Treatment with Insulin is Associated with Worse Outcome in Patients with Chronic Heart Failure and Diabetes

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Abstract

Aims: Up to a third of patients with diabetes mellitus (DM) and heart failure (HF) are treated with insulin. As insulin causes sodium retention and hypoglycaemia, its use might be associated with worse outcomes.

Methods and results: We examined two datasets: (1) 24,012 patients with HF from 4 large randomized trials and (2) an administrative database of 4 million individuals, 103857 with HF. In the former, survival was examined using Cox proportional hazards models adjusted for baseline variables and separately for propensity scores. Fine-Gray competing risk regression models were used to assess the risk of hospitalization for HF. For the latter a case-control nested within a population-based cohort study was conducted with propensity score.

Prevalence of DM at study entry ranged from 25.5% to 29.5% across trials. Insulin alone or in combination with oral hypoglycaemic drugs was prescribed at randomization to 24.4% to 34.5% of the patients with diabetes. The rates of death from any cause and hospitalization for HF were higher in patients with diabetes *vs* no-diabetes, and highest of all in patients prescribed insulin (propensity score pooled HR for all-cause mortality 1.27 [1.16-1.38], for HF hospitalization 1.23 [1.13-1.33]). In the administrative registry, insulin prescription was associated with a higher risk of all-cause death (OR 2.02 95% CI [1.87-2.19]) and re-hospitalization for HF (OR 1.42 95% CI [1.32-1.53]).

Conclusions: Whether insulin use is associated with poor outcomes in HF should be investigated further with controlled trials, as should the possibility that there may be safer alternative glucose lowering treatments for patients with HF and T2DM.

Introduction

The reciprocal relationship between type 2 diabetes mellitus (T2DM) and heart failure (HF) has long been recognized. T2DM is associated with a 2-fold higher risk of new-onset HF in males and up to a 5-fold higher risk in females.[1,2] Conversely, T2DM is present in 30-50% of all patients with HF, compared with approximately 20% of age- and sex-matched controls.[3] Frank diabetes and pre-diabetic dysglycaemia are both associated with worse outcomes in HF.[4-8] Although the benefits of standard treatments for HF are similar in patients with and without T2DM, the converse may not be true and there is much debate about how to safely achieve and maintain glycaemic control in HF patients with T2DM.[9-11] Insulin remains a commonly used second line treatment in up to a third of patients with T2DM and HF. The safety of insulin in patients with HF and T2DM is unknown and there is concern that the sodium retaining action of this treatment[12] along with the significant risk of hypoglycaemia could lead to worse outcomes than with other treatments.[9,13-17] In the absence of a randomized trial, safety can only be assessed using observational data. The limitations of such non-randomized analyses are well known, including confounding by indication where prescription of insulin may be a marker of a more severe T2DM and HF.[9,17] However, whether insulin is safe in HF is an important clinical question. Therefore, to address this question, we examined two complementary types dataset, while correcting as much as possible for confounding. Firstly, we analyzed 4 large randomized HF trials which enrolled 24,012 patients in more than 40 countries worldwide; these trials collected adjudicated outcomes over 2 to 4 years of follow-up, and biomarker data were available in 15,218 patients. Secondly, we analyzed an administrative database including the 4 million people living in the Italian Region of Puglia. In this dataset patients with HF and diabetes were followed for 5 years. The database thus provided a large sample of "real world" patients, well characterized for diabetes duration and micro-and macro-vascular complications, treated in ordinary clinical practice to compare with the more selected patients enrolled in the clinical trials.

Methods

Clinical trials

Data from 4 independent large clinical trials were analyzed: the Valsartan Heart Failure Trial (Val-HeFT),[18] the Controlled Rosuvastatin Multinational Trial in HF (CORONA),[19] the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca – Heart Failure (GISSI-HF) trial,[20] and the Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE).[21] These trials, conducted over the last 20 years, were approved by the local ethics committees at each site, and all participants provided written informed consent.

The Val-HeFT trial was a randomized, placebo-controlled, double-blind, parallel-arm multicentre trial that tested the efficacy of the angiotensin receptor antagonist valsartan on morbidity and mortality in 5010 patients with stable, symptomatic HF with left ventricular systolic dysfunction.[18] The CORONA trial randomized 5011 patients of at least 60 years of age with HF with left ventricular systolic dysfunction due to an ischemic etiology who were in New York Heart Association class II or higher, to rosuvastatin or placebo daily and assessed the effect on morbidity and mortality.[19] GISSI-HF was a randomized, double-blind, placebo-controlled, multicenter trial that enrolled 6975 patients with clinical evidence of stable chronic HF, irrespective of the cause and the level of left ventricular ejection fraction (LVEF), and tested the effect of n-3 polyunsaturated fatty acids or rosuvastatin versus placebo on morbidity and mortality.[20] In ATMOSPHERE, the ACE inhibitor enalapril was compared with the renin inhibitor aliskiren and with the combination of the two treatments in 7016 patients with HF and left ventricular systolic dysfunction on morbidity and mortality.[21]

All events were adjudicated blindly by central endpoint committees in all trials. Two outcomes were used in the present analysis, all-cause mortality and first hospitalization for HF.

Type of diabetes was available only for ATMOSPHERE: patients enrolled with T1DM were 2.3% out of 1944 patients with diabetes. Given this very low prevalence of T1DM and assuming similar prevalence in the other 3 trials, the terms "T2DM" and "diabetes" will be used indifferently throughout the text.

Biomarkers

At randomization, blood samples for biomarkers were collected and the plasma separated and stored at -70°C until analyzed blindly in central laboratories. N-terminal pro-B-type natriuretic peptide (NT-proBNP), a marker of volume overload, was assayed in 3972 patients from Val-HeFT, 3664 from CORONA, 1231 from GISSI-HF, and 6351 from ATMOSPHERE, using a commercial assay (Roche Diagnostics, Basel, Switzerland).

Administrative Registry

We conducted a case-control study nested within a population-based cohort study, using a record-linkage analysis of prescription databases, hospital discharge records, and the civil deaths registry. Data protection was assured by the Healthcare Agency of Puglia. All data were anonymised prior to being accessed by the authors and none of the authors were involved in data anonymisation. In Italy no ethical approval is required for aggregated-anonymous data. A cohort of subjects with HF were identified within the National Health Service Registry of the Puglia Region from 01/01/2008 to 31/12/2013, to allow for at least 1 year of follow up (data available up to the end of 2014). HF was defined according to 2 criteria, hospitalization for HF or NHS-based exemption for disease (characteristic of the patients in Supplemental Tables 1 and 2). Within the cohort of patients with HF, the presence of diabetes was defined as at least one diagnosis of diabetes upon discharge from hospital, or NHS-based exemption for diabetes, or at least 2 prescriptions of hypoglycaemic drugs (ATC: A10) within 12 months from the index date. The relationship between insulin prescription and risk of death or first re-hospitalization for HF was assessed by a case-control (1:1) approach. For each year of observation (2008 through 2014) we identified cases, defined as subjects who were hospitalized for HF or had died, and matched controls. For HF hospitalization, a subject identified as case in one year could not be considered as a control in any subsequent year.

Statistical methods

Categorical variables are presented as proportions, and continuous variables as means (SD) or medians (Q1–Q3), as appropriate. Differences in baseline clinical characteristics according to insulin prescription were compared by the Chi-Square test for categorical variables; for continuous variables, we used a t-test or nonparametric Kruskal–Wallis test.

The associations between insulin prescription and pathophysiological and other characteristics were assessed as follows: congestion score by ordinal logistic regression model, furosemide prescription by a modified Poisson regression model, plasma concentrations of NT-proBNP by linear regression model on the natural logarithm of the values. For each outcome the model was, firstly, adjusted for baseline variables univariately associated ($p < 0.05$) with the outcome of interest (listed in Supplemental Methods 1), and, secondly, was adjusted with the propensity score according to the technique of Inverse Probability of Treatment Weighted (IPTW) that balances the relevant characteristics between insulin and non-insulin treated patients with diabetes.

The propensity scores were estimated, for each outcome, by logistic regression models including all variables associated with the outcome of interest in univariable analyses. The ability of the propensity scores estimates to balance the clinical characteristics between the insulin and non-insulin treated patients was assessed with standardized differences and with the comparison of the empirical distribution function between the insulin groups.

Kaplan–Meier survival analysis was performed by insulin prescription and compared by the log-rank test. Cox proportional hazards models were used to assess the risk of all-cause mortality. All models were adjusted for baseline variables that were associated with outcomes in univariable analysis at a level of $p < 0.05$ (listed in Supplemental Methods 2). Quantitative variables were fitted as a single continuous measurement; variables non-linearly distributed were log-transformed. These models were also adjusted with the propensity score, as previously described. Finally, Fine-Gray competing risk regression models, with or without propensity score adjustment, were used to assess the risk of hospitalization for HF where all-cause mortality was considered as competing event.

A two-sided P value lower than 0.05 was deemed significant. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Meta-analyses of the results of the 4 trials were performed using Review Manager version 5.3 software (Nordic Cochrane Centre, Cochrane Collaboration). The pooled hazard ratio was estimated with generic inverse-variance method with fixed effect. Statistical heterogeneity was quantified using the I^2 statistic and homogeneity by the χ^2 test.

For the nested case-control analysis based on administrative databases, to reduce the bias in the comparison between patients with T2DM treated with insulin and those treated with other glucose lowering drugs, a propensity score–matching algorithm on a 1-to-1 basis was used.

A logistic regression model including age, sex, presence of micro-vascular and macro-vascular complications, overall severity of co-morbid conditions, summarized by the Drug Derived Complexity Index (DDCI), previous hospitalization for arrhythmia, cancer, COPD, and chronic liver disease, year of the event and diabetes duration as covariates was used to predict the probability (propensity score) to receive insulin. The DDCI was previously shown to be a strong predictor of hospitalization, short term mortality, and long term mortality.[22] A 8-to-1 greedy matching algorithm was used to identify a unique matched control for each case according to the propensity score.

The relationships between insulin prescription and risk of death or risk of first re-hospitalization for HF were assessed through matched logistic regression analysis.

Results

Clinical trials

Clinical characteristics

Prevalence of diagnosed diabetes at study entry was similar across the trials: 25.5% (1276/5010) in Val-HeFT, 29.5% (1477/5011) in CORONA, 28.3% (1974/6975) in GISSI-HF, and 27.7% (1944/7016) in ATMOSPHERE (Supplemental Table 1). Insulin alone or in combination with oral hypoglycaemic drugs was prescribed at randomization to these patients as follows: 34.5% (440/1276) in Val-HeFT, 27.3% (403/1477) in CORONA, 27.5% (542/1974) in GISSI-HF, and to 24.4% (475/1944) in ATMOSPHERE (Supplemental Table 1). Age was similar for patients with and without diabetes and for patients with diabetes, irrespective of whether they received insulin. T2DM patients who received insulin were more likely to be women compared to T2DM patients not prescribed insulin and patients without diabetes.

Markers of congestion

Patients with diabetes treated with insulin had more severe heart failure than those not treated with insulin (Supplemental Table 1). In particular, a higher proportion were in NYHA functional class III or IV and they had a higher average creatinine and more signs of congestion, although these differences were not significant after multivariable adjustment (with or without propensity score matching, Supplemental Table 2).

NT-proBNP levels were also higher in T2DM patients treated with insulin compared to T2DM patients not treated with insulin in Val-HeFT, CORONA and GISSI-HF (but not in ATMOSPHERE). Furosemide was prescribed more frequently to patients on insulin, compared to T2DM patients not prescribed insulin, in all 4 trials (Supplemental Tables 1 and 2).

Clinical outcomes

Mortality and HF hospitalization rates were higher in patients with diabetes compared to those without diabetes and were highest of all in those prescribed insulin (Table 1). Survival of patients with

diabetes prescribed insulin was consistently lower than in those not prescribed insulin (Supplemental Figure 1).

Fully adjusted Cox multivariable models showed that insulin was independently associated with worse outcomes in 3 of the 4 trials, with similar trends in Val-HeFT (Table 2). Analysis using propensity score gave similar findings (Table 2). Meta-analysis of the 4 trials showed that insulin treatment was associated with a 32% higher adjusted risk of death and 23% higher risk of heart failure hospitalization, compared with non-insulin treatment of diabetes; the propensity score method gave similar findings (Figures 1 and 2).

Administrative Registry

In the Puglia Region, 103,857 individuals with heart failure, 39,631 (38.2%) of whom had diabetes, were identified with a mean age of 79.3±8.6 years. PPS matching led to the identification of 6,008 cases and 6,008 matched controls for the analysis of death, and 6,385 cases and an equal number of controls for re-hospitalization for HF (Supplemental Figure 2). Patients who died or were hospitalized for HF showed a similar profile of co-morbidities, whether they were on insulin or not (Supplemental Tables 3 and 4).

Logistic regression analysis showed that insulin prescription was associated with a significantly higher risk of all-cause death (OR 2.02 95% CI [1.87-2.19]) and re-hospitalization for HF (OR 1.42 95% CI [1.32-1.53]).

Discussion

The present analysis has several notable strengths, adding significantly to prior studies. Specifically, data were available from 4 large scale clinical trials providing a larger dataset than ever before and one in which all outcomes were adjudicated by independent committees. We had a “real-world” cohort of over 4 million citizens from the Puglia Region of Italy. Moreover, most patients had a measurement of NT-proBNP at randomization which allowed us to use it as an objective marker of congestion.

The principal and remarkably consistent finding, in both the clinical trials examined and in the administrative dataset, was that insulin treatment in HF was associated with a higher risk of death and of HF hospitalization, even after adjusting extensively for other predictors of adverse outcomes. These patients were at greater risk than not only individuals without diabetes but also those with diabetes treated with other glucose lowering drugs.

It is well known that T2DM patients treated with insulin may be sicker and have a longer duration of diabetes which is of greater severity than in those not treated with insulin. These factors may be a major confounder in the assessment of the association between insulin use and adverse clinical outcomes. Duration of diabetes was recorded only in ATMOSPHERE and in the administrative Registry of Puglia. The estimates of risk in analyses adjusted for duration of diabetes were similar to those in analyses not adjusted for duration of diabetes in both ATMOSPHERE and the Puglia dataset. Therefore, information on duration of diabetes in the other trials is unlikely to change our conclusions about the risk related to insulin use, possibly because adjustment for co-morbidities and severity of diabetes reduced the uncontrolled bias of diabetes duration.

Given that insulin may cause water and sodium retention,[13,23] patients with T2DM treated with insulin might be expected to exhibit more signs of congestion, and higher circulating concentrations of NT-proBNP, than individuals not treated with insulin. However, the differences in these variables disappeared after adjustment for the other characteristics of the patients (Supplemental Table 2). The rate of prescription of loop diuretics was significantly higher in patients treated with insulin, compared to those were not and this may have confounded the association with congestion. In relation to this, it is notable that greater use of diuretics is associated with worse outcomes in heart failure, although it is not known whether there is a causal relationship.[24]

Sodium and water retention[12] is not the only potential explanation for the worse outcomes associated with insulin use. Hypoglycaemia is more common in patients treated with insulin,[25] and has several adverse cardiovascular effects such as adrenergic activation, tachycardia, myocardial ischemia, and hypokalemia, all potentially leading to lethal arrhythmias, as well as causing a pro-thrombotic

state.[15,26] Indeed, if there is a causal relationship between insulin use and adverse outcomes, these alternative explanations may be more credible, given the modest difference in measures of congestion described above.

One other potential adverse effect of insulin may also be relevant. Recent evidence suggests that insulin can inhibit cardiac contractility by inducing a G_i-biased β_2-adrenergic signalling in hearts. [27]

There is one large scale randomized trial that might seem to contradict our findings (and those of others). In ORIGIN, 12,537 patients with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes were randomly assigned to insulin glargine or standard care. The incidence of hospital admission for HF was slightly but not significantly lower in the insulin glargine arm.[28] However, this trial enrolled many patients without previously diagnosed diabetes and excluded patients with NYHA class III and IV HF at baseline. Therefore, most of the cases of HF identified during follow-up were incident and had an unknown phenotype. Baseline HbA1c was also quite low at 6.4%, as was the dose of insulin administered, potentially minimizing the risk of fluid retention and hypoglycaemia.

Recently, the sodium glucose cotransporter 2 (SGLT-2)-inhibitor empaglifozin reduced the risk of incident HF and cardiovascular mortality, without a significant effect on myocardial infarction or stroke.[29,30] Cardiovascular benefits of the glucagon-like peptide 1 (GLP-1) analogues[31,32] have been recently questioned.[33,34] Although none of the GLP-1 agonist trials, or the SGLT2 inhibitor trial, enrolled many patients with HF, trials are underway in HF.

The major limitation of the present study, common to all analyses of non-randomized treatments, is the inability to adjust for unmeasured confounders (and even to fully adjust for measured confounders). [35,36] Other specific limitations are the lack of information on type and dose of insulin, which may influence the risk of hypoglycaemia, HbA1c[37], type of diabetes.Details of the oral hypoglycaemic drugs prescribed are available only for the Administrative Registry (see Supplementary Data, page): this did not allow to assess potential confounders of insulin effect in the 4 clinical trials. As most patients included in trials had HF with reduced LVEF (HFrEF), no inferences can

be made about patients with HF and preserved LVEF (HFpEF). The same information is not available from the Registry. However, a recent *post-hoc* analysis of the I-Preserve trial suggests that insulin use is also associated with a higher risk in patients with HFpEF.[6]

In conclusion, insulin use is associated with higher risks of death and hospitalization for worsening of HF in T2DM patients with HFrEF, compared to T2DM patients with HFrEF not treated with insulin. This finding was seen consistently in 4 large clinical trials as well as in a "real world" population. Whether insulin use is associated with poor outcomes in HF should be investigated further with controlled trials, as should the possibility that there may be safer alternative glucose lowering treatments for patients with HF and T2DM.

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Table 1. Incidence rates of adverse clinical outcomes in relation to diabetes and insulin prescription in the 4 clinical trials.

	Val-HeFT (n=5010 patients)		CORONA (n=5011 patients)		GISSI-HF (n=6975 patients)		ATMOSPHERE (n=7016 patients)		All patients (n=24012 patients)	
	Death	**HF hospitalization**	**Death**	**HF hospitalization**	**Death**	**HF hospitalization**	**Death**	**HF hospitalization**	**Death**	**HF hospitalization**
No diabetes	9.8 [9.1 - 10.5]	8.0 [7.4 - 8.7]	11.1 [10.5 - 11.85]	10.4 [9.7 - 11.1]	7.3 [6.9 - 7.6]	8.1 [7.6 - 8.5]	8.4 [8.0 - 8.8]	6.0 [5.6 - 6.4]	**8.7 [8.4 – 8.9]**	**7.7 [7.5 – 8.0]**
Diabetes insulin NO	11.4 [9.7 - 13.1]	12.2 [10.3 - 14.0]	13.0 [11.7 - 14.4]	14.3 [12.8 - 16.0]	8.8 [8.0 - 9.7]	11.4 [10.4 - 12.4]	10.4 [9.5 - 11.3]	8.3 [7.5 - 9.1]	**10.4 [9.9 – 11.0]**	**10.9 [10.3 – 11.4]**
Diabetes insulin YES	14.6 [11.9 - 17.2]	17.0 [13.9 - 20.0]	16.4 [14.0 - 19.2]	19.1 [16.3 - 22.5]	13.9 [12.1 - 15.6]	18.6 [16.2 - 20.9]	13.1 [11.4 - 15.0]	12.6 [10.9 - 14.7]	**14.7 [13.6 – 15.7]**	**16.5 [15.2 – 17.7]**

Incidence Rate (95% CI) per 100 person-years.

Table 2. Clinical outcomes by insulin prescription.

Study	N. of events/N. of pts	Outcome	Univariate Model	Multivariable Model	Multivariable Model with PS (IPTW)
Val-HeFT	293/1276	**All-cause Mortality** HR [95% CI], p-value	1.28 [1.01-1.62], p=0.039	1.18 [0.93-1.50], p=0.175	1.23 [0.98 - 1.55], p=0.079
	284/1276	**HF hospitalization*** HR [95% CI], p-value	1.34 [1.06 – 1.71], p=0.0146	1.28 [0.96 – 1.70], p=0.0888	1.25 [0.97 – 1.61], p=0.0812
CORONA	496/1477	**All-cause Mortality** HR [95% CI], p-value	1.27 [1.05 - 1.53], p=0.014	1.28 [1.05 - 1.56], p=0.013	1.27 [1.05 - 1.53], p=0.014
	467/1477	**HF hospitalization*** HR [95% CI], p-value	1.28 [1.05-1.55], p=0.014	1.17 [0.96-1.42], p=0.129	1.14 [0.95-1.36], p=0.159
GISSI-HF	675/1974	**All-cause Mortality** HR [95% CI], p-value	1.58 [1.35 -1.85], p < 0.0001	1.54 [1.29 - 1.83], p < 0.0001	1.29 [1.10 -1.51], p=0.0014
	712/1974	**HF hospitalization*** HR [95% CI], p-value	1.35 [1.18 – 1.54], p <0.0001	1.18 [1.01 – 1.36], p=0.0319	1.20 [1.06 – 1.35], p=0.0036
ATMOSPHERE	743/1944	**All-cause Mortality** HR [95% CI], p-value	1.27 [1.08 - 1.49], p =0.004	1.25 [1.05 - 1.47], p=0.010	1.26 [1.09 - 1.45]‡, p=0.001
	541/1944	**HF hospitalization*** HR [95% CI], p-value	1.44 [1.20-1.73], p <0.001	1.36 [1.12-1.64], p=0.002	1.34 [1.14-1.58]^, p=0.001

Reference group for all hazard ratios (HR and 95% confidence intervals, CI) are diabetics without insulin prescription.

Covariates used for multivariable models are listed in the Supplemental Methods 2.

IPTW= Inverse Probability of Treatment Weighted; PS=propensity score.

**Fine-Gray competing risk regression models; ‡ when adjusted also for diabetes duration (<5 years and >=5 years), HR=1.21[1.05-1.39]; ^when adjusted also for diabetes duration (<5 years and >=5 years) HR=1.29[1.09-1.52].*

Figure 1. Forest plot: Insulin and all-cause mortality in diabetic patients with chronic HF.

Figure 1.a.

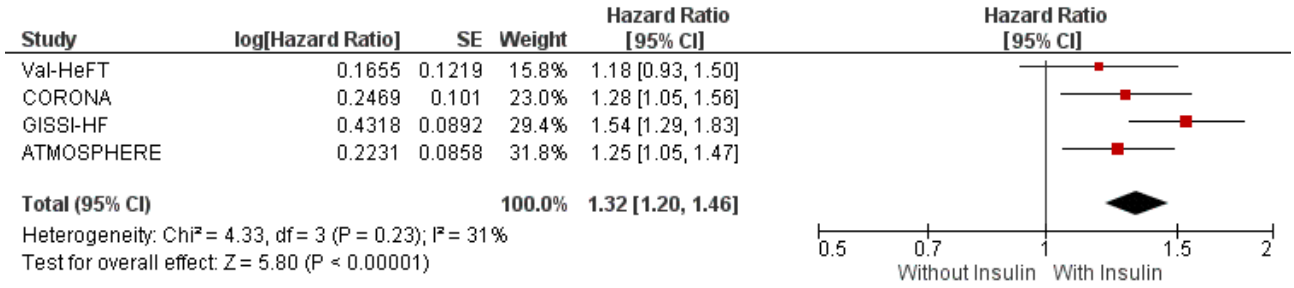
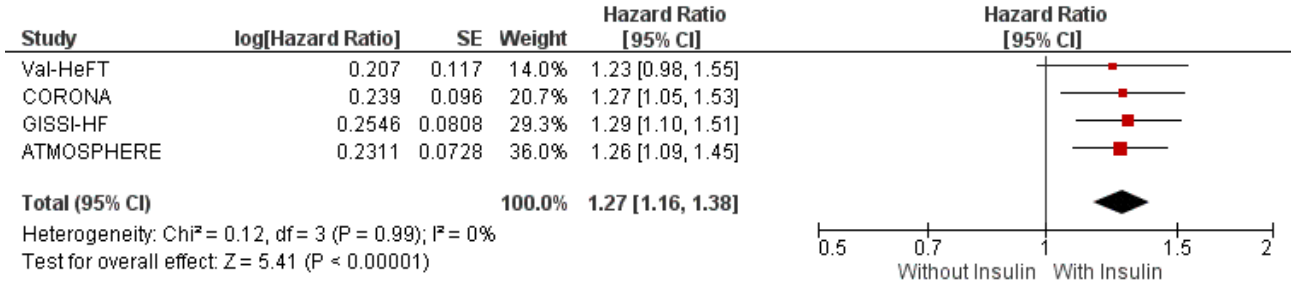


Figure 1.b.



Caption Figure 1. Multivariable Cox model (1.a), and Multivariable Cox model adjusted by propensity score IPTW (Inverse Probability of Treatment Weighted) (1.b). Reference group for all hazard ratios (HR) are diabetics without insulin prescription. The size of the symbols corresponds to the weight assigned to each trial. Trials with lower variance of the risk estimate have higher weight.

Figure 2. Forest plot: Insulin and HF hospitalization in diabetic patients with chronic HF.

Figure 2.a.

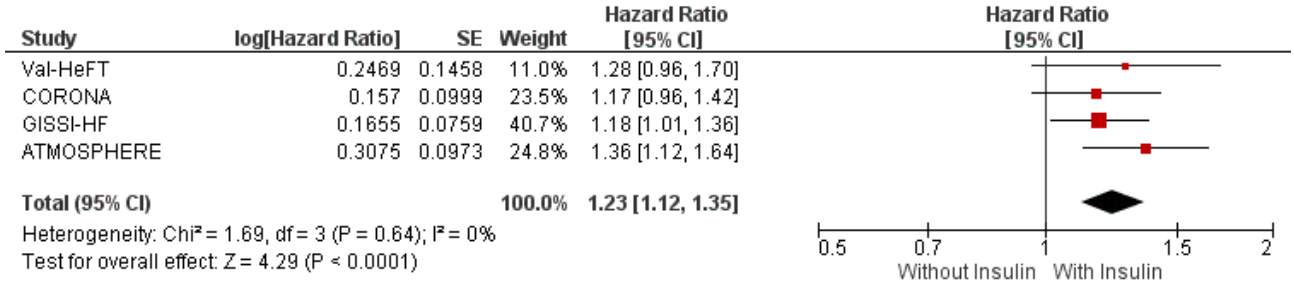
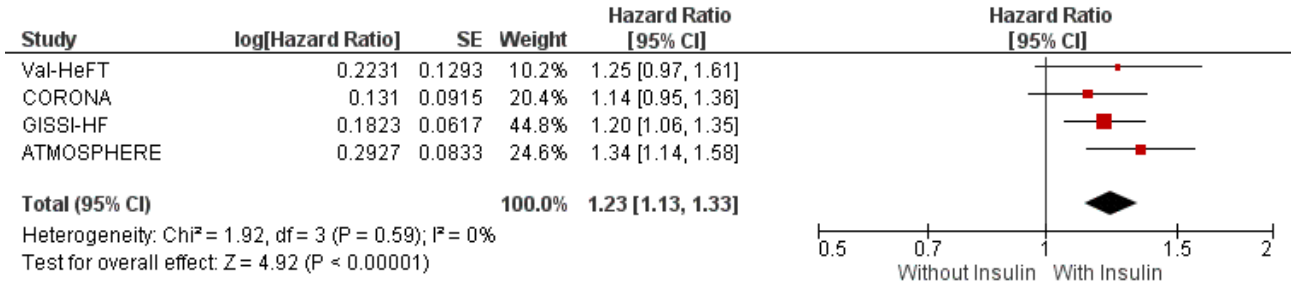


Figure 2.b.



Caption Figure 2. Fine-Gray competing risk regression model (2.a), and Fine-Gray competing risk regression model adjusted by propensity score IPTW (Inverse Probability of Treatment Weighted) (2.b). Reference group for all hazard ratios (HR) are diabetics without insulin prescription. The size of the symbols corresponds to the weight assigned to each trial. Trials with lower variance of the risk estimate have higher weight.