0.9)	11 (1.5)	323 (3.0)	161 (2.0)
Fractures	5 (0.9)	9 (2.0)	385 (5.5)	392 (6.9)	11 (1.4)	28 (3.7)	575 (5.3)	535 (6.6)

AHA, antihyperglycemic agent; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

the estimated reduction of risk with SGLT-2i was 13% for death from any cause, 26% for the composite endpoint of CV death and hospitalization for HF and 38% for renal disease.[8] Our study shows a significant association between SGLT-2i and a reduction in the risk of outcome events when compared with insulin and not with "traditional antidiabetics" as in the placebo group of the two trials listed above.

The ability of SGLT-2 inhibitors to optimize volume status[21] through: (1) glycosuria and (2) inhibition of the sodium-hydrogen exchanger in the kidneys and the heart may result in a cascade of responses including increased natriuresis, reduced subendocardial ischemia, myocardial fibrosis, and increased cardiac contractility.

The difference between SGLT-2i and standard diuretics may be related to a diuretic effect with transient natriuresis,[22] an increase in erythrocyte mass, no vascular contraction and a selective reduction in interstitial fluid that may be unique for SGLT-2i.

On the other hand since the 1980s, investigators have been trying to define the antinatriuretic effects of insulin, and recent evidence suggests that insulin mediates the tubular reabsorption of sodium, acting as an SGLT-2 agonist.[23]

First evidence of long-term use of GLP-1RA in HF

During the 8-year follow-up, there was a reduction in adverse clinical outcomes of GLP-1RA compared with insulin in individuals with HF, with a low rate of adverse events in both regions.

Subgroup analyses of patients with prevalent HF from trials in DM have given contradictory results on the effects of GLP-1RA on major clinical events.[24] In a meta-analysis of seven trials, GLP-1RA showed a modest but significant reduction in MACE (12%), in mortality from any cause (12%), in a kidney composite outcome – in large part due to the effects on albuminuria – (17%) and in admissions for HF (9%).[25]

Two small randomized clinical trials assessed the effects on outcomes of a GLP-1RA (liraglutide and albiglutide) in patients with HF with reduced EF (HFrEF). Both studies, over a six-month follow-up, suggested potential harm with GLP-1RA, although not statistically significant.[26 27] In a third clinical study again, in patients with HFrEF and 6-month follow-up, liraglutide did not change left ventricular function but increased adverse events.[28]

Strengths and limitations

This study is based on administrative databases from large cohorts that allow unbiased assessment of the epidemiology of disease, since all residents are covered by the Italian NHS. The databases offer a high level of completeness regarding drug prescriptions, diagnosis, procedures and length of observation; therefore, our analysis includes all individual with DM and HF. The retrospective analysis of databases shares the potential for bias common to similar studies since diagnosis of HF is based solely on hospitalization.

Conscious that usually older and more severely ill people are treated with insulin, we repeated all risk analysis in propensity matched cohorts to ensure a like-with-like comparison with respect to these biases, confirming the reliability of the HR. Moreover, HR analysis was further adjusted for the covariates that resulted significantly different after matching (online supplemental table 1A–C). As observation was limited to 2015–2018 in the SGLT-2i cohort, we homogenized the calendar years and the period of follow-up in cohorts matched for time in a subsequent Kaplan-Meier analysis for death from any cause and first hospitalization for HF (online supplemental figures 2 and 3). Due to the higher rate of renal disease in the insulin cohort and a difference >10% in the propensity matched cohorts, a sensitivity analyses in the whole and propensity matched cohorts were followed excluding patients with an history of renal disease (online supplemental tables 2 and 3). Overall, the results of these sensitivity analyses are consistent with the main analysis.

SGLT-2i were not indicated in Italy between 2015 and 2018 in subjects with RF, hence one of the reasons for

the small number of RF events in this cohort that subsequently avoid further comparative analyses.

In this study, SGLT-2i and GLP-1RA were prescribed in less than 5% of individuals. Despite the proven effectiveness in CV risk and short-term mortality reduction of these drugs in high CV risk patients, their underprescription is still an open issue.[29]

The most frequently reported side effects are uncomplicated urogenital tract infection for SGLT-2i and gastrointestinal intolerance and increased frequency of gallbladder disease for GLP-1RA, events that do not always require hospitalization and in consequence are not identifiable in our database.

In fact, due to the limitations that are typical of all the studies based on administrative databases, different types of information as those related to biomarker concentrations, out-of-pocket treatments or adverse drug reactions not requiring a specific medical procedure or hospitalization (as hypoglycemia or urinary infections) are not collected.

CONCLUSIONS

This analysis in patients with DM and HF showed that compared with insulin SGLT-2i and GLP-1RA significantly reduce death from any cause, first hospitalization for HF and the composite MACE3 and MACE4. These medications had high safety profiles compared with other-AHAs and particularly with insulin. However, individuals in the insulin cohort were undertreated with other recommended CV medications and metformin. General optimization of antidiabetic and CV treatment is still necessary to reduce major events in this high-risk population.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval In Italy, studies using retrospective aggregated-anonymous data from administrative databases do not require ethics committee/institutional review board approval or notification.

Provenance and peer review Not commissioned; externally peer reviewed.

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