3ο ΠΑΝΕΛΛΗΝΙΟ ΣΥΝΕΔΡΙΟ ΠΝΕΥΜΟΝΙΚΗΣ ΥΠΕΡΤΑΣΗΣ

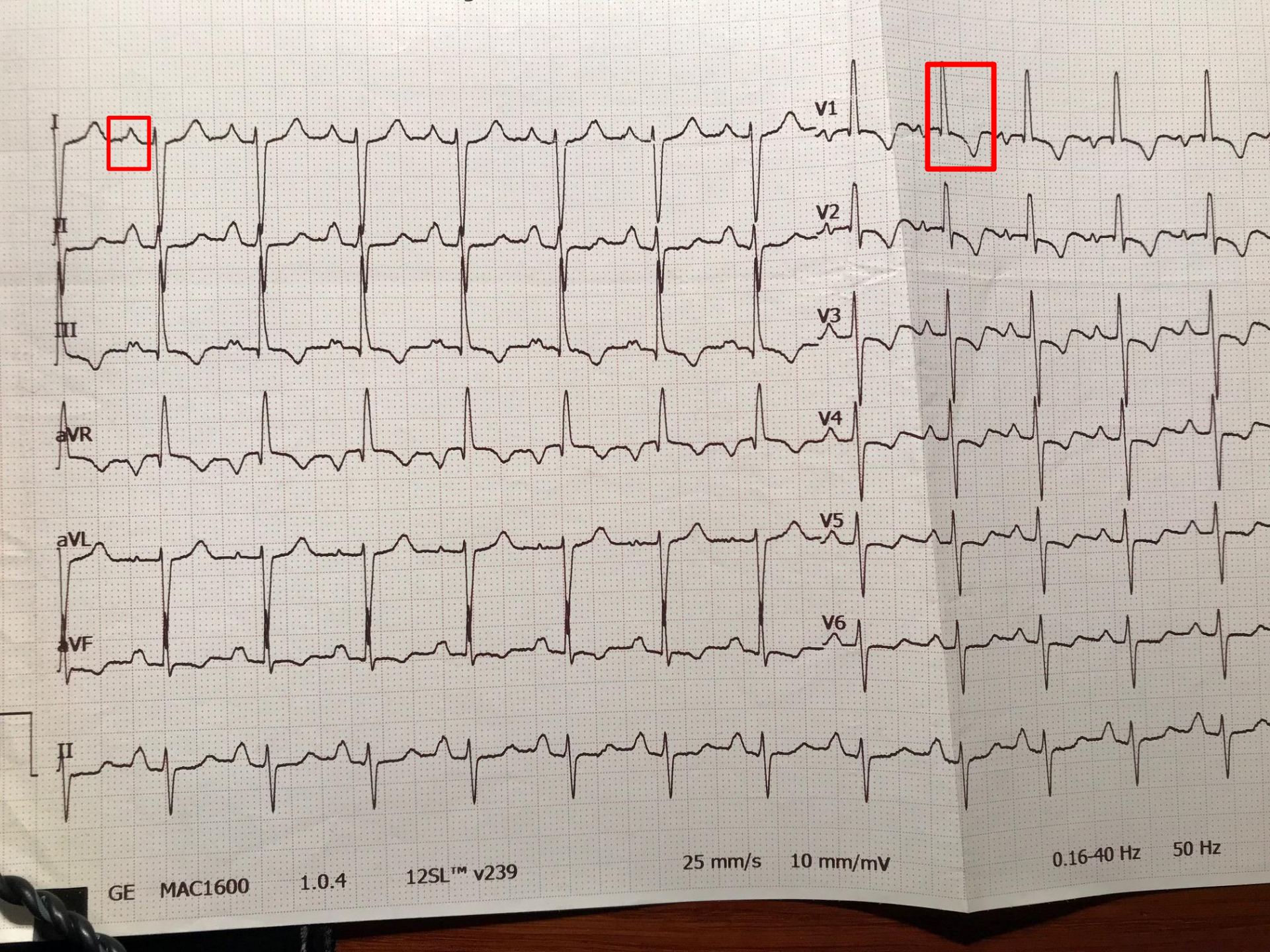
Πνευμονική Υπέρταση και κληρονομικότητα

Φραντζέσκα Φραντζεσκάκη
Πνευμονολόγος – Εντατικολόγος
Διευθύντρια ΕΣΥ
Β' Παν/κή ΜΕΘ «ΑΤΤΙΚΟΝ»

Case Report

- Female, 25 yo (2012), non-smoker
- Familiar history of pulmonary arterial hypertension

  (father dead on triple combination therapy including iv epoprostenol)
- Dizziness after exhaustive physical activity (WHO-FC II)
- Random control during gastroenteritis
- ECG: p pulmonale, RBBB

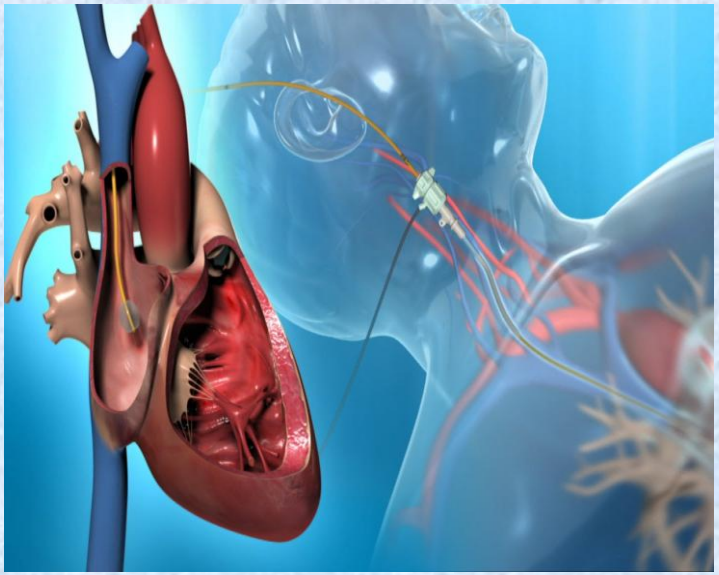

I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
II
GE MAC1600 1.0.4 12SL™ v239
25 mm/s 10 mm/mV
0.16-40 Hz 50 Hz

Echocardiography (2012)

- RA: normal dimension
- RV dilatation (39 mm), severe functional impairment (TAPSE: 15mm, TDI: S=8.5, Ea=5)
- Main pulmonary artery dilatation (30 mm)
- Tricuspid valve regurgitation – VmaxTR: 4.4 m/sec (PASP: 97 mmHg)

RHC: 2012

- RAP: 15 mmHg
- PAP:106/45/67 mmHg (S/D/M)
- Pwedge: 13 mmHg
- CO:2.9 L/min, CI:1.3 L/min/m^2
- PVR: 18.6 Wood Units
- SvO_2: 63%
- SaO_2: 100%
- Acute vasoreactivity test: negative



Laboratory tests

- **6MWD**: 502 m (SaO_2 :96%-98% / FiO_2 0.21)
- **Perfusion lung scanning** : negative for PE
- **Serological testing** for CTD and **thrombophilia** screening: Negative
- **HIV**: Negative
- **Lung function tests**: mild restrictive syndrome, DLCO: 57% pr
- **Cardiopulmonary excercise testing**: VO_2 max: 13.2 ml/kg/min (58% predicted), VE/VCO_2 max: 39 (<34)
- **NT-proBNP**: 2500 ng/L

More laboratory test

- TOE: negative for shunts or defects
- CBC: Hct 55%, WBC: 10750/μL, PLTs:184000/μL
- JAK2VGHF: negative
- Tests for polycythemia vera: negative
- Portal vein Tripplex: negative for portal hypertension
- CTPA-HRCT: No perfusion defects, not important findings from pulmonary parenchyma

TABLE 2 Updated clinical classification of pulmonary hypertension (PH)

1 PAH
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 3)
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers (table 4)
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
- 1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease
- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia
- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

4 PH due to pulmonary artery obstructions (table 6)
- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

5 PH with unclear and/or multifactorial mechanisms (table 7)
- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

Simonneau G et al. *Eur Resp J* 2018

Risk assessment in pulmonary arterial hypertension

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 >15 ml/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%

2015 ESC/ERS Guidelines for the diagnosis and treatment of PH

- Monotherapy with bosentan 125mg x 2 and diuretics
- Reevaluation after 3 mo of treatment:

Echocardiography

VmaxTR:4.5 m/sec (PASP: 80 mmHg)

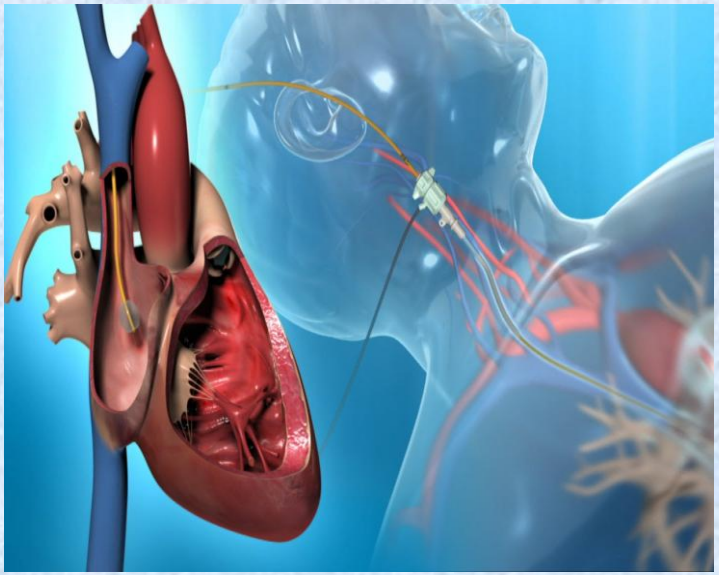
WHO-FC II

6MWD: 542 m

NT-proBNP: 1100 ng/L

RHC: three months later

- RAP: 5 mmHg
- PAP:93/33/55 mmHg (S/D/M)
- Pwedge: 6 mmHg
- CO:4.6 L/min, CI:2.1 L/min/m^2
- PVR: 10.7 Wood Units
- SvO_2: 75.8%
- SaO_2: 100%



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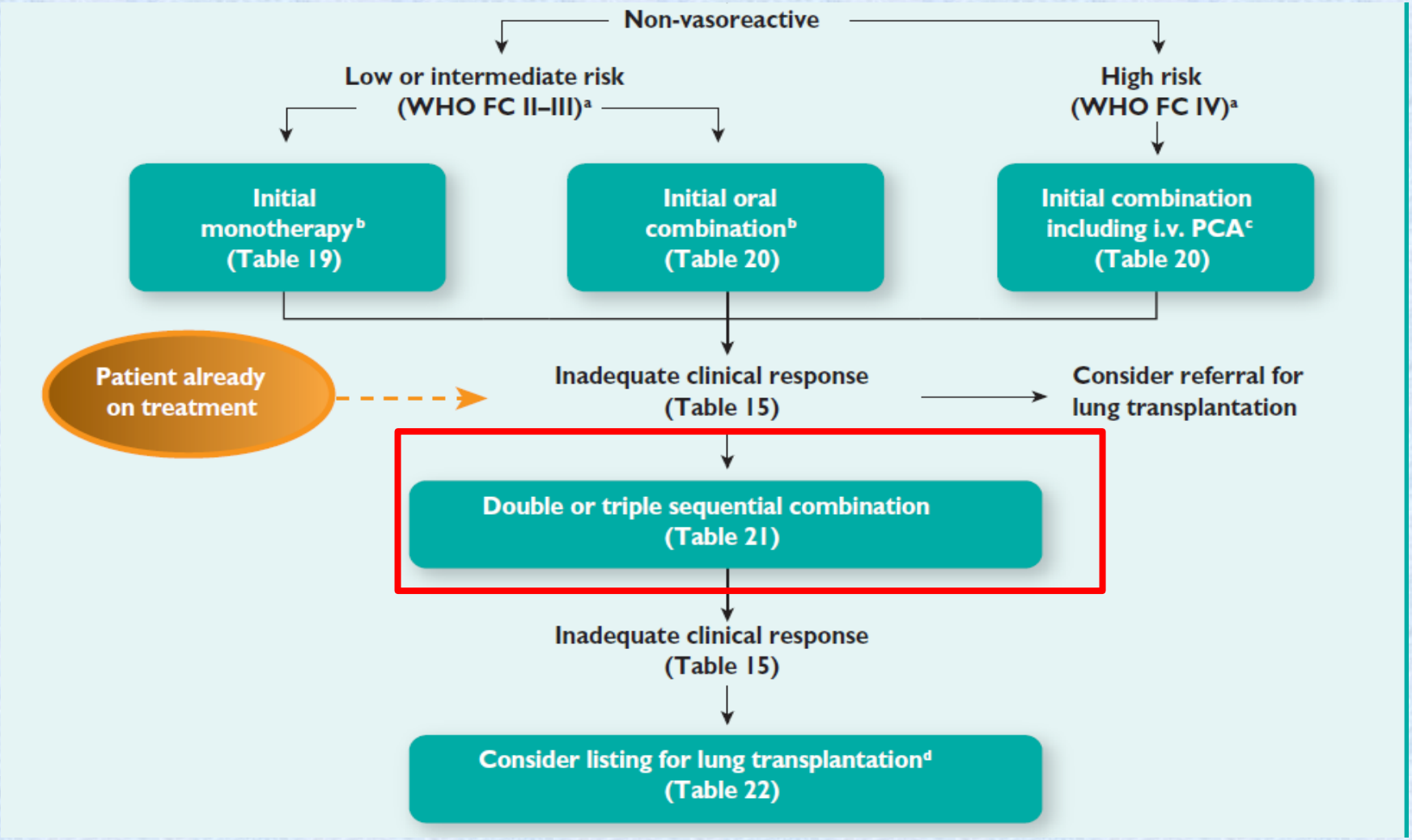
2015 ESC/ERS Guidelines for the diagnosis and treatment of PH

European Heart Journal (2016) 37, 67–119
doi:10.1093/eurheartj/ehv317

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension



	8/2012
NYHA	II
mPAP	67
RAP	15
CI	1.4
PVR	18
6MWT	502
NT-proBNP	2500
Intervention	Add bosentan

	8/2012	11/2012
NYHA	II	II
mPAP	67	50
RAP	15	5
CI	1.4	2.1
PVR	18	10
6MWT	502	542
NT-proBNP	2500	1100
Intervention	Add bosentan	Add sildenafil

	8/2012	11/2012	9/2013
NYHA	II	II	II
mPAP	67	50	50
RAP	15	5	5
CI	1.4	2.1	2.6
PVR	18	10	8.5
6MWT	502	542	570
NT-proBNP	2500	1100	623
Intervention	Add bosentan	Add sildenafil	

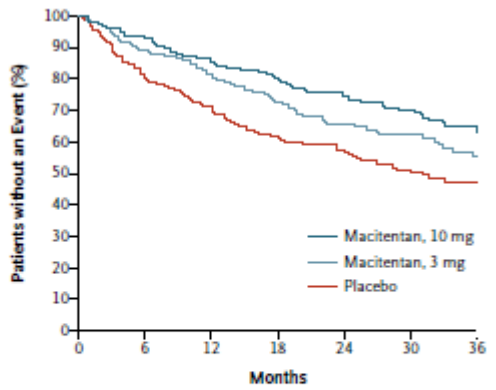
	8/2012	11/2012	9/2013	9/2015
NYHA	II	II	II	II
mPAP	67	50	50	54
RAP	15	5	5	4
CI	1.4	2.1	2.6	2.8
PVR	18	10	8.5	8
6MWT	502	542	570	548
NT-proBNP	2500	1100	623	950
Intervention	Add bosentan	Add sildenafil		Switch to macitentan

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

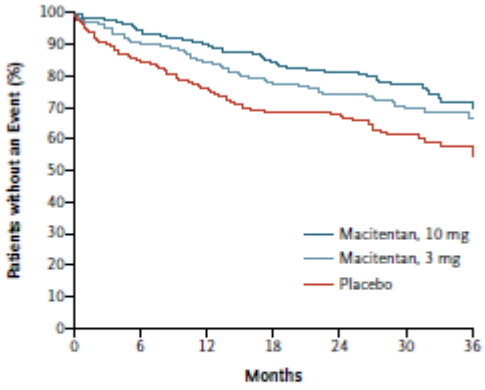
Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension

Tomás Pulido, M.D., Igor Adzerikho, M.D., Richard N. Channick, M.D.,



No. at Risk							
Placebo	250	188	160	135	122	64	23
Macitentan, 3 mg	250	213	188	166	147	80	32
Macitentan, 10 mg	242	208	187	171	155	91	41

Figure 1. Effect of Macitentan on the Composite Primary End Point of a First Event Related to Pulmonary Arterial Hypertension or Death from Any Cause.



No. at Risk							
Placebo	250	188	155	132	119	62	22
Macitentan, 3 mg	250	208	181	159	144	77	31
Macitentan, 10 mg	242	203	183	166	152	86	39

Figure 2. Effect of Macitentan on the Composite Secondary End Point of Death Due to Pulmonary Arterial Hypertension or Hospitalization for Pulmonary Arterial Hypertension as a First Event.

	8/2012	11/2012	9/2013	9/2015	1/2017
NYHA	II	II	II	II	II
mPAP	67	50	50	54	51
RAP	15	5	5	4	5
CI	1.4	2.1	2.6	2.8	2.8
PVR	18	10	8.5	8	7
6MWT	502	542	570	548	564
NT-proBNP	2500	1100	623	950	398
Intervention	Add bosentan	Add sildenafil		Switch to macitentan	Switch to riociguat

RESPITE: switching to riociguat in pulmonary arterial hypertension patients with inadequate response to phosphodiesterase-5 inhibitors

Marius M. Hoeper[1], Gérald Simonneau[2], Paul A. Corris[3], Hossein-Ardeschir Ghofrani[4,5], James R. Klinger[6], David Langleben[7], Robert Naeije[8],

Eur Respir J 2017; 50: 1602425

ABSTRACT A proportion of pulmonary arterial hypertension (PAH) patients do not reach treatment goals with phosphodiesterase-5 inhibitors (PDE5i). RESPITE investigated the safety, feasibility and benefit of switching from PDE5i to riociguat in these patients.

RESPITE was a 24-week, open-label, multicentre, uncontrolled study. Patients in World Health Organization (WHO) functional class (FC) III, with 6-min walking distance (6MWD) 165–440 m, cardiac index <3.0 $L \cdot min^{-1} \cdot m^{-2}$ and pulmonary vascular resistance >400 $dyn \cdot s \cdot cm^{-5}$ underwent a 1–3 day PDE5i treatment-free period before receiving riociguat adjusted up to 2.5 mg maximum *t.i.d.* Exploratory end-points included change in 6MWD, WHO FC, *N*-terminal prohormone of brain natriuretic peptide (NT-proBNP) and safety.

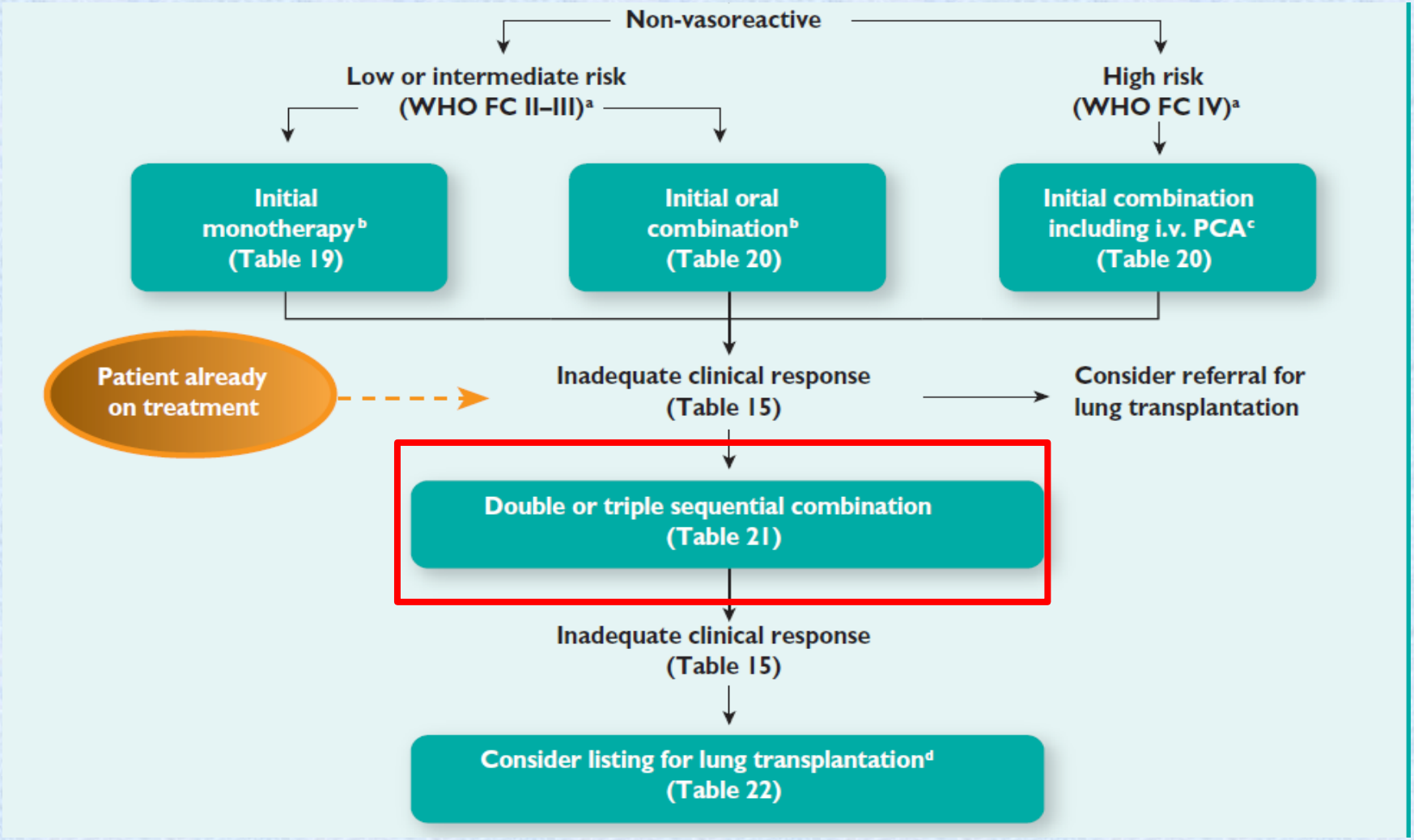
Of 61 patients enrolled, 51 (84%) completed RESPITE. 50 (82%) were receiving concomitant endothelin receptor antagonists. At week 24, mean±SD 6MWD had increased by 31±63 m, NT-proBNP decreased by 347±1235 $pg \cdot mL^{-1}$ and WHO FC improved in 28 patients (54%). 32 patients (52%) experienced study drug-related adverse events and 10 (16%) experienced serious adverse events (2 (3%) study drug-related, none during the PDE5i treatment-free period). Six patients (10%) experienced clinical worsening, including death in two (not study drug-related).

In conclusion, selected patients with PAH may benefit from switching from PDE5i to riociguat, but this strategy needs to be further studied.

	8/2012	11/2012	9/2013	9/2015	1/2017	5/2017
NYHA	II	II	II	II	II	II
mPAP	67	50	50	54	51	52
RAP	15	5	5	4	5	7
CI	1.4	2.1	2.6	2.8	2.8	3.0
PVR	18	10	8.5	8	7	5.7
6MWT	502	542	570	548	564	589
NT-proBNP	2500	1100	623	950	398	400
Intervention	Add bosentan	Add sildenafil		Switch to macitentan	Switch to riociguat	Add selexipag

European Heart Journal (2016) 37, 67–119
doi:10.1093/eurheartj/ehv317

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension



Two years later (2019)

Echocardiography

VmaxTR:4.5 m/sec (PASP: 85 mmHg) / 3.2 m/sec (2017)

WHO-FC III

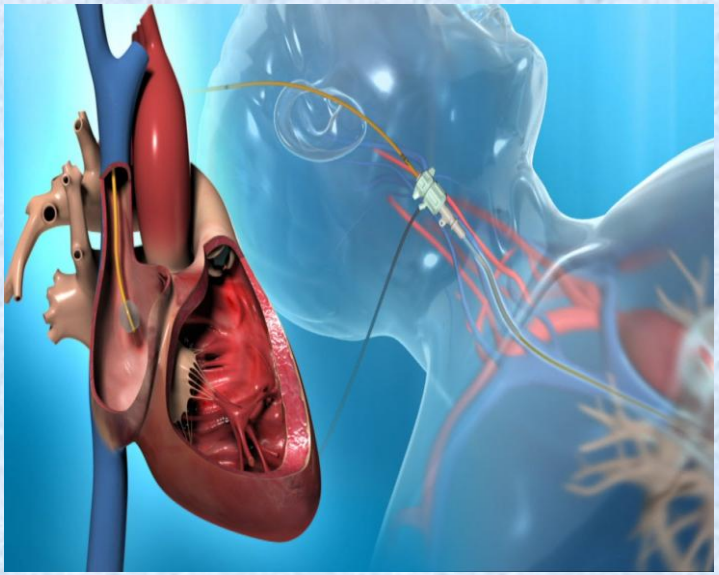
6MWD: 530 m (589 m)

NT-proBNP: 437 (400) ng/L

Macitentan 10mg
Riociguat 2,5 mgx3
Selexipag 1600mcg x2

RHC 2019

- RAP: 11 mmHg
- PAP:123/50/74 mmHg (2017: mPAP 52)
- Pwedge: 12 mmHg
- CO:6 L/min, CI:2.9 (3.4) L/min/m^2
- PVR: 10.3 (5.7)Wood Units
- SvO_2: 70%
- SaO_2: 94%



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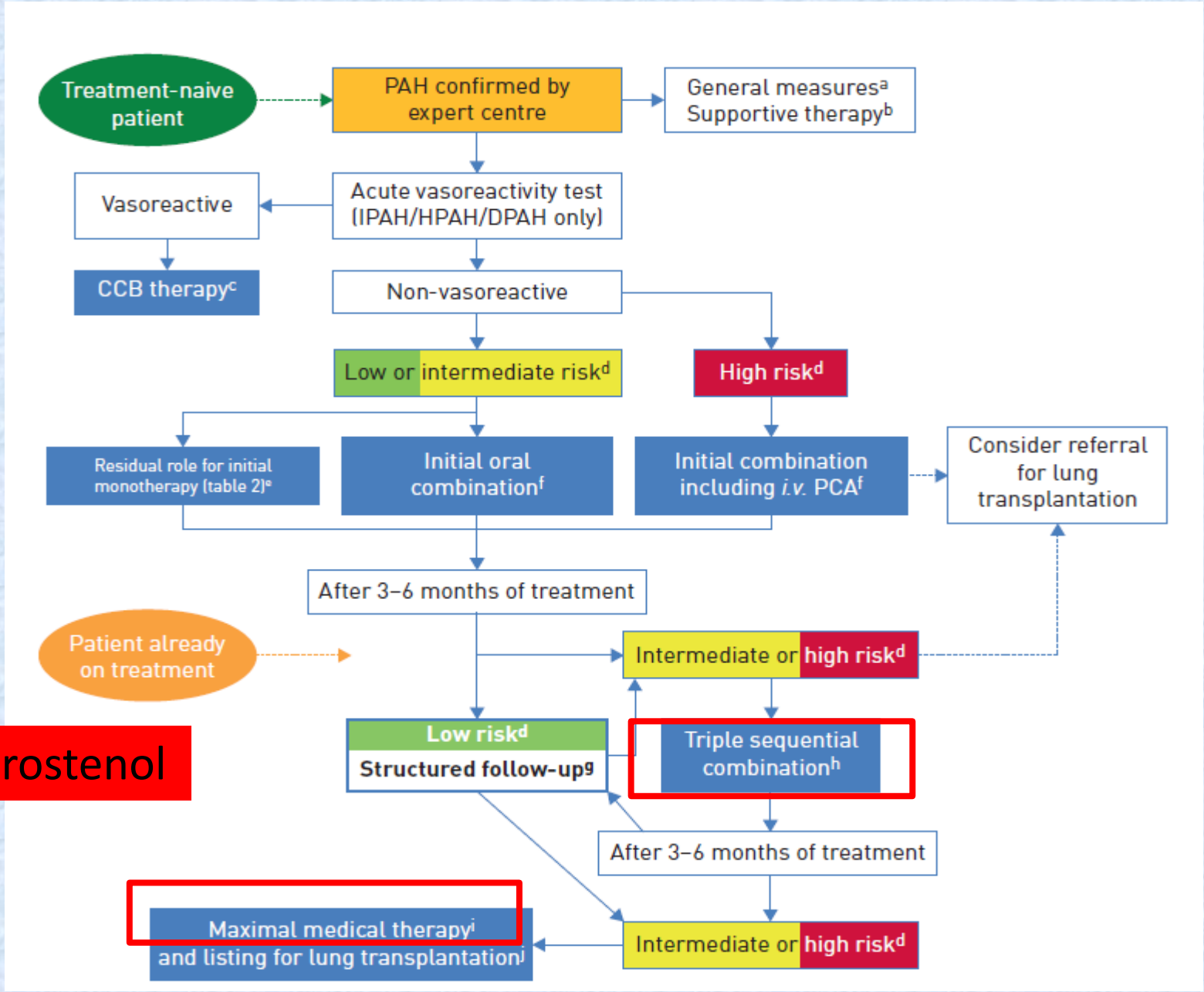
2015 ESC/ERS Guidelines for the diagnosis and treatment of PH



iv epoprostenol

Galie N et al. *Europ Resp J* 2019;53

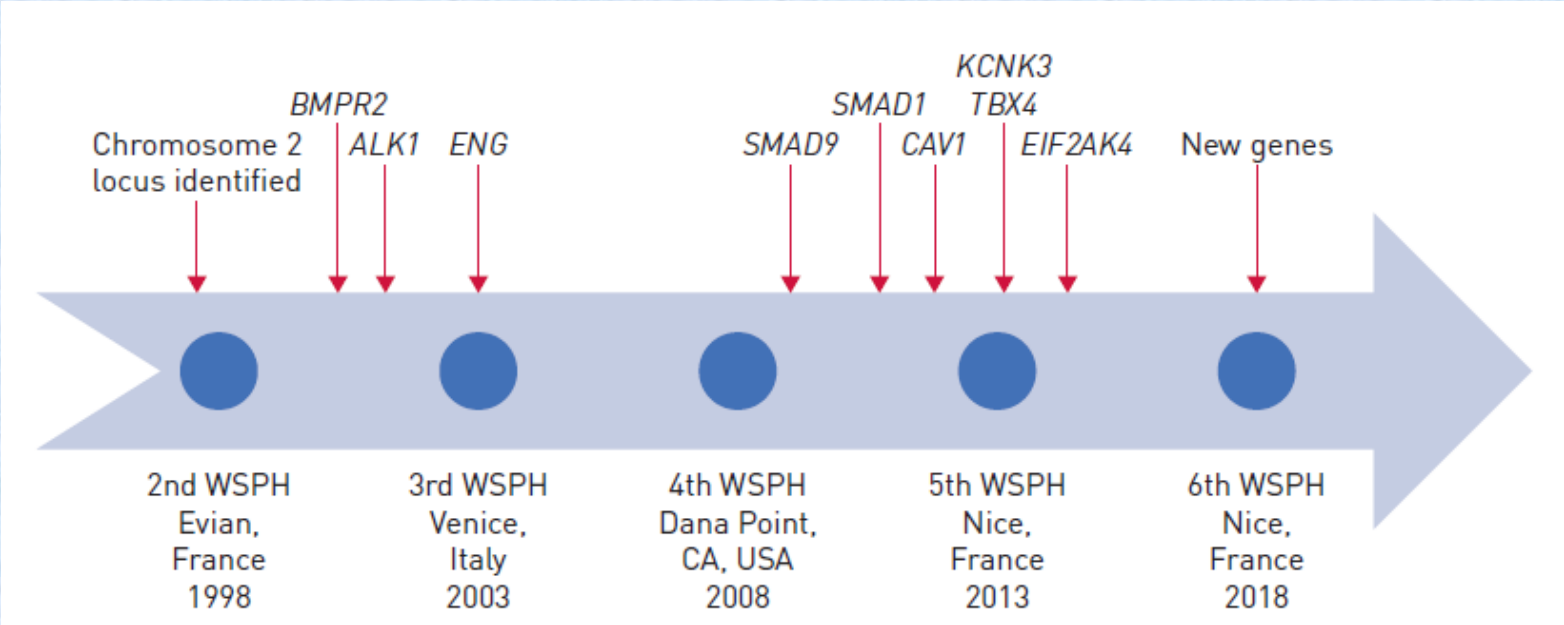
Genetics and genomics of pulmonary arterial hypertension

Nicholas W. Morrell[1], Micheala A. Aldred[2], Wendy K. Chung[3], C. Gregory Elliott[4], William C. Nichols[5], Florent Soubrier[6], Richard C. Trembath[7] and James E. Loyd[8]

Number 2 in the series
"Proceedings of the 6th World Symposium on Pulmonary Hypertension"
Edited by N. Galiè, V.V. McLaughlin, L.J. Rubin and G. Simonneau

IPAH, HPAH,
anorexigen associated,
PVOD/PCH
Children with IPAH
CHD

Eur Respir J 2019; 53: 1801899

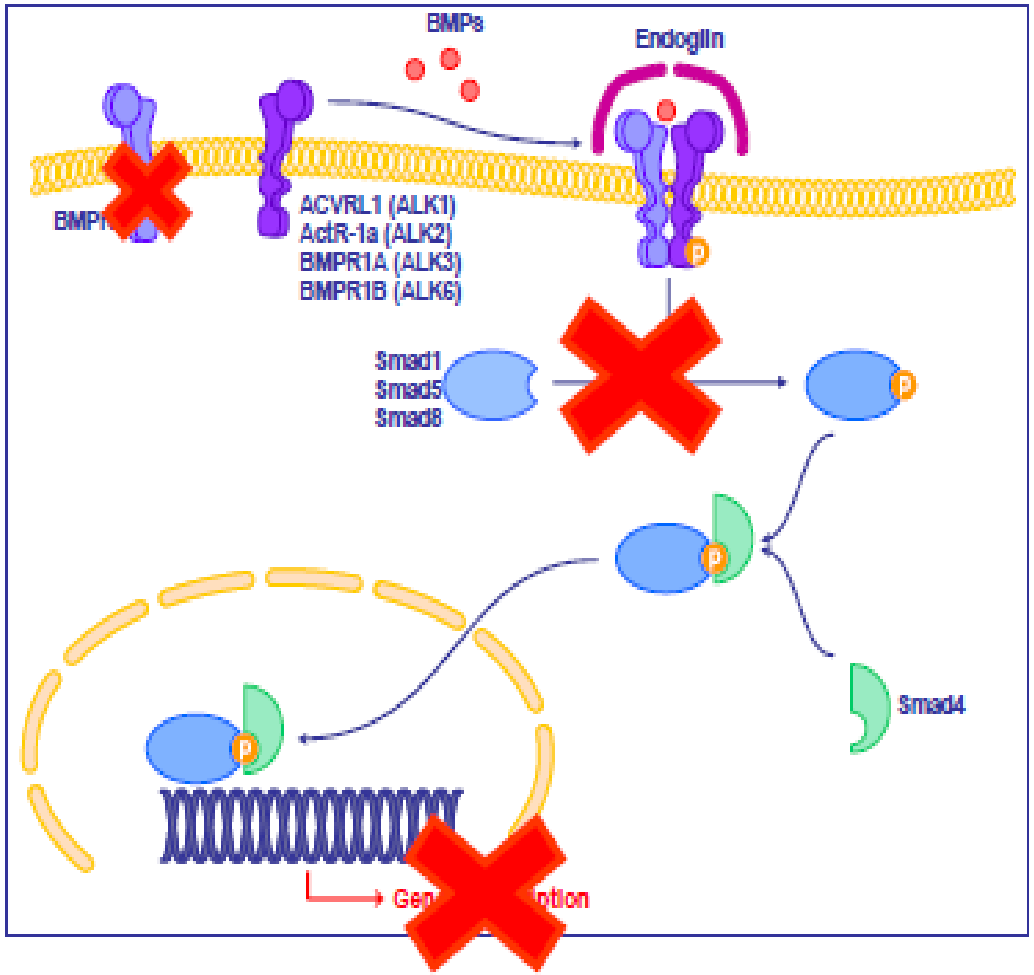


N.Morrell et al. *Eur Resp J* 2019;53

Genetics of PAH

- Family history PAH: 6-10% pts
- *BMPR2* : Bone morphogenetic protein receptor type 2
- 70-80% families with PAH: *BMPR2* mutations
- 10-20% IPAH: *BMPR2* mutations
- Autosomal dominantly inherited-reduced penentrance
- Males 14%, females 42%
- Genetic, epigenetic, environmental factors, female sex
- Inflammatory mediators: TNF-α suppresses *BMPR2* mRNA

Evans JD et al. *Lancet Respir Med* 2016;4:129-137
Cogan J et al. *Circulation* 2012;126: 1907-1916



SMC proliferation
&
EC apoptosis

BMPR2

- Expressed on PVE
- BMP9 protects EC from apoptosis, excessive proliferation and inhibits vascular permeability
- Loss of *BMPR2:* Endothelial dysfunction

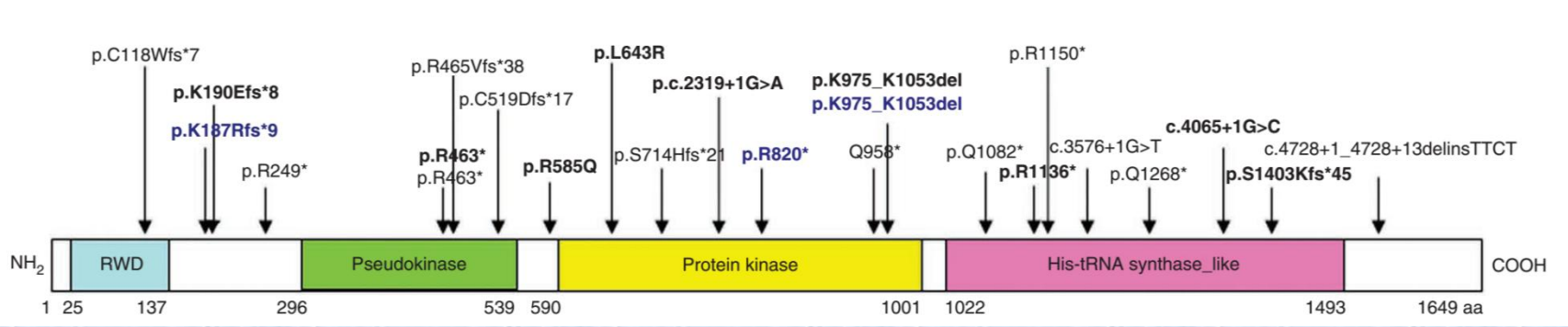
Yang X et al. *Circ Res* 2005;96

Heritable PVOD

EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension

Mélanie Eyries[1–3], David Montani[4–6], Barbara Girerd[4–6], Claire Perret[3,7], Anne Leroy[2], Christine Lonjou[8], Nadjim Chelghoum[8], Florence Coulet[2,3], Damien Bonnet[9,10], Peter Dorfmüller[6,11], Elie Fadel[6,12], Olivier Sitbon[4–6], Gérald Simonneau[4–6], David-Alexandre Tregouët[3,7], Marc Humbert[4–6] & Florent Soubrier[1–3]

nature genetics



Eyries et al. *Nat Genet* 2014

Heritable PVOD

- Eukaryotic translation initiation factor 2 alpha kinase 4
- Activator of cellular stress response pathway
- Autosomal recessive transmission
- 100% of familial cases of PVOD
- 20-25% of sporadic cases
- Penetrance 100%
- Biallelic *EIF2AK4* in PH pt: PVOD

Hadinnapola C et al. *Circulation* 2017; 136:2022-2033

Identification of rare sequence variation underlying heritable pulmonary arterial hypertension

Stefan Gräf et al.#

NATURE COMMUNICATIONS | (2018)9:1416

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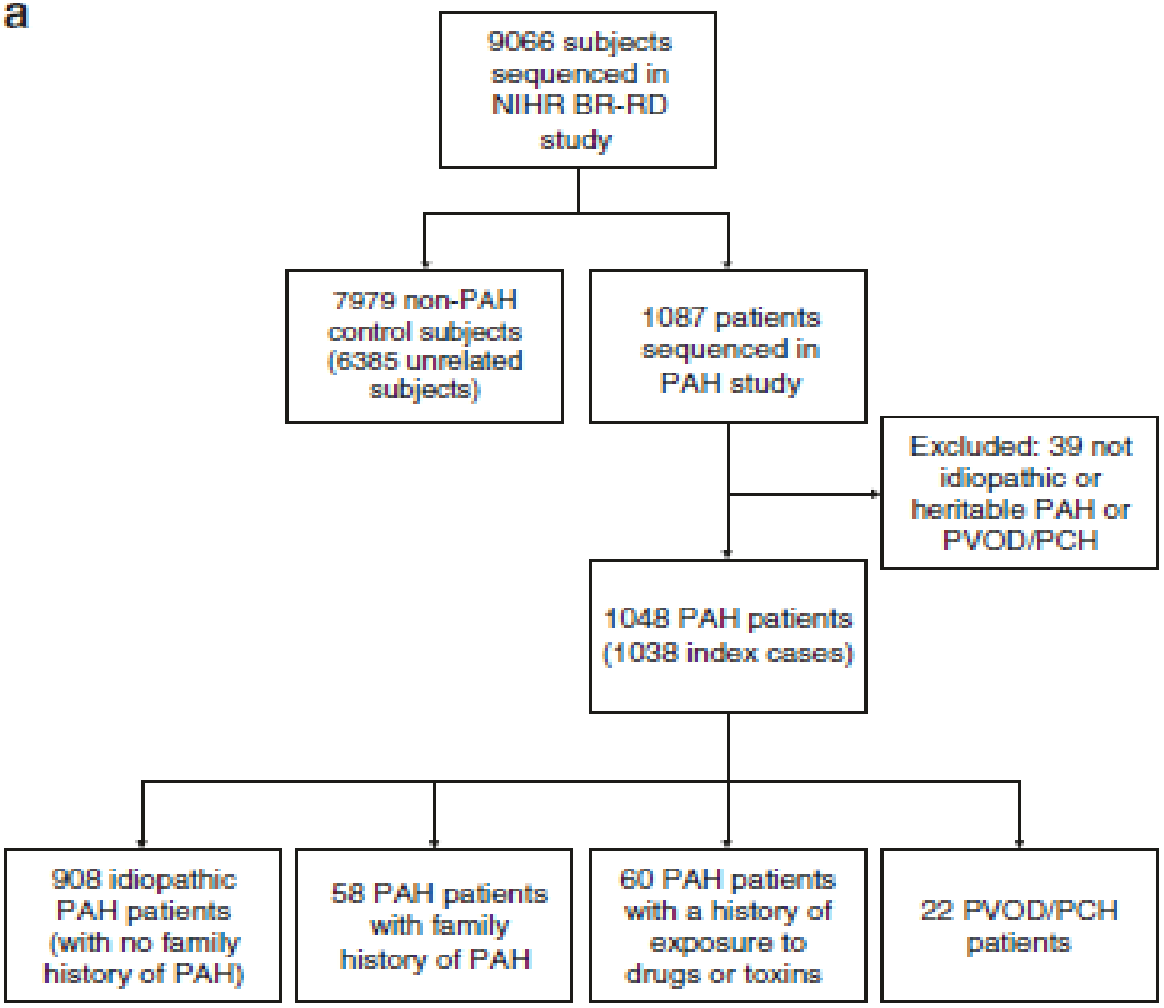
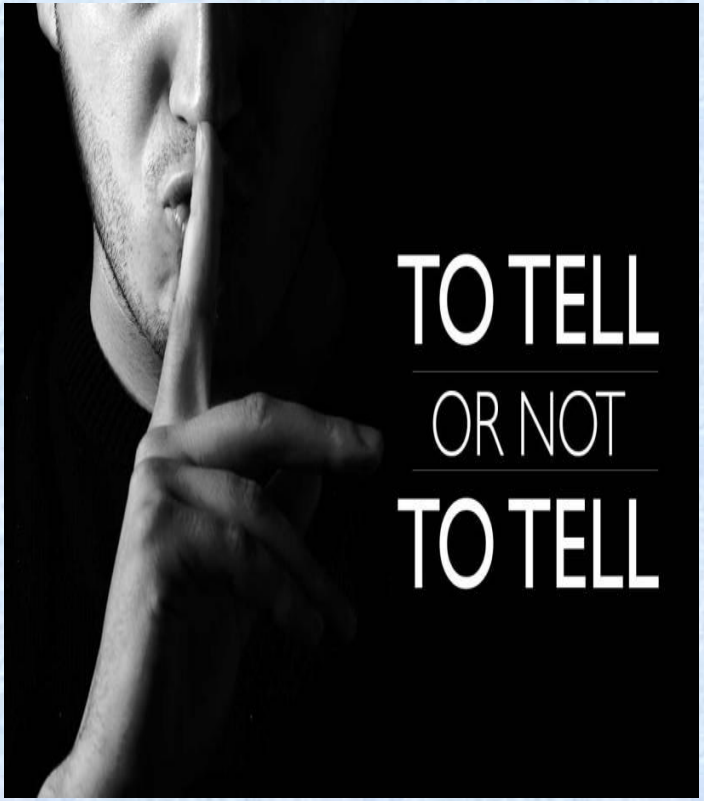


- *BMPR2* 15.3%
- *TBX4* 1,3%
- *ACVRL1* 0.9%
- *ENG* 0.6%
- *SMAD* 0.4%
- *KCNK3* 0.4%

- *P-type ATPase*
- *GDF2*
- *SOX17*
- *Aquaporin 1*

Utility of genetic diagnosis in PAH

- Prognostic reasons
- Genetic counseling
- Therapeutic implications



Link between genotype and phenotype in PAH

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

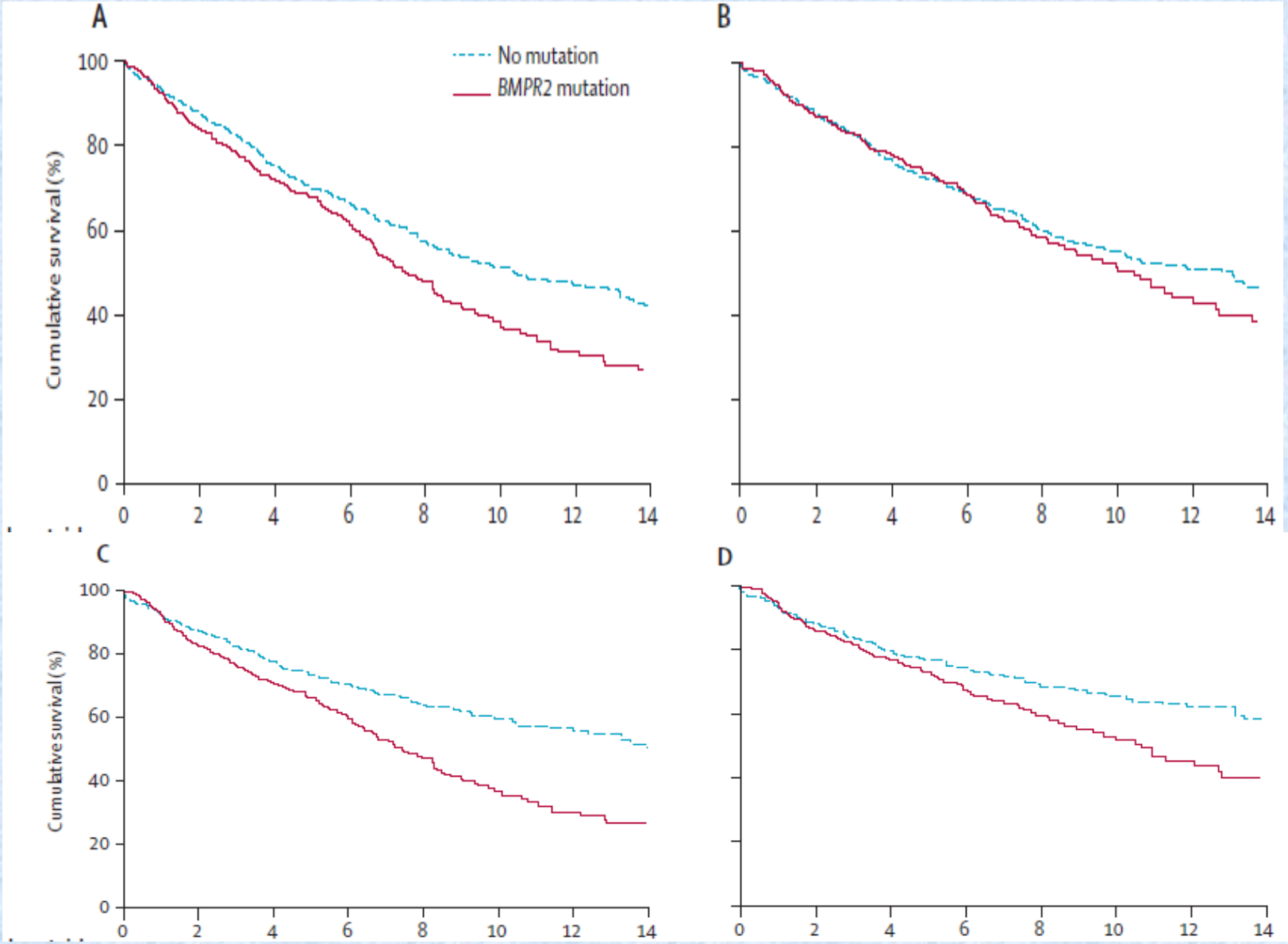
Jonathan D W Evans, Barbara Girerd, David Montani, Xiao-Jian Wang, Nazzareno Galiè, Eric D Austin, Greg Elliott, Koichiro Asano, Ekkehard Grünig, Yi Yan, Zhi-Cheng Jing, Alessandra Manes, Massimiliano Palazzini, Lisa A Wheeler, Ikue Nakayama, Toru Satoh, Christina Eichstaedt, Katrin Hinderhofer, Matthias Wolf, Erika B Rosenzweig, Wendy K Chung, Florent Soubrier, Gérald Simonneau, Olivier Sitbon, Stefan Gräf, Stephen Kaptoge, Emanuele Di Angelantonio, Marc Humbert*, Nicholas W Morrell**

Lancet Respir Med 2016; 4: 129–37

- 1550 pts with IPAH, heritable PAH and anorexigen associated
- 8 cohorts tested for *BMPR2* mutations
- Primary outcome: Death or LTX

	All patients	*BMPR2* mutation status		
		Non-carriers (N=1102)	Carriers (N=448)	p value
Age at diagnosis (N=1447), years	40·1 (17·2)	42·0 (17·8)	35·4 (14·8)	<0·0001
Male sex	440/1545 (28%)	302/1097 (28%)	138/448 (31%)	0·20
Family history of PAH	202/1376 (15%)	..	202/402 (50%)	..
Body-mass index (N=1206), kg/m²	24·9 (9·1)	24·9 (10·6)	24·9 (5·9)	0·99
6-min walk distance (N=1072), m	378 (124)	374 (128)	388 (113)	0·088
NYHA functional class				0·38
I–II	423/1426 (30%)	313/1031 (30%)	110/394 (28%)	
III	896/1426 (63%)	647/1031 (63%)	249/394 (63%)	
IV	107/1426 (8%)	72/1031 (7%)	35/394 (9%)	
Mean pulmonary artery pressure (N=1503), mm Hg	57·6 (15·0)	56·4 (15·3)	60·5 (13·8)	<0·0001
Pulmonary vascular resistance (N=1300), Wood units	14·0 (8·4)	12·9 (8·3)	16·6 (8·3)	<0·0001
Right atrial pressure (N=1253), mm Hg	8·2 (5·5)	8·0 (5·7)	8·6 (5·2)	0·065
Cardiac output (N=1202), L/min	3·98 (1·44)	4·20 (1·50)	3·50 (1·17)	<0·0001
Cardiac index (N=1358), L/min per m²	2·40 (0·88)	2·51 (0·92)	2·11 (0·69)	<0·0001
Vasodilator responder	157/1287 (12%)	147/907 (16%)	10/380 (3%)	<0·0001

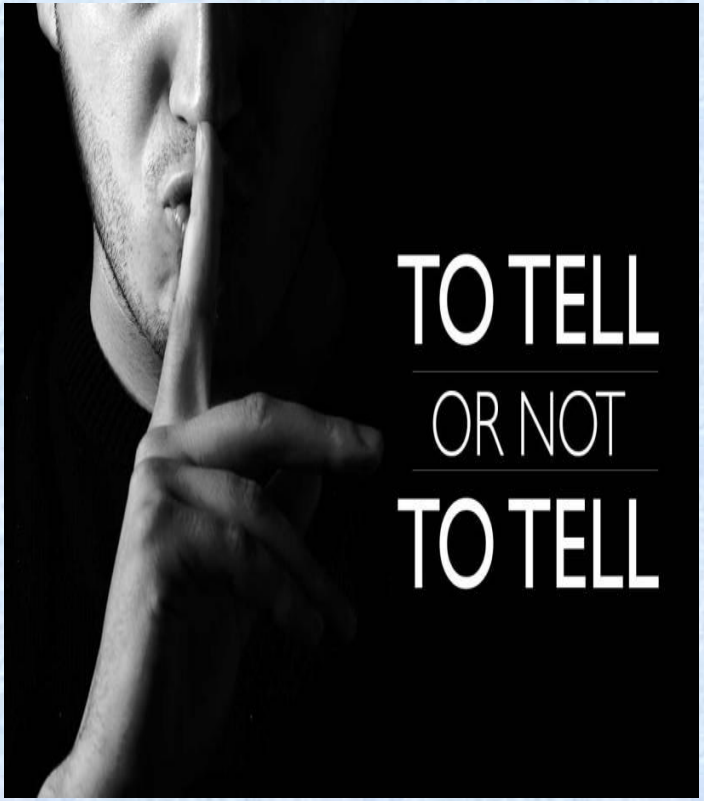
Lancet Respir Med 2016; 4: 129–37



Lancet Respir Med 2016; 4: 129–37

Utility of genetic diagnosis in PAH

- Prognostic reasons
- Genetic counselling
- Therapeutic implications



Genetic counselling

Recommendation (6WSPH)

- "All idiopathic, anorexic and familial PAH and first generation asymptomatic family members of patients with known genetic mutations
- Subsequent evaluation of PAH should be offered (CPET, TTE) for mutation positive individuals
- National databases for genotyping PAH patients"

Aim: Presymptomatic screening-earlier diagnosis

Multidisciniplary approach

Genetic testing: a matter of debate

Dépistage et **E**va**L**uation des facteurs **P**rédictifs de la survenue d'une **H**ypertension artér**I**elle pulmonaire chez les sujets asymptomatiques, porteurs de mutation *BMPR2*

Asymptomatic carriers of *BMPR2 / KCNK3* mutation

Optional at inclusion:
Right Heart Cath
Rest / exercise

Every 12 months or symptoms

Visit
- *NYHA*
- *NT-pro BNP, CRP*
- *ECG*
- *Chest Rx*
- *Genetic counseling*

PFTs
- *VO_2 max*
- *DLCO*
- *DLNO……*

Echo cardio
- *TRJ,*
- *TAPSE,*
- *Tei…..*

Blood samples
- *Plasma/serum,*
- *Biomarkers,*
- *Fibrocytes*
- *Circulating Progenitors,*
- *PDGF, endothelin-1…*

Dyspnea or unexplained syncopa or *Decrease in VO2 max >20% between 2 visits* or *TRJ >2.8 m/s*

No PAH

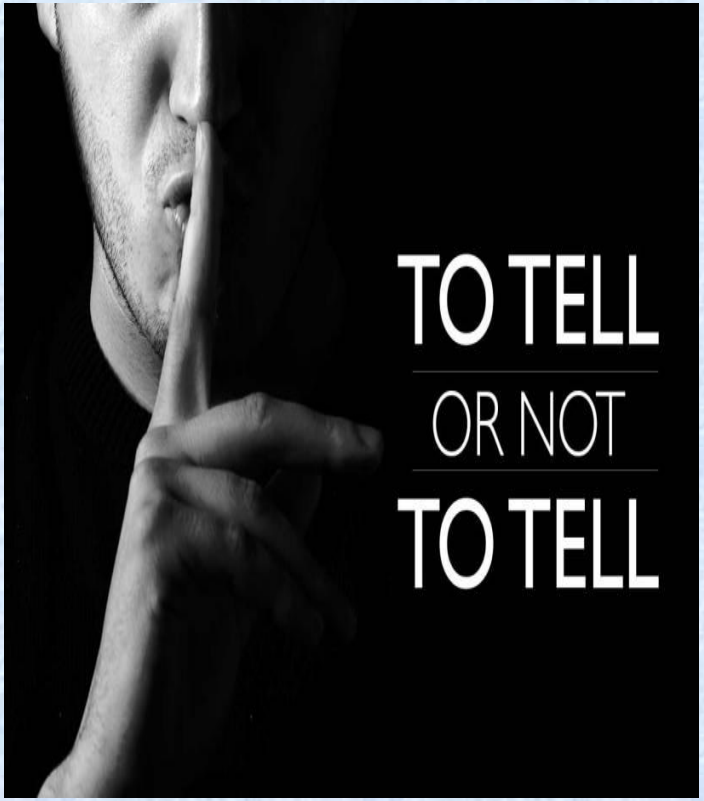
Right Heart Cath
Rest / exercise

Confirmed PAH

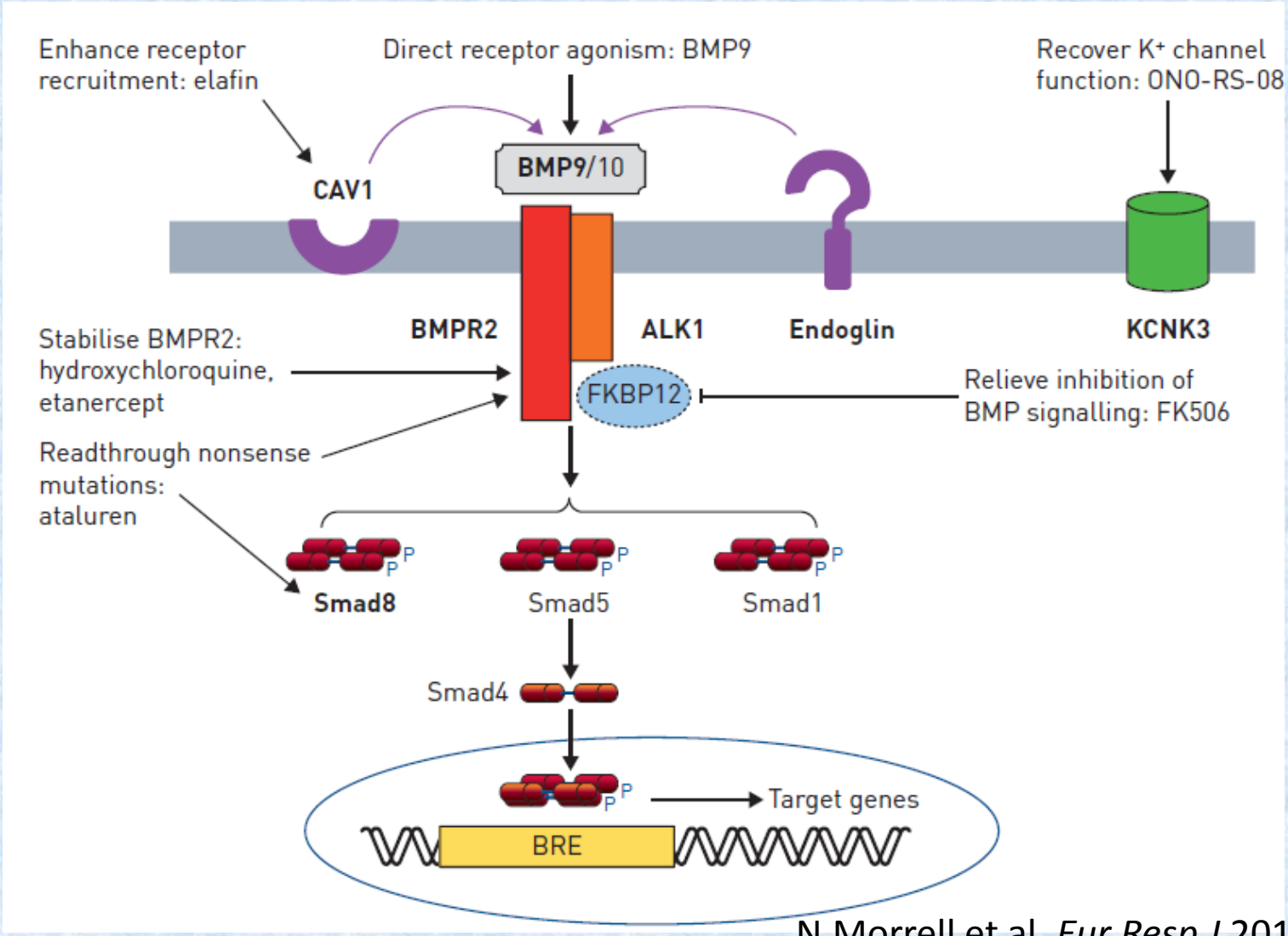
withdrawal from the study
Management according to ERS/ESC guidelines

Utility of genetic diagnosis in PAH

- Prognostic reasons
- Genetic counselling
- Therapeutic implications



From genes to therapies …



N.Morrell et al. *Eur Resp J* 2019;53

Take home messages

- Family history of PAH is observed in 6-10% of PAH patients
- BMPR2 is the most common mutation
- Penetrance is 14% in males and 42% in females
- Carriers show more severe hemodynamics
- Increased risk of death or LTX
- Genetic counselling is important
- Genomic understanding of PH might lead to novel targets for new drugs and prevention strategies

Thank you for your attention