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# Pulmonary Arterial Hypertension: tailoring treatment to risk in the current era

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# 특발성 폐동맥고혈압의 병태생리

Tuberc Respir Dis. 2007 Dec;63(6):475-479

울산대학교 의과대학 서울아산병원 호흡기내과

**나승원, 이상도**

# Cellular and Molecular Pathophysiology of Idiopathic Pulmonary Arterial Hypertension

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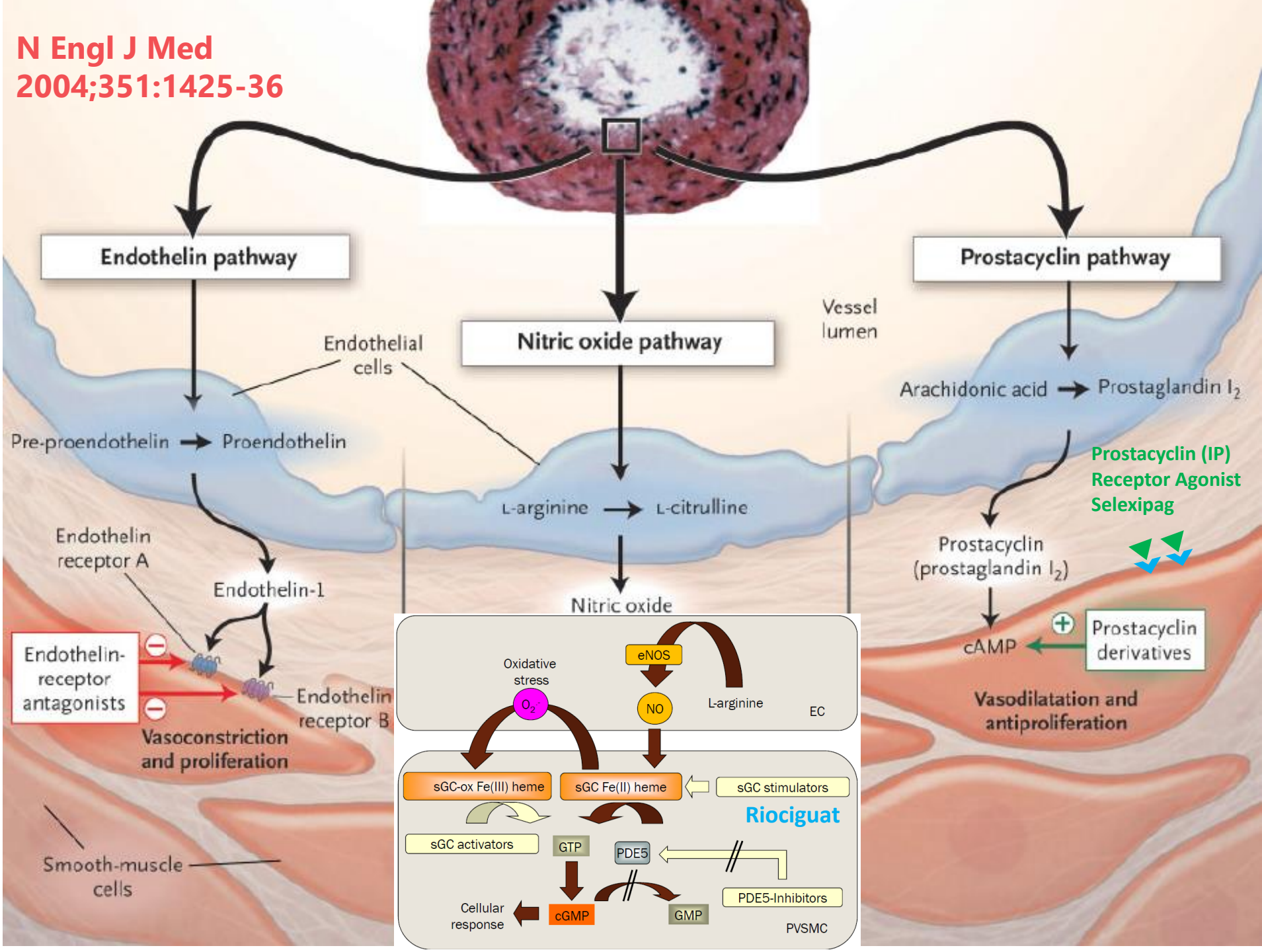
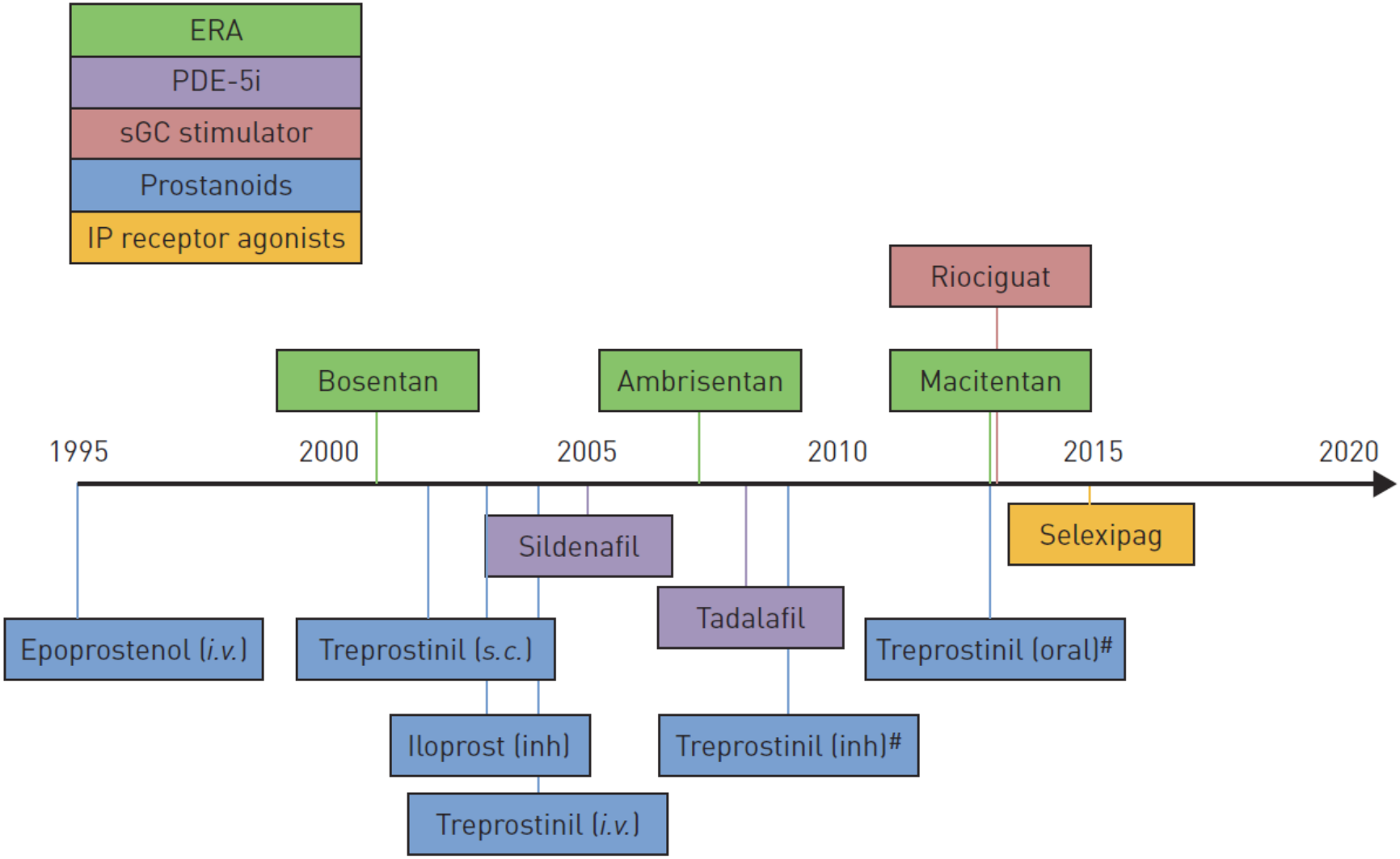
N Engl J Med
2004;351:1425-36



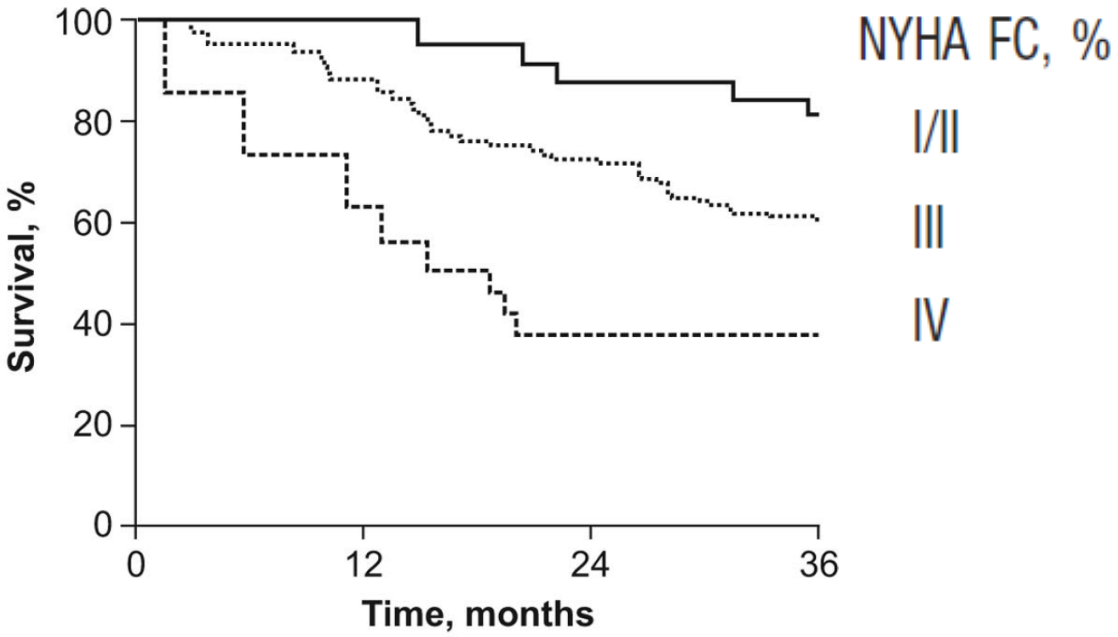
# Timeline of approval of therapies for pulmonary arterial hypertension




Eur Respir Rev 2017; 26: 170095

# Survival in Patients With PAH in the Modern Management Era

| Diagnosis, % | |
|---|---|
| Idiopathic PAH | 87.5 |
| Familial PAH | 5.4 |
| Anorexigen-associated PAH | 7.1 |




Circulation. 2010;122:156-163

# The limitations of the NYHA functional classification system

**Class II** – Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.

Barst RJ, et al. J Am Coll Cardiol 2004;43:S40–S47

**Table 5** Results of the interoperator study

| | | NYHA class for assessor 2 | | |
|---|---|---|---|---|
| | | I | II | III |
| NYHA class for assessor 1 | I | 1 | | |
| | II | 1 | 18 | 10 |
| | III | | 13 | 7 |

NYHA, New York Heart Association.

Heart 2007;93:476–482

# Multivariable Cox PH Model for death

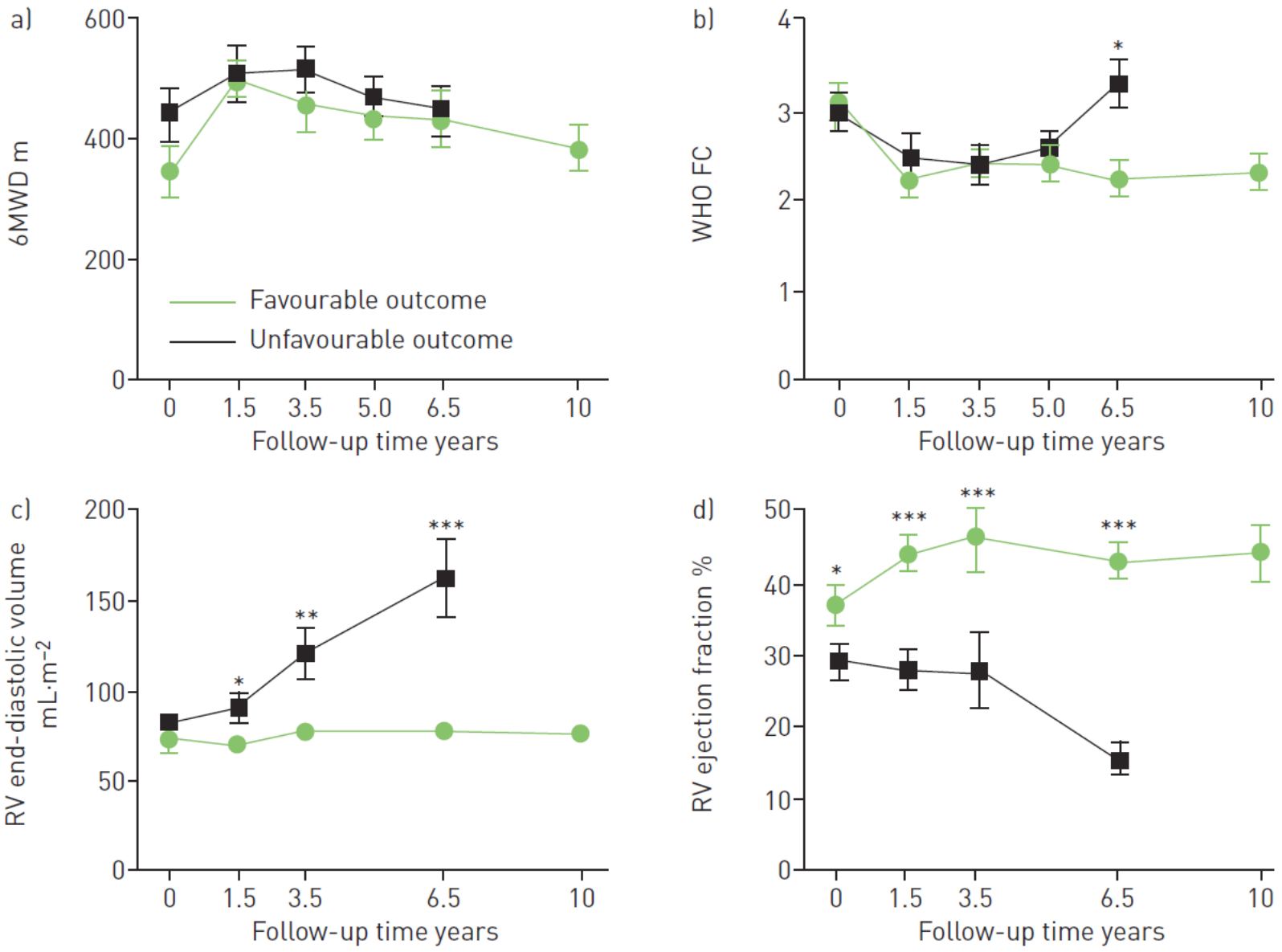
| | HR | 95% CI | *P* |
|---|---|---|---|
| 6MWD | 0.996 | 0.993–0.999 | 0.004 |
| Gender | | | |
| Male | 1 | | |
| Female | 0.375 | 0.212–0.662 | <0.001 |
| Cardiac output | 0.759 | 0.599–0.961 | 0.02 |

**C (concordance) statistics = 0.57 (95% CI, 0.29-0.82 )**

Circulation. 2010;122:156-163

# Disease progression is preceded by RV remodeling

Chest 2015;147:1063–71



# Suggested assessment and timing for the follow-up of patients with pulmonary arterial hypertension

| | At baseline | Every 3–6 months[a] | Every 6–12 months[a] | 3–6 months after changes in therapy[a] | In case of clinical worsening |
|---|---|---|---|---|---|
| Medical assessment and determination of functional class | + | + | + | + | + |
| ECG | + | + | + | + | + |
| 6MWT/Borg dyspnoea score | + | + | + | + | + |
| CPET | + | | + | | +[e] |
| Echo | + | | + | + | + |
| Basic lab[b] | + | + | + | + | + |
| Extended lab[c] | + | | + | | + |
| Blood gas analysis[d] | + | | + | + | + |
| Right heart catheterization | + | | +[f] | +[e] | +[e] |

Eur Respir J 2015;46:903–975
European Heart Journal 2016;37:67–119

# Risk assessment in PAH

| Determinants of prognosis[a] (estimated 1-year mortality) | Low risk <5% | Intermediate risk 5–10% | High risk >10% |
|---|---|---|---|
| Clinical signs of right heart failure | Absent | Absent | Present |
| Progression of symptoms | No | Slow | Rapid |
| Syncope | No | Occasional syncope[b] | Repeated syncope[c] |
| WHO functional class | I, II | III | IV |
| 6MWD | >440 m | 165–440 m | <165 m |
| Cardiopulmonary exercise testing | Peak $VO_2$ >15ml/min/kg (>65% pred.) $VE/VCO_2$ slope <36 | Peak $VO_2$ 11–15 ml/min/kg (35–65% pred.) $VE/VCO_2$ slope 36–44.9 | Peak $VO_2$ <11 ml/min/kg (<35% pred.) $VE/VCO_2$ slope ≥45 |
| NT-proBNP plasma levels | BNP <50 ng/l NT-proBNP <300 ng/l | BNP 50–300 ng/l NT-proBNP 300–1400 ng/l | BNP >300 ng/l NT-proBNP >1400 ng/l |
| Imaging (echocardiography, CMR imaging) | RA area <18 $cm^2$ No pericardial effusion | RA area 18–26 $cm^2$ No or minimal, pericardial effusion | RA area >26 $cm^2$ pericardial effusion |
| Haemodynamics | RAP <8 mmHg CI ≥2.5 l/min/$m^2$ $SvO_2$ >65% | RAP 8–14 mmHg CI 2.0–2.4 l/min/$m^2$ $SvO_2$ 60–65% | RAP >14 mmHg CI <2.0 l/min/$m^2$ $SvO_2$ <60% |

Eur Respir J 2015;46:903–975
European Heart Journal 2016;37:67–119

European Heart Journal (2017) **0**, 1–7
doi:10.1093/eurheartj/ehx257



# A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension

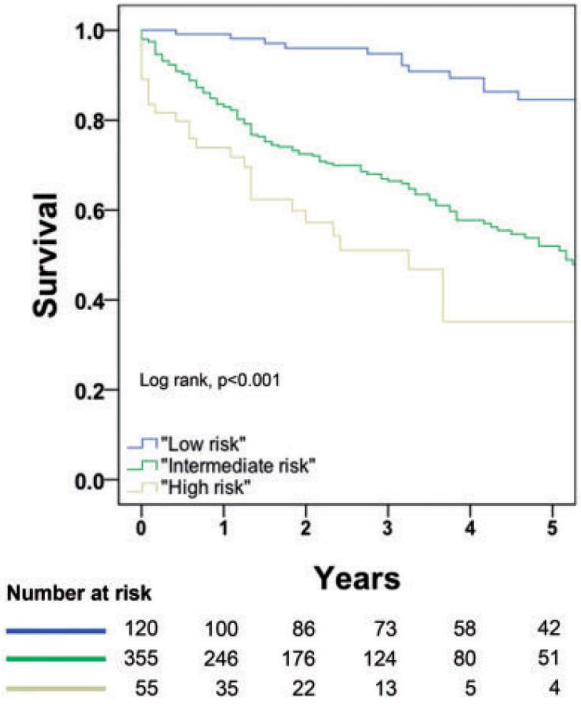
**Table 1 Included variables from the risk assessment instrument from the ESC/ERS 2015 guidelines for the diagnosis and treatment of pulmonary hypertension and their cut-off values**

| Determinants of prognosis | Low risk | Intermediate risk | High risk |
|---|---|---|---|
| WHO functional class | I, II | III | IV |
| 6MWD | >440 m | 165–440 m | <165 m |
| NT-proBNP levels | <300 ng/L | 300–1400 ng/L | >1400 ng/L |
| Imaging (echocardiography) | RA area <18 $cm^2$ | RA area 18–26 $cm^2$ | RA area >26 $cm^2$ |
| | No pericardial effusion | No or minimal pericardial effusion | Pericardial effusion |
| Haemodynamics | RAP <8 mmHg | RAP 8–14 mmHg | RAP >14 mmHg |
| | CI ≥ 2.5 L/min/$m^2$ | CI 2.0–2.4 L/min/$m^2$ | CI < 2.0 L/min/$m^2$ |
| | $SvO_2$ >65% | $SvO_2$ 60–65% | $SvO_2$ <60% |

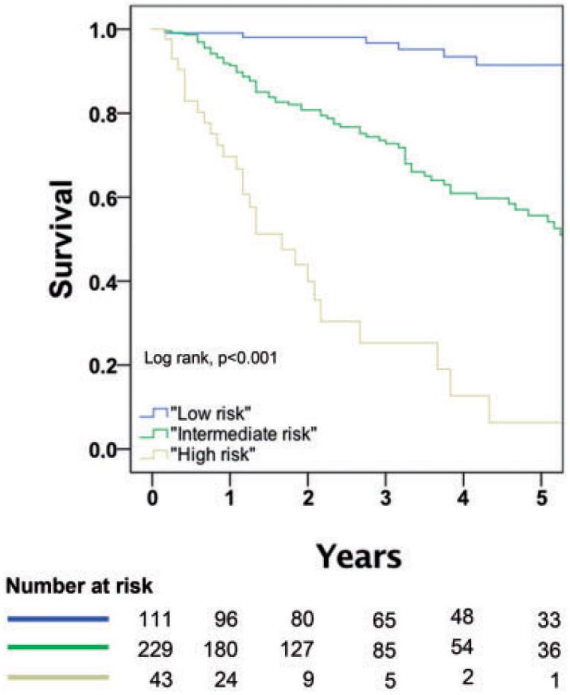
Adopted from the risk assessment instrument from the 2015 ESC/ERS guidelines for the diagnosis and treatment of PH. Reaching a low-risk profile is recommended to be a treatment goal.[19]
6MWD, 6-minute walking distance; CI, cardiac index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RA, right atrium; RAP, right atrial pressure; $S_vO_2$, mixed venous oxygen saturation; WHO, World Health Organization.

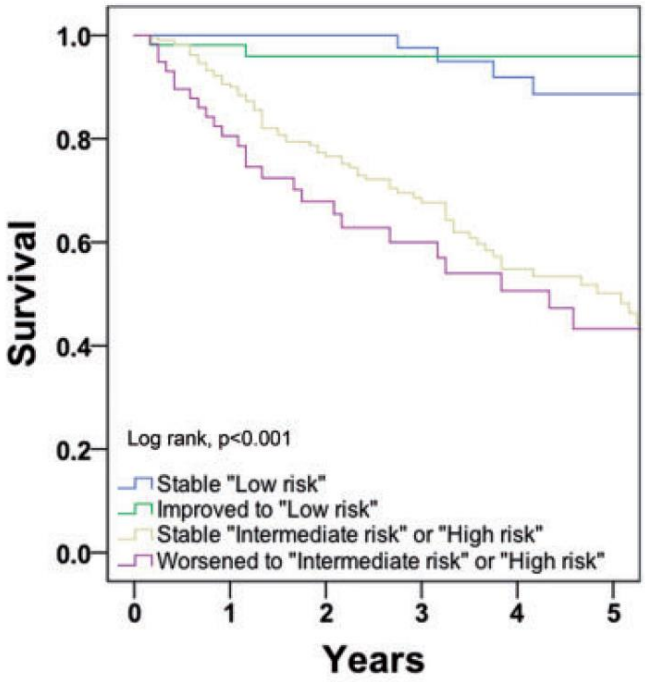
# 5-year survival based on baseline or follow-up risk group

**Baseline risk group (n=530)**



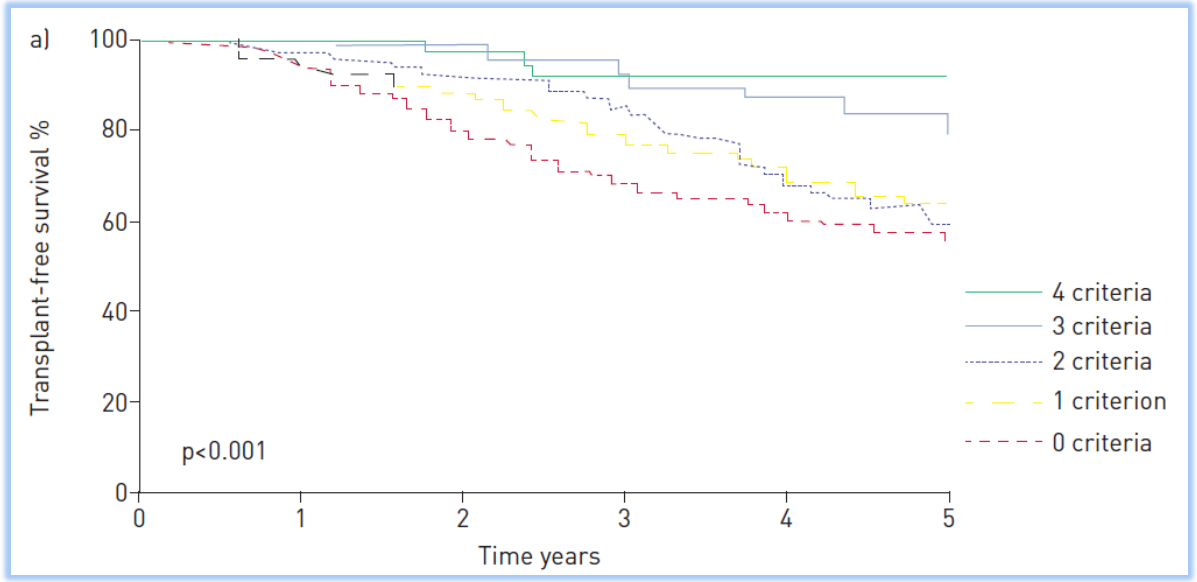

**follow-up risk group (n=383)**

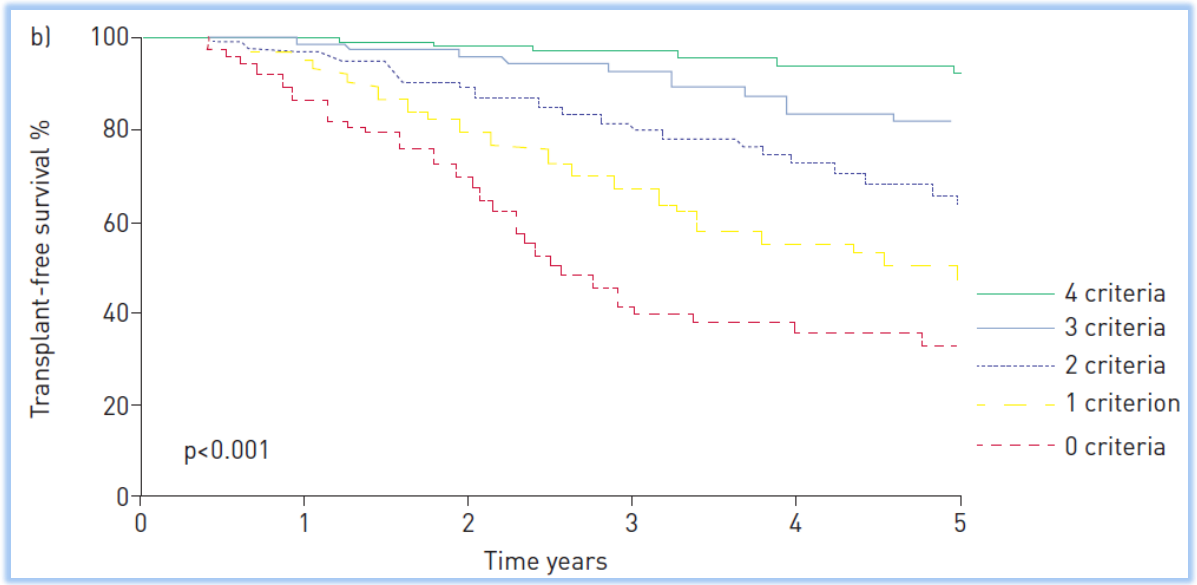



David Kylhammar et al.
European Heart Journal (2017)

# Transplant-free survival according to the number of low-risk criteria



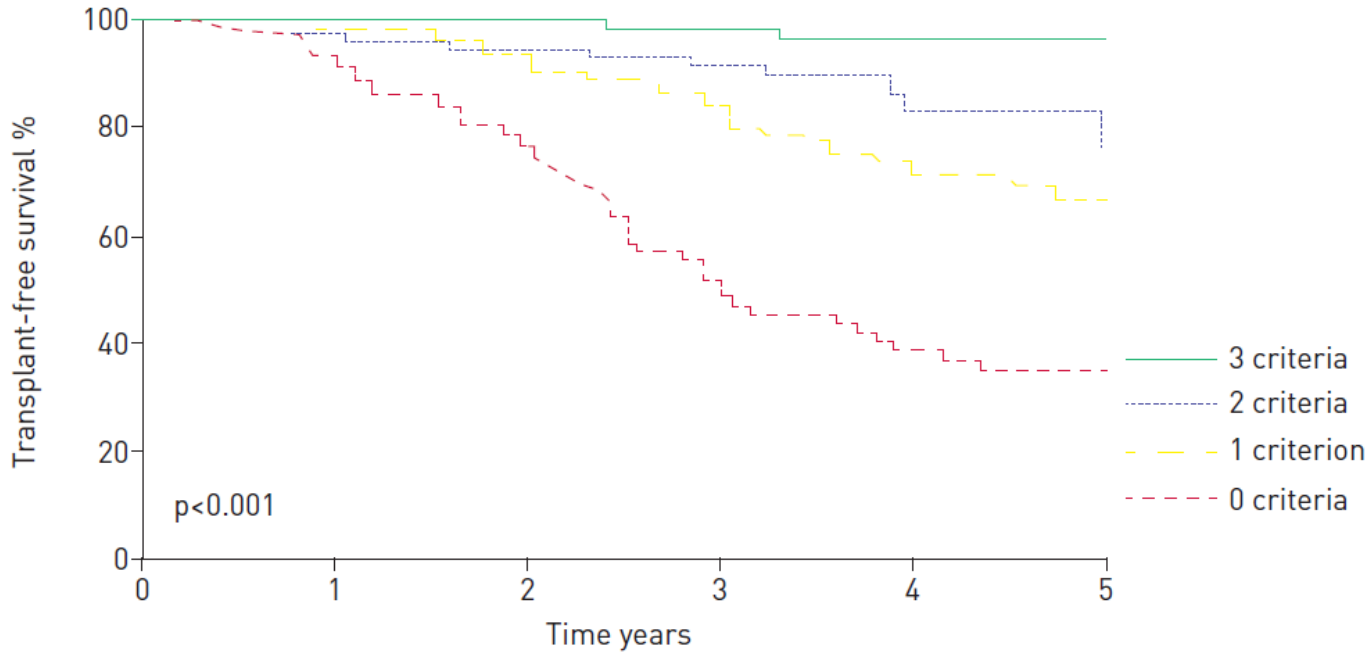




- WHO/NYHA FC I–II
- 6MWT distance >440 m
- RA pressure <8 mmHg
- CI ⩾2.5 L/min/m2

Eur Respir J 2017; 50: 1700889

# Cox analysis of low-risk criteria assessed at first re-evaluation in the subset of patients with available BNP or NT-proBNP measurements

| | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | Hazard ratio (95% CI) | p-value | Hazard ratio (95% CI) | p-value |
| WHO/NYHA FC I–II | 0.28 (0.19–0.42) | <0.001 | 0.47 (0.32–0.71) | <0.001 |
| 6-min walking distance >440 m | 0.17 (0.09–0.31) | <0.001 | 0.32 (0.17–0.60) | <0.001 |
| BNP <50 ng·L$^{-1}$ or NT-proBNP <300 ng·mL$^{-1}$ | 0.21 (0.13–0.34) | <0.001 | 0.31 (0.19–0.52) | <0.001 |
| Right atrial pressure <8 mmHg | 0.45 (0.31–0.65) | <0.001 | | |
| Cardiac index ⩾2.5 L·min$^{-1}$·m$^{-2}$ | 0.44 (0.30–0.65) | <0.001 | | |




Eur Respir J 2017;50:1700889

# Combination therapy data from RCTs

Eur Respir Rev 2016; 25: 408–417

| Study name | Patients | PAH treatment at baseline | Investigational therapy | Comparator | Primary end-point | Study duration | Primary end-point met in overall population |
|---|---|---|---|---|---|---|---|
| **Sequential combination** | | | | | | | |
| PACES-1 [18] | 267 | Epoprostenol *i.v.* 267 (100) | Sildenafil | Placebo | 6MWD | 16 weeks | Yes |
| ZHUANG *et al.* 2014 [21] | 124 | Ambrisentan 124 (100) | Tadalafil | Placebo | 6MWD | 16 weeks | Yes |
| PHIRST [19] | 405 | None 189 (47)<br>Bosentan 216 (53) | Tadalafil | Placebo | 6MWD | 16 weeks | Yes# |
| PATENT-1 [20] | 443 | None 221 (50)<br>ERA 194 (44)<br>Prostanoids¶ 28 (6) | Riociguat | Placebo | 6MWD | 12 weeks | Yes# |
| COMBI [14] | 40 | Bosentan 40 (100) | Inhaled iloprost | None+ | 6MWD | 12 weeks | No |
| STEP [15] | 67 | Bosentan 67 (100) | Inhaled iloprost | Placebo | 6MWD | 12 weeks | No |
| TRIUMPH [17] | 235 | Bosentan 165 (70)<br>Sildenafil 70 (30) | Inhaled treprostinil | Placebo | 6MWD | 12 weeks | Yes |
| FREEDOM-C [23] | 350 | ERA, 106 (30)<br>PDE-5i 88 (25)<br>ERA and PDE-5i 156 (45) | Oral treprostinil | Placebo | 6MWD | 16 weeks | No |
| FREEDOM-C2 [24] | 310 | ERA 53 (17)<br>PDE-5i 132 (43)<br>ERA and PDE-5i 125 (40) | Oral treprostinil | Placebo | 6MWD | 16 weeks | No |
| EARLY [16] | 185 | None 156 (84)<br>Sildenafil 29 (16) | Bosentan | Placebo | PVR and 6MWD | 26 weeks | PVR: yes<br>6MWD: no# |
| COMPASS-2 [25] | 334 | Sildenafil 334 (100) | Bosentan | Placebo | Composite of morbidity/ mortality | Mean 114.4 weeks§ | No |
| SERAPHIN [8] | 742 | None 268 (36)<br>PDE-5i 454 (61)<br>Oral/inhaled prostanoid 40 (5) | Macitentan | Placebo | Composite of morbidity/ mortality | Median 115 weeks | Yes# |
| GRIPHON [10] | 1156 | None 236 (20)<br>ERA 170 (15)<br>PDE-5i 374 (32)<br>ERA and PDE-5i 376 (33) | Selexipag | Placebo | Composite of morbidity/ mortality | Median 67 weeks | Yes# |
| **Initial combination in treatment-naïve patients** | | | | | | | |
| BREATHE-2 [22] | 33 | None | Epoprostenol and bosentan | Epoprostenol and placebo | Total pulmonary resistance | 16 weeks | No |
| AMBITION [9] | 500f | None | Ambrisentan and tadalafil | Ambrisentan or tadalafil | Composite of clinical failure | Mean 73.9 weeks | Yes |

# Combination therapy including a parenteral prostanoid

- Data from **newly diagnosed NYHA FC III/IV PAH** patients (n=19) initiated on upfront **triple combination** therapy (IV epoprostenol, bosentan and sildenafil) were collected retrospectively from a prospective registry.

| | Baseline | Month 4 visit | Final follow-up visit# |
|---|---|---|---|
| **NYHA FC I/II/III/IV n** | 0/0/8/10 | 1/16/1/0** | 4/14/0/0** |
| **6MWD m** | 227±171 | 463±94** | 514±105**,¶ |
| **Haemodynamics** | | | |
| RAP mmHg | 11.9±5.2 | 4.9±4.9** | 5.2±3.5** |
| mPAP mmHg | 65.8±13.7 | 45.7±14.0** | 44.4±13.4** |
| PCWP mmHg | 8.4±3.5 | 6.7±3.2 | 7.9±2.8 |
| Cardiac index $L \cdot min^{-1} \cdot m^{-2}$ | 1.66±0.35 | 3.49±0.69** | 3.64±0.65** |
| PVR $dyn \cdot s \cdot cm^{-5}$ | 1718±627 | 564±260** | 492±209** |
| Mean BP mmHg | 92.1±12.5 | 80.1±11.7** | 84.9±19.4 |
| HR beats per min | 92.3±10.7 | 83.9±9.8** | 79.9±13.4** |
| $Sv_{O_2}$ % | 51.0±8.5 | 69.7±5.2** | 72.2±4.0** |
| **Dose of epoprostenol achieved $ng \cdot kg^{-1} \cdot min^{-1}$** | 0 | 15.9±1.9 | 19.6±6.0 |

Eur Respir J 2014; 43: 1691–1697

# Beyond PAH-specific pharmacological therapy

- Exercise-based rehabilitation
  - ✓ Low-level **aerobic** exercise at home, if it is not feasible.
  - ✓ **Isometric** exercise is **not** recommended
- **IV Iron** supplementation
- **Vitamin D** replacement therapy
- Na-restricted diet to prevent additional water retention
- Anticoagulants – conflicting results
- **Aldosterone antagonists**
- The impact of comorbidities

# Future perspectives: managing transitions

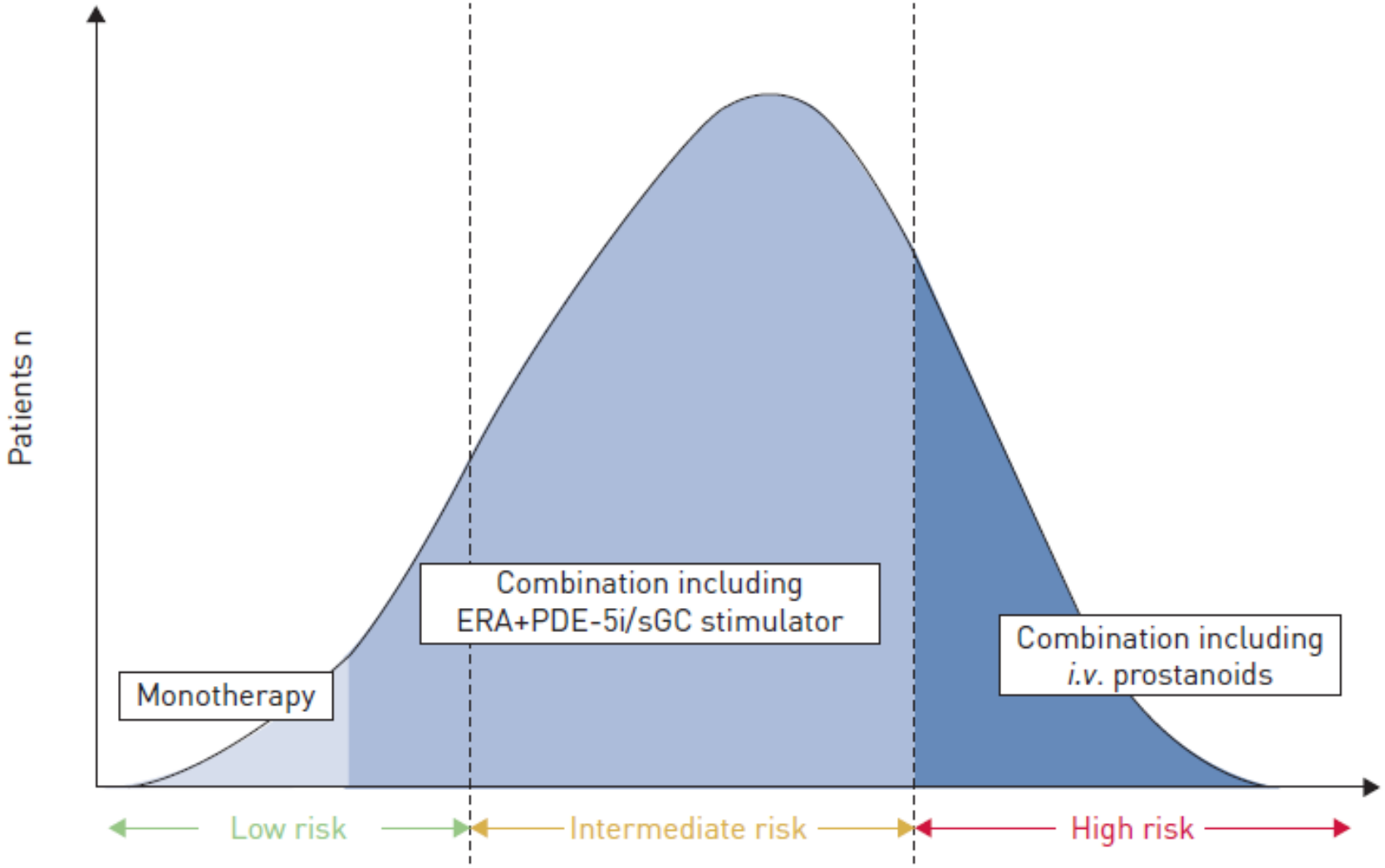
- Transitioned from **IV** or **inhaled** prostacyclins to **oral** treprostinil or selexipag


1. TRANSIT-1 study. Am J Respir Crit Care Med 2017; 195: A2284
2. J Heart Lung Transplant 2017; 36: 193–201
3. Pulm Circ 2016; 6: 132–135
4. Am J Respir Crit Care Med 2017; 195: A2298
5. Am J Respir Crit Care Med 2017; 195: A2278
6. Am J Respir Crit Care Med 2017; 195: A2288
7. Am J Respir Crit Care Med 2017; 195: A2300


- Switching between PDE-5i and sGC stimulator in patients who are not responding to one type of drug.


1. 1. REPLACE trial: Am J Respir Crit Care Med 2017; 195: A2296
2. 2. RESPITE trial: Eur Respir J 2017; 50: 1602425.

# Initial management of PAH in the current era



# 국내 병용투여 보험지침

- 동 약제를 최소 **3개월 이상 단독투여 후** 임상적 반응이 충분하지 않을 때 (다음의 **①~④항 소견 중 최소 1개**와 **⑤~⑨항 중 최소 1개**를 **모두** 만족), 작용기전이 다른 약제 1종과 병용투여를 인정함.

| 지표 | 기준 |
|---|---|
| ① 우심실부전의 임상적 증거 (clinical evidence of RV failure) | 있음 |
| ② 증상진행의 속도 (Rate of progression of symptoms) | 빠름 |
| ③ 실신 (Syncope) | 있음 |
| ④ WHO 기능분류(WHO-FC) | IV단계 |
| ⑤ 6분 보행거리(6MWT) | 300m 미만 |
| ⑥ 운동부하심폐검사 (Cardio-pulmonary exercise testing) | Peak $VO_2$ < 12mL/min/kg |
| ⑦ BNP/NT-proBNP plasma levels | 1800 이상 |
| ⑧ 심초음파검사소견 (Echocardiographic findings) | Pericardial effusion 또는 TAPSE<1.5cm |
| ⑨ 혈류역학검사지표 (Hemodynamics) | RAP>15mmHg 또는 CI≦ 2.0L/min/$m^2$ |

- 치료 효과에 대해 정기적인 평가가 이루어져야 함.