Changements de paradigmes en hypertension pulmonaire:
De la suspicion au traitement

18 novembre 2021

S. Provencher, MD, M.Sc., FRCPC

Groupe de recherche en hypertension pulmonaire (www.phrg.ca)
Institut de cardiologie et de pneumologie de Québec
Université Laval

1

Conflicts of interests
(past 5 years)

	Speaker fees	Consultant	Research grant	Research contracts
Actelion	✔	✔	✔ (IIS*)	✔
Arena				✔
AstraZeneca			✔ (in-kind*)	
Bayer	✔	✔	✔ (IIS*)	✔
Boehringer	✔		✔ (IIS*)	✔
Gilead				✔
GlaxoSK			✔ (IIS*)	✔
Merck		✔		✔
Reata				✔
Resverlogix			✔ (IIS*)	✔
Roche				✔

*Investigator-initiated study

2

Objectifs

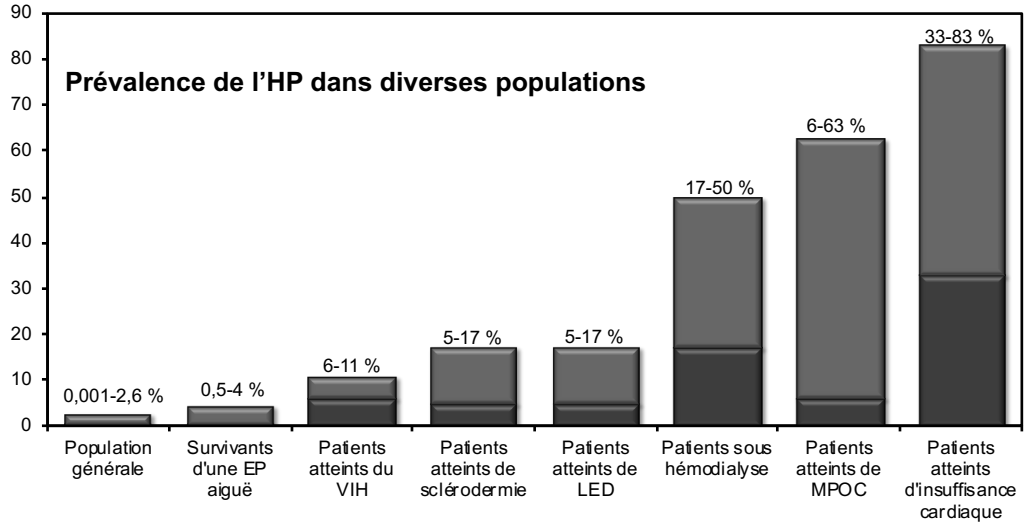
À LA FIN DE LA PRÉSENTATION LE PARTICIPANT SERA EN MESURE DE :

1. Intégrer l'approche probabiliste dans son investigation de l'HTP
2. Nommer ≥2 situations cliniques nécessitant une poursuite de l'investigation d'une l'HTP
3. Réaliser le changement de paradigme dans la prise en charge des patients HTAP
4. Discuter des spécificités de la prise en charge en fonction des caractéristiques des patients souffrant d'HTP

3

Hypertension pulmonaire

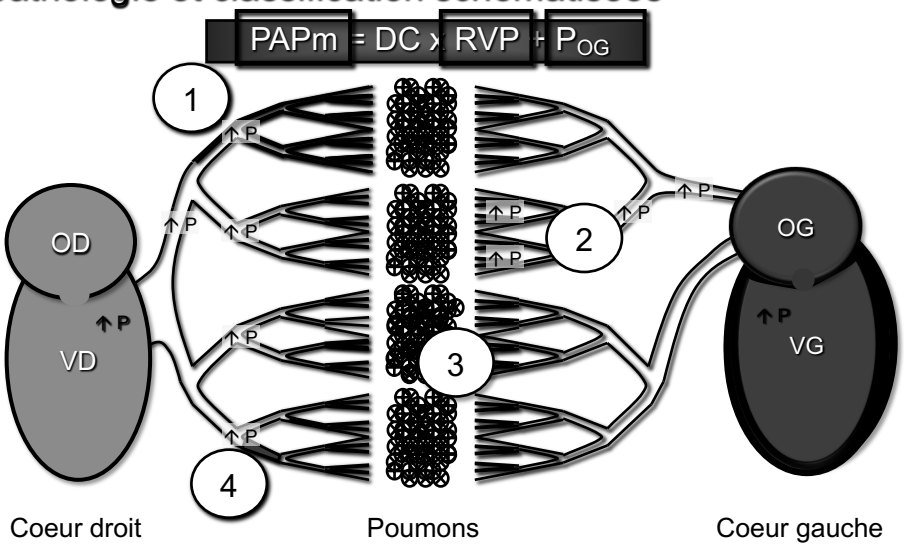
Un problème « fréquent » auquel vous serez confrontés



4

Hypertension pulmonaire

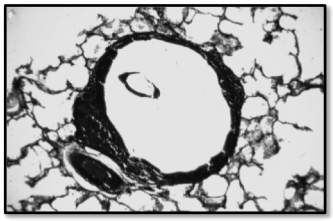
Physiopathologie et classification schématisées

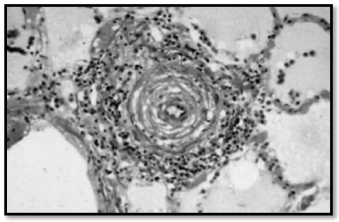


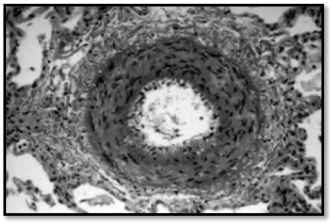
5

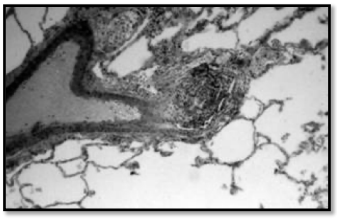
Hypertension artérielle pulmonaire

Plus qu'une simple vasoconstriction


Sujets sains


Anomalies intimales/adventitielles


Hypertrophie de la media


Lésions complexes

6

Diagnosis algorithm

Symptoms, signs tests suggestive of PH

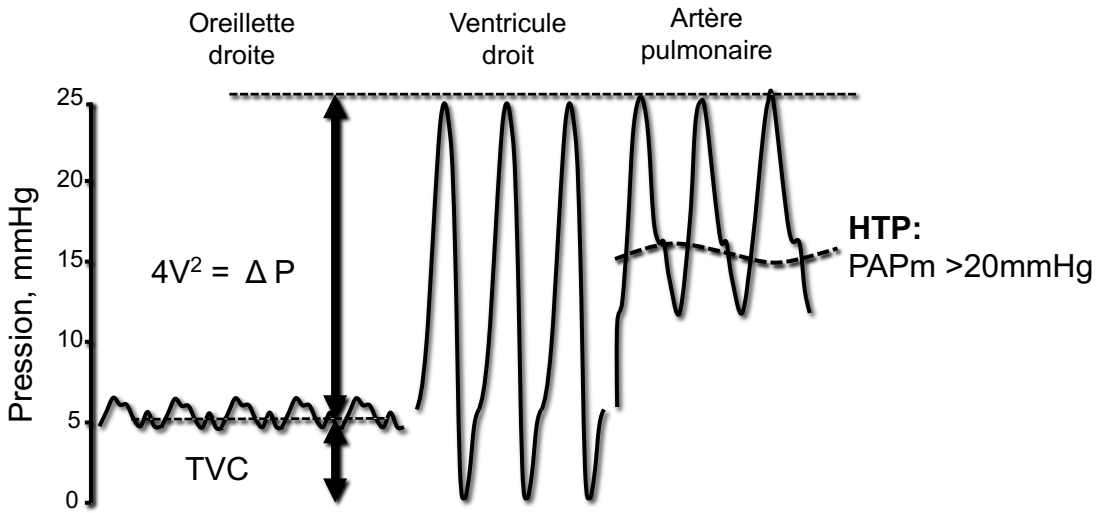
↓

Echocardiographic probability of PH

7

Échocardiographie

Une estimation de la PAP systolique



8

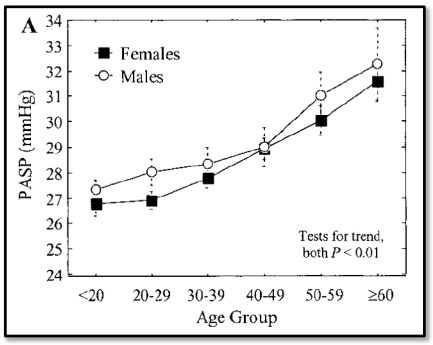
AMERICAN HEART ASSOCIATION Circulation

Clinical Correlates and Reference Intervals for Pulmonary Artery Systolic Pressure Among Echocardiographically Normal Subjects

McQuillan BM, *Circulation* 2001

RV-RA gradient

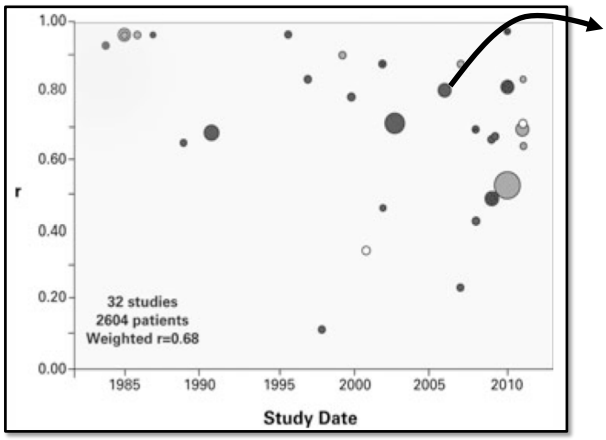
		Women n=2065		Men n=1147	
Variable	n	Mean±SD	95% CI	Mean±SD	95% CI
Age, y					
<20	856	16.4±4.0	8.6, 24.2	17.2±4.6	8.2, 26.2
20 to 29	669	16.8±3.9	9.2, 24.4	18.1±4.2	9.9, 26.3
30 to 39	650	17.5±4.2	9.3, 25.7	18.1±4.8	8.7, 27.5
40 to 49	494	18.7±4.5	9.9, 27.5	18.7±4.9	9.1, 28.3
50 to 59	344	19.8±4.9	10.2, 29.4	20.8±5.0	11.0, 30.6
≥60	199	21.3±5.5	10.5, 32.1	22.4±5.7	11.2, 33.6

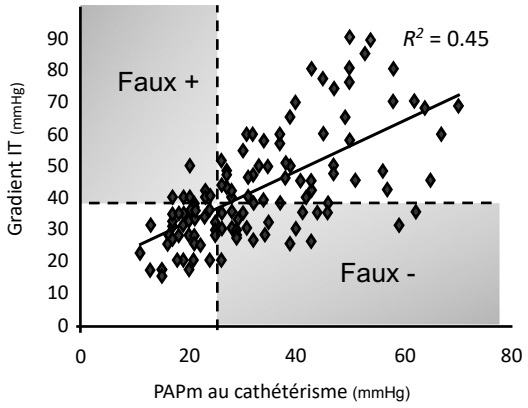


9

D'Andrea A *et al. Chest (in press)*

Limitations and Strengths of Doppler/Echo PA Systolic Pressure–Right Heart Catheterization Correlations: A Systematic Literature Review

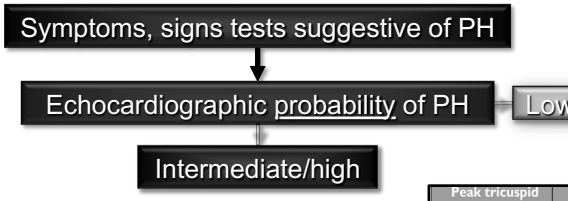




Finkelhor FS *et al. Echocardiography 2014;00:1–9*
Mukerjee D, *et al. Rheumatology* 2004; 43:461-6
Taleb M *et al. Echocardiography 2013;30:258-265*

10

Diagnosis algorithm



Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

11

Classification et implications thérapeutiques

Une approche « doublement » probabiliste

❑ HTAP	**Thérapies spécifiques** (Prostanoids, ERA, PDE-5 inh)
❑ Cardiopathie gauche	**ACE inhibitors, β-blockers, …**
❑ Maladie respiratoire	**Oxygène** Bronchodilatateurs, …
❑ Maladie embolique chronique	**Thromboendarterectomie (Riociguat, BPA, …)**
❑ Autres	???

12

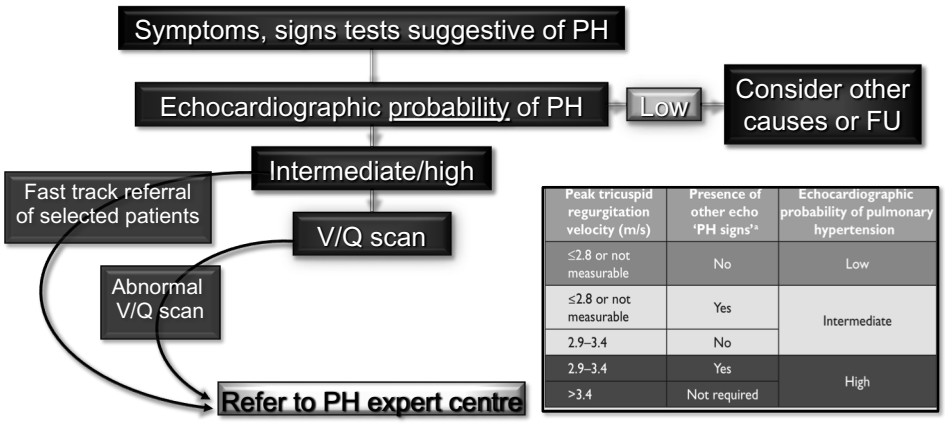
Investigation de l'HTP

Une approche « doublement » probabiliste

	HTAP/HTP-PE	HTP groupes 2/3
Épidémiologie	Fc risque HTAP ATCD TVP/EP	Âge avancé Fc risque cardiaques et respiratoires
ECG/arythmie		FA/flutter
Echocardio.	PAPs très élevée Dilatation/dysfonction modérée-sévère VD Épanch. péricardique	PAPs peu élevée Dilatation OG Absence de dysfonction VD

13

Diagnosis algorithm



Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

14

15

Embolie pulmonaire « aiguë »

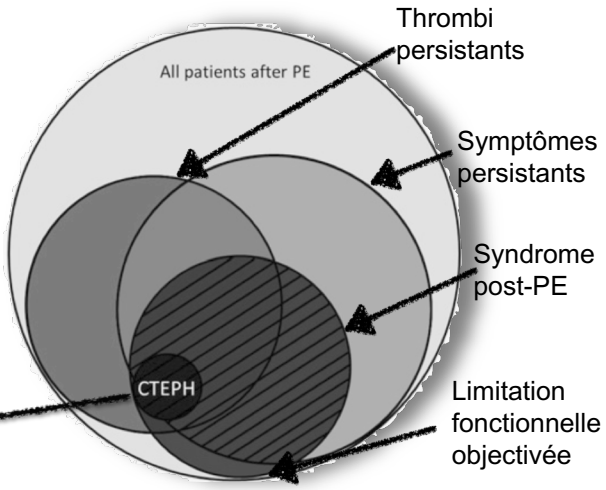
Une maladie pas si aiguë

EP aiguë
Incidence ≈1-2/1000

Déficits perfusionnels persistants
30-40%

Dysfonction VD persistante
20-30%

HTP-PE
0.5-2%



15

Ende-Verhaar et al ERJ 2017; 49: 1601792

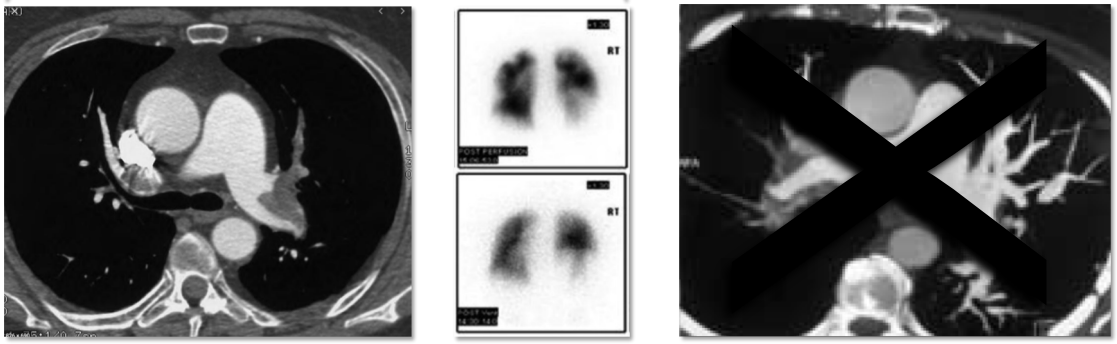
Klok FA *et al. Blood Reviews 28 (2014) 221–226*

HTP chronique post-embolique

Scan V/Q: outil de dépistage de choix

Embolie aiguë

HTP post-embolique



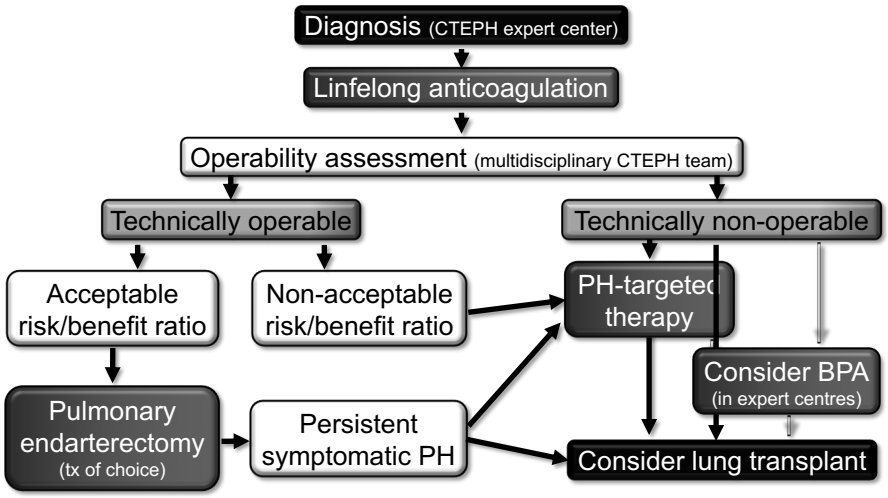
AngioTDM

Scan V/Q

AngioTDM

16

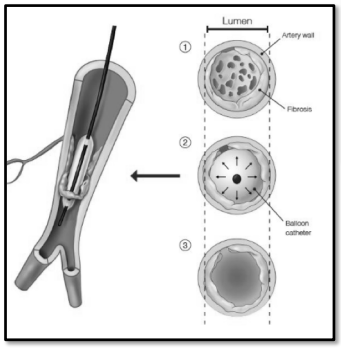
Treatment algorithm of CTEPH

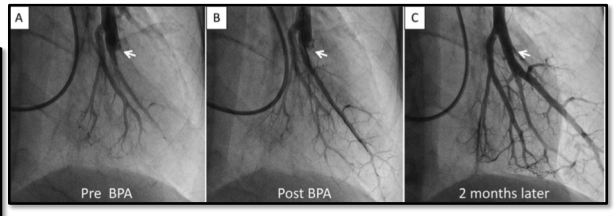


17

Adapted from Galie *et al Eur Heart J 2015*

Emerging role of BPA for CTEPH





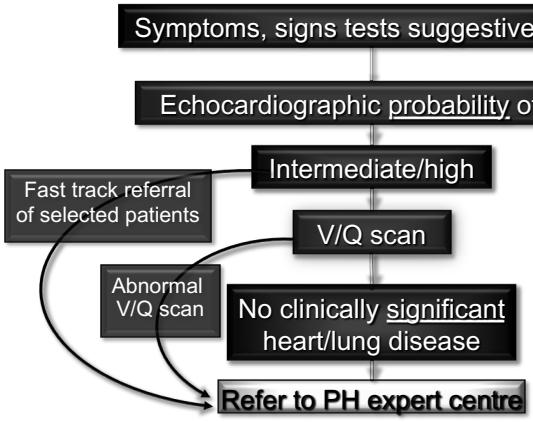
- RACE study (6 months):

	BPA	Riociguat	P value
Delta RVP	**-60%**	-32%	<0.001
Delta 6MWD	N/A	N/A	NS
SAE	50%	26%	<0.01

18

Delcroix M *et al. ERJ (in press)*
Jais X *et al. ERS Madrid 2019*

Diagnosis algorithm

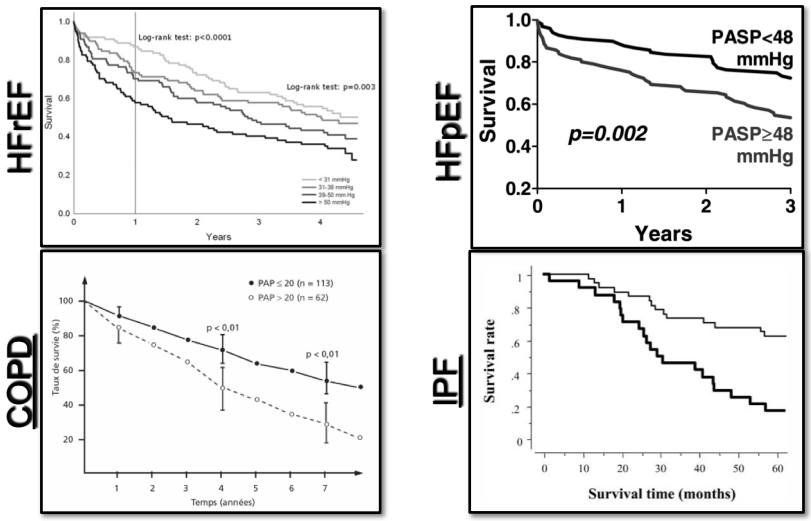


Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

19

PH and chronic cardiac and lung diseases

PH is independently related to mortality

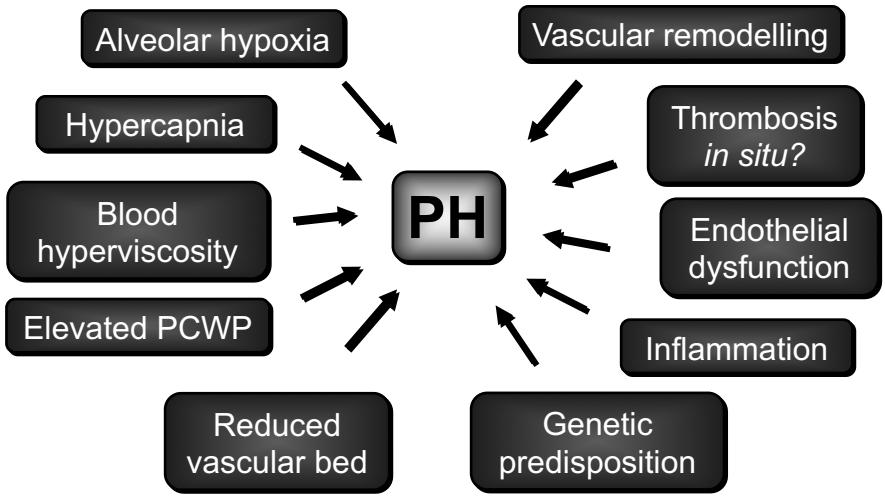


20

Kjaergaard J. *Am J Cardiol 2007;* Lam CSP. *JACC 2009;* Weitzenblum E, *et al. Thorax 1981;* Leuchte HH, *et al. AJRCCM 2006*

PH and chronic lung/heart diseases

More than alveolar hypoxia or elevated wedge pressure



21

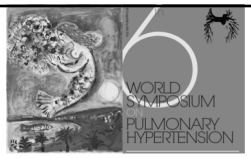
Traiter les HTP de groupe II-III avec les thérapies spécifiques nouvelles?

	Case reports	Case series	"Large-scale" RCTs*
Maladies respiratoires chroniques			
Epoprostenol	✓	✓	↗ shunt
ERA	✓	✓	↗ shunt/excès de mortalité?
PDE5/Riociguat	✓	✓	↗ shunt/excès de mortalité?
Cardiopathies gauches			
Epoprostenol	✓	✓	Excès de mortalité**
ERA	✓	✓	Rétention hydro-sodée**
PDE5/Riociguat	✓	✓	Largement inefficaces

* Ces ECR n'incluaient pas des HTP « disproportionnées »
**Dysfonction systolique. Aucune donnée disponible chez patients avec FEVG préservée

22

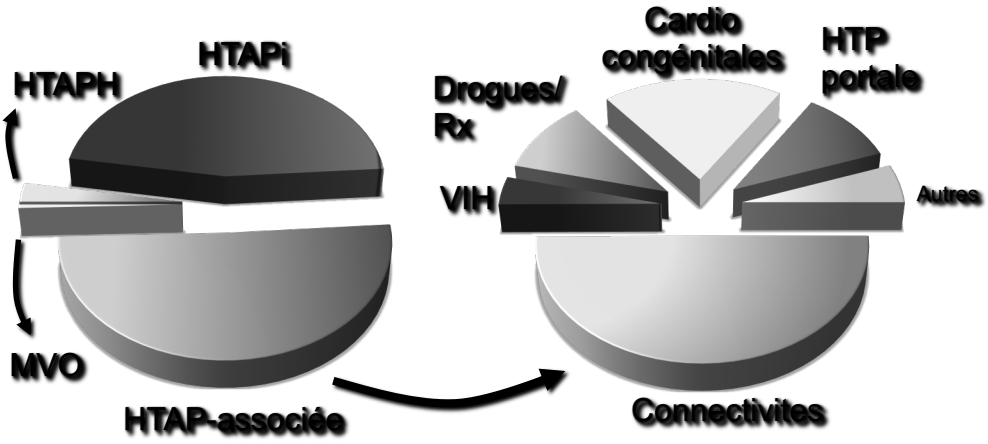
Pulmonary hypertension
Classification – Nice meeting 2018



1. PAH
   - 1.1 Idiopathic PAH
   - 1.2 PAH with vasoreactivity
   - 1.3 Heritable PAH
   - 1.4 Drugs and toxins
   - 1.5 Associated with connective tissue disease, HIV, portal hypertension, congenital heart disease, shistosomiasis
   - 1.6 PAH with overt signs of venous/ capillary involvement
   - 1.7 PPHNB
2. PH due to left heart disease
   - ❑ HF with preserved/reduced EF
   - ❑ Valvular heart disease
   - ❑ Congenital post-capillary obstruction
3. PH due to lung disease and/or hypoxia
   - ❑ Obstructive, restrictive or mixed lung disease
   - ❑ Hypoxia without lung disease
   - ❑ Developmental lung disorders
4. PH due to pulmonary artery obstructions
   - ❑ CTEPH
   - ❑ Other pulmonary artery obstructions
5. PH with unclear mechanisms
   - ❑ Hematologic (e.g. chronic hemolytic anemia, splenectomy)
   - ❑ Systemic (e.g. sarcoidosis)
   - ❑ Metabolic (e.g. Gaucher
   - ❑ Complex congenital heart disease

23

Conditions associées
Fréquentes parmi les patients HTAP



24

Badesch D *et al. Chest 2010;137;376-387*

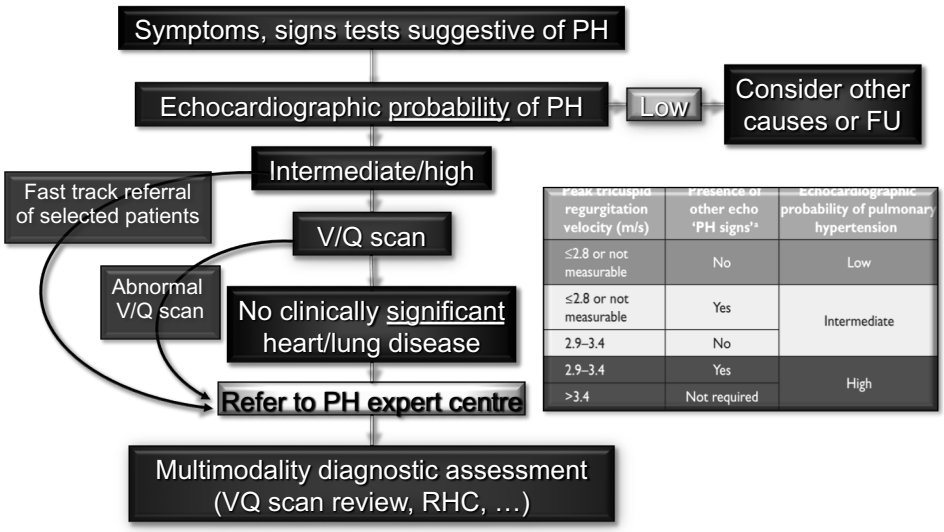
Revision to subgroup: 1.4 D&T (new drugs added)

Definitive	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine*
Dexfenfluramine	St. John's Wort
Toxic rapeseed oil	L_Tryptophan
Benfluorex	Chemotherapeutic agents
Dasatinib	Amphetamine
Methamphetamine	Interferon α and β

*Added agents

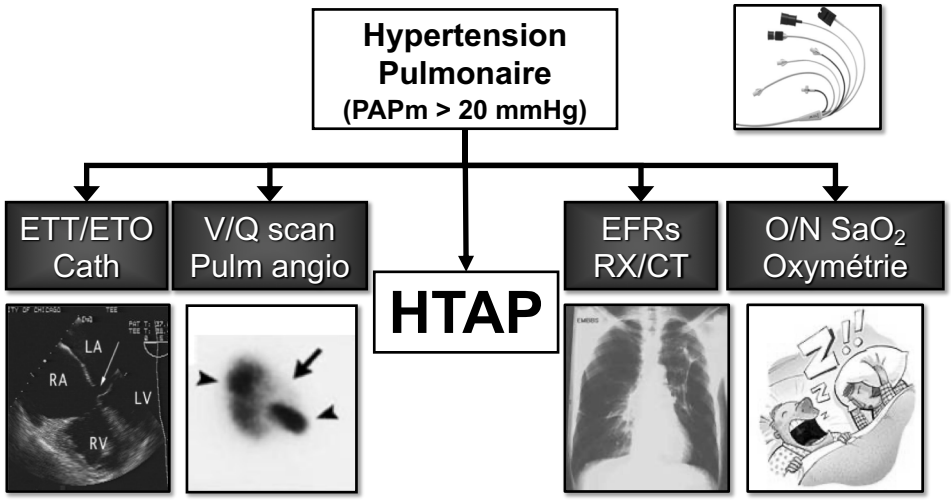
25

Diagnosis algorithm



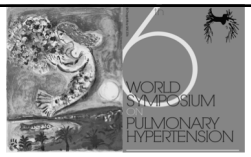
26

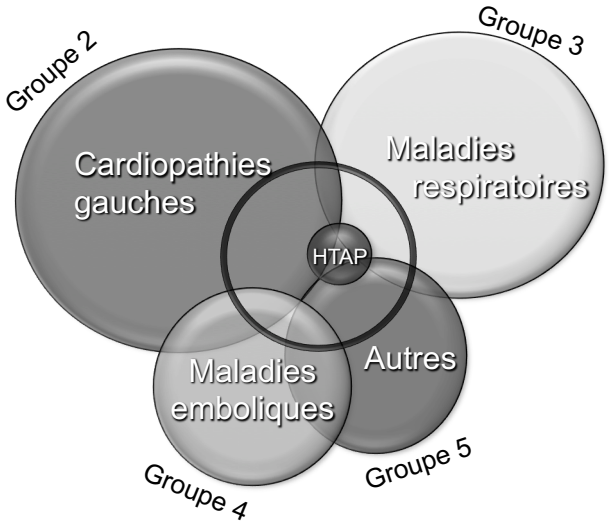
Algorithme diagnostique de l'HTP
Exclusion des causes "secondaires"



27

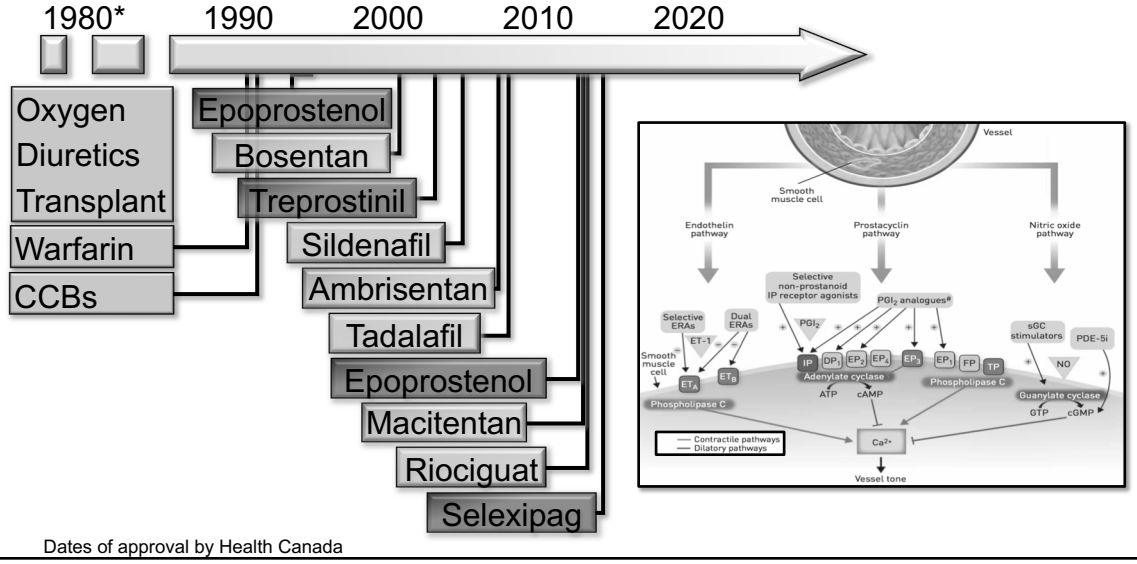
Hypertension pulmonaire
Classification clinique





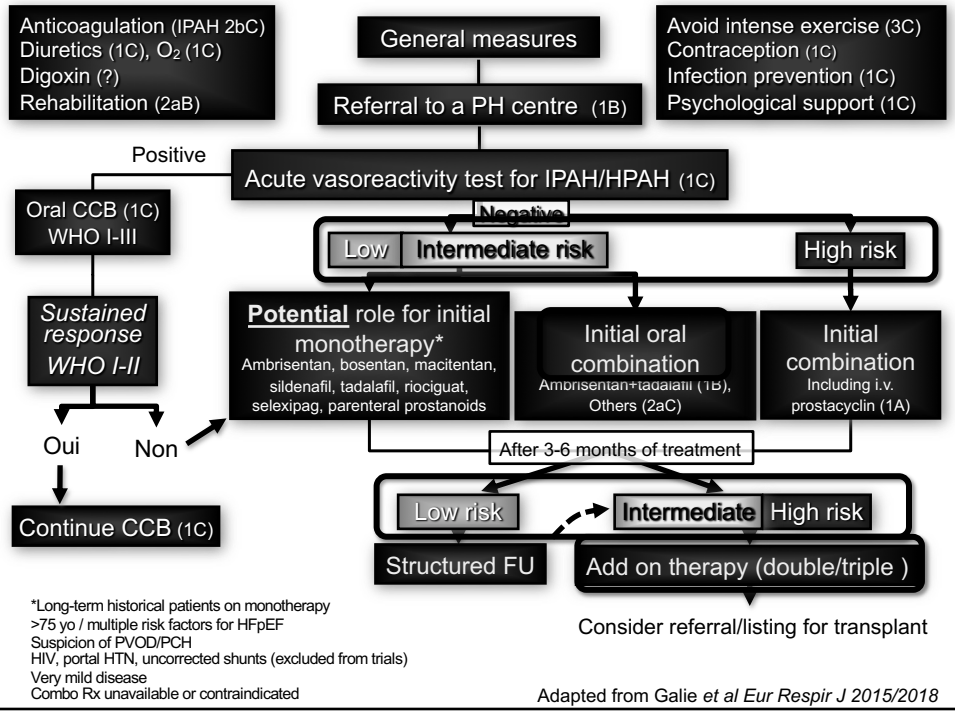
28

The therapeutic approach of PAH has markedly changed over the last decades



29

Dates of approval by Health Canada

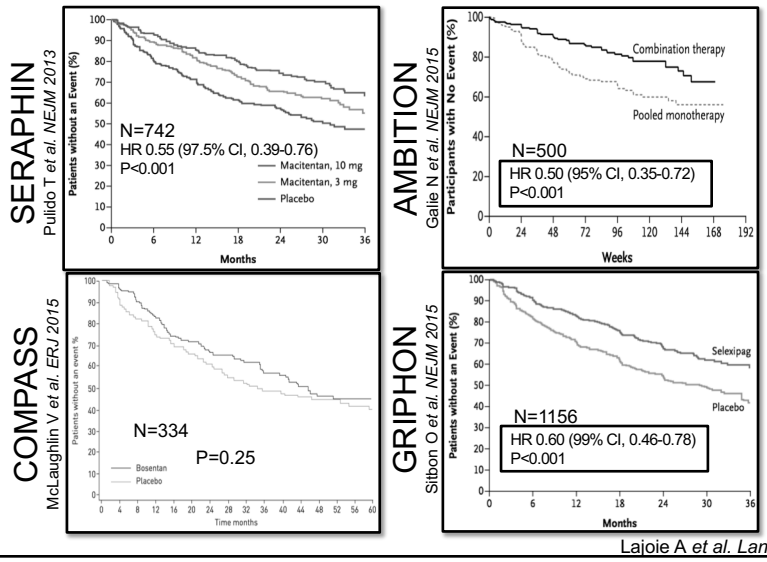


*Long-term historical patients on monotherapy
>75 yo / multiple risk factors for HFpEF
Suspicion of PVOD/PCH
HIV, portal HTN, uncorrected shunts (excluded from trials)
Very mild disease
Combo Rx unavailable or contraindicated

30

Adapted from Galie *et al Eur Respir J 2015/2018*

Combination therapy reduces clinical worsening in long-term trials



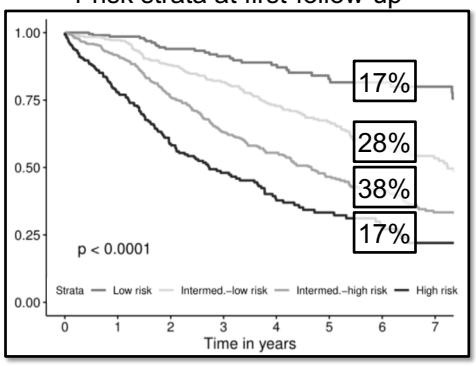
Lajoie A *et al. Lancet Resp Med 2016;4(4):291-305*

31

New models for risk stratification

Prognostic criteria	Low risk	Interm. risk	High risk
WHO FC	I, II	III	IV
6MWD, m	> 440	165-440	<165
NTproBNP, ng/L OR RAP, mmHg	<300 OR < 8	300-1400 OR 8-14	> 1400 OR > 14
CI, L/min/m² OR SvO_2, %	≥ 2.5 OR > 65%	2.0-2.4 OR 60-65%	CI < 2.0 OR < 60%

4-risk strata at first-follow-up

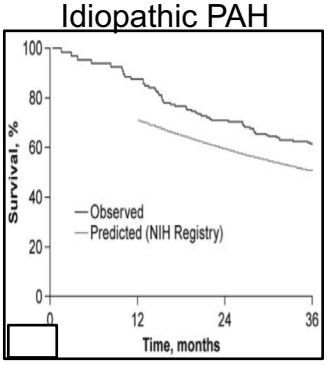


Hoeper M *et al. ERJ (in press)*
Boucly A *et al. ERJ (in press)*

32

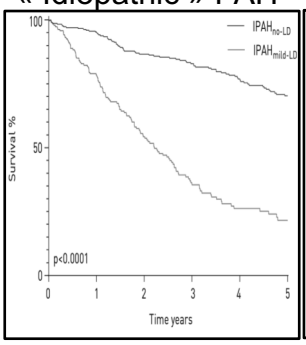
Survival of Incident PAH Patients in the Modern Management Era

Idiopathic PAH



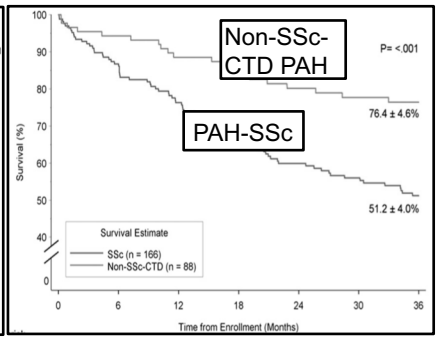
Humbert M, *et al. Circulation 2010*

« Idiopathic » PAH



Lewis RA *et al. ERJ 2020*

PAH-CTD

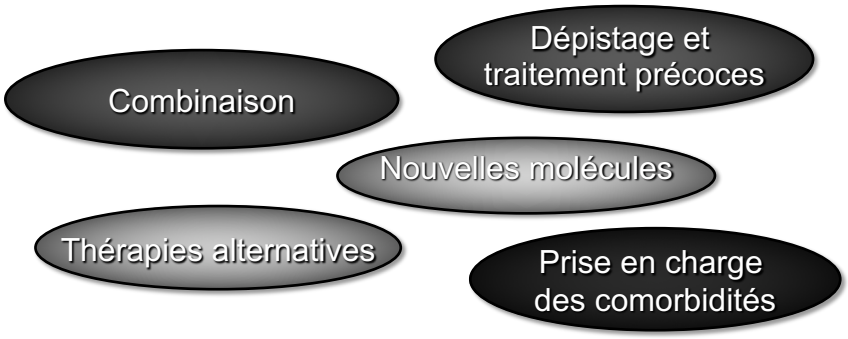


Chung L *et al. Chest 2014*

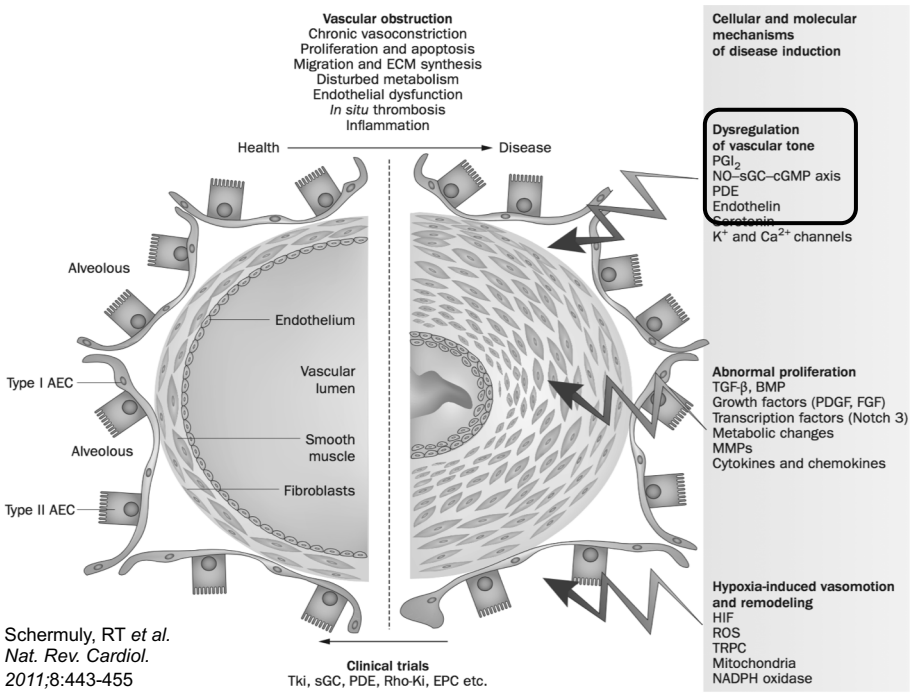
33

Stratégies thérapeutiques futures

- La survie à long terme et la qualité de vie sont toujours à améliorer:
  - L'algorithme de traitement est encore appelé à se modifier

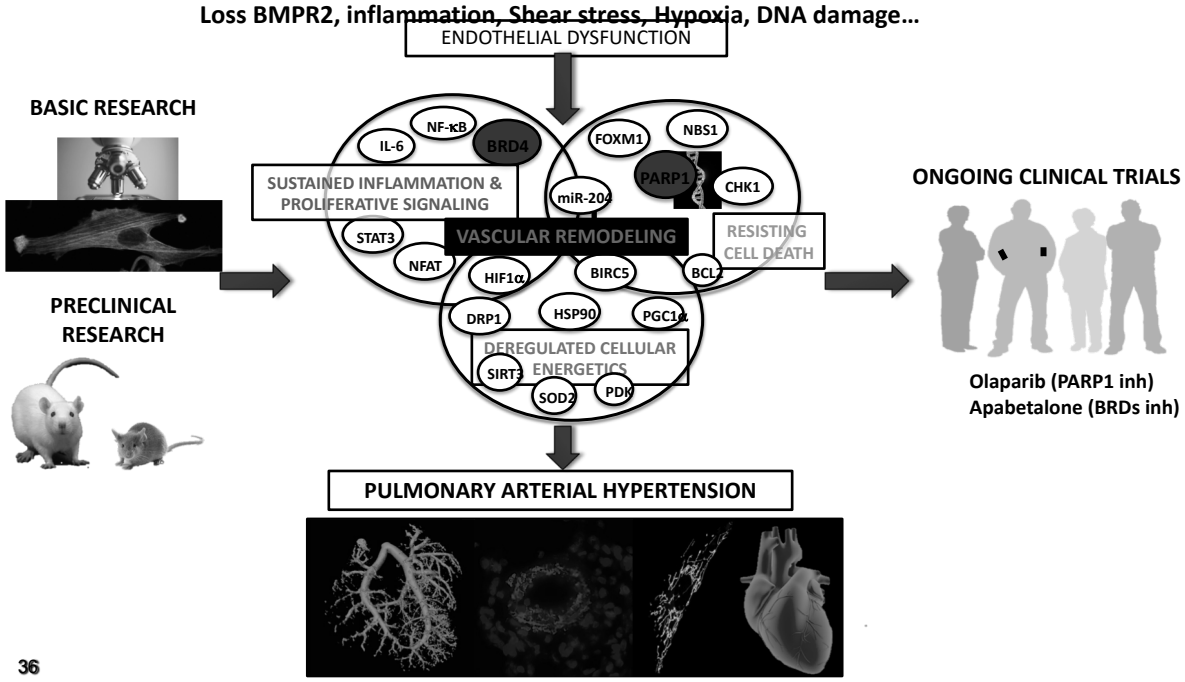


34



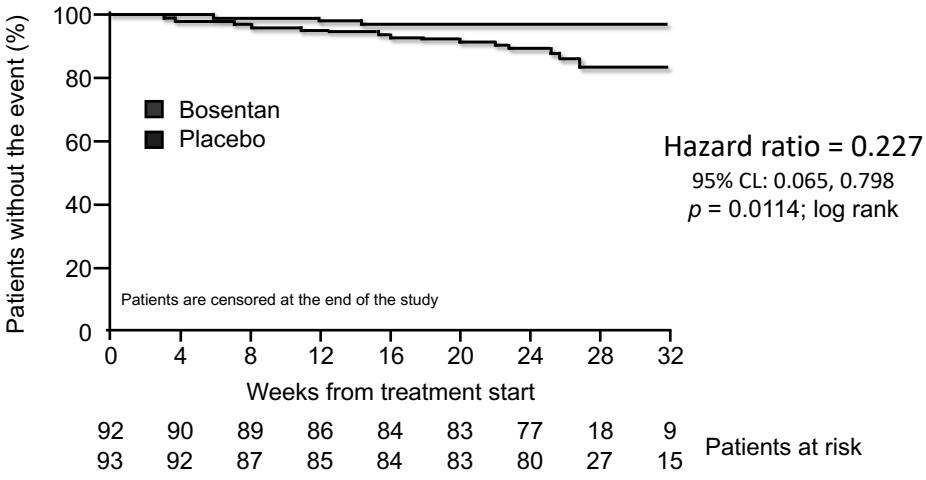
Schermuly, RT *et al.* *Nat. Rev. Cardiol.* *2011;*8:443-455

35



36

Amélioration du pronostic
Diagnostic et traitement précoce



Hazard ratio = 0.227
95% CL: 0.065, 0.798
p = 0.0114; log rank

37

*death 1/1, hospitalisation 3/1, PAH progression 9/1

Galie N *et al. Lancet 2008;391:2093-2100*

Systematic screening in CTD
Current recommendations

- Cardiac ecohgraphy + pulmonary function tests annually
  - Scleroderma (low QE)
  - SSc-spectrum patients (very low QE)

Khanna D. *et al. Arthritis&Rheumatism 2013;65(12):3194-3201*

	Estimated incidence (no. of cases per 100 patient-years)	95% CI
All forms of pulmonary hypertension	1.37	0.74–2.00
Pulmonary arterial hypertension	0.61	0.26–1.20
Among patients with lcSSc	0.40	0.11–1.03
Among patients with dcSSc	1.25	0.34–3.20
Postcapillary pulmonary hypertension	0.61	0.26–1.20
Pulmonary hypertension secondary to pulmonary fibrosis	0.15	0.02–0.55

*Cas incidents d'HTAP étaient tous symptomatiques

38

Hachulla E. *et al. Arthritis Rheum 2009; 60(6):1831–1839*

An evidence-based strategy to screen for pulmonary arterial hypertension in systemic sclerosis

Semalulua T *et al. Sem Arth & Rheum 2020*

Probability: exp(X)/(1+exp(X))
where X= -3.4909+0.2190*SOB-0.0433*DLCO+0.3656*log(BNP)

All SSc-PAH cases: estimated probability of PAH of >1.1%

Meune C *et al. Arthritis Rheum 2011;63(9):2790-2796*

Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study

Annals of the RHEUMATIC DISEASES

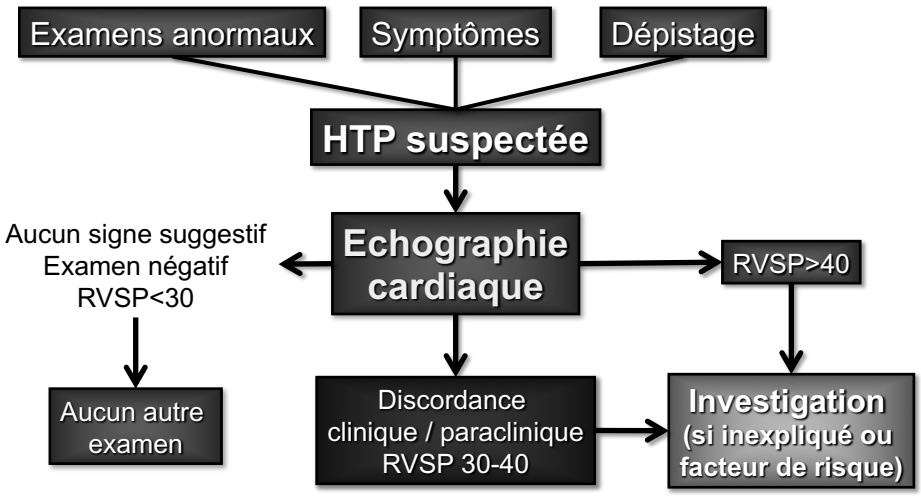
Coglan JG *et al. Ann Rheum Dis 2014;73(7):1340-9*

- 466 SSc patients at high risk of PAH (SSc > 3 ans; DLCO <60%)
  - Overall prevalence: 19%
- **Negative predictive value of TTE alone: 71%**

39

Poursuite de l'investigation

En fonction de la probabilité pré-test



40

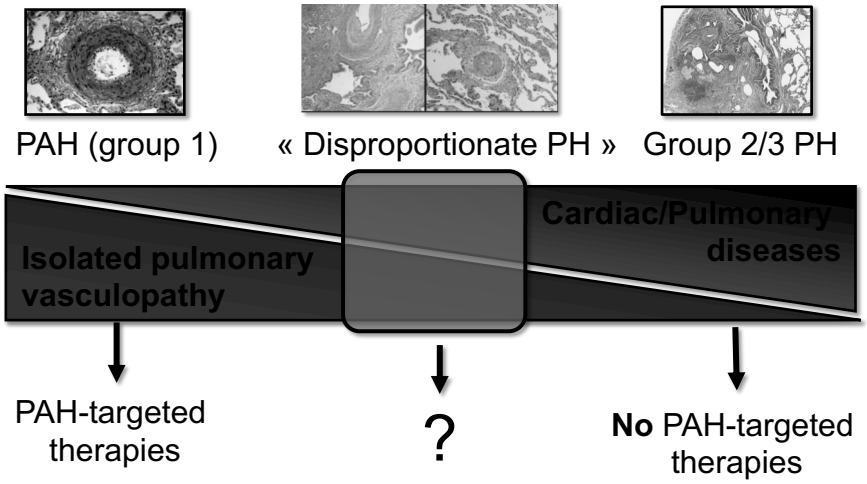
Adapté de Hachulla E *et al. Arthritis Rhumatol* 2005;52(12):3792–3800.

Classification clinique
Implications thérapeutiques

❑ HTAP	**Thérapies spécifiques** (Prostanoids, ERA, PDE-5 inh)
❑ Cardiopathie gauche	**ACE inhibitors, β-blockers, …**
❑ Maladie respiratoire	**Oxygène** Bronchodilatateurs, …
❑ Maladie embolique chronique	**Thromboendarterectomie (Riociguat, BPA, …)**
❑ Autres	???

41

Management of "out of proportion" PH
A "niche" for PAH targeted therapies?



Fartoukh M, Humbert M, *et al. AJRCCM 2000*
Nunes H, Humbert M, *et al. Thorax 2006*

42

Conclusions

- Une dyspnée ne doit pas rester inexpliquée (ou faussement attribuée au déconditionnement) sans investigation appropriée
  - Échocardiographie: bon outil… à interpréter selon le contexte clinique
- Combinaison thérapeutique (d'emblée ou séquentielle), basée sur une stratification systématique du risque devient la norme en HTAP
- Améliorations majeures avec les traitements actuels, surtout si précoces
  - Dépistage ciblé (HTAP) et scan V/Q (HTP-PE) à privilégier
- Options thérapeutiques limitées en HTP de groupe 2 et 3

43

Merci

Canada Foundation for Innovation
Fondation canadienne pour l'innovation
CIHR IRSC
HEART & STROKE FOUNDATION OF CANADA
FONDATION DES MALADIES DU CŒUR DU CANADA
Finding answers. For life. À la conquête de solutions.
Fonds de la recherche en santé du Québec
Québec
1955-2015
CENTRE DE RECHERCHE INSTITUT UNIVERSITAIRE DE CARDIOLOGIE ET DE PNEUMOLOGIE DE QUÉBEC

http://www.pulmonaryarterialhypertension.ca
http://swrsr.crc.chus.qc.ca/en/tissue_bank.asp (FRQS tissue bank)

44