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International Meeting on
PULMONARY RARE DISEASES
AND ORPHAN DRUGS

« Angioplasty & Riociguat for the treatment of non-operable chronic thromboembolic pulmonary hypertension»

Gerald Simonneau

National Reference Center for Pulmonary Hypertension

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Potential COI of Gerald Simonneau

Actelion: consultancy, board or advisory committee, speaker, research support

Jansen: consultancy, board or advisory committee, speaker, research support

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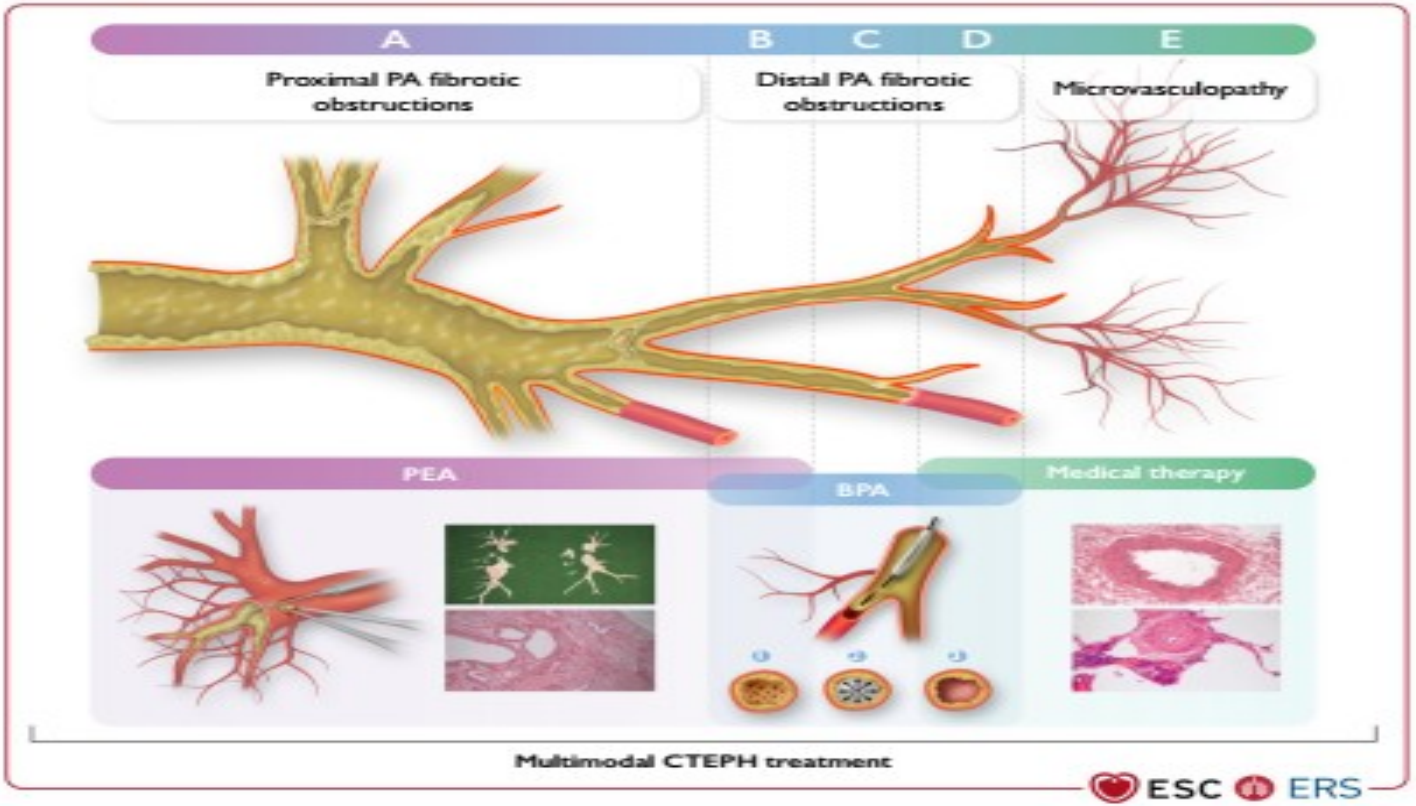
Treatment of CTEPH: Site of action of Surgery (PEA), Angioplasty (BPA) and medical therapy (Riociguat)



M Humbert et al.ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.Eur Respir J 2022

Medical Therapy for CTEPH

- Riociguat, a Guanylate cyclase stimulator (NO pathway), approved in 2015 [1] for the treatment of inoperable CTEPH or for persistent/recurrent PH after surgery PEA.The efficacy is maintained at long-term [2]
- Subcutaneous Treprostinil (Prostacyclin pathway) approved in 2020 [3] providing a parenteral treatment option for patients in FC III/IV and those who do not tolerate other therapies or need combination treatment

1.Ghofrani HA, *et al.* N Engl J Med 2013. 2. Simonneau G*, et al.* Lancet Respir Med 2016
2. Sadushi-Kolici R *et al*. Lancet Respir Med 2019

Balloon pulmonary angioplasty(BPA) for non-perable CTEPH

- BPA was first developed for treating PA congenital stenosis [1]
- A 1st case series of 18 patients from USA was reported in 2001[2] with a treatment effect less than those obtained with PEA and with a high rate of severe complications
- Over the last 10 years , several centers in Japan (Okayama, Osaka, Kobe, Tokyo ..and others) have refined the BPA procedure leading to improvement in efficacy and safety of this treatment option for inoperable patients with CTEPH[3]
- And today BPA for non operable is widely used in Europe[4] and USA with a great efficacy on pulmonary hemodynamic. Regarding safety this technic needs to be performed in large volume center to decrease the rate of complications remaing an issue

1.Lock HE et al . Circulation 1983. 2. Feinstein JA et al . Circulation 2001.
3.A Ogawa & H Matsubara. Reviews in Medicine 2015.4. Brenot Fet al.Eur Respir J 2019.

Balloon pulmonary angioplasty versus riociguat in inoperable chronic thromboembolic pulmonary hypertension (MR BPA): an open-label, randomised controlled trial

Takashi Kawakami, Hiromi Matsubara*, Toshiro Shinke, Kohtaro Abe, Shun Kohsaka, Kazuya Hosokawa, Yu Taniguchi, Hiroto Shimokawahara, Yoshitake Yamada, Masaharu Kataoka, Aiko Ogawa, Mitsushige Murata, Masahiro Jinzaki, Kenichi Hirata, Hiroyuki Tsutsui, Yasunori Sato, Keiichi Fukuda*

www.thelancet.com/respiratory **Published online August 1, 2022** **https://doi.org/10.1016/S2213-2600(22)00171-0**

Balloon pulmonary angioplasty versus riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension (RACE): a multicentre, phase 3, open-label, randomised controlled trial and ancillary follow-up study

Xavier Jaïs, Philippe Brenot, Hélène Bouvaist, Mitja Jevnikar, Matthieu Canuet, Céline Chabanne, Ari Chaouat, Vincent Cottin, Pascal De Groote, Nicolas Favrolt, Delphine Horeau-Langlard, Pascal Magro, Laurent Savale, Grégoire Prévot, Sébastien Renard, Olivier Sitbon, Florence Parent, Romain Trésorier, Cécile Tromeur, Céline Piedvache, Lamiae Grimaldi, Elie Fadel, David Montani, Marc Humbert, Gérald Simonneau**

www.thelancet.com/respiratory **Published online August 1, 2022** **https://doi.org/10.1016/S2213-2600(22)00214-4**

Balloon pulmonary angioplasty versus riociguat in inoperable chronic thromboembolic pulmonary hypertension (MR BPA): an open-label, randomised controlled trial

- Open-label RCT conducted in 4 volumes centres in Japan
- Patients 20-80 yo with inoperable CTEPH, WHO FC II or III
- Randomly assigned (1:1) to BPA or Rociguat
- Primary EP: change in mean PAP from Baseline to 1year
- Between 2016 and 2019, 61 Pts were enrolled (32BPA vs 29 Rio)

Kawakami T et al.Lancet Respir Med 2023

www.thelancet.com/respiratory Published online August 1, 2022 https://doi.org/10.1016/S2213-2600(22)00171-0

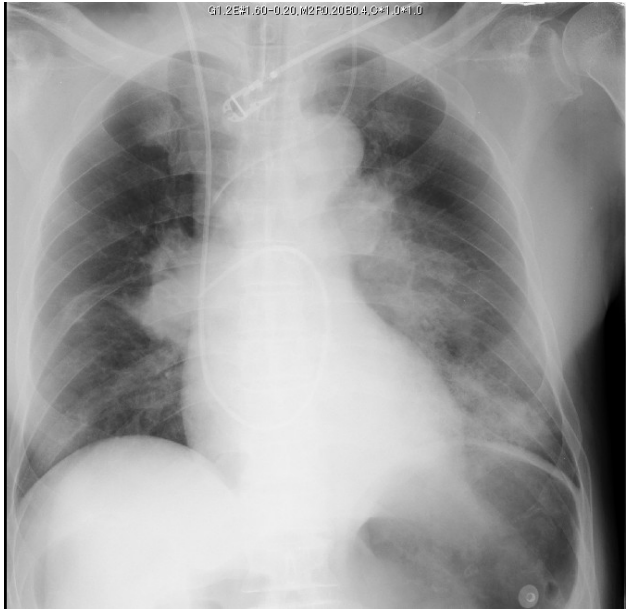
Japanese Study:Results at 1 year

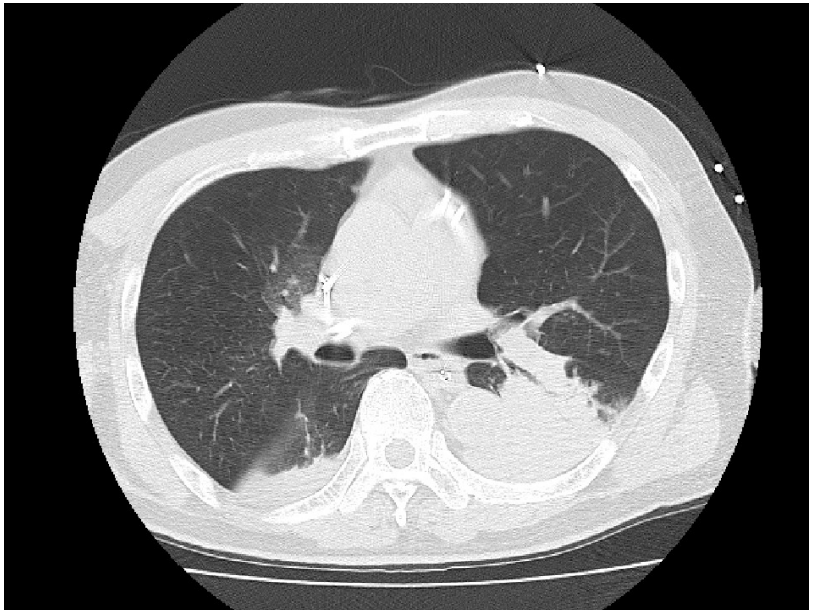
- At 1year mean PAP decreased by 16.3 mmHg in the BPA group vs 7mmHg in the Riociguat group , a difference-9.3 mmHg in favor of BPA [95% CI -12.7 to 5.9 mm Hg; p<0.0001]
- PVR decreased By 54% in the BPA group versus 40% in the Riociguat group (P=0.0004) Cardiac output increased by 3.5% with BPA vs 15% in the Riociguat Group (P=0.0013)
- A case of clinical worsening in the Riociguat group vs none in BPA group
- No deaths observed among the 2 treatment groups
- The most frequent adverse event was pulmonary vascular injury with or without haempoptysis affecting 14patients (44%) in the BPA group vs 1(4%) in the riociguat group

Conclusion: Compared with Riociguat, BPA was associated with a greater improvement in mean pulmonary artery pressure pressure in patients with inoperable CTEPH but this treatment was frequently associated with frequent complications related to the procedure.

Kawakami T et al.Lancet Respir Med 2023

lung injury after BPA





- Characterised by localised and dense lung opacities on CT SCAN
- Immediatly or few hours after BPA
- Severity highly variable
- With or without hemoptysis

Reference(s)

Balloon pulmonaRy angioplasty versus riociguAt for the treatment of inoperable Chronic thromboembolic pulmonary hypertension **(RACE): a multicentre, Phase 3, open-label RCT and ancillary follow-up study**

Xavier Jaïs, Philippe Brenot, Hélène Bouvaist, Mitja Jevnikar, Matthieu Canuet, Céline Chabanne, Ari Chaouat, Vincent Cottin, Pascal De Groote, Nicolas Favrolt, Delphine Horeau-Langlard, Pascal Magro, Laurent Savale, Grégoire Prévot, Sébastien Renard, Olivier Sitbon, Florence Parent, Romain Trésorier, Cécile Tromeur, Céline Piedvache, Lamiae Grimaldi, Elie Fadel, David Montani, Marc Humbert, Gérald Simonneau**

- Enrollement of treatment-naive patients (18-80 yo), newly diagnosed inoperable CTEPH and PVR >320 dyn.s/cm ^{5}
- Primary EP: change in PVR at week 26 expressed as % of baseline PVR
- At week 26 it was offered to pts who completed the RACE trial, remaining with symptoms with PVR> 4WU to continue into an ancillary 26-week follow-up study
- Patients initialy treated with BPA 1st line could benefit from add-on riociguat or add-on BPA for those initialy treated with riociguat. A complete re-evaluation was performed at 1 year after inclusion the Race trial

Jais X et al.Lancet Respir Med 2023

RACE: Study design

Patients with newly diagnosed CTEPH evaluated in a multidisciplinary meeting

Non-operable and eligible for BPA & Riociguat

RACE Study

Randomization 1:1

Riociguat

BPA

Evaluation at 6 months

extended follow-up

Add-on therapy in patients with persistent symptomatic PH (PVR>4 WU)

BPA

Riociguat

Second evaluation at 6 months (1 year from baseline)

Baseline Characteristics

Characteristic	Riociguat (N = 53)	BPA (N = 52)	All patients (N = 105)
Female sex – n (%)	27 (51)	26 (50)	53 (50.5)
Age, years – mean ± SD	66.8 ± 10.5	68.1 ± 9.4	67.4 ± 9.9
6MWD, meters – mean ± SD	390 ± 124	380 ± 103	385 ± 114
WHO FC – n (%)			
II	10 (19)	12 (23)	22 (21)
III	43 (81)	38 (73)	81 (77)
IV	0 (0)	2 (4)	2 (2)
Mean pulmonary arterial pressure, mmHg	45 ± 10	46 ± 8	46 ± 9
Cardiac output, L/min	4.4 ± 1.2	4.2 ± 0.9	4.3 ± 1.1
PVR, dyn·sec·cm^{-5} – mean ± SD	**679 ± 273**	**767 ± 251**	**722 ± 265**
NT-proBNP, pg/mL	1455 ± 1701 (N=45)	1887 ± 2370 (N=44)	1669 ± 2059 (N=89)

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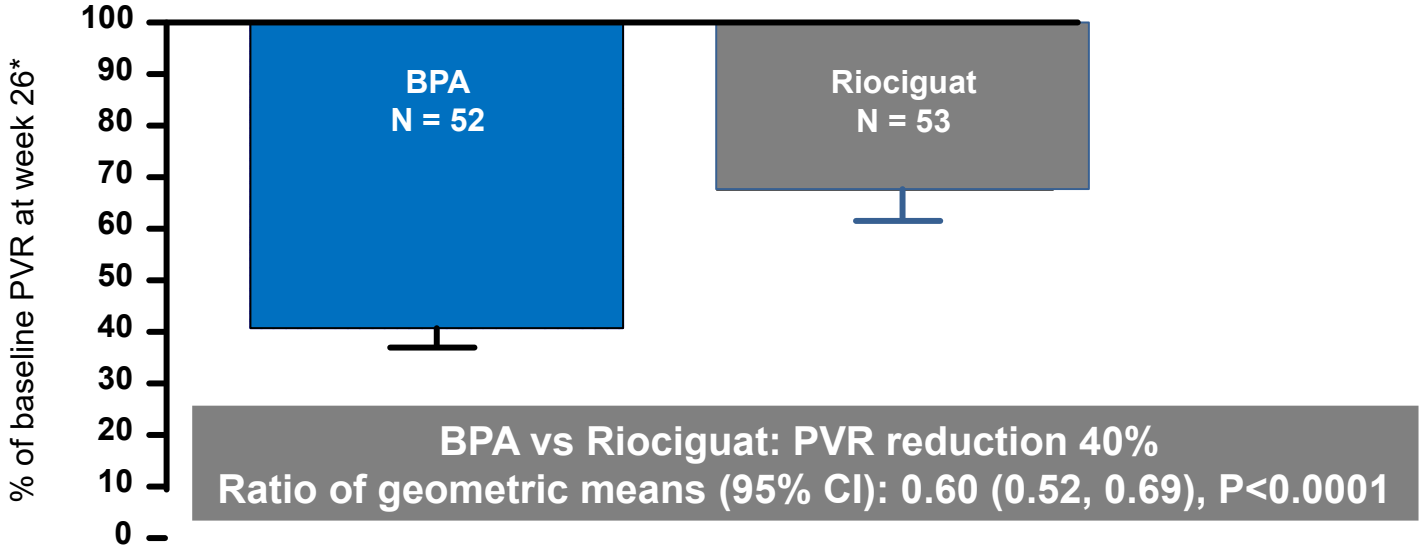
Primary endpoint - Change in PVR at week 26

At week 26 geometric mean PVR decreased to 39.9 % from baseline value in the BPA group

At week 26 geometric mean PVR decreased to 66,7% from baseline value in the Riociguat group



BPA vs Riociguat: PVR reduction 40%
Ratio of geometric means (95% CI): 0.60 (0.52, 0.69), P<0.0001

*Geometric mean plus 95% CI

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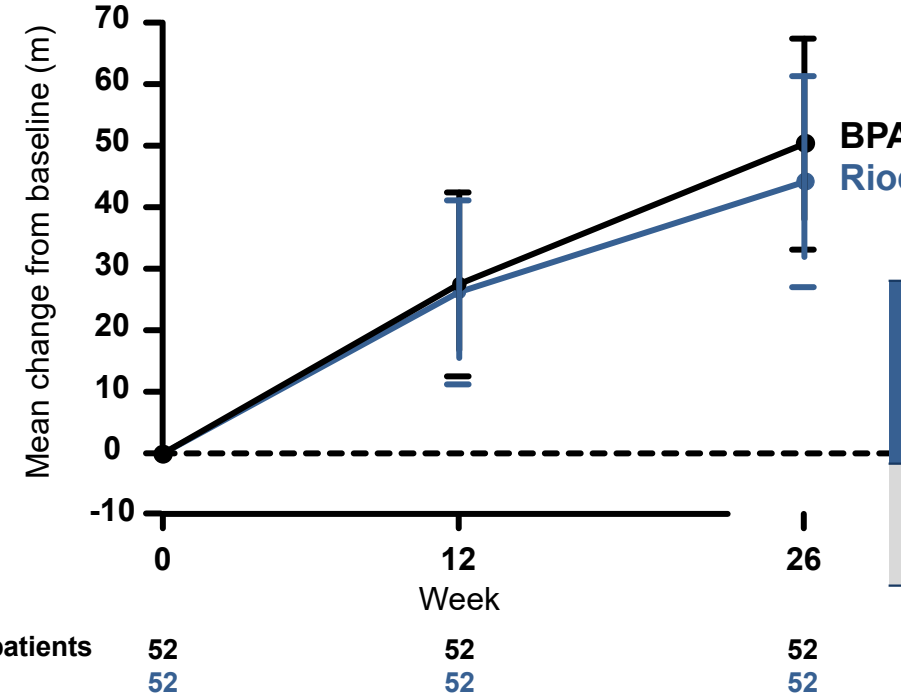
Secondary endpoint - Change in 6MWD at week 26



Treatment effect (95% CI):
6.0 m (-18.1, 30.4), P=0.62

	Riociguat (N = 52)		BPA (N = 52)	
	Baseline	Change	Baseline	Change
6MWD, m Mean (SD)	390 (124)	**44** (27)	380 (103)	**50** (33)

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Secondary endpoints
Change in other haemodynamic parameters at week 26

	Riociguat (N = 53)		BPA (N = 52)		Treatment effect (95% CI)	P value
	Baseline mean ± SD	Change mean ± SD	Baseline mean ± SD	Change mean ± SD		
Cardiac output, L/min	4.4 ± 1.2	1.08 ± 0.97	4.2 ± 0.9	0.72 ± 0.86	**-0.36 (-0.72, 0)**	0.049
PAWP, mmHg	10 ± 3	0.68 ± 3.9	9 ± 3	0.75 ± 3.33	-0.46 (-1.69, 0.76)	0.45
mPAP, mmHg	45 ± 10	-4.23 ± 8.64	46 ± 8	-18.58 ± 9.26	**-13.61 (-16.76, -10.46)**	<0.0001
mRAP, mmHg	8 ± 3	-0.53 ± 4.6	9 ± 4	-3.19 ± 4.12	**-2.2 (-3.54, -0.87)**	0.0014
mSAP, mmHg	101 ± 16	-10.02 ± 14.5	101 ± 16	-2.67 ± 14.63	7.14 (2.92, 11.36)	0.0011

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Safety

	Riociguat N=53	BPA N=52
Patients with ≥1 AE – n (%)	38 (72)	33 (63)
Patients with ≥1 SAE – n (%)	14 (26)	26 (50)
Patients with ≥1 treatment-related SAE – n (%)	5 (9)	22 (42)
Patients with AEs leading to treatment discontinuation – n (%)	0 (0)	0 (0)

* No deaths in the 2 treatment groups

Jais X et al. Lancet Respir Med 2022

Safety: Most frequent adverse events

	Riociguat (N = 53)	BPA (N = 52)
Most frequent AEs (≥3 patients in either group) – n (%)		
Gastroesophageal reflux	10 (19)	0 (0)
Dizziness	9 (17)	1 (2)
Haemoptysis	0 (0)	**8 (15)**
Headache	8 (15)	0 (0)
Vomiting	8 (15)	0 (0)
Cough	7 (13)	0 (0)
Lung injury	0 (0)	**6 (11.5)**
Peripheral edema	6 (11)	4 (8)
Dyspepsia	6 (11)	0 (0)
Nausea	5 (9)	0 (0)
Diarrhea	5 (9)	1 (2)
Chest pain	5 (9)	1 (2)
Palpitations	1 (2)	3 (6)
Epistaxis	3 (6)	2 (4)
Lower respiratory tract infection	2 (4)	3 (6)
Constipation	3 (6)	0 (0)
Urinary tract infection	0 (0)	3 (6)

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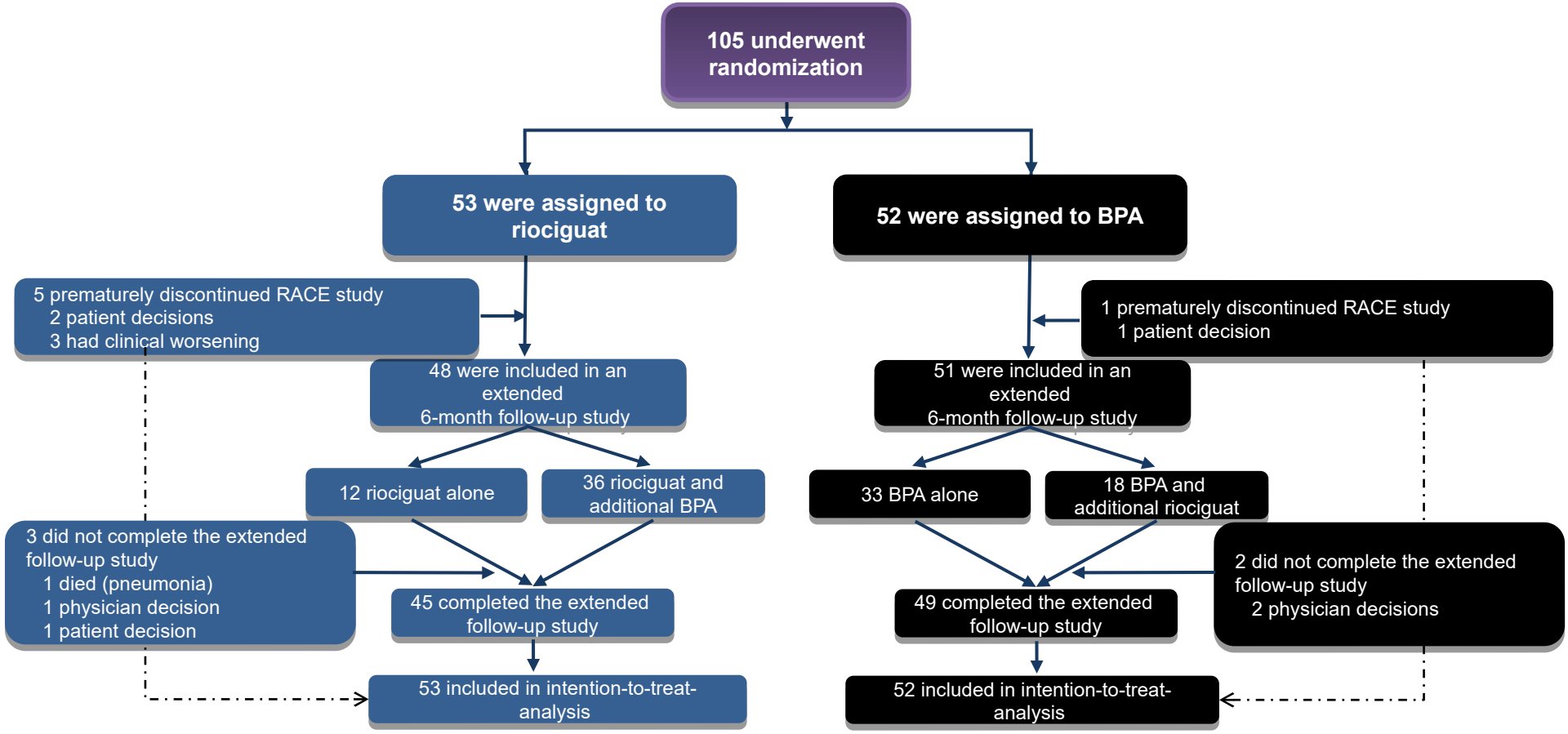
Race Study: Conclusions

- RACE study clearly showed that in inoperable newly diagnosed CTEPH the two treatment strategies (riociguat vs BPA) tested are effective
- BPA led to a significantly higher reduction in PVR compared to riociguat; however the mechanism is different and complementary (BPA lowering mainly mean PAP and Riocguat increasing mainly cardiac output)
- Improvement in 6MWD was not statistically different between the 2 groups
- BPA was associated with more serious adverse events

Ancillary follow-up study profile



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Change in PVR at week 52 according to first-line treatment (ITT analysis)

	Riociguat (N = 53)			BPA (N = 52)			Treatment effect (95% CI)	P value
	Baseline	Post-baseline (W 52)	Change	Baseline	Post-baseline (W 52)	Change		
PVR, WU	8.5 (3.4)	3.51 (1.93)	-4.98 (3.3) 38.6% of baseline* (95% CI 35-42.6)	9.6 (3.1)	3.24 (1.25)	-6.35 (3.1) 35% of baseline* (95% CI 31.7-38.7)	0.91¶ (0.79 to 1.04)	0.18

Data are mean (SD). Post-baseline values were obtained at week 52. *Change was expressed as a percentage of the baseline value (geometric mean [95%CI]). ¶The treatment effect was expressed as the BPA:riociguat ratio of geometric mean (95% CI). PVR: pulmonary vascular resistance; WU: Wood Units.

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Safety of BPA according to a pre-treatment with riociguat or not (serious adverse events)

	First-line Riociguat then BPA 2nd line (N = 36)	First-line BPA (N = 52)	P value
Patients with ≥1 SAE related to BPA- n(%)	5 (14)	22 (42)	0.0045
Patients with ≥1 severe BPA procedure-related complication– n(%)	3 (8)	18 (35)	0.0045

Characteristics of the 2 groups prior to BPA

Characteristic	Second-line BPA after 6 months riociguat (N=36)	First-line BPA (N = 52)	P value
Female sex – n (%)	22 (61)	25 (48)	0.23
Age, years – mean ± SD	67.4 ± 8.8	68.1 ± 9.4	0.54
6MWD, meters – mean ± SD	**427 ± 111**	**380 ± 103**	**0.0487**
WHO FC – n (%) II III IV	 **21(58)** **15 (42)** **0 (0)**	 **12 (23)** **38 (73)** **2 (4)**	**0.0017**
Right atrial pressure, mmHg	7.6 ± 3.4	8.7 ± 3.9	0.1773
Mean pulmonary arterial pressure, mmHg	43.3 ± 9.5	46.5 ± 8.4	0.102
Cardiac output, L/min	**5.2 ± 1.2**	**4.2 ± 0.9**	**< 0.0001**
PVR, Wood Units – mean ± SD	**6.7 ± 2.5**	**9.6 ± 3.1**	**< 0.0001**
NT-proBNP, pg/mL	1200.8 ± 1653	1886.7 ± 2370 *	0.095

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Comparison of hemodynamic variables between patients with or without lung injury

Variables Per session	*Lung injury* + (n=53)	*Lung injury* - (n=87)	*p*
mPAP *(mmHg)*	**42 (38-50)**	**33 (28-41)**	**<0.0001**
PVR *(WU)*	9,2 (7-14,6)	6,1 (3,9-8,7)	<0.0001
CI *(L/min/m²)*	2,5 (1,9-2,7)	2,6 (2,4-3,3)	0,006

Inami T *et al. JACC Cardiovasc Interv* 2013.

Variables Per patient	*Lung injury* + (n=58)	*Lung injury* - (n=18)	*p*
mPAP *(mmHg)*	**44.2±11.9**	**36.2±10.5**	**0.013**
PVR *(WU)*	11.3 (7.5-14.6)	8 (4.8-11.7)	0.043
CI *(L/min/m²)*	2.1±0.6	2.3±0.7	0.31

Ejiri K *et al. Circ Cardiovasc Interv* 2018.

6 months follow up study after Race trial:Summary

- The 6 months extended follow-up study after the randomized RACE trial suggest that in non-operable CTEPH, the hemodynamic effects of the sequential association BPA and Riociguat is very effective (around 65% fall of PVR) regardless the order of administration
- The rate of SAE related to BPA is much lower when BPA is preceded by a 6 months treatment with Riociguat
- At the time of BPA initiation, patients pre-treated with Riociguat present a less severe hemodynamic profile than patients treated with first line BPA

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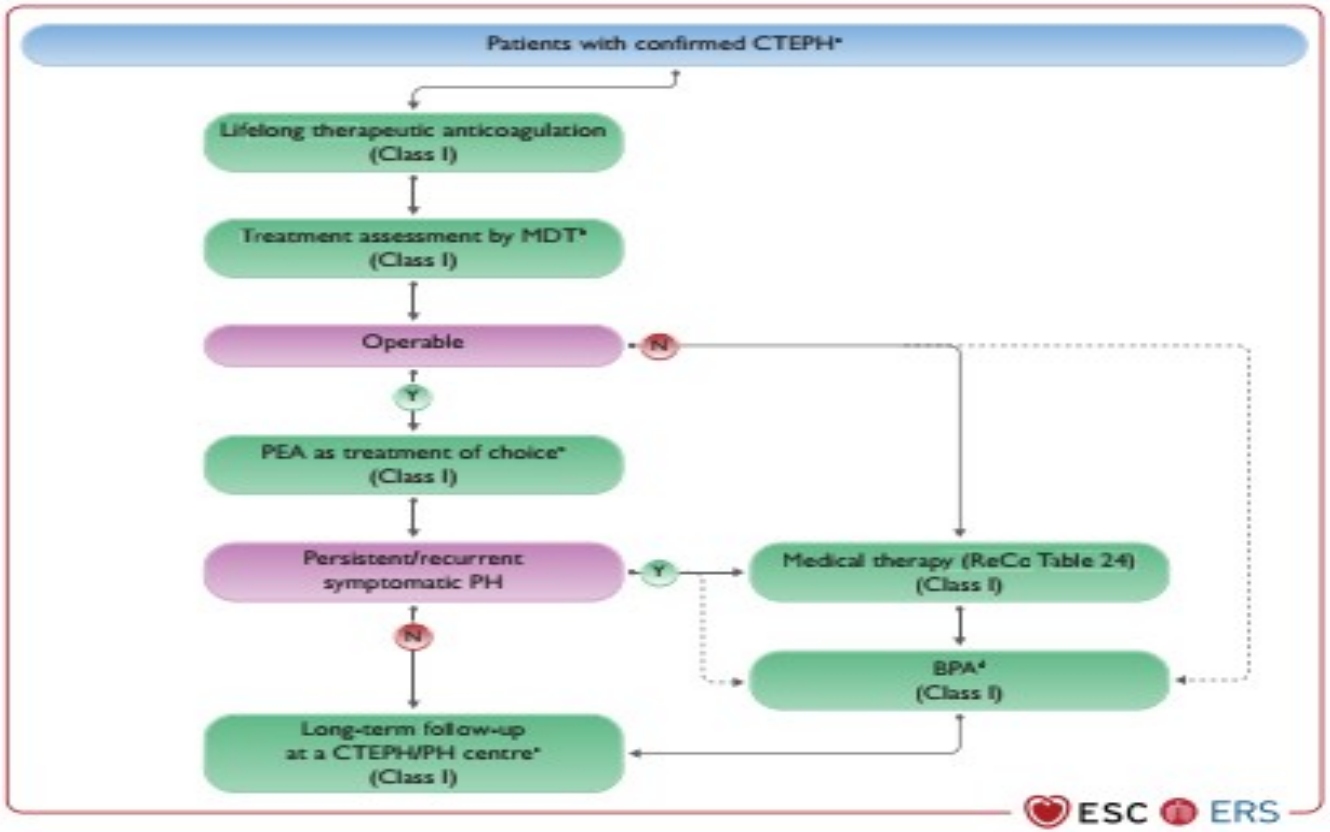
Mamagement of inoperable CTEPH: Summary

- In inoperable CTEPH, PH is due to the combination of fibrotic obstruction of distal PA downstream of subsegmental arteries, non accessible to surgery but accessible to BPA and of a microvasculopathy of muscular PA< 0.5mm diameter (similar to that observed in PAH) and targeted with Riociguat
- Today these two treatments have to be combined in non-operable to increase efficacy on pulmonary hemodynamic but also to improve safety of BPA and rather than opposing both therapies, it is likely that this multimodality approach will become the preferred strategy for most patients with non-operable CTEPH
- Recent observations[1,2] suggest that prognosis of inoperable CTEPH has recently improved significantly with this strategy, the 3-years survival rate improving from 70% to 90%

1.Taniguchi Y, Jais X et al. Predictors of survival in patients with not-operated CTEPH. J Heart Lung Transplant 2019. 2. Widenroth CD et al. Riociguat and Balloon Pulmonary Angioplasty improve prognosis of patients with inoperable CTEPH. J Heart Lung Transplant 2023

Management Strategy of CTEPH



M Humbert et al.ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.Eur Respir J 2022