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ORIGINAL ARTICLE

Prescription of potentially inappropriate medications to elderly hemodialysis patients: prevalence and predictors

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ABSTRACT

Background. In elderly hemodialysis (HD) patients, the risk of medication-related problems is particularly high. Thus, certain medications should generally not be prescribed to those patients. The Beers criteria for potentially inappropriate medications (PIMs) have been publicized. Still, with regard to elderly HD patients, the prevalence and risk factors for prescription of PIMs are unknown.

Methods. This was a cross-sectional study of data from the Japan Dialysis Outcomes and Practice Patterns Study (2002–08). Patients were included if they were 65 years old or older and were currently receiving HD treatment at a hospital or clinic. We counted the number of patients who were prescribed at least one PIM, as defined by the modified Beers criteria. We used multiple logistic regression analysis to determine which patient characteristics and facility characteristics were associated with prescription of PIMs.

Results. Data from 1367 elderly patients were analyzed. More than half of the patients (57%) had been prescribed a PIM. The three most frequently prescribed PIMs were H2 blockers (33%), antiplatelet agents (19%) and α-blockers (13%). PIM prescriptions were less likely at facilities that conducted multidisciplinary rounds {adjusted odds ratio (AOR): 0.67 [95% confidence interval (CI): 0.48–0.93]} and at teaching hospitals [AOR: 0.59 (95% CI, 0.39–0.90)]. PIM prescriptions are more likely if more than one physician has clearance to alter the HD regimen [AOR: 1.65 (95% CI, 1.12–2.44)].

Conclusions. PIMs were prescribed to many elderly HD patients in Japan. Nephrologists should become more aware of PIMs. Multidisciplinary rounds could benefit patients by reducing the prescription of PIMs.

Keywords: adverse drug events, DOPPS, elderly patients, hemodialysis, potentially inappropriate medication

INTRODUCTION

Issues associated with medication administration remain a major healthcare concern, particularly among elderly patients. A 2005

study in the USA found that adverse drug events (ADEs) occurred relatively frequently among ambulatory patients, with 27.6% found to be avoidable [1]. Hemodialysis (HD) patients are considered to be at higher risk for medication-related problems than the general population for several reasons, including impaired drug clearance [2], increased frequency of polypharmacy, increased number of comorbidities and increased proportion of receiving drugs that require therapeutic drug monitoring [3]. However, while the previous studies have revealed that 98% of HD patients had at least one medication-related problem [4], no efficient solutions have yet been proposed.

Identifying drugs carrying high risk of ADEs is one possible strategy for managing medication-related problems. In theory, reducing the likelihood of physicians prescribing such drugs consequently reduces the incidence of medication-related problems and ADEs [5]. These high-risk drugs are called 'potentially inappropriate medication (PIM)' and are defined as 'medication with no clear evidence-based indication, and which carry a substantially higher risk of adverse side effects or are not cost effective' [6]. Several sets of criteria for PIMs have been developed specifically for use with elderly patients, with the Beers criteria most commonly used in previous epidemiological studies [6]. Akazawa *et al.* [7] reported that the frequency of prescribing PIM, as defined using a modified version of the Beers criteria reflecting regional clinical practice and available medications in Japan, was 43.6% among elderly patients in Japan. However, this study population was made up of beneficiaries covered by the employees' health insurance system, which included healthier individuals than may be found in the general elderly population. As such, prescription patterns of PIM for patients with severe disease remain unclear.

Previous reports on the employees' health system have all involved relatively heterogeneous general elderly populations, failing to account for the fact that prescription patterns of PIMs may differ according to patients' comorbidities. A study surveying prescription patterns of these medications of elderly HD patients may, therefore, provide important information on the subject of the difference between healthy elderly patients and elderly patients with severe disease. Here, we attempted to determine the prevalence of and identify risk factors for prescribing PIMs in elderly HD patients.

MATERIALS AND METHOD

Study design and data source

We obtained all data from Phases II (2002–04) and III (2005–08) of the Dialysis Outcome Practice Pattern Study in Japan (J-DOPPS II and J-DOPPS III), which were large cohort studies involving detailed data from adult HD patients at >50 randomly selected dialysis facilities in Japan. The DOPPS originally sought to determine dialysis practices that most contributed to improved mortality and hospitalization rates, health-related quality of life and vascular access outcomes after adjusting for the effects of comorbid disease and other demographic confounding factors. The dialysis facilities included in the DOPPS constitute a nationally representative sample. To ensure variation in practice patterns and outcomes, a stratified random sample of HD facilities was selected. DOPPS's methodology has been detailed previously [8, 9], and all institutional review boards approved its conduct in each facility, as required.

Prescribed drug information and patients' demographic data were surveyed at study enrollment. This study was cross sectional in design to examine the association between PIM and other factors.

Study population

To ensure a representative national sample, two-staged random sampling method was used in the J-DOPPS. After first randomly selecting our 50 HD facilities of focus, we then randomly selected patients at those facilities in each study phase. Inclusion criteria for the present study were an age of 65 years or older and currently receiving chronic HD treatment. Patients receiving transient dialysis were excluded.

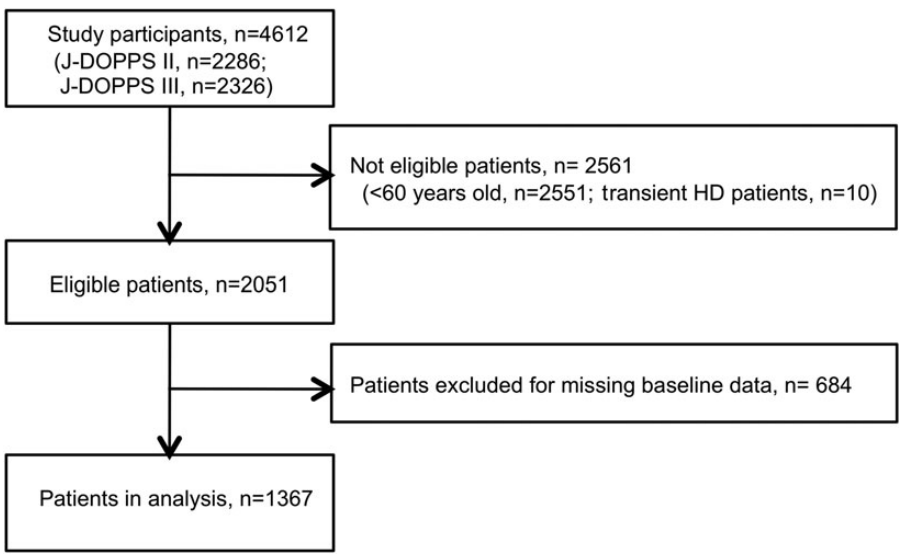

FIGURE 1: Patient flow chart. HD, hemodialysis.

Outcome measurement

We used the modified Beers criteria for elderly Japanese populations to define PIMs [7], identifying a total of 47 PIMs as selected by nine expert panel members. The criteria consisted of either medications that should be always avoided or those which should be avoided only in particular situations. Participants receiving drug prescription classified as PIM only if prescribed long term were additionally examined at 1 year after enrollment. Given that non-critical comorbidities such as insomnia were not recorded correctly in these studies, we defined insomniac patients as those who were prescribed hypnotic agents and constipated patients as those who were prescribed laxative agents. Medications that were to be avoided in patients with incontinence or urinary retention were excluded, as most HD patients are generally accepted to be anuric.

The primary outcome was prescription of at least one PIM as defined by the modified Beers criteria. Prevalence of PIM prescription was estimated. To evaluate changes over time in PIM prescription, we also compared the frequency of PIM prescription between J-DOPPS II and J-DOPPS III.

Table 1. Patients characteristics

Characteristics	J-DOPPS II (2002) ($n = 595$) (%)	J-DOPPS III (2005) ($n = 772$) (%)	Overall ($n = 1367$) (%)
Sex			
Male	57	60	59
Primary cause of ESRD			
DM	32	34	33
Age (years)			
65–69	31	36	34
70–74	34	27	30
75–79	20	21	20
80–84	9	10	10
≥85	5	6	6
Vintage (year)			
<1	15	23	19
1–4	45	34	39
≥5	40	43	42
Number of comorbidities[a]			
0	6	5	5
1–2	18	37	29
3–4	42	30	35
≥5	33	28	30
Number of medications			
<6	33	26	29
6–7	18	26	23
8–9	24	24	24
≥10	25	24	24
Past history of depression	1	1	1
High dependency in ADL (e.g. using a wheelchair)	13	12	12
Living alone	9	10	10
Receiving HD at large medical institution (number of HD stations ≥30)	b	43	
Receiving HD at teaching hospitals	b	23	
Receiving HD at medical institution with multidisciplinary rounds conducted	b	62	
Receiving HD treatment by more than one physician	b	70	

ESRD, end-stage renal disease; ADL, activities in daily living; HD, hemodialysis; DM, diabetes mellitus.

[a]Number of comorbidities: angina, myocardial infarction, arrhythmia, congestive heart failure, hypertension, hyperlipidemia, cerebrovascular disease, transient ischemic attacks, peripheral vascular disease, aortic aneurysm, claudication, past history of deep vein thrombosis, diabetes, chronic obstructive pulmonary disease, seizure disorder, dementia and other cognitive impairment, peripheral neuropathy, Parkinson's disease, depression, history of hip fractures, carpal tunnel syndrome, peptic ulcer disease, recent history gastrointestinal bleed, diabetic gastroparesis, ascites, viral hepatitis, recurrent cellulitis/skin infection/gangrene, cancer and HIV/AIDS.

[b]Not measured.

Statistical analysis

Differences in distributions of primary outcome within categorical valuables were compared using the χ^2 test. Multiple logistic regression analysis was performed to determine patient characteristics associated with PIMs; the model included age, sex, vintage, number of comorbidities, number of medications, dependency in activities in daily living (ADL; defined by using a wheelchair or similar aids), past history of depression and living alone. Numbers of comorbidities and numbers of medications were divided into four groups based on variable quartile.

Given that facility characteristics were measured only in the J-DOPPS III cohort, we conducted subgroup analysis using only patients participating in J-DOPPS III to determine facility characteristic associated with prescription of PIMs. In this subgroup analysis, logistic regression analysis including the above-mentioned patient characteristics and facility characteristics was performed. The number of HD stations was divided into dichotomous variables based on the median value. To estimate cluster effects of each facility, two-stage random-effect logistic regression analysis was also performed as sensitivity analysis.

Differences or associations with a two-sided P-value of <0.05 were considered statistically significant. All analyses were performed using STATA version 11.2 (StataCorp LP, College Station, TX, USA).

RESULTS

A total of 1367 elderly patients were deemed eligible for this study (Figure 1), and their characteristics are shown in Table 1. Characteristics of patients were strikingly similar across both

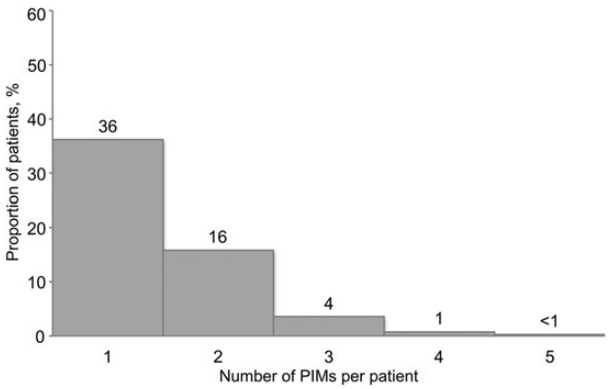

FIGURE 2: Distribution of numbers of PIM.

phases of J-DOPPS. Median age was 72 (range 65–98) years, and 33% of patients were found to have diabetes as the primary cause of end-stage renal disease. Only 1% of patients had a history of definite diagnosis of depression. Details of facility characteristics in J-DOPPS III cohort are available in the online supplementary material. Teaching hospitals made up 26% of facilities examined, and almost half of all facilities conducted multidisciplinary rounds (57%). At least two physicians decided on dialysis treatment in 67% of all facilities.

Figure 2 shows the distribution of the number of PIMs prescribed, revealing that most patients were prescribed one or two PIMs (52%). Table 2 shows the frequency of prescription of PIM and detailed lists of medications among this population. More than half of patients were prescribed PIM—most often H2 blockers. A total of 38% of patients were prescribed famotidine at or exceeding 20 mg daily, the usual dose for patients with normal kidney function. The second most frequently prescribed PIM was cardiovascular drugs (Table 2), primarily antiplatelet drugs such as ticlopidine (19%) and α-blockers (13%). As with patient characteristics, no remarkable differences in details of PIM were noted between the two J-DOPPS phases.

Table 3 describes proportions of PIM prescription stratified by patient characteristics (socio-demographic characteristics,

Table 2. Prescribed PIM list

	J-DOPPS II (2002) *n* = 595	J-DOPPS III (2005) *n* = 772	Overall *n* = 1367
Any PIM (%)	58	56	57
Cardiovascular drugs			
Antihypertensive drugs (%)	14	12	13
Doxazosin (%)	11	12	12
Prazosin hydrochloride (%)	<1	<1	<1
Methyldopa (%)	2	2	2
Clonidine (%)	1	1	1
Antiarrhythmic drugs	5	3	4
Pilsicainide hydrochloride (%)	<1	1	<1
Disopyramide (%)	2	1	1
Amiodarone hydrochloride (%)	<1	<1	<1
Digoxin (%)	<1	<1	<1
Digitoxin (%)	1	<1	1
Propranolol hydrochloride (%)	1	1	1
Verapamil hydrochloride (%)	2	1	1
Antiplatelet drugs (%)	19	19	19
Aspirin (%)	1	6	4
Short-acting dipyridamole (%)	<1	2	1
Ticlopidine hydrochloride (%)	19	14	16
Central nervous system depressant drugs	5	6	6
Etizolam (%)	1	<1	<1
Benzodiazepine class (%)	5	3	4
Diazepam (%)	2	1	2
Ethyl loflazepate (%)	<1	<1	<1
Triazolam (%)	<1	<1	<1
Flunitrazepam (%)	2	1	2
Nitrazepam (%)	<1	<1	<1
Brotizolam (%)	<1	<1	<1
Alprazolam (%)	<1	<1	<1
Amitriptyline hydrochloride (%)	<1	<1	<1
Milnacipran hydrochloride (%)	<1	<1	<1
H_2 blockers (%)	33	30	31
Famotidine (%)	17	18	17
Ranitidine hydrochloride (%)	8	4	5
Cimetidine (%)	3	2	3
Nizatidine (%)	1	1	1
Lafutidine (%)	2	4	3
Roxatidine acetate hydrochloride (%)	2	1	1
Miscellaneous drugs (%)	4	2	3
Loxoprofen sodium (%)	<1	<1	<1
Indomethacin (%)	<1	<1	<1
Zaltoprofen (%)	<1	0	<1
Ampiroxicam (%)	0	<1	<1
Diphenhydramine (%)	<1	0	<1
Chlorpheniramine maleate (%)	3	1	2
Promethazine (%)	<1	<1	<1
Dihydroergotoxine mesilate (%)	<1	<1	<1
Propantheline bromide chlorophyll combined drug (%)	<1	<1	<1
Propiverine hydrochloride (%)	<1	<1	<1

Table 3. Univariate analysis of PIM and patient factors

	Overall (J-DOPPS II & III)		
	Inappropriate medication		P-value
	Yes (%)	No (%)	
Sex			
Female	57	43	0.930
Male	57	43	
Primary cause of ESRD			
non-DM	54	46	0.006
DM	62	38	
Age (year)			
65–69	57	43	0.603
70–74	54	46	
75–79	57	43	
80–84	62	38	
≥85	55	45	
Vintage (year)			
<1	47	53	0.002
1–4	59	41	
≥5	59	41	
Number of comorbidities			
0	45	55	0.001
1–2	51	49	
3–4	58	42	
≥5	63	37	
Number of medications			
<6	34	66	<0.001
6–7	56	44	
8–9	66	34	
≥10	75	25	
Past history of depression			
No	56	44	0.097
Yes	76	24	
Low ADL (e.g. wheelchair bound)			
No	57	43	0.154
Yes	52	49	
Living alone			
No	57	43	0.936
Yes	56	44	

ESRD, end-stage renal disease; DM, diabetes mellitus; ADL, activities in daily living.

health status and number of all medications prescribed) whereas Figure 3 presents the results of multivariable logistic regression analysis. Longer vintage of HD was associated with increased proportion of inappropriate medication prescription {<1 year—47%, adjusted odds ratio (AOR): reference; 1–4 years—59%, AOR: 1.58 [95% confidence interval (CI): 1.15–2.17]; >5 years—59%, AOR: 1.77 (95% CI, 1.28–2.44)}. An increase in proportion of prescribed any medication at all was also associated with prescription of PIMs. While a number of comorbidities seemed to be associated with prescription of PIMs, the degree was not statistically significant in multivariable analysis. Of note, dependency in ADL (equal to or less than ADL when using a wheel chair) was negatively associated with prescription of PIMs [AOR: 0.56 (95% CI, 0.39–0.82)]. No significant association was noted between prescription of PIMs and age, sex, past history of depression and living alone.

Table 4 presents the results of univariate analysis, and Figure 4 presents the results of multivariable analysis including facility factors in the J-DOPPS III cohort. Patients receiving HD at a facility with multidisciplinary rounds conducted [AOR: 0.67 (95% CI, 0.48–0.93)] and at teaching hospital [AOR: 0.59 (95% CI, 0.39–0.90)] were less frequently prescribed PIM. Patients receiving HD at a facility in which more than one physician had clearance to change the dialysis regimen had a higher risk of prescribed PIM [AOR: 1.65 (95% CI, 1.12–2.44)] than those receiving treatment as directed by one physician. Sensitivity analysis with two-staged random-effect model showed no significant clustering at the facility level.

DISCUSSION

The overall frequency of PIMs was 57% among Japanese elderly HD patients, a finding similar between both the J-DOPPS phases examined. The most frequently prescribed PIMs in our study were H2 blockers, antiplatelet agents and α-blocker agents. We noted no remarkable differences in details of PIM between the two different phases of J-DOPPS. Patients on HD for a relatively long time, prescribed many medications or treated by more than one physician were at greater risk of PIM prescription than those not meeting these criteria. In contrast, patients treated at teaching hospitals or hospitals conducting multidisciplinary rounds were at relatively low risk of PIM prescription. Taken together, these findings suggest that elderly HD patients were prescribed PIM more frequently than previously reported for the general elderly population [7].

A previous study reported that 2.7% of general elderly patients were prescribed antiplatelet agents classified as a PIM [7], compared with a proportion of 15% among elderly HD patients in the present study. Elderly HD patients were prescribed antiplatelet agents more often than non-HD patients, given the increased incidence of vascular disease among elderly patients on HD. However, a previous study on antiplatelet therapy in vascular disease (ischemic stroke, coronary artery disease and peripheral arterial disease) suggested that aspirin or clopidogrel should be used as first-line agents for the majority of the patients, as ticlopidine usage is limited by its life-threatening hematological adverse reactions including neutropenia, thrombotic thrombocytopenic purpura and aplastic anemia. Although clopidogrel, a possible alternative to ticlopidine, was not available in Japan at study enrollment for either cohort, we considered that ticlopidine should be prescribed more carefully.

Frequent use of H2 blockers was deemed one of the reasons for the high frequency of prescription of PIMs in the present study. Previous report from worldwide DOPPS reveals that proton-pump inhibitors (PPIs) were used much less often than H2 blockers in Japan (0.8 versus 31.6%, respectively), and the frequency of prescription is very low compared with other countries (14.0–27.3%) [10]. In Japan, the usual prescription of PPIs for gastric and duodenal ulcers is limited to 8 weeks. This limitation may affect the relatively high frequency of prescription of H2 blockers. H2 blockers are associated with mental status changes such as delirium and decline in cognitive function in elderly patients [11]; indeed, a previous study revealed that ∼10% of adult end-stage renal disease patients with prescription of famotidine had shown mental status changes during >7 years of follow-up [12]. While dose adjustment may decrease the frequency of ADE, 38% of patients

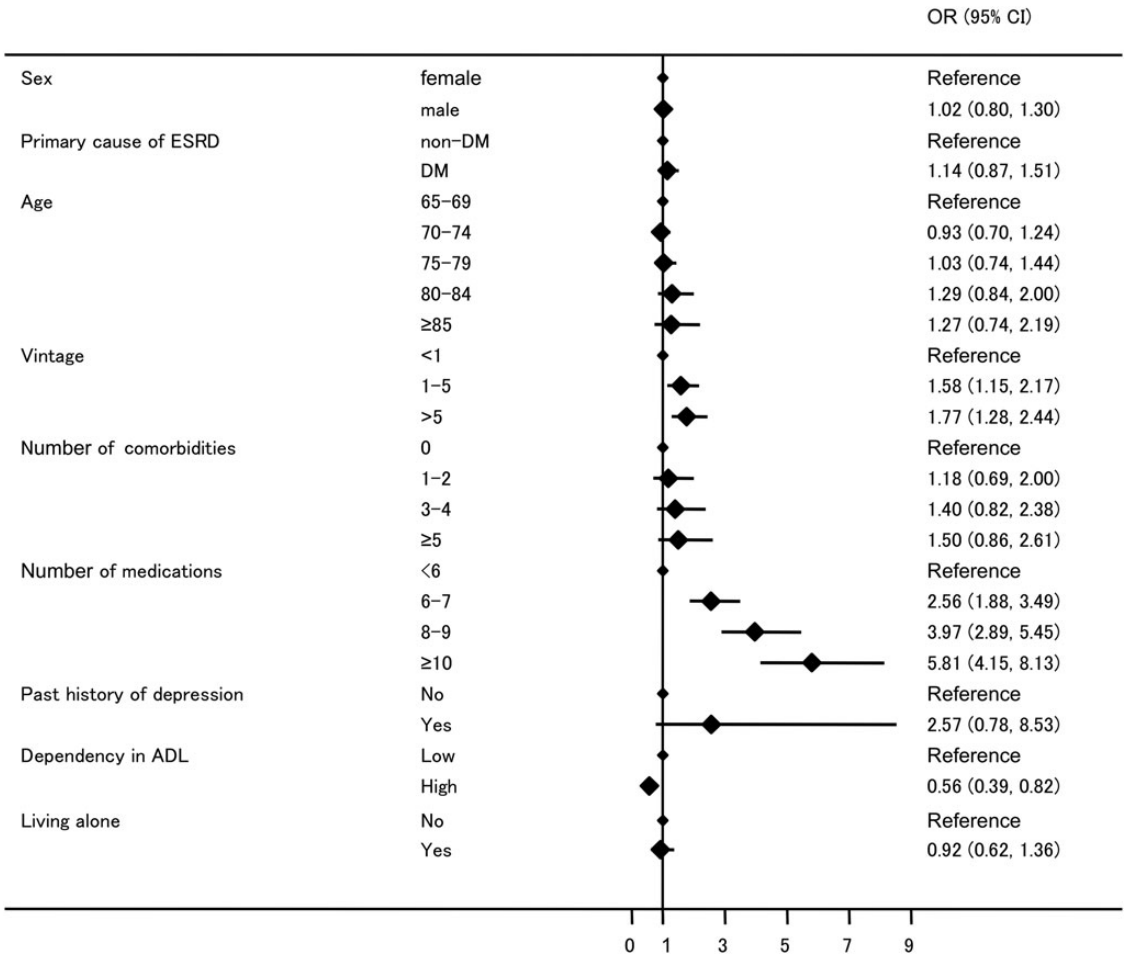

FIGURE 3: Multivariable analysis of PIM and patient factors ($n = 1367$). ADL, activities in daily living; DM, diabetes mellitus; ESRD, end-stage renal disease; OR, odds ratio; CI, confidence interval.

Table 4. Univariate analysis of PIM and facility factors in J-DOPPS III group ($n = 772$)

	Inappropriate medication		P-value
	Yes (%)	No (%)	
Number of HD stations			
<30	59	41	0.043
≥30	52	48	
Teaching hospital			
No	58	43	0.066
Yes	50	50	
Multidisciplinary rounds conducted			
No	58	43	0.085
Yes	50	50	
HD regimen able to be changed by more than one physician			
No	55	45	0.766
Yes	56	44	

HD, hemodialysis.

were prescribed the usual dose of famotidine in the present study (20–40 mg daily).

While Akazawa *et al.* [7] reported that 2.8% of general elderly patients were prescribed α-blockers classified as a PIM, 12% of elderly HD patients were prescribed these drugs in our study. Report from DOPPS reveals that vasodilators are less often prescribed for HD patients in Japan than other countries [13]. Another previous study reported that α-blockers approximately tripled the risk of falling [14], and a previous observational study showed that HD patients with α-blocker prescriptions had slightly higher mortality independent of variables such as age, sex, race, years of end-stage renal disease or prevalence of comorbidities [13]. Other antihypertensive drugs such as angiotensin-converting enzyme inhibitors [15], angiotensin receptor blockers and β-blockers [13], which are all associated with reduced mortality risk in HD patients, should be prescribed instead of α-blockers.

Under the modified Beers criteria, the following analgesics are classified as PIMs: indomethacin, pentazocine, long-term use of full-dosage long half-life non-COX-selective non-steroidal anti-inflammatory drugs (NSAIDs) and general NSAIDs prescription in patients with gastric or duodenal ulcers. As such, analgesic drugs classified as PIMs were rarely prescribed in the present study.

Here, we identified several factors associated with prescription of PIM, with our findings for polypharmacy and dependency in ADL consistent with those of previous studies [16]. Our findings also suggested that longer vintage may be associated with time-dependent increase of cardiovascular or gastrointestinal complications; therefore, patients receiving HD for a relatively

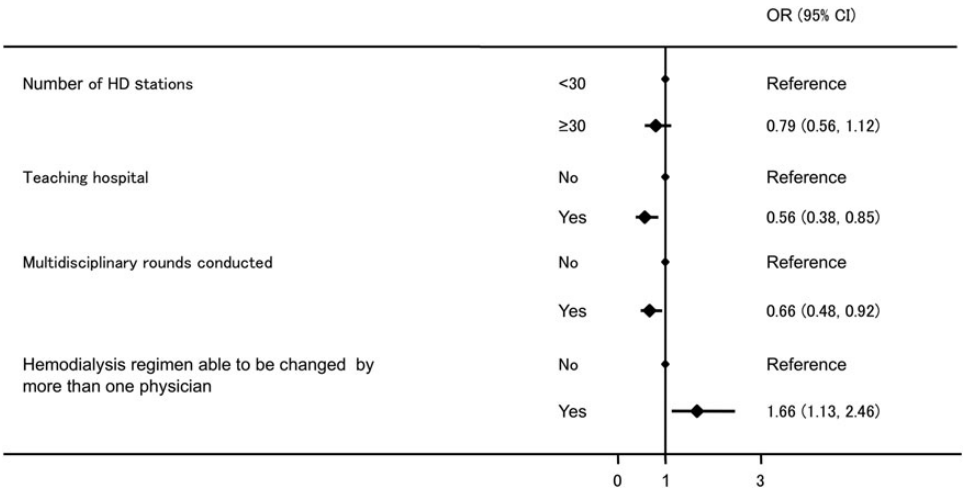

FIGURE 4: Multivariable analysis of PIM and facility factors ($n = 772$). HD, hemodialysis; OR, odds ratio; CI: confidence interval.

long period of time may have more chances to be prescribed PIMs than those with shorter vintage. In contrast, several variables (number of comorbidities, age, sex, past history of depression and living alone) already known to be associated with prescription of PIMs [16] were not found to be statistically significantly associated in the present study. We believe that the number of comorbidities was not an important factor influencing PIMs in the present study because HD status involves serious comorbidities. Given that markedly few patients had a definite history of depression or were older than 85 years, we were unable to detect statistically significant differences in the frequency of PIMs among this population.

In multivariable analysis of the J-DOPPS III cohort, PIM prescription was found to be associated with several facility factors. Patients at teaching hospital may receive relatively high-quality treatment, thereby avoiding many medication-related problems. We further believe that multidisciplinary rounds were useful in facilitating sharing of information about ADEs between physicians and other healthcare providers, possibly resulting in avoiding prescription of PIM; this finding is consistent with the previous studies, further underscoring the efficacy of a multidisciplinary team in avoiding PIM [17]. Having more than one dialysis physician make the decision to change HD regimen may increase the opportunity to be prescribed PIMs. Taken together, these findings suggest that prescription of PIM was affected by modifiable practice patterns.

Six major limitations to the present study warrant mention. First, because of the cross-sectional study design, causal inferences cannot be made. However, as mentioned earlier, variation in these facility factors (teaching hospital, multidisciplinary rounds conducted or changing of the HD regimen by more than one physician) cannot logically be deemed to be due to prescription of PIM. We thought that these factors were the cause or preventive factors of PIM. Second, information regarding patient disease history was limited to 29 diseases, thereby reducing the frequency of PIMs to be taken into account in patients with certain disease such as hyponatremia. This limitation may have thereby led to underestimation of the frequencies of PIM. Third, as we used Beers criteria to identify PIMs, other medications that are at high risk for ADEs in HD patients may not be included. This limitation may also lead to underestimation of the frequencies of PIM. Fourth, some patients may have been redundantly selected for both the J-DOPPS II and J-DOPPS III through random sampling. However, we assume that the percentage of such patients is negligible. Fifth, the present study used data from Japanese HD patients; as such, global application of our findings will require further investigation. Sixth, the association between PIMs and clinical outcome was unclear in elderly HD patients [18]. Further study will be needed to clearly determine the clinical impact of PIMs in this patient population.

In conclusion, the fact that PIMs were prescribed to more than half of the patients in this study underscores the importance of medication management in elderly people receiving HD. Nephrologists should be aware of the frequency and dangers of prescribing PIMs. In addition, we realize that for all HD facilities to implement all of the practices that are common in teaching hospitals might be impractical. Further research should be done on the practices that are common in teaching hospitals, to find out which among them most strongly inhibit the prescription of PIMs. We believe that, as a minimum, multidisciplinary rounds should be conducted at all facilities where they are possible.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

T. Akizawa receives consulting fees from Chugai, Kyowa Kirin, Bayer, Astellas, REATA and Abbott, and grants/funds from

Chugai Kyowa Kirin, Bayer, Astellas and Daiichi-Sankyo. S. Fukuhara is an advisor on epidemiology studies for Kyowa Hakko Kirin and receives consulting fees from Kyowa Hakko Kirin. Other authors have nothing to declare.

(See related article by Gallieni and Cancarini. Drugs in the elderly with chronic kidney disease: beware of potentially inappropriate medications. *Nephrol Dial Transplant* 2015; 30: 342–344.)

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Ranking of factors determining potassium mass balance in bicarbonate haemodialysis

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ABSTRACT

Background. One of the most important pathogenetic factors involved in the onset of intradialysis arrhytmias is the alteration in electrolyte concentration, particularly potassium (K^+).

Methods. Two studies were performed: Study A was designed to investigate above all the isolated effect of the factor time *t* on intradialysis K^+ mass balance (K^+MB): 11 stable prevalent