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Comparison of the effects on cardiovascular events between use of metformin and dipeptidyl peptidase-4 inhibitors as the first-line hypoglycaemic agents in Japanese patients with type 2 diabetes mellitus: a claims database analysis

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ABSTRACT

Objectives To compare the risk of cardiovascular events from the initiation of therapy between metformin and dipeptidyl peptidase-4 inhibitors (DPP-4i) as first-line therapy.

Design Retrospective cohort study using two claims databases.

Setting The MDV database (provided by Medical Data Vision) comprised data from acute care hospitals, and the JMDC database (provided by JMDC) comprised data from individuals covered by health insurance societies.

Participants Those who were diagnosed with type 2 diabetes at ≥18 years, prescribed metformin or DPP-4i as the first-line hypoglycaemic agent, had medical records of ≥6 months before the index prescription and had available glycated haemoglobin (HbA1c) data for the period, including the index date and 30 days before it (defined as the baseline) were included. Those diagnosed with type 1 diabetes and/or a history of myocardial infarction (MI) or cerebrovascular diseases were excluded.

Primary and secondary outcome measures The outcomes were cumulative risks from Kaplan-Meier curves or HRs of patients prescribed metformin compared with DPP-4i. The primary endpoint was the diagnosis of MI or stroke associated with hospitalisation. Patient demographics, prescribed drugs and laboratory test values of HbA1c and estimated glomerular filtration rate at baseline were adjusted. The study period starting from the index included treatment after initial monotherapy.

Results Overall, 2089 and 6686 patients in the MDV database and 1506 and 3635 in the JMDC database were prescribed metformin and DPP-4i, respectively. The HR of the primary endpoint was 0.879 with no statistical significance (95% CI 0.534 to 1.448, p=0.613) in the MDV database, while it was significantly lower, 0.398 (95% CI 0.213 to 0.742, 0.004) in the JMDC database.

Conclusions Patients who received metformin as first-line therapy may have reduced cardiovascular events than those receiving DPP-4i. This study conforms to previous Japanese database studies, despite the consideration of its limitation being an observational design.

Strengths and limitations of this study

- ► Two Japanese claims databases, one comprising data from acute care hospitals and one comprising data from individuals covered by health insurance societies, were included.
- ► A large number of patients were analysed using the nationwide claims databases.
- ► Adjustments were made for confounding factors, including test values of serum glycated haemoglobin (HbA1c) and estimated glomerular filtration rate using propensity scores and explanatory variables for the proportional hazard analysis.
- ► The generalisability of the results may be limited because of characteristic differences in the data included in the databases and the exclusive inclusion of patients with available HbA1c data.
- ► Despite adjusting for confounding factors, not all confounders may have been included.

INTRODUCTION

The number of patients with diabetes has been increasing over the years in Japan, and it was estimated to reach 10 million in 2016.[1] One of the therapeutic goals in type 2 diabetes is the prevention of complications in addition to the maintenance of the quality of life and life expectancy comparable to that of healthy people.[2]

Currently, the most common initial treatment of type 2 diabetes in Japan includes dipeptidyl peptidase-4 inhibitors (DPP-4i), which were introduced in 2009.[3] Several non-Japanese clinical trials have verified the safety

of DPP-4i in patients with type 2 diabetes at risk of cardiovascular complications.[4–6] However, these studies did not demonstrate the efficacy of DPP-4i in preventing the risk of these complications.

Several studies have investigated the effects of metformin, a type of biguanide, in reducing cardiovascular complications. In UK Prospective Diabetes Study, intensive treatment with metformin was suggested to reduce the incidence of heart attack in patients with type 2 diabetes compared with sulfonylureas and insulin.[7] A large international multicentred, registration-based joint observational study indicated significantly fewer total deaths in patients with diabetes with established atherothrombosis who were receiving metformin compared with those not receiving metformin.[8] A randomised controlled trial reported statistically significant effects of metformin in suppressing complex cardiovascular events in Chinese patients with coronary artery disease compared with glipizide, a sulfonylurea.[9] A cohort study in Taiwan revealed a significantly lesser incidence of stroke in the metformin-prescribed group compared with that in the non-metformin-prescribed group.[10] Metformin is often used following DPP-4i in Japan and is recommended for most patients with type 2 diabetes in American and European countries as a first-line hypoglycaemic agent.[11]

A retrospective cohort study compared DPP-4i and metformin as first-line treatments using an American health insurance claims database. It reported that metformin was significantly associated with a lower probability of adding a second glucose-lowering therapy, but not with a significant reduction in the risk of cardiovascular events compared with DPP-4i.[12] In Japan, a study using a claims database provided by Medical Data Vision (MDV database) reported that initial treatment with a biguanide was associated with a reduction in cardiovascular diseases, while that with DPP-4i did not demonstrate a significant difference compared with sulfonylureas. However, metformin and DPP-4i were not directly compared with each other.[13] A 2019 study comparing biguanide and DPP-4i for initial treatment reported that the risk of myocardial infarction (MI) and heart failure (HF) requiring hospitalisation was significantly higher with DPP-4i than with biguanides.[14] The study used the National Database of Health Insurance Claims and Specific Health Checkups of Japan, which is operated by the Ministry of Health, Labour and Welfare since 2009 and comprises claims data from almost all Japanese individuals and some annual medical check-up data. Therefore, the study could be considered to include a sufficient sample size with almost no bias. In the study, adjustments were made for confounders based on diagnoses and prescribed drugs; however, laboratory results, including serum glycated haemoglobin (HbA1c), were not considered. Additionally, the study period involved only the continuous period of first-line monotherapy treatment with a duration of approximately 1 year. Therefore, we sought to examine the differences in the risk of cardiovascular events between these two popular medications as first-line therapy by including different factors from previous studies to provide additional information for selecting the first-line treatment in Japanese patients with type 2 diabetes.

This study aimed to compare the risk of cardiovascular events after initiating treatment with metformin or DPP-4i as first-line therapy using two Japanese claims databases.

METHODS

Study design

This retrospective cohort study was performed using multiple claims databases. We compared the incidences of cardiovascular events in patients with type 2 diabetes who were on monotherapy with either metformin or DPP-4i as the first-line antidiabetic drug using Kaplan-Meier curves and proportional hazards models. The date of the first prescription was defined as the index date and the drug as the index drug.

Data source

We used two claims databases—the MDV database between April 2008 and November 2018 as the main database and a database provided by JMDC (JMDC database) between January 2005 and August 2018 as the secondary database. Although both databases were mainly composed of claims data, the characteristics of population were different from each other.

The MDV database consisted of data from both inpatients and outpatients services in acute care hospitals that used the Diagnosis Procedure Combination/Per-Diem Payment System (DPC)[15] and are called DPC hospitals. The database contains approximately 28 million patients from 385 DPC hospitals, including approximately 22% of acute care hospitals (as of August 2019).[16] Laboratory data were also available from some of the hospitals. The MDV database included patients regardless of age and type of health insurance.

The JMDC database contained data of individuals covered by health insurance societies. The total number of people insured during the study period was 5 840 945 (table 1). Since the JMDC database included employees of the companies that subscribed to the health insurance societies and their family members, it includes few people aged 65 years or older and even fewer people aged 75 years or older. The JMDC database included comprehensive records of all diagnoses and treatments as long as they were with one insurance society. There were no records of deaths apart from the reason for termination of observation. Although the JMDC database did not contain laboratory data, it contained annual medical check-up data for some people.

Patient identification

Eligible patients were those (1) diagnosed with type 2 diabetes coded as E11 or E14 according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10)[17] at least

Table 1 Patient identification and the number of patients in each step

		MDV database	JMDC database
1	Total number of patients in the dataset	2 760 067	5 840 945
2	Patients with a diagnosis of type 2 diabetes	2 726 437	443 245
3	Patients with available index date	298 256	55 218
4	Patients older than 18 years on the index date	297 755	55 137
5	Patients with >6 months of observation period before the index date	104 674	34 129
6	Patients without a diagnosis of type 1 diabetes during observation period	104 112	33 869
7	Patients without a diagnosis of myocardial infarction or cerebrovascular diseases during hospitalisation before the index date	91 200	33 190
8	Patients with available HbA1c data during the baseline period (Target patients)	8775	5141

The dataset of the MDV database consisted of patients with any diagnosis of diabetes that was coded as E10–E14 according to ICD-10. The dataset of JMDC consisted of all included members.
HbA1c, glycated haemoglobin; ICD-10, International Statistical Classification of Diseases, 10th revision; MDV, Medical Data Vision.

once; (2) aged 18 years or older on the index date; (3) prescribed either metformin defined by the generic name, metformin hydrochloride, or DPP-4i defined by the Anatomical Classification of Pharmaceutical Products (ATC) code: A10N1 as the first-line antidiabetic drug coded as A10 for monotherapy after the diagnosis of type 2 diabetes; (4) with available medical records of at least 6 months before the index date and (5) with available HbA1c data during the baseline period, which was the time period including the index date and the preceding 30 days. Those who met any of the following criteria were excluded: (1) diagnosed with type 1 diabetes coded as E10 during the observation period; or (2) hospitalised with any diagnosis of MI (coded as I12x) or cerebrovascular disease (coded as I60x–I69x) before the index date.

Study period

The observation period of each patient was from the first medical record until the last medical record in the MDV database and the insurance period in the JMDC database. The study period for the main analysis was defined as the entire observation period after the index date for each patient. We also conducted subanalyses for the period where the index drug was continuously prescribed as monotherapy. We defined continuation of treatment as the period with <60 day intervals between the prescriptions.

Outcomes

The outcomes were time-to-event data displayed using Kaplan-Meier curves for the metformin group and DPP-4i group and HRs of the metformin group compared with the DPP-4i group for the below endpoints.

The primary endpoint was the incidence of MI or stroke. We referred to 3-point major adverse cardiovascular events: a composite of death from cardiovascular causes, non-fatal MI and non-fatal stroke, commonly used in randomised controlled trials as the endpoint.[18 19] Since the databases do not have records of death besides those recorded as the outcome of hospital discharge in the MDV database; we used the diagnosis of MI or stroke, regardless of fatal or non-fatal, associated with hospitalisation. The secondary endpoints were the incidence of (1) MI, (2) stroke, (3) HF and (4) angina in both databases; (5) death due to cardiovascular diseases—either MI or stroke—as discharge outcome; and (6) total deaths as the outcome of hospital discharge in the MDV database. The incidence of the diseases was defined as follows: (1) MI: hospitalisation with a diagnosis coded as I21x by ICD-10; (2) stroke: hospitalisation with a diagnosis coded as I60x–I64x; (3) HF: hospitalisation with a diagnosis coded as I50; and (4) angina: any procedures including 'percutaneous coronary arteries' in the name with the diagnosis coded as I20 in the same month of the procedure. The diagnoses associated with hospitalisation were those recorded as the greatest-resource consuming condition, trigger-for-hospitalisation condition, or the main condition in the MDV database.

Statistical analysis

We computed the Kaplan-Meier curves for each endpoint and compared the groups after adjusting for confounding factors of the metformin group and DPP-4i group using propensity scores. The propensity scores were calculated using a logistic regression model with metformin prescription as the explained variable, and the following items at baseline as the explanatory variables: age; sex; Charlson Comorbidity Index[20 21]; hypertension—defined by the prescription of antihypertensive agents coded as C03, C07, C08 or C09 by ATC; dyslipidaemia—defined by the prescription of statins or other antihyperlipidaemic agents; prescription of antithrombotic drugs, such as aspirin, novel oral anticoagulants defined by generic name, or other antithrombotic agents coded as B01; HbA1c data; and estimated glomerular filtration rate (eGFR). Missing data on eGFR were imputed by the multiple imputation method using the SAS PROC MI.

The patients were divided into five quintiles based on the propensity score, and then weights were adjusted for each quintile.[22] Statistical significance was tested using the log-rank test.

We calculated the HRs using proportional hazard analyses with each endpoint as an explained variable and variables used for developing the propensity score and the presence or absence of metformin as explanatory variables. In a sensitivity analysis, we calculated the HRs applying the propensity score, instead of each variable, as explanatory variable.

We used Microsoft Excel 2010 (Microsoft, Redmond, Washington, USA) and SAS V.9.4 (SAS Institute) for the analyses.

Patient and public involvement

Patients were not directly involved in this study.

RESULTS

Patients

Table 1 summarises the study design of identifying the target patients and the numbers of patients in each step. Patients diagnosed with type 2 diabetes were 2 726 437 and 443 245 in the MDV and JMDC databases, respectively. The number of patients in the metformin and DPP-4i groups was 2089 and 6686 in the MDV database and 1506 and 3635 patients in the JMDC database, respectively (table 2).

The baseline characteristics, including the explanatory variables (marked with†), are summarised in table 2. Patients who had no records of eGFR during the baseline period were 1212 in the MDV database and 2756 in the JMDC database, and the values of eGFR were imputed. The mean ages (±SD) of participants in the DPP-4i group were 68.6±12.1 and 53.8±8.3 years in the MDV and JMDC databases, respectively, which were higher than those in the metformin group (59.1±13.1 and 51.0±8.5 years, respectively) and the difference between the groups was smaller in the JMDC database. The HbA1c value was higher in the metformin group (7.9%±1.6%) than that in the DPP-4i group (7.4%±1.3%) in the MDV database and the values between the groups were relatively similar in the JMDC database (8.0%±1.7% for the metformin group and 7.9%±1.6% for the DPP-4i group). The study period was longer than 2 years for both groups; the periods in the JMDC database (34.0±26.5 and 31.5±22.0 months for the metformin and DPP-4i groups, respectively) were longer than those in the MDV database (28.1±23.5 and 25.8±21.4 months, respectively). The continuation periods of the initial monotherapy of the index drug were similar between both groups in both databases. Values of the explanatory variables between both groups were relatively similar in the JMDC database, while the difference between both groups was larger in some variables, such as Charlson Comorbidity Index, prescription of antithrombotic drugs, and eGFR in the MDV database compared with that in the JMDC database.

The number of patients for each propensity score quintile is summarised in table 3, and the distribution of patients by the score is shown in online supplemental figure S1. After adjusting for confounding factors using propensity scores, differences in most of the baseline characteristics, including mean age at index date (65.6 and 66.6 for the metformin and DPP-4i groups in the MDV database, and 52.7 and 53.1 for JMDC database, respectively), HbA1c value (7.54% and 7.47%, and 7.96% and 7.96%, respectively), study period (27.2 and 26.2 months, and 33.0 and 31.9 months, respectively) became small (online supplemental table S1).

Risk of MI or stroke

The number of events observed in patients prescribed metformin was 20 and in those prescribed DPP-4i was 116 in the MDV database, and 12 and 74, respectively, in the JMDC database. Figure 1 illustrates the Kaplan-Meier curves for cumulative risk of MI or stroke in each treatment group. According to the log-rank test, there was no significant difference between the treatment groups in the MDV database (p=0.064) (figure 1A). The HR of the metformin group compared with the DPP-4i group was 0.879 (95% CI 0.534 to 1.448) with no statistical significance (p=0.613) (table 4). In the JMDC database, a significant difference was observed in the Kaplan-Meier curves between the DPP-4i group and the metformin group (p<0.001) (figure 1B). The HR was 0.398 (95% CI 0.213 to 0.742) with statistical significance (p=0.004) (table 4). Similar results were observed in both databases using sensitivity analysis; the HR of the metformin group to the DPP-4i group was 0.812 (95% CI 0.496 to 1.331, p=0.409) in the MDV database and 0.406 (95%CI: 0.218 to 0.756, p=0.005) in the JMDC database (online supplemental table S2). Subanalysis for the monotherapy period demonstrated different tendencies in each database; the HR was 1.167 (p=0.703) in the MDV database and 0.763 (p=0.559) in the JMDC database, although there were no significant differences in either of them.

Secondary outcomes

The number of events at each endpoint is shown in online supplemental table S3. In the MDV database, the HRs of all events for diseases except HF were <1 and were not statistically significant. The HR of deaths due to cardiovascular disease as an outcome of hospital discharge did not have statistical significance, while that of total deaths was significantly <1 (HR=0.707, p=0.035) (table 4). In the JMDC database, HRs were lower than 1 for all events; they were significant for MI (HR=0.192, p=0.006) and not significant for others (table 4). The sensitivity analysis showed similar results other than the absence of statistical significance from total deaths in the MDV database, although HR was lower than 1 (HR=0.769, p=0.108) (online supplemental table S2).

Table 2 Baseline demographic data and explanatory variables used for propensity scores

		MDV database			JMDC database		
		Metformin	DPP-4i	P value	Metformin	DPP-4i	P value
Number of patients		2089	6686		1506	3635	
Percentage of female	Mean	39.8%	40.3%	0.361	21.2%	20.5%	0.291
	SD	49.0%	49.0%		40.9%	40.4%	
Age at index date*, years	Mean	59.09	68.56	<0.001	51.02	53.84	<0.001
	SD	13.14	12.12		8.54	8.29	
Index year and month	Mean	201 509	201 511	<0.001	201 506	201 509	<0.001
	SD	26.0	23.7		29.2	23.3	
HbA1c value*	Mean	7.90	7.37	<0.001	8.04	7.93	0.014
	SD	1.57	1.27		1.69	1.62	
Study period, months	Mean	28.1	25.8	<0.001	34.0	31.5	<0.001
	SD	23.5	21.4		26.5	22.0	
	Median	23.0	21.0		28.0	27.0	
Continuation period of the initial monotherapy	Mean	16.8	16.6	0.320	19.1	19.3	0.342
	SD	19.2	19.6		20.3	18.8	
	Median	10.0	9.0		13.0	13.0	
Charlson Comorbidity Index*	Mean	1.51	2.22	<0.001	1.80	1.80	0.500
	SD	1.70	2.17		1.09	1.12	
Diuretic agents*	Mean	0.03	0.07	<0.001	0.02	0.03	0.020
	SD	0.16	0.25		0.15	0.18	
Beta-blockers*	Mean	0.03	0.05	<0.001	0.06	0.06	0.500
	SD	0.16	0.22		0.24	0.24	
Calcium antagonists*	Mean	0.06	0.10	<0.001	0.20	0.22	0.054
	SD	0.24	0.30		0.40	0.42	
Agents acting on the renin–angiotensin system*	Mean	0.07	0.10	<0.001	0.25	0.32	<0.001
	SD	0.25	0.30		0.43	0.46	
Statins*	Mean	0.06	0.07	0.052	0.24	0.32	<0.001
	SD	0.24	0.26		0.42	0.47	
Antihyperlipidaemic agents*	Mean	0.02	0.02	0.500	0.10	0.12	0.015
	SD	0.13	0.14		0.29	0.32	
Aspirin*	Mean	0.02	0.04	<0.001	0.02	0.03	0.016
	SD	0.14	0.20		0.14	0.18	
NOAC*	Mean	0.01	0.02	<0.001	0.00	0.01	<0.001
	SD	0.08	0.13		0.06	0.08	
Antithrombotic drugs*	Mean	0.05	0.12	<0.001	0.01	0.03	<0.001
	SD	0.21	0.33		0.12	0.17	
eGFR*†	Mean	79.41	66.26	<0.001	82.73	79.80	<0.001
	SD	22.82	25.61		15.58	15.52	

*Explanatory variables used for calculating the propensity score.
†The percentage of patients with eGFR value were 83% and 87% for metformin and DPP-4i in the MDV database, and 47% and 46% in the JMDC database, respectively.
DPP-4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; MDV, Medical Data Vision; NOAC, novel oral anti coagulants.

DISCUSSION

We compared the risk of cardiovascular events between metformin and DPP-4i when used as first-line treatment based on the analyses of two Japanese claims databases. For the primary outcome of the incidence of MI or stroke, HR of metformin compared with DPP-4i was <1

Table 3 Number of patients for each propensity score quintile in each treatment group

	MDV database				JMDC database			
	Propensity score		Number of patients		Propensity score		Number of patients	
	Min	Max	Metformin	DPP-4i	Min	Max	Metformin	DPP-4i
1	0.000	0.082	88	1317	0.000	0.218	184	762
2	0.082	0.123	195	1355	0.219	0.266	278	821
3	0.123	0.175	340	1456	0.266	0.318	338	794
4	0.175	0.264	542	1378	0.318	0.389	367	798
5	0.265	1.000	924	1180	0.389	1.000	339	460

DPP-4i, dipeptidyl peptidase-4 inhibitors; MDV, Medical Data Vision.

in both databases, although it was not significant in the MDV database. Although no significant difference was observed for each cardiovascular event, the HRs of the events besides HF were <1 in the MDV database. In the JMDC database, the HRs were <1 for all outcomes, and it was significant for MI. Regarding deaths as the outcome of hospital discharge in the MDV database, the HR of total deaths was <1 with statistical significance, and that of deaths due to cardiovascular diseases was not statistically significant. For the monotherapy period, HR for the primary outcome of metformin compared with DPP-4i was >1 in the MDV database, while it was <1 in the JMDC database, with no significant differences.

Some differences in the results between the databases are probably due to the differences in the characteristics of data included in each database. Since the MDV database consisted of data from the DPC hospitals, which are large hospitals, the patients included in this database might have more severe disease status or complications than general Japanese patients with type 2 diabetes. Each patient had a record of diagnoses and treatments only provided at the same hospital, implying that the events diagnosed outside of the hospital, such as those associated with emergency hospitalisation, could not be included in the database. In the JMDC database, there was a limited number of older patients; however, the events could be captured regardless of the settings unless the patients changed the insurance society. We found that the baseline characteristics, including values of the explanatory variables between the metformin group and DPP-4i group, were relatively similar in the JMDC database compared with those in the MDV database. Although we adjusted for confounding factors between the groups by the methods of propensity scores or proportional hazard analysis, the difference in the baseline characteristics could still affect the results with statistical significance. Considering the similar baseline characteristics between the groups, although target patients were restricted to those excluding older patients, the JMDC database might be more suitable for comparing the treatments in this study. In the JMDC database, metformin showed a preferable effect on the primary outcome. The results of the secondary outcomes in the JMDC database and those in the MDV database were almost consistent, although no statistical significance was seen in most of the outcomes. Thus, metformin as first-line treatment may be associated with a reduced risk of cardiovascular complications.

Our results on the risk of cardiovascular events are consistent with those of previous Japanese studies that also used claims databases,[13 14] where the effect on reduction in the event tended to be lower with biguanide than with DPP-4i as the first-line therapy. However, there are some differences in the study methods. In a 2019 study, a significant difference was observed in the reduction in the incidence of MI and HF with metformin as the first-line monotherapy[14]; however, in the current study, a significant difference was not observed in the MDV database, and a significant difference was observed only for MI in the JMDC database during the entire study period. For the period of monotherapy, which is the same as that of the previous study, no significant difference was observed in both databases. One of the reasons for the difference is probably the differences between the two databases. Another reason may be associated with the study methods, including the study period and the availability of laboratory data. Despite the differences, our results support those of previous studies.

Regarding the study period, the previous Japanese studies[13 14] evaluated the effects for the period of continued initial therapy as monotherapy. Meanwhile, since we focused on the choice of the initial treatment for type 2 diabetes in this study, the study period of the main analysis included the entire period after initial treatment as monotherapy. It means that the period after discontinuation of the initial treatment and/or addition of another therapy was also included. The reason for including this period was to evaluate the comprehensive effects of the first-line drugs, including adherence and acceptability of adding another class of drug as well as the type of drugs added as second-line therapy or later. We believe that this study, which aimed to evaluate the comprehensive effects and not only the efficacy of the drug itself on the risk of cardiovascular events, could aid in choosing first-line therapies in clinical practice.

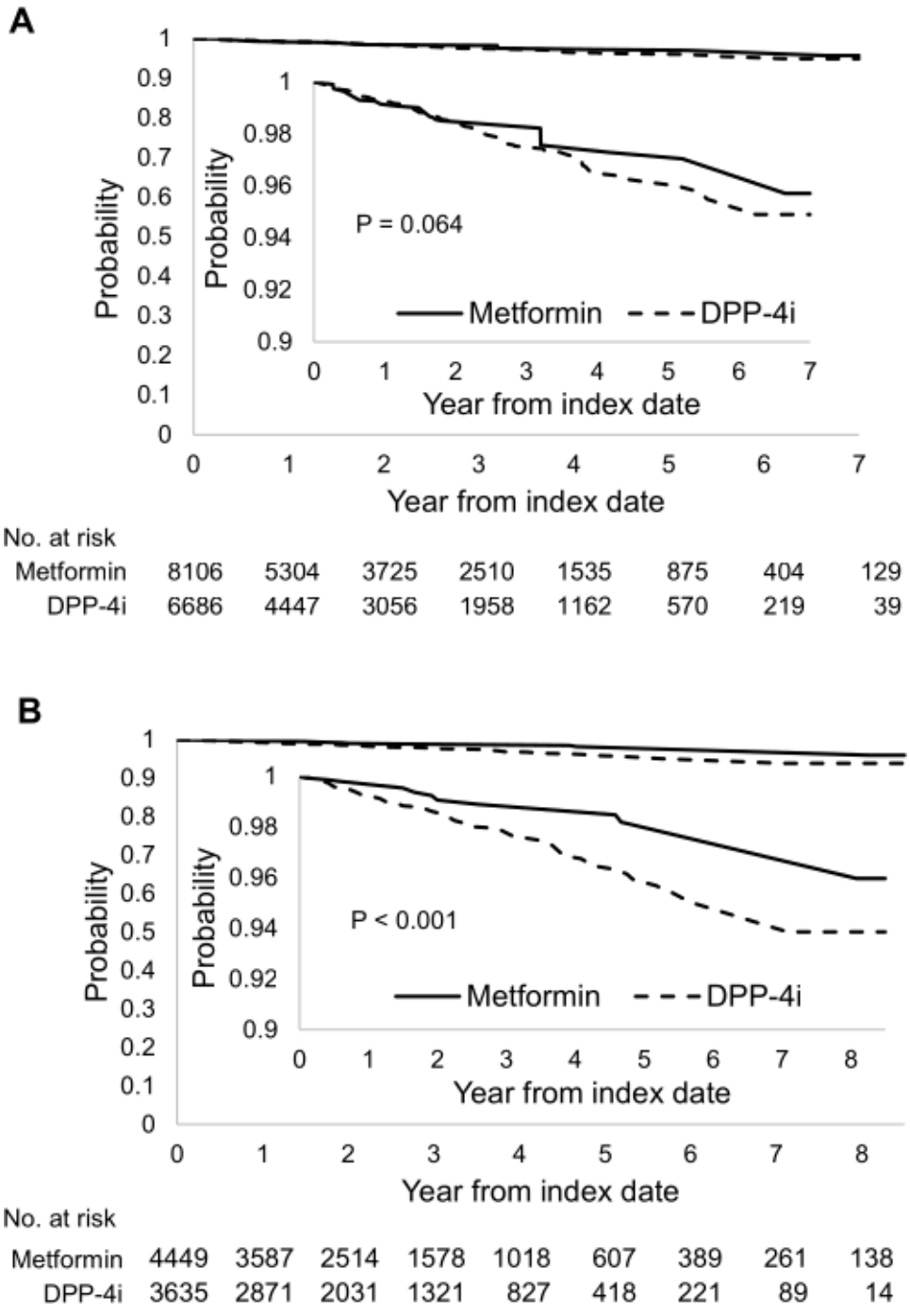

Figure 1 Kaplan-Meier curves for the incidence of myocardial infarction or stroke in the metformin group (solid lines) and DPP-4i group (dotted lines), respectively. Results of the (A) MDV and (B) JMDC database analyses, respectively. DPP-4i, dipeptidyl peptidase-4 inhibitors; MDV, Medical Data Vision.

Strengths and limitations

We used claims databases to compare the risks of cardiovascular outcomes between metformin and DPP-4i in real-world settings. The databases we used in this study include nationwide data from a large number of patients. Currently, several databases are available for such outcome studies in Japan, and each database has different advantages and disadvantages associated with the population, settings and type of data. Therefore, we used two databases to confirm the results between them. In addition, we included laboratory data of HbA1c and eGFR that could be associated with the cardiovascular events as adjustments for confounders, which is a strength of this study compared with previous Japanese studies.

Several limitations should be considered in interpreting the results of this study. Since this study was based on the secondary use of claims data, the accuracy of diagnoses and treatments relies on the accuracy of the records of the databases, which may affect the internal validity. We calculated propensity scores or conducted proportional hazard

Table 4 HR of the metformin group in comparison with the DPP-4i group for each event

Event	MDV database		JMDC database	
	HR (95% CI lower limit, upper limit)	P value	HR (95% CI lower limit, upper limit)	P value
Myocardial infarction or stroke	0.879 (0.534 to 1.448)	0.613	0.398 (0.213 to 0.742)	0.004
Myocardial infarction	0.984 (0.348 to 2.777)	0.975	0.192 (0.059 to 0.626)	0.006
Stroke	0.855 (0.483 to 1.513)	0.590	0.600 (0.294 to 1.225)	0.161
Heart failure	1.201 (0.771 to 1.872)	0.418	0.697 (0.384 to 1.264)	0.234
Angina	0.767 (0.524 to 1.124)	0.174	0.663 (0.328 to 1.339)	0.251
Deaths due to cardiovascular disease as the outcome of hospital discharge	0.872 (0.250 to 3.039)	0.829	–	–
Total deaths as the outcome of hospital discharge	0.707 (0.512 to 0.976)	0.035	–	–

DPP-4i, dipeptidyl peptidase-4 inhibitors; MDV, Medical Data Vision.

analyses to adjust for the confounding factors from the databases; however, not all the important confounders may have been included. We defined the study period as that until the end of the observation period for the main analysis and as the continuation period of monotherapy with the index drug for subanalysis in each patient. Consequently, the length of the period may be related to the results. Notably, additional treatment (availability and types of agents) was not adjusted between treatments because this study aimed to assess the risk between treatments, including the difference in the additional treatment, which may also be related to the results. Since we considered the baseline HbA1c value as one of the important confounders, we only included patients with available baseline HbA1c data. Therefore, patients who measured the value in certain hospitals in the MDV database and those who underwent annual medical check-ups in the baseline period in the JMDC database were included, which resulted in reduced sample size and could affect the external validity of these results. It is noted that the availability of laboratory data depended on the contract between each hospital and MDV. Furthermore, each database includes different risks of potential bias that could affect external validity due to the characteristics of the included data. As described in the Discussion section, in the MDV database, patients might have had more severe disease status or complications than general patients. Since the JMDC database included only company employees and their families, the age structure and social background could have also affected the results.

Conclusions

The results of this study suggest that patients with type 2 diabetes who received metformin as the first-line therapy may have a reduced risk of cardiovascular events compared with those who received DPP-4i during the entire observation period. This finding is only associated with the type of first-line treatment and without continuous therapy periods or the addition of second-line or later drugs. Moreover, some limitations should be considered, including the accuracy of recorded data, a possible insufficient confounding factors adjustment, and generalisability of each database in interpreting the results because these results are based on observational data. Therefore, further studies considering these factors are required to validate the findings of this study. Nevertheless, we believe that our findings may help select the first-line treatment for patients with type 2 diabetes in Japan.

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