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Hospitalisation for heart failure and mortality associated with dipeptidyl peptidase 4 (DPP-4) inhibitor use in an unselected population of subjects with type 2 diabetes

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Short Title: Heart failure and mortality in DPP-4i users

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ABSTRACT

Objective. The SAVOR TIMI–53 study reported a significant increase in the risk of hospitalization for heart failure (HF) in patients treated with a DPP-4 inhibitor (DPP-4i) in comparison with placebo. A recent case-control study in part confirmed this risk signal. Our aim was to compare the occurrence of HF in relation to DPP-4i use versus any antidiabetic treatment.

Design. Population-based matched case-control study conducted using administrative data.

Setting. The Italian Region of Piedmont (4.4 million inhabitants).

Participants From a database of 282,000 patients treated with antidiabetic drugs, we identified 14,613 hospitalizations for HF, 7212 incident cases, and 1727 hospital re-admissions between 2008 and 2012; each case was matched for gender, age and antidiabetic therapy with ten controls; cases and controls were compared for exposure to DPP-4i.

Outcome measures Odds ratios (OR) and 95% confidence intervals were calculated by fitting a conditional logistic model. All analyses were adjusted for available risk factors for HF.

Results. We found no increased risk of hospitalisation for HF associated with the use of DPP-4i (OR for admission for HF 1.00 [0.94-1.07], incident HF1.01 [0.92-1.11], recurrent HF 1.02 [0.84-1.22]). All-cause mortality was 6% lower in DPP-4i users, whereas insulin users showed an excess of risk for any type of hospital admission (19%) and death (20%).

Conclusions. Our findings suggest that, in an unselected population of diabetic patients, the use of DPP-4i is not associated with an increased risk of HF. The favourable impact on all-cause mortality should be viewed with caution and also other explanations investigated.

Keywords: DPP-4 inhibitors, heart failure hospitalization, all-cause mortality, safety in diabetes treatment, case-control study.

Short title: A nested case-control study in a European setting

Strengths and limitations of this study

- This study suggest that, in an unselected population of diabetic patients, the use of DPP-4i is not associated with an increased risk of HF
- The study population was representative of the real type 2 diabetes population seen in Europe, without any selection based on insurance claims or age cut-off which distinguish it from other published studies.
- Hospitalization for HF was evaluated as admission, incidence or recurrence and all five drugs currently available on the market were included
- The main limitation is that weak associations between DPP-4i use and heart failure cannot be ruled out; but if they do exist, they are not so large.
- While looking forward to the results of ongoing trials, practitioners can be reassured that the unexpected association reported in the SAVOR TIMI study has not been confirmed in the real world.

Introduction

DPP-4 inhibitors (DPP-4i), or gliptins, are oral agents that delay the catabolism of native GLP-1 by inhibiting the endogenous enzyme dipeptidyl peptidase 4 (DPP-4), thus extending the life of native GLP-1. They have attracted growing interest as first line therapies for type 2 diabetes largely because they are effective in controlling HbA1c while reducing the risk of hypoglicaemia and weight gain. Currently available data suggest that they also exert a protective effect on cardiovascular risk (1). In the first published trial with cardiovascular endpoints (2), saxagliptin did not increase the risk of a composite of nonfatal myocardial infarction (MI), nonfatal stroke or cardiovascular death, thereby meeting the primary safety objective. However, as compared with placebo, saxagliptin was unexpectedly associated with a 27% excess risk of hospitalization for heart failure (HF) (overall hazard ratio [HR] 1.27 [95% confidence interval [CI] 1.07-1.51]). Detailed sub-analyses (3,4) revealed that the absolute difference between groups was mainly seen during the first 6 months of therapy and that there was no increased risk of death due to heart failure. No clinically relevant factors predictive of increased relative risk with saxagliptin treatment could be definitively identified (5). A subsequent meta-analysis of all registrative trials with DPP-4i failed to rule out an association between the use of this class of drugs and an increased risk of heart failure (6).

Evidence for an association between sitagliptin use and hospitalization for heart failure in some specific conditions comes from a recent observational study by Weir et al. (7) in which the authors

reported that in a case-control study, based on an administrative database of U.S. middle-aged adults with type 2 diabetes, treatment with sitagliptin was associated with an increased probability of hospitalization for heart failure only among patients with pre-existing heart failure.

This safety issue is relevant for diabetes care because the rates of heart failure and hospitalization are higher in patients with type 2 diabetes than in the non-diabetic population, regardless of treatment (8,9,10). Further complicating the question is that several drugs commonly used in the treatment of type 2 diabetes have been suspected to increase the risk of heart failure (11).

In light of the concerns over a possible HF risk associated with DPP-4i, we thought it useful to perform a matched case-control study to explore whether the same increased risk as seen in the SAVOR-TIMI study could be detectable in the real world and in an unselected population. To the best of our knowledge, no such analysis has been performed on data from European administrative databases which, by virtue of the universalistic care of European national health systems, encompass the whole population and include all types of available DPP-4i.

Methods

Study design and participants

We conducted a population-based nested case-control study using regional administrative data from Piedmont (population about 4.4 million). The population is covered by an automated system of databases containing the records of all drugs dispensed from all regional pharmacies and hospital discharges reimbursed by the Italian National Health System. These archives can be linked together by a unique anonymous identifier that is encrypted to protect the patient's privacy. Because this automated system is anonymous, ethical committee approval and informed consent for this study were not required.

Procedures

We extracted information from the regional drug prescription database for individuals aged 56 years or older who were dispensed at least one dose of any drug to treat diabetes between January 1, 2009 and December 31, 2013 (DPP-4i were not available in Italy before 2008). Only Piedmont residents were included. To minimise the chance of inclusion of patients with type 1 diabetes, we linked the database to the regional hospital discharge database, which contains the records of all hospital admissions between 1995 and 2013. Excluded were individuals with an International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) code for type 1 diabetes mellitus (250.x1 or 250.x3). Furthermore, as glitazones (TZD) increase the risk of heart failure, all patients who had received a prescription for TZD during the study period were excluded.

Selection of cases

We used four different definitions for cases. First, we identified all patients who had at least one discharge for heart failure, defined as ICD-9-CM codes 402.01, 402.11, 402.91, 425.4, 425.5, 425.9, 428 or 518.4 as the primary discharge diagnosis at any time after the first exposure to antidiabetic drugs (i.e., date of dispensation). For patients with more than one discharge for heart failure, we only included the first episode (i.e., the hospital admission closest to January 1 2009). Second, we identified "incident" cases of heart failure, defined as patients discharged with a diagnosis of heart failure (defined as above) during the study period, without a previous hospitalization for heart failure in the discharge diagnosis (either main or secondary) during the previous 60 months. Third, similarly to the study by Weir et al. (7) we followed up incident cases (defined as above) to identify "first re-hospitalisations" of those patients who had been admitted to hospital for a diagnosis of heart failure. Finally, we considered as cases all deaths (of any cause) that occurred in the population during the study period. Also included were Piedmont residents discharged from any hospital located outside Piedmont because information on exposure to dispensed drugs is available for all patients residing in the region. Similarly, we included the deaths of Piedmont residents wherever they occurred in Italy.

Selection of controls

To identify controls, we randomly selected ten controls from the same population source for each case, matched for year of birth (within a 5-year age band), sex, and year of first exposure to antidiabetic drugs. Controls were selected one subject at a time with replacement. The process was repeated for each outcome. Matching was done by the study statistician (RP) with the use of an automated computer program.

Exposure to DPP-4 inhibitors

We used the regional drug database to identify cases and controls who had been prescribed DPP-4i at any time in the 6 months before the hospital admission date. We used the hospital admission date of cases to calculate the exposure windows for controls. DPP-4i were selected according to the Anatomical Therapeutic Chemical (ATC) Classification System; ATC codes A10BH01 + A10BD07 (Sitagliptin), A10BH02 + A10BD08 (Vildagliptin), A10BH03 + A10BD10 (Saxagliptin), and A10BH05 + A10BD11 (Linagliptin) were considered.

Ascertainment of potential confounders

We defined potential confounders from the regional hospital discharge database as hospital admissions that occurred up to 5 years before the index date for ischemic heart diseases (ICD-9-CM 410-414). Likewise, we also included individuals who had been treated with glimepiride (ATC code A10BB12) or glibenclamide (ATC code A10BB01) in the 6 months prior to the date of hospital

admission. Treatment with insulin (ATC A10A) in the 6 months prior to the date of hospital admission was regarded as proxy of severity of disease.

Statistical analysis

We calculated the proportions of categorical variables in cases and controls and assessed the differences in baseline characteristics with the chi square test. We estimated the risk of the four different outcomes associated with dispensation of any DPP-4i by fitting conditional logistic regression models, expressed as odds ratios (ORs), and corresponding 95% confidence intervals (CI). We adjusted the statistical models for the aforementioned confounders. Confounders included in the final models were past history of ischemic heart disease, insulin use, and glimepiride or glibenclamide (considered together) use. In the sensitivity analyses, we assessed the use of DPP-4i at any time before hospital admission or death. All analyses were done with the SAS PHREG procedure version 9.2.

Results

During the study period, 14,613 cases of hospital admission for heart failure, 7212 incident cases of heart failure, 1727 cases of re-admission, and 38,248 deaths occurred within this population of patients with type 2 diabetes. Compared with controls, the use, as well as the type, of DPP-4i did not differ between cases and controls for heart failure outcomes (between 1.8 and 2.0% of both cases and controls were on gliptins), whereas the use of insulin, but not of glibenclamide, was more frequent among the cases. There was a higher prevalence of ischemic heart disease among the cases. When mortality was considered as an outcome, exposure to DPP-4i was lower among the cases than the controls (0.8% vs. 1.8%) (Table 1).

After adjustment for available confounders, the use of gliptins up to 6 months before any of the outcomes considered was not associated with the risk of hospitalization for heart failure (OR 1.00, 95% CI 0.94-1.07; p = 0.9832), incident heart failure (OR 1.01, 95% CI 0.92-1.11; p = 0.7808), hospital re-admission for heart failure (OR 1.02, 95% CI 0.84-1.22; p = 0.8745), or death of any cause (OR 0.94, 95% CI 0.90-0.98; p = 0.0021). A history of ischemic heart disease or insulin use was associated with an increased risk of all the outcomes considered, except for hospital re-admission for heart failure (Table 2). In the sensitivity analysis, in which the time window was extended to include DPP-4i use at any time before the outcomes under study, the ORs were unchanged for all outcomes: hospital admission (OR 0.99, 95% CI 0.94-1.05; p = 0.8048), incident heart failure (OR 1.01, 95% CI 0.93-1.09; p = 0.8775), hospital re-admission (OR 0.97, 95% CI 0.85-1.16; p = 0.9558), or death (OR 0.94, 95% CI 0.91-0.98; p = 0.0018).

Discussion

The question whether therapy with DPP-4i may increase the risk of heart failure has raised concern over the safety of these drugs among practitioners (4). The key message of our analysis is that, in a large unselected population of treated individuals with type 2 diabetes, no association was found, regardless of casuality and as borne out by the neutral OR independent of the subgroup considered (Any admission, Incident or Re-admission for heart failure).

Our findings are in line with a very recent paper by Yu et al. who reported no association between the use of these incretin-based therapies, studied as a whole DPPi and GLP1 receptor agonists, and incident heart failure in patients with type 2 diabetes (12). The same concordance exists with the general message from animal studies and pathophysiological investigations which found no detrimental effect of DPP-4i on cardiac function (13,14). However, it's a puzzling link because two other recent physiopathological studies in patients produced unanticipated findings that treatment with DPP-4i could exacerbate heart failure (15,16). Moreover, since no plausible explanation for the SAVOR TIMI 53 finding has been forthcoming, it is difficult to speculate on the reasons for the differences between their and our findings in the drug-associated risk of heart failure.

Weir et al. found a significantly increased risk of hospitalization for heart failure associated with the use of sitagliptin among adults with type 2 diabetes, but only in patients with pre existing heart failure, with a relevant 84% excess of risk (7). One possible, though still speculative, explanation for this discrepancy could be an indication bias in that, before the SAVOR TIMI results were published, DPP-4i were well regarded and considered particularly safe in patients with left ventricular dysfunction or renal insufficiency. On closer analysis, the two study populations differ in average age (78 versus 54 years) and background antidiabetes therapies. An additional difference is in the study design: Weir's case-control study addressed only the effects of one gliptin (sitagliptin) and in a rather selected population of young insured individuals.

The favourable impact of DPP-4i use on all-cause mortality is welcome but still warrants caution. It could confirm recent observational data that suggested a reduction of mortality in the Danish diabetic population on incretins (17). It should also be remembered, however, that DPP-4i use can represent a marker of better specialty care (18).

Our analysis, by contrast, beyond the expected role of previous ischemic heart disease as a factor underlying impaired myocardial performance, revealed an important link between insulin use and risk of heart failure for both first and recurrent hospitalisation. This finding is neither new nor surprising. In the last years, numerous observational studies have found insulin to be a marker of poor cardiovascular outcomes, including heart failure (19). Perplexing is why the outcomes of

insulin use in observational studies clash with the findings from randomised controlled trials such as the UKPDS (20) and ORIGIN (21) and seem to dismiss the role insulin can play in preventing complications. For instance, the DAI study, the largest cohort study on complications of diabetes in Italy, found a correlation between insulin therapy and the occurrence of coronary disease and stroke (22). Similar conclusions were reported for heart failure (23). A simple explanation would be that there is a typical indication bias. A more complex one would point to the problem of clinical inertia: insulin in the real world is given late, after chronic exposure to high glucose levels, thus marking subjects with poor irreversible legacy. In other words, the outcome after insulin therapy in observational studies may reflect the fact that it is initiated too late rather than its appropriate use.

Our study has several strengths. It was conducted using data retrieved from a population-based database representative of the real type 2 diabetes population seen in Europe, without any selection based on insurance claims, and, in particular, with no age cut-off, two factors which distinguish it from other published studies using administrative data. Our approach thus eliminated recall bias and minimised selection bias. All five drugs currently available on the market were included. Furthermore, as DPP-4i are dispensed and reimbursed only by prescription, we are confident to have included all dispensations.

Our study also has potential limitations, however. Though the sample size is rather large, this shouldn't be a concern: with the use of a one-sided test at the alpha = 5% level, the smallest risk, greater than one, that could be detected with 80% power is OR = 1.16 for hospital admissions, 1.24 for incident heart failure, and 1.49 for hospital re-admissions. We are aware that a weaker association between DPP-4i use and heart failure cannot be ruled out; but if it does exist, it is not so large. Another weakness is the missing data on metabolic control and other clinical variables such as NT-pro BNP levels, hypertension, heart valve defects, and renal failure, all of which could have impacted on hospitalisation rates for heart failure. Nonetheless, there is no reason why this could have favoured the control group and thus masked the association. As a proxy of diabetes severity, we adjusted for cardiovascular disease and level of therapy. We did not consider medication dose or adherence to therapy, and, given the low prevalence of exposed individuals, we were unable to factor in the effect of the different compounds separately. In addition, the use of a database of dispensed drugs rather than usage data might have overestimated the use of DPP-4i; however, it is unlikely that this would have affected cases and controls differently. Finally, only severe cases of heart failure hospitalisation were considered, leaving open the question whether milder episodes of cardiac insufficiency, not resulting in hospital admission, could have been increased in DPP-4i users.

Ongoing trials including the Sitagliptin Cardiovascular Outcome Study (24) and the Functional Impact of GLP-1 for Heart Failure Treatment (25) may help to clarify the conflicting findings. Meanwhile, practitioners can be reassured that the unexpected association reported in the SAVOR TIMI study has not been confirmed in the real world.

Contributors' Statement

CBG literature search, study design, data collection, data interpretation, writing.; RP data collection, data analysis; BT, LM and AA literature search, writing assistance; GC data interpretation, writing; RG literature search, study design, data collection, data interpretation, writing. CBG, RP, GC and RG had access to the raw data. The corresponding author had full access to all the data in the study and the final responsibility for the decision to submit for publication.

All authors approved the final version.

Competing interest statement

We have now read and understood BMJ policy on declaration of interests and declare that we have no competing interest.

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REFERENCES

1. Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2014;16:38-47
2. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I;; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317-26
3. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis

BS, McGuire DK, Davidson J, Steg PG, Bhatt DL; for the SAVOR-TIMI 53 Steering Committee and Investigators. Heart Failure, Saxagliptin and Diabetes Mellitus: Observations from the SAVOR - TIMI 53 Randomized Trial. Circulation. 2014 Oct 28;130(18):1579-88. doi: 10.1161

4. Fonarow GC. Diabetes Medications and Heart Failure: Recognizing the Risk. Circulation. 2014
5. Scirica BM, Raz I, Cavender MA, Steg PG, Hirshberg B, Davidson J, et al., on behalf of the SAVOR-TIMI 53 Steering Committee and Investigators. Outcomes of patients with type 2 diabetes and known congestive heart failure treated with saxagliptin: Analyses of the SAVOR-TIMI 53 Study. Poster number 5082 presented at American Heart Association 2013, Dallas, Texas, USA on 17 th November 2013.
6. Monami M, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and heart failure: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis. 2014;24:689-97.
7. Weir DL, McAlister FA, Senthilselvan A, Minhas-Sandhu JK, Eurich DT. Sitagliptin Use in Patients With Diabetes and Heart Failure: A Population-Based Retrospective Cohort Study. JACC Heart Fail. 2014. doi: 10.1016/j.jchf.2014.04.005.
8. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol. 1974; 34:29-34.
9. Chae CU, Glynn TJ, Manson JE, Guralnik JM, Taylor JO, Pfeffer MA. Diabetes predicts congestive heart failure risk in the elderly. Circulation. 1998; 98:721.
10. Bell DS. Heart failure: the frequent, forgotten, and often fatal complication of diabetes. Diabetes Care. 2003; 26:2433-41.
11. Eurich DT, McAlister FA, Blackburn DF, Majumdar SR, Tsuyuki RT, Varney J, Johnson JA. Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. BMJ. 2007;335:497. Review
12. Yu OH, Filion KB, Azoulay L, Patenaude V, Majdan A, Suissa S. Incretin-based drugs and the risk of congestive heart failure. Diabetes Care. 2015 Feb;38(2):277-84. doi: 10.2337/dc14-1459. Epub 2014 Sep 9.
13. Ussher JR, Drucker DJ. Cardiovascular actions of incretin-based therapies. Circ Res. 2014; 114:1788-803.
14. Khan MA, Deaton C, Rutter MK, Neyses L, Mamas MA. Incretins as a novel therapeutic strategy in patients with diabetes and heart failure. Heart Fail Rev. 2013;18:141-148.
15. http://www.escardio.org/congresses/hf2013/congress-to-you/Pages/vildagliptin-shows-no-adverse-effect-ejection-fraction-diabetic-patients-with-heart-failure.aspx. Last access November 18,2014
16. Ayaori M, Iwakami N, Uto-Kondo H, Sato H, Sasaki M, Komatsu T, Iizuka M, Takiguchi S, Yakushiji E, Nakaya K, Yogo M, Ogura M, Takase B, Murakami T, Ikewaki K. Dipeptidyl vasodilatation in type 2 diabetic patients. J Am Heart Assoc. 2013;2:e003277.
17. Mogensen UM, Andersson C, Fosbol EL, Schramm TK, Vaag A, Scheller NM, Torp-Pedersen C, Gislason G, Kober L. Cardiovascular safety of combination therapies with incretin-based drugs and metformin compared with a a combination of metformin and sulphonylurea in type 2 diabetes mellitus – a retrospective nationwide study. Diabetes Obes Metab. 2014; 16:1001-8.
18. Giorda C, Picariello R, Elisa Nada E, Tartaglino B, Marafetti L, Costa G, Gnavi R. The Impact of Adherence to Screening Guidelines and of Diabetes Clinics Referral on Morbidity and Mortality in Diabetes. PLoS One. 2012; 7:e33839
19. Giorda CB. Could clinical inertia in part explain the unexpected association of insulin therapy with poorer cardiovascular outcomes in observational studies on diabetes? Diabetes Res Clin Pract. 2011; 92:e47-8.

20. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008; 359:1577-89.
21. The ORIGIN Trial Investigators. Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia. N Engl J Med. 2012; 367:319-328.
22. Giorda CB, Avogaro A, Maggini M, Lombardo F, Mannucci E, Turco S, Alegiani SS, Raschetti R, Velussi M, Ferrannini E and for the Diabetes and Informatics Study Group. Incidence and risk factors for stroke in type 2 diabetic patients: the DAI study. Stroke. 2007;38:1154–60.
23. Nichols GA, Hillier TA, Erbey JR, Brown JB. Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. Diabetes Care. 2001; 24:1614–9.
24. Green JB, Bethel MA, Paul SK, Ring A, Kaufman KD, Shapiro DR, Califf RM, Holman RR. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. Am Heart J. 2013; 166:983-989.
25. Margulies KB, Anstrom KJ, Hernandez AF, Redfield MM, Shah MR, Braunwald E, Cappola TP; Heart Failure Clinical Research Network. GLP-1 agonist therapy for advanced heart failure with reduced ejection fraction: design and rationale for the functional impact of GLP-1 for heart failure treatment study. Circ Heart Fail. 2014; 7:673-9.

Table 1. Baseline Characteristics

	Any admission for HF			Incident HF			Re-admission for HF			All-cause mortality		
	Cases (n =14,613)	Controls (n =14,6130)	p value	Cases (n =7212)	Controls (n =72,120)	p value	Cases (n =1727)	Controls (n =17,222)	p value	Cases (n =38,248)	Controls (n =382,313)	p value
Age at recruitment, years	78.0 (8.3)	77.9 (8.4)		78.3 (8.4)	78.2 (8.4)		77.9 (8.4)	77.9 (8.5)		80.2 (9.1)	79.9 (9.0)	
Sex male	7690 (52.6)	76,900 (52.6)		3577 (49.6)	35,770 (49.6)		914 (52.9)	9102 (52.9)		19,215 (50.2)	19,1983 (50.2)	
DPP-4i use (6 months)	256 (1.8)	2881 (2.0)	0.0672	135 (1.9)	1285 (1.8)	0.5820	37 (2.1)	338 (2.0)	0.6090	306 (0.8)	6717 (1.8)	<.0001
DPP-4i use (any)	328 (2.2)	3636 (2.5)	0.0702	171 (2.4)	1657 (2.3)	0.6917	47 (2.7)	470 (2.7)	0.9853	477 (1.3)	8491 (2.2)	<.0001
Previous disorders or treatments												
Ischemic heart disease (in the past 5 years)	3371 (23.1)	10,237 (7.0)	<.0001	879 (12.2)	5492 (7.6)	<.0001	281 (16.3)	2361 (13.7)	0.0034	4270 (11.2)	23,938 (6.3)	<.0001
Glimepiride or glibenclamide (in the past 6 months)	1531 (10.5)	16,756 (11.5)	0.0003	916 (12.7)	8144 (11.3)	0.0003	172 (10.0)	1691 (9.8)	0.8516	3428 (9.0)	46,327 (12.1)	<.0001
Insulin (in the past 6 months)	5363 (36.7)	24,108 (16.5)	<.0001	2177 (30.2)	12,042 (16.7)	<.0001	730 (42.3)	4459 (25.9)	<.0001	14,159 (37.0)	64,477 (16.9)	<.0001

HF denotes heart failure.

Data are mean (SD) or no. (%)

Table 2. Matched Odd Ratios (OR) of different outcomes associated with exposure to DPP-4i in the 6 months before index date.

	Any admission for HF		Incident HF		Re-admission for HF		All-cause mortality	
	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value
DPP-4i use	0.99 (0.92-1.05); p=0.6383	1.00 (0.94-1.07); p=0.9832	1.01 (0.92-1.11); p=0.8867	1.01 (0.92-1.11); p=0.7808	1.01 (0.84-1.22); p=0.8944	1.02 (0.84-1.22); p=0.8745	0.93 (0.89-0.97); p=0.0005	0.94 (0.90-0.98); p=0.0021
Previous disorders or treatments								
Ischemic heart disease (in the past 5 years)	1.36 (1.31-1.40); p=<.0001	1.34 (1.29-1.38); p=<.0001	1.09 (1.04-1.14); p=0.0003	1.08 (1.03-1.13); p=0.0014	1.03 (0.96-1.11); p=0.4455	1.02 (0.95-1.10); p=0.6067	1.11 (1.09-1.14); p=<.0001	1.09 (1.07-1.12); p=<.0001
Glimepiride or glibenclamide (in the past 6 months)	0.99 (0.96-1.02); p=0.3555	1.01 (0.98-1.04); p=0.4844	1.02 (0.98-1.06); p=0.3520	1.03 (0.99-1.08); p=0.0998	1.00 (0.92-1.09); p=0.9614	1.02 (0.93-1.11); p=0.6751	0.96 (0.95-0.98); p=<.0001	0.98 (0.97-1.00); p=0.0540
Insulin (in the past 6 months)	1.21 (1.18-1.24); p=<.0001	1.19 (1.17-1.22); p=<.0001	1.13 (1.10-1.17); p=<.0001	1.13 (1.10-1.17); p=<.0001	1.12 (1.06-1.19); p=0.0001	1.12 (1.06-1.19); p=0.0002	1.20 (1.19-1.22); p=<.0001	1.20 (1.18-1.21); p=<.0001

HF denotes heart failure

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Hospitalisation for heart failure and mortality associated with dipeptidyl peptidase 4 (DPP-4) inhibitor use in an unselected population of subjects with type 2 diabetes. A nested case-controll study.

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Hospitalisation for heart failure and mortality associated with dipeptidyl peptidase 4 (DPP-4) inhibitor use in an unselected population of subjects with type 2 diabetes. A nested case-controlled study.

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Short Title: Heart failure and mortality in DPP-4i users

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ABSTRACT

Objective. The SAVOR TIMI–53 study reported a significant increase in the risk of hospitalization for heart failure (HF) in patients treated with a DPP-4 inhibitor (DPP-4i) in comparison with placebo. A recent case-control study in part confirmed this risk signal. Our aim was to compare the occurrence of HF in relation to DPP-4i use versus any antidiabetic treatment.

Design. Population-based matched case-control study conducted using administrative data.

Setting. The Italian Region of Piedmont (4.4 million inhabitants).

Participants From a database of 282,000 patients treated with antidiabetic drugs, we identified 14,613 hospitalizations for HF, 7212 incident cases, and 1727 hospital re-admissions between 2008 and 2012; each case was matched for gender, age and antidiabetic therapy with ten controls; cases and controls were compared for exposure to DPP-4i.

Outcome measures Odds ratios (OR) and 95% confidence intervals were calculated by fitting a conditional logistic model. All analyses were adjusted for available risk factors for HF.

Results. We found no increased risk of hospitalisation for HF associated with the use of DPP-4i (OR for admission for HF 1.00 [0.94-1.07], incident HF1.01 [0.92-1.11], recurrent HF 1.02 [0.84-1.22]). All-cause mortality was 6% lower in DPP-4i users ($p<0.001$), whereas insulin users showed an excess of risk for any type of hospital admission (19%) and death (20%) ($p<0.001$).

Conclusions. Our findings suggest that, in an unselected population of diabetic patients, the use of DPP-4i is not associated with an increased risk of HF. The favourable impact on all-cause mortality should be viewed with caution and also other explanations investigated.

Keywords: DPP-4 inhibitors, heart failure hospitalization, all-cause mortality, safety in diabetes treatment, case-control study.

Short title: A nested case-control study in a European setting

Strengths and limitations of this study

- This study suggest that, in an unselected population of diabetic patients, the use of DPP-4i is not associated with an increased risk of HF
- The study population was representative of the real type 2 diabetes population seen in Europe, without any selection based on insurance claims or age cut-off which distinguish it from other published studies.
- Hospitalization for HF was evaluated as admission, incidence or recurrence and all five drugs currently available on the market were included
- The main limitation is that weak associations between DPP-4i use and heart failure cannot be ruled out; but if they do exist, they are not so large.
- While looking forward to the results of ongoing trials, practitioners can be reassured that the unexpected association reported in the SAVOR TIMI study has not been confirmed in the real world.

Introduction

DPP-4 inhibitors (DPP-4i), or gliptins, are oral agents that delay the catabolism of native GLP-1 by inhibiting the endogenous enzyme dipeptidyl peptidase 4 (DPP-4), thus extending the life of native GLP-1. They have attracted growing interest as first line therapies for type 2 diabetes largely because they are effective in controlling HbA1c while reducing the risk of hypoglicaemia and weight gain. Data from trials with glycemic endpoints suggest that they also exert a protective effect on cardiovascular risk (1). In the first published trial with cardiovascular endpoints (2), saxagliptin neither increase, nor reduce, the risk of a composite of nonfatal myocardial infarction (MI), nonfatal stroke or cardiovascular death, thereby meeting the primary safety objective. However, as compared with placebo, saxagliptin was unexpectedly associated with a 27% excess risk of hospitalization for heart failure (HF) (overall hazard ratio [HR] 1.27 [95% confidence interval [CI] 1.07-1.51]). Detailed sub-analyses (3,4) revealed that the absolute difference between groups was mainly seen during the first 6 months of therapy and that there was no increased risk of death due to heart failure. No clinically relevant factors predictive of increased relative risk with saxagliptin treatment could be definitively identified (5). A subsequent meta-analysis of all registrative trials with DPP-4i showed an association between the use of this class if drugs and increased risk of HF which disappears when excluding cardiovascular outcome trials. (6).

Conflicting evidence for an association between sitagliptin use and hospitalization for heart failure in some specific conditions comes from recent observational studies. Wang et al (7) found an increased risk of hospitalization for HF in with sitagliptin use in Taiwanese insured individuals whereas Chen et al. (8) reported no increased risk in patient with history of chronic kidney disease and myocardial infarction. Weir et al. (9) in particular reported that in a case-control study, based on an administrative database of U.S. middle-aged adults with type 2 diabetes, treatment with sitagliptin was associated with an increased probability of hospitalization for heart failure only among patients with pre-existing heart failure.

This safety issue is relevant for diabetes care because the rates of heart failure and hospitalization are higher in patients with type 2 diabetes than in the non-diabetic population, regardless of treatment (10,11,12). Further complicating the question is that several drugs commonly used in the treatment of type 2 diabetes have been suspected to increase the risk of heart failure (13).

In light of the concerns over a possible HF risk associated with DPP-4i, we thought it useful to perform a matched case-control study to explore whether the same increased risk as seen in the SAVOR-TIMI study could be detectable in the real world and in an unselected population. To the best of our knowledge, no such analysis has been performed on data from European administrative databases which, by virtue of the universalistic care of European national health systems, encompass the whole population and include all types of available DPP-4i.

Methods

Study design and participants

We conducted a population-based nested case-control study using regional administrative data from Piedmont (population about 4.4 million). The population is covered by an automated system of databases containing the records of all drugs dispensed from all regional pharmacies and hospital discharges reimbursed by the Italian National Health System. These archives can be linked together by a unique anonymous identifier that is encrypted to protect the patient's privacy. Because this automated system is anonymous, ethical committee approval and informed consent for this study were not required.

Procedures

We extracted information from the regional drug prescription database for individuals aged 56 years or older who were dispensed at least one dose of any drug to treat diabetes between January 1, 2009 and December 31, 2013 (DPP-4i were not available in Italy before 2008). Only Piedmont residents were included. To minimise the chance of inclusion of patients with type 1 diabetes, we linked the database to the regional hospital discharge database, which contains the records of all hospital admissions between 1995 and 2013. Excluded were individuals with an International Classification

of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) code for type 1 diabetes mellitus (250.x1 or 250.x3). Furthermore, as glitazones (TZD) increase the risk of heart failure, all patients who had received a prescription for TZD during the study period were excluded.

Selection of cases

We used four different definitions for cases. First, we identified all patients who had at least one discharge for heart failure, defined as ICD-9-CM codes 402.01, 402.11, 402.91, 425.4, 425.5, 425.9, 428 or 518.4 as the primary discharge diagnosis at any time after the first exposure to antidiabetic drugs (i.e., date of dispensation). For patients with more than one discharge for heart failure, we only included the first episode (i.e., the hospital admission closest to January 1 2009). Second, we identified "incident" cases of heart failure, defined as patients discharged with a diagnosis of heart failure (defined as above) during the study period, without a previous hospitalization for heart failure in the discharge diagnosis (either main or secondary) during the previous 60 months. Third, similarly to the study by Weir et al. (9) we followed up incident cases (defined as above) to identify "first re-hospitalisations" of those patients who had been admitted to hospital for a diagnosis of heart failure. Finally, we considered as cases all deaths (of any cause) that occurred in the population during the study period. Also included were Piedmont residents discharged from any hospital located outside Piedmont because information on exposure to dispensed drugs is available for all patients residing in the region. Similarly, we included the deaths of Piedmont residents wherever they occurred in Italy.

Selection of controls

To identify controls, we randomly selected ten controls from the same population source for each case, matched for year of birth (within a 5-year age band), sex, and year of first exposure to antidiabetic drugs. Controls were selected one subject at a time with replacement. The process was repeated for each outcome. Matching was done by the study statistician (RP) with the use of an automated computer program.

Exposure to DPP-4 inhibitors

We used the regional drug database to identify cases and controls who had been prescribed DPP-4i at any time in the 6 months before the hospital admission date. We used the hospital admission date of cases to calculate the exposure windows for controls. DPP-4i were selected according to the Anatomical Therapeutic Chemical (ATC) Classification System; ATC codes A10BH01 + A10BD07 (Sitagliptin), A10BH02 + A10BD08 (Vildagliptin), A10BH03 + A10BD10 (Saxagliptin), and A10BH05 + A10BD11 (Linagliptin) were considered.

Ascertainment of potential confounders

We defined potential confounders from the regional hospital discharge database as hospital admissions that occurred up to 5 years before the index date for ischemic heart diseases (ICD-9-CM 410-414). Likewise, we also included individuals who had been treated with glimepiride (ATC code A10BB12) or glibenclamide (ATC code A10BB01) in the 6 months prior to the date of hospital admission. Treatment with insulin (ATC A10A) in the 6 months prior to the date of hospital admission was regarded as proxy of severity of disease.

Statistical analysis

We calculated the proportions of categorical variables in cases and controls and assessed the differences in baseline characteristics with the chi square test. We estimated the risk of the four different outcomes associated with dispensation of any DPP-4i by fitting conditional logistic regression models, expressed as odds ratios (ORs), and corresponding 95% confidence intervals (CI). We adjusted the statistical models for the aforementioned confounders. Confounders included in the final models were past history of ischemic heart disease, insulin use, and glimepiride or glibenclamide (considered together) use. In the sensitivity analyses, we assessed the use of DPP-4i at any time before hospital admission or death. All analyses were done with the SAS PHREG procedure version 9.2.

Results

During the study period, 14,613 cases of hospital admission for heart failure, 7212 incident cases of heart failure, 1727 cases of re-admission, and 38,248 deaths occurred within this population of patients with type 2 diabetes. Compared with controls, the use, as well as the type, of DPP-4i did not differ between cases and controls for heart failure outcomes (between 1.8 and 2.0% of both cases and controls were on gliptins), whereas the use of insulin, but not of glibenclamide, was more frequent among the cases. There was a higher prevalence of ischemic heart disease among the cases. When mortality was considered as an outcome, exposure to DPP-4i was lower among the cases than the controls (0.8% vs. 1.8%) (Table 1).

After adjustment for available confounders, the use of gliptins up to 6 months before any of the outcomes considered was not associated with the risk of hospitalization for heart failure (OR 1.00, 95% CI 0.94-1.07; p = 0.9832), incident heart failure (OR 1.01, 95% CI 0.92-1.11; p = 0.7808), hospital re-admission for heart failure (OR 1.02, 95% CI 0.84-1.22; p = 0.8745), or death of any cause (OR 0.94, 95% CI 0.90-0.98; p = 0.0021). A history of ischemic heart disease or insulin use was associated with an increased risk of all the outcomes considered, except for hospital re-admission for heart failure (Table 2). In the sensitivity analysis, in which the time window was extended to include DPP-4i use at any time before the outcomes under study, the ORs were

unchanged for all outcomes: hospital admission (OR 0.99, 95% CI 0.94-1.05; p = 0.8048), incident heart failure (OR 1.01, 95% CI 0.93-1.09; p = 0.8775), hospital re-admission (OR 0.97, 95% CI 0.85-1.16; p = 0.9558), or death (OR 0.94, 95% CI 0.91-0.98; p = 0.0018).

Discussion

The question whether therapy with DPP-4i may increase the risk of heart failure has raised concern over the safety of these drugs among practitioners (4). The key message of our analysis is that, in a large unselected population of treated individuals with type 2 diabetes, no association was found, regardless of casuality and as borne out by the neutral OR independent of the subgroup considered (Any admission, Incident or Re-admission for heart failure).

Our findings are in line with a very recent paper by Yu et al. who reported no association between the use of these incretin-based therapies, studied as a whole DPPi and GLP1 receptor agonists, and incident heart failure in patients with type 2 diabetes (14). The same concordance exists with the general message from animal studies and pathophysiological investigations which found no detrimental effect of DPP-4i on cardiac function (15,16). However, it's a puzzling link because two other recent physiopathological studies in patients produced unanticipated findings that treatment with DPP-4i could exacerbate heart failure (17,18). Moreover, since no plausible explanation for the SAVOR TIMI 53 finding has been forthcoming, it is difficult to speculate on the reasons for the differences between their and our findings in the drug-associated risk of heart failure.

Weir et al. found a significantly increased risk of hospitalization for heart failure associated with the use of sitagliptin among adults with type 2 diabetes, but only in patients with pre existing heart failure, with a relevant 84% excess of risk (9). One possible, though still speculative, explanation for this discrepancy could be an indication bias in that, before the SAVOR TIMI results were published, DPP-4i were well regarded and considered particularly safe in patients with left ventricular dysfunction or renal insufficiency. On closer analysis, the two study populations differ in average age (78 versus 54 years) and background antidiabetes therapies. An addiotionl difference lies in the selection of cases with the American population appearing as a rather selected population of young selected insure individuals.

The favourable impact of DPP-4i use on all-cause mortality is welcome but still warrants caution. It could confirm recent observational data that suggested a reduction of mortality in the Danish diabetic population on incretins (19). It should also be remembered, however, that DPP-4i use can represent a marker of better specialty care (20).

Our analysis, by contrast, beyond the expected role of previous ischemic heart disease as a factor underlying impaired myocardial performance, revealed an important link between insulin use and risk of heart failure for both first and recurrent hospitalisation. This finding is neither new nor surprising. In the last years, numerous observational studies have found insulin to be a marker of poor cardiovascular outcomes, including heart failure (21) raising the question of the possible pathogenetic role of hypoglycaemic events Perplexing is why the outcomes of insulin use in observational studies clash with the findings from randomised controlled trials such as the UKPDS (22) and ORIGIN (23) and seem to dismiss the role insulin can play in preventing complications. For instance, the DAI study, the largest cohort study on complications of diabetes in Italy, found a correlation between insulin therapy and the occurrence of coronary disease and stroke (24). Similar conclusions were reported for heart failure (25). A simple explanation would be that there is a typical indication bias. A more complex one would point to the problem of clinical inertia: insulin in the real world is given late, after chronic exposure to high glucose levels, thus marking subjects with poor irreversible legacy. In other words, the outcome after insulin therapy in observational studies may reflect the fact that it is initiated too late rather than its appropriate use.

Our study has several strengths. It was conducted using data retrieved from a population-based database representative of the real type 2 diabetes population seen in Europe, without any selection based on insurance claims, and, in particular, with no age cut-off, two factors which distinguish it from other published studies using administrative data. Our approach thus eliminated recall bias and minimised selection bias. All five drugs currently available on the market were included. Furthermore, as DPP-4i are dispensed and reimbursed only by prescription, we are confident to have included all dispensations.

Our study also has potential limitations, however. Though the sample size is rather large, this shouldn't be a concern: with the use of a one-sided test at the alpha = 5% level, the smallest risk, greater than one, that could be detected with 80% power is OR = 1.16 for hospital admissions, 1.24 for incident heart failure, and 1.49 for hospital re-admissions. We are aware that a weaker association between DPP-4i use and heart failure cannot be ruled out; but if it does exist, it is not so large. Another weakness is the missing data on metabolic control and other clinical variables such as NT-pro BNP levels, hypertension, heart valve defects, and renal failure, all of which could have impacted on hospitalisation rates for heart failure. Nonetheless, there is no reason why this could have favoured the control group and thus masked the association. As a proxy of diabetes severity, we adjusted for cardiovascular disease and level of therapy. We did not consider medication dose or adherence to therapy, and, given the low prevalence of exposed individuals, we were unable to

factor in the effect of the different compounds separately. In addition, the use of a database of dispensed drugs rather than usage data might have overestimated the use of DPP-4i; however, it is unlikely that this would have affected cases and controls differently. Finally, only severe cases of heart failure hospitalisation were considered, leaving open the question whether milder episodes of cardiac insufficiency, not resulting in hospital admission, could have been increased in DPP-4i users.

Ongoing trials including the Sitagliptin Cardiovascular Outcome Study (26) and the Functional Impact of GLP-1 for Heart Failure Treatment (27) may help to clarify the conflicting findings. Meanwhile, practitioners can be reassured that the unexpected association reported in the SAVOR TIMI study has not been confirmed in the real world.

Contributorship Statement

CBG literature search, study design, data collection, data interpretation, writing.; RP data collection, data analysis; BT, LM and AA literature search, writing assistance; GC data interpretation, writing; RG literature search, study design, data collection, data interpretation, writing. CBG, RP, GC and RG had access to the raw data. The corresponding author had full access to all the data in the study and the final responsibility for the decision to submit for publication.

All authors approved the final version.

Competing interests

We have now read and understood BMJ policy on declaration of interests and declare that we have no competing interest.

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Data sharing statement

Technical appendix, statistical code, and dataset were not made available in the Dryad repository. However these data can be requested to corresponding author.

REFERENCES

1. Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2014;16:38-47
2. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I;; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317-26
3. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis BS, McGuire DK, Davidson J, Steg PG, Bhatt DL; for the SAVOR-TIMI 53 Steering Committee and Investigators. Heart Failure, Saxagliptin and Diabetes Mellitus: Observations from the SAVOR - TIMI 53 Randomized Trial. Circulation. 2014 Oct 28;130(18):1579-88. doi: 10.1161
4. Fonarow GC. Diabetes Medications and Heart Failure: Recognizing the Risk. Circulation. 2014
5. Scirica BM, Raz I, Cavender MA, Steg PG, Hirshberg B, Davidson J, et al., on behalf of the SAVOR-TIMI 53 Steering Committee and Investigators. Outcomes of patients with type 2 diabetes and known congestive heart failure treated with saxagliptin: Analyses of the SAVOR-TIMI 53 Study. Poster number 5082 presented at American Heart Association 2013, Dallas, Texas, USA on 17 th November 2013.
6. Monami M, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and heart failure: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis. 2014;24:689-97.
7. Wang KL, Liu CJ, Huang CM, Wu CH, Chen SJ, Yeh CM, Chen TJ, Lin SJ and Chiang CE. Sitagliptin and the risk of hospitalization for heart failure: A population-based study. Int J Cardiol. 2014; 177: 86–90
8. Chen DY, Wang SH, Mao CT, Tsai ML, Lin YS, Chou CC, Wen MS, Wang CC, Hsieh IC, Hung KC, Chen TH. Sitagliptin and cardiovascular outcomes in diabetic patients with chronic kidney disease and acute myocardial infarction: A nationwide cohort study. Int J Cardiol. 2015 Feb 15;181:200-6. doi: 10.1016/j.ijcard.2014.12.029.
9. Weir DL, McAlister FA, Senthilselvan A, Minhas-Sandhu JK, Eurich DT. Sitagliptin Use in Patients With Diabetes and Heart Failure: A Population-Based Retrospective Cohort Study. JACC Heart Fail. 2014. doi: 10.1016/j.jchf.2014.04.005.
10. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol. 1974; 34:29-34.
11. Chae CU, Glynn TJ, Manson JE, Guralnik JM, Taylor JO, Pfeffer MA. Diabetes predicts congestive heart failure risk in the elderly. Circulation. 1998; 98:721.
12. Bell DS. Heart failure: the frequent, forgotten, and often fatal complication of diabetes. Diabetes Care. 2003; 26:2433-41.
13. Eurich DT, McAlister FA, Blackburn DF, Majumdar SR, Tsuyuki RT, Varney J, Johnson JA. Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. BMJ. 2007;335:497. Review

14. Yu OH, Filion KB, Azoulay L, Patenaude V, Majdan A, Suissa S. Incretin-based drugs and the risk of congestive heart failure. Diabetes Care. 2015 Feb;38(2):277-84. doi: 10.2337/dc14-1459. Epub 2014 Sep 9.
15. Ussher JR, Drucker DJ. Cardiovascular actions of incretin-based therapies. Circ Res. 2014; 114:1788-803.
16. Khan MA, Deaton C, Rutter MK, Neyses L, Mamas MA. Incretins as a novel therapeutic strategy in patients with diabetes and heart failure. Heart Fail Rev. 2013;18:141-148.
17. http://www.escardio.org/congresses/hf2013/congress-to-you/Pages/vildagliptin-shows-no-adverse-effect-ejection-fraction-diabetic-patients-with-heart-failure.aspx. Last access November 18,2014
18. Ayaori M, Iwakami N, Uto-Kondo H, Sato H, Sasaki M, Komatsu T, Iizuka M, Takiguchi S, Yakushiji E, Nakaya K, Yogo M, Ogura M, Takase B, Murakami T, Ikewaki K. Dipeptidyl vasodilatation in type 2 diabetic patients. J Am Heart Assoc. 2013;2:e003277.
19. Mogensen UM, Andersson C, Fosbol EL, Schramm TK, Vaag A, Scheller NM, Torp-Pedersen C, Gislason G, Kober L. Cardiovascular safety of combination therapies with incretin-based drugs and metformin compared with a a combination of metformin and sulphonylurea in type 2 diabetes mellitus – a retrospective nationwide study. Diabetes Obes Metab. 2014; 16:1001-8.
20. Giorda C, Picariello R, Elisa Nada E, Tartaglino B, Marafetti L, Costa G, Gnavi R. The Impact of Adherence to Screening Guidelines and of Diabetes Clinics Referral on Morbidity and Mortality in Diabetes. PLoS One. 2012; 7:e33839
21. Giorda CB. Could clinical inertia in part explain the unexpected association of insulin therapy with poorer cardiovascular outcomes in observational studies on diabetes? Diabetes Res Clin Pract. 2011; 92:e47-8.
22. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008; 359:1577-89.
23. The ORIGIN Trial Investigators. Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia. N Engl J Med. 2012; 367:319-328.
24. Giorda CB, Avogaro A, Maggini M, Lombardo F, Mannucci E, Turco S, Alegiani SS, Raschetti R, Velussi M, Ferrannini E and for the Diabetes and Informatics Study Group. Incidence and risk factors for stroke in type 2 diabetic patients: the DAI study. Stroke. 2007;38:1154–60.
25. Nichols GA, Hillier TA, Erbey JR, Brown JB. Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. Diabetes Care. 2001; 24:1614–9.
26. Green JB, Bethel MA, Paul SK, Ring A, Kaufman KD, Shapiro DR, Califf RM, Holman RR. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. Am Heart J. 2013; 166:983-989.
27. Margulies KB, Anstrom KJ, Hernandez AF, Redfield MM, Shah MR, Braunwald E, Cappola TP; Heart Failure Clinical Research Network. GLP-1 agonist therapy for advanced heart failure with reduced ejection fraction: design and rationale for the functional impact of GLP-1 for heart failure treatment study. Circ Heart Fail. 2014; 7:673-9.

Table 1. Baseline Characteristics

	Any admission for HF			Incident HF			Re-admission for HF			All-cause mortality		
	Cases (n =14,613)	Controls (n =14,6130)	p value	Cases (n =7212)	Controls (n =72,120)	p value	Cases (n =1727)	Controls (n =17,222)	p value	Cases (n =38,248)	Controls (n =382,313)	p value
Age at recruitment, years	78.0 (8.3)	77.9 (8.4)		78.3 (8.4)	78.2 (8.4)		77.9 (8.4)	77.9 (8.5)		80.2 (9.1)	79.9 (9.0)	
Sex male	7690 (52.6)	76,900 (52.6)		3577 (49.6)	35,770 (49.6)		914 (52.9)	9102 (52.9)		19,215 (50.2)	19,1983 (50.2)	
DPP-4i use (6 months)	256 (1.8)	2881 (2.0)	0.0672	135 (1.9)	1285 (1.8)	0.5820	37 (2.1)	338 (2.0)	0.6090	306 (0.8)	6717 (1.8)	<.0001
DPP-4i use (any)	328 (2.2)	3636 (2.5)	0.0702	171 (2.4)	1657 (2.3)	0.6917	47 (2.7)	470 (2.7)	0.9853	477 (1.3)	8491 (2.2)	<.0001
Previous disorders or treatments												
Ischemic heart disease (in the past 5 years)	3371 (23.1)	10,237 (7.0)	<.0001	879 (12.2)	5492 (7.6)	<.0001	281 (16.3)	2361 (13.7)	0.0034	4270 (11.2)	23,938 (6.3)	<.0001
Glimepiride or glibenclamide (in the past 6 months)	1531 (10.5)	16,756 (11.5)	0.0003	916 (12.7)	8144 (11.3)	0.0003	172 (10.0)	1691 (9.8)	0.8516	3428 (9.0)	46,327 (12.1)	<.0001
Insulin (in the past 6 months)	5363 (36.7)	24,108 (16.5)	<.0001	2177 (30.2)	12,042 (16.7)	<.0001	730 (42.3)	4459 (25.9)	<.0001	14,159 (37.0)	64,477 (16.9)	<.0001

HF denotes heart failure.

Data are mean (SD) or no. (%)

Table 2. Matched Odd Ratios (OR) of different outcomes associated with exposure to DPP-4i in the 6 months before index date.

	Any admission for HF		Incident HF		Re-admission for HF		All-cause mortality	
	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value
DPP-4i use	0.99 (0.92-1.05); p=0.6383	1.00 (0.94-1.07); p=0.9832	1.01 (0.92-1.11); p=0.8867	1.01 (0.92-1.11); p=0.7808	1.01 (0.84-1.22); p=0.8944	1.02 (0.84-1.22); p=0.8745	0.93 (0.89-0.97); p=0.0005	0.94 (0.90-0.98); p=0.0021
Previous disorders or treatments								
Ischemic heart disease (in the past 5 years)	1.36 (1.31-1.40); p=<.0001	1.34 (1.29-1.38); p=<.0001	1.09 (1.04-1.14); p=0.0003	1.08 (1.03-1.13); p=0.0014	1.03 (0.96-1.11); p=0.4455	1.02 (0.95-1.10); p=0.6067	1.11 (1.09-1.14); p=<.0001	1.09 (1.07-1.12); p=<.0001
Glimepiride or glibenclamide (in the past 6 months)	0.99 (0.96-1.02); p=0.3555	1.01 (0.98-1.04); p=0.4844	1.02 (0.98-1.06); p=0.3520	1.03 (0.99-1.08); p=0.0998	1.00 (0.92-1.09); p=0.9614	1.02 (0.93-1.11); p=0.6751	0.96 (0.95-0.98); p=<.0001	0.98 (0.97-1.00); p=0.0540
Insulin (in the past 6 months)	1.21 (1.18-1.24); p=<.0001	1.19 (1.17-1.22); p=<.0001	1.13 (1.10-1.17); p=<.0001	1.13 (1.10-1.17); p=<.0001	1.12 (1.06-1.19); p=0.0001	1.12 (1.06-1.19); p=0.0002	1.20 (1.19-1.22); p=<.0001	1.20 (1.18-1.21); p=<.0001

HF denotes heart failure

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3 and 4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4 and 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 and 6
Bias	9	Describe any efforts to address potential sources of bias	4 and 5 and 13 (table 1) and 14 (table 2)
Study size	10	Explain how the study size was arrived at	Discussed on page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	No subgroups were considered and no interactions were

			examined
		(*c*) Explain how missing data were addressed	No missing data
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, and 13 (table 1)
		(b) Give reasons for non-participation at each stage	Doesn't apply: the study is based on administrative data
		(c) Consider use of a flow diagram	We didn't use a flow diagram.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13 (table 1)
		(b) Indicate number of participants with missing data for each variable of interest	No missing data
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	6 and 13 (table 1)
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6, 7 and 14 (table 2)
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not done
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6 and 7
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8 and 9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8

Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.