

RESEARCH ARTICLE

Open Access



Relationship between antihypertensive drug use and number of people with high blood pressure in FY 2018: a descriptive epidemiological study based on the National Database of Health Insurance Claims and Specific Health Checkups of Japan open data

Kanako Mizuno¹, Ryo Inose¹, Yukina Yoshimura¹ and Yuichi Muraki^{1*} 

Abstract

Background In most countries barring Japan, antihypertensive drug use has been reported using the defined daily doses/1000 inhabitants/day (DID). Although DID has been shown to allow for the assessment of the number of patients treated with a particular drug, the relationship between DID and the number of patients with hypertension has not been clarified. This study aimed to clarify the relationship between antihypertensive drug use and the number of people with high blood pressure based on the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) open data.

Methods DID was calculated by extracting the use of oral antihypertensive drugs from outpatient prescriptions in the NDB Open Data in FY 2018. The number of people with high blood pressure was calculated using the number of enrollees in each sex–age group for systolic and diastolic blood pressure in the 40–74 years age group. The correlation between the DID of antihypertensive drugs and the number of people with high blood pressure by sex and age class was evaluated using Spearman's rank correlation coefficient.

Results The use of antihypertensive drugs increased with age in both men and women. Furthermore, in both sexes, dihydropyridine derivatives, calcium antagonists, and angiotensin II receptor blockers were the main drugs used from the age of 20 years onward. In addition, a very strong positive correlation was found between the number of people with high systolic blood pressure and DID in both sexes (men: $r = 1$, $P < 0.05$; women: $r = 1$, $P < 0.05$). In contrast, there was no significant correlation between the number of people with high diastolic blood pressure and DID in both sexes (men: $r = -0.214$, $P > 0.05$; women: $r = 0.393$, $P > 0.05$).

Conclusions To our knowledge, this study is the first to investigate the use of oral antihypertensive drugs in outpatient settings in Japan. In addition, the DID of antihypertensive drugs can be used as an alternative indicator of the number of people with high systolic blood pressure.

*Correspondence:

Yuichi Muraki

y-muraki@mb.kyoto-phu.ac.jp

Full list of author information is available at the end of the article



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Keywords National Database of Health Insurance Claims and Specific Health Checkups of Japan open data, Antihypertensive drug, Defined daily doses/1000 inhabitants/day, Systolic blood pressure, Diastolic blood pressure, Hypertension

Background

The number of patients with hypertension worldwide has doubled in approximately 30 years as the population grows and ages [1]. Hypertension is a lifestyle-related disease known to cause complications including cerebrovascular diseases and renal dysfunction [2]. Among these, cerebrovascular disease is the fourth leading cause of death in Japan, with hypertension considered its greatest risk factor [3]. Therefore, the treatment of hypertension is extremely important for the prevention of cerebrovascular disease and should be based on guidelines for the management of hypertension. The guidelines for the management of hypertension in Japan published in 2019 recommend the selection of antihypertensive drugs according to the presence of concomitant diseases and specific patient background characteristics, such as elderly age, pregnancy, and age of less than 18 years. Therefore, the antihypertensive drugs used should be identified and monitored.

The World Health Organization (WHO) recommends defined daily doses (DDD)/1000 inhabitants/day (DID) as an indicator for assessing drug use [4]. Therefore, in the 27 member countries of the Organization for Economic Co-operation and Development (OECD), DID values for antihypertensive drug use have been published over time [5]. Antihypertensive drug use varies across countries. In some OECD member countries, calcium (Ca) channel blockers are used more frequently, whereas in others, the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) is more frequent. Although Japan is a member of the OECD, the DID for antihypertensive drugs in the country has not been clarified, making comparisons with the rest of the world difficult. In addition, DID has been shown to help assess the number of patients being treated with a particular drug [6]. However, the relationship between the DID of antihypertensive drugs and number of hypertensive patients has not been clarified.

To date, drug use has been evaluated using information such as sales data [7] or the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) [8]. The NDB contains various data including the number of drug prescriptions and laboratory values during specific health checkups. Therefore, in Japan, which has universal health insurance, the NDB data can be used to understand the medical trends in the population at a

rate close to that in the total number of general populations [9]. However, NDB users are required to ensure a high-security environment, which is a considerable barrier to the general use of these data [9]. In October 2016, the Ministry of Health, Labour and Welfare (MHLW) published statistical data on the actual status of medical care and results of specific health checkups in Japan as NDB Open Data for the public [9]. The NDB Open Data are suitable for a broad and plain understanding of Japanese healthcare [9]. This study aimed to clarify the relationship between antihypertensive drug use and the number of people with high blood pressure based on the NDB Open Data.

Methods

Data source

The numbers of drug prescriptions by sex, age class, and prefecture were obtained from the NDB Open Data for FY 2018 [10, 11]. The NDB Open Data contain the top 100 drugs with the highest prescription numbers in each efficacy category. Additionally, the actual prescription quantities for products with fewer than 1000 prescriptions are anonymized [12]. These data include only the commodity names of drugs and do not contain information about drug ingredients. In this study, ingredient names were added by linking the National Health Insurance (NHI) Drug Price List published by the MHLW [13] with NHI drug codes in the NDB Open Data. In the NDB Open Data, laboratory values for every 5 years of age and by prefecture for those aged 40–74 years who underwent specific health checkups are available. The number of persons in each age group from 40 to 74 years with systolic and diastolic blood pressure in FY 2018 [11] was obtained.

Study design

In Japan, 99.1% of hypertension treatments are performed in the outpatient department [14]. As such, the target antihypertensive drugs were those prescribed as outpatient (in-hospital or out-of-hospital) oral medications in efficacy categories 214 (antihypertensive drugs) and 217 (vasodilators). The WHO defines the Anatomical Therapeutic Chemical (ATC) classification, which classifies drugs into five levels. In this study, antihypertensive drugs were classified using the fourth level, ATC4 [15],

Table 1 ATC4, generic name, and DDD of antihypertensive drugs

Mechanism of action	ATC4 ^{*1}	Generic name	DDD ^{*2} (g)
Phosphodiesterase inhibitors	B01AC	Dipyridamole	0.400
Organic nitrates	C01DA	Isosorbide mononitrate Isosorbide dinitrate	0.040 0.060
Other vasodilators used in cardiac diseases	C01DX	Dilazep Nicorandil	0.100 0.040
Methyldopa	C02AB	Methyldopa	1.000
Alpha-adrenoreceptor antagonists	C02CA	Doxazosin Urapidil	0.004 0.120
Sulfonamides, plain	C03BA	Indapamide	0.003
Aldosterone antagonists	C03DA	Eplerenone	0.050
Beta-blocking agents, selective	C07AB	Metoprolol	0.150
Alpha- and beta-blocking agents	C07AG	Carvedilol	0.038
Dihydropyridine derivatives	C08CA	Amlodipine Azelnidipine Benidipine Cilnidipine Efonidipine Nifedipine	0.005 0.016 ^{*3} 0.004 ^{*3} 0.010 0.040 ^{*3} 0.030
Phenylalkylamine derivatives	C08DA	Verapamil	0.240
Benzothiazepine derivatives	C08DB	Diltiazem	0.240
ACE ^{*4} inhibitors, plain	C09AA	Enalapril Imidapril	0.010 0.010
ARBs ^{*5} , plain	C09CA	Azilsartan Candesartan Irbesartan Losartan Olmesartan medoxomil Telmisartan Valsartan	0.040 0.008 0.150 0.050 0.020 0.040 0.080
ARBs ^{*5} and diuretics	C09DA	Candesartan and diuretics Losartan and diuretics Telmisartan and diuretics Valsartan and diuretics	1 UD ^{*6}
ARBs ^{*5} and calcium channel blockers	C09DB	Azilsartan and Amlodipine Candesartan and Amlodipine Irbesartan and Amlodipine Olmesartan medoxomil and Azelnidipine Telmisartan and Amlodipine Valsartan and Amlodipine Valsartan and Cilnidipine	

^{*1} ATC Anatomical Therapeutic Chemical, ^{*2} DDD Defined daily dose, ^{*3} DDD is not listed in the ATC/DDD Index 2023 and is defined from the dosage and administration in the package insert. ^{*4} ACE angiotensin-converting enzyme inhibitor, ^{*5} ARB angiotensin II receptor blocker, ^{*6} UD Unit of combination drug

which classifies drugs anatomy, therapy, pharmacology, and chemistry. The ATC4 and DDD of the target antihypertensive drugs used are shown in Table 1. DDD (g) was obtained using the ATC/DDD Index 2023 [16]. The DDDs of azelnidipine, efonidipine, and benidipine hydrochloride are not listed in the ATC/DDD Index 2023; therefore, they are defined as the maximum dose in the Japanese package inserts for these medications.

Calculation of antihypertensive drug use

Antihypertensive drug use was evaluated using the DID. The number of prescriptions of antihypertensive drugs obtained from the NDB Open Data was converted to a titer, and the DID was calculated using the DDD and the population by sex and age class [17] or prefecture [18] in FY 2018, as reported by the Statistics Bureau of Japan, by using the following formula (1):

$$\text{DID (DDDs/1,000 inhabitants/day)} = \text{Annual consumption (g)/DDD (g)/(population/1,000 inhabitants)/365 (days)} \quad (1)$$

Calculation of the number of people with high blood pressure

The number of people with high blood pressure was calculated using formulas (2) and (3) for men and women aged 40–74 years.

Statistical analysis

The correlation between the DID of antihypertensive drugs and the number of people with high blood pressure according to sex and age class was evaluated using Spearman’s rank correlation coefficient. Each prefecture was

$$\begin{aligned} &\text{Number of people with high systolic blood pressure (/1,000 inhabitants)} \\ &= (\text{number of persons with systolic blood pressure of 140 mmHg or higher} \\ &\quad / \text{Number of people whose systolic blood pressure had been registered}) \times 1,000 \end{aligned} \tag{2}$$

$$\begin{aligned} &\text{Number of people with high diastolic blood pressure (/1,000 inhabitants)} \\ &= (\text{number of persons with diastolic blood pressure of 90 mmHg or higher} \\ &\quad / \text{Number of people whose diastolic blood pressure had been registered}) \times 1,000 \end{aligned} \tag{3}$$

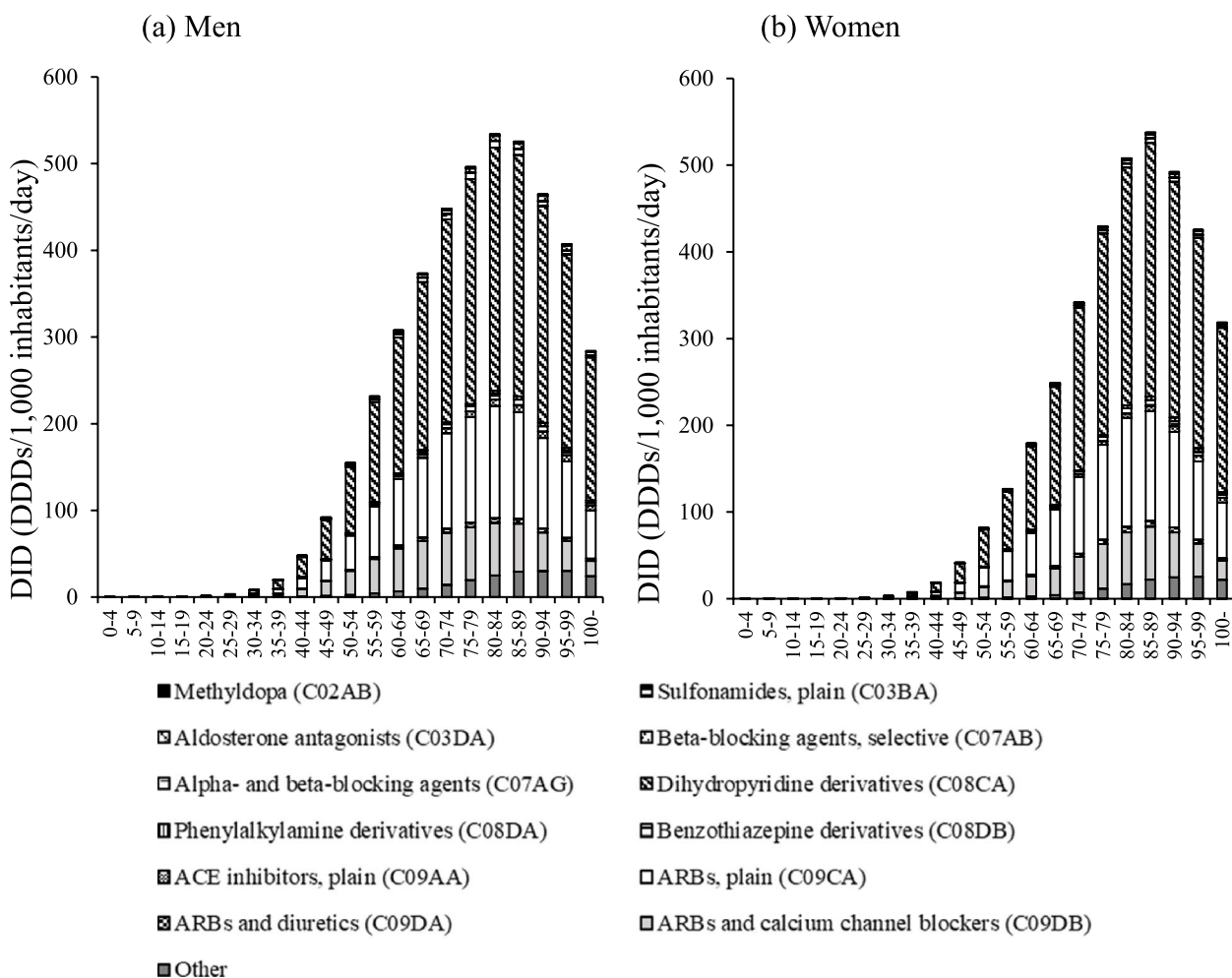


Fig. 1 The trend for antihypertensive drug use stratified by sex and age class. Other: phosphodiesterase inhibitors (B01AC), organic nitrates (C01DA), other vasodilators used in cardiac diseases (C01DX), and alpha-adrenoreceptor antagonists (C02CA). DDD: Defined daily dose

divided into three regions (East, Central, and West), and differences in DID in each category were evaluated using the Kruskal–Wallis test and Bonferroni adjustment. The two-sided significance level was set at 5%, and Easy R (EZR) [19] was used for the analysis.

Ethical consideration

This study was conducted in strict compliance with the “Ethical Guidelines for Medical Research Involving Human Subjects” and was approved by the Ethics Committee of Kyoto Pharmaceutical University (approval number: E21–011).

Results

The use of antihypertensive drugs by sex and age class in FY 2018

The DID for antihypertensive drugs according to sex and age class in FY 2018 is shown in Fig. 1. DID increased with age for both men and women but decreased after peaking at ages 80–84 for men and 85–89 for women.

Antihypertensive drug use was higher among men in the age group of 5–84 years and among women in the age group of ≥ 85 and older age groups.

The proportions of DID for antihypertensive drugs according to sex and age class in FY 2018 is shown in Fig. 2. In both men and women, dihydropyridine (DHP) derivative Ca antagonists (C08CA and C09DB) and ARBs (C09CA, C09DA, and C09DB) were the main drugs used age group of ≥ 20 years. On the other hand, the usage rates of ACE inhibitors, plain (C09AA) and alpha- and beta-blocking agents (C07AG), and others were higher among those aged 0–19 years than among those aged 20 years and higher. Enalapril accounted for more than 90.9% of the ACE inhibitor, plain (C09AA), use in both sexes in the age group of 0–19 years. In addition, alpha- and beta-blocking agents (C07AG) in the age group of 0–19 years included only carvedilol for both sexes.

Among women in their 20s–40s, methyldopa (C02AB) use ranged from 0.2–4.1%, compared with 0.01–0.19% among men in the same age group. The use

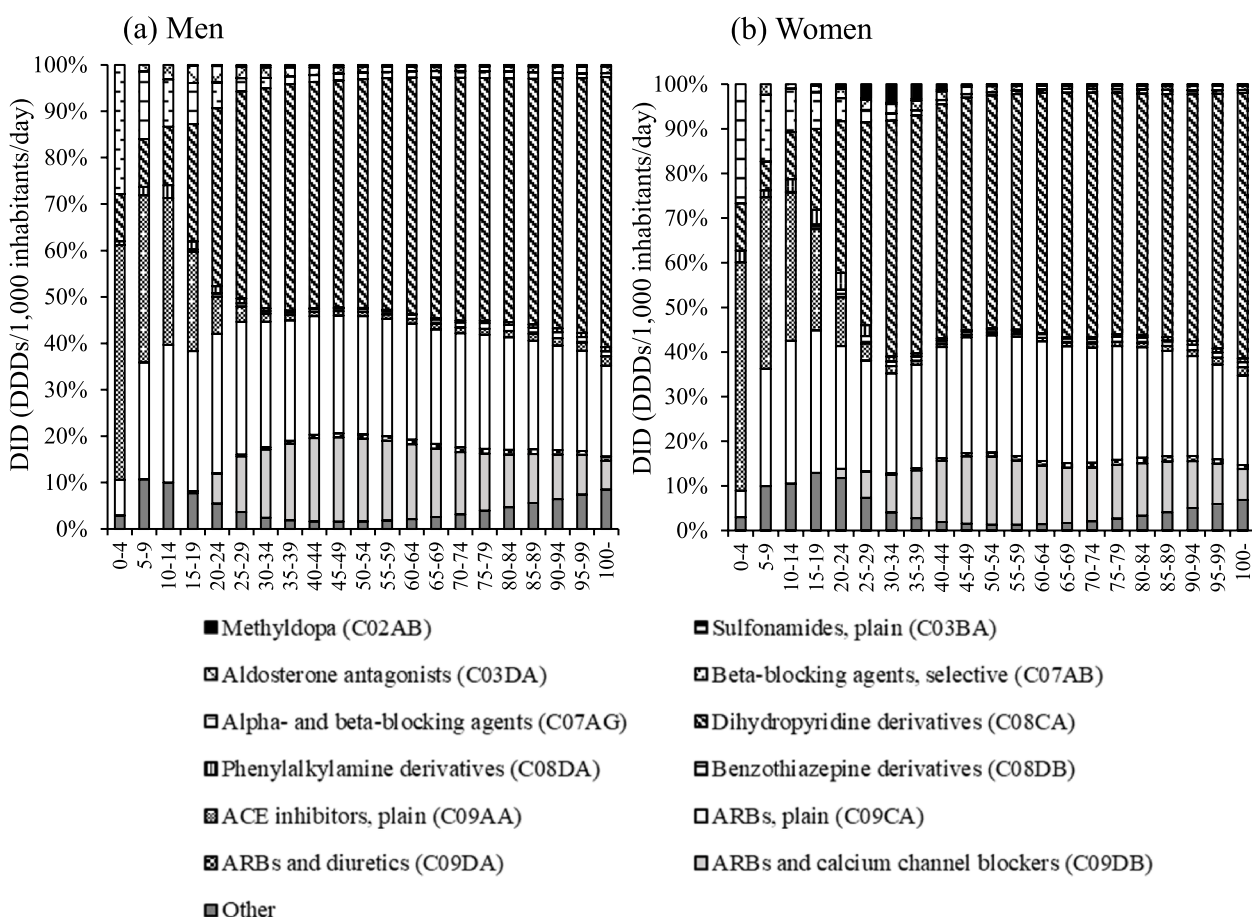


Fig. 2 The proportion of antihypertensive drug use stratified by sex and age class. Other: phosphodiesterase inhibitors (B01AC), organic nitrates (C01DA), other vasodilators used in cardiac diseases (C01DX), and alpha-adrenoreceptor antagonists (C02CA). DDD: Defined daily dose

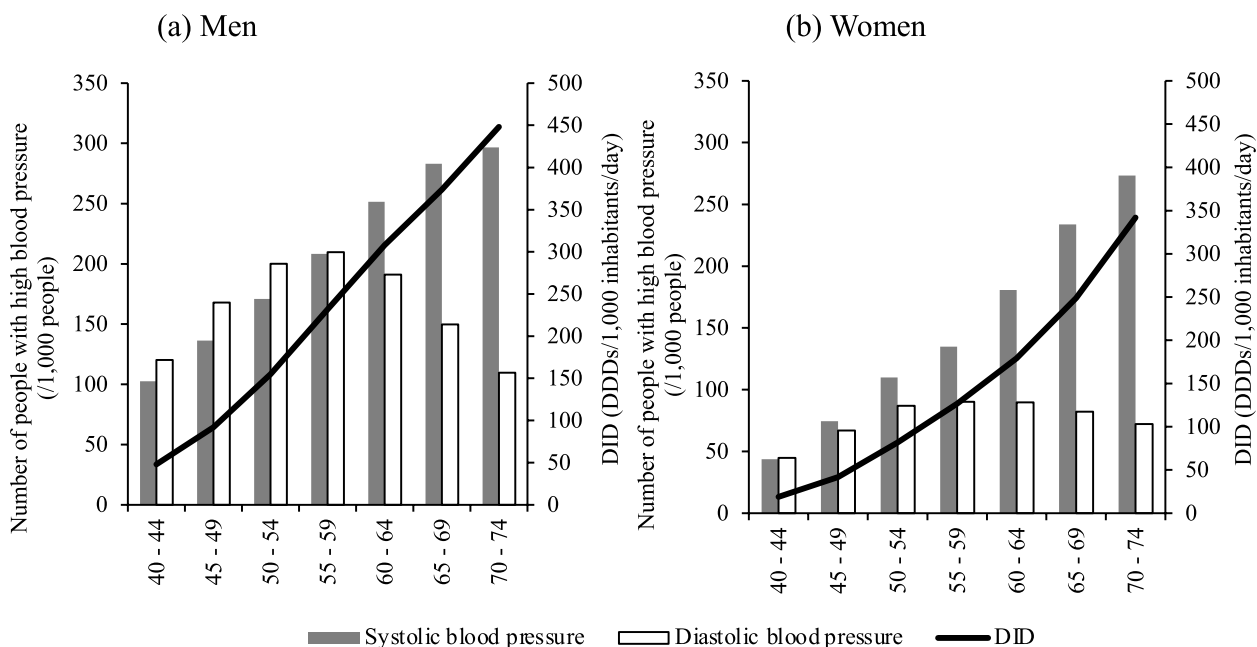


Fig. 3 Relationship between antihypertensive drug use and number of people with high blood pressure. DID: Defined daily dose The x-axis represents age in increments of 5 years

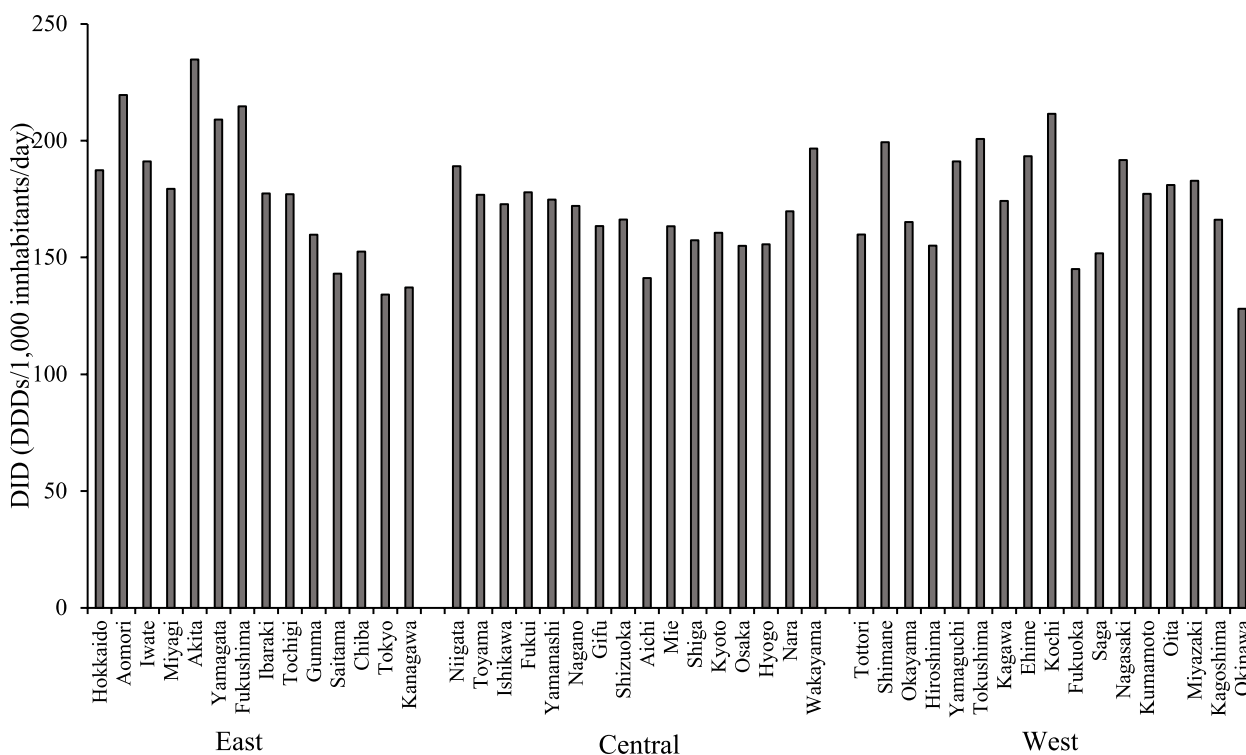


Fig. 4 The trend for antihypertensive drug use stratified by prefecture. DID: Defined daily dose

of ARBs (C09CA, C09DA, and C09DB) ranged from 29.6–41.8%, which was lower than that in men of all ages.

Relationship between the use of antihypertensive drugs and the number of people with high blood pressure

The relationship between DID and the number of people with high blood pressure by sex and age in the 40–74 years age group in FY 2018 is shown in Fig. 3. A very strong positive correlation was found between the number of people with high systolic blood pressure and the DID in both sexes (men: $r=1$, $P<0.05$; women: $r=1$, $P<0.05$). In contrast, there was no significant correlation between the number of people with high diastolic blood pressure and DID in either sex (men: $r=-0.214$, $P>0.05$; women: $r=0.393$, $P>0.05$).

Antihypertensive drug use by prefecture in FY 2018

Figure 4 shows the DID for antihypertensive drugs in each prefecture in FY 2018. The prefecture with the highest DID was Akita (234.7) and that with the lowest DID was Okinawa (128.1). There was a large difference in the DID for each prefecture. The median (range) DID was 178.4 (134.1–234.7), 168.0 (141.2–196.6), and 177.3 (128.1–211.5) in the east, central, and west regions, respectively. No significant differences were found among the regions in terms of DID ($P>0.05$).

Discussion

In this study, the use of antihypertensive drugs in Japan, based on the NDB Open Data, was clarified for the first time using DID. Furthermore, there was a very strong positive correlation between the number of people with high systolic blood pressure and the DID among men and women aged 40–74 years. In addition, this study revealed, for the first time, the use of antihypertensive drugs in each prefecture of Japan. The methodology used in this study may be useful for the continued assessment of antihypertensive drug use and changes in the number of people with high systolic blood pressure based on the changes in antihypertensive drug use.

Antihypertensive drug use increased with age in both men and women (Fig. 1). This is thought to be partly because hypertension is more likely to develop with age owing to a decrease in vascular elasticity and baroreceptor reflex impairment [2]. Furthermore, a very strong positive correlation was found between the number of people with high systolic blood pressure and DID in both men and women aged 40–74 years (Fig. 3). In contrast, there was no significant correlation between the number of people with high diastolic blood pressure and DID (Fig. 3). It has been reported that progression of atherosclerosis leads to an increase in systolic blood pressure

and a decrease in diastolic blood pressure, with the prevalence of isolated systolic blood pressure increasing and that of isolated diastolic hypertension decreasing with advancing age [2, 20]. Therefore, it is possible that the progression of arteriosclerosis associated with advanced age may be a contributing factor. In addition, the use of antihypertensive drugs was higher among men in the age group of 5–84 years and among women in the age group of 85 years and higher (Fig. 1). In the 30–79 years age group hypertension prevalence in men has been reported to be higher than that in women [21]. In addition, women have a longer average life expectancy [22], which may have contributed to this result.

In both men and women, DHP derivative Ca blockers (C08CA and C09DB) and ARBs (C09CA, C09DA, and C09DB) were the main drugs used from the age of 20 years (Fig. 2). These results are similar to those of a previous study using Diagnostic Procedure Combination (DPC) data [23]. Although the DPC data can only capture the use of drugs in some hospitals, the use of NDB Open Data has made it possible to capture the use of drugs nationwide. Guidelines for the management of hypertension in Japan [2] include Ca channel blockers, ARBs, ACE inhibitors, and diuretics as first-line drugs for hypertension management. Among these, DHP derivatives and Ca channel blockers have been reported to have strong hypotensive actions and have been indicated for many patients in Japan [2]. In addition, ARBs have organ-protective effects [24, 25], and the low frequency of adverse effects and high tolerability [26] associated with them are thought to contribute to their widespread use. However, the use of antihypertensive drugs varies across countries [5]. ACE inhibitors are mainly used in foreign countries [27, 28] but not so much in Japan. Dry cough, a side effect of ACE inhibitors, has been shown to develop more frequently in East Asians than in Caucasians [29]. Therefore, the use of ACE inhibitors is considered low in Japan.

Both men and women aged 0–19 years had higher rates of the use of ACE inhibitors, plain (C09AA), alpha- and beta-blocking agents (C07AG), and other drugs than those in their 20s and older (Fig. 2). Enalapril accounted for more than 90.9% of the use of ACE inhibitors plain (C09AA) in both sexes in the age group of 0–19 years (Fig. 2). Enalapril can be administered as early as 1 month of age. Therefore, enalapril is likely used more frequently than other antihypertensive drugs. Furthermore, carvedilol was the only alpha- and beta-blocking agent (C07AG) used in the age group of 0–19 years. In addition to hypertension, carvedilol is indicated for rapid atrial fibrillation, angina pectoris, and chronic heart failure due to ischemic heart disease or dilated cardiomyopathy. Because this study used ATC codes to classify antihypertensive drugs, it was not possible to evaluate the intended

use of antihypertensive drugs with multiple indications, such as carvedilol. In the future, it will be necessary to establish a system for evaluating drug use.

A higher percentage of women in their 20s–40s used methyldopa (C02AB) than their men's counterparts (Fig. 2). Methyldopa is used more frequently in Japan because it is considered one of the first choices for the treatment of gestational hypertension in the Japanese guidelines for the management of hypertension [2]. In addition, ARBs are contraindicated in pregnant women [2] because of fetal and neonatal deaths and malformations that occur in patients who receive ARBs in the second and third trimesters of pregnancy [30, 31]. In this study, the rate of ARB (C09CA, C09DA, and C09DB) use was lower among women in their 20s–40s than in their men's counterparts (Fig. 2).

In this study, a large difference was observed in the use of antihypertensive drugs in each prefecture (Fig. 4), which was determined for the first time. In 2018, the Japanese Society of Hypertension set the goal of reducing the number of patients with hypertension by 7 million over 10 years and extending healthy life expectancy [32]. Previous reports have shown that the trend in drug use in more narrow regions such as municipalities differs from the national and prefectural usage trends [33]. Therefore, it is necessary to understand the trends in antihypertensive drug use in each region and implement appropriate countermeasures [33]. The methodology used in this study can be used to assess changes in the number of people with high systolic blood pressure based on the changes in antihypertensive drug use in a specific region. Therefore, targeted management is considered useful to reduce the number of patients with hypertension.

This study had several limitations. First, information on diagnoses was not available, and drugs prescribed for conditions other than hypertension may have been included in the study. Second, because NDB Open Data were used, factors not included in the data, such as public assistance, could not be considered. In addition, fewer than 1000 prescriptions were anonymized, which may have led to an underestimation of the use of antihypertensive drugs in Japan. Third, the number of people with high blood pressure calculated in this study was based on the results of the specific health checkups and may differ from the actual number of people with high blood pressure. Despite these limitations, this study is useful in understanding the use of antihypertensive drugs in Japan.

Conclusion

In this study, the use of antihypertensive drugs in Japan was clarified for the first time according to sex, age, and prefecture based on the ATC classification. In addition,

our findings suggest that the DID of antihypertensive drugs can be used as an alternative indicator of the number of people with high systolic blood pressure. In the future, the use of antihypertensive drugs in each prefecture will be evaluated over time, making it possible to easily assess the efforts undertaken to reduce the number of people with high blood pressure in each region.

Abbreviations

ACE	Angiotensin-converting enzyme
ARB	Angiotensin II receptor blocker
ATC	Anatomical Therapeutic Chemical
Ca	Calcium
DDD	Defined daily dose
DHP	Dihydropyridine
DID	DDDs/1000 inhabitants/day
DPC	Diagnostic Procedure Combination
MHLW	Ministry of Health, Labour and Welfare
NDB	National Database of Health Insurance Claims and Specific Health Checkups of Japan
NHI	National Health Insurance
OECD	Organization for Economic Co-operation and Development
WHO	World Health Organization

Acknowledgments

We would like to thank Editage (www.editage.jp) for English language editing.

Authors' contributions

K.M. and Y.Y. were responsible for the study design, methodological considerations, and data analysis. K.M. wrote the manuscript. R.I. was responsible for the study design, methodological considerations, and manuscript editing. Y.M. was responsible for the study design, methodological considerations, manuscript editing, and overall supervision. All authors contributed to and approved the final version of the manuscript.

Funding

No funding was received for this study.

Availability of data and materials

The NDB Open Data used in this study are publicly available and can be obtained from the following URL: <https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000177182.html>.

Declarations

Ethics approval and consent to participate

This study was conducted in strict compliance with the "Ethical Guidelines for Medical Research Involving Human Subjects" and was approved by the Ethics Committee of Kyoto Pharmaceutical University (approval number: E21–011).

Consent for publication

Not applicable.

Competing interests

Yuichi Muraki is the editor of the *Journal of Pharmaceutical Health Care and Sciences*. The other authors declare that they have no competing interests.

Author details

¹Laboratory of Clinical Pharmacoepidemiology, Kyoto Pharmaceutical University, 5, Misasagi-Nakauchicho, Yamashina-ku, Kyoto-shi, Kyoto 607-8414, Japan.

Received: 28 August 2023 Accepted: 9 November 2023

Published online: 09 December 2023

References

- World Health Organization. More than 700 million people with untreated hypertension. 2021. <https://www.who.int/news/item/25-08-2021-more-than-700-million-people-with-untreated-hypertension>. Accessed 4 Feb 2022.
- Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, et al. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2019). *Hypertens Res*. 2019;42:1235–481. <https://doi.org/10.1038/s41440-019-0284-9>.
- Ministry of Health, Labour and Welfare. Summary of Vital Statistics Monthly Report Annual Total (approximate number). 2020. <https://www.mhlw.go.jp/toukei/saikin/hw/jinkou/geppo/nengai20/dl/gaikyouR2.pdf>. Accessed 4 Feb 2022.
- Introduction to DDD Indicators. <https://www.who.int/tools/atc-ddd-toolkit/indicators>. Accessed 31 Oct 2023.
- Organisation for economic cooperation and development, OECD. Stat. <https://stats.oecd.org/#>. Accessed 4 Jun 2022.
- WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. 2023. https://www.whocc.no/filearchive/publications/2023_guidelines_web.pdf. Accessed 4 Apr 2023.
- Yamasaki D, Tanabe M, Muraki Y, Kato G, Ohmagari N, Yagi T. The first report of Japanese antimicrobial use measured by national database based on health insurance claims data (2011–2013): comparison with sales data, and trend analysis stratified by antimicrobial category and age group. *Infection*. 2018;46:207–14. <https://doi.org/10.1007/s15010-017-1097-x>.
- Muraki Y, Yagi T, Tsuji Y, Nishimura N, Tanabe M, Niwa T, et al. Japanese antimicrobial consumption surveillance: first report on oral and parenteral antimicrobial consumption in Japan (2009–2013). *J Glob Antimicrob Resist*. 2016;7:19–23. <https://doi.org/10.1016/j.jgar.2016.07.002>.
- Ministry of Health, Labor and Welfare. The 6th NDB Open Data commentary. <https://www.mhlw.go.jp/content/12400000/000821378.pdf>. Accessed 4 Jun 2022.
- Ministry of Health, Labour and Welfare. The 5th NDB Open Data. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000177221_00008.html. Accessed 4 Jun 2022.
- Ministry of Health, Labour and Welfare. The 6th NDB Open Data. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000177221_00010.html. Accessed 4 Jun 2022.
- Ministry of Health, Labor and Welfare. The 5th NDB Open Data commentary. <https://www.mhlw.go.jp/content/12400000/000539646.pdf>. Accessed 4 Jun 2022.
- Ministry of Health, Labour and Welfare. About medicines covered by medical insurance. <https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000078916.html>. Accessed 4 Jun 2022.
- 2017 Patient Survey Summary of Results <https://www.mhlw.go.jp/toukei/saikin/hw/kanja/17/dl/01.pdf>. Accessed 31 Oct 2022.
- WHO Collaborating Centre for Drug Statics Methodology, Structure and principles. 2022. https://www.whocc.no/atc/structure_and_principles/. Accessed 4 Jun 2022.
- WHO collaborating Centre for Drug Statics Methodology. ATC/DDD index 2023. 2023. https://www.whocc.no/atc_ddd_index. Accessed 19 Apr 2023.
- Statistics Bureau of Japan. Population estimate by gender and age. <https://www.e-stat.go.jp/dbview?sid=0003412315/>. Accessed 4 Jun 2022.
- Statistics Bureau of Japan. Population estimate by prefecture. <https://www.e-stat.go.jp/dbview?sid=0003312316/>. Accessed 4 Jun 2022.
- Kanda Y. Investigation of the freely available easy-to-use software “EZR” for medical statistics. *Bone Marrow Transplant*. 2013;48:452–8. <https://doi.org/10.1038/bmt.2012.244>.
- Kim NR, Kim HC. Prevalence and trends of isolated systolic hypertension among Korean adults: the Korea national health and nutrition examination survey, 1998–2012. *Korean Circ J*. 2015;45:492–9. <https://doi.org/10.4070/kcj.2015.45.6.492>.
- Hisamatsu T, Segawa H, Kadota A, Ohkubo T, Arima H, Miura K. Epidemiology of hypertension in Japan: beyond the new 2019 Japanese guidelines. *Hypertens Res*. 2020;43:1344–51. <https://doi.org/10.1038/s41440-020-0508-z>.
- Ministry of Health, Labour and Welfare. Life expectancy at major ages. <https://www.mhlw.go.jp/toukei/saikin/hw/life/life10/01.html>. Accessed 4 Jun 2022.
- Ishida T, Oh A, Hiroi S, Shimasaki Y, Tsuchihashi T. Current prescription status of antihypertensive drugs in Japanese patients with hypertension: analysis by type of comorbidities. *Clin Exp Hypertens*. 2019;41:203–10. <https://doi.org/10.1080/10641963.2018.1465074>.
- Iino Y, Hayashi M, Kawamura T, Shiigai T, Tomino Y, Yamada K, et al. Interim evidence of the renoprotective effect of the angiotensin II receptor antagonist losartan versus the calcium channel blocker amlodipine in patients with chronic kidney disease and hypertension: a report of the Japanese losartan therapy intended for global renal protection in hypertensive patients (JLIGHT) study. *Clin Exp Nephrol*. 2003;7:221–30. <https://doi.org/10.1007/s10157-003-0241-3>.
- Iino Y, Hayashi M, Kawamura T, Shiigai T, Tomino Y, Yamada K, et al. Renoprotective effect of losartan in comparison to amlodipine in patients with chronic kidney disease and hypertension—a report of the Japanese losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) study. *Hypertens Res*. 2004;27:21–30. <https://doi.org/10.1291/hyres.27.21>.
- Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ*. 2003;326:1427. <https://doi.org/10.1136/bmj.326.7404.1427>.
- Rouette J, McDonald EG, Schuster T, Brophy JM, Azoulay L. Treatment and prescribing trends of antihypertensive drugs in 2.7 million UK primary care patients over 31 years: a population-based cohort study. *BMJ Open*. 2022;12:e057510. <https://doi.org/10.1136/bmjopen-2021-057510>.
- Qvarnström M, Kahan T, Kieler H, Brandt L, Hasselström J, Boström KB, et al. Persistence to antihypertensive drug classes: a cohort study using the Swedish primary care cardiovascular database (SPCCD). *Med (Baltim)*. 2016;95:e4908. <https://doi.org/10.1097/MD.0000000000004908>.
- McDowell SE, Coleman JJ, Ferner RE. Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. *BMJ*. 2006;332:1177–81. <https://doi.org/10.1136/bmj.38803.528113.55>.
- Saji H, Yamanaka M, Hagiwara A, Ijiri R. Losartan and fetal toxic effects. *Lancet*. 2001;357:363. [https://doi.org/10.1016/S0140-6736\(00\)03648-5](https://doi.org/10.1016/S0140-6736(00)03648-5).
- Kato K, Okuda M, Ishikawa H, Takahashi T, Hirahara F. Oligohydramnios and pulmonary hypoplasia: a case in which involvement of an angiotensin II receptor antagonist was suspected. *J Obstet Gynaecol Res*. 2008;34:242–6. <https://doi.org/10.1111/j.1447-0756.2008.00762.x>.
- The Japanese Society of Hypertension. Future healthcare plan. <https://www.jpnh.jp/future-plan.html>. Accessed 4 Jun 2022.
- Mizuno K, Inose R, Matsui Y, Takata M, Yamasaki D, Kusama Y, et al. Search for indexes to evaluate trends in antibiotic use in the sub-prefectural regions using the national database of health insurance claims and specific health checkups of Japan. *Antibiotics (Basel)*. 2022;11:763. <https://doi.org/10.3390/antibiotics11060763>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

