Long-term efficacies of selective vasodilators in pulmonary arterial hypertension: A comprehensive comparison using a spontaneous reporting database

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Abstract

Aims: There is no clinical evidence of differences in drugs associated with long-term survival in patients with pulmonary arterial hypertension (PAH) due to a small population and the lack of information on death in the Japanese medical database systems. This study evaluated whether patient data from a spontaneous reporting database could be used for comparing the effects of pulmonary vasodilators on long-term survival in PAH patients. **Methods**: PAH patient data reported in the Japanese Adverse Drug Event Report (JADER) database from April 2004 to July 2022 were extracted. Kaplan-Meier curves were used to compare survival times. Adjusted hazard ratios (aHRs) for all-cause mortality were determined using Cox proportional hazards models. **Results**: Of 1969 PAH patients reported in the JADER database, 1208 patients were included in the survival analyses. The patient demographics were similar to those of the PAH population reported in the Japan Pulmonary Hypertension Registry. Among drugs targeting the prostacyclin pathway, epoprostenol was most associated with long-term survival (aHR: 0.38; 95% confidence interval [CI], 0.23–0.64). The PAH patients treated with endothelin receptor antagonists had improved survival, especially in the macitentan users (aHR: 0.30; 95% CI, 0.22–0.42). Sildenafil was associated with a poor prognosis in the PAH patients (aHR: 1.56; 95% CI, 1.19–2.04). **Conclusion**: Although our results must be interpreted with caution due to several limitations inherent to spontaneous reporting databases, our approach using the JADER database for survival analysis may provide useful information in limited situations such as the treatment of rare diseases including PAH.

1. INTRODUCTION

Evidence for drug treatment strategies that improve mortality in rare disease patients is essential for clinical decision making. In rare diseases, the use of real-world data (RWD) has become a promising approach for evaluating the effects of medications on long-term survival, as large-scale clinical trials are less feasible.[1] Although several RWD sources are available in Japan, the major issue that needs to be resolved is mortality data collection.[2] The National Database of Health Insurance Claims and Specific Health Checkups of Japan, the largest database provided by the Japanese government, has limited information on death.[2]Especially in rare disease patients, efficient approaches for collecting information on death are required to evaluate the long-term survival.

The Japanese Adverse Drug Event Report (JADER) database is a spontaneous adverse event reporting database provided by the Pharmaceuticals and Medical Devices Agency (PMDA).[3] In the JADER database, information on clinical outcomes including death is individually reported with an acceptable missing data rate.[4] The death reports in the JADER database include disease-related death in addition to death due to drug side effects and have been abundantly accumulated since 2004 when the data collection began.[3,5] Patient data reported in spontaneous reporting databases, including the JADER database, are not considered a representative cohort of patients with a particular disease;[6] however, we hypothesized that analysis using patient data from the JADER database as a real-world patient cohort might provide useful information

about associations between medications and all-cause mortality in limited situations such as analysis for rare diseases.

Pulmonary arterial hypertension (PAH) is a rare, progressive disease characterized by pulmonary arterial remodeling, leading to elevated pulmonary vascular resistance, right ventricular failure, and death.[7] Although several PAH-specific vasodilators have been approved over the past two decades, the prognosis of PAH is still poor.[8] The effects of some PAH-specific vasodilators on improvement in PAH mortality were partially evaluated in clinical intervention studies that employed a composite endpoint of a PAH-related complication or all-cause death.[9,10]However, the long-term efficacies of PAH-specific vasodilators remain unclear due to limitations of the study period and evaluation using the composite endpoint.

PAH-specific vasodilators are classified into three categories: drugs targeting the prostacyclin pathway, drugs targeting the nitric oxide (NO) pathway, and drugs targeting the endothelin pathway.[8] Combination therapy of PAH-specific vasodilators targeting different biological pathways reduces the risk of PAH-related events, including all-cause death, compared with monotherapy.[11] Clinical practice guidelines recommend a dual-combination of drugs targeting the NO and endothelin pathway for PAH patients at low risk of death and the addition of a prostacyclin analogue to the dual-combination for high-risk PAH patients.[12] However, there is no consensus on which drug is most associated with long-term survival in PAH patients among pulmonary vasodilators targeting the same biological pathway.[13] Although head-to-head trials directly comparing all drugs in the same category are required, it is difficult to comprehensively conduct large-scale clinical trials comparing all PAH-specific vasodilators targeting the same biological pathway due to PAH being a rare disease.[14] Exploratory analysis using RWD is an efficient approach for comparing the effects of PAH-specific vasodilators on long-term survival prior to conducting clinical trials.

The purpose of this study was to evaluate whether patient data from the JADER database could be used as a real-world cohort for survival analysis of rare disease patients. Moreover, we compared the effects of PAH-specific vasodilators targeting the same biological pathway on long-term survival using PAH patient data from the JADER database. Also, associations between supportive therapy and survival in the PAH patients were examined.

2. METHODS

2.1 Data source

Data reported in the JADER database from April 2004 to July 2022 were obtained from the PMDA website.[3] In Japan, drug adverse events and the clinical outcomes are spontaneously reported to the JADER database by pharmaceutical companies and healthcare workers. Any patient deaths during pharmacotherapy are reportable adverse events for the database. As of July 2022, the JADER database has 1 280 060 adverse event reports, including 86 138 deaths, for 775 566 reported patients.[3] The JADER database consists of four data tables linked by unique identification numbers: DEMO (patient demographics), DRUG (drug names, administration routes, and start and end date of administration), HIST (primary diseases), and REAC (adverse events, onset date, and clinical outcomes).

2.2 Patient data extraction

We extracted the identification numbers of Japanese PAH patients whose primary diseases were reported as idiopathic or heritable PAH in the HIST table. In this study, ethics committee approval and written informed consent were waived because the study design was an observational study using an open access database with patient information fully anonymized by the PMDA.

2.3 Definition of clinical outcomes

Clinical outcomes of respective adverse events are categorized into recovery, remission, non-recovery, sequelae, unknown, and death in the REAC table. We defined the clinical outcomes of the PAH patients with at least one adverse event that resulted in death or without adverse events that resulted in death as death from any cause or non-death, respectively. Preferred terms (PTs), high level group terms (HLGTs),

and high level terms (HLTs) in the Medical Dictionary for Regulatory Activities/Japanese version 25.1 (www.pmrj.jp/jmo/php/indexj.php) were used for coding of adverse events. Death from adverse events reported as the following PTs was defined as PAH-related death: "pulmonary arterial hypertension (PT code: 10064911)", "sudden death (PT code: 10042434)", "condition aggravated (PT code: 10010264)", PTs included in "heart failures (HLGT code: 10019280)", and PTs included in "respiratory failures (excl neonatal) (HLT code: 10052549)".

2.4 Drug information extraction

We evaluated 11 pulmonary vasodilators listed in Supplementary Table S1. The identification numbers of PAH patients treated with these drugs were extracted from the DRUG table. In this study, the PAH patients with concomitant use of PAH-specific vasodilators targeting the same biological pathways were excluded. We also evaluated supportive therapy for PAH, including oxygen therapy, anticoagulant therapy with warfarin or direct oral anticoagulant (DOAC), including apixaban, edoxaban, and rivaroxaban, and diuretic therapy with tolvaptan. Drugs reported in the DRUG table are categorized into "suspected drug", "concomitant drug", and "interacting drug". We employed drug information reported as "suspected drug" and "concomitant drug" for analyses in this study.

2.5 Survival analysis

Figure 1 shows the flow chart of survival analysis in this study. We performed survival analyses using the Kaplan-Meier method to evaluate all-cause mortality in the PAH patients reported in the JADER database. Survival times of the PAH patients with at least one adverse event that resulted in death were calculated from the number of days between the start date of any medication and the first-reported date of death from adverse events. Survival times of the PAH patients without adverse events that resulted in death were censored at the last-reported date of adverse events that resulted in recovery, remission, non-recovery, or sequelae. In the Kaplan-Meier analysis, continuous intravenous epoprostenol or treprostinil, which is recommended for high-risk PAH patients as permanent therapy, was analyzed separately from other drugs targeting the prostacyclin pathway.[12] Patients with missing information about the date of adverse events in the JADER database were excluded from the survival analyses. The log-rank test was used to compare survival times between the PAH patients treated with each pulmonary vasodilator or supportive therapy. Hazard ratios (HRs) of respective therapies evaluated in this study for all-cause mortality in the PAH patients were estimated using Cox proportional hazards models. Based on the results of HRs and Kaplan-Meier curves, the covariates for multivariate analysis were identified by selecting the clinically known variables that may affect all-cause mortality in PAH patients. We also employed a variable of warfarin use for the multivariate analysis, which has been reported as a poor prognostic factor in epoprostenol users.[15,16] A two-sided p value of < 0.05 was considered statistically significant. All statistics were analyzed using R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

2.6 Logistic regression analysis

Binary logistic regression was used to estimate odds ratios (ORs) for death from any cause in the PAH patients treated with each pulmonary vasodilator or supportive therapy. Based on the results of ORs, the variables that may be associated with death from any cause in the PAH patients were confirmed by adjusted ORs calculated from multivariate analysis. The final multivariate model selection was based on the Akaike information criterion (AIC) and receiver operating characteristic (ROC) analysis.

3. RESULTS

3.1 Patient demographics and clinical outcomes

Table 1 summarizes the demographics and clinical outcomes of the PAH patients reported in the JADER database from April 2004 to July 2022. Our study population included 1969 patients, 67.7% of which were female, and the median age was approximately 60 years old. In the PAH patients, 402 (20.4%) cases resulted in death from any cause. There were 542 adverse events reported as causes of death of the PAH patients because some patients with two or more adverse events reported in the JADER database were included.

Among these adverse events, causes of PAH-related death were as follows: 67 cases of "pulmonary arterial hypertension (PT code: 10064911)", 18 cases of "sudden death (PT code: 10042434)", 12 cases of "condition aggravated (PT code: 10010264)", 70 cases of PTs included in "heart failures (HLGT code: 10019280)", and 30 cases of PTs included in "respiratory failures (excl neonatal) (HLT code: 10052549)". The treatment distributions of respective pulmonary vasodilators in the dataset for survival analyses (n = 1208) are shown in Figure 1. Epoprostenol (n = 199), selexipag (n = 329), tadalafil (n = 512), and macitentan (n = 538) were the most frequently used drugs in the classes of parenteral prostacyclin, oral drugs targeting the prostacyclin pathway, drugs targeting the NO pathway, and drugs targeting the endothelin pathway, respectively.

3.2 Associations of PAH-specific vasodilators with long-term survival

A total of 1208 PAH patients were included in the survival analyses. Figure 2 shows Kaplan-Meier curves of PAH-specific vasodilators divided into respective drug classes. The PAH patients treated with epoprostenol had significantly longer survival than those treated with treprostinil and non-user patients ($p < 0.001$). The median survival times (95% confidence interval [CI]) of the PAH patients treated with epoprostenol and treprostinil and the non-user patients were 8.41 years (8.41–not available [NA]), 7.73 years (4.75–NA), and 5.00 years (3.95–6.26), respectively. In contrast, there was no difference in survival between the PAH patients treated with iloprost, beraprost, and selexipag and non-user patients ($p = 0.461$). The median survival times (95% CI) of the PAH patients treated with iloprost, beraprost, and selexipag and the non-user patients were not reached (1.85–NA), 5.11 years (4.33–7.73), 5.55 years (3.48–6.83), and 9.43 years (6.05–NA), respectively. The PAH patients treated with drugs targeting the NO pathway showed significant differences in survival ($p = 0.020$). The median survival times (95% CI) of the PAH patients treated with sildenafil, tadalafil, and riociguat and non-user patients were 4.47 years (3.82–6.05), 6.26 years (5.25–9.43), 6.83 years (6.83–NA), and 10.93 years (6.21–NA), respectively. The PAH patients treated with endothelin receptor antagonists (ERAs) showed significantly longer survival than non-user patients ($p< 0.001$). The median survival times (95% CI) of the PAH patients treated with bosentan, ambrisentan, and macitentan and the non-user patients were 6.05 years (5.00–NA), 4.40 years (3.43–NA), 6.83 years (6.26–NA), and 2.44 years (1.53–NA), respectively.

3.3 Associations of supportive therapy with long-term survival

Figure 3 demonstrates the association between each supportive therapy and survival times in the PAH patients reported in the JADER database. The PAH patients with oxygen therapy had significantly longer survival than non-user patients ($p = 0.004$). The median survival times (95% CI) of the PAH patients with oxygen therapy and the non-users were 10.04 years (6.19–NA) and 6.01 years (4.75–6.32), respectively. The PAH patients with concomitant use of epoprostenol and warfarin had slightly shorter survival compared with the PAH patients treated with only epoprostenol. In the epoprostenol users, the median survival times (95% CI) of the PAH patients treated with warfarin and non-warfarin users were 8.41 years (NA–NA) and 10.04 years (6.21–NA), respectively. In the non-epoprostenol users, the median survival times (95% CI) of the PAH patients treated with warfarin and non-warfarin users were 6.30 years (4.09–NA) and 5.00 years (3.95–6.30), respectively. A significant difference was not observed between the PAH patients treated with DOAC and non-DOAC users ($p = 0.089$). The median survival times (95% CI) of the DOAC users and the non-users were 4.75 years (2.23–NA) and 6.26 years (5.55–8.41), respectively. The PAH patients treated with tolvaptan showed significantly shorter survival than non-user patients ($p < 0.001$). The median survival times (95% CI) of the PAH patients treated with tolvaptan and the non-user patients were 4.75 years (3.61–6.83) and 6.26 years (5.55–10.04), respectively.

3.4 Cox proportional hazards models

Table 2 shows the results of the Cox proportional hazards models examining the risk of all-cause mortality in the PAH patients reported in the JADER database. According to the results of the univariate and the Kaplan-Meier analyses, we selected 12 variables (sex, age, epoprostenol, sildenafil, tadalafil, bosentan, ambrisentan, macitentan, oxygen, warfarin, DOAC, and tolvaptan) for the multivariate analysis (Model 1). The significant variables in Model 1 and the interaction between epoprostenol and warfarin were adjusted in Model 2 as a final model. The HRs of all variables in the univariate analyses were demonstrated in

Supplementary Table S2.

3.5 Predictions of clinical outcomes

A total of 1550 PAH patients were included in logistic regression analyses after excluding the patients with concomitant use of PAH-specific vasodilators targeting the same biological pathways. Table 3 demonstrates the univariate and multivariate logistic regression models that estimate clinical outcomes (death or non-death) of the PAH patients reported in the JADER database. The multivariate model with the interaction term between epoprostenol and warfarin had lower AIC than without the interaction term. The area under the ROC curve of the final model was 0.668. Supplementary Table S3 summarizes the ORs of all variables in the univariate analyses.

4. DISCUSSION

The present study evaluated whether patient data from the JADER database could be used for survival analysis to compare the long-term efficacies of PAH-specific vasodilators targeting the same biological pathway in PAH patients. Our study findings indicate that continuous intravenous epoprostenol and oral ERAs were associated with long-term survival in PAH patients. In contrast, sildenafil, a phosphodiesterase 5 inhibitor (PDE5i), did not associate with improvement in PAH mortality in this study. To the best of our knowledge, this is the first report to comprehensively compare the effects of PAH-specific vasodilators on long-term survival using a spontaneous reporting database. Our results suggest that spontaneous reporting databases partially provide useful information about associations between medications and all-cause mortality in limited situations such as analysis for rare diseases.

The demographics of the PAH patients reported in the JADER database were characterized by a high proportion of females, and most of the patients were idiopathic PAH. Similar demographics of PAH patients were reported in studies using RWD, such as patient registries or medical records.[16–19] Ogawa et al. conducted a retrospective medical chart review assessing 141 Japanese PAH patients and reported that 40 patients died during the study period, and 21 patients died from heart failure.[16] Although the JADER database is a spontaneous adverse event reporting database, the data of PAH patients contain causes of disease-related death, including death from heart failure, as well as just side effects of drugs. In our study population, the percentage of patients whose clinical outcomes were reported as death and the treatment distributions of respective pulmonary vasodilators were similar to the rate of all-cause death and treatments distributions in PAH patients registered in the Japan Pulmonary Hypertension Registry (JAPHR), the largest network of pulmonary hypertension hospitals in Japan.[20,21] In the JAPHR, approximately 20% of the registered patients resulted in death from any causes; the most frequently prescribed drugs in each major drug class were epoprostenol, selexipag, tadalafil, and macitentan, in consistency with our results.[20,21] The high similarity of our study population to other RWD often used for cohort studies indicates the reliability of our results. In limited situations where representative patient population data in rare diseases, such as PAH, are unavailable, patient data from a spontaneous reporting database, with confirmed similarity of the demographics to the whole patient population, may be alternative data for cohort studies.

The present study showed that among drugs targeting the prostacyclin pathway, epoprostenol was most associated with long-term survival in the PAH patients reported in the JADER database. The 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines recommend the addition of epoprostenol or treprostinil to the combination of an ERA and a PDE5i for high-risk PAH patients.[12] The effect of epoprostenol on long-term survival has been confirmed in clinical trials;[22–24]however, there are no clinical trials directly comparing epoprostenol and treprostinil regarding long-term survival. Epoprostenol requires continuous administration via a central venous catheter owing to its short half-life.[25] In contrast, treprostinil is chemically stable, and several delivery systems, including implantable pumps, have been developed.[26,27] Although the long-term efficacy of treprostinil was not fully confirmed in the present study, treprostinil may be an alternative for PAH patients unsuitable for epoprostenol therapy.

The associations of the use of iloprost, beraprost, and selexipag with improved survival were not observed in the present study. The effects of iloprost and beraprost on improvement in PAH mortality have not been

fully elucidated in clinical trials.[28,29] The 2022 ESC/ERS guidelines contain no specific recommendations on the use of iloprost and beraprost in the treatment algorithm for PAH.[12] The guidelines recommend add-on therapy of selexipag for PAH patients at intermediate risk despite receiving the initial combination therapy of an ERA and a PDE5i.[10,12] The JADER database cannot distinguish whether reported drugs are administered as initial or second-line add-on therapy, while 71.1% of the selexipag users were also ERA and PDE5i users in our study (data not shown). The PAH patients reported as selexipag users in the JADER database may include many patients resistant to initial therapy, which might influence our results.

The PAH patients treated with sildenafil were associated with a poor prognosis compared with the patients treated with tadalafil or the non-PDE5i users in the present study. The 2022 ESC/ERS guidelines recommend initial combination therapy with tadalafil and an ERA for PAH patients at low or intermediate risk based on the evidence from a randomized controlled trial that compared the combination of tadalafil and ambrisentan with each monotherapy.[11,12] There is little evidence for the superiority of tadalafil over sildenafil. Tadalafil is a long-acting PDE5i with a half-life of 17.5 hours compared with 4 hours for sildenafil.[30] The longer half-life of tadalafil contributes to stable hemodynamics in PAH patients, which may be associated with our results. The superiority of riociguat, a soluble guanylate cyclase stimulator, over PDE5is was not fully confirmed in the present study. Although the effect of switching to riociguat from PDE5is has been evaluated,[31] initial use of riociguat in newly diagnosed PAH patients should be assessed in future studies.

The PAH patients treated with ERAs, especially macitentan, had significantly better survival than the non-user patients in the present study. There is little information about the comparison of the efficacies of ERAs, while different safety profiles have been observed in clinical trials of each ERA.[9,32,33] The use of bosentan was related to dose-dependent increases in liver transaminases and is not strongly recommended in the 2022 ESC/ERS guidelines compared with other ERAs.[12,33] Ambrisentan and macitentan had low liver toxicity; however, the clinical trials of ambrisentan or macitentan demonstrated an increased incidence of peripheral edema or anemia, respectively.[9,32] Although our data suggest that macitentan was superior to other ERAs for long-term survival, their safety profiles and baseline characteristics of PAH patients should be considered in ERA selection.

Oxygen therapy for PAH patients was not associated with long-term survival in our results. Ulrich et al. reported that oxygen therapy improved exercise capacity in PAH patients.[34] Oxygen therapy is effective for PAH patients as a symptomatic treatment. In the present study, the effect of warfarin on improvement in all-cause mortality was observed in only non-epoprostenol users. Similar tendencies were reported by Ogawa et al.[16] These findings suggest that PAH patients with epoprostenol therapy do not benefit from anticoagulant therapy with warfarin. The relationship between anticoagulant therapy with DOAC and epoprostenol was not assessed in the present study because of the small sample size of DOAC users. The use of tolvaptan was associated with a poor prognosis in our study. Tolvaptan is used for the treatment of right ventricular failure due to PAH in combination with traditional diuretics such as furosemide.[35] Thus, in the present study, PAH patients using tolvaptan potentially have had a poor prognosis owing to the comorbidity of right ventricular failures.

Our study has several limitations. Firstly, high censoring rates were observed in the survival analyses. The JADER database does not include follow-up data for each patient. We used the last-reported date of adverse events as a censoring date to estimate the survival times of the non-death PAH patients. This approach enables large-scale survival analysis using a spontaneous adverse event reporting database, while careful interpretation of the results is needed owing to the tendency to consider non-death patients as censored. Secondly, our study did not assess the effect of combination therapy of PAH-specific vasodilators. We extracted all drug information related to the treatment of PAH from the DRUG table; however, our analyses did not distinguish whether these drugs were administered as mono or combination therapy. The present study performed multivariate analyses to eliminate the influence of covariates including concomitant use of other pulmonary vasodilators. Our results potentially reflect the inherent efficacies of PAH-specific vasodilators as monotherapy. Future clinical trials are required to confirm the effect of combination therapy of PAH-specific vasodilators. Thirdly, the JADER database contains several biases inherent to RWD such

as the potential of missing or wrongly entered data and the duplications of patient data. Additionally, the JADER database is a passive reporting system and is influenced by under-reporting which is the problem that not all occurrences of adverse events are reported to the database. Careful application of our data to clinical decision making is needed.

5. CONCLUSION

Although evidence from our results requires careful application to clinical decision making owing to several limitations inherent to spontaneous reporting databases, our approach using a spontaneous adverse event reporting database for survival analysis may provide useful information on treatment efficacies in limited situations such as the treatment of rare diseases. Among drugs targeting the prostacyclin pathway, epoprostenol was most associated with long-term survival in the PAH patients reported in the JADER database. ERAs, especially macitentan, were associated with improved prognosis compared with non-ERA users. In contrast, the effect of sildenafil on improvement in PAH mortality was not observed in our data, suggesting the relative superiority of tadalafil over sildenafil. Additionally, the long-term efficacy of anticoagulant therapy with warfarin was confirmed in only non-epoprostenol users.

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CONFLICT OF INTEREST STATEMENT

None.

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None.

DATA AVAILABILITY STATEMENT

The majority of the data evaluated during this study are included in this published article and supplementary information. Any other data sets generated during the current study are available from the corresponding author upon reasonable request.

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Table 1 Demographics and clinical outcomes of the patients with pulmonary arterial hypertension reported in the Japanese Adverse Drug Event Report database

Total cases of PAH	1969
Subtypes of PAH, n (%)	
Idiopathic PAH	1958 (99.4)
Heritable PAH	11 (0.6)
Sex, n (%)	
Male	617 (31.3)
Female	1333 (67.7)
Not reported	19 (1.0)
Age, n (%)	

Total cases of PAH	1969
0–19	218 (11.1)
20–39	403 (20.5)
40–59	409 (20.8)
60–79	735 (37.3)
>80	146 (7.4)
Not reported	58 (2.9)
Clinical outcomes reported in the JADER database, n (%)	
Death from any cause[a]	402 (20.4)
Non-death[b]	1567 (79.6)
[a]The clinical outcomes of the PAH patients with at least one adverse event that resulted in death were defined as death from any cause. [b]The clinical outcomes of the PAH patients without adverse events that resulted in death were defined as non-death. PAH, pulmonary arterial hypertension; JADER, Japanese Adverse Drug Event Report.	[a]The clinical outcomes of the PAH patients with at least one adverse event that resulted in death were defined as death from any cause. [b]The clinical outcomes of the PAH patients without adverse events that resulted in death were defined as non-death. PAH, pulmonary arterial hypertension; JADER, Japanese Adverse Drug Event Report.

Table 2 Results of the Cox proportional hazards models examining the risk of all-cause mortality in patients with pulmonary arterial hypertension reported in the Japanese Adverse Drug Event Report database

Variable	Variable	n (%)		Model 1[a]	Model 2[b]
			Crude HR (95%CI)	Adjusted HR (95%CI)	Adjusted HR (95%CI)
Sex	Female	833 (69.0)	ref.	ref.	ref.
	Male	375 (31.0)	1.38 (1.07–1.77)	1.45 (1.13–1.88)	1.44 (1.11–1.86)
Age	<60	581 (48.1)	ref.	ref.	ref.
	[?]60	627 (51.9)	2.34 (1.81–3.03)	2.19 (1.66–2.88)	2.17 (1.65–2.85)
Epoprostenol	Non-user	1009 (83.5)	ref.	ref.	ref.
	User	199 (16.5)	0.47 (0.32–0.69)	0.58 (0.38–0.88)	0.38 (0.23–0.64)
Sildenafil	Non-user	930 (77.0)	ref.	ref.	ref.
	User	278 (23.0)	1.48 (1.15–1.92)	1.60 (1.16–2.20)	1.56 (1.19–2.04)
Tadalafil	Non-user	696 (57.6)	ref.	ref.	-
	User	512 (42.4)	0.76 (0.60–0.98)	1.04 (0.77–1.40)	-
Bosentan	Non-user	984 (81.5)	ref.	ref.	ref.
	User	224 (18.5)	0.75 (0.55–1.04)	0.41 (0.28–0.61)	0.42 (0.28–0.61)
Ambrisentan	Non-user	977 (80.9)	ref.	ref.	ref.
	User	231 (19.1)	1.41 (1.05–1.88)	0.65 (0.45–0.94)	0.67 (0.47–0.96)
Macitentan	Non-user	670 (55.5)	ref.	ref.	ref.
	User	538 (44.5)	0.61 (0.48–0.79)	0.32 (0.22–0.45)	0.30 (0.22–0.42)
Oxygen	Non-user	981 (81.2)	ref.	ref.	-
	User	227 (18.8)	0.61 (0.44–0.85)	0.80 (0.55–1.16)	-
Warfarin	Non-user	916 (75.8)	ref.	ref.	ref.
	User	292 (24.2)	0.87 (0.65–1.16)	0.74 (0.55–0.99)	0.62 (0.45–0.86)
DOAC	Non-user	1154 (95.5)	ref.	ref.	-
	User	54 (4.5)	1.51 (0.93–2.44)	0.93 (0.56–1.54)	-
Tolvaptan	Non-user	1044 (86.4)	ref.	ref.	ref.
	User	164 (13.6)	1.75 (1.29–2.37)	2.02 (1.46–2.80)	1.99 (1.46–2.71)

Variable	Variable	n (%)		Model 1[a]	Model 2[b]
Epoprostenol:Warfarin (Interaction term)	Epoprostenol:Warfarin (Interaction term)	-	-	-	3.94 (1.75–8.86)
[a]All selected variables were adjusted in Model 1. [b]The significant variables in Model 1 and the interaction term were adjusted in Model 2. HR, hazard ratio; CI, confidence interval; ref., reference; DOAC, direct oral anticoagulant	[a]All selected variables were adjusted in Model 1. [b]The significant variables in Model 1 and the interaction term were adjusted in Model 2. HR, hazard ratio; CI, confidence interval; ref., reference; DOAC, direct oral anticoagulant	[a]All selected variables were adjusted in Model 1. [b]The significant variables in Model 1 and the interaction term were adjusted in Model 2. HR, hazard ratio; CI, confidence interval; ref., reference; DOAC, direct oral anticoagulant	[a]All selected variables were adjusted in Model 1. [b]The significant variables in Model 1 and the interaction term were adjusted in Model 2. HR, hazard ratio; CI, confidence interval; ref., reference; DOAC, direct oral anticoagulant	[a]All selected variables were adjusted in Model 1. [b]The significant variables in Model 1 and the interaction term were adjusted in Model 2. HR, hazard ratio; CI, confidence interval; ref., reference; DOAC, direct oral anticoagulant	[a]All selected variables were adjusted in Model 1. [b]The significant variables in Model 1 and the interaction term were adjusted in Model 2. HR, hazard ratio; CI, confidence interval; ref., reference; DOAC, direct oral anticoagulant

Table 3 Logistic regression analysis examining the relationship between the treatment of pulmonary arterial hypertension (PAH) and clinical outcomes of PAH patients reported in the Japanese Adverse Drug Event Report database

Variable	Variable	Outcomes
		Non-death n (%)
Sex	Female	846 (80.0)
	Male	362 (73.4)
Age	<60	677 (85.8)
	[?]60	531 (69.8)
Epoprostenol	Non-use	931 (75.9)
	User	277 (85.8)
Sildenafil	Non-use	971 (79.9)
	User	237 (71.0)
Tadalafil	Non-use	726 (76.0)
	User	482 (81.0)
Riociguat	Non-use	1116 (77.4)
	User	92 (84.4)
Oxygen	Non-use	1004 (76.9)

Variable	Variable	Outcomes
	User	204 (83.3)
Warfarin	Non-use	957 (77.2)
	User	251 (81.0)
Epoprostenol:Warfarin (Interaction term)	Epoprostenol:Warfarin (Interaction term)	-
OR, odds ratio; CI, confidence interval; ref., reference	OR, odds ratio; CI, confidence interval; ref., reference	OR, odds r

FIGURE LEGENDS

Figure 1 Flow chart of survival analysis examining all-cause mortality in patients with pulmonary arterial hypertension (PAH) reported in the Japanese Adverse Drug Event Report database (JADER)

K-M, Kaplan-Meier; DOAC, direct oral anticoagulant

Figure 2 Comparison of the effects of pulmonary vasodilators on long-term survival in patients with pulmonary arterial hypertension reported in the Japanese Adverse Drug Event Report database

A, Kaplan-Meier curves of continuous infusion therapy with drugs targeting the prostacyclin pathway; B, Kaplan-Meier curves of inhalants and oral drugs targeting the prostacyclin pathway; C, Kaplan-Meier curves of drugs targeting the nitric oxide pathway; D, Kaplan-Meier curves of drugs targeting the endothelin pathway. *P* values were determined by the log-rank test.

Figure 3 The effects of supportive therapy on long-term survival in patients with pulmonary arterial hypertension reported in the Japanese Adverse Drug Event Report database

A, Kaplan-Meier curves of oxygen therapy; B, Kaplan-Meier curves of anticoagulant therapy with warfarin (Wf) with or without concomitant epoprostenol (Epo); C, Kaplan-Meier curves of anticoagulant therapy with direct oral anticoagulant (DOAC); D, Kaplan-Meier curves of diuretic therapy with tolvaptan. *P* values were determined by the log-rank test.

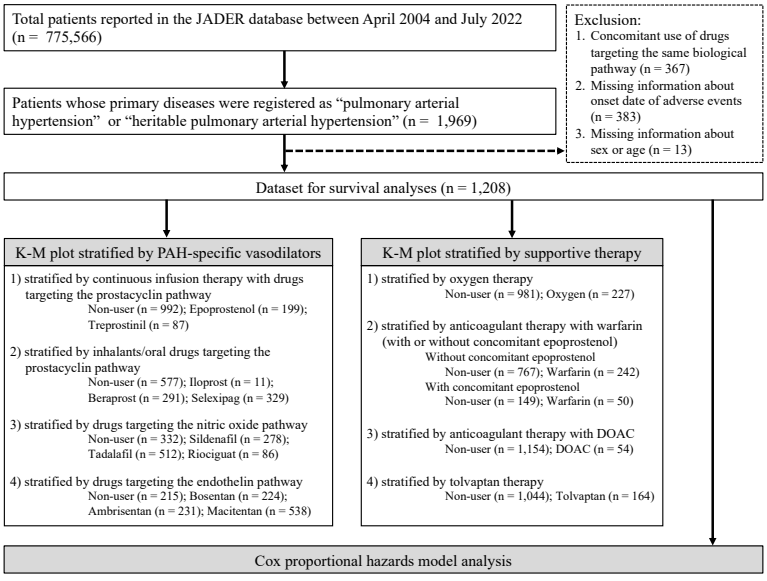

Figure 1

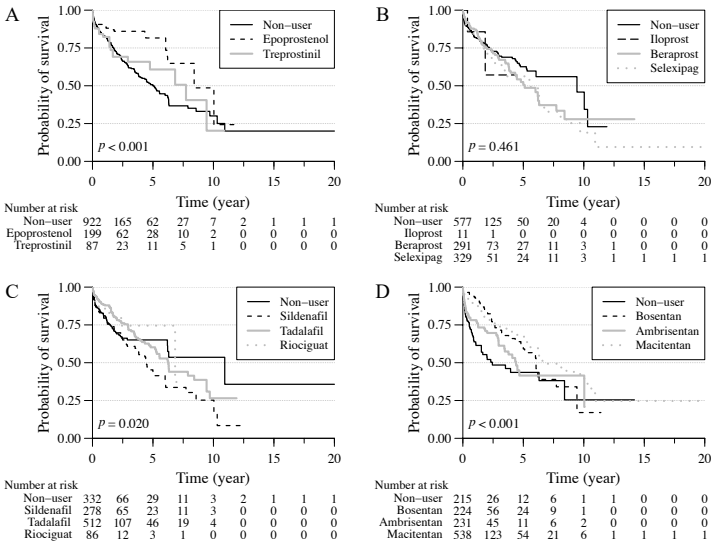

Figure 2

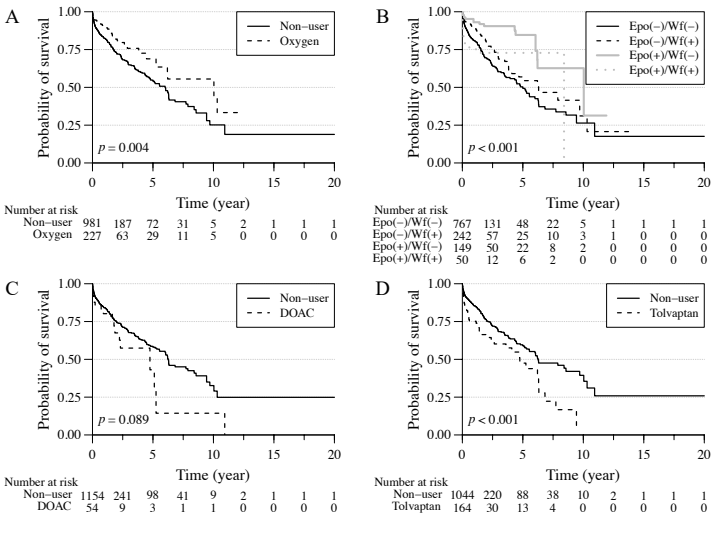

Figure 3