



Comparative Treatment Persistence and Adherence to Endothelin Receptor Antagonists Among Patients with Pulmonary Arterial Hypertension in Japan: A Real-World Administrative Claims Database Study

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ABSTRACT

Introduction: Real-world data on the comparative effectiveness of endothelin receptor antagonists (ERAs; macitentan, bosentan, ambrisentan) for pulmonary arterial hypertension (PAH), particularly in Asian countries, are scarce. We evaluated the persistence of these

These data were previously presented, in part, at the 8th Annual Meeting of the Japanese Society of Pulmonary Hypertension and Pulmonary Circulation General Presentation (JPCPHS23), June 3–4, 2023 in Kobe, Japan.

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ERAs before and after macitentan approval in Japan (2015).

Methods: We used real-world data from the Japanese Medical Data Vision administrative claims database between April 2008 and November 2020. Patients with PAH were identified from the dataset. Persistence to ERA treatment before and after approval of macitentan in Japan was defined as the time between start of the index ERA and treatment discontinuation or death. Propensity score adjustment was applied to minimize confounding effects among treatment groups.

Results: In the pre-macitentan approval cohort, 153 and 51 patients received bosentan and ambrisentan, respectively. In the post-macitentan approval cohort, 331, 284, and 91 patients received macitentan, bosentan, and ambrisentan, respectively. Unadjusted median

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persistence for ambrisentan- and bosentan-treated patients was 19 and 10 months, respectively (adjusted HR 0.87 [95% CI 0.61–1.24]; $P = 0.434$ [bosentan as reference]). In the post-macitentan approval cohort, unadjusted median persistence was 18 months for macitentan-treated patients versus 6 and 8 months for ambrisentan- and bosentan-treated patients, respectively. Adjusted HRs for ambrisentan and bosentan were 1.48 (95% CI 1.12–1.95; $P = 0.006$) and 1.63 (95% CI 1.30–2.04; $P < 0.001$ [macitentan as reference]), respectively.

Conclusions: Real-world data for Japanese patients with PAH showed that persistence was significantly higher for macitentan, versus ambrisentan and bosentan, since its approval.

Keywords: Endothelin receptor antagonists; Japanese patients; Pulmonary arterial hypertension; Real-world data; Treatment persistence

Key Summary Points

Why carry out this study?

Macitentan, ambrisentan, and bosentan are endothelin receptor antagonists (ERAs) that have been approved for use in patients with PAH in Japan.

Real-world data on the comparative effectiveness of ERAs in Japanese patients with PAH are limited.

This study examined the persistence to ERA treatment before and after the approval of macitentan for PAH in Japan in 2015 from the Japanese Medical Data Vision dataset.

What was learned from the study?

Among Japanese patients with PAH in the MDV database, significantly higher persistence to treatment was seen with macitentan versus ambrisentan and bosentan.

These results suggest that macitentan may have a more favorable tolerability profile than ambrisentan or bosentan, but additional research is needed to understand the impact of persistence on long-term outcomes.

INTRODUCTION

Pulmonary arterial hypertension (PAH) causes changes in the production of diverse endothelium-derived vasoactive substances [1]. Existing PAH treatments target one of the three intracellular dysfunctional signaling pathways: prostacyclin, nitric oxide, or endothelin [1]. Five classes of agents that target these pathways are endothelin receptor antagonists (ERAs; e.g., macitentan, ambrisentan, and bosentan), phosphodiesterase type 5 (PDE5) inhibitors (e.g., sildenafil and tadalafil), prostanoids, selective prostacyclin receptor agonists, and soluble guanylate cyclase stimulators [2–6]. Bosentan was the first ERA to be synthesized and is a dual endothelin A and endothelin B receptor antagonist [7, 8]. Ambrisentan is a selective endothelin A receptor antagonist [9], and macitentan is a dual endothelin A and endothelin B receptor antagonist [10, 11]. Because PAH is a progressive disease, treatment persistence is essential to ensure patients receive optimal treatment and the benefits of long-term outcomes.

Several recent network meta-analyses (NMAs) have demonstrated the superior efficacy (e.g., 6-min walking distance [6-MWD], mean pulmonary arterial pressure [mPAP], pulmonary vascular resistance [PVR], mean right atrial pressure [mRAP], cardiac index, World Health Organization [WHO] functional class, clinical worsening, and all-cause mortality) of ERA plus PDE5 inhibitor combination therapy compared with ERA monotherapy in patients with PAH [2–4]. Moreover, current 2015 guidelines for the treatment of PAH from the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) recommend initial or sequential combination therapy with an ERA and a PDE5

inhibitor [6]. Current PAH treatment guidelines from the Japanese Circulation Society and the Japanese Pulmonary Circulation and Pulmonary Hypertension Society [12] are based largely on the European guidelines. As a rule, however, any drugs used in Western countries that are not yet approved for use in Japan were excluded from the Japanese guidelines. Despite the robust literature on the efficacy and tolerability of ERAs and guidelines for their use, few studies have evaluated how these guidelines are implemented in clinical practice.

Studies from France [13], Scotland [14], and the USA [15] estimate the global prevalence of PAH to be approximately 12–50 per million people, but prevalence data from Japan are scarce. A medical records review in 2012 estimated the prevalence of PAH in Japan to be 15.6 per million [16]. In two Japanese registry studies, most patients were female (76–77%) [17, 18]. Data on the comparative effectiveness of ERAs in the real-world setting, particularly in Asian countries such as Japan, also are limited. In Japan, bosentan, ambrisentan, and macitentan were approved for use in patients with PAH in 2005 [19], 2010 [20], and 2015 [21], respectively. The primary aim of this study was to obtain data on persistence with macitentan compared with ambrisentan and bosentan using the Japanese Medical Data Vision (MDV) dataset.

METHODS

Study Design

This retrospective, observational study used real-world data from the MDV database in Japan between April 1, 2008 and November 30, 2020. The primary objective was to compare persistence to ERA treatment (i.e., macitentan, ambrisentan, and bosentan) among Japanese patients with PAH before and after approval of macitentan in Japan in June 2015 [21].

Compliance with Ethics Guidelines

This study was implemented and reported in accordance with the International Conference on Harmonised (ICH) Tripartite Guidelines for Good Clinical Practice with applicable local regulations (including European Directive 2001/20/EC, US CFR 21 and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declarations of Helsinki. As a result of the nature of this type of database, only de-identified data were used, confidentiality of patient records was maintained at all times, and study reports contained aggregate data only without identifying information of individual patients or physicians. Thus, on the basis of Ethical Guidelines for Epidemiological Research issued by the Japanese Ministry of Health, Labor and Welfare, ethics approval and informed consent are not applicable for this study.

Data Sources

The MDV database is Japan's largest administrative claims database, with approximately 10 years of data collected since January 2008. Data represent samples from 426 facilities and approximately 24% of acute care hospitals (diagnosis procedure combination [DPC] hospitals) in Japan [22]. As of October 2020, the database included data from more than 30 million patients, of whom 34% are more than 65 years of age. Approximately 33,000 patients have undergone right heart catheterization (RHC) or echocardiography (ECHO) investigations. Some facilities included in the MDV database were PAH expert centers, which included university hospitals and/or hospitals with more than 500 beds with expertise in PAH with a demonstrated ability to properly diagnose and manage patients with complex PAH.

Patients

Patients were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or ICD-10 coding system for PAH. Patients with PAH were

identified from the MDV dataset using the following inclusion criteria: had a pulmonary hypertension prespecified ICD-9-CM or ICD-10 code (Supplemental Material, Table S1) associated with Japanese disease code 8844804 at least one time and received at least one PAH-specific drug (Supplemental Material, Table S2), had at least one RHC or ECHO before PAH diagnosis code, were at least 18 years old at the time of prescription for any PAH drug, had at least 12 months of follow-up from initiation of treatment for PAH, and had not received ERA treatment for PAH within the preceding 6 months. History of RHC or ECHO prior to PAH diagnosis was used to ensure a sufficient sample size for analysis. Because patients with PAH are often misdiagnosed as having asthma or chronic obstructive pulmonary disease [23], patients with a history of Japanese disease codes for these conditions that were discontinued after any PAH drug was commenced were categorized as misdiagnosed.

Outcome

The primary outcome was persistence to ERA treatment before and after approval of macitentan in Japan for the treatment of patients with PAH. Eligible patients were stratified by when they had received their index (i.e., first prescribed) ERA, either before or after the approval of macitentan (June 9, 2015). For the former, the cohort included patients who started taking bosentan or ambrisentan; for the latter, the cohort included patients who started taking bosentan, ambrisentan, or macitentan. The exposure of interest was treatment with macitentan, ambrisentan, or bosentan. The index date was defined as the date of the first prescription of the index ERA for each patient.

Persistence to ERA treatment was defined as the time, in consecutive days, between the start of bosentan or ambrisentan (before June 9, 2015) or the start of bosentan, ambrisentan, or macitentan (after June 9, 2015) and the time of discontinuation of that treatment, also in consecutive days. An event was defined as treatment discontinuation or death, with two primary reasons for discontinuation assumed to

be adverse events (AEs) and lack of efficacy. The concept of drug persistence (i.e., drug survival) originated from studies evaluating biologics for the treatment of immune-mediated inflammatory diseases (e.g., psoriasis), where drug persistence/survival is frequently a prespecified clinical outcome [24–31]. In the current study, as in many others [24–31], drug persistence includes both treatment discontinuation and death because they both effectively result in the same outcome, end of treatment persistence. Furthermore, the MDV database does not capture all deaths, only those within the same DPC hospital, thus precluding the ability to analyze survival separately.

Patients were censored at the last date of data extraction (censor date). Patients were considered to have discontinued treatment if there was no dispensing of the ERA for at least 6 months after the last dispensing. For example, if a patient was hospitalized for an event with the outcome “transferred to other hospital,” and the patient did not return to the original hospital to fill a prescription within the subsequent 6 months, the patient’s last prescription was considered the date of treatment discontinuation. That is, patient persistence was measured within a DPC hospital. A period of 6 months, instead of 3 months, was selected because, in clinical practice in Japan, patients with PAH typically refill their prescriptions every 3 months. Doubling this time helped achieve a balance between having a refill interval that was too long and having a sufficient number of patients within the pre-index period for analysis.

Treatment adherence was measured by proportion of days covered over 12-month period. Patients with proportion of days covered $\geq 80\%$ of ERA doses were considered adherent, and if days’ supply data was not provided, an assumption was made that each prescription lasted 30 days. Patients who have had fewer than two prescriptions in the 12-month period or have died before the end of 12-month period were categorized as patients with insufficient data and excluded from the analysis.

Statistical Analysis

Baseline demographic and clinical characteristics are summarized descriptively, using means and standard deviations (SDs) or medians (ranges) for continuous variables and frequency distributions, and using percentages for categorical variables. Patient characteristics are summarized separately for those whose ERA index date was before and after June 9, 2015. Exploratory analyses compared baseline demographic and clinical characteristics of patients who received bosentan before and after June 9, 2015, and for patients who received ambrisentan before and after June 9, 2015. Student's *t* tests were used for continuous variables, and chi-square tests were used for categorical variables. Treatment adherence is presented as a proportion of patients who were adherent to treatment using the proportion of days covered method.

Unlike data from randomized controlled trials, real-world data on treatment persistence and adherence among different treatment groups could be biased by confounding variables, including patient characteristics. Therefore, a propensity score model was required to balance the distribution of patients' characteristics and increase the comparability of the three ERA treatment groups. We used a method based on the covariate adjustment approach. Because this method does not actually match patients with similar propensity scores, the comparability of the treatment groups could not be evaluated directly. However, as opposed to the propensity score matching approach, this method has the advantage of preserving sample size.

Separate models were fitted for the two patient subgroups. For the pre-macitentan approval cohort, logistic regression was used to compare ERA assignment among patients who received bosentan or ambrisentan. For the post-macitentan approval cohort, multinomial logistic regression was used to compare ERA assignment among patients who received bosentan, ambrisentan, or macitentan.

Patient demographic and clinical characteristics were used as covariates and fitted within each propensity score model. For the pre-

macitentan approval cohort, the independent variables that served as covariates were gender (male, female); age cohort at the index date (< 50, 50–59, 60–69, 70–79, ≥ 80 years); baseline comorbidities (i.e., hypertension, diabetes, renal disease, arterial disease) as a proxy for overall health status; monotherapy versus combination therapy as an indicator of PAH severity at the start of ERA therapy; first-line therapy versus second or subsequent lines of therapy to identify treatment-naïve patients; and etiology, including idiopathic pulmonary arterial hypertension (IPAH), connective tissue disease (CTD; systemic lupus erythematosus, systemic sclerosis), and coronary heart disease (CHD). For the post-macitentan approval cohort, the covariates were the same except for the exclusion of IPAH etiology, as there were no patients in the ambrisentan group with this type of PAH etiology.

The Kaplan–Meier method was used to determine unadjusted treatment persistence. Differences in adjusted persistence to treatment were assessed using a Cox proportional hazards model with the propensity score as a covariate.

Results were statistically significant if the *P* value was less than 0.05. Persistence and adherence data were analyzed using Prospec-tion's PharmDash software (Prospec-tion, NSW, Australia); all other statistical analyses were performed using R (R Foundation) [32].

RESULTS

Patient Disposition and Characteristics

A total of 8682 patients with a diagnosis code for PAH were identified in the MDV database. Of these, 5330 patients had a prescription receipt code for a PAH-specific medication. After all eligibility criteria were applied, the final cohort was composed of 910 patients. Twenty-eight percent (254/910) of patients had RHC and nearly 100% (908/910) had ECHO before their PAH diagnosis. In the pre-macitentan approval cohort (*n* = 204), 153 and 51 patients had received bosentan and ambrisentan, respectively, as their index ERA. In the post-macitentan approval cohort (*n* = 706), 331,

284, and 91 patients had received macitentan, bosentan, and ambrisentan, respectively, as their index ERA (Fig. 1).

In both cohorts, demographic and clinical characteristics among the three ERA treatment groups were generally comparable. In the pre-macitentan approval cohort (Table 1), there were some notable differences between patients who received bosentan versus ambrisentan, including a lower percentage of patients who used combination therapy in the bosentan versus ambrisentan treatment group (45% versus 67%), and a higher percentage of patients potentially misdiagnosed in the bosentan versus ambrisentan group (18% versus 4%). In the post-macitentan approval cohort (Table 2), there were some notable differences in the bosentan group, compared with the macitentan and ambrisentan groups, where a larger percentage of patients were female (74% versus 62% and 63%), had comorbid arterial disease (63% versus 37% and 42%), and had CTD etiology of PAH (71% versus 46% and 39%). A smaller percentage of patients in the bosentan group used combination therapy compared with those in the macitentan and ambrisentan groups (35% versus 71% and 73%).

Our exploratory analysis revealed some demographic differences within the bosentan and ambrisentan treatment groups before and after the approval of macitentan. Compared with patients who received bosentan in the pre-macitentan approval cohort, patients who received bosentan in the post-macitentan approval cohort had less use of combination therapy, lower rate of CHD etiology, higher rate of CTD etiology, higher rates of comorbid diabetes and arterial disease, and higher use of expert centers (Supplemental Material, Table S3). By contrast, there were fewer differences between ambrisentan-treated patients in the pre- versus post-macitentan approval cohort. Larger percentages of patients in the post-macitentan approval cohort were female, used expert centers, and were potentially misdiagnosed compared with those in the pre-macitentan approval cohort (Supplemental Material, Table S4).

Propensity Scores

In the pre-macitentan approval cohort, the overall mean (SD) propensity score was 0.250 (0.122). Among patients who received bosentan and ambrisentan, mean (SD) propensity scores were 0.231 (0.114) and 0.308 (0.126), respectively. The overall mean (SD) treatment adherence rate was 71.8% (36.9); corresponding rates in the bosentan and ambrisentan groups were 71.1% (36.9) and 73.8% (37.3).

In the post-macitentan approval cohort, the overall mean (SD) propensity scores for patients who received bosentan, macitentan, and ambrisentan were 0.402 (0.226), 0.469 (0.184), and 0.129 (0.072), respectively. The overall mean (SD) treatment adherence rate was 68.6% (37.2); corresponding rates in the bosentan, macitentan, and ambrisentan groups were 64.9% (38.2), 72.7% (35.6), and 65.7% (38.4). Treatment adherence rates by different cutoff thresholds (i.e., 60%, 70%, and 80%) before and after macitentan approval are shown in Fig. 2.

Persistence to ERA Treatment

In the pre-macitentan approval cohort, unadjusted median persistence for patients taking ambrisentan was nearly twice as long (19 months) as that for patients taking bosentan (10 months; $P = 0.28$; Fig. 3). The adjusted hazard ratio (HR) was 0.87 (95% confidence interval [CI] 0.61, 1.24; $P = 0.434$). In the post-macitentan approval cohort, unadjusted median persistence was significantly longer for patients taking macitentan (18 months) compared with those taking ambrisentan (6 months; $P = 0.0067$) or bosentan (8 months; $P = 0.0026$). There was no statistical difference in persistence between ambrisentan- and bosentan-treated patients ($P = 0.5795$; Fig. 4). However, when the propensity score results were applied, adjusted HRs showed that persistence was significantly higher with macitentan compared with ambrisentan (1.48 [95% CI 1.12, 1.95]; $P = 0.006$) and bosentan (1.63 [95% CI 1.30, 2.04]; $P < 0.001$).

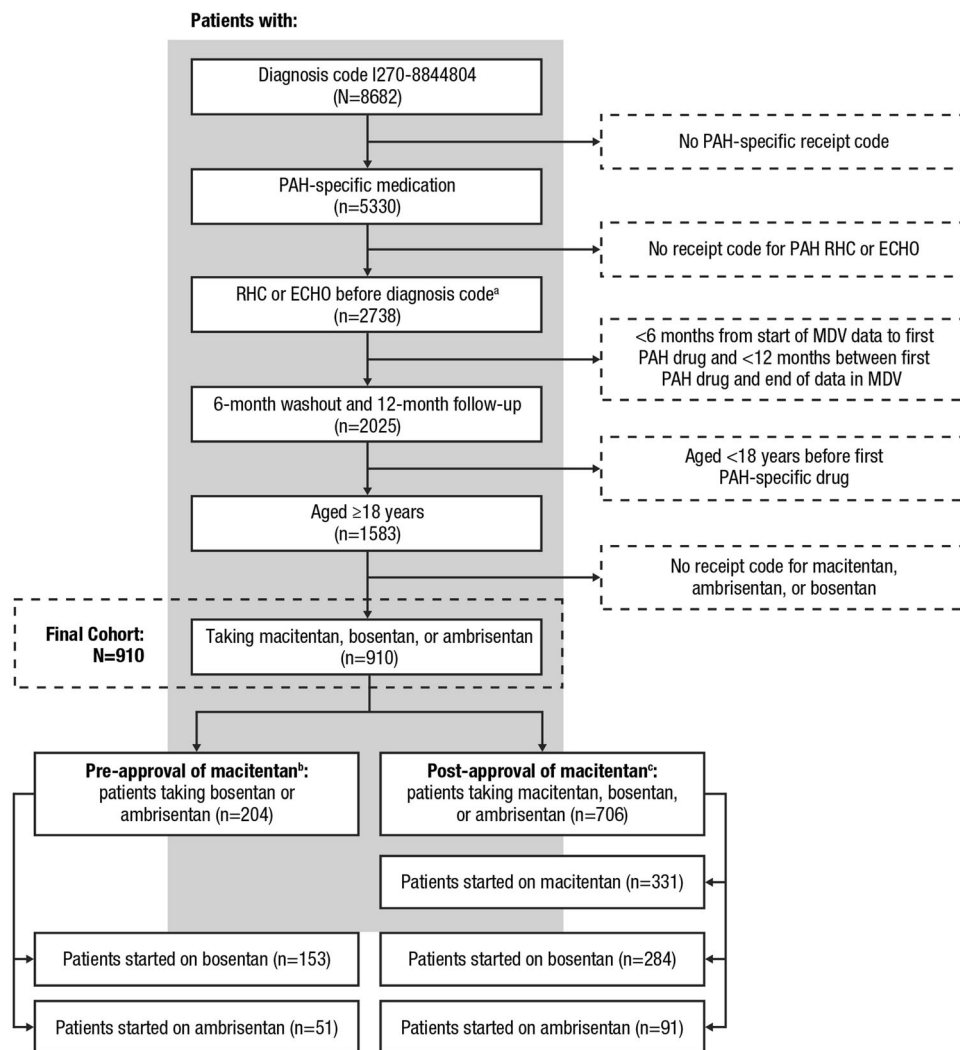


Fig. 1 Patient disposition. *ECHO* indicates echocardiography, *ERA* endothelin receptor antagonist, *MDV* Medical Data Vision database, *PAH* pulmonary arterial hypertension, *RHC* right heart catheterization. ^aBoth RHC and ECHO were considered in the diagnostic algorithm for PAH based on preliminary analysis in MDV with stricter diagnostic criteria for PAH, which demonstrated that with RHC alone, initial treatment for PAH was predominantly monotherapy, with combination therapy not being

observed to increase during treatment. In addition, ECHO is widely used in the real-world setting for the diagnosis of PAH in daily practice. ^bApproval date for macitentan in Japan was June 9, 2015. ERA index date before June 9 was considered as pre-approval use. ^cApproval date for macitentan in Japan was June 9, 2015. ERA index date after June 9 was considered as post-approval use

DISCUSSION

In this study, we used data from the Japanese MDV database to generate real-world evidence comparing adherence and persistence to ERA treatment before and after the approval of macitentan for the treatment of PAH in Japan

(June 9, 2015). Our results showed that before the approval of macitentan, median persistence to treatment appeared to be longer among patients treated with ambrisentan (19 months) compared with those treated with bosentan (10 months). After the approval of macitentan, median persistence to treatment was

Table 1 Pre-approval of macitentan: patient demographic and clinical characteristics

	Bosentan (<i>n</i> = 153)	Ambrisentan (<i>n</i> = 51)	Overall (<i>N</i> = 204)
Female gender, <i>n</i> (%)	103 (67.3)	37 (72.5)	140 (68.6)
Mean (SD) age, years	64.5 (15.0)	61.2 (16.7)	63.6 (15.5)
Median (range)	67.0 (25.0–90.0)	63.0 (20.0–91.0)	65.0 (20.0–91.0)
Age category, <i>n</i> (%)			
< 50 years	25 (16.3)	13 (25.5)	38 (18.6)
50–59 years	23 (15.0)	11 (21.6)	34 (16.7)
60–69 years	41 (26.8)	7 (13.7)	48 (23.5)
70–79 years	40 (26.1)	13 (25.5)	53 (26.0)
≥ 80 years	24 (15.7)	7 (13.7)	31 (15.2)
Therapy line, <i>n</i> (%)			
L1	137 (89.5)	45 (88.2)	182 (89.2)
L2+	16 (10.5)	6 (11.8)	22 (10.8)
Combination therapy, <i>n</i> (%)	69 (45.1)	34 (66.7)	103 (50.5)
Comorbidities, <i>n</i> (%)			
Hypertension	89 (58.2)	29 (56.9)	118 (57.8)
Diabetes	82 (53.6)	31 (60.8)	113 (55.4)
Arterial disease	68 (44.4)	22 (43.1)	90 (44.1)
Renal disease	6 (3.9)	1 (2.0)	7 (3.4)
Etiology, <i>n</i> (%)			
CTD	61 (39.9)	22 (43.1)	83 (40.7)
CHD	20 (13.1)	5 (9.8)	25 (12.3)
IPAH	5 (3.3)	1 (2.0)	6 (2.9)
Expert center, <i>n</i> (%)	0	1 (2.0)	1 (0.5)
Potential misdiagnosis ^a , <i>n</i> (%)	27 (17.6)	2 (3.9)	29 (14.2)

CHD indicates coronary heart disease, *CTD* connective tissue disease, *IPAH* idiopathic pulmonary arterial hypertension, *L1* first line, *L2+* second line or greater, *PAH* pulmonary arterial hypertension, *SD* standard deviation

^aPAH is most often misdiagnosed as asthma or chronic obstructive pulmonary disease [23]

Table 2 Post-approval of macitentan: patient demographic and clinical characteristics

	Bosentan (n = 284)	Macitentan (n = 331)	Ambrisentan (n = 91)	Overall (N = 706)
Female gender, <i>n</i> (%)	210 (73.9)	205 (61.9)	57 (62.6)	472 (66.9)
Mean (SD) age, years	64.7 (15.7)	65.3 (16.1)	64.1 (17.3)	64.9 (16.1)
Median (range) age, years	67.5 (19.0–96.0)	68.0 (18.0–92.0)	70.0 (18.0–91.0)	68.0 (18.0–96.0)
Age category, <i>n</i> (%)				
< 50 years	51 (18.0)	57 (17.2)	21 (23.1)	129 (18.3)
50–59 years	42 (14.8)	41 (12.4)	8 (8.8)	91 (12.9)
60–69 years	67 (23.6)	79 (23.9)	16 (17.6)	162 (22.9)
70–79 years	72 (25.4)	99 (29.9)	32 (35.2)	203 (28.8)
≥ 80 years	52 (18.3)	55 (16.6)	14 (15.4)	121 (17.1)
Therapy line, <i>n</i> (%)				
L1	250 (88.0)	278 (84.0)	76 (83.5)	604 (85.6)
L2+	34 (12.0)	53 (16.0)	15 (16.5)	102 (14.4)
Combination therapy, <i>n</i> (%)	100 (35.2)	234 (70.7)	66 (72.5)	400 (56.7)
Comorbidities, <i>n</i> (%)				
Hypertension	161 (56.7)	182 (55.0)	56 (61.5)	399 (56.5)
Diabetes	183 (64.4)	223 (67.4)	52 (57.1)	458 (64.9)
Arterial disease	179 (63.0)	122 (36.9)	38 (41.8)	339 (48.0)
Renal disease	13 (4.6)	24 (7.3)	3 (3.3)	40 (5.7)
Etiology, <i>n</i> (%)				
CTD	202 (71.1)	153 (46.2)	35 (38.5)	390 (55.2)
CHD	14 (4.9)	21 (6.3)	10 (11.0)	45 (6.4)
IPAH	5 (1.8)	16 (4.8)	0	21 (3.0)
Expert center, <i>n</i> (%)	29 (10.2)	47 (14.2)	8 (8.8)	84 (11.9)
Potential misdiagnosis, <i>n</i> (%)	47 (16.5)	46 (13.9)	11 (12.1)	104 (14.7)

CHD indicates coronary heart disease, *CTD* connective tissue disease, *IPAH* idiopathic pulmonary arterial hypertension, *L1* first line, *L2+* second line or greater, *SD* standard deviation

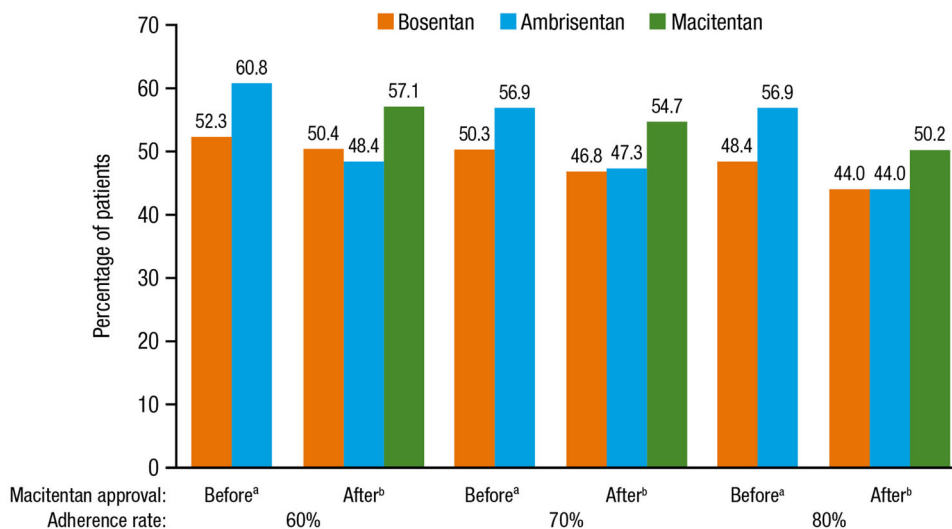


Fig. 2 Adherence rates (60%, 70%, and 80%) among patients by treatment group and time before or after approval of macitentan in Japan. ^aOverall, 20% of patient data were missing. ^bOverall, 17% of patient data were missing

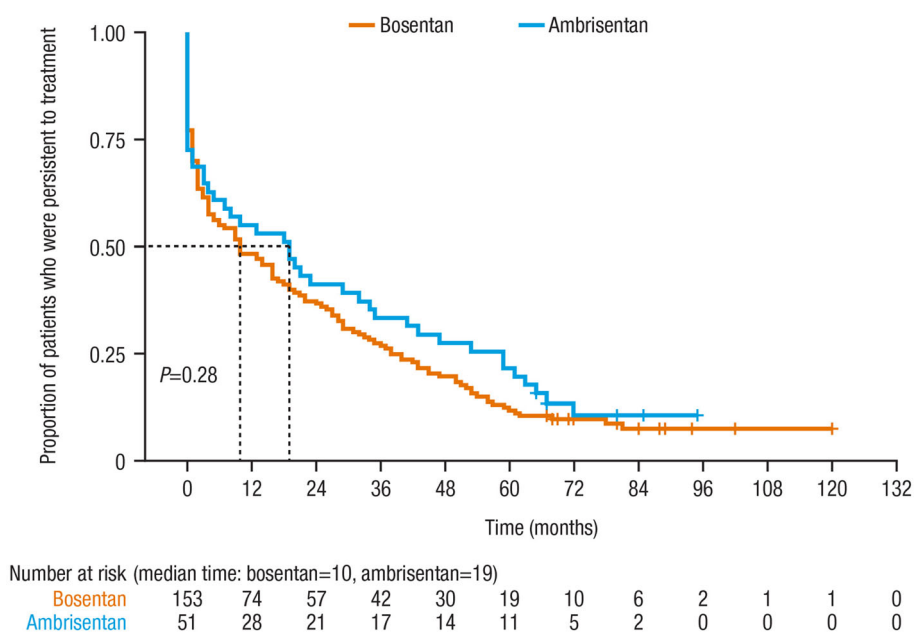


Fig. 3 Pre-approval of macitentan: persistence to treatment. *ERA* endothelin receptor antagonist

significantly longer among patients taking macitentan (18 months) compared with those taking ambrisentan (6 months) or bosentan (8 months).

In the current study, a notably large percentage of patients were female (67.3%), which is consistent with the results from Japanese registry studies (76–79%) [17, 18, 33]. However,

patients in the current study were generally older (mean age 66 years) compared with patients in the Japanese registry studies (mean age 48–53 years) [17, 18, 33]. This difference is important, as it highlights the added value the MDV database provides for identifying and characterizing an older population of Japanese patients with PAH. Moreover, the MDV

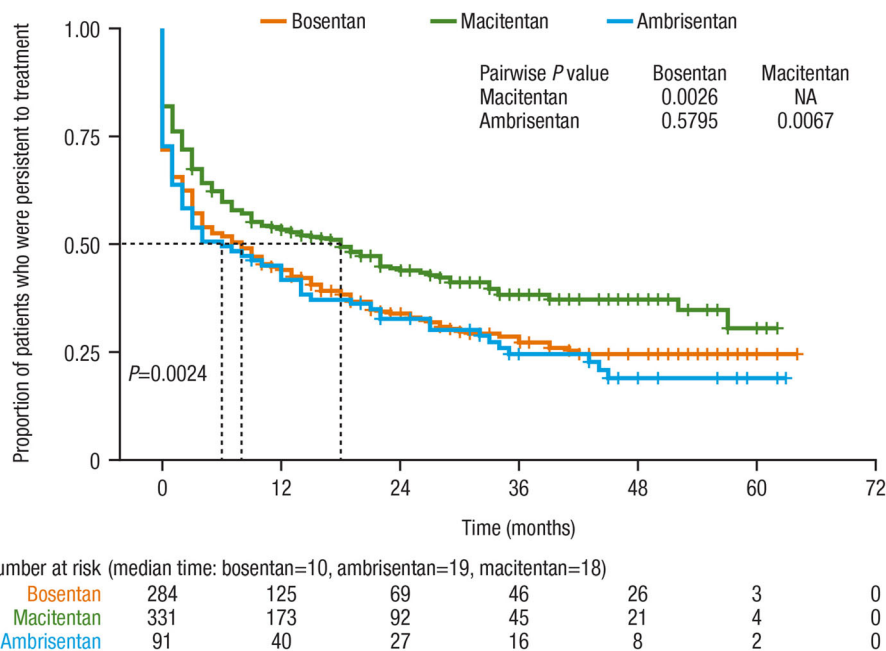


Fig. 4 Post-approval of macitentan: persistence to treatment. *ERA* endothelin receptor antagonist

database includes data from patients seen at PAH specialty centers as well as non-PAH specialty centers, which more closely reflects the real-world PAH management landscape.

Patients who received bosentan in the pre- versus post-macitentan approval cohort had a lower rate of CHD etiology (5% versus 13%) and a higher rate of CTD etiology (71% versus 40%). Only small percentages of patients who received bosentan in the pre- and post-macitentan approval cohort had IPAH (3% and 2%). By contrast, recently published data from the Japan Pulmonary Hypertension Registry (JAPHR) showed idiopathic/heritable pulmonary arterial hypertension was the most common etiology during the two evaluation periods (2008–2015, 50%; 2016–2020, 51%) [33]. The rates of CHD etiology were similar (13% and 7%) and the rates of CTD etiology were notably lower (25% and 32%) [33] compared with those in the current study. These differences may be explained, in part, by characteristics of the MDV database and JAPHR. The current study using the MDV database only presents data from patients receiving ERA treatment and is representative of both PAH and non-PAH expert centers. In contrast, JAPHR includes data for all patients

with PAH, including those who were not prescribed ERA treatment and only captures patients treated at PAH expert centers. Therefore, data availability is a potential study limitation that may have led to differences in population coverage, age distribution, types of hospitals covered, and procedures used for diagnosis of PAH.

Before the approval of macitentan in Japan, persistence to bosentan was notably shorter compared with persistence to ambrisentan (10 versus 19 months). After the approval of macitentan in Japan, persistence to bosentan and ambrisentan shortened considerably (8 and 6 months), while persistence to macitentan was two and three times longer, respectively (18 months). The reason(s) for such a precipitous decline in persistence with bosentan and ambrisentan is(are) not clear from the available MDV data. The decline is unlikely to be due to the use of combination therapy. In bosentan-treated patients, combination therapy decreased from pre- to post-macitentan approval (45–35%); in ambrisentan-treated patients, combination therapy increased from pre- to post-macitentan approval (67–73%). In macitentan-treated patients, combination

therapy was 71%, which was similar to that in ambrisentan-treated patients; however, persistence was three times longer in macitentan-treated patients. In the JAPHR study, macitentan was the most frequently prescribed ERA during the 2016–2020 evaluation period whether it was taken as monotherapy or combination therapy [33].

Recent real-world studies showed that the switch from bosentan or ambrisentan to macitentan was associated with greater efficacy and treatment satisfaction, as measured by the 6-min walk distance, WHO functional class, and quality-of-life questionnaires [34, 35]. Patients treated with macitentan also exhibited fewer adverse effects compared to bosentan and ambrisentan [36]. In our analysis, higher adherence rate and persistence to macitentan were observed compared with bosentan and ambrisentan, which may be related, in part, to the improved efficacy and safety profile also described in these previous studies. Further evaluation is warranted to understand the factors associated with treatment adherence to ERAs.

Current ESC/ERS 2015 guidelines for the treatment of pulmonary hypertension, including PAH, recommend initial or sequential combination therapy with an ERA and a PDE5 inhibitor [6]. Escalation to triple therapy is recommended if there is an inadequate clinical response within 3 to 6 months of follow-up [37]. Macitentan was the first drug to demonstrate efficacy in PAH, including patients with PAH already on treatment, in a clinical trial using morbidity/mortality as the endpoint [38]. Nevertheless, the current analysis suggests that inadequate persistence to therapy is not related to the number of medications being taken to treat PAH. Further real-world studies are warranted to evaluate the potential effects that older age, comorbidities, and drug tolerability might have on persistence to ERAs, as monotherapy or combination therapy. It would also be of value to investigate the consequences of poor persistence, including switching ERA or changing to another drug class or combination of classes. The results of such proposed studies may provide insights into ways to improve persistence on PAH therapy.

Current ESC/ERS guidelines notwithstanding, RHC is invasive and requires a high level of skill to obtain reliable, reproducible, and informative results. RHC also is associated with the risk of serious complications, including bleeding, if not performed at expert centers. The risk of complications associated with RHC is higher in elderly (versus younger) patients and in those with (versus those without) comorbid conditions. Moreover, PAH is diagnosed by ECHO in daily practice, while also accounting for patient factors (e.g., age, comorbidities) and environmental factors (e.g., presence of PAH experts) [39]. Therefore, in this study we included patients who received a diagnosis of PAH after ECHO to better reflect the real-world setting in Japan for the diagnosis and management of PAH. In this study, 28% of patients had RHC and nearly all patients had ECHO before their diagnosis of PAH, which is consistent with clinical practice in Japan.

A large percentage of patients were diagnosed with apparent PAH on the basis of ECHO findings. In fact, many PAH epidemiological studies use ECHO (not RHC) for the diagnosis of PAH. The lack of RHC being conducted for diagnosis may be attributed to the lack of experience in PAH care, which resonates with limited data being available from expert centers. In addition, it is possible that the percentage of patients who had RHC may be underestimated, as patients may have undergone the procedure in another hospital before MDV data were collected for the most recent hospital. Indeed, our data showed that patients with PAH were older and had more comorbidities than those in previous epidemiological studies in Japan [17, 18]. It is possible that advanced age and the presence of comorbidities may have influenced the physicians' choice of diagnostic tests (RHC versus ECHO) for PAH in the clinical setting. Currently, claims databases do not contain sufficient details regarding patients' health status, but further research is certainly warranted to better understand the decision-making process for choosing PAH diagnostic tests among healthcare providers in clinical practice in Japan.

Data on the use of combination therapy in Japanese patients are sparse. One real-world

Japanese study evaluated the long-term efficacy and safety of PAH-specific combination therapy for affected patients [40]. In that study, ambrisentan and a PDE5 inhibitor combination therapy improved hemodynamic parameters in treated patients. The tolerability profile was consistent with that of previous clinical trials conducted in Japanese patients. Results from the recent JAPHR study showed that the use of combination therapies increased from 48% in the 2008–2015 evaluation period to 58% in the 2016–2020 evaluation period [33]. The percentage of patients who were prescribed an ERA (regardless of the combination drug) increased from 90 to 96%, respectively [33].

Our findings should be interpreted with some limitations considered. As a retrospective study based on available database information, the analyses were limited to the data contained therein, and there were likely to be missing patient-level data. We included patients diagnosed with PAH using ECHO or RHC to ensure a robust analysis; however, the study may include some patients who were potentially misdiagnosed. As an example, if patients had RHC performed at one hospital and ECHO performed at another, these data may appear in the MDV database as though patients had received only RHC or ECHO. Patient data are linked longitudinally to a specific hospital; therefore, patient information could be tracked only when patients returned to the same hospital. Therefore, the number of patients with PAH may be underreported or this finding may potentially reflect a change in the clinical picture of PAH in Japan compared to previous studies. Because the propensity score modeling does not actually match patients with similar propensity scores in our analysis, it was not possible to evaluate comparability among the treatment groups and evaluate changes. Additionally, we are unable to adjust for unmeasured or residual confounders that may influence patient compliance, such as patient awareness, economic conditions, and management practices of medical facilities. Finally, only in-hospital mortality data were available. Future research, possibly with a prospective study design, is warranted to address these limitations.

CONCLUSION

The results of this real-world study of patient-level data in the MDV database in Japan support the use of macitentan for treating PAH in clinical practices across the country to improve treatment compliance (persistence and adherence). Our results showed that persistence to treatment was significantly longer among patients with PAH treated with macitentan compared with those treated with ambrisentan or bosentan, suggesting that macitentan may have a better tolerability profile than ambrisentan or bosentan. Additional research is needed in Japan on whether improved persistence with macitentan versus other ERAs leads to improved long-term outcomes and tolerability in a real-world setting.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available. The claims database used for this study can only be obtained by purchasing from a vendor (Medical Data Vision Co., Ltd; <http://www.mdv.co.jp/>).

Declarations

Conflict of Interest. Junichi Omura is an employee of Janssen Pharmaceuticals. Yogeshwar Makanji is an employee of Janssen Pharmaceuticals. Nobuhiro Tanabe has nothing to disclose. Dae Young Yu is an employee of Janssen Pharmaceuticals. Jin Yu Tan is an employee of Janssen Pharmaceuticals. Sooyeol Lim is a former employee of Prospecion, which received funding from Janssen to conduct the study analyses. Mahsa H. Kouhkamari is a former employee of Prospecion, which received funding from Janssen to conduct the study analyses. Jeremy Casorso is a current employee of Prospecion, which received funding from Janssen to conduct the study analyses. David Bin-Chia Wu is an employee of Janssen Pharmaceuticals. Paul Bloomfield was an employee of Janssen Pharmaceuticals at the time of the analysis.

Ethical Approval. This study was implemented and reported in accordance with the International Conference on Harmonised (ICH) Tripartite Guidelines for Good Clinical Practice with applicable local regulations (including European Directive 2001/20/EC, US CFR 21 and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declarations of Helsinki. On the basis of Ethical Guidelines for Epidemiological Research issued by the Japanese Ministry of Health, Labor and Welfare, ethics approval and informed consent are not applicable for this study. Reference: The Ministry of Education, Culture, Sports, Science and Technology, The Ministry of Health, Labour and Welfare. Ethical principles in research ethics and Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects [in Japanese]. <https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf>. Accessed 3 February 2023.

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