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Summary of Study Results Using National Database of Health Insurance Claims (NDB)

August 25, 2026

Study title	Evaluation of the risk of fatal arrhythmia events due to domperidone or metoclopramide
Products investigated	■ **The following oral drugs** Domperidone, metoclopramide
Background	• Domperidone (oral dosage form and suppository) was approved in Japan in 1982 for the indications of diseases such as chronic gastritis and gastrointestinal symptoms (including nausea and vomiting) during administration of drugs. • Overseas, the injectable form of domperidone had also been marketed, but its marketing approval was rescinded in Europe after 1985 because cases of sudden cardiac death after administration of the intravenous injection were reported[1]. • In 2014, the European Medicines Agency instructed a revision of the SmPC (Summary of Product Characteristics) including setting the maximum daily dose of domperidone at 30 mg and contraindicating its use in patients with cardiac disease and during co-administration with CYP3A4 inhibitors[2]. • In Japan, as a result of consideration of the status of adverse reaction reporting and the lower maximum dose of the oral dosage form than that in Europe, precautions have been taken by providing precautionary statements indicating that arrhythmias such as QT prolongation may occur in patients with cardiac disease. • Studies that evaluated the risk of arrhythmia-related events associated with domperidone have been reported overseas. Among them, some suggest a relationship between domperidone and an increased risk of arrhythmia or sudden cardiac death [3,4,5,6,7,8], while others do not suggest such a relationship between domperidone and an increase in these risks[9,10,11]. In addition, no study involving the Japanese population has been reported. Based on the above situation, it was considered necessary to evaluate the risk of fatal arrhythmia and sudden cardiac death due to domperidone using the NDB. • Moreover, based on the results of a previous overseas study [5] comparing the risk of sudden cardiac death between domperidone and metoclopramide, a similar drug with the same indication as domperidone, which found a higher risk with metoclopramide than with domperidone, it was decided to investigate metoclopramide as well as domperidone.

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[11] Zhang Y, Shu M, Liang W, Jiang K, Zhang D, Qiu H, et al. Risk of Serious Ventricular Arrhythmia in Users of Gastrointestinal Medications: A Retrospective Cohort Study in China. Adv Ther. 2020;37(4):1564–78.

Purpose of the study	The purpose is to evaluate the relationship between the timing of domperidone or metoclopramide use and the risk of fatal arrhythmia or sudden cardiac death in patients aged 20 years or older who received a prescription of domperidone or metoclopramide. The relationship between the daily prescribed dose of domperidone and fatal arrhythmia or sudden cardiac death is also evaluated.
Reason for selection of NDB for the study and data period	• Reason for selection: It was selected because it is a nationwide database in Japan, and it is possible to follow up patients across multiple different medical institutions nationwide. • Data period: April 1, 2012 to March 31, 2023
Outline of method	■ **Study population** The nested case-control design was used in this study. Patients who had records of a prescription or dispensing (hereinafter referred to as prescription) of oral domperidone or metoclopramide during the data period from April 1, 2012 to March 31, 2023 and did not meet the following exclusion criteria * were included in this study. The earliest prescription date of domperidone or metoclopramide during the data period was defined as t_0. t_0 was the start date of follow-up, and the end date of follow-up was the index date (described later) or the end date of the month of the last claim data, whichever came first. *Exclusion criteria • Patients aged younger than 20 years at t_0 • Patients with no claims at least 6 months before t_0 • Patients who had the following diseases/injuries before t_0: malignant tumour, Parkinson's disease, or hereditary arrhythmia (congenital long QT syndrome, Brugada syndrome) ■ **Analysis population** Based on the nested case-control design, patients who met the following definitions of a case or a control were included in the analysis population. • Case: Patients with fatal arrhythmia or sudden cardiac death (hereinafter referred to as "composite outcome") during the follow-up period (the earliest onset date was defined as the index date). An analysis limited to fatal arrhythmia as the target event was also performed. Each event was defined as follows. Fatal arrhythmia: An event for which either the prescription of the relevant therapeutic drug (Amiodarone hydrochloride (injection), nifekalant hydrochloride, sotalol hydrochloride, landiolol hydrochloride, isoprenaline hydrochloride (injection), potassium preparation (injection), lidocaine (injection), magnesium sulfate (injection)) or the implementation of treatment (defibrillator, pacing, cardiac massage) was recorded within 14 days before and after the date of diagnosis of the relevant disease/injury, including the date of the diagnosis. Sudden cardiac death: An event for which either the prescription of the relevant therapeutic drug (Amiodarone hydrochloride (injection), nifekalant hydrochloride, sotalol hydrochloride, landiolol hydrochloride, isoprenaline hydrochloride (injection), potassium preparation (injection), lidocaine (injection), magnesium sulfate (injection)) or the implementation of treatment (defibrillator, pacing, cardiac massage) was recorded within 14 days before and after the date of diagnosis of the relevant disease/injury, including the date of the diagnosis. If "shock due to ischaemic heart disease, pulmonary infarction, cerebrovascular disorder, or haemorrhage of the digestive tract" was recorded on the date of diagnosis of the disease/injury corresponding to sudden cardiac death, the event was defined as an event not falling under "sudden cardiac death" in this study. • Control: Among patients who were non-cases at the time of the index date, those with matching factors (sex, age, calendar year of t_0, history of target events) that were consistent with each case (random sampling of up to 10 patients per 1 case)

	■ **Exposure or non-exposure** In this study, two exposure categories were set based on the most recently recorded prescription information of domperidone or metoclopramide before the index date, and the relationship between domperidone or metoclopramide use and the outcome was investigated in the analysis of exposure category 1, and the relationship between the daily prescribed dose of domperidone and the outcome was investigated in the analysis of exposure category 2. In the analysis of exposure category 2, only domperidone was evaluated. • Exposure category 1: Patients were classified as follows based on the temporal relationship between the end date of the prescription period in the most recent prescription information before the index date and the index date. (1) Current use: The end date of the prescription period was within 7 days before the index date or after the index date. (2) Past use: The end date of the prescription period was between 8 and 67 days before the index date. • Exposure category 2: Only domperidone prescriptions classified as Current use in exposure category 1 were classified as follows based on the most recent daily prescribed dose before the index date. (1) High dose: The daily prescribed dose of domperidone was > 30 mg (2) Low dose: The daily prescribed dose of domperidone was 30 mg or lower • Non-exposure (Non-use): The end date of the prescription period was 68 days or more before the index date. ■ **Analysis methods** • As the primary analysis, conditional logistic regression was used to estimate crude exposure odds ratios and adjusted odds ratios [12] and their respective 95% confidence intervals for the composite outcome or fatal arrhythmia only in exposure category 1 (Current or Past use) and exposure category 2 (High dose or Low dose) in comparison with Non-use. • For the primary analysis of domperidone (exposure category 1), analyses by age at t_0 (≥ 65 years/< 65 years), presence or absence of cardiac disease or hepatic impairment before t_0, and presence or absence of concomitant use of strong or moderate CYP3A4 inhibitors at t_0 were performed as subgroup analyses. The analyses were performed in the same manner as the primary analysis to estimate adjusted odds ratios for the composite outcome and 95% confidence intervals. [12] The matched pairs were used as stratification factors, and cardiac disease, hepatic impairment, renal impairment, hypertension, dyslipidaemia, and diabetes mellitus before t_0 and drugs known to have a QT-prolonging effect and strong or moderate CYP3A4 inhibitors at t_0 were used as covariates.
Outline of results	■ **Analysis population** • Of the 19,361,211 patients in the study population, 83,958 cases and 839,190 controls were identified when patients with the composite outcome were defined as cases, and 33,808 cases and 337,698 controls were identified when patients with fatal arrhythmia only were defined as cases. • As for the patient backgrounds in the case and control groups when patients with the composite outcome were defined as cases, standardized differences exceeding 0.1 were observed in the distributions of cardiac disease (cases: 56.3%, controls: 42.0%, the same order applies hereinafter), renal impairment (10.1%, 4.5%), hypertension (59.2%, 48.9%), and diabetes mellitus (18.0%, 11.3%). • When patients with fatal arrhythmia only were defined as cases, standardized differences exceeding 0.1 were observed in the distributions of cardiac disease (cases: 58.6%, controls: 36.6%, the same order applies hereinafter), renal impairment (10.2%, 3.8%), hypertension (57.7%, 42.5%), diabetes mellitus (18.6%, 10.8%) and dyslipidaemia (34.5%, 28.1%) as well. • The odds ratios were estimated by making adjustments for the differences in these patient

backgrounds as described in the analysis methods section.

■ **Associations of the Current or Past use of domperidone or metoclopramide with the outcome (exposure category 1)**

- The results of the relationship between the domperidone use and the composite outcome are as shown in Appendix Figure 1 (see Appendix Tables 1-1 and 2-1). The adjusted odds ratios (95% confidence intervals) for each exposure category in comparison with Non-use were 2.48 (2.39-2.58) in Current use and 1.60 (1.53-1.67) in Past use. In the analysis defining patients with fatal arrhythmia only as cases, the adjusted odds ratios (95% confidence intervals) for each exposure category in comparison with Non-use were 2.37 (2.22-2.53) in Current use and 1.60 (1.50-1.71) in Past use. The results of subgroup analyses were shown in Appendix Figure 2.
- The results of the relationship between the metoclopramide use and the composite outcome are as shown in Appendix Figure 1 (see Appendix Tables 1-1 and 2-1). The adjusted odds ratios (95% confidence intervals) for each exposure category in comparison with Non-use were 2.73 (2.61-2.86) in Current use and 2.00 (1.91-2.10) in Past use. In the analysis defining patients with fatal arrhythmia only as cases, the adjusted odds ratios (95% confidence intervals) for each exposure category in comparison with Non-use were 2.82 (2.62-3.04) in Current use and 2.00 (1.85-2.15) in Past use.

■ **Association of the daily prescribed dose of current domperidone with the composite outcome (exposure category 2)**

- The results of the relationship between the daily prescribed dose of domperidone and the composite outcome are as shown in Appendix Figure 1 (see Appendix Tables 1-2 and 2-2). The adjusted odds ratios (95% confidence intervals) for each exposure category in comparison with Non-use were 1.75 (1.53-1.99) in High dose and 1.91 (1.83-1.99) in Low dose. In the analysis defining patients with fatal arrhythmia only as cases, the adjusted odds ratios (95% confidence intervals) for each exposure category in comparison with Non-use were 1.75 (1.43-2.15) in High dose and 1.71 (1.59-1.83) in Low dose.

■ **Discussion based on the results**

- The results showed an increased risk of the composite outcome associated with Current and Past use of domperidone or metoclopramide in comparison with Non-use. The analysis defining patients with fatal arrhythmia only as cases indicated a similar trend. These results suggested that patients whose prescriptions of domperidone or metoclopramide might have ended between 8 and 67 days before the index date or within 7 days before the index date or after the index date had an increased risk of fatal arrhythmia and sudden cardiac death compared with patients whose prescriptions of domperidone or metoclopramide might have ended earlier than 67 days before the index date.
- The results showed an increased risk of both the composite outcome and fatal arrhythmia only associated with High dose and Low dose of domperidone compared with Non-use. These results suggested that patients whose prescriptions of domperidone ended within 7 days before the index date or after the index date had an increased risk of fatal arrhythmia and sudden cardiac death compared with patients whose prescriptions of domperidone or metoclopramide ended earlier than 67 days before the index date, regardless of whether the daily prescribed dose closest to the index date was above or below 30 mg.
- The subgroup analyses suggested an increased risk of the composite outcome, regardless of age or a history of relevant diseases, with a trend toward lower aORs observed among patients aged 65 years or older and among patients with a history of cardiac disease. The results of the subgroup analysis by the presence or absence of concomitant use of strong or moderate CYP3A4 inhibitors were difficult to interpret because the range of 95% confidence intervals was wide in the population with concomitant use of relevant drugs.

	• It should be noted that there are some limitations in the evaluation of the results, including the following: The outcome definition was set based on previous studies and clinical perspectives. However, the validation study for the definition in the NDB has been unachievable, and the possibility that other potential confounders (e.g., history of drinking, body mass index) and changes in confounders during the follow-up period, which could affect changes in the exposure situation, may have affected the results. As for sudden cardiac death, the outcome may have been misclassified because of the inability to completely capture out-of-hospital deaths and other causes.

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Appendix

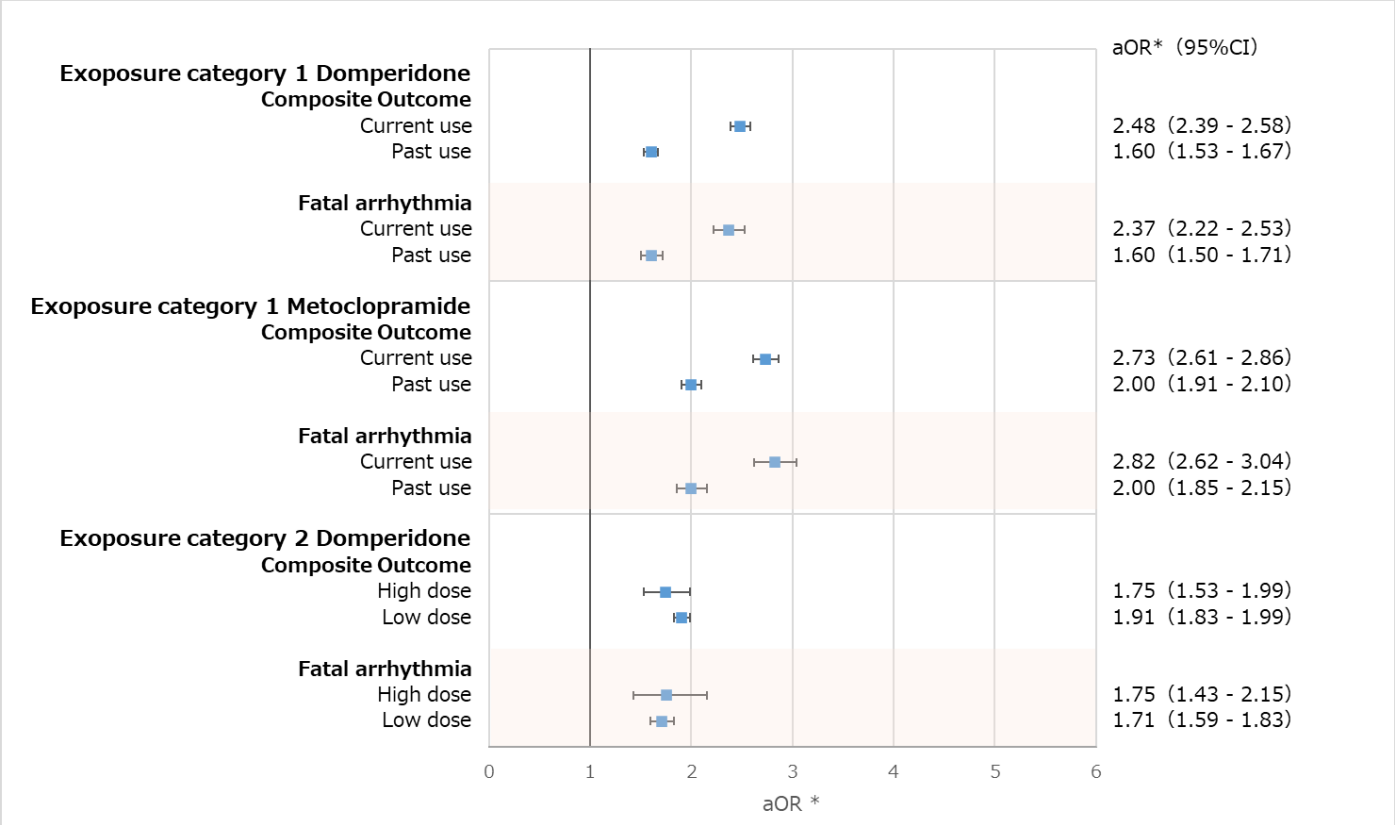

Figure 1. Associations of Current or Past use of domperidone or metoclopramide and the domperidone daily dose with the outcomes (the composite outcome, fatal arrhythmia only)

* aOR: Adjusted odds ratio

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Table 1-1. Number of Composite Outcome Events, Crude Odds Ratios, and Adjusted Odds Ratios by Exposure Category 1

Drug	Exposure category 1*	Case		Control		OR (95%CI)†	aOR (95%CI)†
		(n)	(%)	(n)	(%)		
Domperidone	Current use	4,745	5.65	30,963	3.69	2.57(2.47-2.67)	2.48(2.39-2.58)
	Past use	3,373	4.02	28,911	3.45	1.63(1.56-1.70)	1.60(1.53-1.67)
	Non-use	75,840	90.33	779,316	92.87	Reference	Reference
Metoclopramide	Current use	3,038	3.62	18,252	2.17	2.83(2.70-2.96)	2.73(2.61-2.86)
	Past use	2,555	3.04	16,972	2.02	2.07(1.97-2.17)	2.00(1.91-2.10)
	Non-use	78,365	93.34	803,966	95.80	Reference	Reference

* Current use: The end date of the prescription period was within 7 days before the index date or after the index date. Past use: The end date of the prescription period was within 67 days before the index date, excluding Current use. Non-use: The end date of the prescription period was 68 days or more before the index date.

† Conditional logistic regression was used to estimate crude exposure odds ratios (ORs) and adjusted exposure odds ratios (aORs) and their respective 95% confidence intervals (95% CI) for Current use or Past use in comparison with Non-use. The matched pairs were used as stratification factors, and cardiac disease, hepatic impairment, renal impairment, hypertension, dyslipidaemia, and diabetes mellitus before t_0 and drugs known to have a QT-prolonging effect and strong or moderate CYP3A4 inhibitors at t_0 were used as covariates.

Table 1-2. Number of Composite Outcome Events, Crude Odds Ratios, and Adjusted Odds Ratios by Exposure Category 2

Drug	Exposure category 2*	Case		Control		OR (95%CI)†	aOR (95%CI)†
		(n)‡	(%)	(n)‡	(%)		
Domperidone	High dose	<300	<1.00	2,186	0.28	1.84(1.62-2.09)	1.75(1.53-1.99)
	Low dose	>4,400	>5.00	27,336	3.48	1.96(1.88-2.04)	1.91(1.83-1.99)
	Non-use	>75,800	>94.00	755,422	96.24	Reference	Reference

* High dose: Among patients in Current use, those whose daily prescribed dose in the most recent prescription before the index date is > 30 mg. Low dose: Among patients in Current use, those whose daily prescribed dose in the most recent prescription before the index date is 30 mg or lower.

‡ Among each stratum with matched cases and controls, strata that cannot contribute to the odds ratio estimation (stratum with cases only or controls only) as a result of excluding patients classified as Past use from the analysis were excluded from the tabulation. The data with a value of less than 10 are masked so that the value cannot be identified according to the publication criteria of the NDB.

† Conditional logistic regression was used to estimate crude exposure odds ratios (ORs) and adjusted exposure odds ratios (aORs) and their respective 95% confidence intervals (95% CI) for High dose or Low dose in comparison with Non-use. The matched pairs were used as stratification factors, and cardiac disease, hepatic impairment, renal impairment, hypertension, dyslipidaemia, and diabetes mellitus before t_0 and drugs known to have a QT-prolonging effect and strong or moderate CYP3A4 inhibitors at t_0 were used as covariates.

Table 2-1. Number of Fatal Arrhythmia Events, Crude Odds Ratios, and Adjusted Odds Ratios by Exposure Category 1

Drug	Exposure category 1*	Case		Control		OR (95%CI)†	aOR (95%CI)†
		(n)	(%)	(n)	(%)		
Domperidone	Current use	1,727	5.11	11,989	3.55	2.52(2.37-2.69)	2.37(2.22-2.53)
	Past use	1,428	4.22	12,258	3.63	1.65(1.55-1.76)	1.60(1.50-1.71)
	Non-use	30,653	90.67	313,451	92.82	Reference	Reference
Metoclopramide	Current use	1,230	3.64	7,156	2.12	3.05(2.84-3.28)	2.82(2.62-3.04)
	Past use	1,088	3.22	7,297	2.16	2.10(1.95-2.25)	2.00(1.85-2.15)
	Non-use	31,490	93.14	323,245	95.72	Reference	Reference

* Current use: The end date of the prescription period was within 7 days before the index date or after the index date. Past use: The end date of the prescription period was within 67 days before the index date, excluding Current use. Non-use: The end date of the prescription period was 68 days or more before the index date.

† Conditional logistic regression was used to estimate crude exposure odds ratios (ORs) and adjusted exposure odds ratios (aORs) and their respective 95% confidence intervals (95% CI) for Current use or Past use in comparison with Non-use. The matched pairs were used as stratification factors, and cardiac disease, hepatic impairment, renal impairment, hypertension, dyslipidaemia, and diabetes mellitus before t_0 and drugs known to have a QT-prolonging effect and strong or moderate CYP3A4 inhibitors at t_0 were used as covariates.

Table 2-2. Number of Fatal Arrhythmia Events, Crude Odds Ratios, and Adjusted Odds Ratios by Exposure Category 2

Drug	Exposure category 2*	Case		Control		OR (95%CI)†	aOR (95%CI)†
		(n)‡	(%)	(n)‡	(%)		
Domperidone	High dose	121	<1.00	844	0.27	1.91(1.56-2.33)	1.75(1.43-2.15)
	Low dose	1,606	<5.00	10,561	3.35	1.79(1.67-1.91)	1.71(1.59-1.83)
	Non-use	>30,600	>94.00	303,459	96.38	Reference	Reference

* High dose: Among patients in Current use in exposure category 1, those whose daily prescribed dose in the most recent prescription before the index date is > 30 mg. Low dose: Among patients in Current use, those whose daily prescribed dose in the most recent prescription before the index date is 30 mg or lower.

‡ Among each stratum with matched cases and controls, strata that cannot contribute to the odds ratio estimation (stratum with cases only or controls only) as a result of excluding patients classified as Past use from the analysis were excluded from the tabulation. The data with a value of less than 10 are masked so that the value cannot be identified according to the publication criteria of the NDB.

† Conditional logistic regression was used to estimate crude exposure odds ratios (ORs) and adjusted exposure odds ratios (aORs) and their respective 95% confidence intervals (95% CI) for High dose or Low dose in comparison with Non-use. The matched pairs were used as stratification factors, and cardiac disease, hepatic impairment, renal impairment, hypertension, dyslipidaemia, and diabetes mellitus before t_0 and drugs known to have a QT-prolonging effect and strong or moderate CYP3A4 inhibitors at t_0 were used as covariates.

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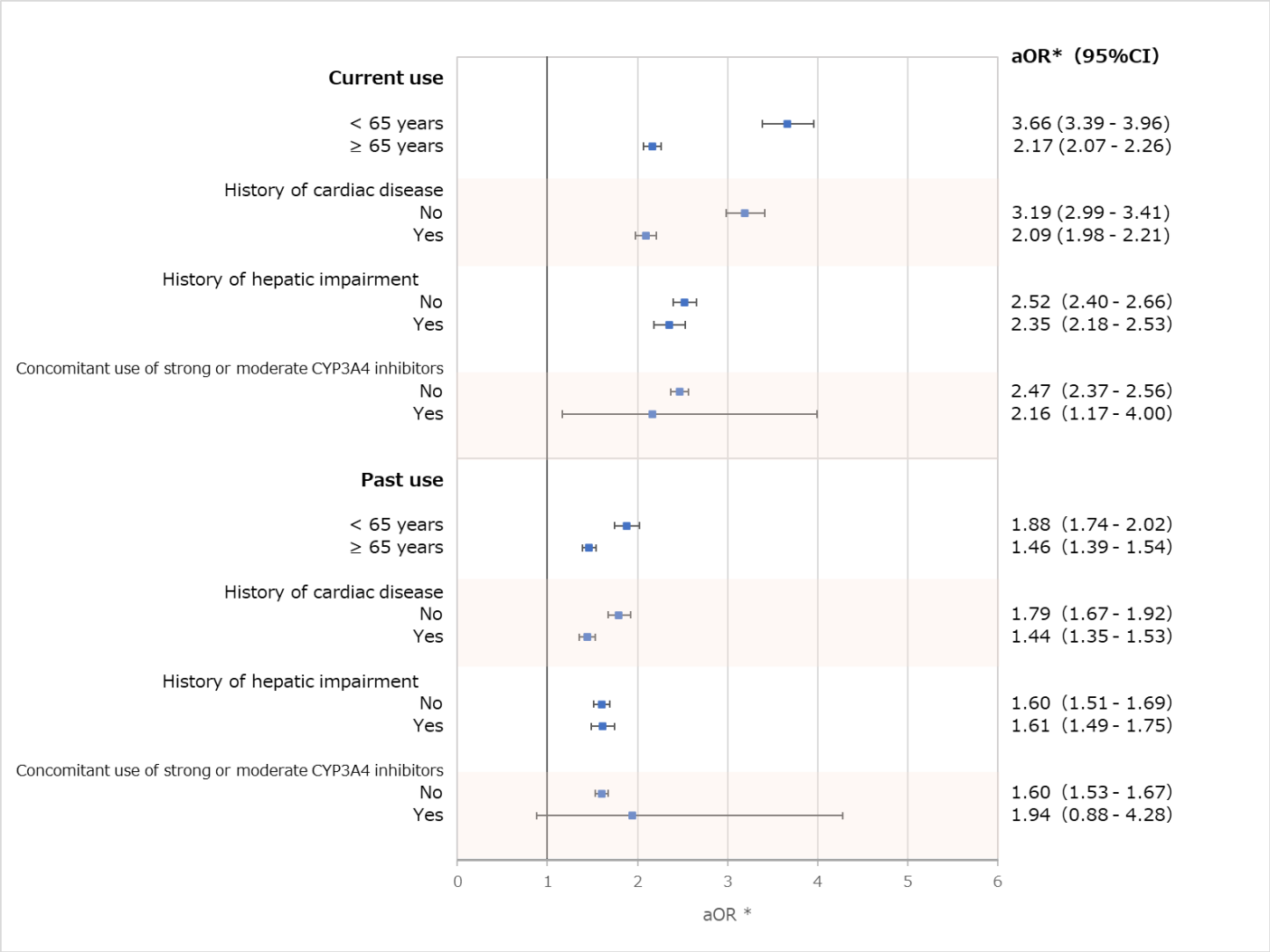

Figure 2. Association between Current or Past use of domperidone and the composite outcome (subgroup analysis results)

* aOR: Adjusted odds ratio