特集 肺高血圧症の病態と治療2016 Up to Date

# レジストリー比較からみた日本における肺高血圧症の治療*

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## はじめに

肺高血圧症治療をグローバルな視点からみると，この2～3年の変革は大きなものとなっている．従来は2005年にHoeperらが行った報告から[1]，運動耐容能の改善を治療の目標におき，その目標を達成できない場合には併用療法を進めていくという治療戦略をGoal Oriented Therapyと呼び，主として運動耐容能で評価した治療のゴール(Treatment Goal)というものが強く意識されてきた．運動耐容能ひいては6分間歩行距離の改善が肺高血圧症治療薬の開発や予後の寄与に改善したことは紛れもない事実である．これは希少疾患である肺高血圧症の治療薬開発において，ほとんど薬剤がない時代に死亡や入院などのいわゆるHard Endpointを設定することは，薬剤開発まで多大な時間を要することを意味するため，倫理的側面からもしかるべき措置であったといえる．しかし薬剤が充実してきた現在では，臨床試験の短期効果の指標としての6分間歩行距離の改善は必ずしも長期予後を反映するものではないこと[2]から，昨今では死亡や肺移植の施行および心不全による入院や症状の悪化に伴う薬剤の増量などをエンドポイントと定義する“Time to Clinical Worsening(TTCW)”という概念が臨床試験のエンドポイントとしても使用されるようになっている．また，後述するように併用療法に関してもエビデンスが整ってきたことから，早期併用療法が積極的に推奨されるようにガイドラインの変更も行われている[3,4]．

そこで本稿では，現在使用されている肺高血圧症治療薬における併用療法のエビデンスを紹介するとともに，今後の世界の潮流となる治療を先取りして行っていた本邦において，併用療法を用いた治療戦術に関してレジストリーから俯瞰した解説を行う．

## Upfront combination therapy

これまで薬剤の開発として行われてきた臨床試験はいずれも単剤の効果を評価するランダム化比較試験であった．したがって現在日本では主流になっている早期からの併用療法に関しては，まだ発展途上にある点が，肺動脈性肺高血圧症(PAH)治療の課題である．2014年はこの早期併用療法の有効性に関する国際的認知を深める意味で，大きな変革の年であった．フランスの国立肺高血圧症センターからは，NYHA Ⅳ度のPAH症例に対して，エポプロステノールを含めた早期併用療法の有効性を示唆する報告[5]が行われ，3年後もhistorical controlと比較して良好な予後を示唆す

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るものであった．

またそれに加えて，早期の併用療法の有効性を評価するランダム化比較試験であるAMBITION studyの結果も報告された[6]．AMBITION studyはタダラフィルとアンブリセンタンによるup-front combination therapyとおのおのの単剤治療を比較した二重盲検下ランダム化比較試験である．NYHA Ⅱ～Ⅲ度の未治療のPAH症例を対象とし，早期併用群では8週間のタイトレーションスケジュールでタダラフィルとアンブリセンタンを最大用量(40 mg/10 mg each)まで増量した．一方，単剤治療群は各薬剤の最大用量を使用した．組み入れ症例数は解析に入った数で605例とPAHを対象とした試験のなかでは大きなものであった．この試験でも死亡およびTTCWが評価の対象であり，入院・肺高血圧症の進行・治療効果不十分の項目をclinical failureと定義し，複合一時エンドポイントとした．clinical failureの発現に関してupfront combination therapy群が単剤治療群に対して50%のrisk reduction (p=0.0002)を実現し，タダラフィル単剤およびアンブリセンタン単剤との比較においておのおの同様の結果であった．ただしこの差はやはり主に入院イベントによってもたらされた(死亡リスクは有意差を認めなかった)．

これらの結果から，最新の欧州のPAHガイドラインにおいてはNYHA Ⅱ～Ⅲ度のPAHに対しては，タダラフィル+アンブリセンタンによるupfront combination therapyが高いレベルで推奨されるようにガイドラインが変更され[3]，NYHA Ⅳ度の例に対してはエポプロステノールを含めた併用療法が推奨されるようになることが期待される．

## レジストリーの意義

以上のようにPAHに対する薬物療法の進歩はめざましく，数多くの患者がその恩恵を受けていることは間違いない．またupfront combination therapyの例のようにEBMの充実という意味での発展もめざましい．それらの観点から，特に軽症で発見されたPAH症例に対する治療法は国際間でも差異がなくなってきている．一方，実臨床で問題になるのは多くの場合初診時よりNYHA Ⅲ～Ⅳ度で高い肺血管抵抗を伴う重症PAH例であるが，これらの例に対するEBMは依然として不足しており，ほとんどのランダム化比較試験にもこういった最重症例の患者は組み入れられていない．そこで多くの肺高血圧症治療薬が手に入るようになった現在でも，各国でどのような治療が行われて，予後がどのようになっているかをレジストリーのデータから検討することは非常に重要である．

また，ここ数年の間に各国で行われているレジストリーの特徴として，Incident caseに関する検討が重要視されるようになったことが挙げられる．Incident caseとは，レジストリー組み入れ開始後に新規に診断された症例を指すものであり，対する用語としてあるPrevalent caseとは，既に診断され存在していた症例のことを指す．PAHは希少疾患であるため，従来は少しでも多くの症例を検討に入れるためにPrevalent caseを用いた検討が行われていたが，特に予後に関してはバイアスがあるため(以前から診断されてその後組み入れ時まで生存している症例しか組み入れられない)，現在ではこの両者を区別して検討することが行われている．事実，多くの症例数が登録されている3つのレジストリーすなわちREVEALレジストリー(Registry to Evaluate Early and Long-Term PAH Disease Management：米国)[7]・フレンチレジストリー(フランス)[8]・COMPERAレジストリー(主にドイツ)[9]では，両者を区別して登録しているか，もしくはIncident caseのみに限っての登録を行っている．また対象疾患に関しては，従来は特発性肺動脈性肺高血圧症(IPAH)のみであったが，上記のような近年のレジストリーにおいてはNice分類の1群に分類されるPAH症例すべてを対象としていることが多い．

レジストリーにおいて最も重要な解析内容は予後の解析である．表1は各国におけるレジストリーからみた1～3年生存率の比較である．前述の米国・フランス・ドイツのデータに加えて，中国[10]および英国[11]におけるデータを併せて記している．これらのデータをみるとPAHに対する薬

表1 各国のレジストリーからみたPAHの1，2，3年生存率

| Registry | Study Cohort | 1 yr. % | | 2 yrs. % | | 3 yrs. % | |
|---|---|---|---|---|---|---|---|
| | | PAH | IPAH | PAH | IPAH | PAH | IPAH |
| フランス | Prevalent case + Incident case | Total 87<br>Prev 88<br>Inc 88 | Total 83<br>Prev 89<br>Inc 89 | Total 76<br>Prev 79<br>Inc 65 | Total 67<br>Prev 77<br>Inc 68 | Total 67<br>Prev 71<br>Inc 51 | Total 58<br>Prev 69<br>Inc 55 |
| 中国 | Incident case | NA | 68 | NA | 57 | NA | 39 |
| 米国(REVEAL) | Prevalent case + Incident case | 85 | 91 | NA | NA | 68 | 74 |
| 英国 | Incident case | 79 | 93 | 68 | 84 | 57 | 73 |
| ドイツ(COMPERA) | Incident case | NA | 92 | NA | 83 | NA | 74 |

Prev：Prevalent case，Inc：Incident case，NA：該当データなし

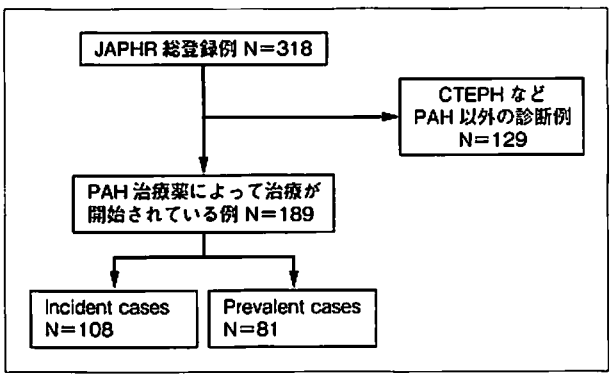


図1 JAPHRにおける症例(2015年3月現在)

剤がまだなかった1980年代のNIHからの報告[12]と比較して，当時がIPAHの1年および3年生存率が68%，48%であったのと比較すると，1年生存率には大きな改善が認められることがわかる．また比較的組み入れが新しい米国やドイツ・英国などのデータをみると3年生存率においても大きな改善が認められていることがわかる．

## 本邦におけるレジストリー Japan PH Registry(JAPHR)

このように諸外国では既にレジストリーが構築されて，数多くのデータの蓄積および臨床現場へのフィードバックがなされてきている．一方で本邦においてはこれまで多施設共同のレジストリーの試みは乏しく，国際的に発信できるデータは皆無であった．そこで厚生労働科学研究費の補助を受けて開始されたのがJapan PH Registry(JAPHR)である．全国における8カ所の肺高血圧症診療施設が参加し，現在までで既に300例以上の肺高血圧症例の登録が行われている．本研究の目的は，本邦における肺高血圧症治療や予後の実態を明らかにするだけではなく，保険償還の自由度の高さから本邦において世界に先行して始まっている多剤併用療法の有用性を評価することにある．

本稿ではJAPHRに登録されたなかから，PAHの診断を受けて肺高血圧症治療薬による治療を受けている計189例に対して解説を行う．

## JAPHRにおける Incident caseとPrevalent case

前述のようにレジストリーの解析を行う際は，Incident caseとPrevalent caseの区別を行うことが重要である．JAPHRにおいては，PAH症例189例のなかで組み入れ時に新たに診断されたIncident caseは合計108例，既に診断・治療が開始されていたPrevalent caseは81例であった(図1)．まずはIncidentおよびPrevalent caseを

表 2　JAPHR 全患者における患者特性(N＝189)

| | |
|---|---|
| 組み入れ時年齢(歳) | 45.1±16.6 |
| 診断時年齢(歳) | 43.9±16.9 |
| 女性　N(%) | 144(76.2) |
| 組み入れ時 6 分間歩行距離(m) | 306±146 |
| 組み入れ時 NYHA 心機能分類 | |
| Ⅰ，N(%) | 4(2.1) |
| Ⅱ，N(%) | 64(33.9) |
| Ⅲ，N(%) | 96(50.8) |
| Ⅳ，N(%) | 25(13.2) |
| 抗凝固療法施行患者，N(%) | 78(41.3) |

併せた 189 例の特徴に関して解説を行う．

まず背景疾患に関しては**図 2** に示す通り，半数あまりが特発性および遺伝性肺動脈性肺高血圧症(I/HPAH)であった．これは他国におけるレジストリーでの分布と大きな差異は認められなかった．またそれに引き続いて膠原病性肺動脈性肺高血圧症，先天性心疾患に伴う肺高血圧症，門脈圧亢進症に伴う肺高血圧症の順に多く認められた．次に患者特性に関してであるが，**表 2** に示す通り診断時の年齢が 40 代前半であり，女性の割合が全体の約 3/4 を占める．米国やフランスのデータと比較すると，PAH の診断時年齢はおのおの 50±15 歳，50±14 歳であり，また女性の割合はおのおの 65%，80% であることから多少のばらつきはあるものの概ね他の先進国のコホートと同様の特性をもっていることが示唆された[7,8]．また 6 分間歩行距離や診断時の NYHA 心機能分類上での重症度に関しても比較すると，米国の Incident case と Prevalent case を合わせた群において組み入れ時の 6 分間歩行距離が 329 m であり NYHA 心機能分類における Ⅲ～Ⅳ 度の割合が 56% であることから，JAPHR のほうがやや重症である可能性が示唆された．血行動態指標に関しては**表 3** に示す通りであるが，組み入れ時の血行動態指標は平均肺動脈圧 48.2 mmHg となっており，これも米国のデータ(51 mmHg)と比較して大きな差異は認められなかった．これらの観点から，JAPHR における PAH コホートは疾患の内訳や男女比だけではなく重症度においてもベースラインでほぼ共通していると考えられた．

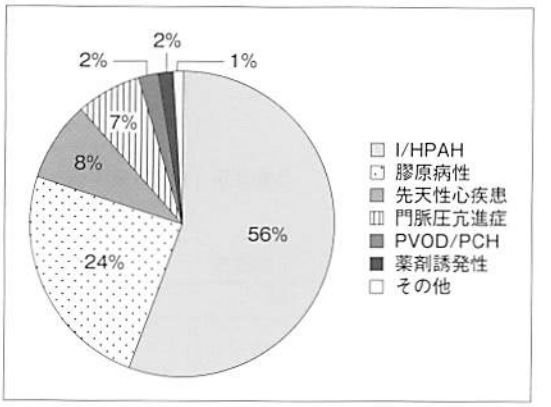


**図 2**　JAPHR における疾患分類(N＝189)
I/HPAH：特発性/遺伝性肺動脈性肺高血圧症，PVOD/PCH：肺静脈閉塞症/肺毛細血管腫症

表 3　JAPHR 全患者における組み入れ時の血行動態指標(N＝189)

| | |
|---|---|
| 混合静脈血酸素飽和度(%) | 66.6±9.7 |
| 平均肺動脈圧(mmHg) | 48.2±13.8 |
| 肺血管抵抗(dyne・sec・cm$^{-5}$) | 1,036±653 |
| 肺動脈楔入圧(mmHg) | 8.3±3.4 |
| 右房圧(mmHg) | 6.6±4.1 |
| 心係数($l$/min/m$^2$) | 2.4±0.8 |

## JAPHR における予後評価

**表 4** に JAPHR 組み入れ時の薬剤使用の割合を示す．組み入れ時においてはおよそ 3/4 の症例は依然として単剤療法を受けていることがわかる．一方で少数ながらも 3 剤併用療法を施行されている症例も認められており，重症度に応じた治療が行われていることがわかる．しかし現在の世界的な潮流は，早期からの多剤併用療法に向かっており，そのことからも今後の組み入れ時の薬剤プロファイリングは変わってくる可能性が高い．

本コホートにおける推定 3 年生存率(カプランマイヤー曲線)を**図 3** に示す．驚くべきことに，ベースラインにおいては欧米のレジストリーと同様の重症度であったにもかかわらず，**表 1** に示した各国の生存率と比較して 3 年生存率は 88% と高い値であることがわかる．やはり肺高血圧症の専門医が従来主張していた通り，本邦における肺高血圧症の予後は良いことが理解される．

表4 JAPHR全患者における組み入れ時薬剤使用特性(N=189)

| | 薬剤組み合わせ | % |
|---|---|---|
| 単剤 | PDE5阻害薬 | 33.3 |
| | エンドセリン受容体拮抗薬 | 27.0 |
| | エポプロステノール | 15.3 |
| 2剤併用 | PDE5阻害薬+エンドセリン受容体拮抗薬 | 15.4 |
| | エポプロステノール+PDE5阻害薬 | 3.7 |
| | エポプロステノール+エンドセリン受容体拮抗薬 | 3.2 |
| 3剤併用 | | 2.1 |
| 計 | | 100.0 |

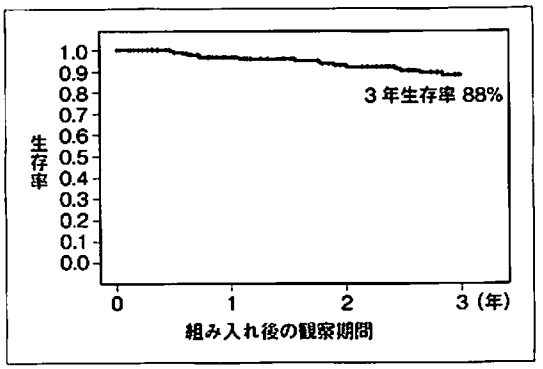


図3 JAPHRにおける3年生存率(N=189)

表5 JAPHR Incident caseにおける患者特性(N=108)

| | |
|---|---|
| 組み入れ時年齢(歳) | 48.8±17.3 |
| 女性 N(%) | 86(79.6) |
| 組み入れ時6分間歩行距離(m) | 281±145 |
| 組み入れ時NYHA心機能分類 | |
| Ⅰ, N(%) | 1(0.9) |
| Ⅱ, N(%) | 36(33.3) |
| Ⅲ, N(%) | 55(50.9) |
| Ⅳ, N(%) | 16(14.8) |
| 抗凝固療法施行患者, N(%) | 46(42.6) |

表6 JAPHR Incident caseにおける組み入れ時の血行動態指標(N=108)

| | |
|---|---|
| 混合静脈血酸素飽和度(%) | 65.0±8.9 |
| 平均肺動脈圧(mmHg) | 46.9±14.4 |
| 肺血管抵抗(dyne・sec・cm$^{-5}$) | 1,106±733 |
| 肺動脈楔入圧(mmHg) | 7.8±3.7 |
| 右房圧(mmHg) | 6.5±4.0 |
| 心係数(l/min/m$^2$) | 2.2±0.7 |

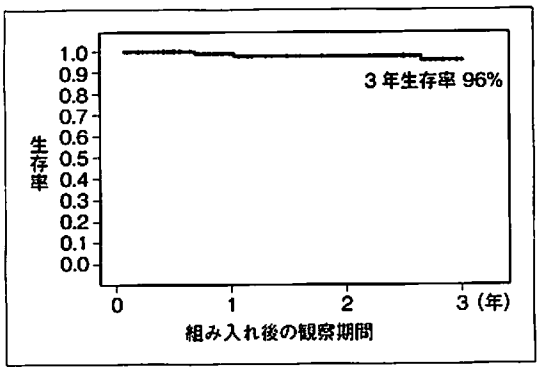


図4 JAPHRにおけるIncident caseコホートでの3年生存率(N=108)

しかしIncident caseとPrevalent caseを合わせた群においては前述のように組み入れ時のバイアスがかかってしまう可能性がある．そこで，Incident caseである108例のみに関して解析を追加した．

## JAPHRにおけるIncident caseの解析

表5・6にIncident caseのコホートにおける重症度および血行動態指標のデータを示す．多くの項目に関して，Incident caseとPrevalent caseを合わせたコホートと同様のデータであることがわかる．したがって，Incident caseのコホートも欧米のレジストリーにおけるコホートと同様の背景をもつことが示唆される．そこで，あらためて本コホートでの推定3年生存率を図4に示す．すると3年という短期間ではほとんどの症例が生存しており，従来の報告と大きく異なる予後を示していることが示唆された．

## 日本のデータから今後の展望を読み解く

最後に，本邦において予後が良好である理由について考察したい．1点目は前述の通り併用療法

の割合が多い点である．Incident caseのコホートにおいては初期から2剤以上の併用療法を行っている割合が31.5%であり，従来の単剤治療から徐々に治療を追加していくやり方とは異なる治療方針で治療が行われていることが明らかになった．また2点目はエポプロステノールの用量である．本コホートにおいてエポプロステノールの持続静注療法を行っている患者の初期ターゲット用量を評価したところ，平均で40 ng/kg/min前後の投与量であり，これも従来の欧米の報告が10～20 ng/kg/minのものが多いことを鑑みると高用量で用いられていることがわかる．肺高血圧症治療においては，現在では特に重症例に対してはthe more, the betterの治療戦略が推進されるようになってきている．本邦における良好な治療成績は，それを先取りしたものであることが示唆される．

これまで述べてきたように，IPAHの治療は積極的な治療介入すなわち多剤併用およびエポプロステノール持続静注療法の積極的な使用を躊躇しないことで，欧米の治療成績と比較してそれを凌駕する成果を実現できる可能性が極めて高い．一方で，希少疾患であることから現在でも診断や積極的な治療介入まで時間を要してしまう症例も数多く存在し，治療抵抗性の例はそういった要素が強い．今後の課題は，早期診断のための疾患啓蒙活動と積極的治療介入という治療戦術の普及にある．

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# Survival of Japanese Patients With Idiopathic/Heritable Pulmonary Arterial Hypertension

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**Idiopathic/heritable pulmonary arterial hypertension has a poor prognosis despite the available therapeutic options. Survival of Japanese patients with this disease entity has not been reported in the multicenter setting. A retrospective study of 141 patients with idiopathic/heritable pulmonary arterial hypertension treated at 3 pulmonary hypertension centers in Japan from 1992 to 2012 investigated survival and determinants of survival. Mean survival time from treatment initiation was 14.7 ± 0.8 years (95% confidence interval, 13.1 to 16.3 years) and the 1-, 3-, 5-, and 10-year survival rates were 97.9%, 92.1%, 85.8%, and 69.5%, respectively. Patients showed significant improvement in exercise capacity and hemodynamics after treatment. Patients with 6-minute walk distance >372 m, mean pulmonary arterial pressure ≤46 mm Hg, and cardiac index >2.5 L/min/m$^2$ at follow-up had a significantly better prognosis. Most patients (99.2%) were receiving pulmonary hypertension-targeted drugs at follow-up. Use of endothelin receptor antagonists and intravenous epoprostenol were related to survival in the univariate analysis. Among the patients who were on intravenous epoprostenol therapy, those with endothelin receptor antagonists had a significantly better prognosis, whereas patients on warfarin had a significantly worse prognosis. In conclusion, survival of Japanese patients with idiopathic/heritable pulmonary arterial hypertension in this study was good, showing improvement in hemodynamic parameters supported by pulmonary hypertension-targeted drugs.**  **(Am J Cardiol 2017;■:■−■)**

Pulmonary arterial hypertension (PAH) is a progressive disease with increased pulmonary vascular resistance (PVR) and pulmonary arterial pressure. The median survival of patients with idiopathic PAH was 2.8 years before PAH-targeted drugs became available.[1] Despite the progression in therapeutic options over the last 2 decades, overall survival continues to be unsatisfactory.[2−5] We previously conducted a retrospective study at a single center in Japan and reported improved survival of Japanese patients with idiopathic/heritable pulmonary arterial hypertension (I/HPAH),[6] whereby patients showed a significant improvement in hemodynamic parameters after treatment. To elucidate the survival of Japanese patients with I/HPAH on a larger scale, we conducted the first multicenter study on survival of Japanese patients with I/HPAH treated at 3 referral centers. This study also aimed to identify determinant factors for the survival of Japanese patients with I/HPAH, including hemodynamic changes and treatment regimen, and to confirm the improvement of hemodynamic parameters after treatment.

## Methods

We conducted a retrospective chart review of patients with I/HPAH. Patients were treated at 3 pulmonary hypertension centers in Japan (National Hospital Organization Okayama Medical Center, Kyorin University Hospital, and Keio University Hospital) between November 1992 and August 2012. Diagnosis was performed using a standard approach for the diagnosis of PAH including physical examination and right heart catheterization.[7,8] The study protocol was approved by the institutional review board of each hospital. The follow-up period for analyses of survival data ended in December 2014. Patients who underwent lung transplantation were censored at the time of operation.

World Health Organization (WHO) functional class, 6-minute walk distance (6MWD), plasma levels of brain natriuretic peptide (BNP), heart rate (HR), oxygen saturation ($SpO_2$), and hemodynamic parameters (mean pulmonary arterial pressure [mPAP], cardiac index [CI], mixed venous oxygen saturation [$SvO_2$], and PVR) were evaluated at baseline. Follow-up data were collected when patients achieved the best values for mPAP with preserved CI. Data regarding the treatment received by patients at follow-up were also collected.

Results are expressed as the mean ± standard deviation or median (minimum−maximum value), unless otherwise specified. The chi-square test was used to assess the

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See page 5 for disclosure information.

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Table 1
Clinical characteristics of patients

| Variable | Baseline (n=141) | Follow-up (n=130) | *P* Value |
|---|---|---|---|
| Male | 37 (26.2%) | | |
| Age at diagnosis (years) | 33.3±14.4 | | |
| Heritable pulmonary arterial hypertension | 12 (8.5%) | | |
| Time between baseline and follow-up, (years) median (min−max) | | 3.3 (0.2−14.4) | |
| WHO functional class (I/II/III/IV), n | 1/18/91/31 | 10/83/34/3 | <.001 |
| 6-minute walk distance (meters) | 267.1±154.4 | 407.9±106.6 | <.001 |
| Brain natriuretic peptide (pg/mL) | 326.2±348.1 | 74.1±172.2 | <.001 |
| Heart rate (bpm) | 78.9±15.7 | 79.0±15.6 | .385 |
| Oxygen saturation (%) | 95.2±4.2 | 96.1±3.5 | .037 |
| Mean pulmonary artery pressure (mm Hg) | 60.3±14.7 | 37.6±11.4 | <.001 |
| Cardiac index (L/min/$m^2$) | 2.1±0.9 | 3.2±1.1 | <.001 |
| Mixed venous oxygen saturation (%) | 63.2±9.9 | 74.0±7.0 | <.001 |
| Pulmonary vascular resistance (dyn•s/$cm^5$) | 1522.7±799.5 | 591.6±426.3 | <.001 |

Values are expressed as mean ± SD unless otherwise specified. Follow-up data were evaluated in patients who underwent follow-up right heart catheterization.

significance of differences between categorical variables. Continuous variables at baseline and follow-up were compared using U tests.

Survival analyses were conducted using the Kaplan-Meier method. Survival time is expressed as mean ± standard error (95% confidence interval). Differences between survival curves were assessed using the log-rank test. A Cox proportional hazards model was used to determine the variables associated with increased mortality. Multivariate stepwise models were applied to candidate explanatory variables that remained significant ($p < 0.1$) in univariate analyses. The hazard ratio and 95% confidence interval were defined. Receiver operating characteristic curves were constructed to determine an optimal cutoff value for 6MWD, mPAP, CI, and HR. All analyses were undertaken with SAS Release 9.4 (SAS Institute, Cary, NC) and IBM SPSS 20 (IBM, Armonk, NY). Statistical significance was defined as $p < 0.05$.

## Results

We conducted a retrospective chart review of 141 consecutive patients with I/HPAH. Patients' characteristics are listed in Table 1. Patients were predominantly women and in their 30s at diagnosis. At baseline, 86.5% of patients were in WHO functional class III or IV. Hemodynamic parameters were severely impaired, with mPAP >60 mm Hg and PVR >1,500 dyn•s/$cm^5$.

Data of 130 patients who underwent follow-up right heart catheterization were collected. At follow-up, WHO functional class, 6MWD, and BNP were significantly improved. HR was unchanged. $SpO_2$ and hemodynamic parameters (mPAP, CI, $SvO_2$, and PVR) were significantly improved over those at baseline ($p < 0.001$).

During the study period, 40 patients died and 7 underwent lung transplantation. Thirty-one patients (22.0%) died from right heart failure, 1 from alveolar hemorrhage, 1 from sudden death, 1 from acute renal failure, and 2 from adverse effects of drugs. In 4 patients, causes of death were unrelated to PAH (malignant lymphoma, esophageal carcinoma, gastrointestinal bleeding, and a traffic accident). The mortality rate related to PAH was 25.5% (Figure 1). Mean survival time from treatment initiation was 14.7 ± 0.8 years (95% confidence interval, 13.1 to

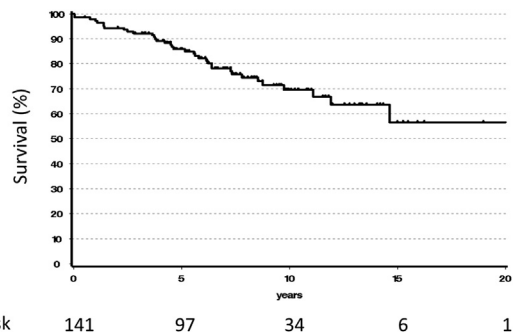


Figure 1. Overall survival. Survival representing mortality with disease-related death. Mean survival time from treatment initiation was 14.7 ± 0.8 years (95% confidence interval, 13.1 to 16.3 years), with 1-, 3-, 5-, and 10-year survival rates of 97.9%, 92.1%, 85.8%, and 69.5%, respectively.

Table 2
Cox proportional hazards analysis

| Variable | Hazard Ratio | 95% Confidence Interval | *P* Value |
|---|---|---|---|
| Baseline | | | |
| Heat rate (bpm) | 1.036 | 1.007−1.065 | .014 |
| At follow-up | | | |
| 6-minute walk distance (meters) | 0.994 | 0.988−0.9997 | .040 |
| Heart rate (bpm) | 1.081 | 1.018−1.149 | .012 |
| Mean pulmonary artery pressure (mm Hg) | 1.058 | 1.003−1.117 | .038 |
| Cardiac index (L/min/$m^2$) | 0.102 | 0.028−0.382 | <.001 |

p Values for each analysis are shown. Since cardiac index (CI) is related to mixed venous oxygen saturation and pulmonary vascular resistance, CI was chosen as a representative variable in multivariate analysis.

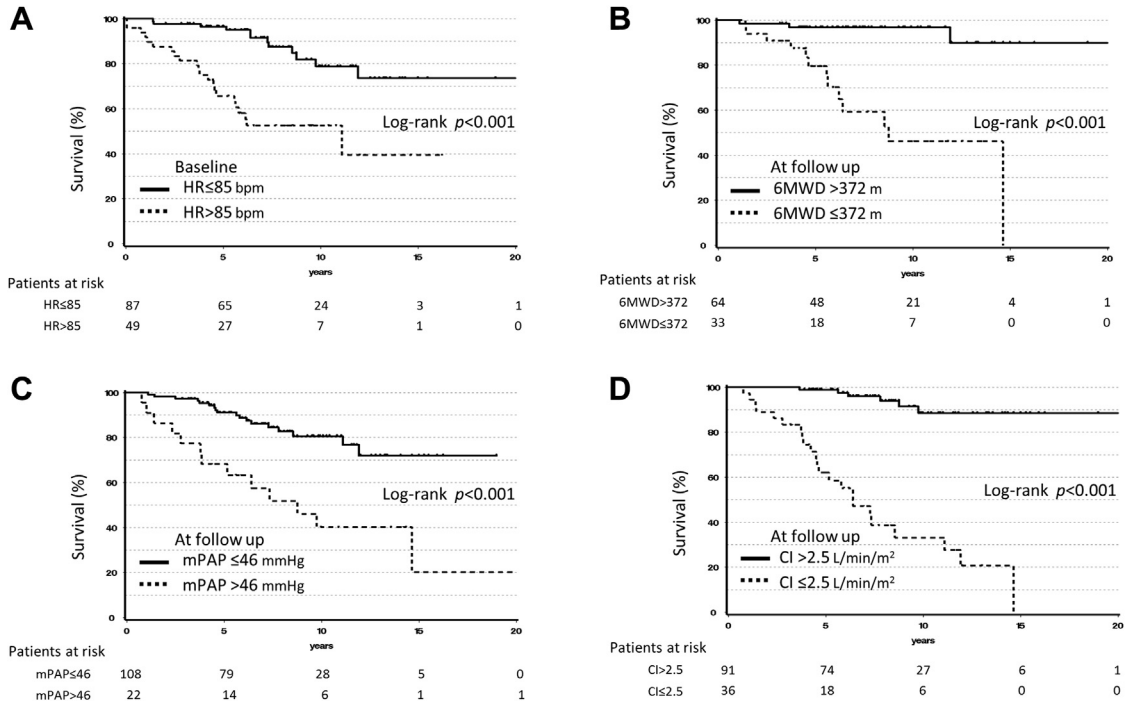


Figure 2. Survival rate of patients stratified by parameters at baseline *(A)* and follow-up *(B to D)*. *(A)* Survival rate of patients with heart rate ≤85 beats/min at baseline was significantly better than that of patients with HR >85 beats/min (p <0.001). *(B)* Survival rate of patients with 6MWD >372 m at follow-up was significantly better than that of patients with 6MWD ≤372 m (p <0.001). *(C)* Survival rate of patients with mPAP ≤46 mm Hg at follow-up was significantly better than that of patients with mPAP >46 mm Hg (p <0.001). *(D)* Survival rate of patients with cardiac index (CI) >2.5 L/min/m$^2$ at follow-up was significantly better than that of patients with CI ≤2.5 L/min/m$^2$ (p <0.001).

Table 3
Treatment at follow-up (n = 130)

| Variable | n (%) |
|---|---|
| Warfarin | 49 (37.7%) |
| Pulmonary arterial hypertension targeted therapy | 129 (99.2%) |
| Oral prostacyclin analog | 20 (15.4%) |
| Intravenous prostacyclin | 102 (78.5%) |
| Endothelin receptor antagonist | 83 (63.8%) |
| Phosphodiesterase type 5 inhibitor | 89 (68.5%) |
| Combination therapy | 103 (79.2%) |
| Double therapy | 41 (31.5%) |
| Triple therapy | 62 (47.7%) |

16.3 years), with 1-, 2-, 3-, 5-, and 10-year survival rates of 97.9%, 94.3%, 92.1%, 85.8%, and 69.5%, respectively.

The Cox proportional hazards model was used to estimate the risk factors for disease-related death based on the baseline data of patients. Age at diagnosis, male gender, HPAH, WHO functional classes III or IV, mPAP, CI, and PVR were not significant in univariate analysis, although 6MWD, BNP, HR, $SpO_2$, and $SvO_2$ were significant. In multivariate analysis, HR was significantly related to survival (Table 2). With regard to follow-up data, WHO functional classes III or IV, 6MWD, BNP, HR, $SpO_2$, mPAP, CI, $SvO_2$, and PVR were significant in the univariate analysis. In multivariate analysis, 6MWD, HR, mPAP, and CI at follow-up were determinants of survival (Table 2).

Based on the area under the curve calculated from the receiver operating characteristic curves, cutoff values were calculated: baseline HR (area under the curve, 0.694; cutoff value, 85 beats/min), 6MWD at follow-up (0.849; 372 m), HR at follow-up (0.664; 77 beats/min), mPAP at follow-up (0.782; 46 mm Hg), and CI at follow-up (0.882; 2.5 L/min/m$^2$). A baseline HR >85 beats/min showed a significantly worse prognosis (p <0.001), although the cutoff value for HR at follow-up did not stratify survival. Patients with 6MWD >372 m, mPAP ≤46 mm Hg, and CI >2.5 L/min/m$^2$ at follow-up had a significantly better prognosis (p <0.001) (Figure 2).

The treatment regimen was evaluated in patients who underwent follow-up catheterization (Table 3). Less than 40% of patients were administered warfarin. Most patients were receiving PAH-targeted drugs: prostacyclin analogs, endothelin receptor antagonists (ERAs), and phosphodiesterase type 5 (PDE5) inhibitors. Intravenous prostacyclin was highly prescribed. All patients received epoprostenol except for 1 patient who received treprostinil. The maximum dose of epoprostenol was 70.6 ± 39.5 ng/kg/min. Approximately 80% of patients were treated with combination therapy.

The Cox proportional hazards model was used to estimate the risk factors for disease-related death with regard to treatment at follow-up. Oral prostacyclin analog, PDE5 inhibitors, and warfarin did not show significance in univariate analysis (p = 0.168, 0.257, and 0.156, respectively). ERA and intravenous epoprostenol were important for survival in the univariate analysis (p = 0.027 and 0.046,

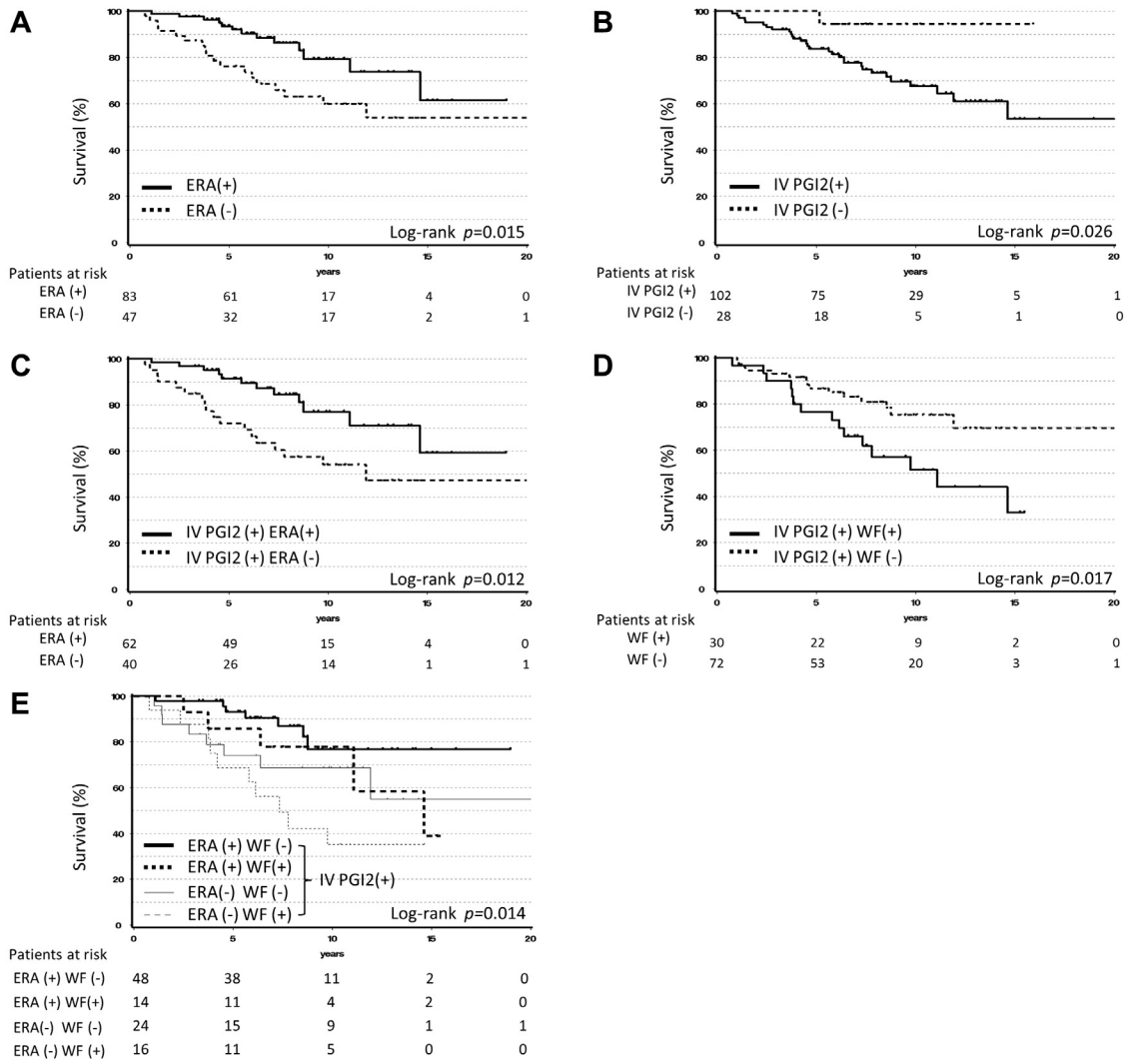


Figure 3. Kaplan-Meier estimates stratified according to treatment at follow-up. *(A)* Survival rate of patients with ERA was significantly better than that of patients without ERA (p = 0.015). *(B)* Survival rate of patients with intravenous (IV) prostacyclin (PGI2) was significantly worse than that of patients without IV PGI2 (p = 0.026). *(C)* Survival rate of patients with ERA was significantly better than that of patients without ERA among patients who were on IV PGI2 therapy (p = 0.012). *(D)* Survival rate of patients with warfarin (WF) was significantly worse than that of patients without warfarin among patients who were on IV PGI2 therapy (p = 0.017). *(E)* Survival rates of patients with and without ERA and with or without warfarin were compared among patients who were on IV PGI2 therapy. Survival rate of patients with warfarin was significantly worse than that of patients with ERA (p = 0.014).

respectively). However, no drug showed significant benefit to survival in the multivariate analysis. In the Kaplan-Meier analysis, patients administered ERA showed significantly better survival (log-rank test, p = 0.015) (Figure 3) with significant improvement of hemodynamics at follow-up (Supplementary Table 1), although patients administered ERA did not show any difference in the baseline data except for HR. Patients who did not need epoprostenol had a better prognosis (log-rank test, p = 0.026) (Figure 3). Among patients who were administered intravenous epoprostenol therapy, those taking ERA had a significantly better prognosis (log-rank test, p = 0.012) (Figure 3); although there was no difference in the baseline data, they showed significant improvement of hemodynamics at follow-up (Supplementary Table 2). Among patients on epoprostenol therapy, patients given warfarin had a significantly worse prognosis (log-rank test, p = 0.017) (Figure 3). There was no difference in the baseline data except for lower $SpO_2$, but patients not given warfarin showed significant improvement of hemodynamics at follow-up (Supplementary Table 3). Furthermore, patients given intravenous prostacyclin were divided into 4 groups: with or without ERA and with or without warfarin (Figure 3). There was a significant difference in survival (log-rank test with a Tukey adjustment, p = 0.014), and a significant difference was found between ERA-only and warfarin-only groups (p = 0.007). Male prevalence and $SpO_2$ were significantly different parameters among these 4 groups at baseline, whereas mPAP, CI, and PVR were significantly different at follow-up (Supplementary Tables 4 and 5).

## Discussion

This is the first multicenter report on survival of Japanese patients with I/HPAH treated at 3 referral centers. The results confirmed our previous report on the high survival rate

of Japanese patients with I/HPAH and significant improvement in hemodynamic parameters after treatment.[6] In patients receiving epoprostenol therapy, concomitant use of ERA was beneficial and warfarin was related to worse survival.

Survival of patients with PAH improved after progress in the use of PAH-targeted drugs, although the results continued to be unsatisfactory.[2–5] Numerous parameters have been reported to be improved by targeted therapies, including WHO functional class, 6MWD, and BNP. It is essential to understand which parameters need to be improved, and to what extent, in achieving better survival.

Among the baseline characteristics, HR is the only prognostic factor in the present study. However, HR did not change after treatment and the importance of HR in patients with I/HPAH may be limited, although HR is a known prognostic factor in left-sided cardiac failure.[9] The improvement in other parameters after treatment is more significant in our patients in comparison with those enrolled in previous studies, although the baseline parameters were comparable with those reported previously.[2–5,10,11] Patients with 6MWD >372 m, mPAP ≤46 mm Hg, and CI >2.5 L/min/$m^2$ at follow-up had a significantly better survival. Improvement in the 6MWD, which has long been considered the end point in most clinical trials, has been shown not to be related to long-term survival.[12] CI was also reported to be a prognostic factor in the first report on survival.[1] Mean PAP was found to be significant in stratifying patients' survival in our previous single-center report.[6] In line with the previous results, the finding that mPAP can be lowered by treatment and is a determinant factor was confirmed by the present study. mPAP improvement may deserve to be recognized as a determinant factor of prognosis, as already is the case for chronic thromboembolic pulmonary hypertension.[13,14]

The significant improvement in pulmonary hemodynamics might be attributed to the high prescription rate and combination therapy including epoprostenol treatment. Epoprostenol is known to be the most potent drug among all the PAH-targeted drugs, reducing mPAP by approximately 8 mm Hg after 1 year of treatment with 21 ng/kg/min monotherapy.[15] We have reported that a rapid uptitration regimen of epoprostenol soon after the initiation of treatment was associated with a continuous decrease in mPAP and better survival compared with the slow uptitration regimen.[16,17] Combination therapy has been shown to be beneficial in PAH.[18–20] In the present study, epoprostenol and combination therapy were chosen for 80% of patients and a reduction in mPAP of 37.6% was achieved. This result is consistent with our previous report of a 44% reduction in mPAP in 75% of patients given epoprostenol treatment[6] and 32.5% reduction in mPAP by upfront combination therapy.[18] This treatment regimen is enabled by the Japanese national health care system, which subsidizes medical care for patients with rare and intractable diseases.

Our results showed that patients who were given ERA showed better survival compared with those not given ERA. Because patients who require epoprostenol are the most severe cases, they showed worse survival than those who did not need it. However, in patients who needed epoprostenol treatment, concomitant use of ERA led to significantly better survival, which was indicated by the BREATHE-2 study, a placebo-controlled combination study of epoprostenol and bosentan that showed a trend toward hemodynamic and clinical improvement.[21] We did not observe a favorable effect on survival when using a PDE5 inhibitor as an add-on therapy to epoprostenol treatment, although the PACES trial demonstrated pulmonary hemodynamic improvement by adding sildenafil to epoprostenol therapy.[22] Many patients included in our study were already diagnosed and treated before PDE5 inhibitors were approved in Japan. Patients able to survive until the approval of PDE5 inhibitors may not have further appreciated its benefit.

The use of anticoagulation is controversial in patients with I/HPAH.[23–25] In the present study, patients given warfarin showed a tendency toward worse survival compared with those not given warfarin (data not shown, $p = 0.06$). Furthermore, among patients who underwent epoprostenol therapy, concomitant use of warfarin was associated with a poor prognosis, despite similar baseline parameters. The exact reason cannot be determined from this study because we did not specifically collect the data regarding warfarin-related adverse events, such as bleeding. We previously reported an increased risk of pulmonary alveolar hemorrhage with >28 ng/kg/min of epoprostenol.[26] Patients in the present study were on high-dose epoprostenol therapy, which can reduce platelet coagulation activity and ultimately may result in adverse effects. The use of anticoagulation in patients with I/HPAH should be considered with caution, especially with epoprostenol therapy.

Another reason for the improvement in survival may be due to racial/ethnic factors. Reports from China and Korea showed higher survival rates than in Western countries.[10,11] It is possible that a difference in genetic background between Asians and Caucasians leads to a different response to treatment. Furthermore, the mean age at diagnosis of patients reported from China, Korea, and in the present study is in the 30s. This also differs from recent reports from Western countries, which consist of patients in their 50s at the time of diagnosis, although the age at diagnosis of patients in the first registry was in the 30s.[1] Differences in ethnicity in patients with I/HPAH and the patient profile of Asian populations therefore need to be evaluated in a larger cohort.

There are several limitations to this study. The fact that this is a retrospective study with a small number of patients precludes control of the baseline characteristics and may thus lead to biased results. Furthermore, the study comprised patients who were diagnosed from 1992 to 2012, whereas the first PAH-targeted drug became available in 1999 in Japan. The possibility of selection bias and survivor bias could not be avoided. Prospective studies to ascertain the results presented herein are warranted.

## Disclosures

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## Supplementary Data

Supplementary data related with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2017.01.015.


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