British Journal of Medicine & Medical Research
20(11): 1-7, 2017; Article no.BJMMR.22039
ISSN: 2231-0614, NLM ID: 101570965

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Dipeptidyl Peptidase-4 Inhibitors and Cardiovascular Risk: Retrospective Study of 50 Type 2 Diabetic Patients with Chronic Heart Failure

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Authors' contributions

This work was carried out in collaboration between all authors. Authors NAA and PH designed the study and wrote the first draft of the manuscript. Authors NAA, PH and EA managed the literature searches and analyses of the data. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2017/22039
Editor(s):
(1) Ricardo Forastiero, Professor of Physiology and Internal Medicine, Haematology, Favaloro University, Argentina.
(2) Salomone Di Saverio, Emergency Surgery Unit, Department of General and Transplant Surgery, S. Orsola Malpighi University Hospital, Bologna, Italy.
Reviewers:
(1) Carlos Martínez Salgado, University of Salamanca, Spain.
(2) Geetanjali Dang, Medical College of Wisconsin, USA.
(3) Jerzy Bełtowski, Medical University, Lublin, Poland.
(4) Mary Grace 'D' Tungdim, University of Delhi, India.
(5) Terry J. Ellapen1, University of KwaZulu-Natal, South Africa.
Complete Peer review History: http://www.sciencedomain.org/review-history/18635

Original Research Article

Received 15th September 2015
Accepted 31st October 2015
Published 14th April 2017

ABSTRACT

Objectives: The choice of antidiabetics in patients with heart failure is a major clinical concern. Some antidiabetic agents such as thiazolidinediones, more or less sulfonamides and insulin increase the risk of exacerbation of heart failure. There is controversy with regard to the cardiovascular risk associated with dipeptidyl peptidase-4 (DPP-4) inhibitors. The aim of this study was to evaluate the cardiovascular risk in patients with diabetes and heart failure treated with these medications.

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Patients and methods: A retrospective study was carried out from January 2014 to April 2015 at the *Centre Hospitalier de Haguenau*. The frequency of re-hospitalizations was studied (primary endpoint), as the duration of hospitalization and death in patients with type 2 diabetes and heart failure. Patients were divided into 2 groups, those treated with DPP-4 inhibitors (cases) and those not treated with DPP-4 inhibitors (controls).
Results: Fifty regularly followed up type 2 diabetic patients with chronic heart failure were included in this study, of whom 32(64%) were men. Their mean age (SD) was 73.7 (± 7.6) years, ranging between 58 and 85 years. Twenty-four cases (48%) were treated with DPP-4 inhibitors. The rate of re-hospitalizations (primary endpoint) was 33.3% in the cases, and 26.9% in the controls (OR: 1.29, CI: 0.38 – 4.35, p=0.575). The duration of first hospitalization was 11.9 (±8.3) days in the cases, and 9.1 (±6.2) days in the controls (Risk ratio: 1.31, p=0.217). In-hospital mortality was not different between the 2 groups.
Conclusion: Treatment with DPP-4 inhibitors was not associated with an increased risk of re-hospitalizations, duration of hospitalizations, and death in type 2 diabetic patients with heart failure.

Keywords: Dipeptidyl peptidase-4 inhibitors; diabetes; cardiovascular morbidity; cardiovascular mortality; heart failure.

1. INTRODUCTION

Diabetes and heart failure (HF) are closely related, and this relationship is bidirectional. On the one hand, diabetes mellitus, particularly type 2 (non-insulin dependent), predisposes to the occurrence of heart failure through different mechanisms, usually involving various risk factors including: abdominal obesity, high blood pressure, coronary heart disease, and specific diabetic cardiomyopathy [1-3]. Diabetic patients are 3 times more likely to develop HF [4]. Conversely, congestive HF is a hemodynamic condition that increases the risk of developing type 2 diabetes through insulin resistance [5,6].

The choice of antidiabetic agents in patients with HF is a major clinical concern. Some antidiabetic agents such as thiazolidinediones (TZDs), more or less sulfonamides and insulin increase the risk of exacerbation of HF [7-9]. This phenomenon seems to be observed with dipeptidyl peptidase-4 (DPP-4) inhibitors, a new therapeutic class in the treatment of type 2 diabetes. Despite large experimental data and small pilot clinical studies that have showed cardiovascular benefit with DPP-4 inhibitors [10,11], their use raises concerns about their cardiovascular safety since the release of the results of the *SAVOR* study [12] on the increased risk of hospitalization for HF with saxagliptin. In the *EXAMINE* trial [13], no difference was observed between the alogliptin and placebo in the risk of hospitalization for HF. Moreover, there were no new cases of HF in this study, and no worsening in the HF in previously known patients before the study. The contradictory results of these two trials therefore do not allow us to define clearly the role of DPP-4 inhibitors in the treatment of diabetic patients with HF.

The aim of this study was to evaluate the potential risk of hospitalization and death in diabetic patients with HF, treated with DPP-4 inhibitors.

2. PATIENTS AND METHODS

2.1 Type and Objectives of Study

This was a retrospective study, conducted at the *Centre Hospitalier de Haguenau* (Haguenau, France), between January 2014 and April 2015. We compared the occurrence of events (frequency of re-hospitalizations, duration of hospitalizations, and death) in type 2 diabetic patients with HF, treated with and without inhibitors of DPP-4.

2.2 Study Population

We included all patients with type 2 Diabetes (T2DM) who fulfilled the following conditions. A glycosylated hemoglobin (HbA1c) between 6.5% and 12%, systolic HF with a left ventricular ejection fraction (LVEF) ≤40% and / or diastolic dysfunction known for at least a year, in class I - III *NYHA*, under standard treatment, aged 18-85 years.

We excluded patients with advanced chronic kidney disease or on maintenance dialysis, pregnant women, patients on DPP-4 inhibitors for <6 months.

2.3 Criteria Studied

The following criteria were studied: frequency of re-hospitalizations (main criterion [MC]), duration of hospitalizations (secondary endpoint [SE]), and death (SE) in 2 populations of diabetic patients with HF, treated with and without DPP-4 inhibitors.

2.4 Definitions

Hospitalizations for heart failure (HF): HF requiring hospitalization was defined as an event that required hospitalization in an inpatient unit or a visit with a minimum stay of 12 hours in the emergency department for clinical manifestations of HF, including at least one of the following signs or symptoms: new or worsening dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, crackles at the lung bases, jugular venous distension, appearance of a third heart sound or gallop rhythm, or radiological signs of worsening HF, and an additional treatment or an increase in the initiation of therapy including diuretics, IV inotropic or vasodilator therapy, an increase in the intravenous treatment if already in progress, initiation of mechanical ventricular assist or surgical treatment, or the use of ultrafiltration, hemofiltration or dialysis for the HF.

Diastolic dysfunction: Diastolic dysfunction was defined as an LVEF >45% (Simpson biplane), associated with an increase in left ventricular filling pressures (I/e' ratio >15 or I/e' ratio between 8 and 15, with left atrium dilation, or Ap – Am >20 ms).

2.5 Procedure

The records of 50 type 2 diabetic patients with HF regularly seen between January 2014 and April 2015 at the *Centre Hospitalier de Haguenau* (Haguenau, France) were reviewed. From the eligible records, we extracted all the clinical data, echocardiographic data, and all further tests and cardiovascular imagings, laboratory tests, and any document with useful information. We collected the following data: demographic and anthropological parameters; past medical history and co-morbidities; the year of diagnosis of diabetes and HF; glycated hemoglobin (HbA1c) at the beginning and end of study (if available); LVEF and diastolic function and ventricular structural abnormalities; NT-pro BNP levels; serum creatinine levels with estimation of the glomerular filtration rate (CKD-EPI formula); the different treatments of HF, diabetes, and co-morbidities; the frequency and duration of HF hospitalizations during the study period, and possible death from cardiovascular events. The selected patients were divided into 2 groups: those treated with DPP-4 inhibitors (cases), and those not treated with DPP-4 inhibitors (controls).

2.6 Statistical Analysis

The data were coded, entered and analyzed using the *SPSS software* for *Windows*, version 20.0 (*IBM Corp*., Armonk New York, USA). We summarized continuous variables as means and standard deviations (SD), and compared using the *t-test*. Categorical variables were summarized as frequencies with their percentages, and compared using *chi-square* tests. The *odds* of events for a patient treated with or without DPP-4 inhibitors was studied using univariate and multivariate logistic regression analysis, adjusted for renal function and basic cardiovascular risk profile. Kaplan-Meier analysis was used to study survival. A p value <0.05 was considered statistically significant.

2.7 Ethical Considerations

This study was approved by the Ethics Committee of *Centre Hospitalier de Haguenau* (Haguenau, France).

3. RESULTS

3.1 Demographics

The clinical records of 50 regularly followed up type 2 diabetic patients with chronic HF fulfilled the inclusion criteria. Of these patients, 32 (64%) were men. Their mean age (SD) was 73.7 (± 7.6) years, and ranged between 58 and 85 years. Women were significantly older (77.6 ± 7.4 years for men *versus* 71.5 ± 6.9 years for women, p = 0.0051). The distribution by age is shown in Fig. 1. Patients aged 70 to 79 were the most represented (54%).

3.2 Therapeutic Data

Twenty-four cases (48%) were treated with DPP-4 inhibitors, and 26 were controls (52%). The prescribed medications in the cases were: sitagliptin (62.5%), vildagliptin (20.8%), and saxagliptin (16.7%]).

3.3 Clinical Features

The clinical characteristics of the patients (cases *versus* controls) are summarized in Table 1. The cases had average glycated hemoglobin (HbA1c) significantly higher, and were more likely to receive oral antidiabetic agents and insulin than the controls. The duration of hypertension was significantly higher in the cases than in the control group, and no significant differences were noted in the use of cardiovascular drugs particularly of HF. A non-significant higher rate of dyslipidemia was noted in the cases.

Patients with LVEF ≤40% were in the majority (n = 41), with a non-significant higher rate in the cases. The mean ejection fraction was not significantly lower in the cases than in the control group. Nearly 60% of patients (n = 29) had a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 of whom the majority were between 30 and 60 ml/min/1.73m², with no significant difference between the 2 groups.

3.4 Outcome Criteria Studied

With regard to the main outcome criteria of the study; the cases had a non-significant higher rate of re-hospitalization (p>0.05) (Fig. 2). The duration of hospitalization (secondary outcome) was not significantly longer (4.6% longer) in the cases (*p*>0.05). The in-hospital mortality (secondary outcome) was 2% (n = 1), and occurred in the control group at day 5 of the first hospitalization (p>0.05). No statistically significant differences were noted between the 2 groups in terms of ischemic heart disease (*p*>0.05).

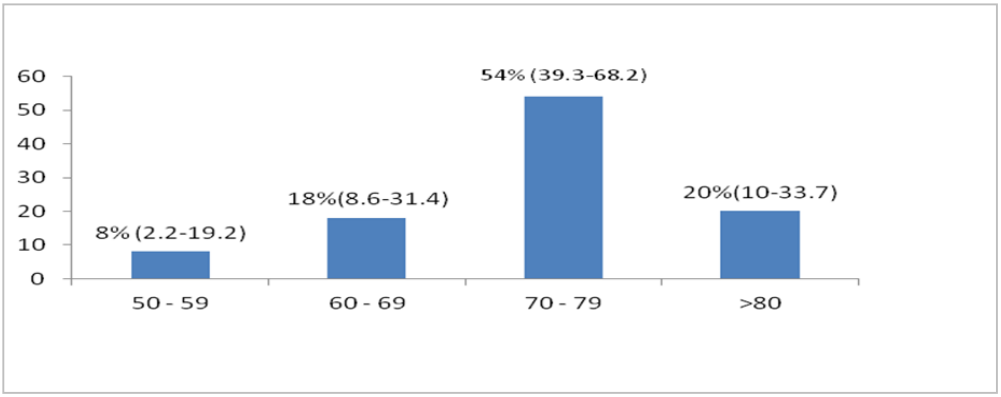

Fig. 1. Age distribution (years) of the study population

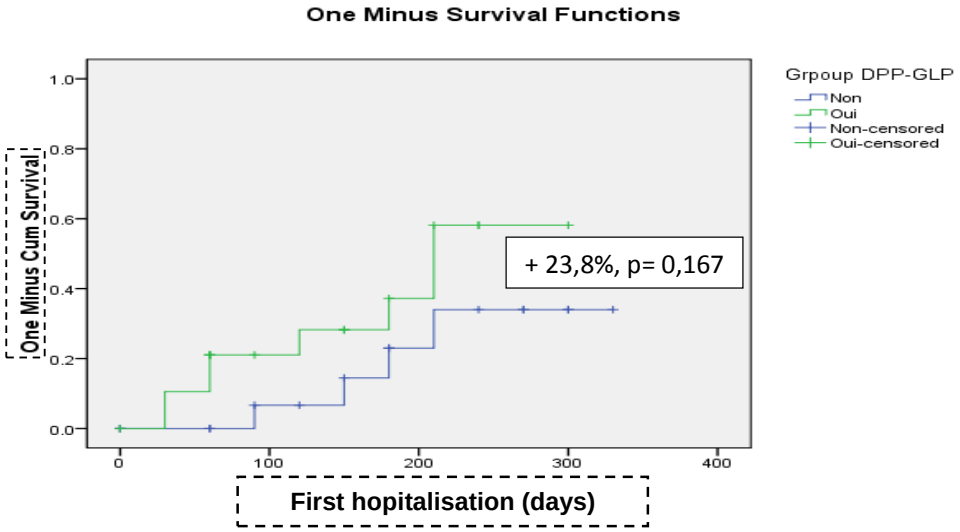

Fig. 2. *Kaplan-Meier* estimates of hospitalizations (days) for heart failure

Table 1. Characteristics of the study population

Characteristics	Overall (N = 50)	Cases (n =24)	Controls (n=26)	P values	Odds*
Hospitalisations, mean (SD)	1.35 (0.8)	1.38 (0.7)	1.32 (0.95)	0.820	1.05*
Re-hospitalisation rate (%)	30	33.3	26.9	0.575	1.29*
Duration of hospitalizations, mean (SD)					
First	10.5 (7.4)	11.9 (8.3)	9.1 (6.2)	0.217	1.31
Second	11 (6.3)	12.3 (5.5)	8.5 (7.8)	0.355	1.45
Third					
Deaths (number)	1	0	1	NA	NA
Age (years), mean (SD)	73.7 (7.6)	73.5 (8.1)	73.9 (7.2)	0.860	NA
Male (%)	64	62.5	65.4	0.532	NA
Weight (kg), mean (SD)	79.6 (17.2)	80.2 (20.1)	79.1 (14.6)	0.817	1.01
BMI (kg/m^2), mean (SD)	28.4 (6.1)	28.8 (6.5)	28.1 (5.7)	0.699	1.03
Obesity (BMI ≥ 30) (%)	38	37.5	38.5	0.969	0.98
Duration of diabetes, mean (SD)	14.7 (10.4)	14.6 (9.8)	14.8 (11.2)	0.948	NA
Hypertension (%)	90	91.7	88.5	0.625	NA
Dyslipidemia (%)	64	75	53.8	0.235	2.36*
Sleep apnea syndrome (%)	22	20.8	23.1	0.980	0.88 *
Ischemic heart disease (%)	60	62.5	57.7	0.614	1.11*
Hypertensive heart disease (%)	40	45.8	34.6	0.489	NA
Ejection fraction base line, mean (SD)	38.1 (12.6)	36 (0)	40.1 (13)	0.248	0.90
Duration of heart failure (years), mean (SD)	5.2 (6.5)	5.4 (6.4)	5.0 (6.7)	0.860	NA
Type of heart failure (%)					
Low ejection fraction	82	87.5	76.9	0.275	2.1*
Normal election fraction	18	12.5	23.5	0.275	0.4*
Previous coronary revascularization, n (%)					NA
Angioplasty	30	29.2	30.8	0.610	
Bypass surgery	18	20.8	15.4	0.568	
Baseline HbA1c, mean (SD)	7.8 (1.1)	8.2 (1.1)	7.4 (1.0)	0.042	NA
GFR levels, n (%)					
< 30 ml/min	10	16.7	3.8	0.332	NA
30 – 60 ml/min	48	50	46.2	0.332	
60 – 90 ml/min	30	20.8	38.5	0.332	
>90ml/min	12	12.5	11.5	0.332	
Albuminuria (mg/24 hour), mean (SD)	394.9 (343.9)	283.3 (92.4)	436.8 (399)	0.539	0.65
Heart failure therapy (%)					
Aspirin	56	58.3	53.8	0.631	NA
ß blockers	76	83.3	69.2	0.387	
ACE inhibitors	70	79.2	61.5	0.313	
ARA II	14	8.3	19.2	0.316	
Diuretics	98	100	96.2	0.520	
Statins	66	79.2	53.8	0.139	
Fibrates	4	8.3	0	0.321	
Digoxine	12	16.7	7.7	0.443	
Anti-aldosterone	56	45.8	65.4	0.183	
Ivabradine	6	8.3	3.8	0.511	
Implantable defibrillator	18	16.7	19.2	0.597	
Pacemaker	10	8.3	11.5	0.571	
Resynchronisation	2	0	2	0.382	
Diabetes medications (%)					
Metformin	60	75	46.2	0.036	NA
Sulfonamides	38	66.7	11.5	<0.001	
Glinides	10	0	10	0.031	
Insulin	46	50	42.3	0.397	

SD: Standard Deviation, n: Frequency, BMI: Body Mass Index, HbA1c: Glycated Hemoglobin, GFR: Glomerular Filtration Rate, MDRD: Modifying Diet in Renal Disease, ACE: Angiotensin Converting Enzyme, ARA: Angiotensin Receptor Blocker

4. DISCUSSION

In this first study including not selected patients with type 2 diabetic patients and documented chronic heart failure (real life world), no statistically significant difference was observed between the two groups concerning the number of HF hospitalizations. In this study with a small

number of patients, no difference was also seen in the rate of in-hospital mortality between the groups, with or without DPP-4 inhibitors.

The relative increase in the number of hospitalizations in the cases may be related, in part, to the use of other antidiabetic agents. Sixty-seven per cent of cases were receiving concomitant sulphonylureas and 50% insulin (Table 1). A significantly high risk of death and congestive HF was observed with sulfonylureas in some studies [14-16]. Similarly in the *SAVE* [17] trial, subjects treated with insulin after myocardial infarction complicated with low LVEF, had a poorer prognosis.

The *SAVOR* trial [12] so far remains the only large clinical trial that has shown an increased risk of hospitalization for heart failure with the use of DPP-4 inhibitors. In this trial, the factors associated with a greater risk of hospitalization with saxagliptin were the history of HF, kidney failure (defined as GFR <60 ml/min) and high levels of NT-based Pro-BNP. In this study of patients with established HF in whom more than half had a GFR <60 ml/min, no significant difference in terms of hospitalizations was observed in the 2 groups (33% *versus* 27%). In the *EXAMINE* trial [13], a non-significant relative increase in HF hospitalization was observed. The recent *TECOS* study [18] reached the primary endpoint of non-inferiority and non-superiority, and sitagliptin was not associated with an excessive risk of HF hospitalizations.

The results of our study, albeit the small sample, seem to corroborate with the findings of large trials such as *EXAMINE*, *TECOS*, and other studies on the absence of excessive HF risk [13,18,19]. Conversely, it should be noted that all these studies have not shown the improvement of cardiovascular prognosis with pharmacological inhibition of DPP-4 as had been demonstrated in the preclinical studies.

With the current debate on the supposed excessive risk of HF, the mechanism by which DPP-4 inhibitors are associated with this risk remains to be clarified, as well as the lack of improvement of the cardiovascular profile. However, pending further results on this subject, treatment with DPP-4 inhibitors in diabetic patients with HF should require caution (precautionary principle) and individual risk-benefit balance of these discussed for each type 2 diabetic patient with chronic HF (personalized medicine).

The multiple antidiabetic treatments observed in the cases probably is a reflection of the difficulty involved in the choice of antidiabetic treatment in HF. Most of these treatments have negative effects, except for metformin, the only treatment currently accepted as having a cardiovascular safety [14].

As in most retrospective studies, the lack of standardization of data is a limitation to this study. Similarly, the small sample size is a weakness. It was almost impossible to ensure compliance with healthy dietary lifestyle measures and the regular practice of physical activity that may also affect the prognosis of patients with HF. Similarly, it was difficult to ensure adherence to treatment. All these limit the interpretation of these results and their generalization.

Nevertheless, this study provides a snapshot of a real life scenario. There was no patient selection, a situation inherent in large randomized studies.

5. CONCLUSIONS

In this retrospective study at *Centre Hospitalier de Haguenau* (Haguenau, France), treatment with DPP-4 inhibitors did not result in an increased risk of HF hospitalizations, duration of hospitalizations, and death in type 2 diabetic patients with chronic heart failure. Additional data are needed to clarify definitely the cardiovascular safety of gliptins and to understand the mechanisms that could explain the absence of positive improvement observed in preclinical and small clinical studies.

CONSENT

All authors declare that oral informed consent was obtained from the patient (or other approved parties) for publication of this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/18635