# Traitement de la fibrose pulmonaire idiopathique


HOPITAL FOCH

**Docteur Alexandre CHABROL le 12/04/2019**

# Liens d'intérêt

- Oxyvie
- LVL
- SOS Oxygène
- Roche
- Astra Zeneca
- Boehinger
- Novartis
- Homeperf
- Elivie

# Introduction

- **La fibrose pulmonaire idiopathique est la plus fréquente des pneumopathie interstitielle chronique**
- **Incidence ( USA + Europe) : 3 à 9 cas pour 100 000 personnes-années.**
- **Pronostic sombre. Médiane de survie de 3ans.**
- **Aucun traitement jusqu'au 2012**

# Tableau clinique

- **Homme de plus de 70 ans fumeur avec des antécédents cardiovasculaires.**
- **Dyspnée chronique, toux sèche.**
- **Présence d'un hippocratisme digital et de crépitants à l'ascultation.**
- **Absence d'atteinte extra pulmonaire.**
- **Maladie limité au poumon**
- **Absence d'expositon professionnelle , domestique ou de prise de médicaments pneumotoxique**

# Explorations recommandées

- **NFS, CRP, fonction rénale , bilan hépatique**
- **CPK, EPP**
- **FAN, anti CCP, Fateur rhumatoide**
- **ANCA**

**selon le tableau**

- **Anti ECT , Anticorps des dermatomyosites Précipitines**

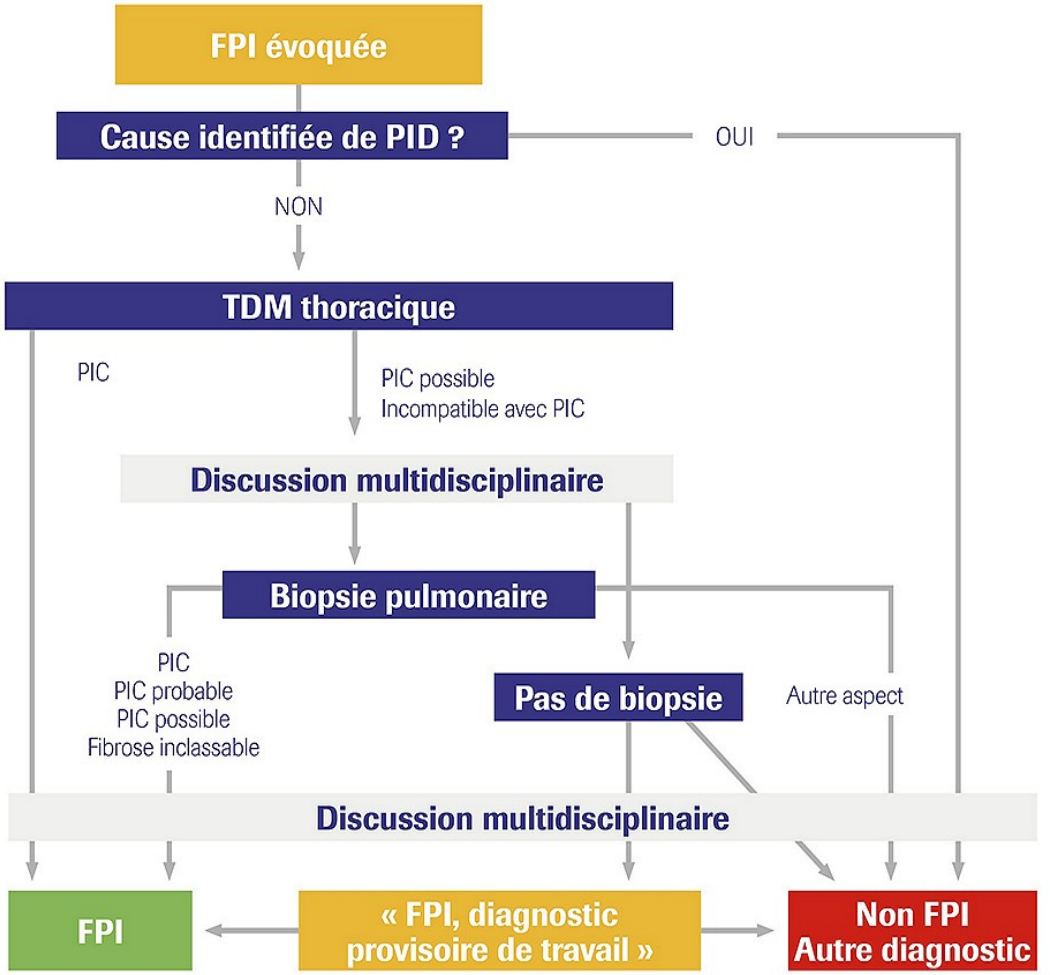
- **Fibroscopie et LBA**
- **EFR**

Recommandations pratiques pour le diagnostic et la prise en charge de la fibrose pulmonaire idiopathique.
Actualisation 2017.
V. Cottin, B. Crestani, J. Cadranel c, et al

# Diagnostic de FPI.

Recommandations pratiques pour le diagnostic et la prise en charge de la fibrose pulmonaire idiopathique. Actualisation 2017.
V. Cottin, B. Crestani, J. Cadranel c, et al

**Algorithme diagnostique de la fibrose pulmonaire idiopathique**




**FPI :** fibrose pulmonaire idiopathique ; **PIC :** pneumopathie interstitielle commune ; **PID :** pneumopathie interstitielle diffuse ; **TDM :** tomodensitométrie

D'après 1.

# Synthèse TDM/ histologie

| | Aspect histologique | | | | | |
|---|---|---|---|---|---|---|
| **Aspect TDM** | **PIC certaine** | **PIC probable** | **PIC possible** | **Fibrose inclassable** | **Non PIC** | **Pas de biopsie** |
| **PIC certaine** | **FPI** | **FPI** | **FPI** | **FPI** | **Non FPI** | **FPI** |
| **PIC possible** | **FPI** | **FPI** | **FPI probable** | **FPI probable** | **Non FPI** | **Selon DMD** |
| **Non PIC** | **FPI** | **Non FPI** | **Non FPI** | **Non FPI** | **Non FPI** | **Selon DMD** |

Recommandations pratiques pour le diagnostic et la prise en charge de la fibrose pulmonaire idiopathique. Actualisation 2017.
V. Cottin, B. Crestani, J. Cadranel c, et al

# Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

**Ganesh Raghu, Martine Remy-Jardin, Jeffrey L. Myers, Luca Richeldi, Christopher J. Ryerson, David J. Lederer,Juergen Behr, Vincent Cottin, Sonye K. Danoff, Ferran Morell, Kevin R. Flaherty, Athol Wells, Fernando J. Martinez,Arata Azuma, Thomas J. Bice, Demosthenes Bouros, Kevin K. Brown, Harold R. Collard, Abhijit Duggal, Liam Galvin,Yoshikazu Inoue, R. Gisli Jenkins, Takeshi Johkoh, Ella A. Kazerooni, Masanori Kitaichi, Shandra L. Knight,George Mansour, Andrew G. Nicholson, Sudhakar N. J. Pipavath, Ivette Buend´ıa-Rold´an, Mois´es Selman,William D. Travis, Simon L. F. Walsh, and Kevin C. Wilson; on behalf of the American Thoracic Society, EuropeanRespiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society**

# Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper

*David A Lynch, Nicola Sverzellati, William D Travis, Kevin K Brown, Thomas V Colby, Jeffrey R Galvin, Jonathan G Goldin, David M Hansell, Yoshikazu Inoue, Takeshi Johkoh, Andrew G Nicholson, Shandra L Knight, Suhail Raoof, Luca Richeldi, Christopher J Ryerson, Jay H Ryu, Athol U Wells*

Lancet Respir Med. 2017 Nov 15

| | Typical UIP CT pattern | Probable UIP CT pattern | CT pattern indeterminate for UIP | CT features most consistent with non-IPF diagnosis |
|---|---|---|---|---|
| Distribution | Basal predominant (occasionally diffuse), and subpleural predominant; distribution is often heterogeneous | Basal and subpleural predominant; distribution is often heterogeneous | Variable or diffuse | Upper-lung or mid-lung predominant fibrosis; peribronchovascular predominance with subpleural sparing |
| Features | Honeycombing; reticular pattern with peripheral traction bronchiectasis or bronchiolectasis*; absence of features to suggest an alternative diagnosis | Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis*; honeycombing is absent; absence of features to suggest an alternative diagnosis | Evidence of fibrosis with some inconspicuous features suggestive of non-UIP pattern | Any of the following: predominant consolidation, extensive pure ground glass opacity (without acute exacerbation), extensive mosaic attenuation with extensive sharply defined lobular air trapping on expiration, diffuse nodules or cysts |

UIP=usual interstitial pneumonia. IPF=idiopathic pulmonary fibrosis. *Reticular pattern is superimposed on ground glass opacity, and in these cases it is usually fibrotic. Pure ground glass opacity, however, would be against the diagnosis of UIP or IPF and would suggest acute exacerbation, hypersensitivity pneumonitis, or other conditions.

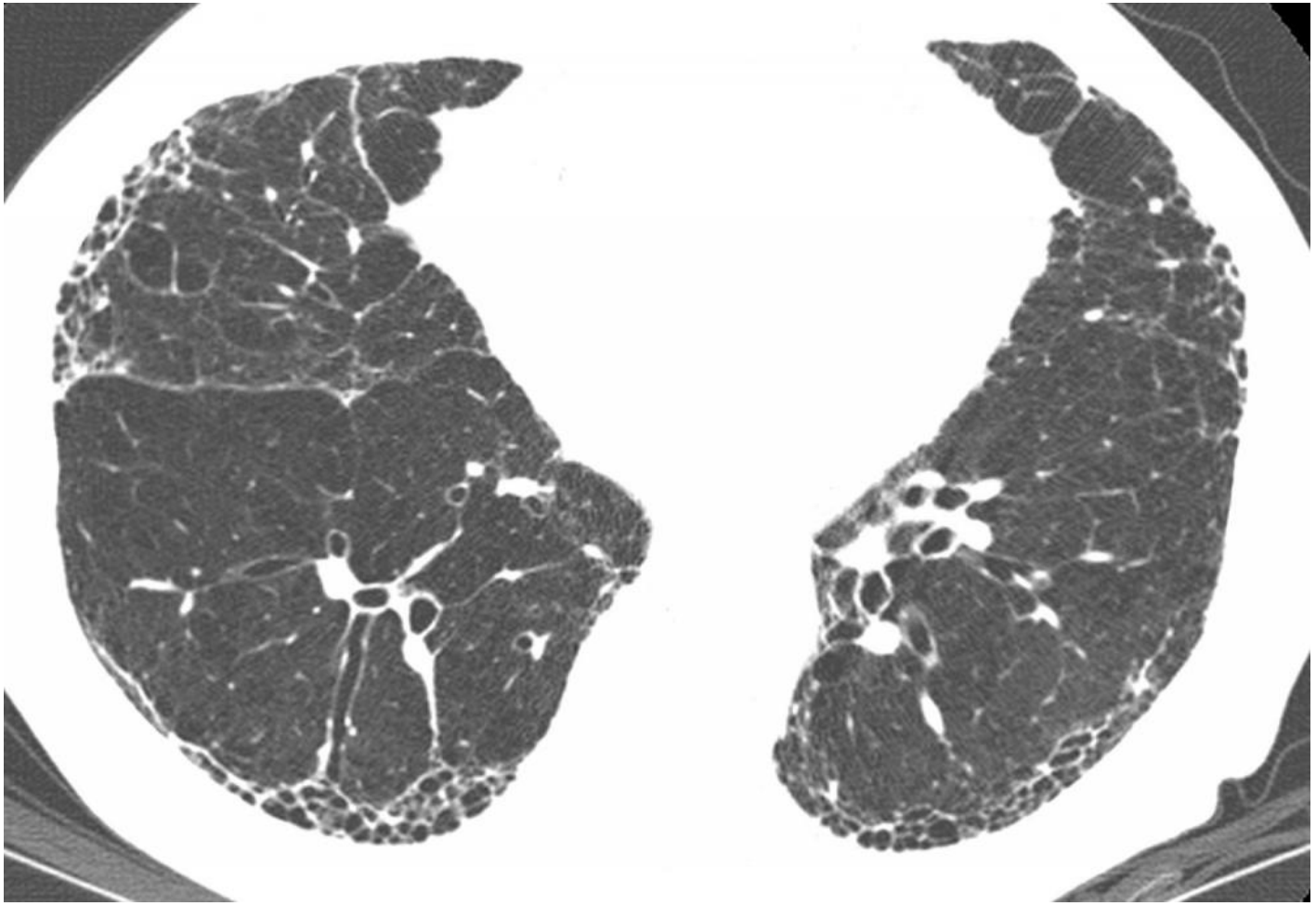
**Table 1:** Diagnostic categories of UIP based on CT patterns

# Eléments évoquant un autre diagnostic

- **C**ondensation
- **A**ir trapping
- **N**odules, micronodules diffus
- **N** verre dépoli
- **O**ther ( kystes)
- **T**op (prédominance lobes supérieurs)
- **B:** épaississement peri **B**ronchovasculaire

+ Respect sous pleurale, épanchement pleural ou péricardique, dilatation de l'oesophage, plaques pleurales, Adénopathies, Erosions claviculaires distales

# PIC certaine



# PIC probable

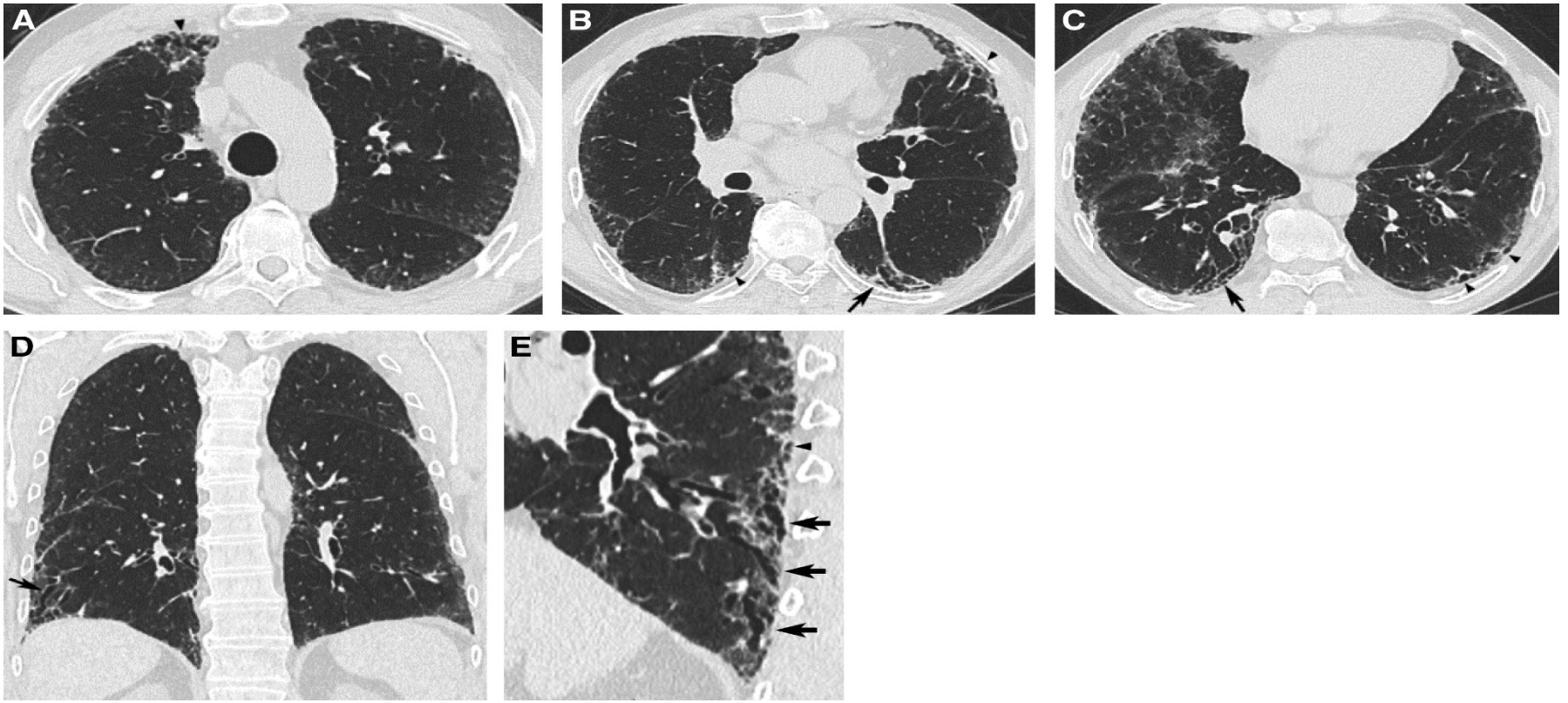



**Figure 2.** Probable usual interstitial pneumonia (UIP) pattern.

Am J Respir Crit Care Med, 2018
Ganesh Raghu; Martine Remy-Jardin; Jeffrey L. Myers; Luca Richeldi; Christopher J. Ryerson; David J. Lederer; Juergen Behr; Vincent Cottin; Sonye K. Danoff; Ferran Morell; Kevin R. Flaherty; Athol Wells; Fernando J. Martinez; Arata Azuma; Thomas J. Bice; Demosthenes Bouros; Kevin K. Brown; Harold R. Collard; Abhijit Duggal; Liam Galvin; Yoshikazu Inoue; R. Gisli Jenkins; Takeshi Johkoh; Ella A. Kazerooni; Masanori Kitaichi; Shandra L. Knight; George Mansour; Andrew G. Nicholson; Sudhakar N. J. Pipavath; Ivette Buendía-Roldán; Moisés Selman; William D. Travis; Simon L. F. Walsh; Kevin C. Wilson; *Am J Respir Crit Care Med* 198e44-e68.

# PIC indeterminée

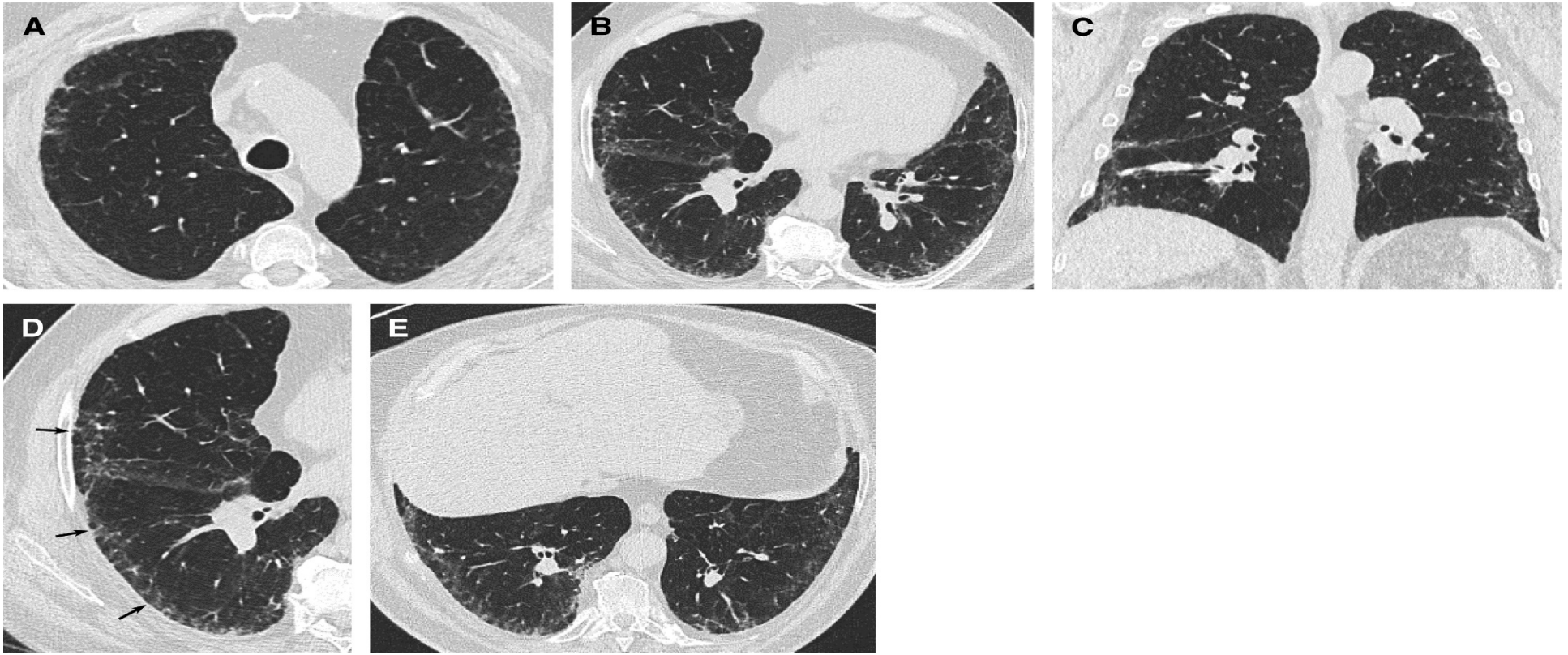



**Figure 3.** Indeterminate for usual interstitial pneumonia (UIP) pattern

Am J Respir Crit Care Med, 2018
Ganesh Raghu; Martine Remy-Jardin; Jeffrey L. Myers; Luca Richeldi; Christopher J. Ryerson; David J. Lederer; Juergen Behr; Vincent Cottin; Sonye K. Danoff; Ferran Morell; Kevin R. Flaherty; Athol Wells; Fernando J. Martinez; Arata Azuma; Thomas J. Bice; Demosthenes Bouros; Kevin K. Brown; Harold R. Collard; Abhijit Duggal; Liam Galvin; Yoshikazu Inoue; R. Gisli Jenkins; Takeshi Johkoh; Ella A. Kazerooni; Masanori Kitaichi; Shandra L. Knight; George Mansour; Andrew G. Nicholson; Sudhakar N. J. Pipavath; Ivette Buendía-Roldán; Moisés Selman; William D. Travis; Simon L. F. Walsh; Kevin C. Wilson; *Am J Respir Crit Care Med* 198e44-e68.
DOI: 10.1164/rccm.201807-1255ST

# Suggestif d'un diagnostic différentiel

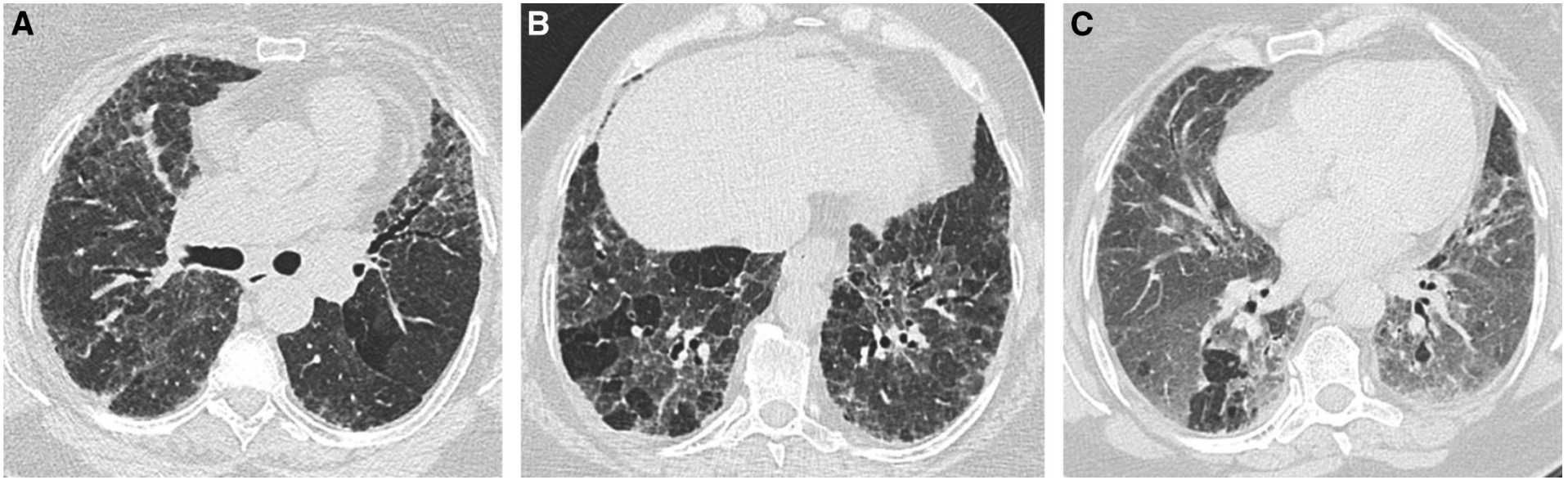



**Figure 5.** Computed tomography (CT) pattern suggestive of an alternative diagnosis for lung fibrosis.

Am J Respir Crit Care Med, 2018
Ganesh Raghu; Martine Remy-Jardin; Jeffrey L. Myers; Luca Richeldi; Christopher J. Ryerson; David J. Lederer; Juergen Behr; Vincent Cottin; Sonye K. Danoff; Ferran Morell; Kevin R. Flaherty; Athol Wells; Fernando J. Martinez; Arata Azuma; Thomas J. Bice; Demosthenes Bouros; Kevin K. Brown; Harold R. Collard; Abhijit Duggal; Liam Galvin; Yoshikazu Inoue; R. Gisli Jenkins; Takeshi Johkoh; Ella A. Kazerooni; Masanori Kitaichi; Shandra L. Knight; George Mansour; Andrew G. Nicholson; Sudhakar N. J. Pipavath; Ivette Buendía-Roldán; Moisés Selman; William D. Travis; Simon L. F. Walsh; Kevin C. Wilson; *Am J Respir Crit Care Med* 198e44-e68.

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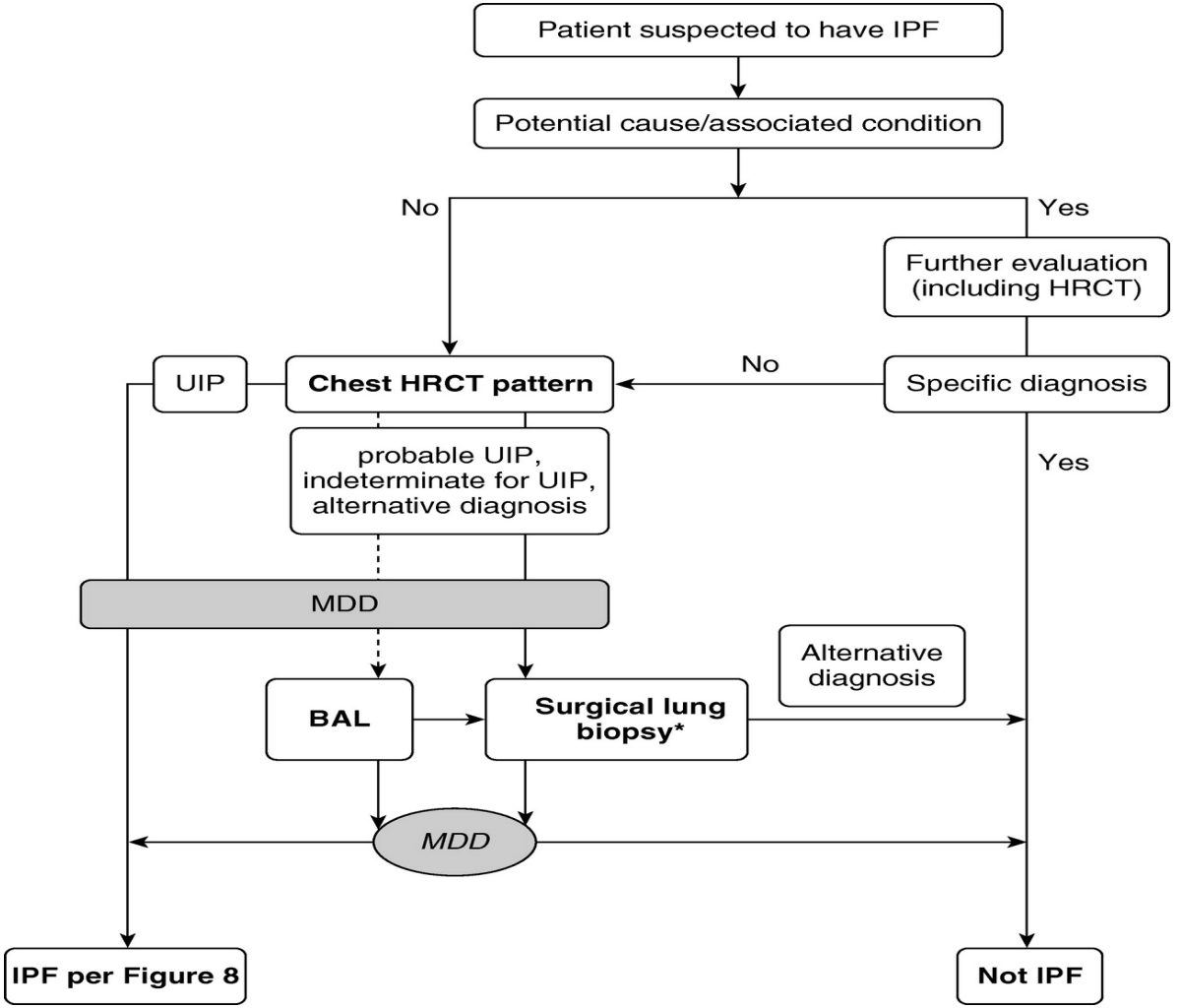



**Figure 9.** Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF).

Am J Respir Crit Care Med, 2018

Ganesh Raghu; Martine Remy-Jardin; Jeffrey L. Myers; Luca Richeldi; Christopher J. Ryerson; David J. Lederer; Juergen Behr; Vincent Cottin; Sonye K. Danoff; Ferran Morell; Kevin R. Flaherty; Athol Wells; Fernando J. Martinez; Arata Azuma; Thomas J. Bice; Demosthenes Bouros; Kevin K. Brown; Harold R. Collard; Abhijit Duggal; Liam Galvin; Yoshikazu Inoue; R. Gisli Jenkins; Takeshi Johkoh; Ella A. Kazerooni; Masanori Kitaichi; Shandra L. Knight; George Mansour; Andrew G. Nicholson; Sudhakar N. J. Pipavath; Ivette Buendía-Roldán; Moisés Selman; William D. Travis; Simon L. F. Walsh; Kevin C. Wilson; *Am J Respir Crit Care Med* 198e44-e68.

# Remarques

- **Fibroscopie et LBA non recommandés si pattern de PIC certaine.**

**Conseillés dans les autres cas**

- **Histologie non recommandée si pattern de PIC certaine et suggerée dans les autres cas même en cas de pattern PIC probable**
- **Biopsie pulmonaire chirurgicale à priviliger par rapport aux cryobiopsies**
- **Role central de la DMD**

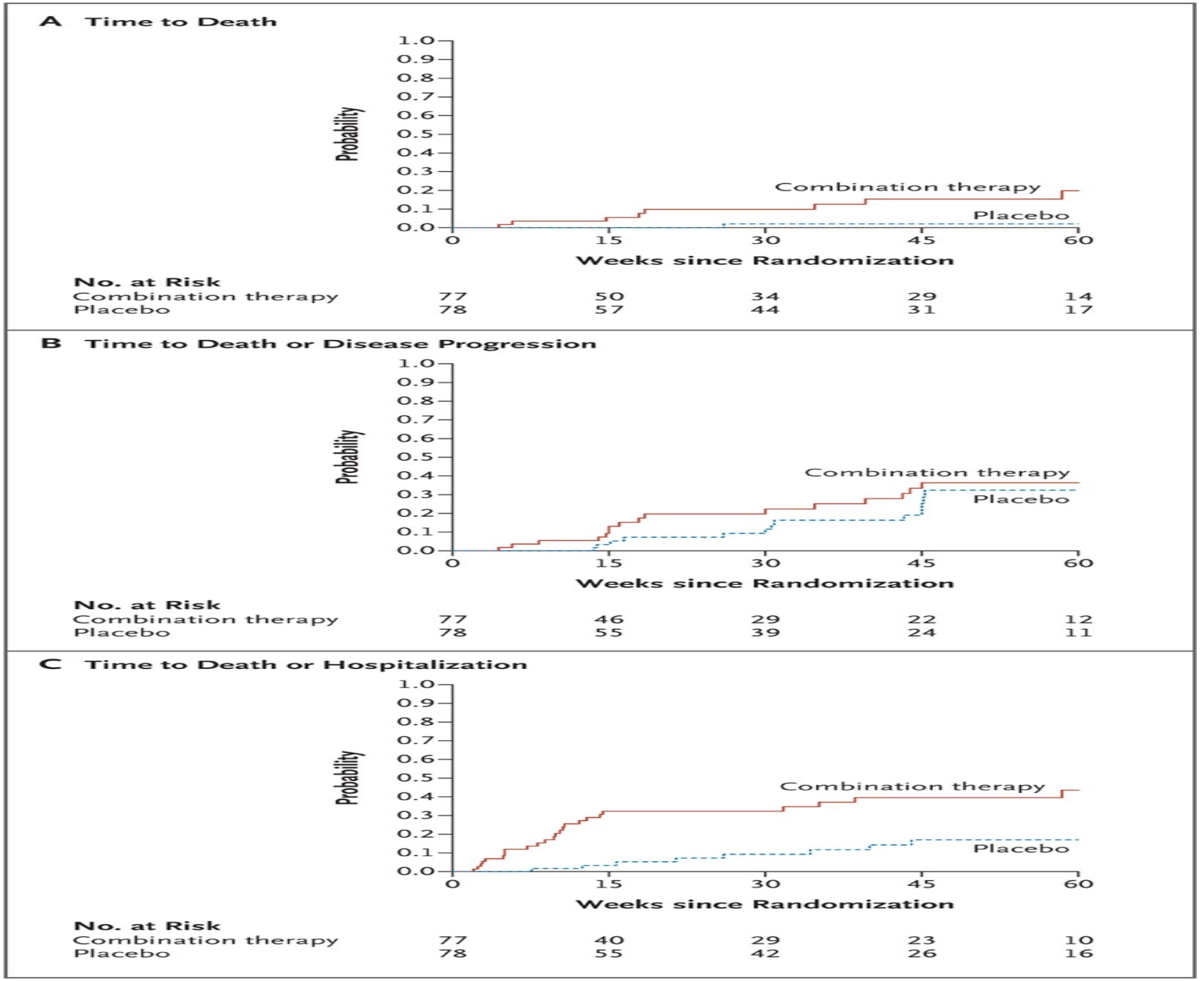
**Diagnostic Ability of a Dynamic Multidisciplinary Discussion in Interstitial Lung Diseases: A Retrospective Observational Study of 938 Cases.De Sadeleer LJ, Meert C, Yserbyt J Chest 2018**

| IPF suspected* | | Histopathology pattern | | | |
|---|---|---|---|---|---|
| | | UIP | Probable UIP | Indeterminate for UIP | Alternative diagnosis |
| HRCT pattern | UIP | IPF | IPF | IPF | Non-IPF dx |
| | Probable UIP | IPF | IPF | IPF (Likely)** | Non-IPF dx |
| | Indeterminate for UIP | IPF | IPF (Likely)** | Indeterminate for IPF*** | Non-IPF dx |
| | Alternative diagnosis | IPF (Likely)** /non-IPF dx | Non-IPF dx | Non-IPF dx | Non-IPF dx |

dx = diagnosis; HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.

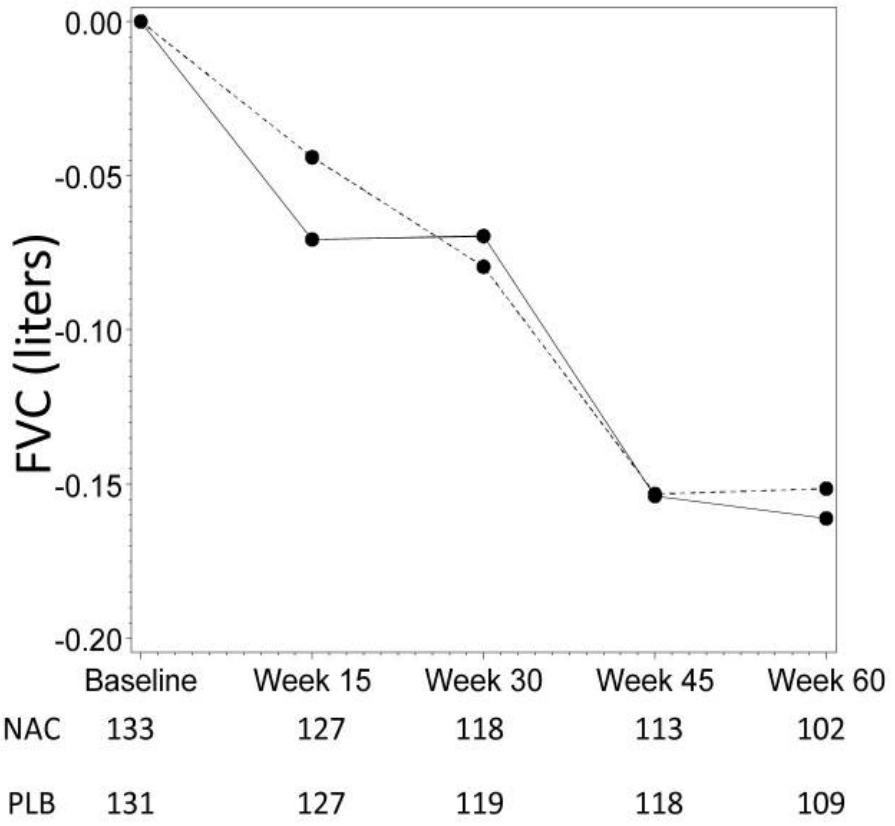
m J Respir Crit Care Med, 2018
Published in: Ganesh Raghu; Martine Remy-Jardin; Jeffrey L. Myers; Luca Richeldi; Christopher J. Ryerson; David J. Lederer; Juergen Behr; Vincent Cottin; Sonye K. Danoff; Ferran Morell; Kevin R. Flaherty; Athol Wells; Fernando J. Martinez; Arata Azuma; Thomas J. Bice; Demosthenes Bouros; Kevin K. Brown; Harold R. Collard; Abhijit Duggal; Liam Galvin; Yoshikazu Inoue; R. Gisli Jenkins; Takeshi Johkoh; Ella A. Kazerooni; Masanori Kitaichi; Shandra L. Knight; George Mansour; Andrew G. Nicholson; Sudhakar N. J. Pipavath; Ivette Buendía-Roldán; Moisés Selman; William D. Travis; Simon L. F. Walsh; Kevin C. Wilson; *Am J Respir Crit Care Med* 198e44-e68.

# 2012 Essai Panther



# NAC

**Figure 2A**




**NAC – solid, Placebo – dashed**

**Pas de différence également sur la mortalité et les exacerbations**

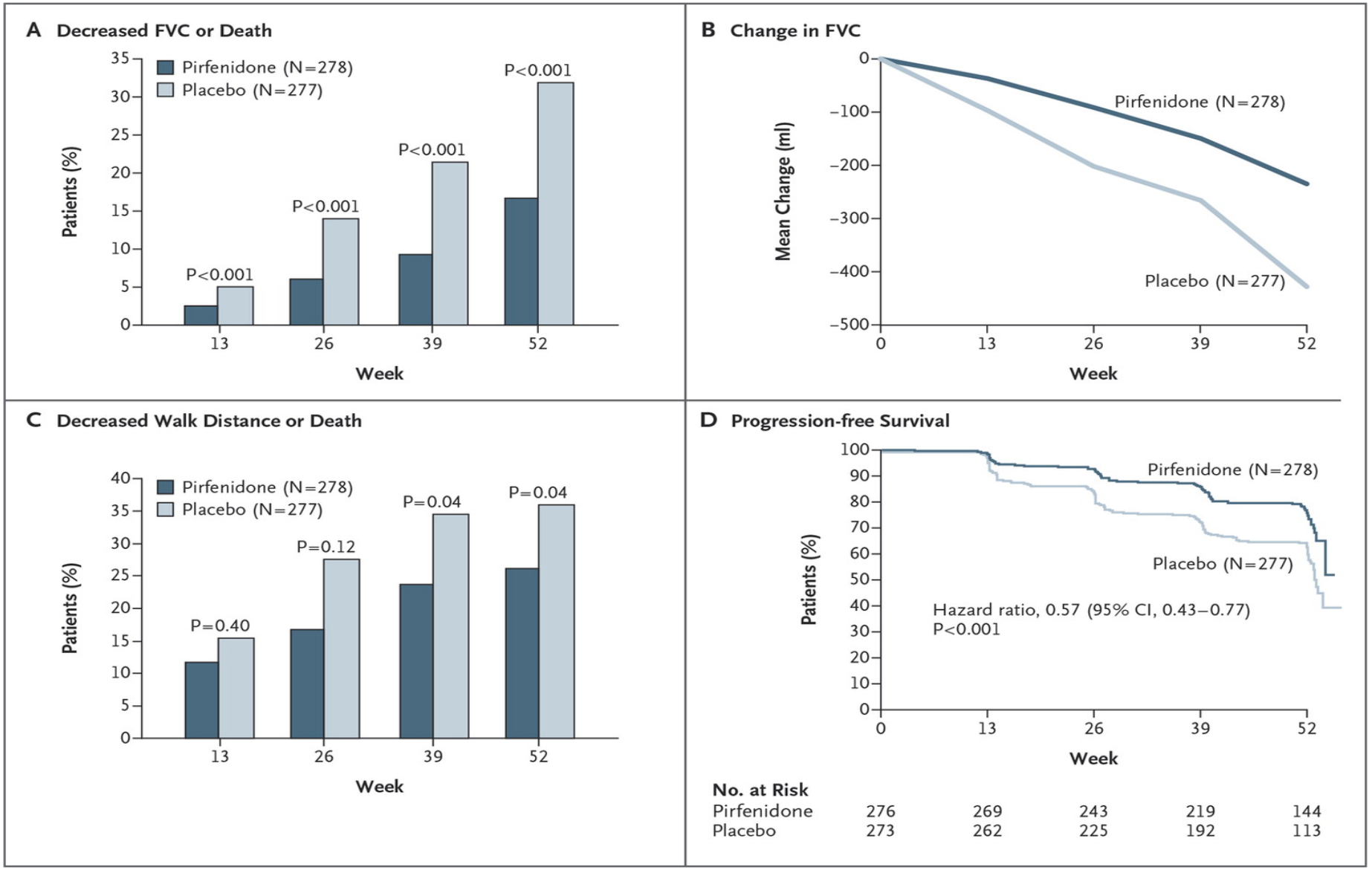
***Martinez FJ, de Andrade JA, Anstrom KJ, King TE Jr, Raghu G.cN Engl J Med 2014 May 29***

# Transplantation pulmonaire

- **Evaluation précoce dans un centre de transplation pulmonaire pour tout patient de moins de 65 ans ayant une FPI en l'absence de contre indication quelque soit les EFR.**
- **Soit dès l'instauration d'un traitement  anti fibrosant**
- **Quand inscrire : Déclin de la CVF de plus de 10% en 10 mois ou déclin de la DLCO de plus de 15% en 6 mois, diminution de 50 m au TM6 en 6 mois ( distance inférieure à 220 m ou désaturation à moins de 88%)**
- **Transplantation bi ou monopulmonaire**
- **Pour les patients de plus de 65 ans : selon l'état général, les comorbidités : à considérer au cas par cas**

**A consensus document for the selection of lung transplant candidates: 2014 - An update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation Well et al**

# Pirfenidone




**Talmadge E. King, JrA Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis, NEJM**

# Pirfenidone

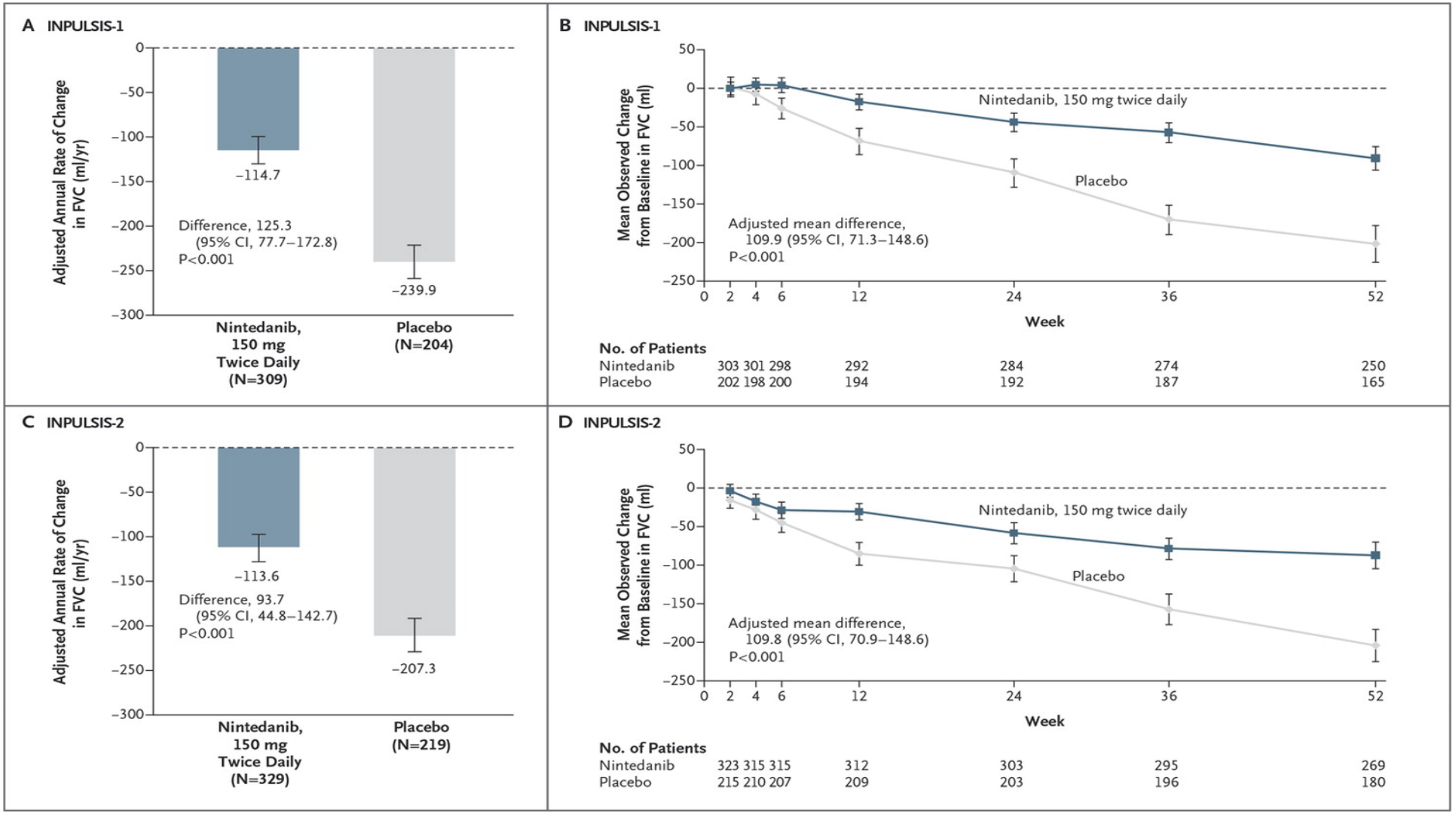
**Table 2. Mortality in the ASCEND and CAPACITY Trials.***

| Variable | Pirfenidone | Placebo | Hazard Ratio (95% CI)† | P Value‡ |
|---|---|---|---|---|
| ASCEND trial | | | | |
| No. of patients | 278 | 277 | | |
| Death — no. (%) | | | | |
| From any cause | 11 (4.0) | 20 (7.2) | 0.55 (0.26–1.15) | 0.10 |
| Related to idiopathic pulmonary fibrosis§ | 3 (1.1) | 7 (2.5) | 0.44 (0.11–1.72) | 0.23 |
| Pooled data from ASCEND and CAPACITY trials | | | | |
| No. of patients | 623 | 624 | | |
| Death — no. (%) | | | | |
| From any cause | 22 (3.5) | 42 (6.7) | 0.52 (0.31–0.87) | 0.01 |
| Related to idiopathic pulmonary fibrosis§ | 7 (1.1) | 22 (3.5) | 0.32 (0.14–0.76) | 0.006 |

* Data from the two CAPACITY studies[8] were censored at 1 year to standardize the follow-up for the three studies.
† Hazard ratios are for the pirfenidone group, as compared with the placebo group, and were calculated with the use of the Cox proportional-hazards model.
‡ P values were calculated with the use of the log-rank test.
§ Death related to idiopathic pulmonary fibrosis was defined as death that occurred during the period from randomization to 28 days after the last dose of the study drug. This category was evaluated in a blinded fashion by an independent mortality-assessment committee in the ASCEND trial and by clinical investigators in the CAPACITY trials.

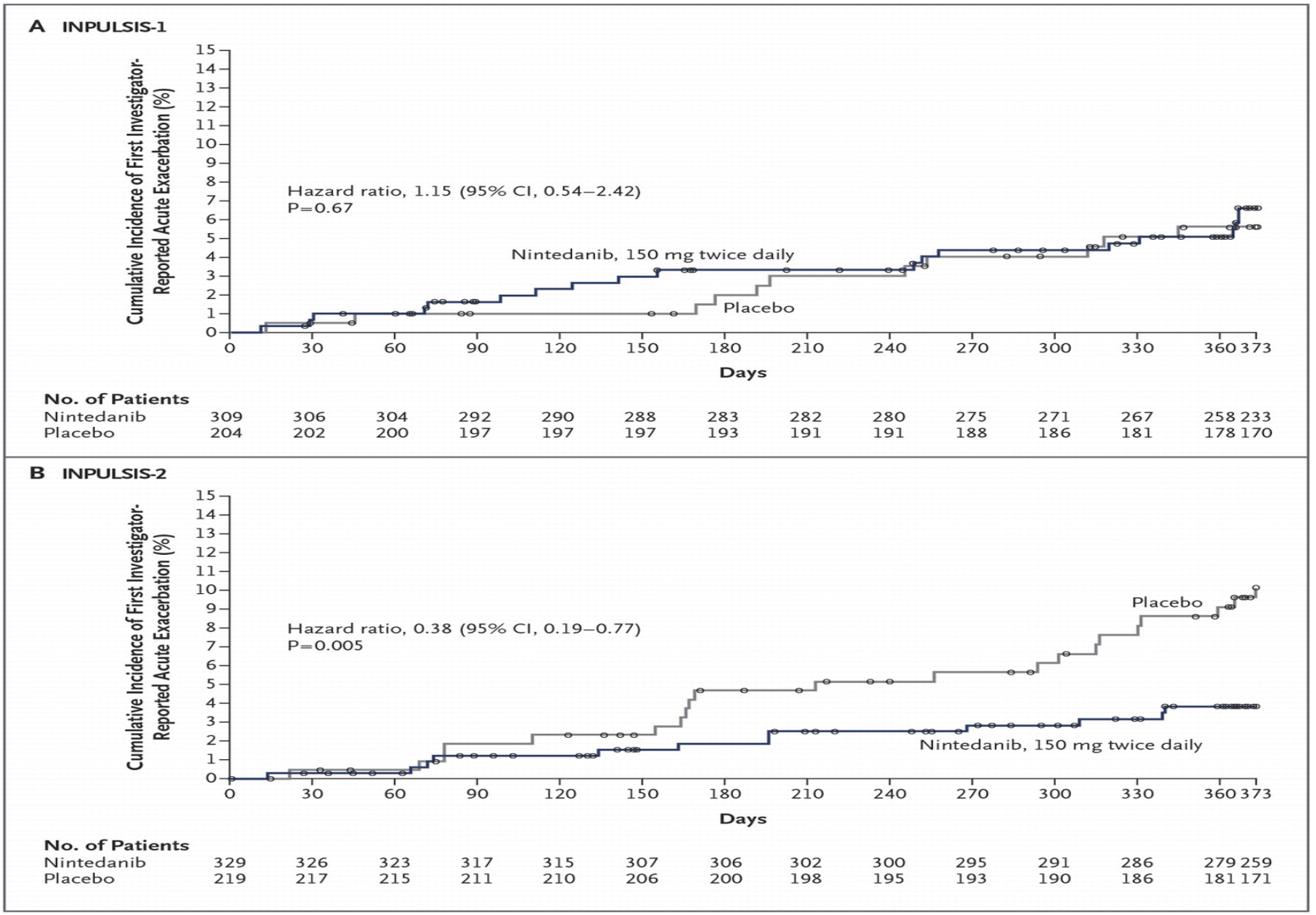
**Talmadge E. King, JrA Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis, NEJM**

# Nintedanib




Luca Richeld, Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis, NEJM

# Nintedanib




Luca Richeld, Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis, NEJM

# Récapitulatif

| | Nintedanib | Pirfenidone |
|---|---|---|
| Objectif | Ralentir declin CVF, diminuer les exacerbations | Ralentir déclin CVF<br>Diminuer les exacerbations |
| Indication | FPI légère à modérée | FPI légère à modérée |
| dose | 150 mg x 2/j | 801mg x 3/j |
| Effets indésirables | diarrhées | Anorexie, nausées, vomissements et photosensibilité |
| Surveillance bilan hépatique | oui | oui |
| Précautions | Majoration du risque de saignement | Diminution de l'efficacité si poursuite du tabagisme<br>Attention aux interactions médicamenteuses et avec le jus de pamplemousse. |

# Association

- **Des 2 antifibrosants :Etudes de tolérance disponibles**

**Pas d'indication pour l'heure à prescrire les deux en assocations**

- **Un antifibrosant et une autre molécule**

**- anti fibrosante en cours de développement (pentraxin 2, GLPG1690**

**Effect of Recombinant Human Pentraxin 2 vs Placebo on Change in Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis: A Randomized Clinical Trial. Raghu G et al. JAMA 2018**

- **Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial. Maher TM et al**

**- Cotrimoxazole** **Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: a randomised controlled trial. Shulgina L et al. Thorax 2013. + EME-TIPAC**

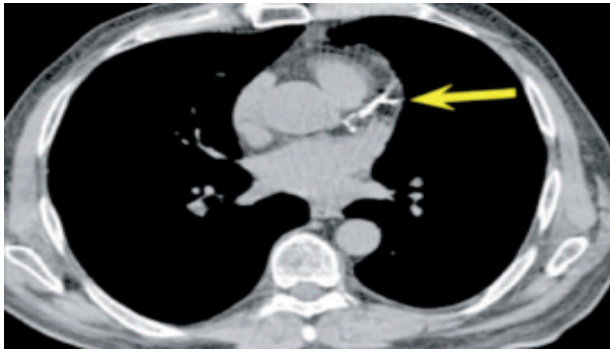
**- IPP**

**- ttt anti HTAP**

- **Nécessité de nouveaux essais**

# Traitement FPI : ne pas oublier

- Sevrage tabagique
- Vaccination grippe et pneumocoque
- Recherche des foyers dentaires et ORL
- Oxygène
- Prise en charge comorbidités :SAS, BPCO, obésité, dénutrition, syndrome dépréssif, pathologies cardiovasculaires ( cardiopathie ischémique notamment)
- Dépistage de l'HTP
- Augmentation du risque de cancer pulmonaire indépendamment du tabagisme. TDM annuel
- Prise en charge du reflux si présent



# Non recommandé

- Colchicine
- AVK
- Ciclosporine
- Simtuzumab
- Étanercept
- Interféron-gamma-1b
- Carlumab
- Antagonistes des récepteurs de l’endothéline-1 ( Ambrisentan)
- Riociguat
- Anti IL13 et IL4

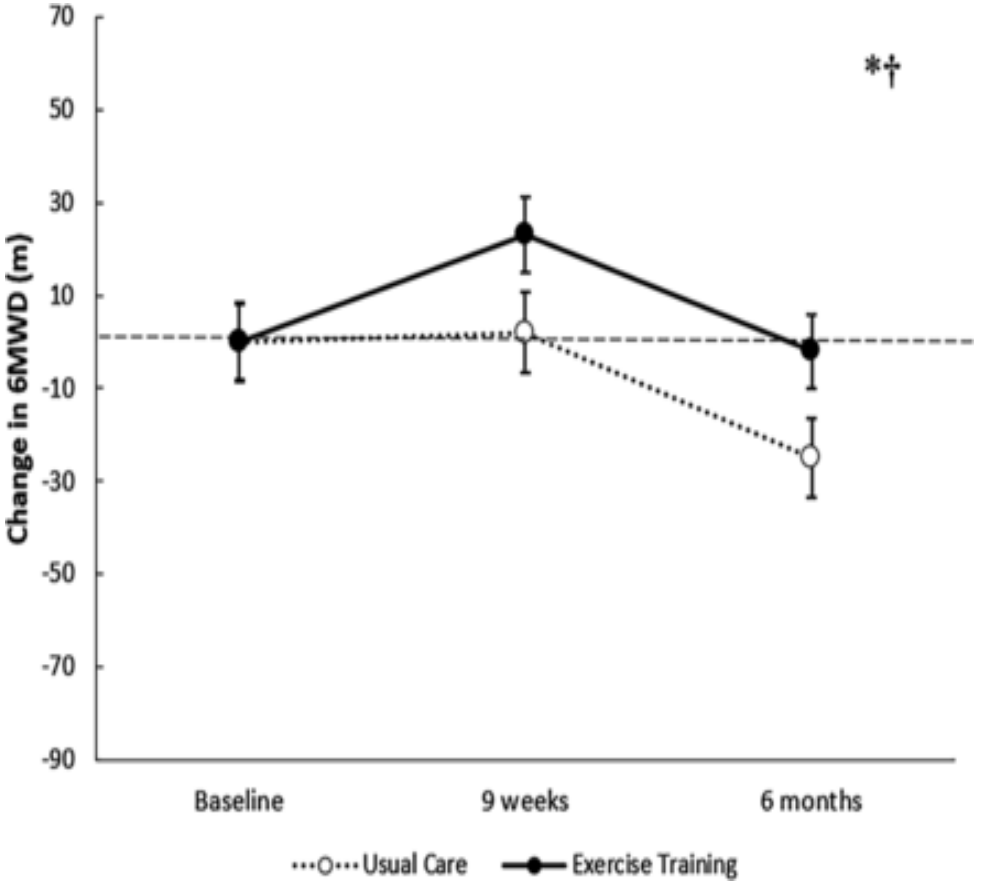
# HTAP

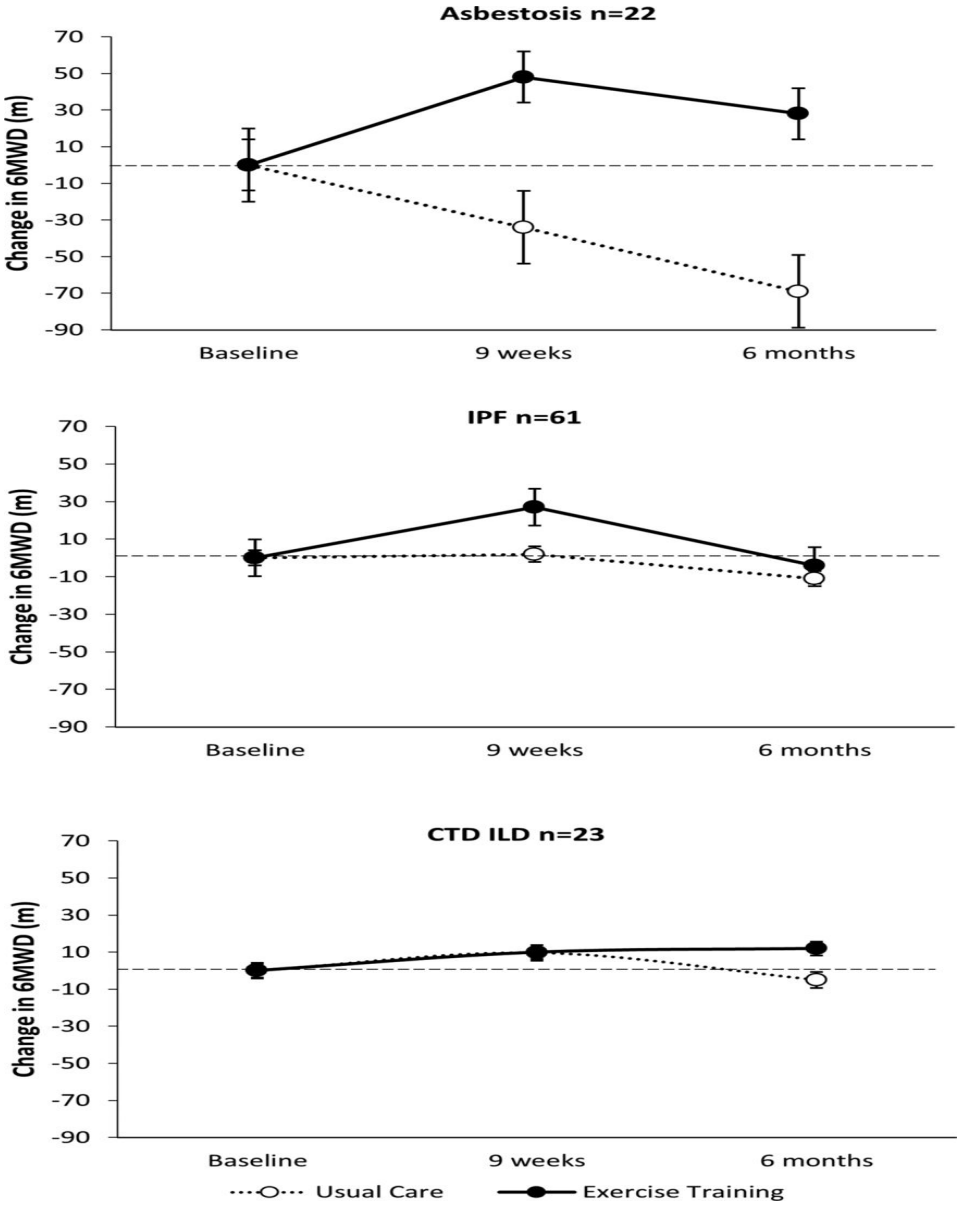
- **Dépistage par ETT**
- **Cathérisme cardiaque droit pour confirmation**
- **En cas d'hypertension artérielle pré capillaire disproportionné,  il n'est pas recommandé de prescrire un traitement de l'HTAP**
- **Contre indication rociguat et ambrisentan**

- **Nintedanib +  sidénafil . FPI  avec DLCO inférieure à 35% pas de différence sur les scores de dyspnée**

*Martin Kolb, M.D., Ganesh Raghu, M.D., Athol U. Wells et al NEJM novembre 2018*

# Réhabilitation




**The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial Leona M Dowman, Christine F McDonald Catherine J Hill et al BMJ 2017**

# Formes génétiques

- **Analyse gène télomères**

**- Age inférieur à 50 ans en l'absence de mutations surfactant**

**- ATCD familiaux**

**- syndrome de téloméropathie personnel ou dans la famille : Atteinte hépatique ; hématologique ou cutanéo muqueuse**

- **Analyse du gène du surfactant**

**- Age inférieur à 50 ans**

**- Détresse respiratoire néonatale chez un patient né à terme**

**- Forme familliale chez un patient de 50 ans sans mutation des gènes des télomères**

# Danazol et téloméropathie

- **Signal positif avec une tendance à la stabilisation CVF et DLCO sous traitement**
- **Faible effectif et pas l'objectif intial de l'étude.**
- **Necessité d'études supplémentaires sur plus de patients et centrées sur le poumon.**
- **PHRC en cours en France**

**Danazol Treatment for Telomere Diseases.Townsley DM et al. N Engl J Med. (2016)**

# Conclusion

- **Pathologie grave**
- **Necessité d'une prise en charge dans des centres spécialisés.**
- **Rôle majeur de la DMD dans le diagnostic**
- **Progrès thérapeutique important durant les 5 dernières années avec les traitements anti fibrosant ( Nintedanib et Pirfenidone)**
- **Toujours se poser la question de la faisabilité d'une transplantation pulmonaire. Si oui adresser précocement les patients.**

# IPAF définitions

- 1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) and,
- 2. Exclusion of alternative aetiologies and,
- 3. Does not meet criteria of a defined connective tissue disease and,
- 4. At least one feature from at least two of these domains:
- A. Clinical domain
- B. Serologic domain
- C. Morphologic domain

- ***Aryeh Fischer and al, An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features***

# Serologic domain

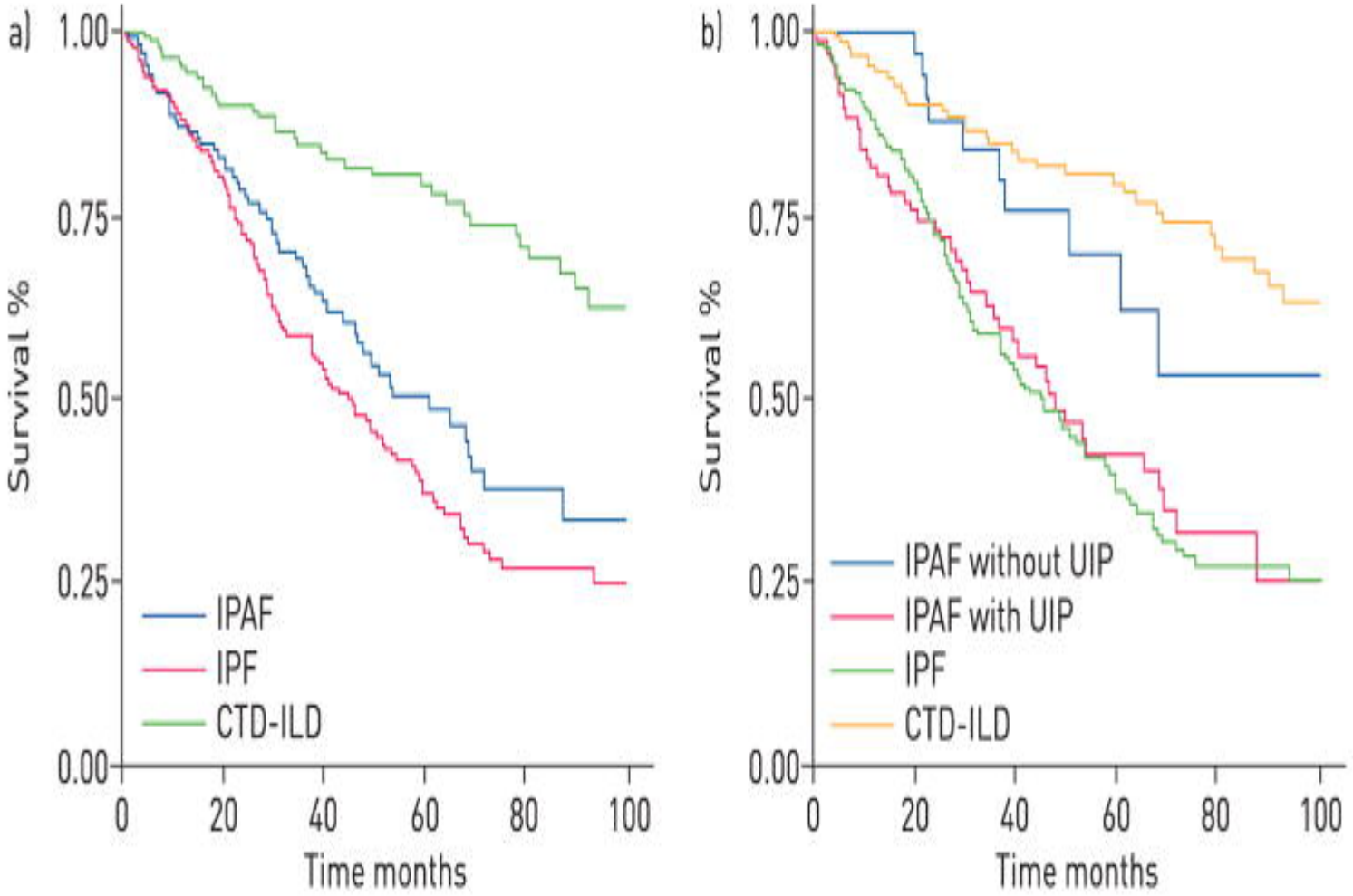
- 1. ANA ⩾1:320 titre, diffuse, speckled, homogeneous patterns or
- a. ANA nucleolar pattern (any titre) or
- b. ANA centromere pattern (any titre)
- 2. Rheumatoid factor ⩾2× upper limit of normal, Anti-CCP
- 4. Anti-dsDNA
- 5. Anti-Ro (SS-A), Anti-La (SS-B)
- 7. Anti-ribonucleoprotein
- 8. Anti-Smith
- 9. Anti-topoisomerase (Scl-70)
- 10. Anti-tRNA synthetase (e.g. Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS), Anti-PM-Scl , Anti-MDA-5

# Morphologic domain

- 1. Suggestive radiology patterns by HRCT
- - NSIP, OP, NSIP with OP overlap,  LIP
- 2. Histopathology patterns or features by surgical lung biopsy:
- - NSIP, OP, NSIP with OP overlap, LIP, Interstitial lymphoid aggregates with germinal centres, Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
- 3. Multi-compartment involvement (in addition to interstitial pneumonia) - - - - Unexplained pleural effusion or thickening,
- - Unexplained pericardial effusion or thickening
- - Unexplained intrinsic airways disease# (by PFT, imaging or pathology)
- - Unexplained pulmonary vasculopathy

# Morphologic domain

- 1. Suggestive radiology patterns by HRCT
- - NSIP, OP, NSIP with OP overlap,  LIP
- 2. Histopathology patterns or features by surgical lung biopsy:
- - NSIP, OP, NSIP with OP overlap, LIP, Interstitial lymphoid aggregates with germinal centres, Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
- 3. Multi-compartment involvement (in addition to interstitial pneumonia) - - - - Unexplained pleural effusion or thickening,
- - Unexplained pericardial effusion or thickening
- - Unexplained intrinsic airways disease# (by PFT, imaging or pathology)
- - Unexplained pulmonary vasculopathy




Justin M. Oldham : Characterisation of patients with interstitial pneumonia with autoimmune features, ERJ 2016