Global Health & Medicine. 2023; 5(5):294-300.
BRIEF REPORT
DOI: 10.35772/ghm.2023.01059

An age-stratified cross-sectional study of antidiabetic and non-antidiabetic drugs prescribed to Japanese outpatients with diabetes

Rena Kuribayashi[1], Shiori Hasebe[1], Daisuke Ishida[1,2], Shinichi Hirose[1,2], Seisuke Mimori[3], Tsuyoshi Takizawa[4], Yuki Yamasaki[5], Satoko Suzuki[1], Tetsuto Kanzaki[1,*]

[1] Department of Drug Informatics, Graduate School and Faculty of Pharmaceutical Sciences, Chiba University, Chiba, Japan;
[2] MatsukiyoCocokara & Co., Matsudo, Chiba, Japan;
[3] Department of Clinical Medicine, Faculty of Pharmacy, Chiba Institute of Science, Choshi, Chiba, Japan;
[4] Department of Biostatistics, Faculty of Pharmacy, Chiba Institute of Science, Choshi, Chiba, Japan;
[5] Division of Food, National Institute of Health Sciences, Kawasaki, Kanagawa, Japan.

Abstract: Polypharmacy, common in patients with diabetes, may cause adverse drug reactions. The number of antidiabetic and non-antidiabetic drugs prescribed to patients in different age groups remains unclear. The aim of this study was to examine the number and class of antidiabetics and non-antidiabetics prescribed to Japanese patients with diabetes, stratified by age for reducing polypharmacy. This cross-sectional study examined all prescriptions of patients prescribed antidiabetics at 257 pharmacies of Matsumotokiyoshi Holdings in Japan from May 2018 to March 2019. Total prescription numbers including antidiabetic drugs were 263,915 in this study. Mean numbers of antidiabetic drugs per prescription were 1.71, 2.17, and 1.52 in the patient age groups of 10–19, 50–59, and 90–99 years, respectively. Count of antidiabetics was not related to age. However, the mean total number of drugs prescribed increased with age, which was 2.22 and 7.99 in the age groups of 10–19 and 90–99 years, respectively. The linear regression coefficient (b) according to age was 0.07 ($p < 0.001$) for 10–99 years. The mean non-antidiabetic number of agents prescribed increased with age among 10–99 years (b = 0.07, $p < 0.001$). Among outpatients treated for diabetes, dipeptidyl peptidase-4 inhibitors (29%) and antihypertensive, β-blocking and renin-angiotensin system blocking drugs (32%) were the most prescribed antidiabetics and non-antidiabetics in all ages, respectively. The number of prescribed antidiabetic agents did not increase with age, whereas the total and non-antidiabetic numbers of medications prescribed increased linearly. For reduction of polypharmacy in older people with diabetes, we need to focus on non-antidiabetics.

***Keywords*:** polypharmacy, diabetes, age-stratified, antidiabetic agents, non-antidiabetic drugs, prescriptions

Introduction

The rate of multimorbidity, whereby patients are affected by multiple chronic illnesses, is increasing in ageing populations (*1*). Older adults with multimorbidity often receive multiple prescriptions. Polypharmacy is defined as the concurrent use of multiple drugs (*2,3*). Polypharmacy enhances clinical benefits while minimising risks, providing treatments that are well-managed (*4*), however, it may increase the risk of adverse drug reactions (ADRs) (*5,6*). Indeed, a growing body of evidence suggests that polypharmacy increases a range of risks, including those of ADRs (*7-9*). Kojima *et al*. reported that outpatients taking five or more drugs are at an increased risk of falling; moreover, inpatients aged ≥ 65 years taking six or more drugs are at an increased risk of ADRs (*10,11*).

Masnoon *et al.* (*12*) reported that in 80.4% of definitions, polypharmacy is defined by the numerical values of daily medications, whereas 10.9% of definitions also consider treatment duration and setting. Although a definitive definition of polypharmacy remains to be established, it commonly refers to the routine use of five or more drugs (*3,12*).

Diabetes is associated with an increased risk of microangiopathy, atherosclerotic diseases, dyslipidaemia, hypertension, and obesity, among others. Patients with diabetes tend to have higher incidence rates of polypharmacy (*8*) than non-diabetics, even when antihyperglycemic drugs are excluded (*2*). Older patients with diabetes are more likely than their younger counterparts to receive polypharmacy (*13-15*). The overall number of drugs prescribed tends to be higher for older patients with diabetes than for their younger counterparts. However, the number and class of antidiabetic and non-antidiabetic drugs prescribed to each age group remain unclear. Understanding the types and counts of drugs that are concurrently prescribed to

patients with diabetes may help reduce inappropriate polypharmacy.

The aim of this study was to examine the number and class of antidiabetic and non-antidiabetic agents prescribed to patients aged 10–99 years, stratified by age (10-year age range) for decreasing polypharmacy. The study used a database of prescriptions handled by dispensing pharmacies of Matsumotokiyoshi Holdings for 1 year.

Materials and Methods

Study design and data source

This cross-sectional observational study was performed using the database of prescriptions dispensed to patients at 257 pharmacies of Matsumotokiyoshi Holdings from 1 April 2018 to 31 March 2019. These pharmacies were mainly located in Honshu where 81% of Japan's population lives. Employees from the participating pharmacy anonymised the prescriptions, and subsequently extracted prescription data, including information on patient age, sex, and medication type and count. Data extraction was approved by the operating officer of Matsumotokiyoshi Holdings. The total prescription count was 3,780,193, of which 263,915 included antidiabetic agents.

The study protocol was approved by the Ethics Committee of Chiba University (No. 206), and it adhered to the tenets of the Declaration of Helsinki. Informed consent was not required because the data were anonymised.

Polypharmacy

We defined polypharmacy as a prescription of five or more drugs with no consideration of treatment duration. Only prescription drugs were included; over-the-counter drugs, complementary medicines, and supplements were excluded.

Data collection

Prescriptions of patients who had been prescribed at least one antidiabetic drug were stratified by age (10-year age range). Drug class and count were assessed per age group. We counted numbers of prescribed drugs per prescription without consideration of dosage and directions of medicine. In other words, if there were 2 tablets of metformin (250 mg) 3 times a day in a prescription, the prescribed drug was counted as one. Antidiabetic agents were classified as dipeptidyl peptidase-4 inhibitors (DDP-4i), biguanides, insulins, sulfonylureas, sodium glucose cotransporter-2 inhibitors (SGLT-2i), α-glucosidase inhibitors (αGI), thiazolidine derivatives (TZD), glinides, glucagon-like peptide-1 (GLP-1) receptor agonists, and combination drugs. The Anatomical Therapeutic Chemical Classification System (ATC) classification (*16*) of these agents is shown in Supplemental Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=70*). "Combination drugs" were defined as those that included two different drug classes from this list.

Non-antidiabetic agents were classified as antihypertensive, β-blocking and renin-angiotensin (RA) system blocking, lipid-modifying, alimentary tract, antithrombotic, psychotropic drugs, and others. ATC codes of antihypertensive, β-blocking and RA system blocking agents were C02, C03, C07, C08, C09, and G04CA03, which were mainly used for hypertension and chronic heart failure in Japan. Lipid-modifying drugs were included in ATC group C10, except for C10BX03. Alimentary tract medications were included in ATC group A, except for A10A and A10B. Antithrombotic agents were included in ATC groups B01A and C10AX06. Psychotropic drugs were coded N05, N06, and C02AC02 (Supplemental Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=70*). "Others" drugs included all other ATC codes in non-antidiabetic agents. Twelve agents without ATC codes were classified based on drug efficacy (Supplemental Table S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=70*).

Outcome

The outcomes of interest were the class and count of drugs prescribed to patients with diabetes included in the pharmacy database, stratified by age (10-year age range).

Statistical analysis

The prevalence of polypharmacy and drug class and count were compared among age groups (10-year age ranges) in the complete dataset. The count of drugs per prescription was described as mean ± standard deviation in each age range. We also expressed the count of antidiabetic or non-antidiabetic drugs prescribed as the mean number and the proportion compared to the total number of agents in each age range. The linear regression of mean number of drugs prescribed by age was analysed. The independent variable was midpoint of age range and the dependent variable was mean number of drugs calculated for each class. The slope of the regression line (b) was estimated and the *p* value was calculated in testing of the null hypothesis that the population linear coefficient was zero. The *p* value was significant below 0.05. Sex stratification was omitted owing to insignificant differences between prescriptions for males and females. The number of prescriptions in the age groups of 0–9 years and 100–109 years was 179 and 36, respectively, with the overall prescription rate below 0.1%; therefore, we excluded these data from the

study. Statistical Analysis System (SAS) software version 9.4 was used for the statistical analysis.

Results and Discussion

Prevalence of polypharmacy

The total number of prescriptions for patients taking at least one antidiabetic drug increased with age from 0–79 years and then decreased in patients of ≥ 80 years. The highest number of prescriptions was 73,431 in the age group of 70–79 years (Table 1). The overall rate of polypharmacy was 57.5%, of which 45.3% was 5-9 drugs and 12.2% was ≥ 10 drugs, and it increased with age. Older patients were more likely than younger patients to receive 10 or more drugs (Table 1).

The rate of polypharmacy in patients with diabetes had a strong relationship with age (Table 1); this is consistent with the results of previous studies (*7,13,15*). The class and count of drugs prescribed remain unclear and should be examined in age-stratified analysis to support policies aimed at reducing instances of inappropriate polypharmacy.

Mean drug count of prescriptions including antidiabetic agents

The overall mean counts of drugs per prescription were 2.22 and 7.99 in individuals aged 10–19 and 90–99, respectively (Table 2). The number of drugs prescribed linearly increased with patients' age between 10–99 years (Figure 1). The linear regression coefficient (b) was 0.07 ($p < 0.001$). The mean count of non-antidiabetic agents prescribed also increased with patient age from 10–99 years (b = 0.07, $p < 0.001$) (Table 2). However, the relationship of antidiabetic drugs with age differed. Comparing patients aged 10–19, 50–59 and 90-99 years, the mean count of antidiabetic prescriptions was 1.71, 2.17 and 1.52, respectively, and the prescription count did not increase linearly with age (b = -0.002, p = 0.489). The maximum mean count of antidiabetic agents was observed in the 50–59-year-old patients (2.17), decreasing to patients aged 90–99 years (Table 2).

A multicenter cross-sectional survey in Italy (METABOLIC Study) showed that 49.6% of diabetic patients were treated with only one oral antidiabetic drug and 12.5% were treated with three or more, indicating

Table 1. Age-stratified prevalence of polypharmacy on prescriptions including antidiabetic agents

Age (years)	Numbers of all drugs prescribed				*n*
	1–4	≥ 5	5-9	≥ 10	
All ages	42.5(%)	57.5 (%)	45.3 (%)	12.2 (%)	263,915
10–19	92.0	8.0	7.9	0.1	736
20–29	86.0	14.0	12.3	1.6	1,980
30–39	74.6	25.4	21.7	3.7	8,430
40–49	58.1	41.9	36.0	5.9	26,442
50–59	49.2	50.8	42.4	8.4	44,385
60–69	41.5	58.5	47.5	11.1	72,268
70–79	29.5	70.5	51.9	18.6	73,431
80–89	20.0	80.0	55.3	24.7	33,324
90–99	17.9	82.1	49.5	32.6	2,704

Numbers show the proportion of prescriptions in each age range/total number of prescriptions in corresponding age range. *n* indicates the total number of prescriptions including antidiabetic agents.

Table 2. Mean drug count of prescriptions including antidiabetic agents by age

Age (years)	Count of antidiabetics prescribed	Count of non-antidiabetics prescribed	Overall count of drugs prescribed	*n*
All ages	1.99 ± 1.05	3.67 ± 3.18	5.60 ± 3.25	263,915
10–19	1.71 ± 0.81	0.60 ± 1.19	2.22 ± 1.33	736
20–29	1.88 ± 0.96	0.82 ± 1.37	2.73 ± 2.01	1,980
30–39	1.96 ± 1.03	1.62 ± 2.52	3.51 ± 2.76	8,430
40–49	2.13 ± 1.14	2.31 ± 2.56	4.51 ± 2.84	26,442
50–59	2.17 ± 1.14	2.96 ± 2.87	5.12 ± 3.04	44,385
60–69	2.07 ± 1.10	3.40 ± 2.93	5.44 ± 3.05	72,268
70–79	1.92 ± 0.99	4.10 ± 3.16	6.07 ± 3.27	73,431
80–89	1.77 ± 0.89	5.23 ± 3.40	7.02 ± 3.40	33,324
90–99	1.52 ± 0.76	6.46 ± 3.50	7.99 ± 3.62	2,704
Linear regression coefficients				
b	-0.002	0.07	0.07	
p	0.489	< 0.001	< 0.001	

Count of drugs per prescription is shown as means ± standard deviation in each age range. Overall count of drugs prescribed indicates the number of all drugs including antidiabetic and non-antidiabetic ones per prescription. *n* indicates the total number of prescriptions including antidiabetic agents. Linear regression coefficient (b) is calculated between the mean number of drugs and midpoint of age range.

that the mean count of antidiabetics was approximately 1.7 per person over 65 years old (*14*). There was another report about antidiabetic drug prescription from National Center Diabetes Database in Japan. It stated that only one antidiabetic agent was prescribed in about 30% of diabetic patients, two antidiabetics were used in about 30% of patients, and three or more antidiabetics were used in about 40% below the 65 years age group, suggesting that the mean number of antidiabetics prescribed was about 2.2 per person in this report (*17*). Mean drug count of antidiabetics per prescription was 1.99 in all ages of our study, which is almost consistent with the data of these papers.

The reasons for the different patterns observed between antidiabetic and overall drug use in association with age remains unclear. Combination drugs are not the reason because its use did not increase with age among patients aged 50–99 years (Table 3). However, international guidelines on diabetes management recommend different haemoglobin A1c (HbA1c) values, depending on patient age (*18-20*). Blood glucose and HbA1c levels may differ depending on disease management and complications in older patients with diabetes. Strict blood glucose control may not reduce the risk of cardiovascular disease-related death in older adults with diabetes (*21*), consequently, the recommended HbA1c levels of patients with complications are higher in older patients than in younger counterparts. Furthermore, the prevalence of diabetes increases rapidly in people over 50 years old age. Blood glucose levels in aged patients newly diagnosed might not be higher than those in younger patients. These things might be related to the discrepancies in the associations of the antidiabetics and overall prescription drugs with age.

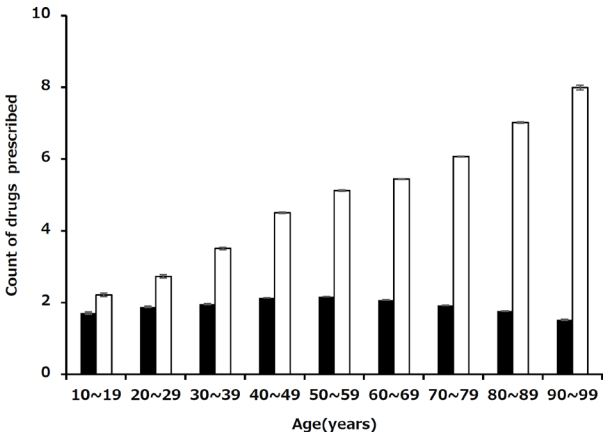

Figure 1. Mean drug count of antidiabetic and overall prescription drugs by age. The number of prescribed drugs is expressed as mean ± standard error. Mean drug count of antidiabetics is shown as closed column, and that of overall agents prescribed is as open column.

Classification and count of antidiabetic prescriptions

Table 3 shows the age-stratified proportions of antidiabetic agent use. In all age groups, DDP-4i (29.2%) was the most used agent, followed by biguanides (16.8%), insulins (12.5%), sulfonylureas (10.8%), SGLT-2i (9.0%), and αGI (7.3%). Insulin prescription rates were 69.9% and 39.2% in the 10–19 and 20–29 years age groups, respectively, which were most frequently prescribed in these age groups. The rates of biguanide use were 25.3% and 21.4%, highest among prescribed drugs in the age groups of 30–39 and 40–49 years, respectively. The DDP-4i prescription rates were 5.5% and 51.8% in the 10–19 and 90–99 years age groups, respectively. This was the most prescribed drug in patients aged 50–99 years. TZD, glinides, and GLP-1 receptor agonists accounted for < 5% of antidiabetic drugs. Combination drugs were used at 8.1% in the 50–59 years age group,

Table 3. Classification and proportion of count of antidiabetic and non-antidiabetic drugs in prescriptions by age

Age (years)	All ages	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99
Antidiabetics										
DPP-4i (%)	29.2	5.5	9.7	14.4	19.9	23.5	28.6	34.6	41.0	51.8
Biguanides (%)	16.8	12.2	23.2	25.3	21.4	20.0	18.5	13.5	9.0	5.1
Insulins (%)	12.5	69.9	39.2	24.7	15.2	11.9	11.3	11.3	10.2	7.8
Sulfonylureas (%)	10.8	0.5	2.0	4.3	6.4	9.1	11.0	13.0	14.3	14.1
SGLT-2i (%)	9.0	2.9	12.0	14.2	16.4	13.8	8.9	5.0	2.8	1.9
αGl (%)	7.3	3.9	4.8	4.2	5.0	6.1	7.2	8.6	9.2	9.2
TZD (%)	3.2	1.1	1.5	2.1	3.1	3.0	3.3	3.2	3.7	2.2
Glinides (%)	2.7	0.6	1.5	1.2	1.9	2.2	2.6	3.2	4.0	4.4
GLP-1 receptor agonists (%)	1.8	1.9	2.6	2.9	2.9	2.4	1.5	1.3	1.5	0.9
Combination drugs (%)	6.8	1.5	3.6	6.7	7.8	8.1	7.1	6.3	4.4	2.7
Non-antidiabetics										
Antihypertensive, β-blocking and RA system blocking agents (%)	32.0	5.1	17.1	23.4	31.2	33.9	35.1	32.4	28.8	24.6
Lipid modifying agents (%)	17.1	5.9	19.8	21.7	23.5	22.5	20.3	16.5	10.9	5.7
Alimentary tract agents (%)	16.9	21.6	17.7	13.6	13.7	13.1	14.7	17.3	21.2	22.1
Antithrombotic agents (%)	9.3	0.0	0.1	2.1	4.1	6.6	9.4	10.7	10.6	9.1
Psychotropic agents (%)	6.1	3.4	3.7	7.2	3.8	4.6	4.6	6.7	7.9	8.7
Others (%)	18.7	64.0	41.7	32.0	23.7	19.4	15.9	16.3	20.6	29.8

Numbers show the proportion of each drug number in age range/total number of diabetic or non-antidiabetic agents in the corresponding age range.

which was decreasing in patients aged 90–99 years (2.7%). The count of DDP-4i prescribed increased linearly with patient age from 10–99 years (b = 0.009, $p < 0.001$) (Table 4). Biguanides and SGLT-2i were the most prescribed agents in the age groups of 30–39 and 40–49 years, respectively, compared to other age ranges; older patients were less likely to receive these drugs. Insulin use rates were inversely related to age from 10–99 years (b = -0.011, $p = 0.003$). Sulfonylurea and αGI use positively related to age, yielding linear regression coefficients of 0.003, $p < 0.001$ and 0.002, $p < 0.001$, respectively in both cases (Table 4).

A consensus statement from the Japan Diabetes Society (JDS) is based on the concept of the differences in diabetes pathology and pharmacotherapy between Japan, Asians, and Westerners (*22*). DDP-4i has the lowest ADR risk and effectively reduces HbA1c levels in Asian patients but not in non-Asian populations (*23*). These drug properties may account for the popularity of DDP-4i among older adults with diabetes in Japan. In fact, Bouchi *et al.* (*24*) reported that DDP-4i accounts for > 60% of first prescriptions among patients with diabetes included in the National Database of Health Insurance Claims and Specific Health Check-ups of Japan. The estimates of DPP-4i use in Japanese patients reported by Bouchi *et al.* (*24*) differ from those in this study. This is likely because different target populations were studied. For instance, Bouchi *et al.* (*24*) analysed newly introduced antidiabetic medications only but we analysed total prescribed antidiabetic drugs in this study. Additionally, our calculations included insulin and combination drugs administered through both oral and other routes, whereas Bouchi *et al.* (*24*) restricted the analysis to oral antidiabetics except injectable formulations of GLP-1 receptor agonists.

The decline in biguanide use in individuals aged 30–99 years may be associated with the contraindications of renal insufficiency (estimated glomerular filtration rate of < 30 mL/min), severe heart failure, and severe liver damage (*18*), which increase with age. Insulin is universally prescribed for patients with type 1 diabetes, which has an incidence rate of 2.3/100,000 children in Japan (*25*), this incidence is comparable to patients aged 0–60 years (*26*). The incidence of type 2 diabetes is 3.0/100,000 children (*27*), whereas the number increases rapidly among patients aged ≥ 20 years. Therefore, the ratio of patients with type 1/type 2 diabetes is higher among younger people than among older people in Japan, likely accounting for the high frequency of insulin use among patients aged 10–29 years.

Japanese guidelines on diabetes management in older patients state that insulin and sulfonylurea should be used with caution in cases associated with multiple complications (*18*). Sulfonylureas were prescribed to > 10% of patients aged 60–99 years in our study. Future studies are required to evaluate the safety and efficacy profiles of this approach. SGLT-2i may reduce the risks of heart failure and chronic kidney disease; herein, the associated prescription rate was 9.0% overall. SGLT-2i has been previously reported as first-line treatment in 7.6% of patients (*24*). This rate will likely increase in Japan in the future.

Classification and count of non-antidiabetic prescriptions

Table 3 shows the age-stratified proportions of non-antidiabetic drugs prescribed. The proportion of antihypertensive, β-blocking and RA system blocking agents was 32.0%, the most prescribed group of non-antidiabetic medications in all age groups. Overall, five

Table 4. Classification and count of antidiabetic and non-antidiabetic drugs in prescriptions by age

Age (years)	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99	b	*p*
Antidiabetics											
DPP-4i	0.10	0.18	0.29	0.43	0.51	0.59	0.66	0.72	0.80	0.009	< 0.001
Biguanides	0.21	0.44	0.50	0.46	0.44	0.38	0.26	0.16	0.08	-0.003	0.102
Insulins	1.22	0.74	0.49	0.33	0.26	0.23	0.22	0.18	0.12	-0.011	0.003
Sulfonylureas	0.01	0.04	0.09	0.14	0.20	0.23	0.25	0.25	0.22	0.003	< 0.001
SGLT-2i	0.05	0.23	0.28	0.36	0.30	0.19	0.10	0.05	0.03	-0.002	0.254
αGl	0.07	0.09	0.08	0.11	0.13	0.15	0.17	0.16	0.14	0.002	< 0.001
TZD	0.02	0.03	0.04	0.07	0.07	0.07	0.06	0.07	0.03	0.000	0.239
Glinides	0.01	0.03	0.02	0.04	0.05	0.05	0.06	0.07	0.07	0.001	< 0.001
GLP-1 receptor agonists	0.03	0.05	0.06	0.06	0.05	0.03	0.03	0.03	0.01	0.000	0.075
Combination drugs	0.03	0.07	0.13	0.17	0.18	0.15	0.12	0.08	0.04	0.000	0.950
Non-antidiabetics											
Antihypertensive, β-blocking and RA system blocking agents	0.03	0.12	0.33	0.62	0.82	0.97	1.06	1.29	1.54	0.019	< 0.001
Lipid modifying agents	0.03	0.15	0.31	0.47	0.55	0.56	0.54	0.49	0.36	0.005	0.036
Alimentary tract agents	0.11	0.13	0.19	0.27	0.32	0.40	0.57	0.95	1.39	0.014	0.001
Antithrombotic agents	0.00	0.00	0.03	0.08	0.16	0.26	0.35	0.48	0.57	0.008	< 0.001
Psychotropic agents	0.02	0.03	0.10	0.08	0.11	0.13	0.22	0.36	0.54	0.006	0.001
Others	0.32	0.30	0.45	0.47	0.47	0.44	0.54	0.93	1.87	0.014	0.019

Numbers present the mean count of each drug per prescription in age range. Linear regression coefficient (b) is calculated between midpoint of age range and the mean count of each drug.

groups which were antihypertensive, β-blocking and RA system blocking, lipid-modifying, alimentary tract, antithrombotic, and psychotropic agents accounted for 81.3% of non-antidiabetic drugs. In patients aged 10–39 and 90–99 years, 'others' in non-antidiabetic medications, excluding these five most prescribed ones, were the most highly prescribed. However, in patients aged 40–89 years, antihypertensive, β-blocking and RA system blocking agents were the most highly prescribed medications. Lipid-modifying drugs were prescribed most commonly in 40–49-year-olds compared to other age ranges.

The counts of these five frequently used drugs except lipid modifying ones increased with patient age (Table 4). The number of antihypertensive, β-blocking and RA system blocking drugs, and antithrombotic drugs showed strong relation to age ($b = 0.019$, $p < 0.001$; and $b = 0.008$, $p < 0.001$, respectively) (Table 4).

The counts of antihypertensive, β-blocking and RA system blocking agents, and antithrombotic agents increase with age, likely owing to the increases in the occurrence of vascular complications associated with diabetes. The proportion of lipid-modifying agent use decreased in patients aged ≥ 40 years. O'Keeffe *et al.* (*28*) reported slight HbA1c level increases and low-density lipoprotein cholesterol (LDL-C) decreases in women aged 53–69 years in the United Kingdom, suggesting that glucose and LDL-C do not respond synergistically. The relationship between HbA1c and LDL-C levels and age should be elucidated. The use of psychotropic medicines, especially benzodiazepines, is known to increase with age (*29*), these findings are consistent with those of this study. The most prescribed drugs in the age group of 10–39 years were in the category "others". The composition of this category remains unclear and should be evaluated.

Our data on the different patterns between antidiabetic and non-antidiabetic drug use with age, suggests that antidiabetic agents are not targets for reduction of polypharmacy in older people with diabetes. As for non-antidiabetic drugs, those excluding lipid-modifying agents increased with patient age. From these results alone, it is hard to determine which class of drugs we need to focus on for reducing inappropriate polypharmacy. Generally, the increase of prescribed drugs is closely related with the potentially inappropriate medication (PIM) (*15*). Large parts of PIM are benzodiazepines in psychotropic drugs and H_2-receptor antagonists in alimentary tract agents seen in a survey in Japan (*30*). Our data demonstrated that the prescription of alimentary tract and psychotropic medications increased with patient age. Therefore, we think that it is important to be careful using benzodiazepines and H_2-receptor antagonists to reduce inappropriate polypharmacy closely related with PIM.

This study had some limitations. First, we only examined patients with diabetes who were taking antidiabetic drugs; thus, rates of polypharmacy in patients with diabetes who were not taking such drugs remain unclear. Second, patient clinical signs and symptoms were not evaluated in this study; therefore, the rates of suitable and unsuitable polypharmacy remain unclear. Third, we could not distinguish between type 1 and type 2 diabetes mellitus. It is important to recognise diabetic types because the treatments and causes of the diseases differ. Fourth, it is possible that a patient visited two or more departments in different hospitals to treat complications and received several prescriptions dispensed from different pharmacies. In these cases, the accurate number of non-antidiabetic drugs would be higher than that determined in our study. Finally, as our study was observational, the true causes of different patterns of antidiabetic and non-antidiabetic drug use associated with age could not be determined.

In conclusion, among Japanese patients with diabetes, the mean overall and non-antidiabetic number of drugs per prescription increased with age. However, the count of antidiabetic drugs did not relate to age and the highest number of these prescriptions was observed in the age group of 50–59 years, suggesting that antidiabetic drugs are not targets for reducing inappropriate polypharmacy in older people with diabetes. We need to aim non-antidiabetic agents with PIM. DDP-4i, and antihypertensive, β-blocking and RA system blocking drugs were the most prescribed antidiabetic and non-antidiabetic agents in the studied patients, respectively.

Acknowledgements

The authors thank Ms. Yuna Nobuoka, Ms. Kanae Kon, Ms. Miyu Sakazume, Ms. Riho Hosoi, and Mr. Kei Aoki for technical help and useful discussions.

Funding: None.

Conflict of Interest: There are no conflicts of interest to disclose except for Ishida D and Hirose S. They are employees of MatsukiyoCocokara & Co. and belong to the Department of Drug Informatics, Graduate School and Faculty of Pharmaceutical Sciences, Chiba University.

References

1. Navickas R, Petric VK, Feigl AB, Seychell M. Multimorbidity: What do we know? What should we do? J Comorb. 2016; 6:4-11.
2. Huang YT, Steptoe A, Wei L, Zaninottob P. Polypharmacy difference between older people with and without diabetes: Evidence from the English longitudinal study of ageing. Diabetes Res Clin Pract. 2021; 176:108842.
3. World Health Organization. Medication safety in polypharmacy: technical report, 2019 *https://www.who.int/publications/i/item/WHO-UHC-SDS-2019.11* (accessed March 18, 2022).
4. Cadogan CA, Ryan C, Francis JJ, Gormley GJ, Passmore

P, Kerse N, Hughes CM. Development of an intervention to improve appropriate polypharmacy in older people in primary care using a theory-based method. BMC Health Serv Res. 2016; 16:661.
5. Arai S, Ishikawa T, Kato H, Koshizaka M, Maezawa Y, Nakamura T, Suzuki T, Yokote K, Ishii I. Multidrug use positively correlates with high-risk prescriptions in the Japanese elderly: A longitudinal study. J Pharm Health Care Sci. 2019; 5:20.
6. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: Population database analysis 1995–2010. BMC Med. 2015; 13:74.
7. Höhn A, Jeyam A, Caparrotta TM, *et al*. The association of polypharmacy and high-risk drug classes with adverse health outcomes in the Scottish population with type 1 diabetes. Diabetologia. 2021; 64:1309-1319.
8. Dobrică EC, Găman MA, Cozma MA, Bratu OG, Stoian AP, Diaconu CC. Polypharmacy in type 2 diabetes mellitus: Insights from an internal medicine department. Medicina (Kaunas). 2019; 55:436.
9. Al-Musawe L, Torre C, Guerreiro JP, Rodrigues AT, Raposo JF, Mota-Filipe H, Martins AP. Polypharmacy, potentially serious clinically relevant drug-drug interactions, and inappropriate medicines in elderly people with type 2 diabetes and their impact on quality of life. Pharmacol Res Perspect. 2020; 8:e00621.
10. Kojima T, Akishita M, Nakamura T, Nomura K, Ogawa S, Iijima K, Eto M, Ouchi Y. Polypharmacy as a risk for fall occurrence in geriatric outpatients. Geriatr Gerontol Int. 2012; 12:425-430.
11. Kojima T, Akishita M, Kameyama Y, Yamaguchi K, Yamamoto H, Eto M, Ouchi Y. High risk of adverse drug reactions in elderly patients taking six or more drugs: Analysis of inpatient database. Geriatr Gerontol Int. 2012; 12:761-762.
12. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017; 17:230.
13. Alwhaibi M, Balkhi B, Alhawassi TM, Alkofide H, Alduhaim N, Alabdulali R, Drweesh H, Sambamoorthi U. Polypharmacy among patients with diabetes: A cross-sectional retrospective study in a tertiary hospital in Saudi Arabia. BMJ Open. 2018; 8:e020852.
14. Noale M, Veronese N, Cavallo Perin P, Pilotto A, Tiengo A, Crepaldi G, Maggi S. Polypharmacy in elderly patients with type 2 diabetes receiving oral antidiabetic treatment. Acta Diabetol. 2016; 53:323-330.
15. Oktora MP, Alfian SD, Bos HJ, Schuiling-Veninga CCM, Taxis K, Hak E, Denig P. Trends in polypharmacy and potentially inappropriate medication (PIM) in older and middle-aged people treated for diabetes. Br J Clin Pharmacol. 2021; 87:2807-2817.
16. World Health Organization. ATC/DDD classification (temporary). WHO Drug Inf. 2019; 33:226-232.
17. Yamamoto-Honda R, Takahashi Y, Mori Y, *et al.* Changes in antidiabetic drug prescription and glycemic control trends in elderly patients with type 2 diabetes mellitus from 2005-2013: An analysis of the National Center Diabetes Database (NCDD-03). Intern Med. 2018; 57:1229-1240.
18. Araki E, Goto A, Kondo T, Noda M, Noto H, Origasa H, Osawa H, Taguchi A, Tanizawa Y, Tobe K, Yoshioka N. Japanese clinical practice guideline for diabetes 2019. J Diabetes Investig. 2020; 11:1020-1076.
19. Leung E, Wongrakpanich S, Munshi MN. Diabetes management in the elderly. Diabetes Spectr. 2018; 31:245-253.
20. LeRoith D, Biessels GJ, Braithwaite SS, Casanueva FF, Draznin B, Halter JB, Hirsch IB, McDonnell ME, Molitch ME, Murad MH, Sinclair AJ. Treatment of diabetes in older adults: An Endocrine Society* clinical practice guideline. J Clin Endocrinol Metab. 2019; 104:1520-1574.
21. Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, Miller ME, *et al.* Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008; 358:2545-2559.
22. Bouchi R, Kondo T, Ohta Y, Goto A, Tanaka D, Satoh H, Yabe D, Nishimura R, Harada N, Kamiya H, Suzuki R, Yamauchi T. A consensus statement from the Japan Diabetes Society (JDS): a proposed algorithm for pharmacotherapy in people with type 2 diabetes. Diabetol Int. 2023; 14:1-14.
23. Seino Y, Kuwata H, Yabe D. Incretin-based drugs for type 2 diabetes: Focus on East Asian perspectives. J Diabetes Investig. 2016; 7(Suppl 1):102-109.
24. Bouchi R, Sugiyama T, Goto A, Imai K, Ihata-Sugiyama N, Ohsugi M, Yamauchi T, Kadowaki T, Ueki K. Retrospective nationwide study on the trends in first-line antidiabetic medication for patients with type 2 diabetes in Japan. J Diabetes Investig. 2022; 13:280-291.
25. Onda Y, Sugihara S, Ogata T, Yokoya S, Yokoyama T, Tajima N. Incidence and prevalence of childhood-onset type 1 diabetes in Japan: The T1D study. Diabet Med. 2017; 34:909-915.
26. Nishioka Y, Noda T, Okada S, Myojin T, Kubo S, Higashino T, Ishii H, Imamura T. Incidence and seasonality of type 1 diabetes: A population- based 3- year cohort study using the National Database in Japan. BMJ Open Diabetes Res Care. 2020; 8:e001262.
27. Tajima N, Morimoto A. Epidemiology of childhood diabetes mellitus in Japan. Pediatr Endocrinol Rev. 2012; 10 (Suppl 1): 44-50.
28. O'Keeffe LM, Kuh D, Fraser A, Howe LD, Lawlor D, Hardy R. Age at period cessation and trajectories of cardiovascular risk factors across mid and later life. Heart. 2020; 106:499-505.
29. Brett J, Pearson SA, Daniels B, Wylie CE, Buckley NA. A cross sectional study of psychotropic medicine use in Australia in 2018: A focus on polypharmacy. Br J Clin Pharmacol. 2021; 87:1369-1377.
30. Fujie K, Kamei R, Araki R, Hashimoto K. Prescription of potentially inappropriate medications in elderly outpatients: A survey using 2015 Japanese Guidelines. Int J Clin Pharm. 2020; 42:579-587.

Received May 16, 2023; Revised August 18, 2023; Accepted August 28, 2023.

Released online in J-STAGE as advance publication September 17, 2023.

Address correspondence to:
Tetsuto Kanzaki, Department of Drug Informatics, Graduate School and Faculty of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8675, Japan.
E-mail: tkanzaki@cis.ac.jp