Echocardiography for the Detection of Valvulopathy Associated with the Use of Ergot-Derived Dopamine Agonists in Patients with Parkinson's Disease

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Abstract

Objective The ergot-derived dopamine agonists, cabergoline and pergolide, are associated with valvulopathy risk. In Japan, product labels were revised in April 2007 to recommend periodic echocardiography for patients taking these dopamine agonists, however, the compliance of physicians to follow through with this recommendation is unknown. This study assessed changes in echocardiography evaluation of patients with Parkinson's disease (PD) taking cabergoline or pergolide before and after the label revision and examined the factors related with echocardiography performance.

Methods and Patients Medical claim data from January 2005 to December 2008 were used. Patients were divided into a C-P group (prescribed either cabergoline or pergolide) or reference group (prescribed other anti-PD drugs), and further classified based on whether they were prescribed these drugs "pre-revision" or "post-revision." The Cochran-Armitage trend test was used to compare the proportion of echocardiograms obtained amongst these groups before and after the revision. The frequencies of echocardiograms performed among the treatment groups for each period were compared by Fisher's exact test.

Results A total of 222 subjects (C-P, 73; reference, 149) were assessed. The proportion of C-P patients undergoing echocardiography increased from 4.8% to 27.9% after revision of product labels ($p=0.001$), which was higher than those in the reference group following label revisions (11.0%) ($p=0.014$). Prescription duration of C-P after the revision was longer in the patients with echocardiography than without echocardiography ($p=0.026$).

Conclusion Although echocardiography evaluations increased, more than 70% of PD patients prescribed cabergoline or pergolide did not undergo such assessment despite the product label recommendation. Adherence to drug safety recommendations should be facilitated with more feasible and effective measures.

Key words: Parkinson's disease, valvulopathy, dopamine agonist, safety information, echocardiography, database research

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder (1). The prevalence of PD (per

100,000 people) in Japan is 175-180 according to the previous studies (2, 3). Levodopa remains the most effective drug against PD symptoms, but results in adverse effects such as motor fluctuations. Therefore, dopamine agonists are also being used increasingly as first-line treatment for PD (4, 5).

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Table 1. Overview of Official Approval Status and Risk Mitigation Measures on Valvulopathy Risk with Cabergoline and Pergolide in Japan, United States, and European Union

Approval status and Risk mitigation measure	Anti-PD drugs	Japan	United States	European Union
Maximum recommended dose (following revision of product labels)	Cabergoline	PD treatment: Reduced to 3 mg/day Hyperprolactinemic disorders [†] : 1 mg/week	1 mg/twice a week	Reduced to 3 mg/day
	Pergolide	1.25 mg/day	3 mg/day*	Reduced to 3 mg/day
Diseases approved for drug treatment	Cabergoline	PD Hyperprolactinemic disorders [†]	Hyperprolactinemic disorders	PD
	Pergolide	PD	PD	PD
Risk mitigation strategy	Cabergoline	Revised product labels	Continues to be sold on the market	Revised product labels
	Pergolide	Revised product labels	Voluntarily withdrawn from the market	Revised product labels
Evidence associating drug use with valvulopathy (~2008)	Cabergoline	Yes	No clear risk for patients treated for hyperprolactinemia	Yes
	Pergolide	No	Yes	Yes

* Prior to withdrawal from the market.

[†] Hyperprolactinemic disorders: galactorrhea, hyperprolactinemic ovulatory dysfunction, pituitary prolactinoma, and suppression of postpartum milk secretion.

PD, Parkinson's disease

Dopamine agonists are classified as ergot-derived agents such as bromocriptine, cabergoline, and pergolide, or non-ergot-derived agents such as ropinirole, talipexole, and pramipexole. Since cabergoline and pergolide have a high affinity for Dopamine 2 receptors specifically, they are thought to be effective with only mild adverse effects (4).

In 2002, however, pergolide use was reported to be associated with valvulopathy (6, 7). By 2004, several comparative studies further supported a high prevalence of valvulopathy among patients with PD treated with pergolide followed by cabergoline (8-11). In Japan, two observational studies reported an association between high dosage and long-term use of cabergoline and increasing frequency of valvulopathy (12, 13).

In response to these safety concerns, several risk mitigation measures were taken during 2007 and 2008. Pergolide was voluntarily withdrawn from the United State (US) market after consultation with the US Food and Drug Administration (FDA) (14). On the other hand, cabergoline remains on the US market because it is approved for the treatment of hyperprolactinemia. In Japan, the Ministry of Health, Labour, and Welfare (MHLW) notified manufacturers to revise the product label for cabergoline and pergolide in April 2007 (15). In brief, labels were revised to include the risk of valvulopathy associated with cabergoline and pergolide use, to add contraindication against patients with a history of valvulopathy, to restrict use of these medications as second-line treatment for PD patients, and to recommend periodic echocardiograms to detect valvulopathy before and during medication intake. Likewise, the European Medicines

Agency issued a similar safety recommendation in June 2008 (16) (Table 1).

To date, however, the effectiveness of these safety notifications has not been adequately reported. Questionnaires of Japanese and European neurologists revealed over 90% awareness of valvulopathy notifications related to pergolide use and 70% adherence to periodic echocardiographic monitoring (17, 18). However, those results may be overestimated as they only encompass voluntarily responding physicians. Thus, it is necessary to objectively evaluate the effectiveness of these safety measures.

Medical claim data, which reflect actual clinical practice, have been increasingly used to monitor adverse drug events, evaluate medical resource utilization, and delineate the impact of guidelines (19-21). Recently in Japan, the cooperative effort of universities and industry has made several databases available for research purposes (22).

This study aimed to evaluate whether revision of drug product labels resulted in an increase of echocardiograms performed on patients with PD who were prescribed cabergoline or pergolide by using medical claim databases, and to explore factors associated with echocardiography assessment.

Methods

Data sources

This study utilized a medical claim database maintained by the Japan Medical Data Center Co., Ltd. (JMDC, Tokyo,

Japan) entitled the JMDC Medical Data Bank (MDB). In the Japanese healthcare system, all citizens are covered by public health insurance programs (23). This universal health insurance system is composed of two types of insurance programs, the Employees' Health Insurance program (*hiyosha hoken*) and the National Health Insurance program (*kokumin kenkou hoken*). The company-provided Employees' Health Insurance program (*kenkou hoken kumiai*) enrolls employees of large-scale companies and their dependents. JMDC-MDB is comprised of medical claim data from approximately 530,000 patients from multiple company-provided Employees' Health Insurance programs (22).

The JMDC-MDB provides data on patient demographics, test orders, treatments, drugs prescribed, and medical establishments for ambulatory and inpatient care. Drugs are coded according to the Anatomical Classification of Pharmaceutical Products (ATC) of the European Pharmaceutical Market Research Association (EphMRA). Diagnoses for insurance claims are coded by the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).

Study subjects

Patients prescribed one of the following anti-PD drugs at least once between January 2005 and December 2008 were eligible for study inclusion: levodopa, dopamine agonists (cabergoline, pergolide, bromocriptine, pramipexole, ropinirole, and talipexole), or monoamine oxidase inhibitor (selegiline). Other drugs used for treatment of PD, such as anticholinergic drugs, amantadine, catechol-O-methyltransferase, and droxidopa, were not included for purposes of patient selection since these drugs have other indications such as treatment of extrapyramidal side effects associated with psychotropic drugs and influenza (4, 24).

Patient exclusion criteria included: 1) Age younger than 30 years, since the average onset of PD is at 62.7 years with 90.2% of PD patients being 40 years or older (5). 2) Consumption of less than 15 mg of cabergoline per month throughout the survey period. Since the maintenance dose of cabergoline for PD is 0.5-3 mg/day, such lower doses may reflect treatment for hyperprolactinemia or hypogalactia. The relationship between use of cabergoline in patients with hyperprolactinemia and increased risk of valvulopathy remains unclear (25-27). 3) Prescription for bromocriptine in the absence of concomitant use of other anti-PD drugs and without a recorded diagnosis of PD. These patients may have been prescribed bromocriptine for indications such as hyperprolactinemia, hypogalactia, and acromegaly.

The study protocol was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee.

Definition of variables

The variables examined in this study included gender, age, prescription of cabergoline and pergolide (C-P), assessment of echocardiogram, existence of valvulopathy and other heart diseases, PD duration, type of medical establish-

ment, concomitant use of anti-PD drugs other than C-P, daily dose of C-P, and duration of C-P prescribed between April 2007 and December 2008. Age was determined in January 2007, because only birth year and month were available in the database. Existence of valvulopathy was defined as the presence of one or more ICD-10 codes for "non-rheumatic mitral valve disorder" (I34), "non-rheumatic aortic valve disorder" (I35), "non-rheumatic tricuspid valve disorder" (I36), "non-rheumatic pulmonary valve disorder" (I37), and "endocarditis, valve unspecified" (I38). Existence of other heart diseases was defined as one or more ICD-10 codes for "ischemic heart diseases" (I20-I25) and "other types of heart diseases" (I30-I52) aside from "valvulopathy" (I34-I38). PD duration was defined as starting from the time of official diagnosis until the last recorded diagnosis. The type of medical establishment was classified as either clinic (0-19 beds) or hospital (20 or more beds). When patients visited multiple establishments, the medical establishment predominantly prescribing the anti-PD drugs was selected for classification. Combination use of anti-PD drugs was defined as use of at least one PD medication other than C-P according to the ATC classification system (code N04A) in addition to either cabergoline or pergolide. Mean daily dosage during April 2007 to December 2008 was calculated for cabergoline or pergolide individually. A low daily dose was defined as under 2.5 mg/day for cabergoline and less than 0.75 µg/day for pergolide; a high daily dose was defined as above 2.5 mg/day for cabergoline and above 0.75 µg/day for pergolide. Prescription duration was defined as the period starting from the month of initial C-P prescription during the period of April 2007 to December 2008 until the last month when these drugs were prescribed.

Statistical analysis

First, study patients were divided into two treatment groups: the C-P group and a reference group (for other anti-PD drugs). Second, the C-P group was divided into a cabergoline subgroup and a pergolide subgroup. Patient demographics and performance of echocardiography were summarized for the C-P group, cabergoline subgroup, pergolide subgroup, and reference group. The proportion of echocardiograms obtained amongst these groups before and after the 2007 label revision was compared using the Cochran-Armitage trend test. The period from January 2005 to March 2007 was termed "pre-revision," while April 2007 to December 2008 was deemed "post-revision." In the C-P group, patients were classified as "pre-revision" or "post-revision" based on when they were prescribed cabergoline or pergolide during these periods. Classification was carried out in a similar way for the cabergoline subgroup, pergolide subgroup, and reference group (prescribed other anti-PD drugs). Assessment of echocardiograms was subdivided by period and treatment groups. Patient age during the "pre-revision" period was determined as of January 2006, and age during the "post-revision" period was determined as of January 2008. Comparisons of the frequency of echocardiograms

Figure 1. Patient distribution. Note that some patients met more than one criterion for exclusion.

performed among treatment groups were made using Fisher's exact test for each survey period. In addition, since the revised product labels recommended obtaining echocardiograms to monitor valvulopathy at least once every 6-12 months while taking the drugs, the number of echocardiograms undergone by patients on C-P for 12 or more months during the "post-revision" period was calculated.

The C-P group in the "post-revision" period was divided based on whether or not echocardiogram was performed to examine potential associated factors. In that regard, continuous variables (age, PD duration, and prescription duration of C-P in "post-revision") were examined using the Wilcoxon rank sum test and categorical variables (gender, existence of other heart diseases, combined use of other anti-PD drugs, daily dose of C-P, and type of medical establishment) were examined using Fisher's exact test.

We used SPSS 16.0 for Windows (SPSS Inc., Chicago, Illinois) and SAS 9.1 (SAS Institute Inc., Cary, North Carolina) for data analyses. All reported *p*-values were two-tailed and the threshold for significance was *p* < 0.05.

Results

Of the 1,201 patients prescribed anti-PD drugs in the database, a total of 222 PD patients (91 men, 131 women; mean age, 61.1 years) were eligible for this study. Among them, 73 patients fell into the C-P group (57 in the cabergoline subgroup, 20 in the pergolide subgroup, 4 patients received both cabergoline and pergolide), and 149 patients in the reference group (Fig. 1, Table 2).

Proportions of echocardiograms performed in each group "pre-revision" and "post-revision" were as follows. In the C-P group, the proportion increased from 3/62 (4.8%) to 12/43 (27.9%) (*p*=0.001) overall. Among these, the cabergoline subgroup experienced a rise from 3/47 (6.4%) to 7/34 (20.6%, *p*=0.055), while the pergolide subgroup experienced an increase from 0/18 (0%) to 5/10 (50%, *p*=0.001). In contrast, the proportion of echocardiograms performed did not change in the reference group, with 11/103 (10.7%) pre-

revision and 12/109 (11.0%) post-revision (*p*=0.957, Table 3). In the "pre-revision" period, the frequency of echocardiograms in each treatment group was not significantly different from that in the reference group (*p*=0.255 vs. the C-P group, *p*=0.367 vs. the cabergoline subgroup, *p*=0.550 vs. the pergolide subgroup). In the "post-revision" period, the proportion of patients undergoing echocardiography was significantly higher in the C-P group (*p*=0.014) and the pergolide subgroup (*p*=0.001) than in the reference group, but not significantly different in the cabergoline subgroup (*p*=0.158).

Twenty-two patients continued receiving C-P for 12 or more months in the "post-revision" period with 2 undergoing echocardiography twice. The duration of drug prescription was significantly longer in the echocardiography (+) subgroup than in the echocardiography (-) subgroup (*p*=0.026) during "post-revision." Performance of echocardiography was not found to be associated with gender, age, existence of other heart diseases, concomitant use of other anti-PD drugs, type of medical establishment, daily dose, or PD duration (Table 4).

Discussion

In order to evaluate the impact of risk mitigation measures for valvulopathy risk associated with cabergoline and pergolide use, this study focused on an objectively measurable action for the early detection of adverse effect. We used the medical claim database to calculate the proportion of PD patients taking cabergoline or pergolide who underwent echocardiograms before and after the revision of product labels recommending testing for early detection of valvulopathy. We also explored potential factors associated with echocardiography performance. The proportion of echocardiography performance did indeed increase significantly after the label revision. However, only 27.9% of patients prescribed these drugs underwent echocardiography evaluation even after the revision. Furthermore, those who did undergo echocardiography evaluation had a longer duration of ergot-

Table 2. Demographics of Patients with Parkinson's Disease by Treatment Group (n=222)

Group:		Cabergoline and/or pergolide group			Reference group
		Total	Cabergoline subgroup	Pergolide subgroup	
Number of patients	Total	73	57	20	149
	Pre-revision	62	47	18	103
	Post-revision	43	34	10	109
Age (years), mean [SD]	Total	59.7 [12.9]	59.3 [14.4]	61.6 [8.17]	61.8 [15.3]
	Pre-revision	58.8 [12.1]	58.1 [13.3]	60.3 [8.5]	61.7[15.5]
	Post-revision	58.4 [14.1]	57.8 [15.7]	59.1 [6.2]	61.6 [15.6]
Gender (men), n (%)	Total	32 (43.8%)	21 (36.8%)	13 (65.0%)	59 (39.6%)
	Pre-revision	30 (48.4%)	20 (42.6%)	12 (66.7%)	37 (35.9%)
	Post-revision	19 (44.2%)	13 (38.2%)	7 (70.0%)	47 (43.1%)
Valvulopathy, n (%)		11 (15.1%)	8 (14.0%)	3 (15.0%)	18 (12.1%)
Heart diseases, n (%)		38 (52.1%)	29 (50.9%)	11 (55%)	89 (59.7%)
Parkinson's disease duration (months), mean [SD] (median, IQR)		45.0 [47.3] (32.0, 12.0-63.0)	36.9 [37.3] (30.0, 9.5-49.5)	64.0 [61.6] (38.0, 20.3-96.3)	32.2 [41.6] (17.0, 6.0-43.0)
Medical establishment (hospital), n (%)		54 (74.0%)	42 (73.7%)	16 (80.0%)	90 (60.4%)

Four patients were prescribed both cabergoline and pergolide during the survey period. Reference group: patients who were prescribed anti-Parkinson's disease (PD) medications other than cabergoline or pergolide. "Pre-revision": patients who received anti-PD medications between January 2005 and March 2007. "Post-revision": patients who received anti-PD medications between April 2007 and December 2008. Some patients were categorized as both "pre-revision" and "post-revision." SD, standard deviation. IQR, interquartile ranges.

Table 3. Proportions of Patients with Parkinson's Disease Undergoing Echocardiography by Treatment Group before and after Cabergoline and Pergolide Product Label Revisions for Valvulopathy Risk

Echocardiography, n (%)	Cabergoline and/or pergolide group			Reference group
	Total	Cabergoline subgroup	Pergolide subgroup	
Total	17/73 (23.2%)	11/57 (19.3%)	6/20 (30.0%)	26 /149 (17.4%)
Pre-revision	3 /62 (4.8%)	3 /47 (6.4%)	0/18 (0%)	11 /103 (10.7%)
Post-revision	12 /43 (27.9%)	7/34 (20.6%)	5/10 (50.0%)	12/109 (11.0%)
p-value (pre- vs. post-)	0.001	0.055	0.001	0.957

"Pre-revision": patients who received anti-Parkinson's disease (PD) medications between January 2005 and March 2007. "Post-revision": patients who received anti-PD medications between April 2007 and December 2008. Some patients were categorized as both "pre-revision" and "post-revision." p-value, proportion of echocardiograms performed among pre-revision subjects vs. post-revision subjects (Cochran-Armitage trend test).

derived medication prescription "post-revision."

Echocardiography performance

The present study revealed that less than 30% of PD patients who were prescribed cabergoline or pergolide underwent echocardiography after the 2007 product label revision. This suggests that the recommended safety measures against valvulopathy concerns, specifically regular echocardiographic monitoring, are not sufficiently implemented in clinical practice (15). Furthermore, only 2 of 22 patients receiving the ergot-derived agents for 12 or more months underwent periodic echocardiograms per product label recommendations. In other words, there is insufficient follow-up monitoring for valvulopathy with echocardiography in these patients. Even though patients who did not undergo echocar-

diography may have been examined by auscultation, periodic echocardiography should still be conducted according to product label recommendations to screen potential valvulopathy with greater accuracy.

In the pergolide subgroup, echocardiography performance during the "post-revision" period was significantly enhanced relative to the "pre-revision" period, and was better than that of the corresponding period of the reference group. However, no significant difference was seen for the cabergoline subgroup. Although the possibility of chance cannot be denied due to our limited sample size, several factors may explain this observation. First, it may have been influenced by the fact that the association between ergot-derived dopamine agonists and valvulopathy was first observed in relation to pergolide in a series of European and US stud-

Table 4. Factors Associated with Echocardiography Assessment in Patients with Parkinson's Disease Prescribed Cabergoline and/or Pergolide after Product Label Revisions for Valvulopathy Risk

Variable	Echocardiography(+) n=12	Echocardiography(-) n=31	p-value
Gender (men: women)	8 : 4	11 : 20	0.091*
Age (years)	59.5 (55.3-66.5)	61.0 (45-70)	0.373
Comorbid heart disease (n)	6	10	0.313*
Concomitant use of other anti-Parkinson's disease drugs (n)	11	20	0.130*
Cabergoline subgroup			
n	7	27 [†]	
Daily dose (mg)	2.21 (2.00-3.89)	2.00 (1.00-2.00)	
< 2.5mg : ≥ 2.5mg	4:3	21:6	0.348*
Pergolide subgroup			
n	5	5 [†]	
Daily dose (μg)	0.750 (0.690-0.945)	0.417 (0.075-0.608)	
< 750μg : ≥ 750μg	2:3	5:0	0.167*
Parkinson's disease duration (months)	59.5 (55.3-66.5)	42.5 (11.8-71.8)	0.112
Prescription duration during "post-revision" (months)	18.5 (11.3-20.8)	8.0 (3.0-19.0)	0.026
Prescribing medical establishment (clinic: hospital)	1:11	11:20	0.130*

Age was determined at January 2007. Values are expressed as medians with interquartile ranges in parentheses. *p-values were calculated by Fisher's exact test. Other p-values were calculated by Wilcoxon rank-sum test. [†]One patient had prescriptions for both cabergoline and pergolide.

ies (8, 11, 28). In addition to these studies, the fact that pergolide was withdrawn from the market in the US and Canada may have strongly influenced Japanese physicians' decisions on whether or not to perform echocardiographic monitoring (29, 30). In Japan, however, the increased risk of valvulopathy was reported for patients taking cabergoline, but not for pergolide, whose approved dose is lower than that in Europe and the US (12, 13). However, of note is that the product labels of cabergoline and pergolide were revised similarly at the same time in Japan. Other factors may be considered, such as stage of PD, type of department, or differences in risk mitigation strategies by drug distribution companies, which were not examined in the present study. In Japan, cabergoline was received by a greater number of PD patients at higher doses in comparison to pergolide. The patients receiving the higher or accumulated doses of cabergoline were reported to be at an increased risk of valvulopathy (12, 13). It would be necessary to attract more attention of the practitioners into echocardiographic monitoring of the patients taking cabergoline. Additionally, the appropriate follow-up monitoring is warranted in practice taking patient's age, choice of medicine, and the doses into consideration.

The prescription duration of cabergoline or pergolide during the "post-revision" period was shorter in patients in the absence of echocardiography than with echocardiography, with a shift to other anti-PD drugs that do not require echocardiographic monitoring. This may relate to the 2007 label revision to restrict the use of these drugs only to second-line treatment. In addition, previous studies showed the cumulative dose-response relationship between cabergoline and the risk of valvulopathy (12, 13). Therefore, there is a possibility that physicians may have performed echocardiography selectively for patients receiving long-term medication, rather than uniformly.

An insignificant but substantial difference in the propor-

tions of echocardiograms performed during "post-revision" period was observed between clinics and hospitals, although this insignificant result would be ascribable to the limited number of patients observed. Clinics may fail to perform echocardiograms possibly because of lack of echocardiography equipment and the burden of patient referral to another institution.

Limitations and strengths

This study has several limitations due to the use of medical claim data from company-provided Employees' Health Insurance programs. First, PD occurs mostly in elderly populations (1), but a large portion of enrollees in these programs is comprised of middle-aged people. Furthermore, some patients may have left their jobs due to age or illness, and were thus removed from this database. Because JMDC-MDB is composed of a younger and healthier population than the target PD population, our sample is likely to be composed of younger and healthier patients than the general Japanese PD patients. Therefore, physicians may have elected not to perform echocardiography in our study patients due to their better health, leading to the consequent low adherence rate with respect to echocardiography. The proportions of echocardiograms may be increased if the enrollees in the National Health Insurance program were added in the analysis which covers more elderly enrollees such as retired employees than the company-provided Employees' Health Insurance program. On the other hand, elderly patients have a higher risk of cardiac disease than young patients and are more likely to undergo echocardiography for examination of common cardiac issues rather than detecting drug-related valvulopathy. Consequently, the relationship between clinicians' intention to follow the safety instructions and implementation of echocardiography might be obscured among these elderly patients. To this end, there is an advantage of using the present data to interpret

clinicians' intention to follow safety instructions, although the assessed patients were rather young. We also used drug prescription data as inclusion criteria. Therefore, some patients without PD may have been included in this study based on their medication patterns. However, it is unlikely that this possibility would introduce serious bias since echocardiographic monitoring should be based on the use of cabergoline or pergolide, even if not in a PD patient.

Use of the large-scale medical claim database provides several advantages. First, we were able to enroll 222 patients with PD, which is relatively rare among the general population. The prevalence of PD is 37.7 per 100,000 population in this 530,000 patient database, which is lower than the prevalence of PD in Japan (2, 3). This is likely due to the fact that JMDC-MDB is biased toward younger people. Second, because we used data from patients at multiple facilities and medical establishments, including both ambulatory and inpatient care, our results are not significantly biased by the specific influence of a particular medical establishment. Third, the use of objective outcome variables such as echocardiography performance and prescription drugs in claim records undoubtedly reflects actual clinical practice (31).

In Europe and the US, researchers have made use of public health insurance data such as Medicaid claims data in order to evaluate the effectiveness of drug safety information (32-34). The present findings are compatible with other studies that demonstrated lack of full adherence to drug safety recommendations in performing tests to monitor adverse effects in clinical practice (35, 36).

In conclusion, the proportion of echocardiography performance to detect valvulopathy increased after issuing safety recommendations, but remained at less than 30% compliance among the target population. To facilitate physician adherence to recommended safety measures by pharmaceutical companies and regulatory agencies, it would be helpful to optimize hospital information systems, facilitate pharmacist communication with physicians regarding drug safety recommendations, and embed a prescription warning system in electronic health records (37, 38).

Author's disclosure of potential Conflicts of Interest (COI).

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