**BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis**


**Summary**

**Background** Mutations in the gene encoding the bone morphogenetic protein receptor type II (BMPR2) are the commonest genetic cause of pulmonary arterial hypertension (PAH). However, the effect of BMPR2 mutations on clinical phenotype and outcomes remains uncertain.

**Methods** We analysed individual participant data of 1550 patients with idiopathic, heritable, and anorexigen-associated PAH from eight cohorts that had been systematically tested for BMPR2 mutations. The primary outcome was the composite of death or lung transplantation. All-cause mortality was the secondary outcome. Hazard ratios (HRs) for death or transplantation and all-cause mortality associated with the presence of BMPR2 mutation were calculated using Cox proportional hazards models stratified by cohort.

**Findings** Overall, 448 (29%) of 1550 patients had a BMPR2 mutation. Mutation carriers were younger at diagnosis (mean age 35·4 [SD 14·8] vs 42·0 [17·8] years), had a higher mean pulmonary artery pressure (60·5 [13·8] vs 56·4 [15·3] mm Hg) and pulmonary vascular resistance (16·6 [8·3] vs 12·9 [8·3] Wood units), and lower cardiac index (2·11 [0·69] vs 2·51 [0·92] L/min per m²; all p<0·0001). Patients with BMPR2 mutations were less likely to respond to acute vasodilator testing (3% [10 of 380] vs 16% [147 of 907]; p<0·0001). Among the 1164 individuals with available survival data, age-adjusted and sex-adjusted HRs comparing BMPR2 mutation carriers with non-carriers were 1·42 (95% CI 1·15–1·75; p=0·0011) for the composite of death or lung transplantation and 1·27 (1·00–1·60; p=0·046) for all-cause mortality. These HRs were attenuated after adjustment for potential mediators including pulmonary vascular resistance, cardiac index, and vaso-reactivity. HRs for death or transplantation and all-cause mortality associated with BMPR2 mutation were similar in men and women, but higher in patients with a younger age at diagnosis (p=0·0030 for death or transplantation, p=0·011 for all-cause mortality).

**Interpretation** Patients with PAH and BMPR2 mutations present at a younger age with more severe disease, and are at increased risk of death, and death or transplantation, compared with those without BMPR2 mutations.

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Evidence before this study

In the year 2000, mutations in the BMPR2 gene were identified as the major genetic cause of pulmonary arterial hypertension (PAH). Some small studies have examined the effect of BMPR2 mutations on the presentation, haemodynamic profile, and outcomes in patients with PAH. These studies suggested that those with BMPR2 mutations present at a younger age with more severe derangements of cardiopulmonary haemodynamics. Due to a lack of statistical power, lack of adjustment for important factors such as age and sex, and confounding from inclusion of prevalent cases without necessary adjustments in many of these studies, the effect of BMPR2 mutations on long-term outcomes has not been reliably established.

Added value of this study

By harmonising individual participant data from 1550 patients in eight published and unpublished studies, with updated follow-up, this study provides the most definitive assessment of the effect of BMPR2 mutations on the haemodynamic profile at diagnosis and long-term outcomes in patients with PAH. This study has shown that possession of a BMPR2 mutation is associated with an increased risk of death or transplantation and all-cause mortality. This association appears to be mediated by a more severe haemodynamic profile measured at diagnosis with the greatest proportion of the risk accounted for by the lower cardiac index in BMPR2 mutation carriers. There was a strong interaction between the effect of a BMPR2 mutation and age at diagnosis, such that the increased risk of death or transplantation and all-cause mortality associated with possession of a BMPR2 mutation was greater in younger patients.

Implications of all the available evidence

Patients with PAH with underlying BMPR2 mutations are younger at diagnosis, have more severe disease, and have a worse prognosis than patients without BMPR2 mutations. The role of routine genetic testing for BMPR2 mutations on the management of patients with PAH deserves further study.

Research in context

Low penetrance of BMPR2 mutations (20–30%) and the occurrence of de novo mutations.11

Recent European guidelines for the management of PAH recommend offering genetic counselling and screening for BMPR2 mutations to patients diagnosed with idiopathic, heritable, and anorexigen-associated PAH, mainly to enable predictive genetic testing of relatives.12 Studies have suggested that patients with PAH carrying causal BMPR2 mutations present at an earlier age with more severe haemodynamic compromise.13–17 Although this might be expected to confer a worse survival, robust evidence describing the effect of BMPR2 mutations on long-term outcomes in these patients is lacking, primarily due to the limited power of individual studies and survival bias.18,19

We established the BMPR2 Studies Collaboration to investigate the effect of BMPR2 mutations on clinical phenotypes and long-term outcomes in patients with PAH. This international consortium has allowed central collation and harmonisation of participant data on 1550 patients with PAH from eight cohorts based in six different countries.
consistent with prevailing international guidelines at the time of recruitment, at the discretion of the clinical team in each institution. Data regarding initial and subsequent PAH targeted therapy were not available for this analysis. Cohorts comprised a combination of incident patients, defined for the purposes of this study as those who were enrolled in their respective study and thus committed to genotyping within 6 months of PAH diagnosis, and prevalent patients who were enrolled more than 6 months after PAH diagnosis.

Patients were excluded from the analysis if they had PAH associated with conditions such as connective tissue disease, HIV, congenital heart disease, or portal hypertension. Furthermore, to avoid potential confounding from mutations in other genes or undetected BMPR2 mutations, patients with a family history of PAH but with no identifiable BMPR2 mutation were also excluded. Patients with a history of anorexigen exposure were included since BMPR2 mutations have been recorded in these patients, and the disease is indistinguishable from idiopathic PAH.4,22

Outcomes
The primary outcome was the composite of death or lung transplantation. All-cause mortality was the secondary outcome. Patients contributed only the first outcome recorded during follow-up (ie, deaths preceded by transplantation were not included) because data regarding post-transplant survival were not available. Outcomes were censored if a patient was lost to follow-up or reached the end of the follow-up period. In analysis of all-cause mortality, patients were censored at the time of transplantation. Date of PAH diagnosis was defined as the date of diagnostic right heart catheterisation.

Statistical analysis
Baseline characteristics of patients according to BMPR2 mutation status were compared using t test for continuous variables and χ² test for categorical variables. Associations of BMPR2 mutation status with risk of death or transplantation and all-cause mortality recorded during follow-up were assessed using Cox proportional hazards regression models stratified by cohort and timing of study entry (ie, incident or prevalent). We used a one-stage stratified model rather than two-stage random effects model for our primary analysis because of the small number of participants in some studies. As a sensitivity analysis, we pooled data using a two-stage random effects model rather than two-stage random effects model for our primary analysis. Cox proportional hazards regression models and survival curves were fitted allowing for left truncation arising from the interval between diagnosis and enrolment. These patients were only included in the risk set from the time of study entry and were excluded if they entered the study more than 10 years after diagnosis. In patients for whom the date of enrolment in the study was not available, patients entered the risk set on the date they were genotyped for BMPR2 mutations. Given that worse survival has been reported in incident patients compared with prevalent patients in

Figure 1: Study and patient selection

unadjusted Kaplan-Meier estimates and compared using the log-rank test.

To restrict the scope for potential bias due to inclusion of prevalent patients (ie, those diagnosed with PAH more than 6 months before study enrolment), Cox proportional hazards regression models and survival curves were fitted allowing for left truncation arising from the interval between diagnosis and enrolment. These patients were only included in the risk set from the time of study entry and were excluded if they entered the study more than 10 years after diagnosis. In patients for whom the date of enrolment in the study was not available, patients entered the risk set on the date they were genotyped for BMPR2 mutations. Given that worse survival has been reported in incident patients compared with prevalent patients in
observational studies, and a higher risk of PAH-related death or admission to hospital was reported in incident patients in a clinical trial population. Cox models were also stratified by timing of study entry. Data pertaining to familial clustering of individuals and mutations were not available; however, to account for this, survival models were adjusted for clustering by sets of individuals with the same mutation from the same cohort. Two studies were adjusted for clustering by sets of individuals with the same mutation but were included in the survival analysis due to insufficient survival data but were included in the description of demographic and haemodynamic characteristics.

We explored interactions between the effect of BMPR2 mutation with age at diagnosis and sex within the one-stage stratified Cox models. The interaction with age at diagnosis was assessed with age as a continuous variable, with cases separated into three post-hoc groups according to age at diagnosis for illustrative purposes (<30 years, 30–50 years, and >50 years).

To assess the degree to which the association of BMPR2 mutations with outcome was mediated by haemodynamic characteristics at diagnosis, we calculated the percentage of excess risk mediated (PERM) by three mediators thought likely to be in the causal pathway: pulmonary vascular resistance, cardiac index, and vasodilator responsiveness. Each of these mediators was added to the age-adjusted and sex-adjusted Cox proportional hazards models individually, and then all three simultaneously. The PERM, that is the degree to which the HR is attenuated by addition of the mediator in question, was calculated using the equation:

\[
\text{PERM} = \left( \frac{HR_{\text{without mediator}} - HR_{\text{with mediator}}}{HR_{\text{without mediator}} - 1} \right) \times 100
\]

For this analysis, missing covariate data were imputed using multiple imputation by chained equations in those individuals included in the survival analysis, to generate ten datasets with complete covariates. Cox proportional hazards models were fitted within each imputed dataset and combined using Rubin’s rules. This analysis was repeated using only cases that had complete data for all three mediators as a sensitivity analysis.

In an exploratory analysis, we compared haemodynamic parameters at presentation (compared using one-way ANOVA) and survival in patients by BMPR2 mutation type. Mutations were assigned to one of five categories (frameshift, stop-gained, splice site or intronic, large deletions or exonal duplications, missense).

A two-sided p value less than 0.05 was considered statistically significant throughout. Statistical analyses were done using Stata (version 14; StataCorp, College Station, TX, USA).

**Role of the funding source**

No funding bodies had any role in the design, conduct, analysis of this study, or writing of the manuscript. The corresponding author had full access to the data and had the final responsibility for the decision to submit this manuscript with the permission of all coauthors.

**Results**

Figure 1 shows the inclusion and exclusion of studies and patients. Of ten studies identified, one eligible cohort (that involved 61 patients and was available only in abstract form) did not contribute data to the current analysis, and one cohort was excluded because it exclusively included 47 patients younger than 16 years. We analysed data from a total of 1550 patients with idiopathic, heritable, and anorexigen-associated PAH from eight cohorts (appendix). The mean age at diagnosis was 40·1 (SD 17·2) years, 72% (1105/1545 [data for five patients were unavailable]) were women, 60% (931/1550) were from western Europe, 18% (276/1550) from North America, and 22% (343/1550) from east Asia. Overall, 448 (29%) of 1550 patients had an identified BMPR2 mutation and 86 (6%) of 1550 patients had a recorded history of anorexigen exposure. Histograms of the dates during which patients included in the survival analyses were diagnosed and recruited into these studies are shown in the appendix.

<table>
<thead>
<tr>
<th>Table 1: Demographics and clinical measurements at diagnosis</th>
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<tbody>
<tr>
<td><strong>All patients</strong></td>
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<td></td>
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<tr>
<td>Age at diagnosis (N=1447), years</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Family history of PAH</td>
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<tr>
<td>Body-mass index (N=1206), kg/m²</td>
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<tr>
<td>6-min walk distance (N=1072), m</td>
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<td>NYHA functional class</td>
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<td>I–II</td>
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<tr>
<td>III</td>
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<tr>
<td>IV</td>
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<tr>
<td>Mean pulmonary artery pressure (N=1503), mm Hg</td>
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<tr>
<td>Pulmonary vascular resistance (N=1300), Wood units</td>
</tr>
<tr>
<td>Right atrial pressure (N=1253), mm Hg</td>
</tr>
<tr>
<td>Cardiac output (N=1202), L/min</td>
</tr>
<tr>
<td>Cardiac index (N=1358), L/min per m²</td>
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<tr>
<td>Vasodilator responder</td>
</tr>
</tbody>
</table>

Data are n/N (%) or mean (SD), unless otherwise stated. PAH=pulmonary arterial hypertension. NYHA=New York Heart Association.
The proportion of patients with BMPR2 mutations varied between studies (appendix). In patients with no recorded family history of PAH, a BMPR2 mutation was identified in 17% (200/1174), whereas in patients with a family history of PAH a mutation was identified in 82% (202/247). Patients with a BMPR2 mutation were younger at diagnosis (mean age 35·4 years vs 42·0 years, p<0·0001) and the proportion of patients with a BMPR2 mutation was greater in those diagnosed at a younger age (37% [162/434] in those aged <30 years, 33% [187/562] in those aged 30–50 years, and 17% [75/451] in those aged >50 years at diagnosis; p<0·0001). A comparison of haemodynamic and functional parameters measured at the time of diagnosis between carriers and non-carriers of a BMPR2 mutation is shown in table 1. Those carrying a BMPR2 mutation

Figure 2: Kaplan–Meier survival curves according to BMPR2 mutation status
(A) Transplant-free survival, all patients (p=0·0016). (B) Overall survival, all patients (p=0·32). (C) Transplant-free survival, younger than 50 years at diagnosis (p=0·0001). (D) Overall survival, younger than 50 years at diagnosis (p=0·0032). (E) Transplant-free survival, older than 50 years at diagnosis (p=0·07). (F) Overall survival, 50 years or older at diagnosis (p=0·16). Survival curves are not adjusted for age at diagnosis or sex and are not stratified by study cohort.
had a higher mean pulmonary artery pressure and pulmonary vascular resistance, and lower cardiac index. No difference was recorded in the severity of symptoms assessed by New York Heart Association functional class or exercise capacity assessed by 6 min walk distance. Patients with a BMPR2 mutation were less likely to respond to acute vasodilator testing (table 1).

Characteristics of the 1164 patients from the six studies that contributed to the survival analysis are shown in the appendix. Survival curves by BMPR2 mutation status in the combined dataset are shown in figure 2. Of the 1164 patients, 723 (62%) were incident cases and 441 (38%) were prevalent cases. The median interval between diagnosis and study entry in the prevalent patients was 1·8 years (IQR 1·1–4·5). During 5870 person-years at risk (median duration of follow-up from diagnosis 5·4 years [IQR 3·0–8·2]), there were 354 deaths and 74 patients underwent lung transplantation. Age-adjusted and sex-adjusted HRs comparing BMPR2 mutation carriers with non-carriers were 1·42 (95% CI 1·15–1·75; p=0·0011) for the composite of death or lung transplantation and 1·27 (1·00–1·60; p=0·046) for all-cause mortality (table 2). HRs were unchanged after adjusting for previous exposure to anorexigen. Addition of each of the three mediators assessed to the age-adjusted and sex-adjusted models attenuated the HRs associated with BMPR2 mutation for both death or transplantation and all-cause mortality (table 2). Cardiac index mediated the greatest proportion of excess risk, accounting for 65% and 79% of the increased HR for death or transplantation and all-cause mortality, respectively. The PERM by the combination of pulmonary vascular resistance, cardiac index, and vasodilator responsiveness was 71% for death or transplantation and 100% for all-cause mortality. In the complete case sensitivity analysis (913 patients; appendix) the PERM by each mediator was similar.

HRs associated with possession of a BMPR2 mutation were similar in men and women (p=0·576 for death or transplantation, p=0·636 for all-cause mortality), but higher in patients with a younger age at diagnosis (p=0·0030 for death or transplantation, p=0·011 for all-cause mortality; figure 3, appendix). The interaction of BMPR2 and age at diagnosis persisted after adjustment for potential mediators (appendix).

Similar results were recorded with meta-analysis using a two-stage approach with random effects (appendix). Between-study heterogeneity was modest, both for death or transplantation (I²=36·9% [95% CI 0·70]; p=0·16) and all-cause mortality (I²=20·1% [0·65]; p=0·28).

There were no significant differences in haemodynamic parameters at diagnosis between those with different mutation subtypes (appendix). Patients with missense mutations were slightly younger at diagnosis. No significant difference was recorded in the risk of death or transplantation or all-cause mortality among carriers of different types of BMPR2 mutations (appendix).

Discussion
To our knowledge, this meta-analysis of individual participant data from published and unpublished studies provides the most comprehensive standardised assessment of associations of BMPR2 mutations with long-term outcomes in patients with idiopathic, heritable, and anorexigen-associated PAH.

We have shown that patients diagnosed with PAH have an increased risk of death or transplantation and all-cause mortality if they possess a mutation in the BMPR2 gene. HRs associated with possession of a BMPR2 mutation were similar in males and females, but greater with younger age at diagnosis. Furthermore, we have confirmed in this analysis the previously reported observations that patients with BMPR2 mutations present at a younger age, have more severe haemodynamic compromise at diagnosis with higher mean pulmonary artery pressure and pulmonary vascular

<table>
<thead>
<tr>
<th>Death or transplantation</th>
<th>HR (95% CI) for BMPR2 mutation</th>
<th>p value</th>
<th>PERM</th>
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<tbody>
<tr>
<td>Pulmonary vascular resistance</td>
<td>Adjusted for age and sex</td>
<td>1·42 (1·15–1·75)</td>
<td>0·0011</td>
</tr>
<tr>
<td></td>
<td>Adjusted for age, sex, and pulmonary vascular resistance</td>
<td>1·28 (1·03–1·58)</td>
<td>0·024</td>
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<tr>
<td>Cardiac index</td>
<td>Adjusted for age and sex</td>
<td>1·42 (1·15–1·75)</td>
<td>0·0011</td>
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<tr>
<td></td>
<td>Adjusted for age, sex, and cardiac index</td>
<td>1·18 (0·95–1·47)</td>
<td>0·14</td>
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<tr>
<td>Vasoreactivity</td>
<td>Adjusted for age and sex</td>
<td>1·42 (1·15–1·75)</td>
<td>0·0011</td>
</tr>
<tr>
<td></td>
<td>Adjusted for age, sex, and vasoreactivity</td>
<td>1·26 (1·02–1·57)</td>
<td>0·036</td>
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<tr>
<td>Combined model</td>
<td>Adjusted for age and sex</td>
<td>1·42 (1·15–1·75)</td>
<td>0·0011</td>
</tr>
<tr>
<td></td>
<td>Adjusted for age, sex, pulmonary vascular resistance, cardiac index, and vasoreactivity</td>
<td>1·12 (0·89–1·41)</td>
<td>0·33</td>
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<table>
<thead>
<tr>
<th>All-cause mortality</th>
<th>HR (95% CI) for BMPR2 mutation</th>
<th>p value</th>
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<tr>
<td>Pulmonary vascular resistance</td>
<td>Adjusted for age and sex</td>
<td>1·27 (1·00–1·60)</td>
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<td></td>
<td>Adjusted for age, sex, and pulmonary vascular resistance</td>
<td>1·13 (0·89–1·43)</td>
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<tr>
<td>Cardiac index</td>
<td>Adjusted for age and sex</td>
<td>1·27 (1·00–1·60)</td>
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<td></td>
<td>Adjusted for age, sex, and cardiac index</td>
<td>1·06 (0·83–1·35)</td>
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<td>Vasoreactivity</td>
<td>Adjusted for age and sex</td>
<td>1·27 (1·00–1·60)</td>
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<td></td>
<td>Adjusted for age, sex, and vasoreactivity</td>
<td>1·14 (0·89–1·45)</td>
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<td>Combined model</td>
<td>Adjusted for age and sex</td>
<td>1·27 (1·00–1·60)</td>
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<tr>
<td></td>
<td>Adjusted for age, sex, pulmonary vascular resistance, cardiac index, and vasoreactivity</td>
<td>1·00 (0·77–1·29)</td>
</tr>
</tbody>
</table>

Hazard ratios (HRs) associated with possession of a BMPR2 mutation after addition of each mediator individually to age-adjusted and sex-adjusted Cox proportional hazards models with the percentage of excess risk mediated (PERM) by each mediator. Missing data for mediators generated by multiple imputation.

Table 2: Proportion of excess risk mediated by haemodynamic variables at diagnosis
resistance and lower cardiac index, and are less likely to respond to acute vasodilator testing and more likely to undergo lung transplantation.\(^{11,12,26}\)

The precise mechanisms underlying the difference in survival in those with a \(\text{BMPR2}\) mutation remain unclear. We have found that after adjusting for pulmonary vascular resistance, cardiac index, and vasodilator responsiveness, HRs for death or lung transplantation and all-cause mortality were attenuated. The low number of \(\text{BMPR2}\) mutation carriers having vasodilator responsiveness, a phenotype associated with a good prognosis when treated with calcium-channel blocker therapy,\(^{29,30}\) is consistent with a predominance of extensive vascular remodelling rather than vasoconstriction. Given that the greatest percentage of the excess risk associated with a \(\text{BMPR2}\) mutation was accounted for by reduced cardiac index at diagnosis, impaired right ventricular adaptation to increased afterload in those with \(\text{BMPR2}\) mutations could be an important factor, as has been suggested in preclinical studies.\(^{31}\)

Our finding of a greater proportion of \(\text{BMPR2}\) mutations in younger age groups is consistent with the common observation that diseases with a major genetic contribution tend to present with an earlier onset. The strong interaction between \(\text{BMPR2}\) mutation status and age at diagnosis is of great interest and has not been reported before. Patients carrying a \(\text{BMPR2}\) mutation in which PAH manifests at a younger age might have a more severe mutation that not only results in more extensive pulmonary vascular remodelling or impaired right ventricular adaptation at diagnosis, but also results in more rapid progression of the disease process. This hypothesis is supported by the observation that the worse prognosis associated with a \(\text{BMPR2}\) mutation in patients diagnosed before the age of 30 years in this study was not completely attenuated after adjustment for pulmonary vascular resistance, cardiac index, and vasoreactivity.

Data from the UK PAH registry\(^7\) suggest that patients with PAH diagnosed after the age of 50 years are phenotypically distinct compared with younger patients. Older patients have a higher prevalence of cardiovascular comorbidities including systemic hypertension, atrial fibrillation, and diabetes. In the present study, although we did not collect data on comorbidities, we found that the proportion of patients with a \(\text{BMPR2}\) mutation is lower in those diagnosed after the age of 50 years than in younger patients. Additionally, we show that after adjusting for age and sex, mutations do not affect survival in these older patients, and prognosis might even be better in those with mutations. \(\text{BMPR2}\) mutations present in those who do not develop PAH until later in life might be less deleterious. Alternatively, in the older age group, comorbidities might outweigh the effect of \(\text{BMPR2}\) mutations on survival.

Our study confirms the relatively high frequency of \(\text{BMPR2}\) mutations in idiopathic and heritable PAH, and supports a central role for the \(\text{BMPR2}\) pathway in the initiation of this disease. Moreover, the effect of \(\text{BMPR2}\) mutation on survival suggests a role for BMPR-II dysfunction in the clinical progression of the disease. Both of these observations support further investigations into the potential targeting of the BMPR-II pathway for therapeutic intervention in PAH.\(^{11,14}\)

The main reason to test for the presence or absence of a \(\text{BMPR2}\) mutation in a patient with PAH is to guide prognostic genetic testing in unaffected relatives. Although our findings show that \(\text{BMPR2}\) mutations are associated with a worse survival, the usefulness of this result for prognostic purposes might be restricted in the clinic, since the majority of this risk appears to be accounted for by the known haemodynamic predictors of mortality measured during the diagnostic assessment during right heart catheterisation. Despite this, in younger patients, in which the increased risk appears to persist after adjustment for these factors, albeit only in subgroup analyses, screening for mutations might add value, and this warrants further investigation.

Our analysis has major strengths. We had access to data for more than 95% of participants from eligible cohorts. We analysed individual participant data to avoid limitations of literature-based reviews. We had information on both all-cause mortality and death or transplantation. We studied clinically relevant subpopulations (such as by age and sex) reliably, exploiting the study’s considerable statistical power. We avoided potential over-adjustment in the primary analysis by not adjusting for variables (eg, pulmonary

![Figure 3: Hazard ratios (HRs) for the effect of a BMPR2 mutation on death or transplantation and all-cause mortality by age at diagnosis and sex](image-url)
vascular resistance, cardiac index, and vasoactivity) that could mediate associations between BMPR2 and death or transplantation and all-cause mortality. We ensured generalisability by studying cohorts located across east Asia, Europe, and North America.

Our analysis has some limitations. Studies included differed in their methods of recruitment and data collection, and in the proportion of familial cases and individuals with BMPR2 mutations, which might explain the heterogeneity recorded between studies. Nevertheless, we obtained similar results to those in our primary analysis based on a stratified Cox proportional hazards model when we used a two-stage random effects meta-analysis model in sensitivity analysis. Additionally, given the evidence for interaction recorded between mutation status and age, the differences in age at diagnosis in different studies could partly explain the heterogeneity recorded in two-stage meta-analyses. The inclusion of prevalent patients in survival analyses can introduce bias; however, we addressed this in the Cox proportional hazards model by allowing for left truncation arising from the interval between diagnosis and study entry and also stratifying by timing of enrolment. Additionally, we observed no interaction between BMPR2 mutation status and timing of enrolment. Finally, the lack of data regarding the timing and use of PAH-directed therapies might introduce some bias, although we believe any effect is likely to be very small. Indeed, if patients with BMPR2 mutations were treated more aggressively due to their more severe haemodynamic derangements at diagnosis, this could have resulted in an attenuation of the association we have recorded.

By harnessing data from observational studies done worldwide, we have shown that in patients with idiopathic, familial, and anorexigen-associated PAH, the presence of a mutation in the BMPR2 gene is associated with an increased risk of death or lung transplantation and all-cause mortality, particularly in those diagnosed at a younger age. Our analysis suggests that this association is largely mediated by the more severe haemodynamic derangements and low frequency of vasodilator responsiveness at diagnosis seen in those with BMPR2 mutations.

**Contributors**

JDWE and NWM conceived the study. JDWE, EDAn, MH, and NWM designed the study. BG, DM, X-JW, NG, EDAn, GE, KA, EG, YY, Z-CJ, AM, MP, LAW, IN, TS, CE, KH, MW, EBR, WKC, FS, GS, OS, and MH collected the data. JDWE and NWM coordinated the study. JDWE, SG, and SK analysed the data. All authors interpreted the results. JDWE, EDAn, MH, and NWM drafted the manuscript with critical revisions for important intellectual content from all authors. All authors approved the final version.

**Declaration of interests**

BG reports personal fees from Actelion, GlaxoSmithKline, and Pfizer, outside of the submitted work. DM reports grants and personal fees from Actelion and Bayer, and personal fees from GlaxoSmithKline, Pfizer, Novartis, and BMS, outside of the submitted work. GE reports grants from NIH, during the conduct of the study; personal fees from Bellerophon, Actelion, and Bayer, and grants from Actelion, Gilead, and United Therapeutics, outside of the submitted work. GS reports grants and personal fees from Actelion, GlaxoSmithKline, and Bayer, and personal fees from Pfizer, outside of the submitted work. OS reports grants, personal fees, and non-financial support from Actelion, GlaxoSmithKline, and Bayer, and grants and personal fees from Pfizer, and personal fees and non-financial support from United Therapeutics, outside of the submitted work. EDAn reports grants from The British Heart Foundation, Medical Research Council, NHS Blood and Transplant, National Institute for Health Research, and European Union, and personal fees from Elsevier (France), outside of the submitted work. MH reports personal fees and non-financial support from Actelion and Pfizer, and grants, personal fees, and non-financial support from Bayer and GlaxoSmithKline, outside of the submitted work. JDWE, X-JW, NG, EDAn, KA, EG, YY, Z-CJ, AM, MP, LAW, IN, TS, CE, KH, MW, EBR, WKC, FS, GS, SK, and NWM declare no competing interests.

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**References**


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