A cross-sectional survey of hospitalization and blood tests implementation status in patients who received tolvaptan under 75 years of age using a Japanese claims database

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Abstract

Background: Hypernatremia and liver injury are typical adverse effects of tolvaptan. Therefore, hospitalization and frequent monitoring of serum sodium concentration and liver function are necessary for tolvaptan initiation. We performed a cross-sectional survey to evaluate these situations.

Research design and methods: We employed the Japanese claims database, which contains data of patients aged < 75 years. Patients who were newly prescribed tolvaptan for fluid accumulation induced by chronic heart failure (FA-CHF) or liver cirrhosis (FA-LC) from January 2011 to June 2017 were included. We evaluated the hospitalization status and implementation of serum sodium and liver function tests in the evaluation period, based on the Japanese package insert.

Results: Of 1,173 patients, 347 and 117 were enrolled in FA-CHF and FA-LC groups, respectively. Among them, 10.7% (FA-CHF group) and 5.13% (FA-LC group) were prescribed tolvaptan without hospitalization. In the FA-CHF group, 11.0% and 17.6% did not undergo serum sodium and liver function tests even once in the evaluation period, respectively, compared with 12.0% and 12.8% in the FA-LC group.

Conclusions: Our results highlight the deviation from Japanese package insert recommendations. This approach can be applied to other drugs and provides important perspectives on pharmacovigilance research.

Keywords: blood test, hypernatremia, insurance claims, liver injury, tolvaptan

1. Introduction

Tolvaptan is a nonpeptide orally selective antagonist of the vasopressin V2 receptor that increases dilute urine production in a dose-dependent manner [1]. Tolvaptan is used for the treatment of the following diseases under the Japanese medical insurance [2]: (1) fluid accumulation induced by chronic heart failure (FA-CHF), (2) fluid accumulation induced by liver cirrhosis (FA-LC), (3) autosomal dominant polycystic kidney disease (ADPKD), and (4) hyponatremia-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH). In Japan, tolvaptan was first approved in October 2010 for FA-CHF. Then, it was additionally approved for treating FA-LC in September 2013. However, the use of tolvaptan for these indications is not approved in other countries and regions [2-8]. Further, tolvaptan is prescribed at lower doses (7.5 or 15 mg daily) for these indications than for ADPKD (60 mg daily).

Hypernatremia and liver injury are known, typical side effects of tolvaptan. Even at lower doses (i.e., 7.5 or 15 mg daily), tolvaptan can sometimes result in marked increases in serum sodium concentrations. For example, Kinugawa *et al*. reported that the incidence of hypernatremia (defined as serum sodium ≥ 150 mEq/L) was 3.65% in patients with FA-CHF [9]. Hirai *et al*. surveyed the risk factors of hypernatremia (defined as serum sodium ≥ 147 mEq/L) that targeted mainly patients with FA-CHF; they reported that hypernatremia was observed in 25.6% of enrolled patients and identified three factors including an initial and average daily dose of tolvaptan > 7.5 mg that affect the occurrence of hypernatremia [10]. Meanwhile, most of the reports regarding liver injury are associated with high doses of tolvaptan for patients with

ADPKD, although there are exceptions [11-13]. Therefore, frequent monitoring of serum sodium concentration and liver function is recommended for most patients, despite differences based on the indications, countries, and regions (Table 1).

Among them, the Japanese package insert states that hospitalization is required during the initial administration of tolvaptan for each indication (Table 1). Serum sodium must be evaluated 4–6 hours and 8–12 hours after initiation, followed by every day for at least a week in patients with FA-CHF and SIADH. In patients with FA-LC, serum sodium must be evaluated 4–8 hours, followed by 2 and 3 to 5 days after initiation. Furthermore, liver function should be monitored before tolvaptan initiation and at least every two weeks thereafter in patients with FA-CHF, FA-LC, and SIADH. However, in patients with ADPKD, these parameters can be monitored less frequently. For providing safe tolvaptan therapy, clinicians should comply with these regulations.

In our pharmaceutical practice, tolvaptan treatment is sometimes initiated without hospitalization, and blood tests may be performed independently. However, the overall nationwide trends are unclear and should be evaluated for appropriate pharmacovigilance. Recently, several epidemiological surveys evaluating inappropriate drug use have been performed using medical big data sources, such as claims databases [14–16]. By employing medical big data, it may be possible to obtain generalized evidence. Accordingly, in this study, we used a large Japanese claims database to perform a cross-sectional survey to evaluate the hospitalization status and blood test implementation in patients who received tolvaptan treatment.

2. Patients and methods

2.1 Data sources

This cross-sectional study was performed using the JMDC claims database (JMDC Inc., Tokyo, Japan), which has de-identified individual-level data of employees from large companies and their families excluding business owners or welfare recipients. This database comprises approximately 7.3 million individuals [17]. Additionally, the database contains limited data for patients aged 65 years or older and no data for patients aged 75 years or older. Several patient parameters can be obtained from this database, including encrypted personal identifiers, year and month of birth, sex, the period over which the data were obtained, diagnoses, consultations, drugs, and medical procedures. The JMDC claims database does not contain laboratory data. Drugs are registered based on the Anatomical Therapeutic Chemical Classification System (ATC) codes.

2.2 Study population

Patients who were newly prescribed tolvaptan from January 2011 to June 2017 with a prescription duration of at least 14 days were included. In addition, among the four Japanese indications of tolvaptan [2], we targeted only the patients who were presumed to be prescribed tolvaptan for FA-CHF or FA-LC. There are two reasons for this selection criteria. First, the use of tolvaptan in hyponatremia induced by

SIADH was approved in June 2020 in Japan, i.e., after the study period. Second, in our preliminary survey, we found that the number of patients with ADPKD who received tolvaptan was too small for evaluation. To identify new prescriptions, we screened data from 1 year before the first prescription of tolvaptan for each patient. Enrolled patients were observed for up to 15 days from the day of prescription. The exclusion criteria were as follows: (1) patients who were registered in the JMDC claims database within 1 year before the start of tolvaptan; (2) patients who were prescribed tolvaptan occasionally (which made it difficult to calculate the administration period); and (3) patients with missing values. The occasional use of tolvaptan was detected using the "occasional use flag" in the JMDC claims database.

2.3 Outcomes

First, enrolled patients were classified into FA-CHF and FA-LC groups. Second, the following situations were evaluated in each group: (1) hospitalization status at the time of initial prescription of tolvaptan; (2) implementation status of serum sodium measurement before tolvaptan initiation (day -14 to -1) through day 6 (FA-LC group) and day 8 (FA-CHF group) of prescription; and (3) implementation status of liver function tests before tolvaptan initiation (day -14 to -1) through day 15 of prescription in both groups. Finally, we assessed whether these situations complied with the Japanese package insert recommendation. Although periodic blood tests are necessary even after these periods, we focused on the early phase of administration owing to the need for special attention during this time. Because the prescription start date

is not always the administration start date, accurate evaluation of the implementation of serum sodium measurement and liver function tests was difficult in the claims database. For example, the prescription date may be the start date of administration; however, administration can also start 1 or 2 days after the prescription. Therefore, evaluation periods should be set such that even patients whose administration started 2 days after the prescription can be evaluated. As another possibility, even if the prescription period was 14 days, drug administration may be stopped during the period. Thus, if blood tests (serum sodium measurement and liver function tests) were not performed even once in the given periods, we considered that these did not comply with the package insert recommendation [2]: (1) serum sodium tests on the day of initiation (day 0) through day 6 (FA-LC group) and day 8 (FA-CHF group) and (2) liver function tests before tolvaptan initiation (day -14 to -1) through day 15. We defined these cases as "without serum sodium tests" and "without liver function tests." Additionally, we considered "prescription for outpatient" cases when tolvaptan was prescribed in patients who were not hospitalized. We hypothesized that "prescription for outpatients" may be associated with "without serum sodium tests" and "without liver function tests"; therefore, we sought to validate this hypothesis. Further, outcomes were analyzed when patients were classified based on whether or not the initial daily dose of tolvaptan exceeded the Japanese package insert recommendation (FA-CHF: 15 mg daily, FA-LC: 7.5 mg daily). Moreover, we evaluated outcomes based on the prescription start year (e.g., 2011, 2012).

2.4 Data collection

Tolvaptan was identified using the ATC code C03XA01. Liver function tests were defined as the implementation of the following four blood tests on the same day: (1) aspartate aminotransferase, (2) alanine aminotransferase, and (3) gamma-glutamyl transpeptidase, and (4) total bilirubin. Baseline data for patients, including age, sex, and the daily dose of tolvaptan, were collected. The baseline was defined as the day of the first tolvaptan prescription. The two indications of tolvaptan prescription were detected by diagnostic names using the International Classification of Diseases, 10th Revision (ICD-10): codes I50 (chronic heart failure) and K74 (liver cirrhosis).

2.5 Data analyses

Pearson's chi-squared or Fisher's exact tests were used for the comparison of categorical variables, such as proportions of prescription for outpatient, without serum sodium tests and liver function tests. Fisher's exact test was performed when more than 20% of cells had an expected frequency of under 5 [18]. For multiple comparisons, *P* values were adjusted using Bonferroni corrections. A statistically significant difference was defined by a *P* value (including adjusted *P* value) less than 0.05. All statistical analyses were performed using JMP 14 software (SAS Institute, Inc., Cary, NC, USA).

2.6 Ethics Approval

The institutional review board of the Faculty of Pharmaceutical Sciences of Hokkaido University waived the requirement for informed consent as the study did not involve human subjects and the data were de-identified.

3. Results

3.1 Enrolled patients

Of 1,173 patients who were newly prescribed tolvaptan from January 2011 to June 2017, 425 patients were enrolled and classified into FA-CHF (n=347) and FA-LC (n=117) groups (Fig 1). Thirty-nine patients who received both diagnoses were enrolled in both groups, resulting in minor overlapping. Tolvaptan was prescribed by 222 and 97 facilities in FA-CHF and FA-LC groups, respectively (1–14 FA-CHF and 1–3 FA-LC patients per facility). Patient characteristics are shown in Table 2.

3.2 Hospitalization and blood tests implementation

As shown in Fig 2A, 37 (10.7%) FA-CHF and 6 (5.13%) FA-LC patients belonged to the "prescription for outpatients" category. The numbers of patients who did not undergo serum sodium tests were 38 (11.0%) and 14 (12.0%) in FA-CHF and FA-LC groups, respectively. Similarly, the number of patients who did not undergo liver function tests were 61 (17.6%) and 15 (12.8%), respectively. The proportions of those without liver function tests were significantly higher in outpatients than in hospitalized patients but the difference

was not significant for serum sodium tests (Figs 2B and 2C). When patients were classified according to their initial daily dose of tolvaptan, the difference in each outcome was not significant (Figs 3A–C).

Considering the distribution of the number of patients, we categorized them according to their prescription start year, i.e., before 2013 (January 2011 to December 2013), 2014 to 2015 (January 2014 to December 2015), and after 2016 (January 2016 to June 2017) (Figs 4A–C). The results showed that there were no significant differences between these evaluation periods for all endpoints. As shown in Figs 5A and 5B, the proportions of implementation of serum sodium and liver function tests tended to gradually decrease after tolvaptan initiation.

4. Discussion

Tolvaptan is an important therapeutic option for patients such as those with FA-CHF who do not respond sufficiently to other diuretics [19]. Therefore, the safe use of this drug may be beneficial for the patient. In this study, we examined the hospitalization status and implementation of serum sodium measurement and liver function tests in patients who were prescribed tolvaptan. When tolvaptan is used in hyponatremia, the rationale behind monitoring serum sodium levels is to prevent overly rapid correction of hyponatremia that may cause osmotic demyelination. The reported risk factors of overly rapid serum sodium correction include low baseline serum sodium levels (< 125 mmol/L) [20]. However, in Japan, tolvaptan is commonly prescribed for FA-CHF and FA-LC. Since these patients usually do not have hyponatremia at baseline, it

can be inferred that their risk of hypernatremia is higher than that in patients with hyponatremia [9, 10]. Thus, monitoring of serum sodium level is essential for tolvaptan use in FA-CHF and FA-LC. Meanwhile, as liver injury usually occurs with relatively high doses (i.e., ≥ 60 mg daily) [11, 12], it is unclear whether frequent liver function monitoring is clinically necessary for low doses in patients with FA-CHF or FA-LC (i.e., 7.5 or 15 mg daily) [2]. Further, the requirement of hospitalization for tolvaptan initiation varies across countries and regions [2-8]. Therefore, we cannot simply conclude that deviations from the Japanese package insert recommendations are "clinically inappropriate." However, from a pharmacovigilance perspective, we believe it is important to investigate the compliance with these recommendations.

As the prescription start date is not always the administration start date, it is difficult to assess the status of the implementation of blood tests. Thus, we defined a case as "without serum sodium and liver function tests" if blood tests were not performed even once from the day of prescription to the end of each evaluation period. We presumed that these cases did not comply with the package insert recommendations. Although the number of patients was not large, we included patient data from more than 300 institutions in total; thus, our results may be generalized. Among FA-CHF and FA-LC groups, proportions of patients without blood tests ranged from 11.0 to 17.6%. Of these, liver function tests in the FA-CHF group tend to be ignored. Nasuhara *et al*. investigated the implementation of blood tests in patients who were prescribed thiamazole at a single hospital in Japan [21] and found that the proportion of outpatients who never received blood tests was 3.9% during the 6-month evaluation period. For thiamazole, a "blue letter" (a healthcare professional

letter of rapid safety information from a regulatory agency) was issued in February 2004 to perform periodic monitoring of white blood cells. Although a simple comparison is difficult, a “blue letter” may be related to differences in the proportions of patients without blood tests.

When the hospitalization status was assessed, the proportions of those without liver function tests were significantly higher in outpatients than in hospitalized patients. Notably, a majority of outpatients in the FA-LC group did not undergo liver function tests. A similar trend was observed in serum sodium tests, although the difference was not significant. In addition to the problem of prescribing tolvaptan without hospitalization, these patients were also identified to be “without blood tests”, further supporting our hypothesis that the implementation of blood tests was low in outpatients prescribed tolvaptan.

Considering previous reports [9-12], the occurrence of hypernatremia and liver injury induced by tolvaptan seems to be dose-dependent. In this study, we evaluated the association between the daily dose and outcome based on whether or not the administered dose exceeded the daily dose recommended by the Japanese package [2]. However, the number of patients whose daily dose exceeded the recommended dose was small, and a clear trend could not be observed.

The use of tolvaptan for FA-CHF and FA-LC were approved in Japan in October 2010 and September 2013, respectively [2], and tolvaptan prescription in outpatient settings and without blood tests was expected to increase over time. Although these proportions were not on the rise in the present study, “the number of patients” receiving tolvaptan was highest in after 2016 (January 2016 to June 2017), even though

this period was approximately 6 months shorter than the others (i.e., before 2013 and 2014 to 2015). These results suggest that “the number of patients” who received tolvaptan prescription in outpatient settings and without blood tests tended to increase. In our analysis of the daily status of serum sodium and liver function tests, the proportions tended to gradually decrease after the start of tolvaptan administration, although they were relatively high before tolvaptan initiation. This result is similar to the previous report of thiamazole [21]. Moreover, our results indicated that only 20–30% of patients underwent serum sodium tests after day 3 in both groups. The proportion of patients undergoing liver function tests was even lower than this. Although we enrolled patients whose prescription was continued for 14 days or longer, there may have been discontinuations that were not reflected in the prescription. Even when considering these factors, we believe that the proportion of patients who underwent serum sodium and liver function tests was low. Notably, with regard to serum sodium tests for patients with FA-CHF, the Japanese package insert recommends that patients with FA-CHF should be tested daily for 7 days after tolvaptan initiation [2].

Considering these observations, it is important to educate clinicians who prescribe tolvaptan on the importance of blood tests. Additionally, community pharmacists who dispense tolvaptan should play an important role in preventing inappropriate tolvaptan use. In particular, pharmacists should make pharmacy inquiries to clinicians when tolvaptan is newly prescribed to outpatients and alert clinicians that hospitalization and proper blood tests are necessary for these patients.

Our study had some limitations. First, because the JMDC claims database does not have data for patients

aged 75 years and older, elderly patients could not be included [17]. In addition, since this database comprises employees from large companies and their families, there may be some selection bias. Second, since tolvaptan administration was detected based on prescriptions, the actual use could not be evaluated. Third, we did not evaluate the implementation status of blood tests beyond the evaluation period; however, we succeeded in assessing when the serum sodium and liver function tests were performed, as described in the Japanese package insert [2]. Fourth, the occurrence of side effects could not be evaluated because the JMDC claims database does not contain laboratory data, such as serum sodium levels. Fifth, in our study, we only evaluated results in Japanese patients with FA-CHF and FA-LC; therefore, additional studies are required to adapt these findings to other indications and countries. Sixth, we defined patients with FA-CHF and FA-LC based on the ICD-10 codes corresponding to their underlying diseases. However, the accuracy of these codes was not validated. Also, the actual purpose of the prescription could not be identified in 39 patients who received both diagnoses. Finally, most recent datasets could not be evaluated because our database contains data only up to June 2017.

Despite these limitations, our findings provided important insights into the hospitalization status and the implementation of serum sodium measurement and liver function tests in patients prescribed tolvaptan, using large medical data. Our approach also establishes important perspectives on pharmacovigilance research.

5. Conclusion

Among patients who received new tolvaptan prescriptions, 10.7% and 5.13% were prescribed tolvaptan without hospitalization in FA-CHF and FA-LC groups, respectively. In addition, the proportions of patients who did not undergo blood tests ranged from 11.0–17.6% in these groups. Moreover, our results indicated that the implementation of serum sodium measurement and liver function tests was low in outpatients who were prescribed tolvaptan. These results highlight the deviation from the package insert recommendations of tolvaptan in Japan.

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None.

Author Contributions

SI and YT conceived the study idea and designed the study. KM, HK, TM, YS, and SM assisted with the research design. KM provided epidemiological data. SI and YT performed the statistical analyses. KM, HK, TM, YS, and SM assisted with performing statistical analyses. SI and YT wrote the manuscript. KM, HK, TM, YS, and SM contributed equally to this work. All authors have read and approved the final version of the manuscript.

Declaration of interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available because they are proprietary but may be available from the corresponding author upon reasonable request.

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* This study revealed that the proportion of outpatients who never received blood tests was 3.9% in patients with thiamazole during their evaluation period.

Table 1. The regulatory status of tolvaptan in various countries and regions

Regulatory authorities	Indications	Hospitalization requirement for initiation	Serum sodium test requirement	Liver function test requirement	Initial daily dose (in adults)	Approval date	Others
Pharmaceuticals and Medical Devices Agency (Package insert, Japan) [2]	Fluid accumulation induced by chronic heart failure	Required	Must be monitored: 1. Initially, 4–6 hours and 8–12 hours after administration 2. Every day at least about one week after the initiation 3. After that, as appropriate	Must be monitored: 1. Before the initiation 2. Frequently for at least two weeks after the initiation 3. After that, as appropriate	15 mg once daily	27 October 2010	
	Fluid accumulation induced by liver cirrhosis	Required	Must be monitored: 1. Initially, 4–8 hours after administration 2. Then, 2 days and 3 to 5 days after the initiation 3. After that, as appropriate	Must be monitored: 1. Before the initiation 2. Frequently for at least two weeks after the initiation 3. After that, as appropriate	7.5 mg once daily	13 September 2013	

ADPKD with already increased renal volume and rapidly increasing renal volume	Required	Must be monitored: 1. Each visit to the hospital during the dose-escalation period 2. Once a month at least	Must be monitored: 1. Before the initiation 2. Once a month at least	45 mg in the morning and 15 mg in the evening	24 March 2014	Only doctors who have taken the training program and registered can prescribe
Hyponatremia-induced by SIADH	Required	Must be monitored: 1. Initially, 4–6 hours and 8–12 hours after administration 2. Every day for at least one week after the initiation 3. After that, as appropriate	Must be monitored: 1. Before the initiation 2. Frequently at least two weeks after the initiation 3. After that, as appropriate	7.5 mg once daily	29 June 2020	

U.S. Food and Drug Administration (label, United States) [3, 4]	Clinically significant hypervolemic and euvolemic hyponatremia, including patients with heart failure and SIADH	Recommended	Should be monitored during initiation and after titration	Not stated	15 mg once daily	19 May 2009	
	Adults at risk of rapidly progressing ADPKD	Not required	Must be monitored: 1. Ensure that abnormalities in sodium concentrations are corrected before initiation 2. If serum sodium level increases above the normal range, suspend tolvaptan until serum sodium is within the normal range	Must be monitored: 1. Measure transaminases (ALT, AST) and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation 2. Then, monthly for the first 18 months and every 3 months thereafter	45 mg taken upon waking, and 15 mg taken approximately 8 hours later	23 April 2018	Tolvaptan should not be prescribed or used outside of the FDA-approved Risk Evaluation and Mitigation Strategy (REMS) for ADPKD patients

Health Canada (Product Monograph, Canada) [5, 6]	Clinically important, non-hypovolemic hyponatremia	Recommended	Must be monitored: 1. No later than 4–6 hours after treatment initiation 2. During the first 1–2 days and until the tolvaptan dose is stabilized at least every 6 hours	Must be monitored: 1. Before starting treatment 2. Every month for the first 18 months 3. Every 3 months for the next 12 months 4. Every 3–6 months thereafter during treatment	15 mg once daily	25 July 2011	
	ADPKD	Not required	Must be monitored frequently during treatment initiation	Must be monitored: 1. Before starting treatment 2. Every month for the first 18 months 3. Every 3 months for the next 12 months 4. Every 3–6 months thereafter during treatment	45 mg taken upon waking, and 15 mg taken approximately 8 hours later	23 February 2015	Tolvaptan is available for the treatment of patients with ADPKD only through a manufacturer and product-specific controlled hepatic safety monitoring and distribution (HSMD) program

European Medicines Agency (Summaries of product characteristics, European Union) [7, 8]	Hyponatremia secondary to the SIADH	Recommended	Must be monitored: 1. No later than 4–6 hours after treatment initiation 2. During the first 1–2 days and until the tolvaptan dose is stabilized at least every 6 hours	Not stated	15 mg once daily	3 August 2009	
	ADPKD in adults with chronic kidney disease stage 1 to 4 at the initiation of treatment with evidence of rapidly progressing disease	Not required	Must be monitored: 1. Before and after initiation 2. At least every three months during long-term treatment	Must be monitored: 1. Before initiation 2. Every month for the first 18 months 3. Every 3 months thereafter	45 mg in the morning and 15 mg in the evening	27 May 2015	Only doctors who are specialized in the treatment of ADPKD can prescribe

ADPKD: autosomal dominant polycystic kidney disease, SIADH: syndrome of inappropriate antidiuretic hormone secretion.

Table 2. Baseline characteristics of the study population

Description	CHF group (n = 347)	Liver cirrhosis group (n = 117)
Age (years), median (IQR)	56 (45–64)	60 (53–64)
Sex (male), n (%)	227 (65.4)	80 (68.4)
Daily dose of tolvaptan (mg), median (IQR)	7.5 (3.75–7.5)	7.5 (3.75–7.5)

Overlap was observed in 39 patients because they received both diagnoses. CHF: chronic heart disease, IQR: interquartile range.

Figure Legends

Fig. 1. Flowchart of patients enrolled in this study.

FA-CHF: fluid accumulation induced by chronic heart failure, FA-LC: fluid accumulation induced by liver cirrhosis.

Fig. 2. Status of hospitalization and blood tests implementation.

A: Evaluation of all enrolled patients in fluid accumulation induced by chronic heart failure (FA-CHF) and liver cirrhosis (FA-LC) groups. B: Comparison of proportions of patients without serum sodium tests based on hospitalization status. C: Comparison of proportions of patients without liver function tests based on hospitalization status. Without serum sodium tests: serum sodium tests were not performed even once from the day of prescription through day 6 (FA-LC group) and day 8 (FA-CHF group). Without liver function tests: liver function tests were not performed even once before the day of prescription (day -14 to -1) through day 15. *$P \leq 0.05$.

Fig. 3. Status of hospitalization and blood test implementation when patients were classified according to the initial daily dose of tolvaptan.

A–C: Comparison of the proportions of prescriptions for outpatients and without serum sodium and liver function tests based on the initial daily dose of tolvaptan. The cutoff values of daily dose were based on the

Japanese package insert recommendations [fluid accumulation induced by chronic heart failure (FA-CHF): 15 mg daily, fluid accumulation induced by liver cirrhosis (FA-LC): 7.5 mg daily]. Without serum sodium tests: serum sodium tests were not performed even once from the day of prescription through day 6 (FA-LC group) and day 8 (FA-CHF group). Without liver function tests: liver function tests were not performed even once before the day of prescription (day -14 to -1) through day 15.

Fig. 4. Status of hospitalization and blood test implementation when classified according to prescription start year.

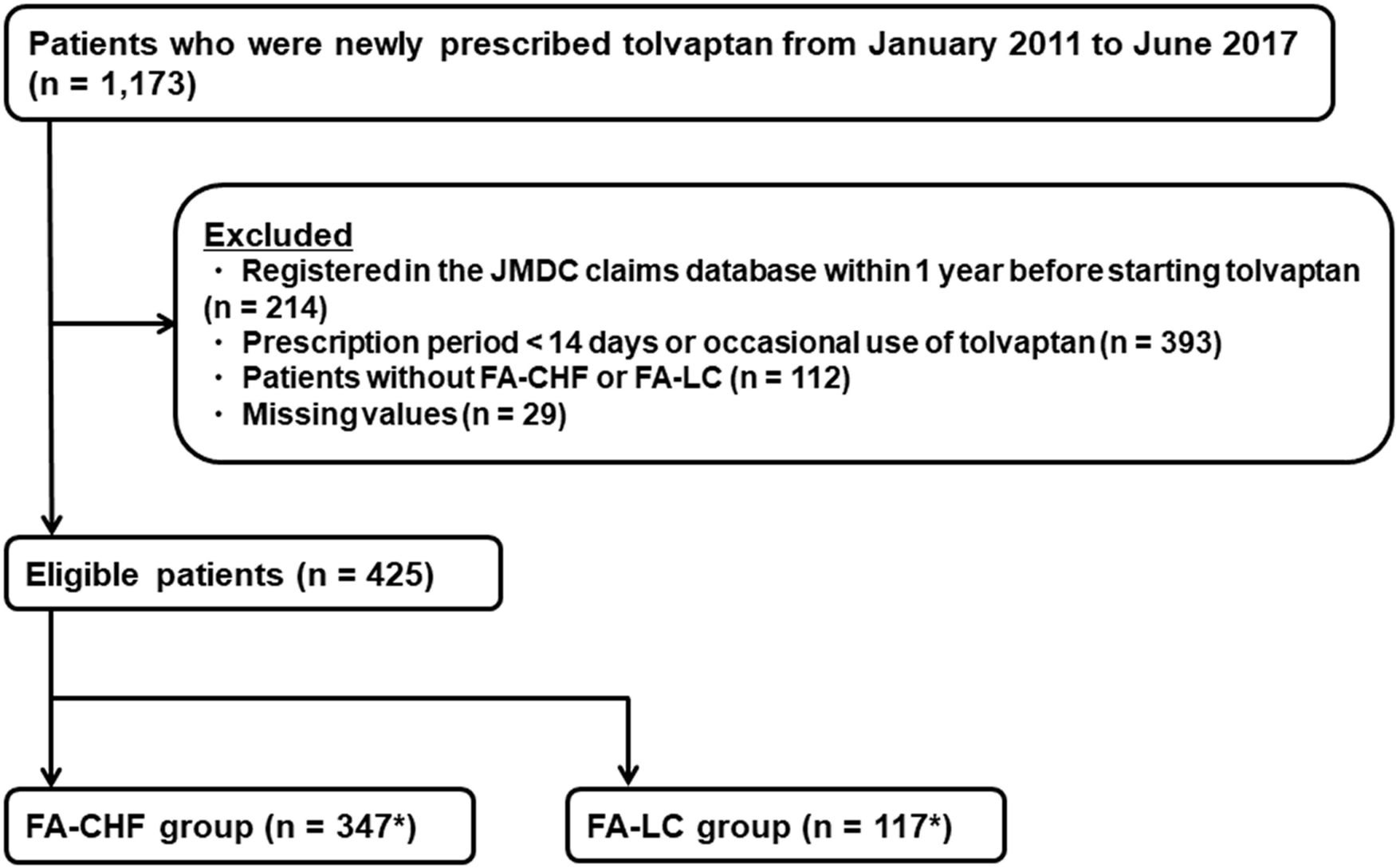
A–C: Comparison of the proportions of prescriptions for outpatients and without serum sodium and liver function tests when classified according to prescription start year. Before 2013: January 2011 to December 2013, 2014 to 2015: January 2014 to December 2015, after 2016: January 2016 to June 2017. Without serum sodium tests: serum sodium tests were not performed even once from the day of prescription through day 6 [fluid accumulation induced by liver cirrhosis (FA-LC) group] and day 8 [fluid accumulation induced by chronic heart failure (FA-CHF) group]. Without liver function tests: liver function tests were not performed even once before the day of prescription (day -14 to -1) through day 15.

Fig. 5. Daily status of serum sodium and liver function tests.

A: Daily status of serum sodium tests before tolvaptan initiation (day -14 to -1) through day 6 [fluid

accumulation induced by liver cirrhosis (FA-LC) group] and day 8 [fluid accumulation induced by chronic heart failure (FA-CHF) group] of prescription. B: Daily status of liver function tests before tolvaptan initiation (day -14 to -1) through day 15 of prescription in both groups.

Fig. 1



*Thirty-nine patients received both diagnoses

Fig. 2

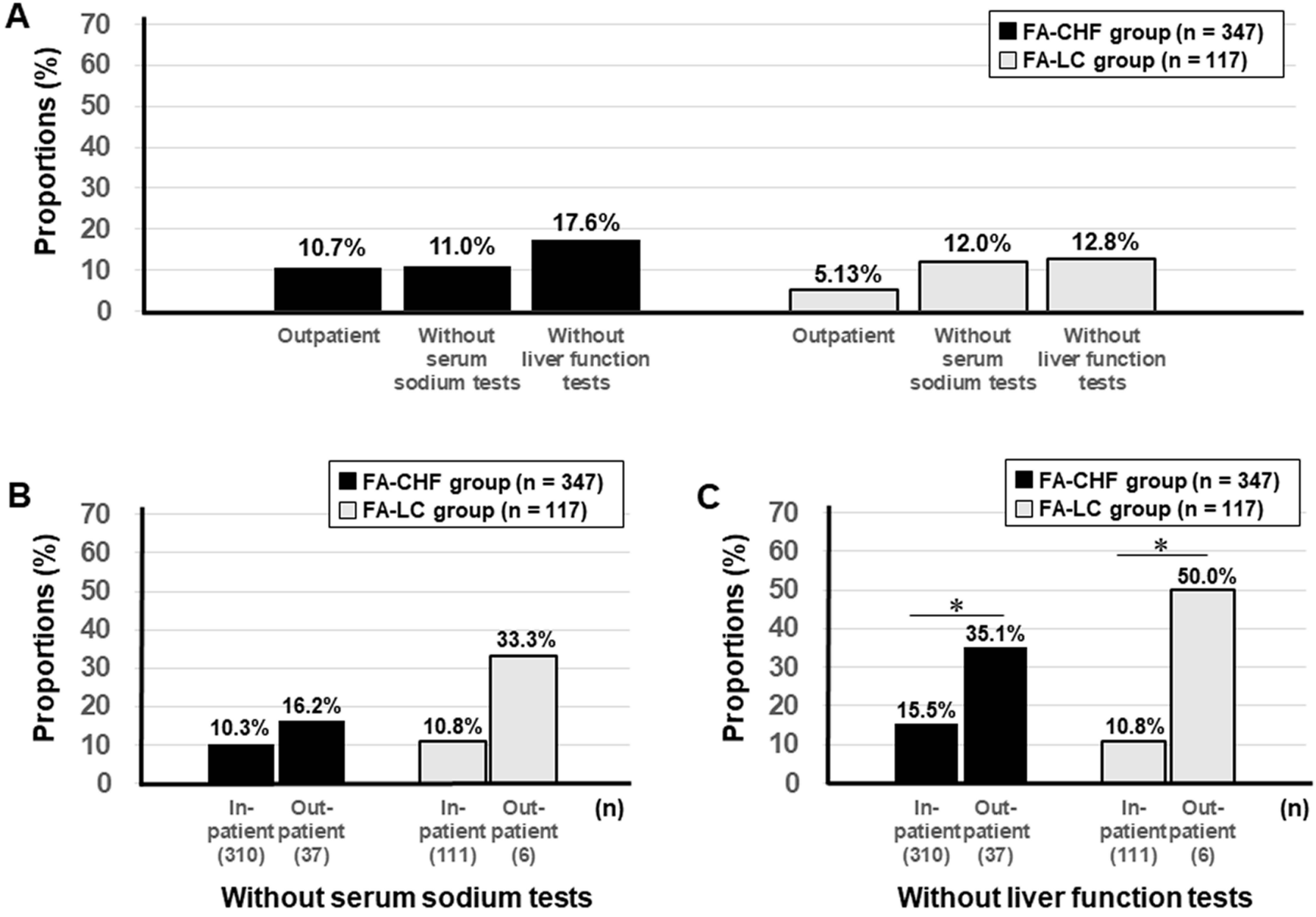

A
Proportions (%)
70
60
50
40
30
20
10
0
FA-CHF group (n = 347)
FA-LC group (n = 117)
10.7%
11.0%
17.6%
5.13%
12.0%
12.8%
Outpatient
Without serum sodium tests
Without liver function tests
Outpatient
Without serum sodium tests
Without liver function tests
B
Proportions (%)
FA-CHF group (n = 347)
FA-LC group (n = 117)
10.3%
16.2%
10.8%
33.3%
In-patient (310)
Out-patient (37)
In-patient (111)
Out-patient (6)
(n)
Without serum sodium tests
C
Proportions (%)
FA-CHF group (n = 347)
FA-LC group (n = 117)
*
*
15.5%
35.1%
10.8%
50.0%
In-patient (310)
Out-patient (37)
In-patient (111)
Out-patient (6)
(n)
Without liver function tests

Fig. 3

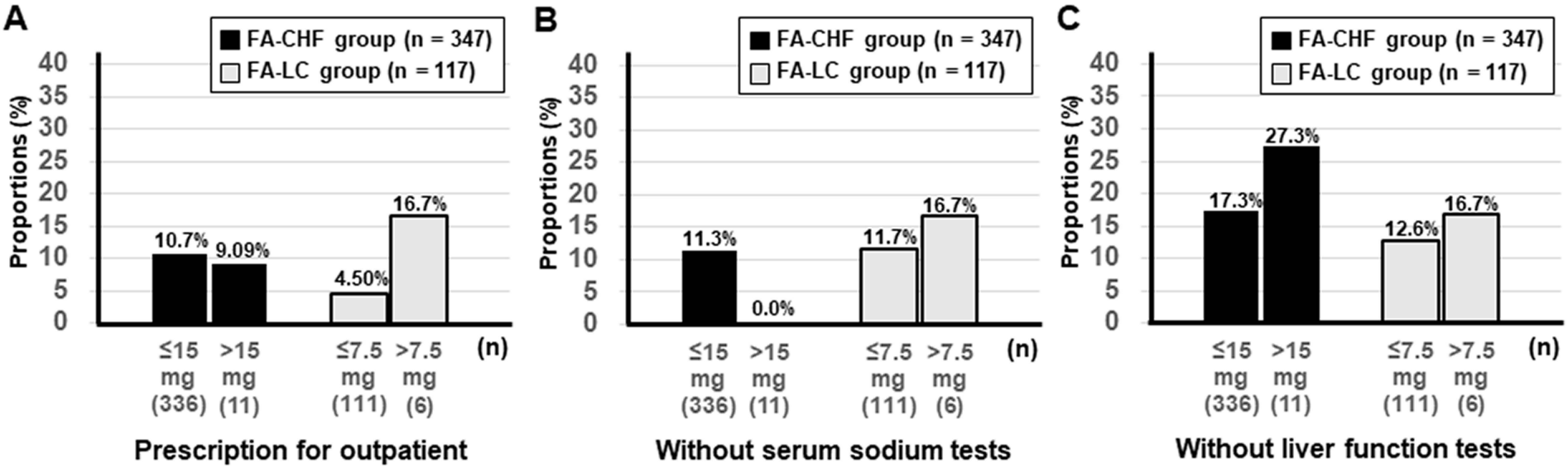

A
FA-CHF group (n = 347)
FA-LC group (n = 117)
Proportions (%)
40
35
30
25
20
15
10
5
0
10.7%
9.09%
4.50%
16.7%
≤15 mg (336)
>15 mg (11)
≤7.5 mg (111)
>7.5 mg (6)
(n)
Prescription for outpatient
B
FA-CHF group (n = 347)
FA-LC group (n = 117)
Proportions (%)
11.3%
0.0%
11.7%
16.7%
(n)
Without serum sodium tests
C
FA-CHF group (n = 347)
FA-LC group (n = 117)
Proportions (%)
17.3%
27.3%
12.6%
16.7%
(n)
Without liver function tests

Fig. 4

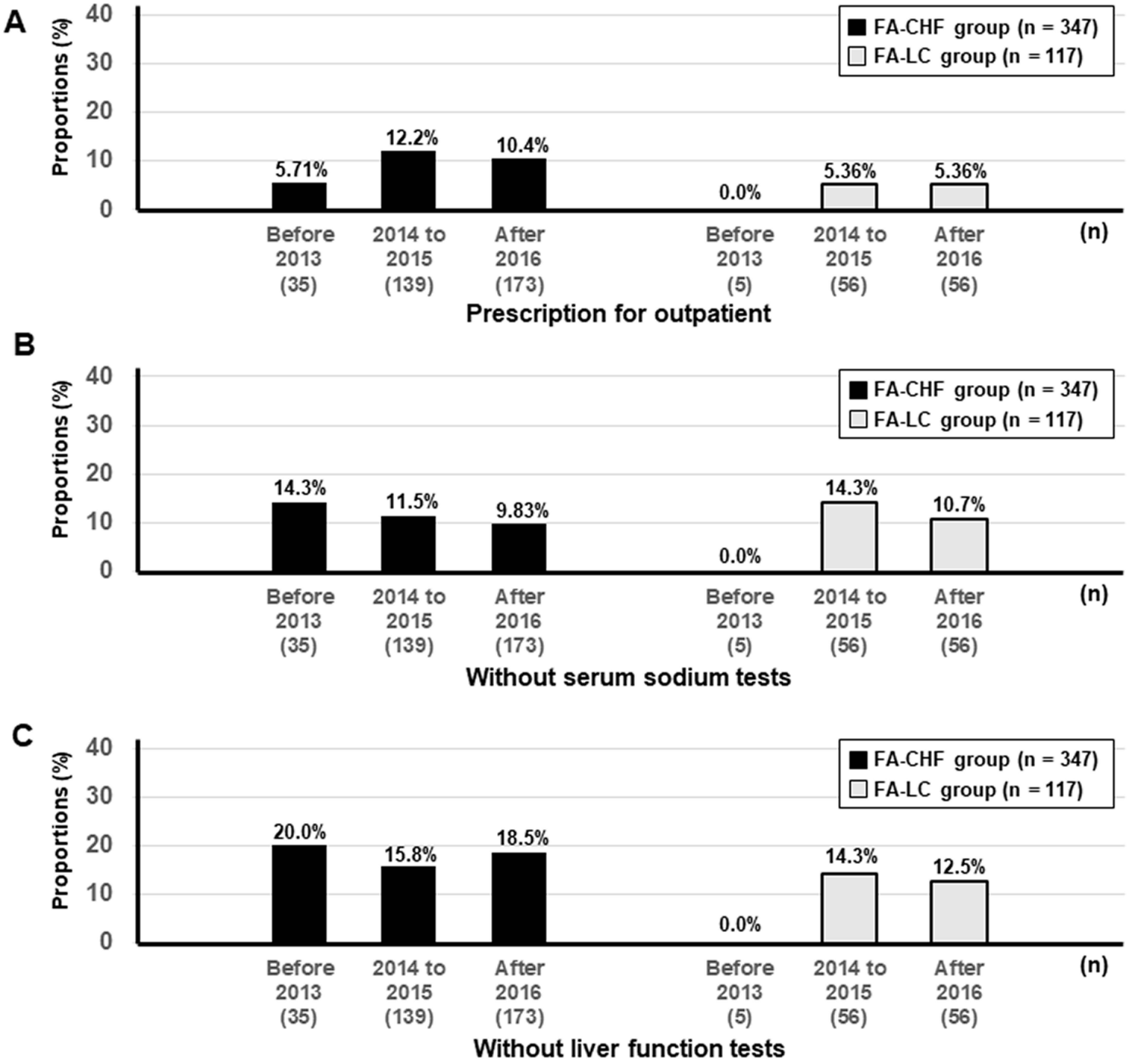
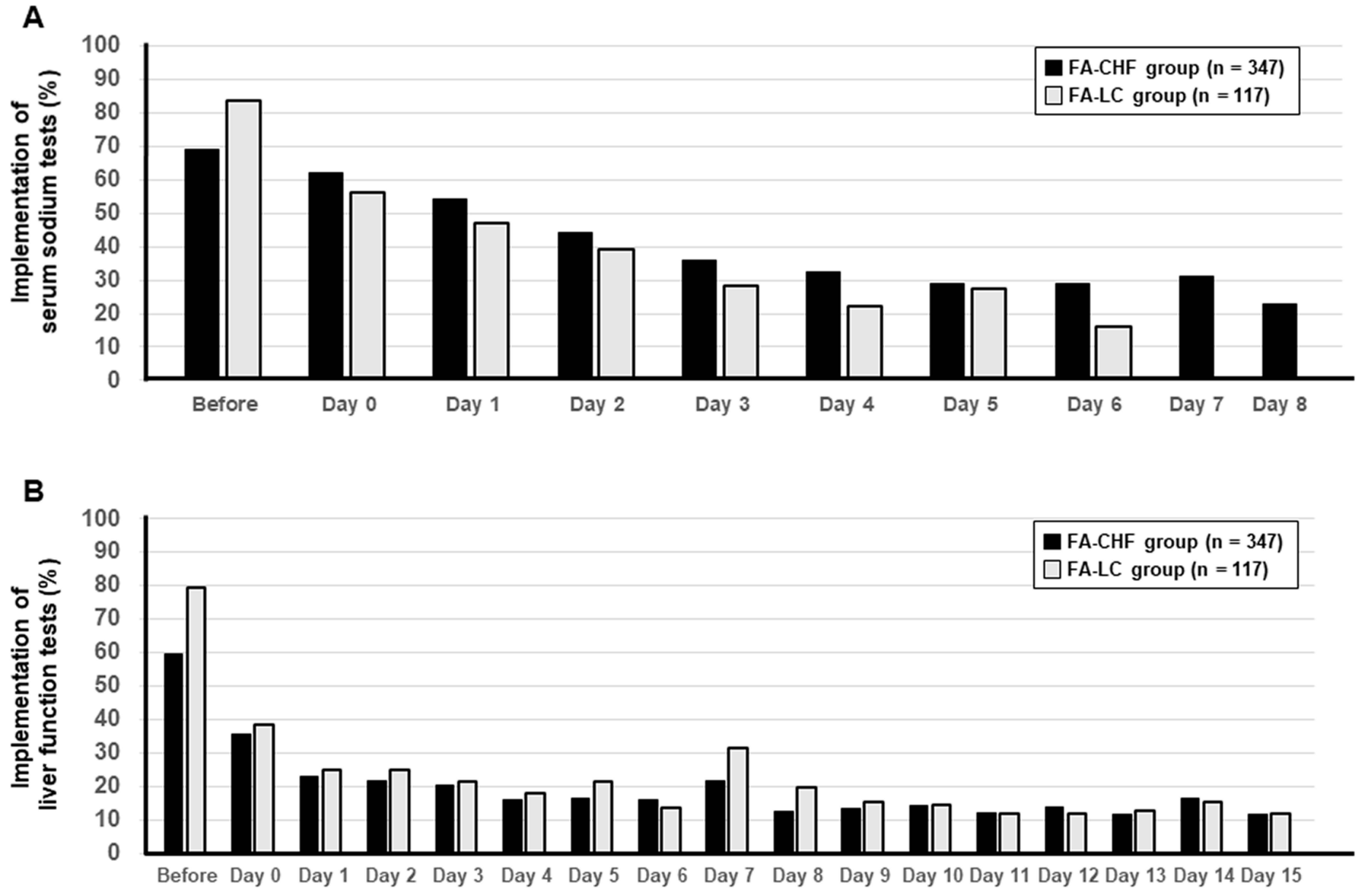

A
Proportions (%)
40
30
20
10
0
FA-CHF group (n = 347)
FA-LC group (n = 117)
5.71%
12.2%
10.4%
0.0%
5.36%
5.36%
Before 2013 (35)
2014 to 2015 (139)
After 2016 (173)
Before 2013 (5)
2014 to 2015 (56)
After 2016 (56)
(n)
Prescription for outpatient
B
Proportions (%)
FA-CHF group (n = 347)
FA-LC group (n = 117)
14.3%
11.5%
9.83%
0.0%
14.3%
10.7%
Before 2013 (35)
2014 to 2015 (139)
After 2016 (173)
Before 2013 (5)
2014 to 2015 (56)
After 2016 (56)
(n)
Without serum sodium tests
C
Proportions (%)
FA-CHF group (n = 347)
FA-LC group (n = 117)
20.0%
15.8%
18.5%
0.0%
14.3%
12.5%
Before 2013 (35)
2014 to 2015 (139)
After 2016 (173)
Before 2013 (5)
2014 to 2015 (56)
After 2016 (56)
(n)
Without liver function tests

Fig. 5


A
Implementation of serum sodium tests (%)
100
90
80
70
60
50
40
30
20
10
0
FA-CHF group (n = 347)
FA-LC group (n = 117)
Before
Day 0
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
B
Implementation of liver function tests (%)
100
90
80
70
60
50
40
30
20
10
0
FA-CHF group (n = 347)
FA-LC group (n = 117)
Before
Day 0
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Day 9
Day 10
Day 11
Day 12
Day 13
Day 14
Day 15