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Summary of MID-NET® study No.2020-001

August 27, 2024

Study title

Evaluation of the effect of ACE inhibitors on liver function test abnormal using MID-NET®

Products investigated

- Alacepril
- Imidapril hydrochloride
- Enalapril maleate
- Captopril
- Quinapril hydrochloride
- Cilazapril hydrate
- Temocapril hydrochloride
- Delapril hydrochloride
- Trandolapril
- Benazepril hydrochloride
- Perindopril erbumine
- Lisinopril hydrate

Background:

- Angiotensin-converting enzyme [ACE] inhibitors are drugs widely used for hypertension. Based on the results of clinical studies, etc., a precaution about liver disorder-related events is included in the "Other Adverse Reactions" section in the package insert.
- On the other hand, descriptions of the precaution in the "Clinically Significant Adverse Reactions" section differs among ACE inhibitors (drugs for which the precaution is included are enalapril maleate, temocapril hydrochloride, trandolapril, benazepril hydrochloride, and lisinopril hydrate).

Purpose of the study

To evaluate differences in the risk of liver function test abnormal among ACE inhibitors by comparing the occurrences of abnormal test values related to liver disorder after prescription of ACE inhibitors

Reason to select MID-NET® for the study and data period

Reason to select: To perform evaluation with laboratory test results as an index

Data from all healthcare organizations cooperating with MID-NET® (22 hospitals at 10 healthcare organizations) whose data were available throughout the data period

Data period: January 1, 2009 to December 31, 2019

Outline of method

The occurrence of liver function test abnormal defined by abnormally elevated liver function test values during the follow-up period was evaluated in patients who were prescribed ACE inhibitors during the data period. Patients who met any of the following criteria during the 90 days prior to the new prescription of ACE inhibitors (including the start date of the new prescription) were excluded from the study population: (1) Patients who had a grade 2[†] or higher abnormality in any of the liver function test values (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], or total bilirubin [T-BIL]) (assessed by the test value measured at the closest timepoint to the start date of the new prescription for each test value), (2) patients who were prescribed anticancer drugs or received radiotherapy, (3) patients who were prescribed antiviral drugs for hepatitis B or C, and (4) patients who could not be followed up after the new prescription of ACE inhibitors. Depending on the drugs prescribed at the start date of the new prescription, enalapril maleate was treated as a comparator group, and other drugs as respective exposure groups.

[†] The criteria was based on the "Criteria of Severity of Adverse Drug Reactions for Drugs, etc." (PAB/SD Notification No. 80 issued by the Director of Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated June 29, 1992) (AST, grade 1 or lower: less than 100 U/L, grade 2 or higher: 100 U/L or higher; ALT, grade 1 or lower: less than 100 U/L, grade 2 or higher: 100 U/L or higher; ALP, grade 1 or lower: less than 805 U/L, grade 2 or higher: 805 U/L or higher; T-BIL, grade 1 or lower: less than 3.0 mg/dL, grade 2 or higher: 3.0 mg/dL or higher).

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- **Definition of new prescription:**

  The new prescription was defined as the earliest prescription of ACE inhibitors during the data period. In order to appropriately identify a new prescription, patients without any medical records at least 91 days before the new prescription were also excluded from the study population.

- **Definition of follow-up period:**

  A follow-up period started the next day of the start date of a new prescription of an ACE inhibitor and ended at the earliest day of the following: (1) 30 days after the end date of the last prescription of the ACE inhibitor, (2) the date of a prescription of an ACE inhibitor other than the one prescribed on the day of a new prescription, or (3) the date of the last medical record entry within the data period.

- **Definition of liver function test abnormal:**

  <Outcome (1)>

  Outcome (1) was defined as meeting a) or b) below, and all liver function test values must be grade 1[†] or lower during the 90 days prior to the date of meeting any of the criteria below (a or b).

  a) Grade 2[†] or higher AST and ALT was recorded on the same day.

  b) Grade 2[†] or higher ALP and T-BIL was recorded on the same day.

  The date of first meeting these definitions during the follow-up period is defined as the date of occurrence date of outcome (1).

  <Outcome (2)>

  Outcome (2) was defined as the grade 3[‡] or higher abnormality in any of the liver function test values (AST, ALT, ALP, or T-BIL). The date of first meeting these definitions during the follow-up period is defined as the date of occurrence date of outcome (2).

[‡] The criteria were set based on the Japanese translation of Common Terminology Criteria for Adverse Events version 5.0 by the Japan Clinical Oncology Group.

- **Analyses and methods:**
  - The number of patients and median follow-up period with an interquartile range were tabulated for each group. In addition, for the implementation status of tests during the follow-up period[§], the median numbers of tests per 100 person-days with an interquartile range were tabulated.
  - Regarding the occurrence of outcomes, the number and percentage of patients meeting the outcome definitions during the follow-up period were calculated for each group. For the duration to the occurrence of outcome, the median duration and interquartile range were calculated for each group.
  - To compare the risk of liver function test abnormal between the comparator group (enalapril maleate) and each exposure group, crude hazard ratios and adjusted hazard ratios with their 95% confidence intervals for outcome (1) and (2) were estimated using the Cox proportional hazard model. Adjusted hazard ratios were estimated using inverse probability weighting based on the high-dimensional propensity scores calculated by logistic regression for each combination between the comparator and exposure groups. Gender, age (65 years or older or not), past history of abnormal liver function tests[†], presence or absence of prescription of antidiabetic drugs, presence or absence of prescription of antihyperlipidemic drugs, and comorbidity of heart failure were included in the model for calculation of high-dimensional propensity scores as basic covariates. In addition, for each combination between the comparator and exposure groups, analyses restricted to the population with an overlapping high-dimensional propensity score between groups were performed. Due to differences in indications among drugs (e.g., enalapril maleate and lisinopril hydrate have indications related to heart failure), similar analyses were performed as sensitivity analyses in populations restricted to patients without heart failure but with a diagnosis of hypertension.

[§] Implementation status of tests was defined on the presence or absence of testing that can judge the occurrence of outcomes. In the evaluation of outcome (1), implementation of tests was defined as the measurement of AST and ALT on the same day or measurement of ALP and T-BIL on the same day. In the evaluation of outcome (2), implementation of tests was defined as the measurement of AST, ALT, ALP, or T-BIL.

Outline of results

■ Study population

- A total of 34,070 patients[**] were newly prescribed an ACE inhibitor during the data period, 29,817 of whom did not meet the exclusion criteria. The largest number of patients were prescribed enalapril maleate, a comparator group with 12,448 patients (Appendix Table 1). As for outcome (1) assessment, the median follow-up periods were 30-166.5 days, and the median numbers of tests per 100 person-days were 1 or more in all groups but exposure group 1 (captopril). For exposure group 1 (captopril), most patients were prescribed only once (median follow-up period was 30 days), with no tests performed during the follow-up period (Appendix Table 1). As for outcome (2) assessment, similar trends were observed (Appendix Table 2).

■ Comparison of occurrences of liver function test abnormal

- For outcome (1), the adjusted hazard ratios for exposure group 1 (captopril), exposure group 2 (alacepril), exposure group 4 (cilazapril hydrate), exposure group 7 (perindopril erbumine), and exposure group 10 (temocapril hydrochloride) compared with enalapril maleate were 0.68-1.37, with the 95% confidence interval including 1.00 (Appendix Figure 1). The adjusted hazard ratios for exposure group 5 (imidapril hydrochloride) and exposure group 8 (lisinopril hydrate) were 0.72 and 0.69, respectively, with the upper limit of the confidence interval less than 1.00 (Appendix Figure 1). For exposure group 3 (delapril hydrochloride), the adjusted hazard ratio was 4.91, with the confidence interval including 1.00. For exposure group 11 (trandolapril), the adjusted hazard ratio was 3.44, with the lower limit of the confidence interval exceeding 1.00 (Appendix Figure 1). For exposure group 6 (quinapril hydrochloride) and exposure group 9 (benazepril hydrochloride), no occurrence of the outcome was observed. The analysis restricted to the population with an overlapping high-dimensional propensity score between groups also showed a similar trend as the results of the primary analysis.
- For outcome (2), the adjusted hazard ratios for exposure group 1 (captopril), exposure group 2 (alacepril), exposure group 5 (imidapril hydrochloride), exposure group 7 (perindopril erbumine), and exposure group 10 (temocapril hydrochloride) compared

** Patients prescribed more than one ACE inhibitor at the start date of the new prescription are excluded from the study population.

with enalapril maleate were 0.84-1.42, with the 95% confidence interval including 1.00 (Appendix Figure 2). For exposure group 4 (cilazapril hydrate), the adjusted hazard ratio was 0.37, but the confidence interval included 1.00. For exposure group 8 (lisinopril hydrate), the adjusted hazard ratio was 0.74, with the upper limit of the confidence interval less than 1.00 (Appendix Figure 2). For exposure group 3 (delapril hydrochloride), the adjusted hazard ratio was 3.33, but the confidence interval included 1.00. For exposure group 11 (trandolapril), the adjusted hazard ratio was 2.77, with the lower limit of the confidence interval exceeding 1.00 (Appendix Figure 2). For exposure group 6 (quinapril hydrochloride) and exposure group 9 (benazepril hydrochloride), no occurrence of the outcome was observed. The analysis restricted to the population with an overlapping high-dimensional propensity score between groups also showed a similar trend as the results of the primary analysis.

- In the analysis restricted to hypertension patients, the adjusted hazard ratio for the outcome (1) in exposure group 5 (imidapril hydrochloride) was 1.14 (0.82-1.59), which was different from the trend in the primary analysis (hazard ratio (95% confidence interval): 0.72 (0.55-0.93)). The other groups showed similar trends for both outcomes (1) and (2) to the results of the primary analysis.
- The median duration to the occurrence of outcomes was 24.0-72.0 days for outcome (1) (Appendix Table 1) and 32.0-53.0 days for outcome (2) (Appendix Table 2) in the groups with 10 or more cases of outcomes, excluding exposure group 10 (temocapril hydrochloride). For exposure group 10 (temocapril hydrochloride), the median durations to the occurrence of outcome (1) and outcome (2) were 245.0 days and 224.5 days, respectively.

■ **Discussion based on the results**

- Regarding the risk of liver function test abnormal, no increasing or decreasing trends of consistently significant risks were observed with other ACE inhibitors in both outcome definitions, except for exposure group 8 (lisinopril hydrate), exposure group 11 (trandolapril), and exposure group 6 (quinapril hydrochloride) and exposure group 9 (benazepril hydrochloride), where no occurrence of liver function test abnormal was observed, compared with the risk in enalapril maleate, which has already included a precaution in the “Clinically Significant Adverse Reactions” section in the package insert.

A relatively large hazard ratio was observed in exposure group 3 (delapril hydrochloride) and exposure group 11 (trandolapril), and a relatively small hazard ratio was observed in exposure group 4 (cilazapril hydrate). Since the number of patients and occurrences of liver function test abnormal were limited and the confidence interval of the hazard ratio was wide in these groups, these results should be carefully interpreted. It was considered that the difference in these relative risks of liver function test abnormal from enalapril maleate could not necessarily be determined.

- Although the median occurrence timing of liver function test abnormal varied among the drugs, it was considered that there were no major differences among them considering the variations in the interquartile ranges and follow-up periods, which suggests that most liver function test abnormal occur within two to three months after prescription.
- For exposure group 1 (captopril), considering the situation of prescription, the drug might have been prescribed not for hypertension but as a captopril challenge test[††] for a functional confirmatory test of primary hyperaldosteronism.
- In this study, confounding factors were adjusted as much as possible by using the high-dimensional propensity score method. However, it is necessary to keep in mind that the possibility that potential confounding factors (e.g., severity of hypertension, past history of abnormal liver function tests, etc.) may affect the results cannot be ruled out and that there are certain limitations such as inadequate adjustment for confounding due to the small number of patients in some groups. In addition, it should be noted that the hazard ratios of each exposure group in this study do not necessarily indicate the magnitudes of the risks of liver function test abnormal between exposure groups because the high-dimensional propensity scores were estimated for a combination of each exposure group and the comparator group and the comparability between each exposure group is not warranted.

[††] Edited by the Guideline Committee of the Japanese Society of Hypertension: Guidelines for the Management of Hypertension 2019. Life Science Publishing Co., Ltd., Tokyo, 2019.

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Appendix

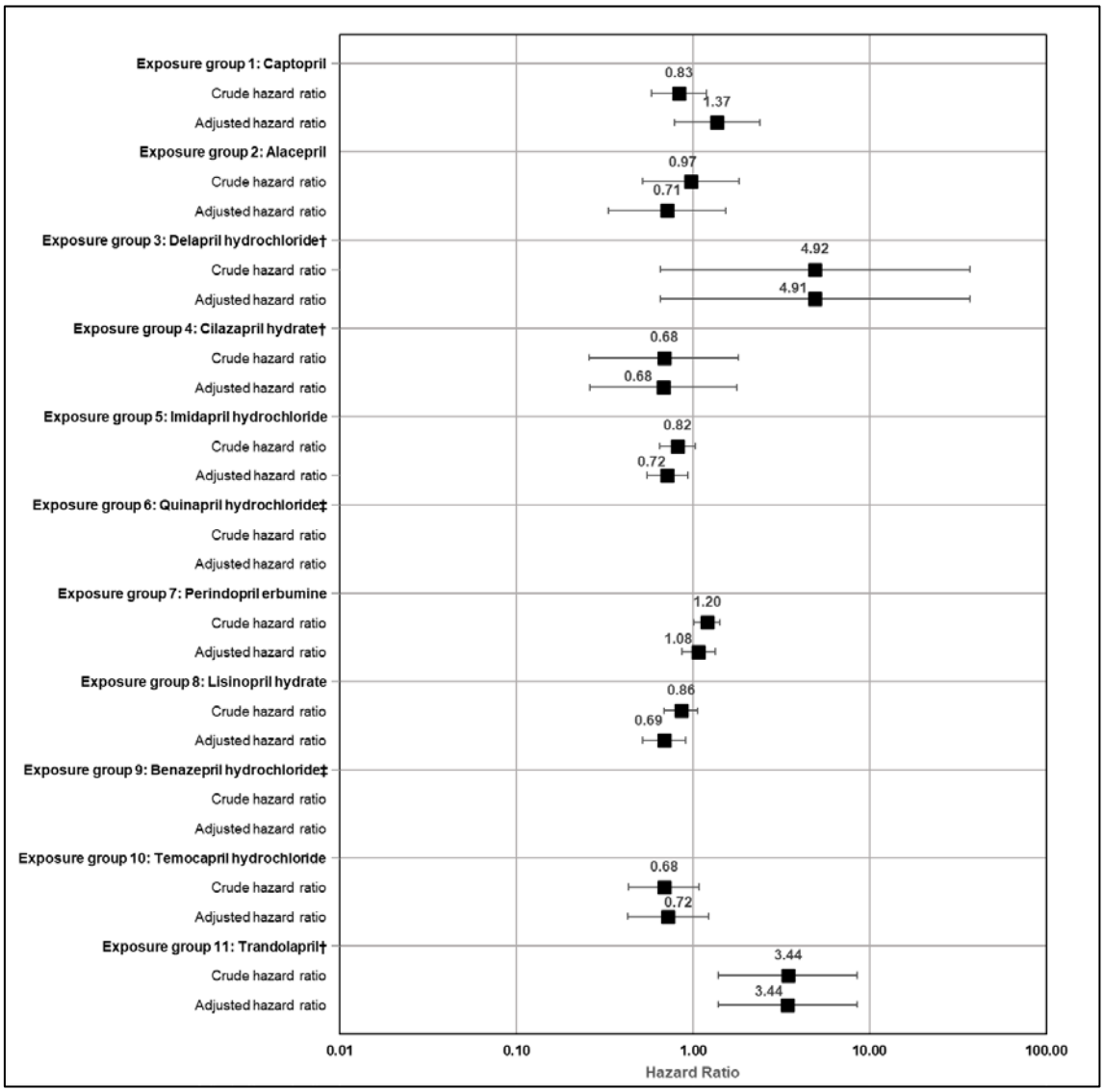

Figure 1. Hazard ratio with their 95% confidence interval for each exposure group compared with comparator group (enalapril maleate) for outcome (1)

Adjusted hazard ratios were estimated using inverse probability weighting based on the high-dimensional propensity scores calculated by logistic regression for each combination between the comparator and exposure groups.

† The estimation accuracy of the adjusted hazard ratio is low for groups with a small number of patients.

‡ Hazard ratios and 95% confidence intervals for the exposure group 6 (quinapril hydrochloride) and 9 (benazepril hydrochloride) were not plotted because no occurrence of the outcome was observed.

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Appendix

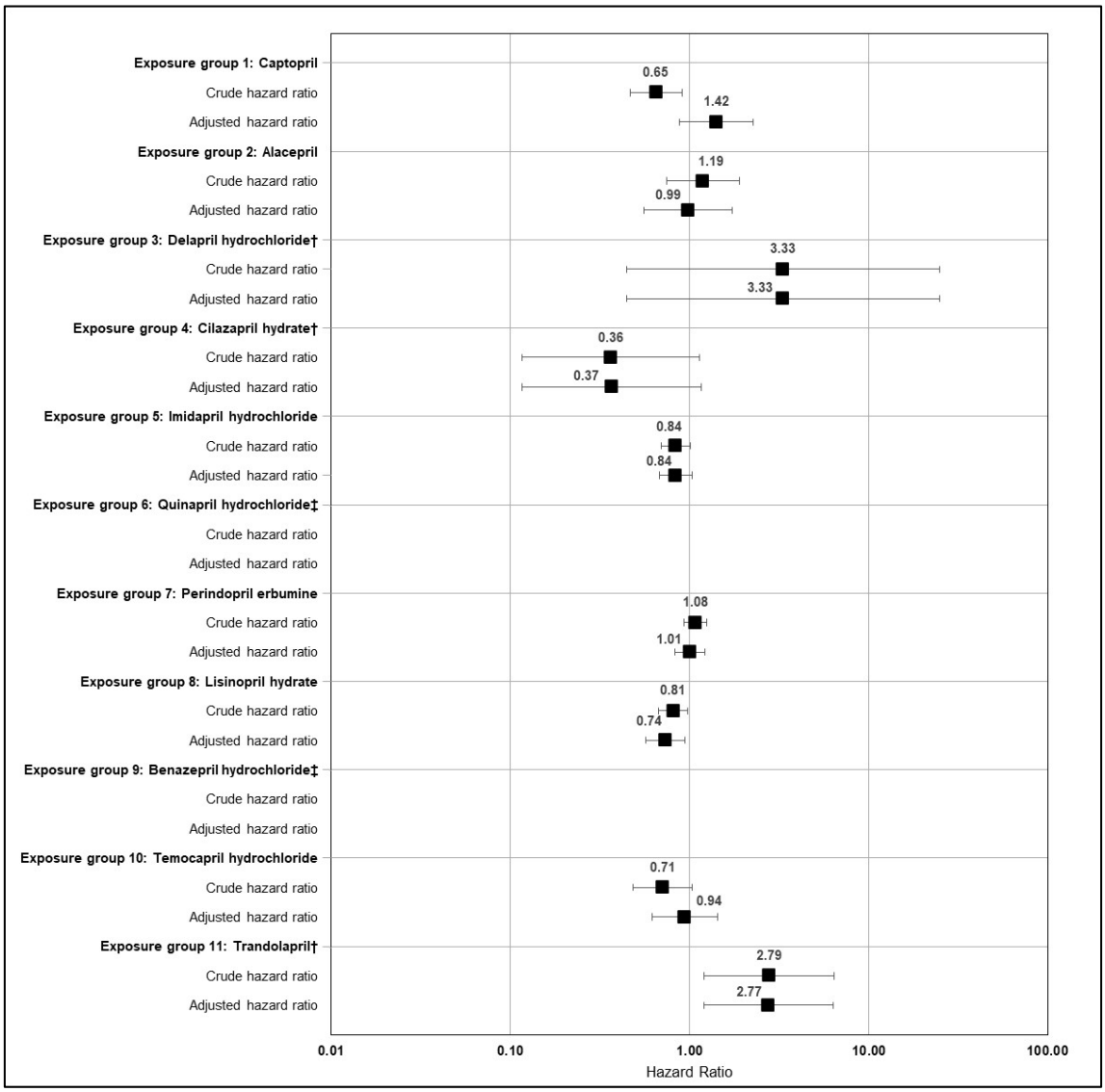

Figure 2. Hazard ratio with their 95% confidence interval for each exposure group compared with comparator group (enalapril maleate) for outcome (2)

Adjusted hazard ratios were estimated using inverse probability weighting based on the high-dimensional propensity scores calculated by logistic regression for each combination between the comparator and exposure groups.

† The estimation accuracy of the adjusted hazard ratio is low for groups with a small number of patients.

‡ Hazard ratios and 95% confidence intervals for the exposure group 6 (quinapril hydrochloride) and 9 (benazepril hydrochloride) were not plotted because no occurrence of the outcome was observed.

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Appendix

Table 1. Follow-up periods for outcome (1), implementation status of tests, and duration to occurrence of outcome

	Number of patients	Follow-up period (days)	Implementation status of tests (/100-person days)	Number of outcome (%)†	Duration to occurrence of outcome (days)
		Median (Interquartile range)	Median (Interquartile range)		Median (Interquartile range)
Comparator group: Enalapril maleate	12,448	92.0 (46.0 - 412.0)	4.0 (1.0 - 12.0)	404 (3.25)	70.0 (13.0 - 517.0)
Exposure group 1: Captopril	3,242	30.0 (30.0 - 31.0)	0.0 (0.0 - 1.0)	38 (1.17)	24.0 (3.0 - 54.0)
Exposure group 2: Alacepril	408	59.5 (36.0 - 179.5)	2.0 (0.0 - 6.0)	10 (2.45)	25.0 (13.0 - 98.0)
Exposure group 3: Delapril hydrochloride	18	32.5 (9.0 - 38.0)	1.0 (0.0 - 3.0)	<10*	1.0 (* - *)
Exposure group 4: Cilazapril hydrate	128	166.5 (69.5 - 1088.0)	3.0 (1.0 - 16.5)	<10*	789.5 (* - *)
Exposure group 5: Imidapril hydrochloride	3,621	79.0 (42.0 - 351.0)	3.0 (1.0 - 10.0)	90 (2.49)	35.5 (7.0 - 294.0)
Exposure group 6: Quinapril hydrochloride	17	30.0 (5.0 - 36.0)	1.0 (1.0 - 3.0)	0 (0.00)	(-)
Exposure group 7: Perindopril erbumine	5,294	119.0 (53.0 - 368.0)	5.0 (2.0 - 13.0)	195 (3.68)	68.0 (11.0 - 325.0)
Exposure group 8: Lisinopril hydrate	3,822	87.0 (46.0 - 364.0)	4.0 (1.0 - 10.0)	100 (2.62)	72.0 (15.0 - 424.5)
Exposure group 9: Benazepril hydrochloride	26	116.0 (44.0 - 596.0)	4.5 (1.0 - 12.0)	0 (0.00)	(-)
Exposure group 10: Temocapril hydrochloride	716	131.5 (44.0 - 626.0)	4.0 (1.0 - 14.0)	19 (2.65)	245.0 (10.0 - 874.0)
Exposure group 11: Trandolapril	77	41.0 (28.0 - 74.0)	3.0 (1.0 - 6.0)	<10*	6.0 (* - *)

† Representing the number and percentage of patients meeting the outcome definition during the follow-up period.
* When a value was < 10, it was shown as an aggregated value based on the MID-NET® publication rule.

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Appendix

Table 2. Follow-up periods for outcome (2), implementation status of tests, and duration to occurrence of outcome

	Number of patients	Follow-up period (days)	Implementation status of tests (/100-person days)	Number of outcome (%)†	Duration to occurrence of outcome (days)
		Median (Interquartile range)	Median (Interquartile range)		Median (Interquartile range)
Comparator group: Enalapril maleate	12,448	92.0 (45.0 - 407.0)	4.0 (1.0 - 12.0)	584 (4.69)	51.0 (16.5 - 344.5)
Exposure group 1: Captopril	3,242	30.0 (30.0 - 31.0)	0.0 (0.0 - 1.0)	43 (1.33)	32.0 (6.0 - 67.0)
Exposure group 2: Alacepril	408	60.0 (36.0 - 179.5)	2.0 (0.0 - 6.0)	18 (4.41)	42.5 (20.0 - 84.0)
Exposure group 3: Delapril hydrochloride	18	32.5 (9.0 - 38.0)	1.0 (0.0 - 3.0)	<10*	1.0 (* - *)
Exposure group 4: Cilazapril hydrate	128	166.5 (66.0 - 1088.0)	3.0 (1.0 - 16.5)	<10*	91.0 (* - *)
Exposure group 5: Imidapril hydrochloride	3,621	78.0 (42.0 - 350.0)	3.0 (1.0 - 10.0)	134 (3.70)	48.5 (8.0 - 289.0)
Exposure group 6: Quinapril hydrochloride	17	30.0 (5.0 - 36.0)	1.0 (1.0 - 3.0)	0 (0.00)	(-)
Exposure group 7: Perindopril erbumine	5,294	118.0 (51.0 - 367.0)	5.0 (2.0 - 13.0)	260 (4.91)	49.0 (14.0 - 246.5)
Exposure group 8: Lisinopril hydrate	3,822	87.0 (46.0 - 358.0)	4.0 (1.0 - 10.0)	139 (3.64)	53.0 (16.0 - 352.0)
Exposure group 9: Benazepril hydrochloride	26	116.0 (44.0 - 596.0)	4.5 (1.0 - 12.0)	0 (0.00)	(-)
Exposure group 10: Temocapril hydrochloride	716	128.5 (44.0 - 626.0)	4.0 (1.0 - 14.5)	28 (3.91)	224.5 (9.5 - 853.0)
Exposure group 11: Trandolapril	77	41.0 (24.0 - 74.0)	3.0 (1.0 - 6.0)	<10*	6.0 (* - *)

† Representing the number and percentage of patients meeting the outcome definition during the follow-up period.
* When a value was < 10, it was shown as an aggregated value based on the MID-NET® publication rule.

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