Early View

Original article

Risk Assessment in Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension

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Risk Assessment in Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension

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Author Contributions: MH conceived the idea for the analyses detailed in this manuscript. RLB and HF were also involved in the conceptualization of these analyses in the PATENT and CHEST study databases. MH, HF, HAG, MMH and CM contributed to the design and data collection in the PATENT and CHEST studies. DB undertook statistical analyses of the data in the manuscript. All authors contributed to drafting and critical review of the manuscript. All authors approved the manuscript for submission.

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Running head: Risk Assessment in PAH and CTEPH

9.35 Pulmonary Hypertension: Clinical Diagnosis/Pathogenesis/Outcome

At A Glance Commentary

Scientific Knowledge on the Subject: Current treatment guidelines advocate a goal-oriented treatment strategy of achieving a low-risk profile in patients with pulmonary arterial hypertension (PAH). Retrospective registry studies in patients with incident PAH highlight the favorable prognostic outcome of ‘low-risk’ vs. other risk categories. However, such a strategy has not been validated in a prospective clinical study database, or in a
prevalent PAH population. In addition, there is currently no recommendation for risk assessment in patients with chronic thromboembolic pulmonary hypertension (CTEPH).

**What This Study Adds to the Field:** We evaluated 3 abbreviated versions of the ESC/ERS PAH risk stratification model in patients from the PATENT studies of riociguat. This post hoc analysis showed that the methods can discriminate for survival and clinical worsening-free survival over 2 years. To our knowledge, this is the first validation of these risk stratification methods in a mostly prevalent PAH population from a pivotal efficacy study. Our findings suggest that the methods may be clinically relevant for assessing patients receiving PAH therapy. We also explored these methods in patients with inoperable or persistent/recurrent CTEPH from the CHEST studies; findings were similar to those in PAH, warranting further investigation of these risk assessment tools in CTEPH.

**Abstract**

**Rationale:** Current pulmonary hypertension treatment guidelines recommend use of a risk stratification model encompassing a range of parameters, allowing patients to be categorized as low, intermediate, or high risk. Three abbreviated versions of this risk stratification model were previously evaluated in patients with pulmonary arterial hypertension in the French, Swedish, and COMPERA registries.

**Objective:** To investigate 3 abbreviated risk stratification methods for patients with mostly prevalent pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, in patients from the PATENT-1/-2 and CHEST-1/-2 studies of riociguat.
**Methods:** Risk was assessed at baseline and at follow-up in PATENT-1 and CHEST-1. Survival and clinical worsening-free survival were assessed in patients in each risk group/strata.

**Measurements and Main Results:** With all 3 methods, riociguat improved risk group/strata in patients with pulmonary arterial hypertension after 12 weeks. The French non-invasive and Swedish/COMPERA methods discriminated prognosis for survival and clinical worsening-free survival at both baseline and follow-up. Furthermore, patients achieving ≥1 low-risk criteria or a low-risk stratum at follow-up had a significantly reduced risk of death and clinical worsening, compared with patients achieving no low-risk criteria or an intermediate-risk stratum. Similar results were obtained in patients with inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension.

**Conclusions:** This analysis confirms and extends the results of the registry analyses, supporting the value of goal-oriented treatment in pulmonary arterial hypertension. Further assessment of these methods in patients with chronic thromboembolic pulmonary hypertension is warranted.

**Key words:** riociguat, PAH, CTEPH, registry, long term outcomes
Introduction

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are subtypes of pre-capillary pulmonary hypertension (PH), a rare but debilitating condition [1, 2]. Despite improvements in the short-term survival of patients with PAH, the condition remains incurable. By contrast, CTEPH is potentially curable by pulmonary endarterectomy (PEA) [1-5]; however, up to 50% of patients are considered inoperable and up to 51% develop persistent/recurrent PH after undergoing PEA [6-11].

For patients with PAH, the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) treatment guidelines and the 2018 Proceedings of the 6th World Symposium on Pulmonary Hypertension recommend regular comprehensive risk assessment at expert PH centers using a range of clinical, echocardiographic, exercise, biochemical, and hemodynamic parameters. As such, patients can be categorized as low, intermediate, or high risk, with an estimated 1-year mortality of <5%, 5–10%, and >10%, respectively. Achieving and maintaining a low-risk profile is the recommended goal of PAH treatment[1, 12].

Recently, 3 abbreviated versions of the 2015 ESC/ERS risk stratification model have been evaluated retrospectively in newly diagnosed (incident) PAH cohorts of the French, Swedish, and COMPERA registries [13-15]. The French registry invasive method classifies patients according to the number of ESC/ERS low-risk criteria present for World Health Organization (WHO)/New York Heart Association (NYHA) functional class (FC), 6-minute walking distance (6MWD), right atrial pressure (RAP), and cardiac index. The French registry non-invasive method classifies patients according to the number of ESC/ERS low-risk criteria present for WHO/NYHA FC, brain natriuretic peptide (BNP)/ N-terminal prohormone of BNP.
(NT-proBNP), and 6MWD. The Swedish/COMPERA method grades 6MWD, WHO FC, NT-proBNP, RAP, cardiac index, and mixed venous oxygen saturation (SvO₂) from 1 to 3 (1=low, 3=high) using the ESC/ERS risk thresholds. The rounded mean of these grades is then used to define patient risk stratum. Each model demonstrated a favourable prognostic outcome for patients with a greater number of low-risk criteria or patients in the ‘low-risk’ strata vs. other strata, at both baseline and follow-up [13-15].

There is currently no recommendation regarding how to assess risk in patients with inoperable CTEPH; however, in addition to its common and well-validated use in assessing risk in patients with PAH, the REVEAL risk score (RRS) has shown utility as a prognostic tool in patients with CTEPH [16], and a recent study suggested that the Swedish/COMPERA method predicts mortality in non-operated patients with CTEPH [17].

Riociguat is a soluble guanylate cyclase (sGC) stimulator [18-22] approved for the treatment of both PAH and inoperable or persistent/recurrent CTEPH [23-28]. In the 12-week PATENT-1 study, riociguat significantly improved exercise capacity and a range of secondary endpoints in patients with mostly prevalent PAH [29]. Similar benefits of riociguat were observed in patients with inoperable or persistent/recurrent CTEPH in the 16-week CHEST-1 study [23, 24]. The improvements in 6MWD, WHO FC, and NT-proBNP observed in the PATENT-1 and CHEST-1 studies were maintained at 2 years of riociguat treatment in the long-term extension studies PATENT-2 and CHEST-2 [25-28]. Patients in both studies were well-characterized by invasive and non-invasive assessment at baseline and at the end of the double-blind study period, with patients being followed for a median of 139 weeks in PATENT-2 and 116 weeks in CHEST-2.
These studies provided an opportunity to conduct a post hoc analysis of the three abbreviated risk assessment methods in patients with mostly prevalent PAH and inoperable or persistent/recurrent CTEPH to explore the association between patient risk group or stratum, before and after riociguat treatment, and long-term outcomes.

**Methods**

**Patients and Studies**

PATENT-1 (NCT00810693), was a 12-week, Phase III, double-blind study in which patients with PAH were randomly assigned to placebo, riociguat individually dose adjusted to a maximum of 2.5 mg 3 times daily (tid), or an exploratory dose of 1.5 mg riociguat tid (not included in the risk assessment analyses). CHEST-1 (NCT00855465) was a 16-week, Phase III, double-blind study in which patients with inoperable CTEPH or persistent/recurrent PH were randomly assigned to placebo or riociguat individually adjusted to a maximum of 2.5 mg tid. Patients completing PATENT-1 and CHEST-1 without ongoing study drug-related serious adverse events were eligible to enter the PATENT-2 (NCT00863681) and CHEST-2 (NCT00910429) open-label extension studies in which all patients received riociguat 2.5 mg tid–maximum. Details of these trials are included in the online supplement and published elsewhere [23, 24]. The present analyses included patients who completed PATENT-1 or CHEST-1 and participated in PATENT-2 or CHEST-2.

The PATENT and CHEST studies were conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The institutional review board at each participating center approved the study protocol and all patients gave written informed consent.
Risk Assessment

Six of the 13 variables recommended for PAH risk stratification in the 2015 ESC/ERS treatment guidelines were collected prospectively in PATENT-1 and CHEST-1 (6MWD, WHO FC, NT-proBNP, RAP, cardiac index, SvO₂). Using these variables, the French invasive, French non-invasive, and Swedish/COMPERA models described above were assessed post hoc in the PATENT and CHEST populations at baseline and follow-up. The resultant risk groups/strata were assessed for association with long-term outcomes (survival and clinical worsening-free survival).

Clinical worsening was prospectively defined as first occurrence of any of the following events: death, heart/lung transplantation, atrial septostomy in PATENT or rescue PEA due to worsening of PH in CHEST, hospitalization due to worsening of PH, start of new specific PH treatment, persistent decrease of >15% from baseline in 6MWD (or >30% compared with last study-related measurement), and persistent worsening of WHO FC. Independent adjudication of events was not undertaken.

Statistical Analysis

Data from patients in the riociguat 2.5 mg tid–maximum group were included in all analyses detailed in this manuscript. Data from patients in the riociguat 1.5 mg tid–maximum group in PATENT-1 were included in baseline demographics but excluded from all other analyses. Data from patients in the placebo group were included in baseline demographics and allocation of patients to risk group/strata, but excluded from any long-term assessments (Kaplan-Meier or Cox proportional hazards ratio analyses). All results are presented as observed, with no imputation for missing data.
Patients were grouped according to the number of low-risk criteria achieved (French registry methods) or assigned a risk stratum based on the rounded mean of risk grades (Swedish/COMPERA method) at baseline and follow-up in PATENT-1 and CHEST-1.

Kaplan–Meier analyses of observed data from patients in PATENT-1 and CHEST-1 were used to determine survival and clinical worsening-free survival in PATENT-2 and CHEST-2, respectively, according to the number of low-risk criteria achieved/risk stratum at baseline or follow-up of PATENT-1/CHEST-1. Discrimination between Kaplan–Meier curves (prognostic groups) was determined using log-rank tests.

Cox proportional hazards models were performed in patients from PATENT-1 and CHEST-1 to assess the risk of death and clinical worsening over 2 years according to the number of low-risk criteria achieved/risk stratum (full details online supplement). Only patients who completed PATENT-1 and CHEST-1 and entered PATENT-2 and CHEST-2, respectively, were included in the current post hoc analyses.

Due to the small number of patients in the high-risk stratum using the Swedish/COMPERA model, patients in this group were excluded from all analyses evaluating statistical significance.

Throughout the text, the term “baseline” refers to PATENT-1 and CHEST-1 baseline, and “follow-up” refers to PATENT-1 Week 12 or CHEST-1 Week 16.

Results

PATENT Studies of Patients with PAH

Of 443 patients included in PATENT-1, 396 entered PATENT-2. In the PATENT-2 population at baseline, the majority of patients were female (80%), white (61%), had
idiopathic PAH (62%), and were in WHO FC III (54%), with a mean (SD) age of 50 (16) years. At entry into PATENT-1, approximately 50% of the overall population were pretreated with a PAH therapy and the mean time since diagnosis was 2.4 years (1.9 years in treatment-naïve and 3.0 years in pretreated patients), indicating a predominantly prevalent population. A total of 340 patients who participated in PATENT-2 were included in this analysis. Patient achievement of parameters according to baseline ESC/ERS risk stratification groups are shown in Table 1.

Assessment of the patient demographics in each risk group/strata at baseline and follow-up showed no difference between patients in each group/strata, and thus no obvious confounding factors that may have influenced long-term outcomes could be identified (data not shown).

Risk stratification at baseline and association with long-term outcomes. Risk stratification at baseline according to the 3 abbreviated methods is summarized in Figure 1a and b. Using the French non-invasive method, when stratified by number of low-risk criteria achieved at PATENT-1 baseline, there was a significant difference between prognostic groups for both survival ($P = 0.0283$) and clinical worsening-free survival ($P = 0.0036$), whereas the French invasive method did not discriminate between prognostic groups for either outcome (Figures E1 and E2). Discrimination between prognostic groups for both survival ($P = 0.0355$) and clinical worsening-free survival ($P = 0.0236$) based on baseline risk strata was also observed with the Swedish/COMPERA method (Figures E1 and E2).

Figure 2a and c show Cox proportional hazards analyses of the risk of death or clinical worsening in PATENT-2 according to the number of low-risk criteria/risk strata at baseline. The French invasive and non-invasive methods showed lower risks of death or
clinical worsening as more low-risk criteria were present at baseline. Compared with achieving no low-risk criteria, these reductions were statistically significant for clinical worsening in patients who met 3 criteria with the invasive strategy or 2 or more criteria with the non-invasive strategy. Using the Swedish/COMPERA approach, patients categorized as low risk at baseline had a 64% lower risk of death and a 44% lower risk of a clinical worsening event over 2 years than patients in the intermediate-risk group.

*Risk stratification at follow-up and association with long-term outcomes.* In PATENT-1, treatment with riociguat increased the number of low-risk criteria achieved (French invasive and non-invasive methods) and improved risk strata using the Swedish/COMPERA method at follow-up (Figure 1a and b).

When patients were stratified by the number of low-risk criteria achieved at PATENT-1 follow-up, the French non-invasive method was able to discriminate between prognostic groups for both survival ($P = 0.0126$) and clinical worsening-free survival ($P = 0.0001$), whereas the invasive method only discriminated for clinical worsening-free survival ($P = 0.0078$). Based on risk strata at follow-up, the Swedish/COMPERA method discriminated between prognostic groups for both survival ($P = 0.0099$) and clinical worsening-free survival ($P = 0.0023$) (Figures 3 and 4). Estimated survival rates over 3 years according to the number of low-risk criteria achieved or risk strata achieved at follow-up are shown in Table E1.

For the French invasive method, achieving ≥2 low-risk criteria at PATENT-1 follow-up was associated with a significantly lower risk of clinical worsening compared with achieving none (Figure 2d). Using the French non-invasive method, achieving ≥1 low-risk criteria at follow-up was associated with a significant reduction in the risk of death. Similar results
were seen for clinical worsening (although no significant difference in clinical worsening was seen when patients achieving 2 low-risk criteria were compared with those achieving none). Using the Swedish/COMPERA method, patients categorized as low risk at PATENT-1 follow-up had a 59% lower risk of death and a 46% lower risk of a clinical worsening event than patients in the intermediate-risk group (Figure 2b and d).

**CHEST Studies of Patients with Inoperable or Persistent/Recurrent CTEPH**

Of the 261 CTEPH patients entering CHEST-1, 237 participated in CHEST-2 and were included in the analyses. At CHEST-1 baseline, the majority were female (65%), white (70%), and in WHO FC III (65%), and mean (SD) patient age was 59 (13) years; 73% were inoperable and 27% had persistent/recurrent CTEPH. At entry into CHEST-1, the mean (SD) time since diagnosis was 2.1 (3.1) years, and the time since operation in the post-operative patients (n = 65) was 3.3 (3.0) years.

With the abbreviated methods, patients receiving riociguat in CHEST-1 met more low-risk criteria or improved their risk strata at follow-up compared with baseline (Figure 1c and d). Risk stratification using all 3 abbreviated models at CHEST-1 follow-up discriminated prognostic groups for both survival and clinical worsening-free survival in CHEST-2 (Figures 5 and 6).

The risk of death and clinical worsening in CHEST-2 according to the number of low-risk criteria or risk strata at follow-up (Cox proportional hazards analyses) is summarized in Figure 7. According to both French registry methods, achieving ≥1 low-risk criteria was associated with a reduction in both the risk of death and clinical worsening over 2 years, compared with achieving no low-risk criteria. For the Swedish/COMPERA method, patients
stratified as low-risk at Week 16 had a decreased risk of death or clinical worsening compared with those in the intermediate-risk strata.

**Discussion**

Current ESC/ERS PH treatment guidelines recommend a goal-oriented treatment strategy, with periodic assessment of patients using a risk stratification model with a number of modifiable parameters [1, 12]. Retrospective studies from 3 registries (French, Swedish, and COMPERA), collectively evaluating over 3,000 patients with incident PAH, assessed abbreviated methods of the ESC/ERS risk stratification model. These registry analyses have consistently highlighted the favorable prognostic outcome of ‘low-risk’ vs. other risk categories [13-15]. While these observational studies support a goal-oriented treatment strategy with a low-risk profile as the overall objective, such a strategy has not yet been validated prospectively, in a clinical trial setting, or in a prevalent PAH population [30]. The current post hoc analysis is the first to assess these abbreviated methods in a mostly prevalent population of patients with PAH from a pivotal clinical study.

Analysis of patients with PAH enrolled in the PATENT studies found that only a small number of patients achieved all of the assessed ESC/ERS low-risk criteria at PATENT-1 follow-up [31]. However, 12 weeks of riociguat treatment increased the number of patients achieving a greater number of low-risk criteria (French methods) or a low-risk strata (Swedish/COMPERA method), compared with patients receiving placebo.

Assessment of long-term outcomes of patients with PAH grouped according to the number of low-risk criteria or risk strata found that the French non-invasive and the Swedish/COMPERA methods discriminated prognosis for both survival and clinical worsening-free survival over 2 years in the PATENT-2 study. Patients achieving ≥1 low-risk
non-invasive criteria at follow-up had a significant reduction in the risk of death, based on Cox proportional hazards ratios. Similar results were seen for clinical worsening. However, using the invasive method there was a significant reduction in the risk of clinical worsening only. The Swedish/COMPERA method found a significant reduction in the risk of death and clinical worsening in the low-risk group compared with the intermediate-risk group at follow-up. Interestingly, the French non-invasive approach was recently found to be more accurate than the Swedish/COMPERA model in identifying patients with an excellent long-term survival [32]. In the present study, however, both tools seemed to have a similar predictive value. It is important to note that many patients remained in the intermediate risk group at all timepoints, and further research is necessary to provide additional discrimination and guidance on which patients in this category would benefit from intervention.

The results of the present analysis were consistent with previous studies of risk assessment in PAH. The RRS was developed as a simplified calculator for everyday clinical use to predict survival in patients with PAH, based on data from the REVEAL Registry [33]. Studies have shown that the RRS has good discriminatory ability for predicting survival in patients with newly or previously diagnosed PAH, and that changes in RRS over a 12-month period are also predictive of survival[33, 34]. Assessment of the PATENT patient populations using the RRS showed results in line with the current post-hoc analyses [35]. In patients with PAH, RRS and risk stratum were significantly improved by riociguat between baseline and follow-up. Moreover, RRS at baseline and at PATENT-1 follow-up, and change in RRS during PATENT-1, were all significantly associated with both survival and clinical worsening-free survival [35]. The RRS has been further refined recently to allow better risk delineation and include new clinically useful variables [36]. Another predictive equation that has been
developed in PAH is that from French Pulmonary Hypertension Network (FPHN) registry, which like the RRS and the risk assessment methods analysed in the present paper, has shown good discrimination and calibration for prediction of survival in patients with PAH [37, 38].

The results of the present analysis show a number of implications for clinical practice in the management of PAH. For example, registry findings with the French non-invasive method demonstrated that invasive measures may not always be essential for risk assessment. Our study also demonstrated discrimination between prognostic groups for both survival and clinical worsening-free survival using the French non-invasive method at both baseline and PATENT-1 follow-up, while the discrimination ability of the French invasive method was limited to just clinical worsening-free survival. This is also true of the RRS, which does not require hemodynamic parameters for calculation [34]. In clinical practice, it is important that individual patient risk should be assessed by experienced treating physicians, as patients may achieve a low-risk category for some parameters and not others. However, while the ESC/ERS risk stratification model allows for comprehensive assessment of patients with PAH [1, 12], the current post hoc analysis suggests that as few as 3 non-invasive parameters may be of use for initial patient risk assessment, potentially before a more comprehensive assessment takes place. Importantly, the use of abbreviated tools in clinical practice is still under discussion and until further studies are undertaken, clinicians should use currently available risk assessment tools, finding the best balance of discriminatory power and ease of use for making treatment decisions for the individual patient. Another way in which these tools could be used, as demonstrated by the association of patient risk group or strata with long-term outcomes shown in our analyses and the registry analyses, is
in the development of new, goal-oriented clinical trial endpoints. However, this needs to be validated in the context of a prospective clinical study [30].

Risk assessment is more challenging in patients with CTEPH than in those with PAH due to the multiple treatment options available for CTEPH, including PEA, balloon pulmonary angioplasty, and medical therapy. Furthermore, there may be prognostic factors specific to CTEPH that are not included in the existing risk models. However, each of the three abbreviated tools in the current post hoc analysis had the ability to discriminate prognosis for survival and clinical worsening-free survival among patients with inoperable or persistent/recurrent CTEPH following 16 weeks of treatment with riociguat, although further analyses would need to be performed to statistically compare the discriminatory ability of the tools. These observations are in line with similar results found when the RRS was applied to the CHEST study database, in which riociguat significantly improved RRS and risk stratum vs placebo from baseline to Week 16 [16]. In addition, RRS at baseline and Week 16, and change in RRS during CHEST-1 were significantly associated with survival and clinical worsening-free survival over 2 years in CHEST-2. Further study of the challenges and tools for assessing risk in CTEPH is warranted with multiple therapeutic options used alone, sequentially, or in combination [1, 39]. A recent study has shown that the Swedish/COMPERA model can be used to predict mortality in patients with non-operated CTEPH [17], however, it may be more appropriate to develop a risk assessment tool specific to CTEPH and test it in contemporary cohorts of patients recruited in the modern management era.

Limitations of the ESC/ERS risk assessment model, also common to the abbreviated models presented here, include the lack of weighting of the various risk criteria, and the reliance on
expert consensus regarding parameter inclusion, rather than on results of statistical modeling.[40] Although the thresholds used for the abbreviated risk models could statistically discriminate patient cohorts for outcome, the statistical assessment of patient groups may be of limited value for the individual patient. Furthermore, the ESC/ERS low-risk thresholds used here have been identified using regression analyses in specific study populations and therefore may not be as useful in other patient populations. A further limitation of the current post hoc analysis is the lack of C-indices, which were not calculated, meaning that the methods cannot be compared statistically. It should also be noted that there were differences between the patient populations in the different analyses used in the present study. For example, a far higher percentage of patients in the French non-invasive assessment had one or more low-risk criteria than were identified as ‘low risk’ in the Swedish/COMPERA method. While it may not therefore be possible to compare specific data directly between the different methods, the overall results for each method were broadly similar. In addition, the patient numbers in some subgroups were very small, including the cohorts with zero low-risk criteria. This, combined with the low numbers of events (deaths or clinical worsening events), resulted in large confidence intervals, increasing the uncertainty of the results. Finally, the analysis excluded patients who did not complete the original PATENT-1/CHEST-1 studies. As long-term outcomes in these patients may have been worse than those who completed the original studies and were included in the analysis, this may have affected our findings.

In conclusion, this post hoc analysis confirms the results of previous registry evaluations when each abbreviated model was applied to a prospective pivotal clinical study database of mostly prevalent PAH patients. Achieving ≥1 low-risk criteria using the French non-invasive method or a low-risk strata according to the Swedish/COMPERA method at
follow-up conferred a significantly reduced risk of death or experiencing a clinical worsening event. Observations in patients with inoperable and persistent/recurrent CTEPH demonstrated the potential utility of PAH risk prediction tools in this population.

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References


Figures and tables

Table 1. ESC/ERS Risk Assessment Parameters in the PATENT-2 Study Population at Baseline and Follow-up of PATENT-1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>6MWD risk group, n (%)</th>
<th>WHO FC risk group, n (%)</th>
<th>NT-proBNP risk group, n (%)</th>
<th>RAP risk group, n (%)</th>
<th>Cardiac index risk group, n (%)</th>
<th>SvO₂ risk group, n (%)</th>
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<td></td>
<td>Baseline (n = 231)</td>
<td>Follow-up (n = 109)</td>
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<td>Follow-up (n = 109)</td>
<td>Missing (n = 231)</td>
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<td>1 (&lt;1)</td>
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<td>26 (11)</td>
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<td>15 (14)</td>
<td>32 (29)</td>
<td>32 (29)</td>
<td>1 (1)</td>
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<tr>
<td>Intermediate: 165–440m</td>
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<td>152 (66)</td>
<td>94 (86)</td>
<td>76 (70)</td>
<td>76 (70)</td>
<td>76 (70)</td>
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<td>1 (1)</td>
<td>1 (1)</td>
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<td>142 (61)</td>
<td>57 (52)</td>
<td>62 (57)</td>
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<td>Intermediate: FC III</td>
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<td>34 (31)</td>
<td>34 (31)</td>
<td>34 (31)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (&lt;1)</td>
<td>2 (1)</td>
<td>5 (5)</td>
<td>6 (6)</td>
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</tr>
<tr>
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<td>131 (57)</td>
<td>138 (60)</td>
<td>62 (57)</td>
<td>51 (47)</td>
<td>51 (47)</td>
<td>51 (47)</td>
</tr>
<tr>
<td>Intermediate: 8–14 mm Hg</td>
<td>72 (31)</td>
<td>74 (32)</td>
<td>37 (34)</td>
<td>39 (36)</td>
<td>39 (36)</td>
<td>39 (36)</td>
</tr>
<tr>
<td>High: &gt;14 mm Hg</td>
<td>27 (12)</td>
<td>17 (7)</td>
<td>5 (5)</td>
<td>13 (12)</td>
<td>13 (12)</td>
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</tr>
<tr>
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<td>4 (2)</td>
<td>5 (5)</td>
<td>6 (6)</td>
<td>6 (6)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Low: ≥2.5 L/min/m²</td>
<td>102 (44)</td>
<td>172 (74)</td>
<td>52 (48)</td>
<td>46 (42)</td>
<td>46 (42)</td>
<td>46 (42)</td>
</tr>
<tr>
<td>Intermediate: 2.0–2.5 L/min/m²</td>
<td>83 (36)</td>
<td>40 (17)</td>
<td>21 (19)</td>
<td>30 (28)</td>
<td>30 (28)</td>
<td>30 (28)</td>
</tr>
<tr>
<td>High: &lt;2.0 L/min/m²</td>
<td>43 (19)</td>
<td>15 (6)</td>
<td>31 (28)</td>
<td>27 (25)</td>
<td>27 (25)</td>
<td>27 (25)</td>
</tr>
<tr>
<td>Missing</td>
<td>26 (11)</td>
<td>11 (5)</td>
<td>12 (11)</td>
<td>11 (10)</td>
<td>11 (10)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Low: &gt;65%</td>
<td>106 (46)</td>
<td>154 (67)</td>
<td>56 (51)</td>
<td>47 (43)</td>
<td>47 (43)</td>
<td>47 (43)</td>
</tr>
<tr>
<td>Intermediate: 60–65%</td>
<td>46 (20)</td>
<td>36 (16)</td>
<td>26 (24)</td>
<td>25 (23)</td>
<td>25 (23)</td>
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<tr>
<td>High: &lt;60%</td>
<td>53 (23)</td>
<td>30 (13)</td>
<td>15 (14)</td>
<td>26 (24)</td>
<td>26 (24)</td>
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</tr>
</tbody>
</table>

Definition of abbreviations: 6MWD, 6-minute walking distance; ERS, European Respiratory Society; ESC, European Society of Cardiology; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RAP, right atrial pressure; SvO₂, mixed venous oxygen saturation; WHO FC, World Health Organization functional class.
**Figure 1.** Proportion of patients in each risk stratum at baseline and follow-up in PATENT-1 and CHEST-1, according to the 3 abbreviated versions of the European Society of Cardiology/European Respiratory Society risk stratification model.

Data may not add up to 100% due to rounding.

Only patients who participated in PATENT-2 and CHEST-2 were included in the analysis. The analysis is based on observed data with no imputation.

**French registry invasive method:** Number of low-risk criteria fulfilled: 6MWD >440 m, WHO FC I/II, right atrial pressure <8 mmHg, cardiac index ≥ 2.5 L/min/m²; **French registry non-invasive method:** Number of low-risk criteria fulfilled: 6MWD >440 m, WHO FC I/II, NT-proBNP <300 pg/mL; **Swedish/COMPERA method** mean of grades (1–3: low, intermediate, high) of 6 available criteria (6MWD, WHO FC, NT-proBNP, RAP, cardiac index and SvO₂) as defined in the European Society of Cardiology/European Respiratory Society 2015 treatment guidelines, rounded to the nearest integer.
**Figure 2.** Forest plots comparing survival in PATENT-2 expressed as hazard ratios (95% CI) for mortality comparing patients who achieved one or more low-risk criteria compared with those who achieved no low-risk criteria at a) baseline and b) follow-up in PATENT-1, and clinical worsening-free survival in PATENT-2 expressed as hazard ratios (95% CI) for clinical worsening comparing patients who achieved one or more low-risk criteria compared with those who achieved no low-risk criteria at c) baseline and d) follow-up in PATENT-1.

CI = confidence interval.

Only patients receiving riociguat 2.5 mg tid–maximum in PATENT-1 who participated in PATENT-2 were considered in this analysis.

*Due to the small number of patients in the high-risk category at baseline and follow-up according to the Swedish/COMPERA method, these patients were not included in this analysis.

Due to no or few events in some risk groups/strata, hazards ratios could not be calculated in some cases.

**French registry invasive method:** Number of low-risk criteria fulfilled: 6MWD >440 m, WHO FC I/II, right atrial pressure <8 mmHg, cardiac index ≥ 2.5 L/min/m²; **French registry non-invasive method:** Number of low-risk criteria fulfilled: 6WMD >440 m, WHO FC I/II, NT-proBNP <300 pg/mL; **Swedish/COMPERA method** mean of grades (1–3: low, intermediate, high) of 6 available criteria (6MWD, WHO FC, NT-proBNP, RAP, cardiac index and SvO₂) as defined in the European Society of Cardiology/European Respiratory Society 2015 treatment guidelines, rounded to the nearest integer.
**Figure 3.** Kaplan–Meier curves for survival in patients based on risk stratification at PATENT-1 follow-up: a) French registry invasive method; b) French registry non-invasive method; and c) Swedish/COMPERA method.

Only patients receiving riociguat 2.5 mg tid–maximum in PATENT-1 who participated in PATENT-2 were considered in this analysis.

Data were based on observed cases with no imputation.

Day 0 = start of extension study.

Only 3 patients were in the Swedish/COMPERA high-risk group at PATENT-1 follow-up and are therefore not included in the analysis for this method.

**French registry invasive method:** Number of low-risk criteria fulfilled: 6MWD >440 m, WHO FC I/II, right atrial pressure <8 mmHg, cardiac index ≥ 2.5 L/min/m$^2$; **French registry non-invasive method:** Number of low-risk criteria fulfilled: 6WMD >440 m, WHO FC I/II, NT-proBNP <300 pg/mL; **Swedish/COMPERA method** mean of grades (1–3: low, intermediate, high) of 6 available criteria (6MWD, WHO FC, NT-proBNP, RAP, cardiac index and SvO$_2$) as defined in the European Society of Cardiology/European Respiratory Society 2015 treatment guidelines, rounded to the nearest integer.

**Log-rank test:** Invasive $P = 0.5595$, non-invasive $P = 0.0126$, Swedish/COMPERA $P = 0.0099$. 
Figure 4. Kaplan–Meier curves for clinical worsening-free survival in patients based on risk stratification at PATENT-1 follow-up: a) French registry invasive method; b) French registry non-invasive method; and c) Swedish/COMPERA method.

Only patients receiving riociguat 2.5 mg tid–maximum in PATENT-1 who participated in PATENT-2 were considered in this analysis.

Data were based on observed cases with no imputation.

Day 0 = start of extension study.

Only 3 patients were in the Swedish/COMPERA high-risk group at PATENT-1 follow-up and are therefore not included in the analysis for this method.

**French registry invasive method**: Number of low-risk criteria fulfilled: 6MWD >440 m, WHO FC I/II, right atrial pressure <8 mmHg, cardiac index ≥ 2.5 L/min/m²; **French registry non-invasive method**: Number of low-risk criteria fulfilled: 6WMD >440 m, WHO FC I/II, NT-proBNP <300 pg/mL; **Swedish/COMPERA method** mean of grades (1–3: low, intermediate, high) of 6 available criteria (6MWD, WHO FC, NT-proBNP, RAP, cardiac index and SvO₂) as defined in the European Society of Cardiology/European Respiratory Society 2015 treatment guidelines, rounded to the nearest integer.

**Log-rank test**: Invasive $P = 0.0078$, non-invasive $P = 0.0001$, Swedish/COMPERA $P = 0.0023$. 
**Figure 5.** Kaplan–Meier curves for survival in patients based on risk stratification at CHEST-1 follow-up: a) French registry invasive method; b) French registry non-invasive method; and c) Swedish/COMPERA method.

Only patients receiving riociguat 2.5 mg tid–maximum in CHEST-1 who participated in CHEST-2 were considered in this analysis.

Data were based on observed cases with no imputation.

Day 0 = start of extension study.

Only 5 patients were in the Swedish/COMPERA high-risk group at CHEST-1 follow-up and are therefore not included in the analysis for this method.

**French registry invasive method:** Number of low-risk criteria fulfilled: 6MWD >440 m, WHO FC I/II, right atrial pressure <8 mmHg, cardiac index ≥ 2.5 L/min/m²; **French registry non-invasive method:** Number of low-risk criteria fulfilled: 6WMD >440 m, WHO FC I/II, NT-proBNP <300 pg/mL; **Swedish/COMPERA method** mean of grades (1–3: low, intermediate, high) of 6 available criteria (6MWD, WHO FC, NT-proBNP, RAP, cardiac index and SvO₂) as defined in the European Society of Cardiology/European Respiratory Society 2015 treatment guidelines, rounded to the nearest integer.

**Log-rank test:** Invasive P < 0.0001, non-invasive P = 0.0231, Swedish/COMPERA P < 0.0001.
Figure 6. Kaplan–Meier curves for clinical worsening-free survival in patients based on risk stratification at CHEST-1 follow-up: a) French registry invasive method; b) French registry non-invasive method; and c) Swedish/COMPERA method.

Only patients receiving riociguat 2.5 mg tid–maximum in CHEST-1 who participated in CHEST-2 were considered in this analysis.

Data were based on observed cases with no imputation.

Day 0 = start of extension study.

Only 5 patients were in the Swedish/COMPERA high-risk group at CHEST-1 follow-up and are therefore not included in the analysis for this method.

**French registry invasive method:** Number of low-risk criteria fulfilled: 6MWD >440 m, WHO FC I/II, right atrial pressure <8 mmHg, cardiac index ≥ 2.5 L/min/m²; **French registry non-invasive method:** Number of low-risk criteria fulfilled: 6WMD >440 m, WHO FC I/II, NT-proBNP <300 pg/mL; **Swedish/COMPERA method** mean of grades (1–3: low, intermediate, high) of 6 available criteria (6MWD, WHO FC, NT-proBNP, RAP, cardiac index and Svo2) as defined in the European Society of Cardiology/European Respiratory Society 2015 treatment guidelines, rounded to the nearest integer.

**Log-rank test:** Invasive P < 0.0001, non-invasive P < 0.0001, Swedish/COMPERA P < 0.0001
**Figure 7.** Forest plots comparing survival in CHEST-2 expressed as hazard ratios (95% CI) for mortality comparing patients who achieved one or more low-risk criteria compared with those who achieved no low-risk criteria at a) baseline and b) follow-up in CHEST-1, and clinical worsening-free survival in CHEST-2 expressed as hazard ratios (95% CI) for clinical worsening comparing patients who achieved one or more low-risk criteria compared with those who achieved no low-risk criteria at c) baseline and d) follow-up in CHEST-1.

CI = confidence interval.

Only patients receiving riociguat 2.5 mg tid–maximum in CHEST-1 who participated in CHEST-2 were considered in this analysis.

*Due to the small number of patients in the high-risk category at baseline and follow-up according to the Swedish/COMPERA method, these patients were not included in this analysis.

Due to no or few events in some risk groups/strata, hazards ratios could not be calculated in some cases.

**French registry invasive method:** Number of low-risk criteria fulfilled: 6MWD >440 m, WHO FC I/II, right atrial pressure <8 mmHg, cardiac index ≥ 2.5 L/min/m²; **French registry non-invasive method:** Number of low-risk criteria fulfilled: 6WMD >440 m, WHO FC I/II, NT-proBNP <300 pg/mL; **Swedish/COMPERA method** mean of grades (1–3: low, intermediate, high) of 6 available criteria (6MWD, WHO FC, NT-proBNP, RAP, cardiac index and SvO₂) as defined in the European Society of Cardiology/European Respiratory Society 2015 treatment guidelines, rounded to the nearest integer.
<table>
<thead>
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<th>Model</th>
<th>Baseline</th>
<th>CHEST-1</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>French registry invasive model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of low-risk criteria met</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>French registry non-invasive model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of low-risk criteria met</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>Swedish/COMPERA model</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No. of low-risk criteria met</td>
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<td>Intermediate risk</td>
<td>High risk</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>75</td>
<td>11</td>
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<td>French registry invasive model</td>
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</tr>
<tr>
<td>No. of low-risk criteria met</td>
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<td>3</td>
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<tr>
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<td>1</td>
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<td></td>
<td>24</td>
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<td>9</td>
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<tr>
<td>Swedish/COMPERA model</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No. of low-risk criteria met</td>
<td>Low risk</td>
<td>Intermediate risk</td>
<td>High risk</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>82</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>65</td>
<td>15</td>
</tr>
</tbody>
</table>
French registry invasive model

4 criteria vs. 0 criteria
3 criteria vs. 0 criteria
2 criteria vs. 0 criteria
1 criterion vs. 0 criterion

French registry non-invasive model

3 criteria vs. 0 criterion
2 criteria vs. 0 criterion
1 criterion vs. 0 criterion

Swedish/COMPERA model*
Low risk vs. intermediate risk

Hazard ratio 95% CI p-value

0.462 0.158–1.354 0.160
0.867 0.393–1.914 0.724
0.903 0.395–2.065 0.809
0.495 0.208–1.178 0.112
0.797 0.418–1.520 0.491
0.359 0.151–0.854 0.021
0.324 0.087–1.208 0.093
0.462 0.149–1.433 0.181
0.554 0.180–1.701 0.302
0.691 0.211–2.263 0.541
0.178 0.059–0.536 0.002
0.457 0.219–0.954 0.037
0.447 0.207–0.963 0.040
0.409 0.215–0.779 0.007
French registry invasive model
4 criteria vs. 0 criteria
Hazard ratio: 0.076, 95% CI: 0.016–0.371, p-value: 0.002
3 criteria vs. 0 criteria
Hazard ratio: 0.128, 95% CI: 0.043–0.385, p-value: <0.001
2 criteria vs. 0 criteria
Hazard ratio: 0.199, 95% CI: 0.066–0.600, p-value: 0.004
1 criterion vs. 0 criteria
French registry non-invasive model
3 criteria vs. 0 criteria
Hazard ratio: 0.164, 95% CI: 0.036–0.752, p-value: 0.020
2 criteria vs. 0 criteria
Hazard ratio: 0.227, 95% CI: 0.062–0.831, p-value: 0.025
1 criterion vs. 0 criterion
Swedish/COMPERA model
Low risk vs. intermediate risk
Hazard ratio: 0.155, 95% CI: 0.036–0.675, p-value: 0.013
<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p-value</th>
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<td>French registry invasive model</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4 criteria vs. 0 criteria</td>
<td>0.070</td>
<td>0.019-0.260</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 criteria vs. 0 criteria</td>
<td>0.038</td>
<td>0.008-0.178</td>
<td>&lt;0.001</td>
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<td>2 criteria vs. 0 criteria</td>
<td>0.185</td>
<td>0.080-0.430</td>
<td>&lt;0.001</td>
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<td>1 criterion vs. 0 criteria</td>
<td>0.371</td>
<td>0.166-0.826</td>
<td>0.015</td>
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<tr>
<td>French registry non-invasive model</td>
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</tr>
<tr>
<td>3 criteria vs. 0 criteria</td>
<td>0.061</td>
<td>0.014-0.262</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 criteria vs. 0 criteria</td>
<td>0.233</td>
<td>0.098-0.557</td>
<td>0.001</td>
</tr>
<tr>
<td>1 criterion vs. 0 criteria</td>
<td>0.313</td>
<td>0.159-0.617</td>
<td>&lt;0.001</td>
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<tr>
<td>Swedish/COMPERA model</td>
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<tr>
<td>Low risk vs. intermediate risk</td>
<td>0.164</td>
<td>0.064-0.420</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Online data supplement

PATENT-1 and -2

PATENT-1 was a 12-week, double-blind, randomized Phase III study that enrolled 443 patients with pulmonary arterial hypertension (PAH). Patients were randomly assigned (4:2:1) to riociguat individually dose adjusted according to tolerability up to 2.5 mg three times daily (tid), placebo, or riociguat 1.5 mg tid (exploratory dose). The primary endpoint was change from baseline to Week 12 in 6-minute walking distance (6MWD). After completing PATENT-1, eligible patients were invited to participate in an open-label extension study, PATENT-2. All patients in PATENT-2 received riociguat individually adjusted up to 2.5 mg tid in an 8-week blinded phase (the former riociguat 2.5 mg–maximum arm underwent sham titration), followed by an open-label study phase that will continue until all patients transition to the commercially available drug.

CHEST-1 and -2

CHEST-1 was a 16-week, double-blind, randomized Phase III study that enrolled 261 patients with chronic thromboembolic pulmonary hypertension (CTEPH). Patients were excluded if they had received an endothelin-receptor antagonist, prostacyclin analog, phosphodiesterase type 5 inhibitor, or nitric oxide donor within the 3 months before study entry. Patients were randomly assigned (2:1) to riociguat, individually adjusted according to tolerability up to 2.5 mg tid, or placebo. The primary endpoint was change from baseline to Week 16 in 6MWD. After completing CHEST-1, eligible patients were invited to participate in an open-label extension study, CHEST-2. All patients in CHEST-2 received riociguat
individually adjusted up to 2.5 mg tid in an 8-week blinded phase (the former riociguat arm underwent sham titration), followed by an open-label study phase that will continue until all patients transition to the commercially available drug.

**Cox Proportional Hazards Analyses**

Cox proportional hazards analyses were undertaken in patients who were receiving riociguat (2.5 mg tid-maximum) in PATENT-1/CHEST-1, and went on to participate in PATENT-2/CHEST-2.

The Cox proportional hazards analyses performed assessed the change in risk of death or clinical worsening in patients achieving ≥1 low-risk criteria, compared with those achieving none (according to the French registry methods), and the number of patients achieving a low-risk stratum, compared with those achieving an intermediate-risk stratum (according to the Swedish/COMPERA method). Due to no or few events in some risk groups/strata, hazards ratios could not be calculated in some cases.

Analyses were based on observed cases without imputation.
**Table E1.** Estimated survival rates over 3 years based on risk stratification at PATENT-1 follow-up

<table>
<thead>
<tr>
<th>Number of low-risk criteria/risk stratum achieved according to abbreviated ESC/ERS risk stratification methods</th>
<th>Estimated survival rate (95% CI)</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
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<tbody>
<tr>
<td>French invasive method</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 criteria</td>
<td>91.7 (53.9–98.8)</td>
<td>91.7 (53.9–98.8)</td>
<td>91.7 (53.9–98.8)</td>
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<tr>
<td>1 criterion</td>
<td>92.8 (79.3–97.6)</td>
<td>90.2 (76.0–96.2)</td>
<td>87.6 (72.6–94.6)</td>
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</tr>
<tr>
<td>2 criteria</td>
<td>100.0</td>
<td>93.4 (83.5–97.5)</td>
<td>85.0 (73.1–91.9)</td>
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<tr>
<td>3 criteria</td>
<td>100.0</td>
<td>93.8 (84.2–97.6)</td>
<td>91.9 (81.6–96.6)</td>
<td></td>
</tr>
<tr>
<td>4 criteria</td>
<td>97.0 (80.4–99.6)</td>
<td>93.8 (77.5–98.4)</td>
<td>90.6 (73.6–96.9)</td>
<td></td>
</tr>
<tr>
<td>French non-invasive method</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 criteria</td>
<td>95.9 (84.7–99.0)</td>
<td>86.7 (72.6–93.8)</td>
<td>76.6 (60.7–86.8)</td>
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<tr>
<td>1 criterion</td>
<td>96.8 (87.8–99.2)</td>
<td>93.4 (83.4–97.5)</td>
<td>88.0 (76.4–94.1)</td>
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<tr>
<td>2 criteria</td>
<td>100.0</td>
<td>93.4 (83.4–97.5)</td>
<td>91.5 (80.8–96.4)</td>
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</tr>
<tr>
<td>3 criteria</td>
<td>97.7 (84.9–99.7)</td>
<td>97.7 (84.9–99.7)</td>
<td>95.2 (82.2–98.8)</td>
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</tr>
<tr>
<td>Swedish/COMPERA method</td>
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<td></td>
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<tr>
<td>Intermediate-risk</td>
<td>96.4 (90.6–98.6)</td>
<td>90.3 (82.8–94.7)</td>
<td>84.0 (75.1–89.9)</td>
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</tr>
<tr>
<td>Low-risk</td>
<td>99.1 (93.6–99.9)</td>
<td>95.2 (88.8–98.0)</td>
<td>92.0 (84.6–95.9)</td>
<td></td>
</tr>
</tbody>
</table>

*Definitions of abbreviations: CI, confidence interval; ERS, European Respiratory Society; ESC, European Society of Cardiology*

Only patients receiving riociguat 2.5 mg tid–maximum in PATENT-1 who participated in PATENT-2 were considered in this analysis.

**French registry invasive method:** Number of low-risk criteria fulfilled: 6MWD >440 m, WHO FC I/II, right atrial pressure <8 mmHg, cardiac index ≥ 2.5 L/min/m²; **French registry non-invasive method:** Number of low-risk criteria fulfilled: 6WMD >440 m, WHO FC I/II, NT-proBNP <300 pg/mL; **Swedish/COMPERA method** mean of grades (1–3: low, intermediate, high) of 6 available criteria (6MWD, WHO FC, NT-proBNP, RAP, cardiac index and Svo2) as defined in the European Society of Cardiology/European Respiratory Society 2015 treatment guidelines, rounded to the nearest integer.
**Figure E1.** Kaplan–Meier curves for survival in patients based on risk stratification at PATENT-1 baseline: a) French registry invasive method; b) French registry non-invasive method; and c) Swedish/COMPERA method.
Only patients receiving riociguat 2.5 mg tid–maximum in PATENT-1 who participated in PATENT-2 were considered in this analysis.

Data were based on observed cases with no imputation.

Day 0 = start of extension study.

Only 12 patients were in the Swedish/COMPERA high-risk group at PATENT-1 baseline (most of whom died during PATENT-2 follow-up) and are therefore not included in the analysis for this method.

**French registry invasive method:** Number of low-risk criteria fulfilled: 6MWD >440 m, WHO FC I/II, right atrial pressure <8 mmHg, cardiac index ≥ 2.5 L/min/m²; **French registry non-invasive method:** Number of low-risk criteria fulfilled: 6WMD >440 m, WHO FC I/II, NT-proBNP <300 pg/mL; **Swedish/COMPERA method** mean of grades (1–3: low, intermediate, high) of 6 available criteria (6MWD, WHO FC, NT-proBNP, RAP, cardiac index and SvO₂) as defined in the European Society of Cardiology/European Respiratory Society 2015 treatment guidelines, rounded to the nearest integer.

**Log-rank test:** invasive $P = 0.4276$, non-invasive $P = 0.0283$, Swedish/COMPERA $P = 0.0355$. 
Figure E2. Kaplan–Meier curves for clinical worsening-free survival in patients based on risk stratification at PATENT-1 baseline: a) French registry invasive method; b) French registry non-invasive method; and c) Swedish/COMPERA method.
Only patients receiving riociguat 2.5 mg tid–maximum in PATENT-1 who participated in PATENT-2 were considered in this analysis.

Data were based on observed cases with no imputation.

Day 0 = start of extension study.

Only 12 patients were in the Swedish/COMPERA high-risk group at PATENT-1 baseline (most of whom died during PATENT-2 follow-up) and are therefore not included in the analysis for this method.

**French registry invasive method:** Number of low-risk criteria fulfilled: 6MWD >440 m, WHO FC I/II, right atrial pressure <8 mmHg, cardiac index ≥ 2.5 L/min/m²; **French registry non-invasive method:** Number of low-risk criteria fulfilled: 6WMD >440 m, WHO FC I/II, NT-proBNP <300 pg/mL; **Swedish/COMPERA method** mean of grades (1–3: low, intermediate, high) of 6 available criteria (6MWD, WHO FC, NT-proBNP, RAP, cardiac index and SvO₂) as defined in the European Society of Cardiology/European Respiratory Society 2015 treatment guidelines, rounded to the nearest integer.

**Log-rank test:** Invasive $P = 0.0602$, non-invasive $P = 0.0036$, Swedish/COMPERA $P = 0.0236$. 