Appendix 4 Risk of bias of included cohort studies

Author (year)	Ascertainment of type 2 diabetes	Ascertainment of exposure to DPP-4 inhibitors agents	Selection of the non exposed cohort	Ascertainment of other confounding variables	Demonstration that outcome of interest was not present at start of study	Comparability of study controls for important factors	Assessment of outcome	Completeness of outcome and exposure variables
Studies reporting heart failure								
Gitt (2013)[109]	Type 2 diabetes patients identified by physicians	Data collected during the follow up	Drawn from the same population as the exposed cohort	NR	No, more patients in the DPP4 inhibitors groups had heart failure at baseline compared sulfonylurea group (8.9% vs. 3.9%, P< 0.05)	Patient characteristics, blood glucose, blood pressure, and cardiovascular comorbidities were virtually identical	Data collected during the follow up	The available patients follow up data for DPP-4 inhibitors group was 90.1%, and sulfonylurea group was 81.6%
NCT01357135 (2014)[110]	Statement not explicit; type 2 diabetes patients likely identified by general practitioners	Drug prescription in the routine clinical practice	Drawn from the same population as the exposed cohort	NR	NR	Patients had statistical difference in age, and no adjusted analysis were conducted	Statement not explicit; likely from the data collected during the follow up	There were 8 and 0 participants with missing baseline gender in the sitagliptin group and sulfonylureas group, respectively
Kannan (2015)[111]	Statement not explicit; likely from identifying ICD-9 code in the database	Statement not explicit; likely from the drug prescription in the electronic medical records	Drawn from the same population as the exposed cohort	NR	Yes, patients who had a history of cardiovascular disease or congestive heart failure at baseline were excluded	Cox regression model was used to adjust baseline medical history variables (age, sex, race, BMI, number of encounters, median household income, smoking status, systolic and diastolic blood pressure, drugs used, comorbidities and propensity for being on metformin and sulfonylureas at baseline), and laboratory data (lipid profile, estimated glomerular filtration rate)	ICD-9 codes and/or a documentation of a post-baseline left ventricular ejection fraction < 40%	Authors did not mention the completeness of outcome and exposure variable data in the database
Studies reporting hospital admission for heart failure								
Fadini (2015)[13]	Statement not explicit; likely from identifying patients	DPP-4 inhibitors exposure identified by anatomical	Drawn from the same population as the exposed cohort	Confounding variables (e.g., previous	Yes, patients with a previous hospitalization for	Cox proportional hazard regression was used to adjust for age, sex, the use of certain	Hospital discharge event with a primary diagnosis	Authors did not mention the completeness of

	who were prescribed for the first time and at least once a DPP-4 inhibitors, a sulphonylurea, or a glitazone, alone or in combination with metformin	therapeutic chemical classes A10BH/A10BD07/ A10BD08		hospitalization for cardiovascular causes, previous glucose lowering medications use) were identified by ICM-9 and ATC classes	heart failure (hospital discharge ICD-9 code 428) during the 12 months before the index date were excluded	medications, the presence of previous hospitalizations, the Charlson index level grouped into three categories previous oral glucose-lowering medications, the presence of a co-treatment with metformin, and adherence level categorized on the basis of the medication possession ratio	of heart failure (ICD-9 code 428)	outcome and exposure variable data in the database
Fu (2015)[14]	NR	Statement not explicit; likely from the data of pharmacy claims	Drawn from the same population as the exposed cohort	NR	Statement not explicit; analyses were stratified by presence of baseline cardiovascular disease	Propensity score was used to identify control, and the covariates included demographics, general clinical characteristics, and hospitalization for heart failure risk factors from the 1-year baseline; cox models were built to estimate the adjusted hazard ratio stratified by presence of cardiovascular disease	NR	Authors did not mention the completeness of outcome and exposure variable data in the database
Seong (2015)[113]	Diabetic patients were identified by ICD-10 codes (E11-14)	Statement not explicit; likely from the drug prescription in the database	Drawn from the same population as the exposed cohort	Confounding variables including age at index date, gender, duration of diabetes, presence of comorbidities, and use of the medications specified were ascertained by the ICD-10 codes and drug prescription in the database	Yes, patients with a history of cardiovascular disease within the 2.5 years prior to cohort entry were excluded	Propensity score was used to balance confounders (gender, age, duration of diabetes, microvascular complications and other comorbidities in previous year, Charlson score, etc.); weighted cox model based on propensity score values was used to estimate the hazard ratio	ICD-10 code (I50)	Authors did not mention the completeness of outcome and exposure variable data in the database
Suh (2015)[114]	Statement not explicit; likely from identifying patients who received a	Statement not explicit; likely from the drug prescription in the	Drawn from the same population as the exposed cohort	NR	Yes, all hospitalizations for heart failure that occurred before	Cox regression model was used to control for age and sex	ICD-10 code (I50)	Authors did not mention the completeness of outcome and

	prescription of pioglitazone, sitagliptin, or vildagliptin	database			medication was initiated were excluded			exposure variable data in the database
Velez (2015)[115]	Diabetic patients were identified by having a primary diagnosis of diabetes mellitus using the electronic data	Statement not explicit; likely from the data of prescription claims	Drawn from the same population as the exposed cohort	NR	Yes, patients with an earlier diagnosis of heart failure during the study duration were excluded	Multivariable cox proportional hazards regression was used to adjusted for propensity score, number of antidiabetic drugs, duration of diabetes, baseline beta-blocker use, and angiotensinconverting enzyme inhibitor/angiotensin receptor blocker use	Hospital admission for heart failure was the first inpatient admission with a primary discharge diagnosis of heart failure during the period of observation.	Authors did not mention the completeness of outcome and exposure variable data in the database
Wang (2014)[15]	Diabetic patients were identified by the presence of ≥2 medical claims containing International Classification of Diseases, Ninth Revision codes for diabetes mellitus	Statement not explicit; likely from the data of pharmacy claims	Drawn from the same population as the exposed cohort	Comorbidities as hypoglycemia and heart failure was ascertained by the ICD-9 codes in the first 3 positions of the hospital discharge diagnoses, and other comorbidities were confirmed by ICD-9 codes or procedure claims before the index date	Statement not explicit; the rates of patients with heart failure at baseline in sitagliptin and control group were similar (7.1% vs. 6.6%, p=0.218)	Propensity-score matching approach was used to identify control, and the covariates included age, gender, duration of diabetes, antidiabetic drugs used, comorbidities and outpatient visit; cox proportional hazard models were built to estimate the adjusted hazard ratio	ICD-9 codes in the first position of the hospital discharge diagnoses	Authors did not mention the completeness of outcome and exposure variable data in the database

DPP-4=Dipeptidyl peptidase-4; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10=International Classification of Diseases 10th revision; NR=not reported; ATC=Anatomical Therapeutic Chemical.