Broncho-Pneumopathie Chronique Obstructive
Nouveaux concepts

(Photo : J.-Marc Blache/Mission)

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Université Grenoble Alpes Grenoble, France

AER, Lyon, 14-11-2013

Conflits d'intérêts 3 dernières années
déplacements, conférences, fonds de recherche

- **Actélion**
- **Astra Zeneca**
- **Bayer**
- **Boehringer Ingelheim**
- **GlaxoSmithKline**
- **Lilly**
- **Novartis**
- **Pfizer**
- **Pierre Fabre**
- **Sanofi**
- *Therakos*
- *PneumRx, Medwin, Aeris, Holaira*
- *AGIR@dom, Orkyn, Vitalaire, IPS*

Global Initiative for Chronic

**O**bstructive

Lung

Disease

http://www.goldcopd.org

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Definition of COPD

- **COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.**

- **Exacerbations and comorbidities contribute to the overall severity in individual patients.**

Médicine Systémique & Soins innovants
Nouvelle Taxonomie & RCT multimodaux

Qu'est-ce que l'Approche systémique ?

Qualité de vie Symptômes

Fonctionnel

Clinique

Cellulaire

Moléculaire

Auffray *et al*. (2009) Genome Med 2009;1:2 & Chest 2010; 137:1410-6
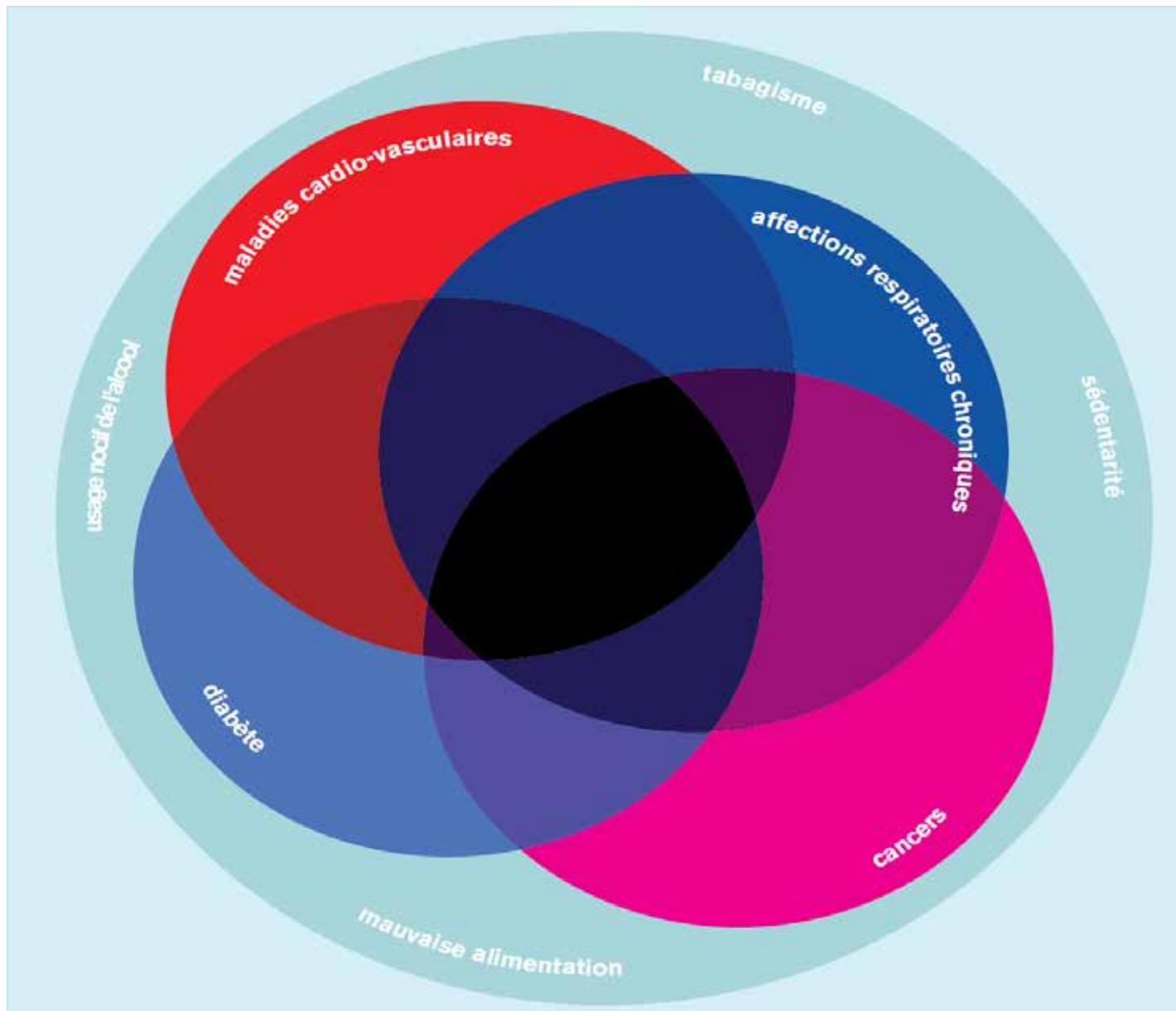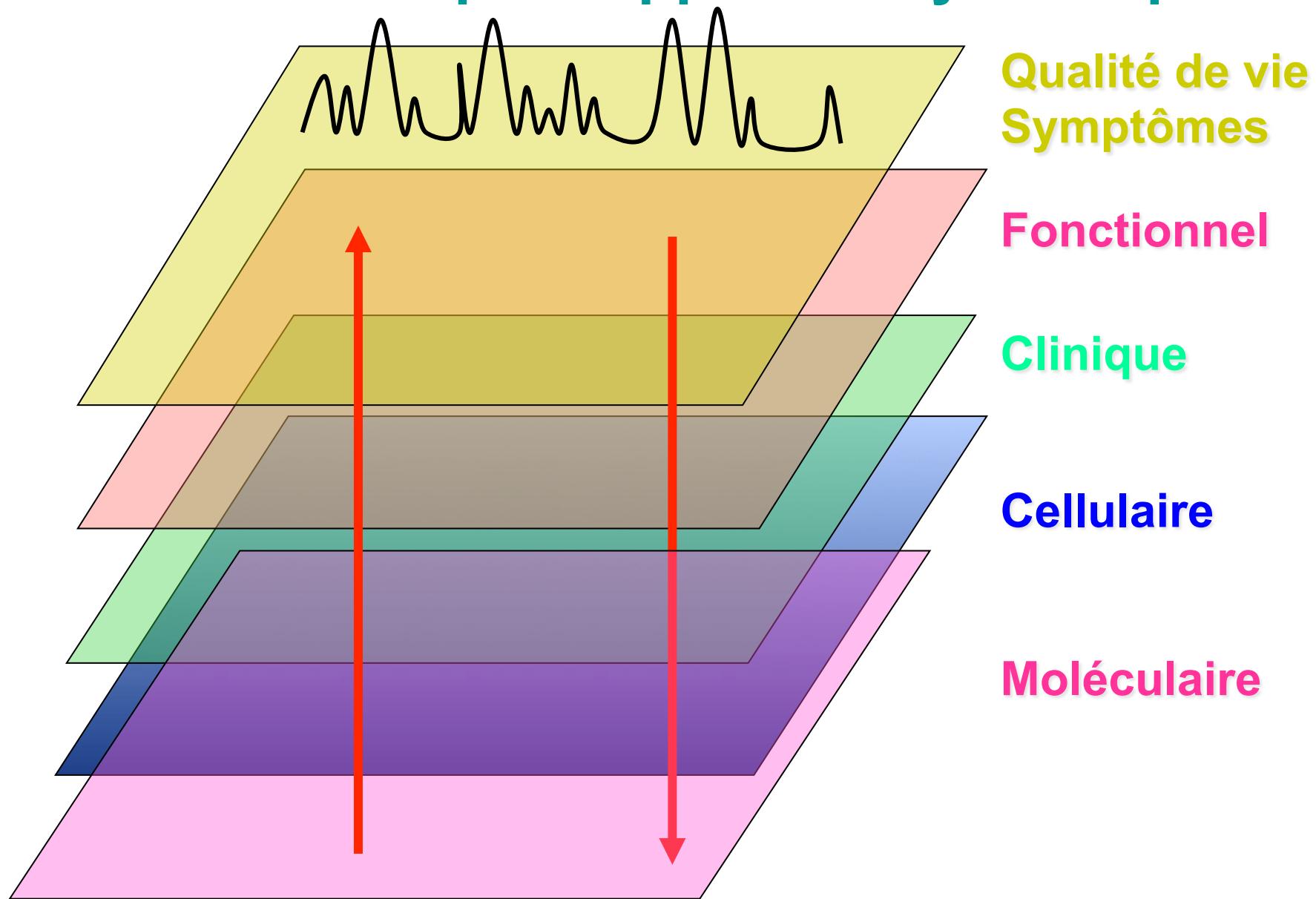
Qu'est-ce que l'Approche Systémique ?

- **Complexité de la biologie et des maladies**

- **3 niveaux de compréhension**
  - **briques ou modules**
  - **interconnexions**   **Fonction *versus* Dysfonction**
  - **dynamique du système**

- **2 types d'informations**
  - **signaux environnementaux : air, exercice, nutrition, sommeil, stress, « exposome »**
  - **informations digitales génomiques**

- **Des informations aux phénotypes: réseaux et machines moléculaires**

Hood *et al.* Biotechnol. J. 2012;7:992-1001   7

Causes décès Monde 2008
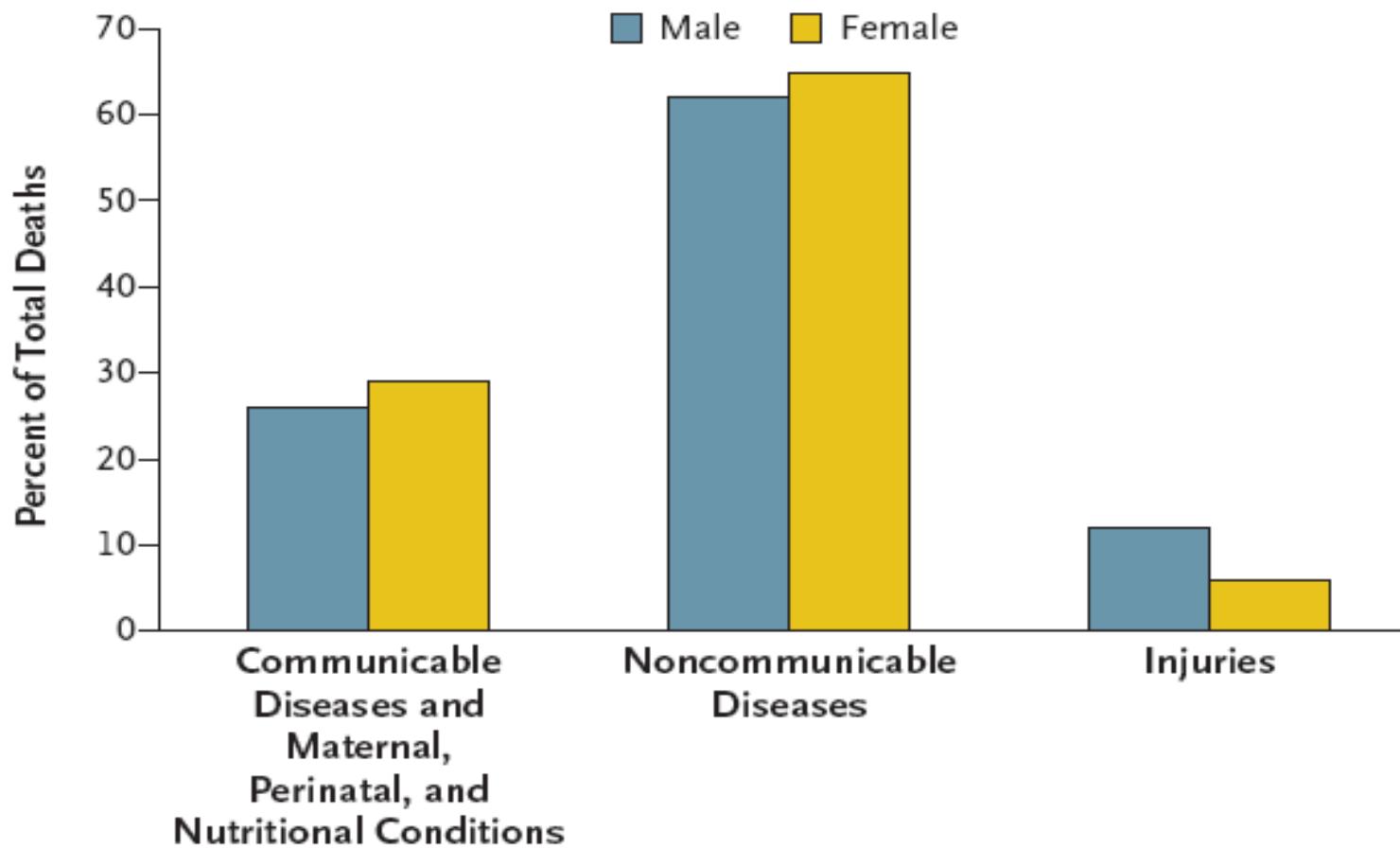
Figure 1. Global Deaths According to Cause and Sex, 2008.
Adapted from the World Health Organization (WHO).[4]

Causes décès et handicaps Monde 2008

A Global Deaths
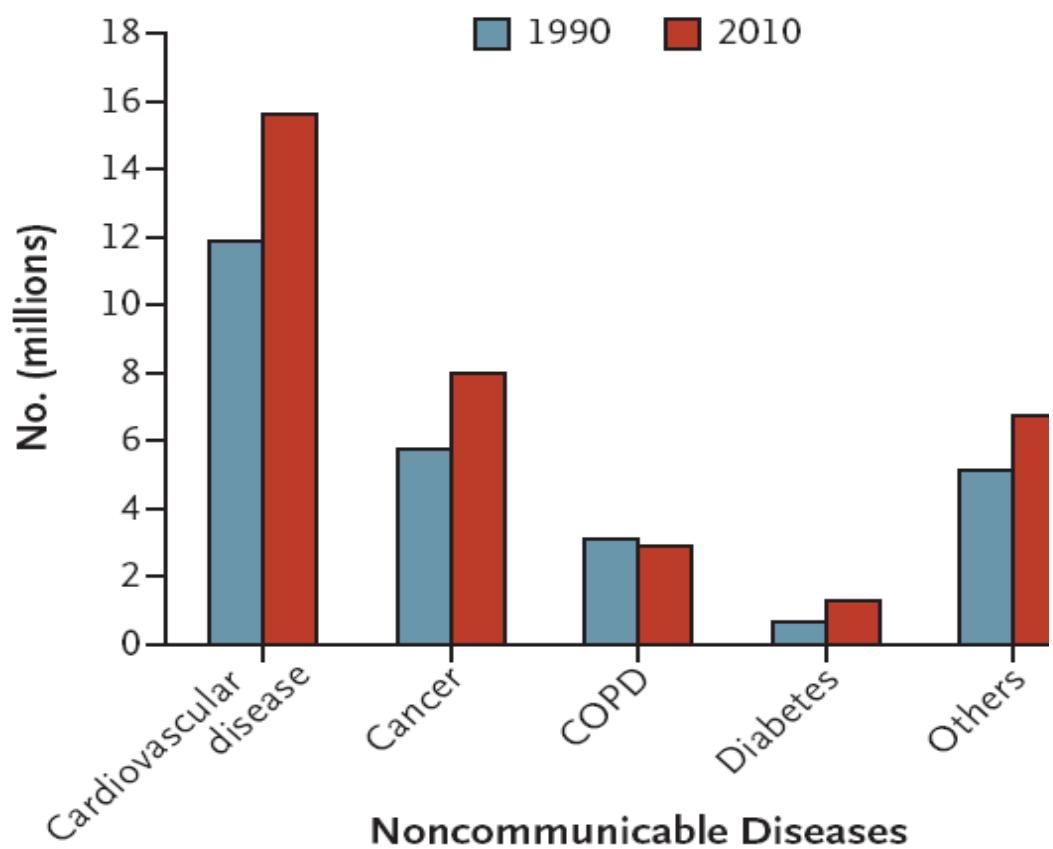
B Global DALYs
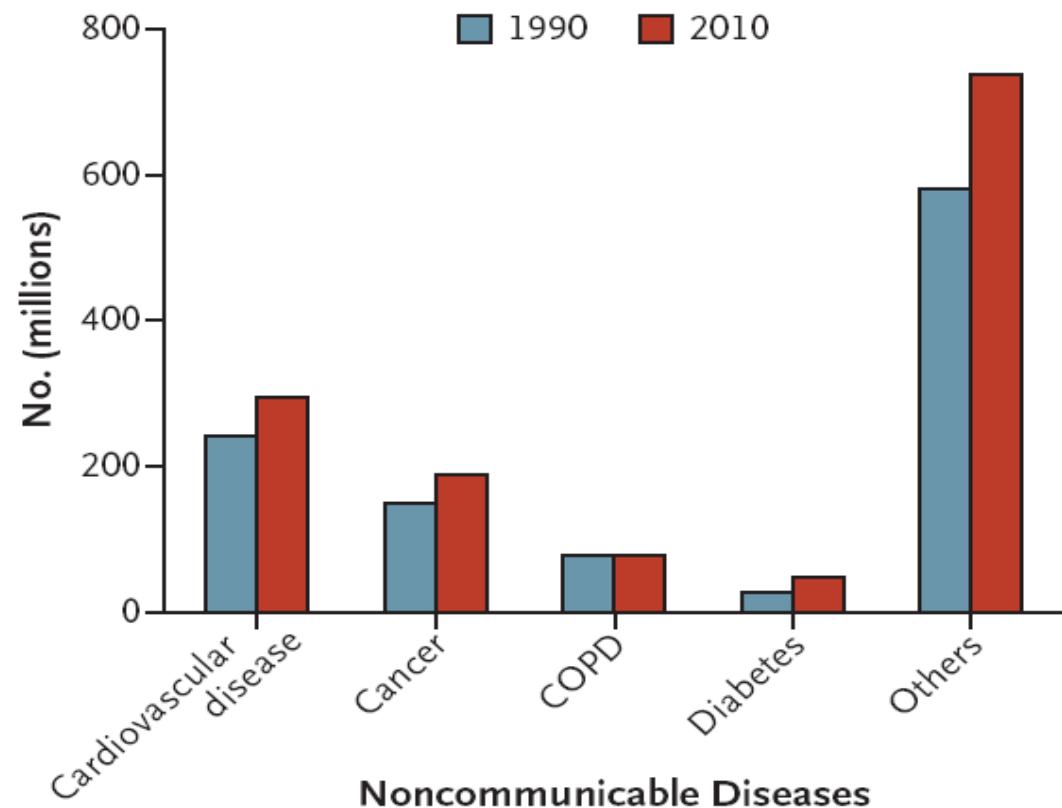
Décès aux USA 1950-2010 / 100 000 h /an


NEJM 2013;369:1336-43
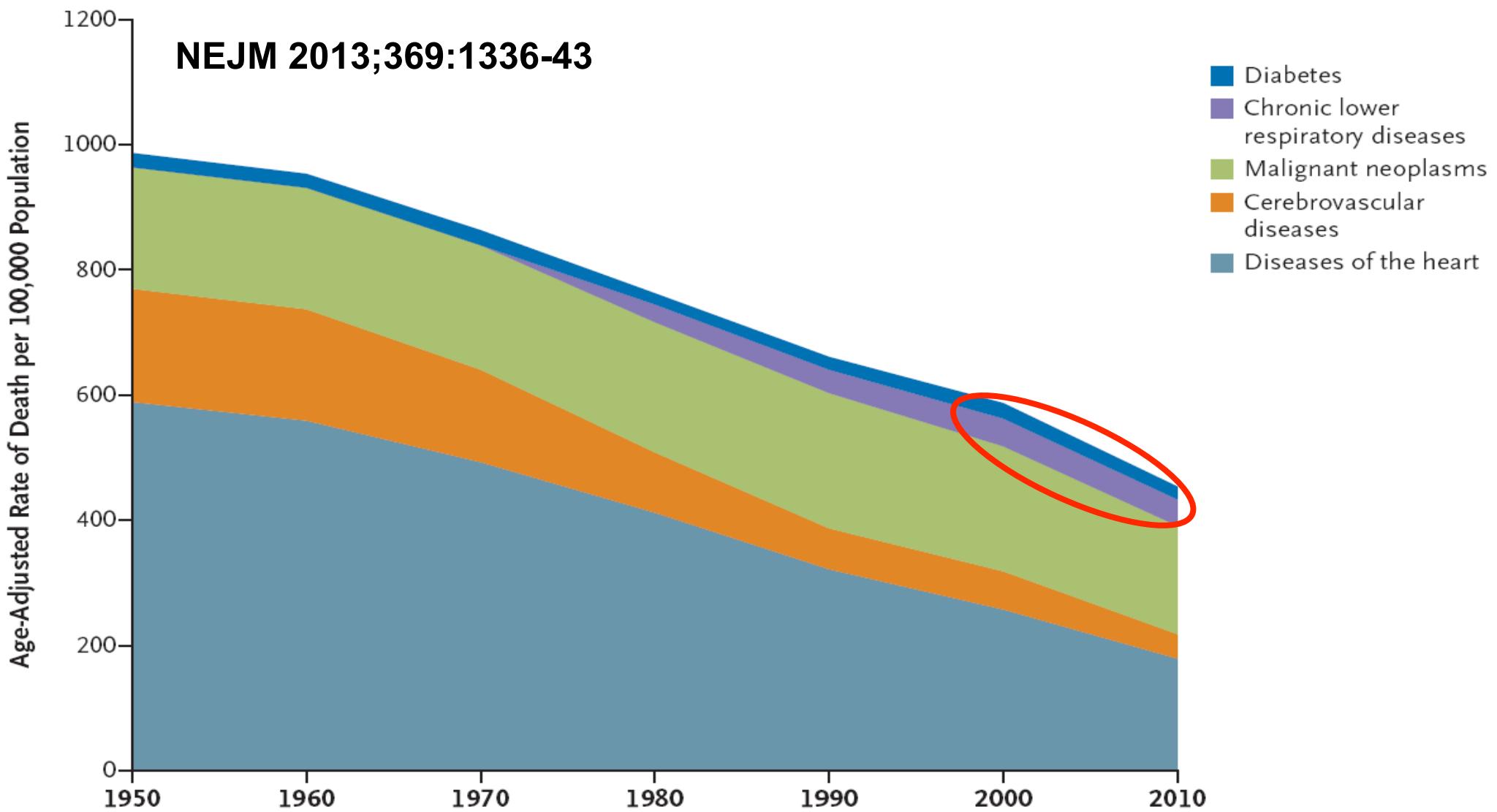
Figure 4. Declines in Rates of Death from Major Noncommunicable Diseases in the United States, 1950 to 2010.
Adapted from the National Center for Health Statistics, Centers for Disease Control and Prevention.[18]

Prévalence

- Mannino DM, Buist AS. Lancet 2007;370:765
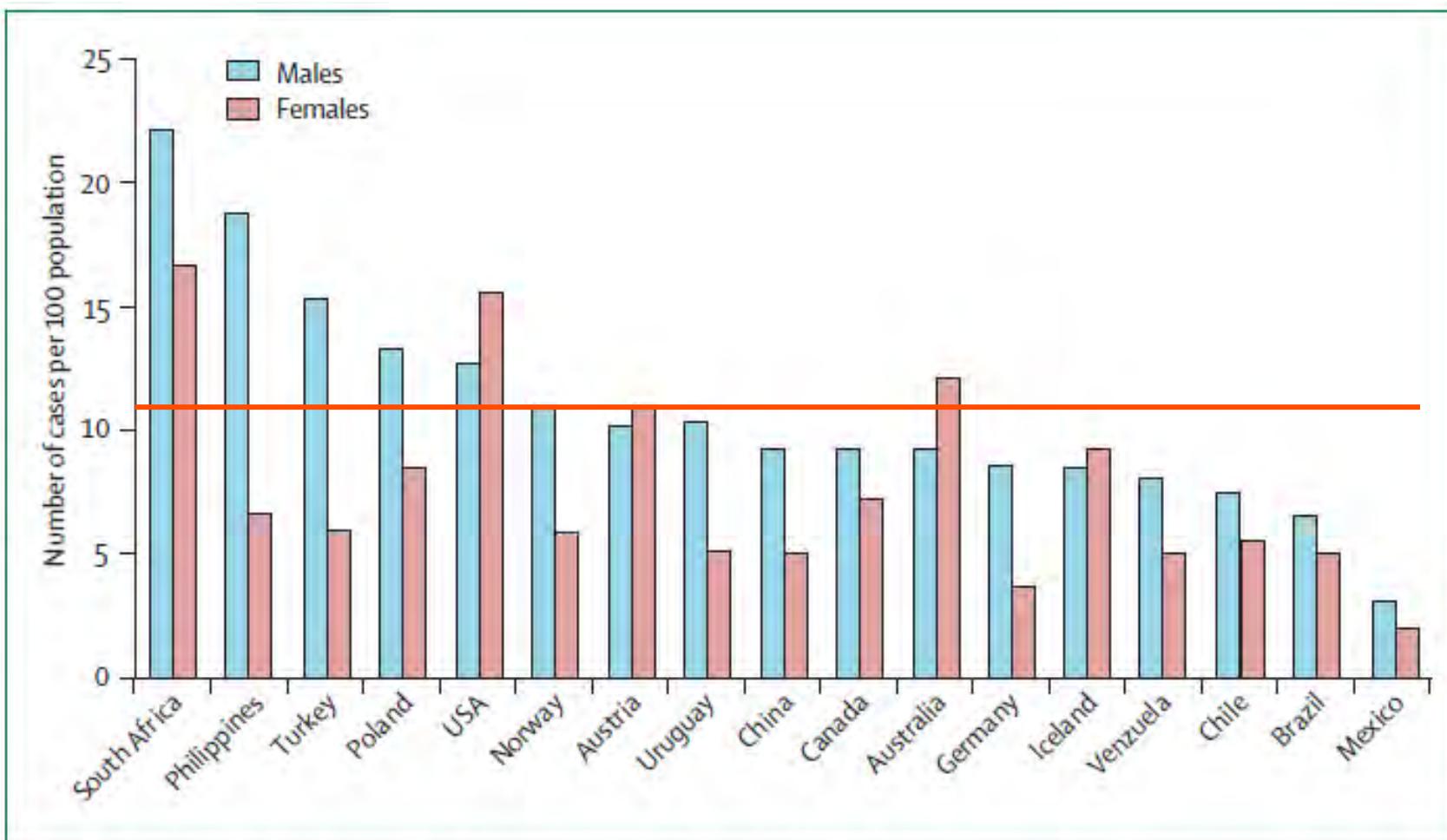
Figure 4: Estimated prevalence of GOLD stage 2 or higher COPD

Data taken from the PLATINO study[60] and the BOLD project.[26] Estimates are for small regions of the listed countries and do not necessarily represent national prevalence estimates.

BPCO en France

- **3,5 millions patients, 10 à 25% des cas reconnus**

- **3,5 milliards € / an**

- **3ème cause d'arrêts de travail**

- **100 000 sujets sous OLD**

- **17 000 décès annuels**

BPCO : réduction des débits expiratoires non totalement réversible, progressive et associée à une réponse inflammatoire anormale des poumons

Classification Internationale du Fonctionnement-CIF, OMS, 2001

Déficience	POUMON Stress Ox-Neutrophil Infl. Hypoxie →	SYSTEMIQUE Stress Ox-Neutrophiles Hypoxie
	VEMS SpO_2	IMC Muscles squelettiques
Activité	**Dyspnée**	**PM6**
Participation	**Qualité de Vie - Morbidité Mortalité**	

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Assessment of COPD: Goals

Determine the severity of the disease, its impact on the patient's health status and the risk of future events (for example exacerbations) to guide therapy. Consider the following aspects of the disease separately:

- current level of patient's symptoms
- severity of the spirometric abnormality
- frequency of exacerbations
- presence of comorbidities.

COPD Assessment Test (CAT)

Exemple: Je suis très heureux (heureuse) ⓪ ⓧ ② ③ ④ ⑤ Je suis très triste

POINTS

Je ne tousse jamais	⓪ ① ② ③ ④ ⑤	Je tousse tout le temps
Je n'ai pas du tout de glaires (mucus) dans les poumons	⓪ ① ② ③ ④ ⑤	J'ai les poumons entièrement encombrés de glaires (mucus)
Je n'ai pas du tout la poitrine oppressée	⓪ ① ② ③ ④ ⑤	J'ai la poitrine très oppressée
Quand je monte une côte ou une volée de marches, je ne suis pas essoufflé(e)	⓪ ① ② ③ ④ ⑤	Quand je monte une côte ou une volée de marches, je suis très essoufflé(e)

COPD Assessment Test (CAT)

Je ne suis pas limité(e) dans mes activités chez moi	0 1 2 3 4 5	Je suis très limité(e) dans mes activités chez moi
Je ne suis pas inquièt(e) quand je quitte la maison, en dépit de mes problèmes pulmonaires	0 1 2 3 4 5	Je suis très inquièt(e) quand je quitte la maison, en raison de mes problèmes pulmonaires
Je dors bien	0 1 2 3 4 5	Je dors mal à cause de mes problèmes pulmonaires
Je suis plein(e) d'énergie	0 1 2 3 4 5	Je n'ai pas d'énergie du tout

Modified MRC (mMRC)Questionnaire

PLEASE TICK IN THE BOX THAT APPLIES TO YOU
(ONE BOX ONLY)

mMRC Grade 0. I only get breathless with strenuous exercise. ☐

mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill. ☐

mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level. ☐

mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level. ☐

mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing. ☐

Spirometry: Obstructive Disease

Classification of Severity of Airflow Limitation in COPD*

In patients with $FEV_1/FVC < 0.70$:

GOLD 1: Mild $\qquad$ $FEV_1 \geq 80\%$ **predicted**

GOLD 2: Moderate $\qquad$ $50\% \leq FEV_1 < 80\%$ **predicted**

GOLD 3: Severe $\qquad$ $30\% \leq FEV_1 < 50\%$ **predicted**

GOLD 4: Very Severe $\quad$ $FEV_1 < 30\%$ **predicted**

Based on Post-Bronchodilator FEV_1
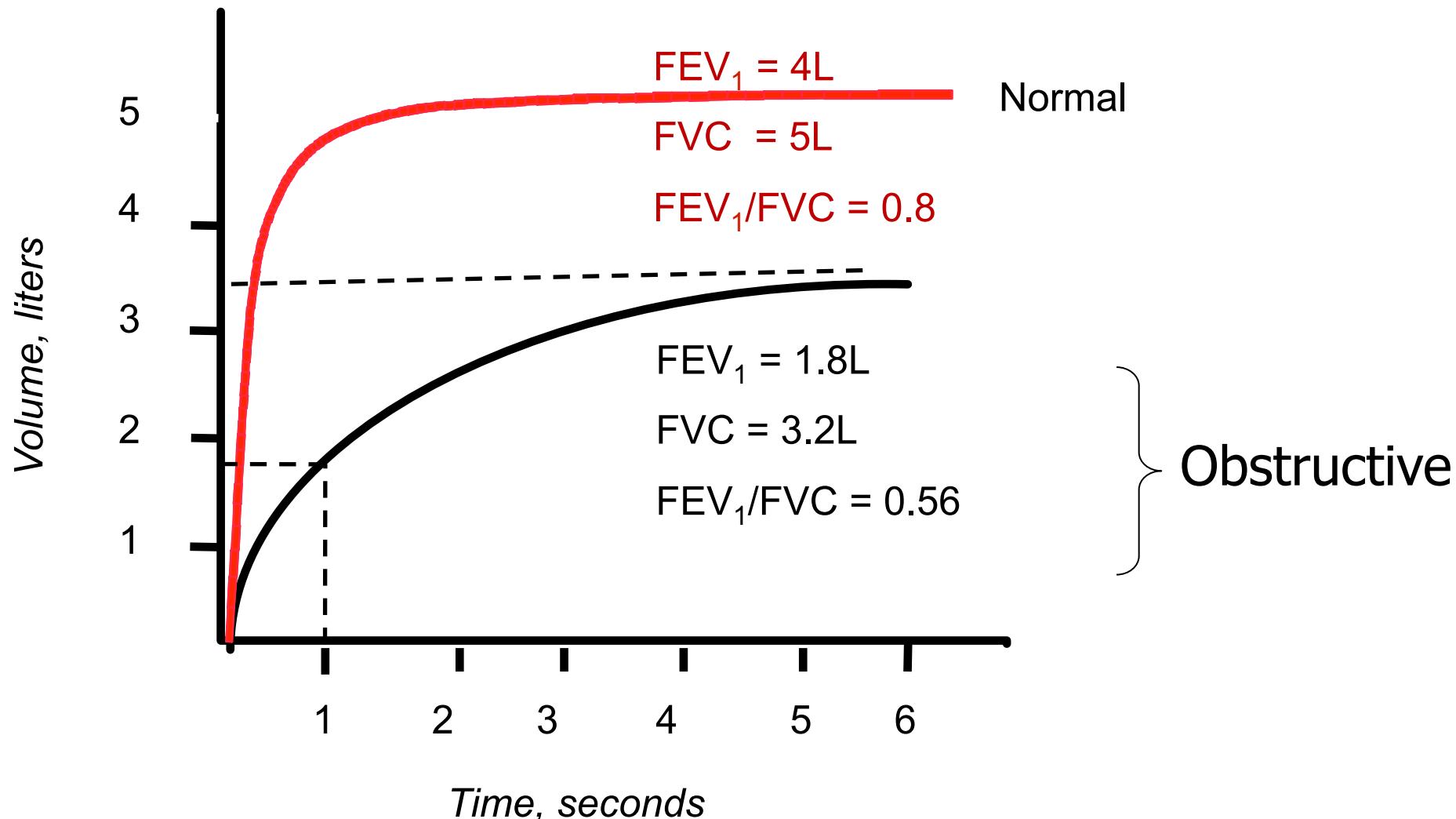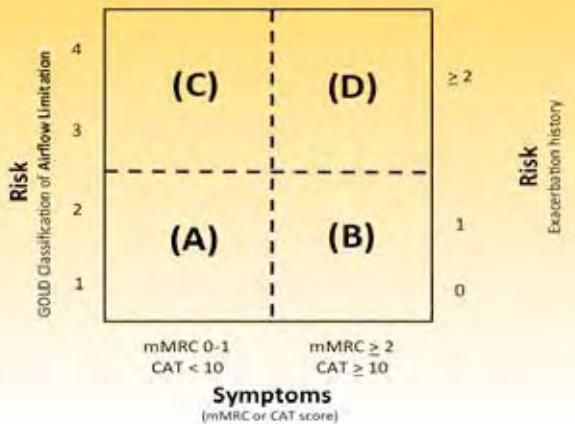
Global Strategy for Diagnosis, Management and Prevention of COPD

Combined Assessment of COPD

*When assessing risk, choose the **highest** risk according to GOLD grade or exacerbation history. One or more hospitalizations for COPD exacerbations should be considered high risk*

Patient	Characteristic	Spirometric Classification	Exacerbations per year	mMRC	CAT
A	Low Risk Less Symptoms	GOLD 1-2	≤ 1	0-1	< 10
B	Low Risk More Symptoms	GOLD 1-2	≤ 1	≥ 2	≥ 10
C	High Risk Less Symptoms	GOLD 3-4	≥ 2	0-1	< 10
D	High Risk More Symptoms	GOLD 3-4	≥ 2	≥ 2	≥ 10

Assess COPD Comorbidities

COPD patients are at increased risk for:

- Cardiovascular diseases
- Osteoporosis
- Respiratory infections
- Anxiety and Depression
- Diabetes
- Lung cancer

These comorbid conditions may influence mortality and hospitalizations and should be looked for routinely, and treated appropriately.

TABLE 1. PATIENTS' CHARACTERISTICS

	All Subjects ($n = 213$)
Age, yrs	63.6 ± 7.0
Male, %	59
BMI, kg/m^2	26.2 ± 5.1
FFMI, kg/m^2	17.0 ± 2.4
mMRC dyspnea grade	2.1 ± 1.09
Current smoker, %	28
Pack-years	46 ± 26
Long-term oxygen therapy, %	17
FEV_1, L	1.40 ± 0.54
FEV_1, % predicted	51.2 ± 16.9
FEV_1/FVC	0.40 ± 0.11
ITGV, % predicted	148 ± 33
TLCO, % predicted	56 ± 17
6MWD, m	470 ± 106
SGRQ, total score	51.3 ± 17.5
Updated BODE score	2.9 ± 2.5
Framingham 10-yr risk, %	9.4 ± 6.7

Clu... ve
Mea... ;
wit...

Lowie
Vanessa
Emiel F

New taxonomy in COPD
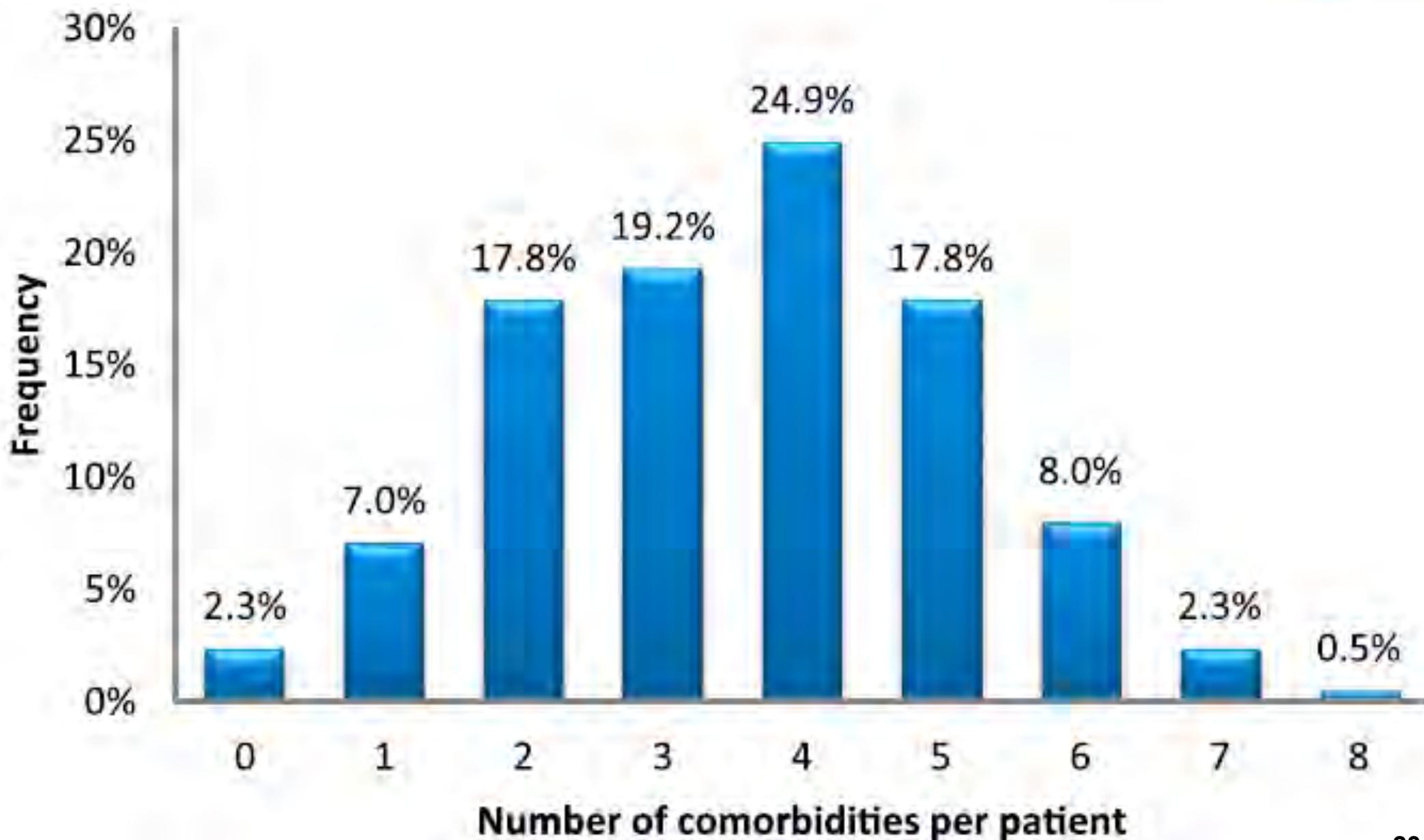
New taxonomy in COPD

TABLE 2. DETAILED DESCRIPTION OF THE FIVE CLUSTERS IN TERMS OF THE NUMBER OF COMORBIDITIES AND THE PREVALENCE OF EACH COMORBIDITY

| Comorbidities	Cluster 1: Less Comorbidity	Cluster 2: Cardiovascular	Cluster 3: Cachectic	Cluster 4: Metabolic	Cluster 5: Psychologic
N	67	49	44	33	20
Number of comorbidities	2.5 ± 1.4*	3.8 ± 1.7	4.2 ± 1.4[†]	4.4 ± 1.1[†]	4.1 ± 1.8
Renal impairment, %	16	24	45[†]	9	5
Anemia, %	9	4	2	3	5
Hypertension, %	3*	98[†]	43	100[†]	5*
Obesity, %	30	14	0*	61[†]	15
Underweight, %	0*	0*	66[†]	3*	0
Muscle wasting, %	12*	10*	98[†]	0*	20
Hyperglycemia, %	52	41*	43	91[†]	60
Dyslipidemia, %	42	16*	25	67[†]	40
Osteoporosis, %	27	37	52[†]	0*	35
Anxiety, %	5*	28	26	0*	84[†]
Depression, %	6*	23	7	6	68[†]
Atherosclerosis, %	56	67[†]	12*	81[†]	53
Myocardial infarction, %	2*	11	7	13	32[†]

Summary variables are presented as mean $\pm$ standard deviation for quantitative variables, and percentage for discrete variables.

*Less prevalent compared with the whole study sample (95% confidence interval).

[†] More prevalent compared with the whole study sample (95% confidence interval).

New taxonomy in COPD

The pulmonologist view of comorbidities

Moving towards a Copernican view of COPD
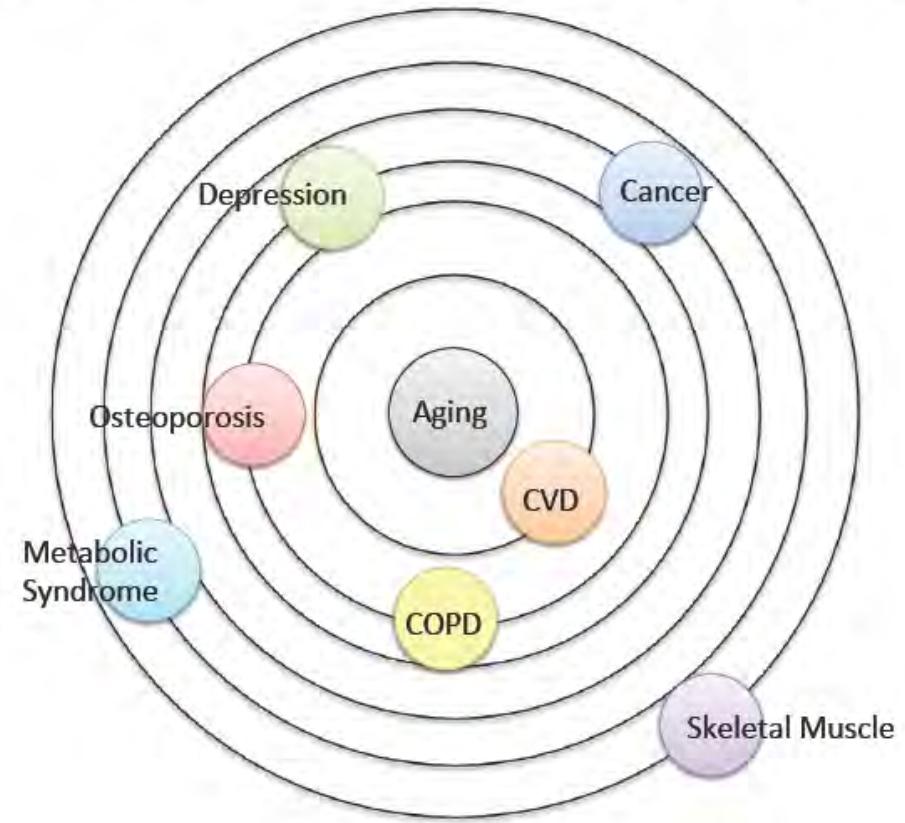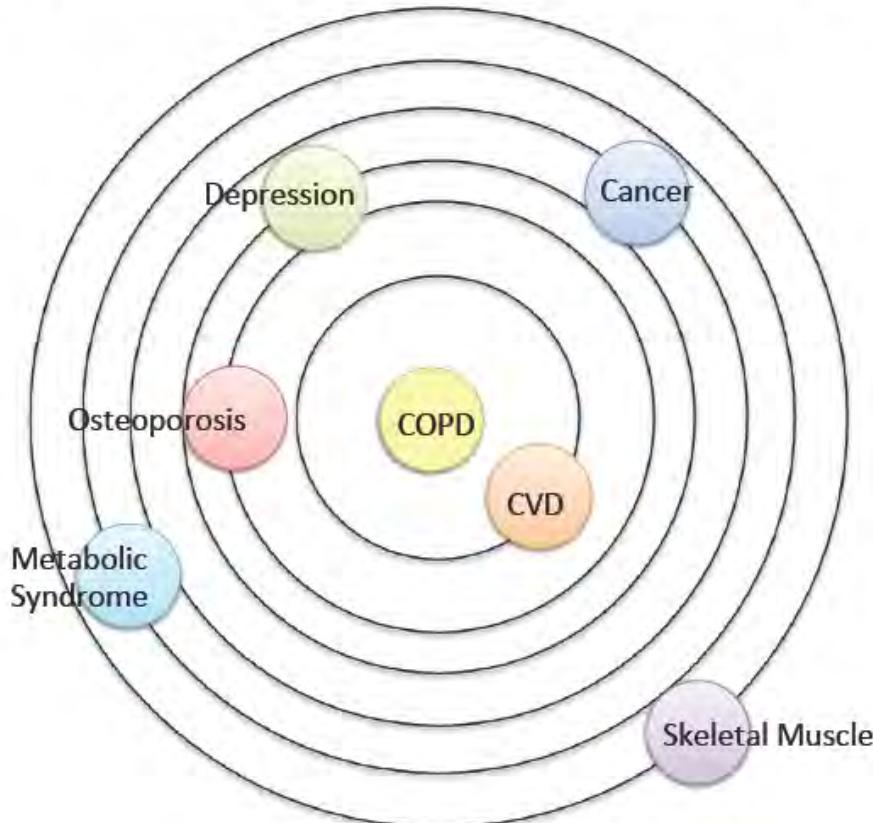
Consultation WEB des Maladies Respiratoires Chroniques

Objectifs

Consultation WEB pour le suivi longitudinal de la BPCO

OUTIL PROFESSIONNEL

BASE DE DONNEES LONGITUDINALES

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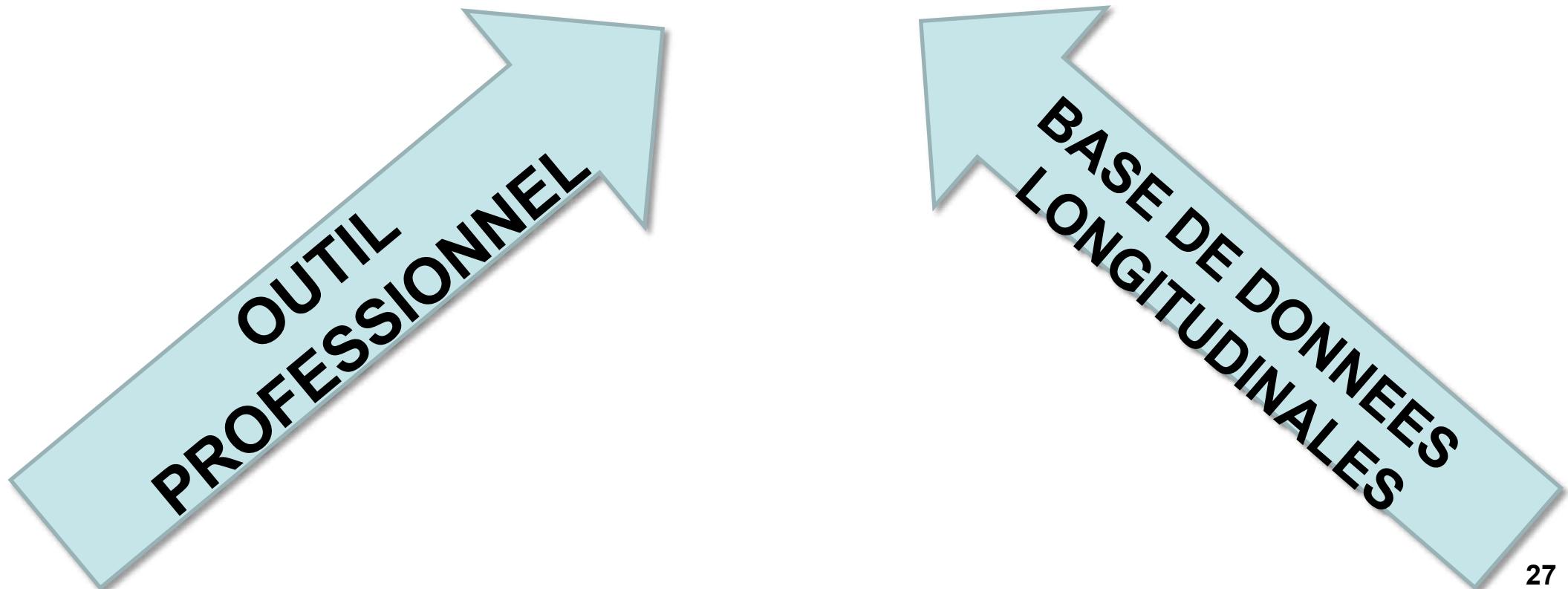
Consultation structurée
Maladie chronique respiratoire

1. Mode de vie
2. Expositions
3. Traitements en cours
4. Antécédents/Co morbidités
5. Consultation du jour
6. EFR/Hématose
7. Questionnaires handicap et qualité de vie
8. Exploration d'exercice
9. Examens complémentaires (TDM-Biolo-..)
10. Prescription du jour

Manage Stable COPD: Pharmacologic Therapy

Patient	Recommended First choice	Alternative choice		Other Possible Treatments
A	SAMA prn *or* SABA prn	LAMA *or* LABA *or* SABA and SAMA		Theophylline
B	LAMA *or* LABA	LAMA and LABA		SABA *and/or* SAMA Theophylline
C	ICS + LABA *or* LAMA	LAMA and LABA *or* LAMA and PDE4-inh. *or* LABA and PDE4-inh.		SABA *and/or* SAMA Theophylline
D	ICS + LABA *and/or* LAMA	ICS + LABA and LAMA *or* ICS+LABA and PDE4-inh. *or* LAMA and LABA *or* LAMA and PDE4-inh.		Carbocysteine *SABA and/or* SAMA Theophylline

Manage Stable COPD: Non-pharmacologic

| Patient Group	Essential	Recommended	Depending on local guidelines
A	Smoking cessation (can include pharmacologic treatment)	Physical activity	Flu vaccination Pneumococcal vaccination
B, C, D	Smoking cessation (can include pharmacologic treatment) Pulmonary rehabilitation	Physical activity	Flu vaccination Pneumococcal vaccination

Réhabilitation Respiratoire : Médecine Systémique

"Pulmonary rehabilitation is an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health care costs through stabilizing or reversing systemic manifestations of the disease." *AJRCCM 2006;173:1390-413*

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Réhabilitation Respiratoire post exacerbation

Figure 4. Forest plot of comparison: I Rehabilitation versus control, outcome: I.2 Mortality.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Troosters 2000	6	24	12	19	67.3%	0.19 [0.05, 0.72]
Man 2004	1	20	2	21	18.8%	0.50 [0.04, 5.99]
Behnke 2000	1	14	1	12	13.9%	0.85 [0.05, 15.16]
Total (95% CI)		58		52	100.0%	0.28 [0.10, 0.84]
Total events	8		15			

Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 2.29 (P = 0.02)

Odds Ratio M-H, Random, 95% CI
0.02   0.1   1   10   50
Favours rehabilitation   Favours control

Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease (Review)

Puhan MA, Gimeno-Santos E, Scharplatz M, Troosters T, Walters EH, Steurer J

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Multimodal RCT in Chronic Organ Failure
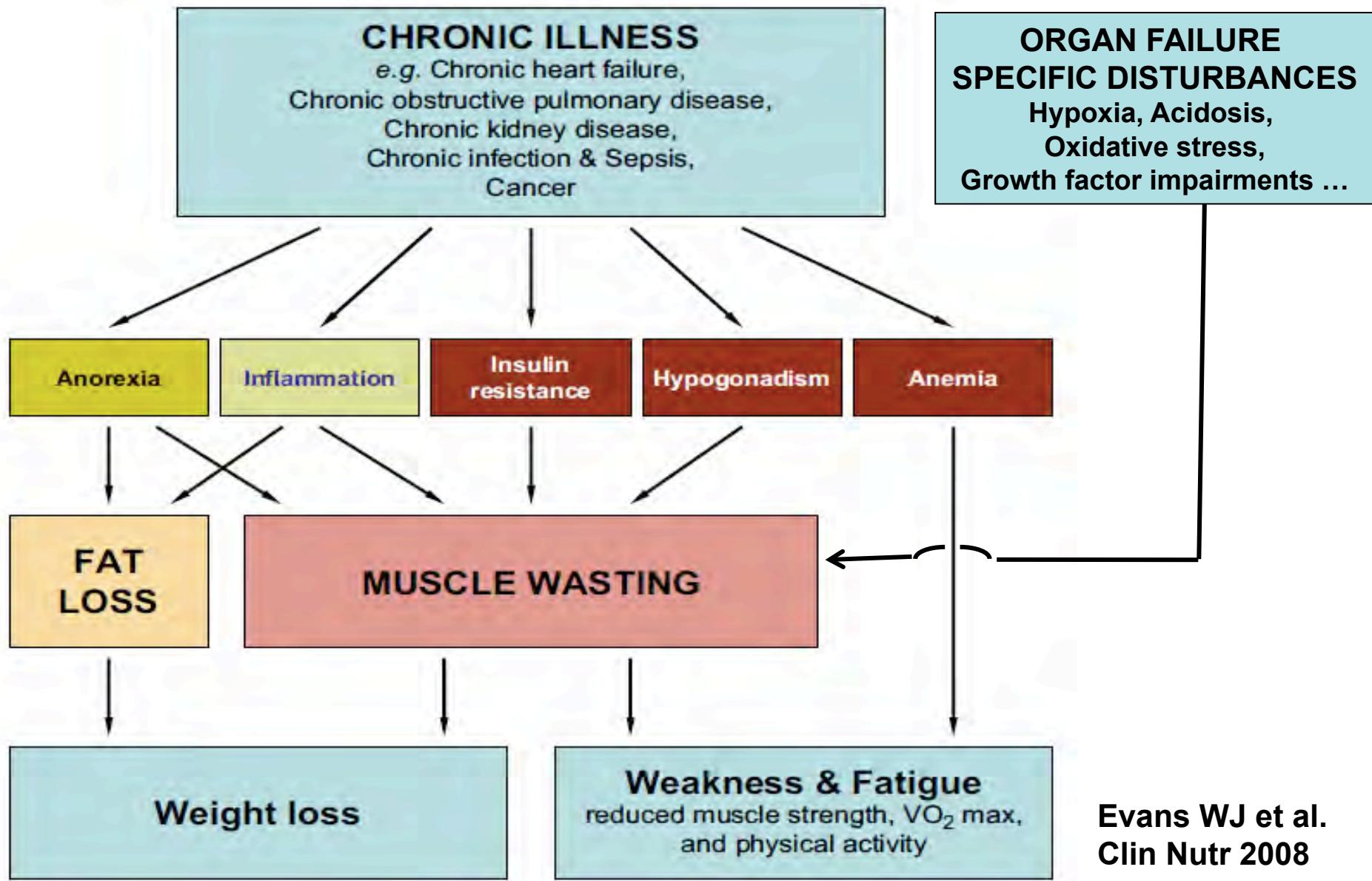
Evans WJ et al.
Clin Nutr 2008

BPCO - Maladie Systémique

- **Sédentarité**
- **Corticothérapie systémique**
- **Troubles ioniques**
- **Dénutrition catabol. / anabolisme**
- **Hypogonadisme**

- **Inflam. systémique**
- **Hypoxémie**
- **Stress oxydatif**
- **Anomalies réactivité vasculaire**
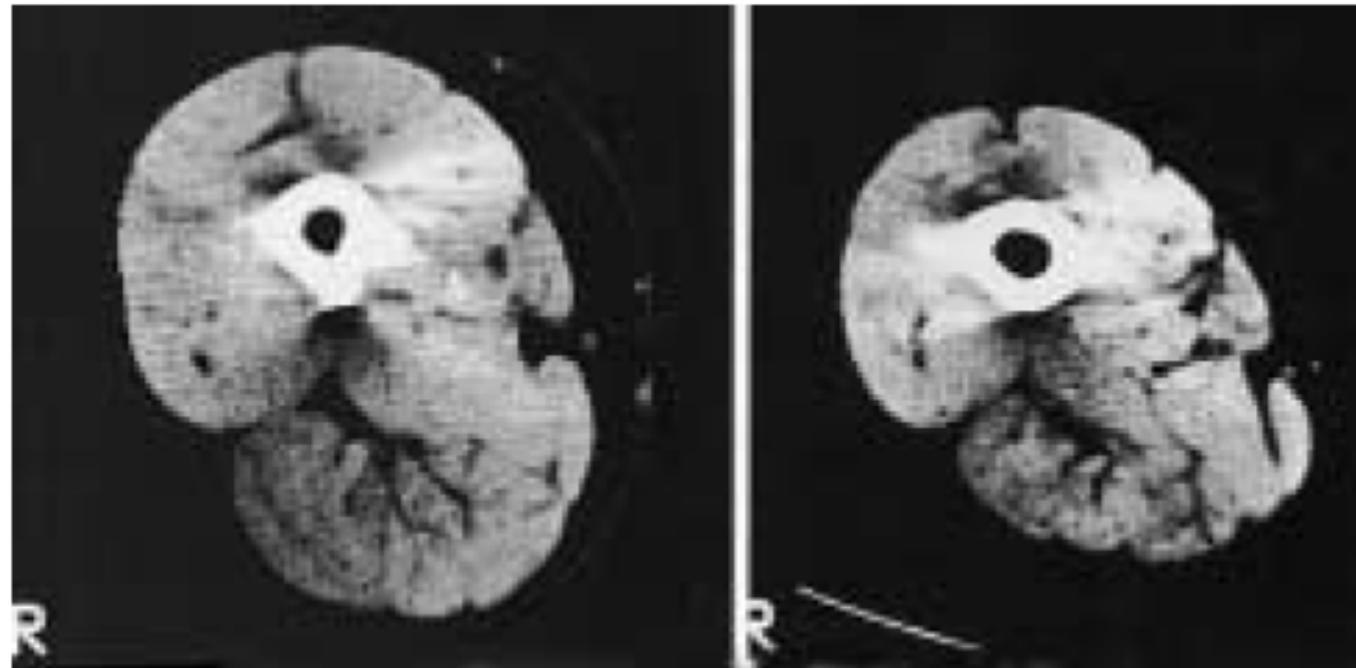
FIG. 1. — Tomographie assistée par ordinateur d'un sujet sain (à gauche) et d'un sujet atteint de BPCO (à droite) appartenant au même groupe d'âge. La surface transversale du muscle de la cuisse est considérablement réduite chez le sujet atteint de BPCO par rapport au sujet sain. Tiré de Bernard *et al. Am J Respir Crit Care Med* 1998;158: 629-4.

Composition corporelle

Composition corporelle

Low FFM

Normal FFM

involuntary weight loss

stable weight

stable weight

involuntary weight loss

BMI

20   25   30   35
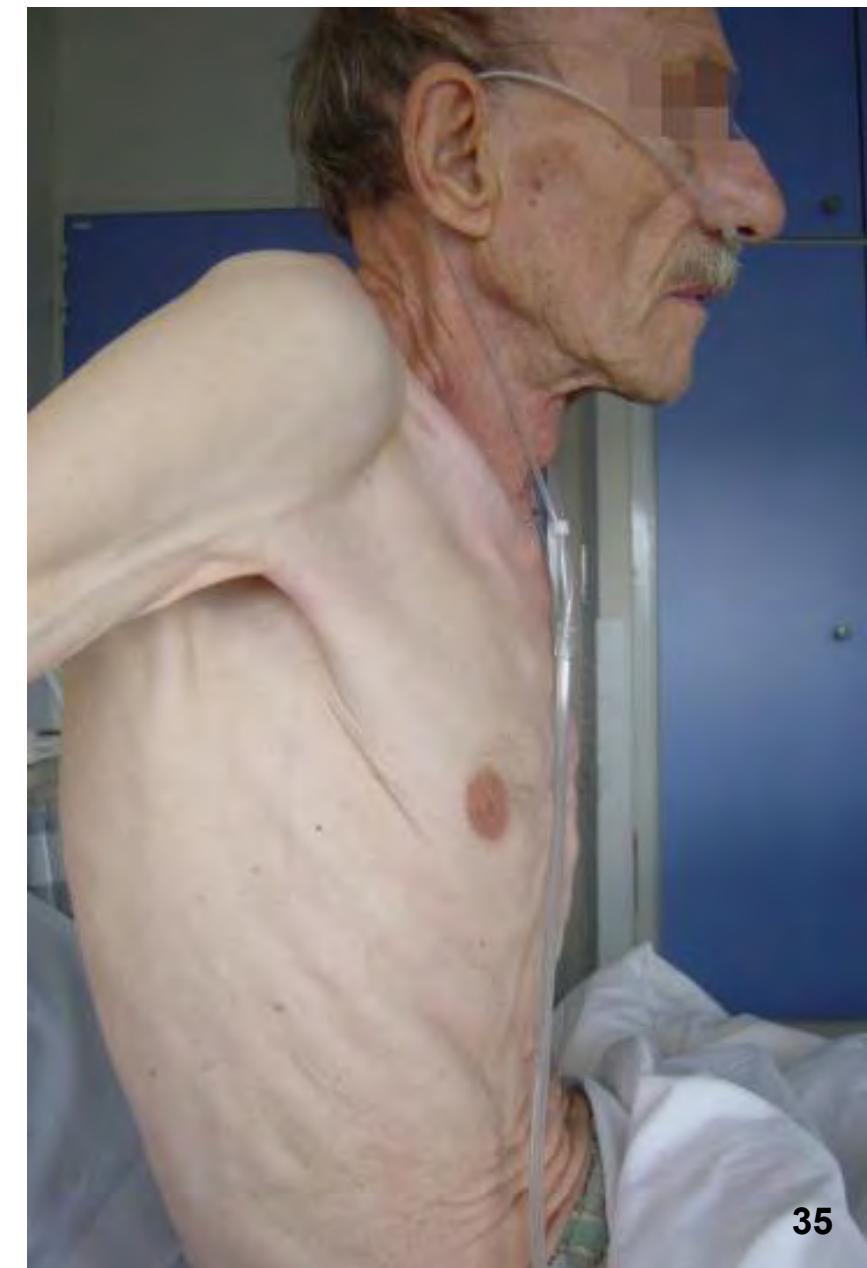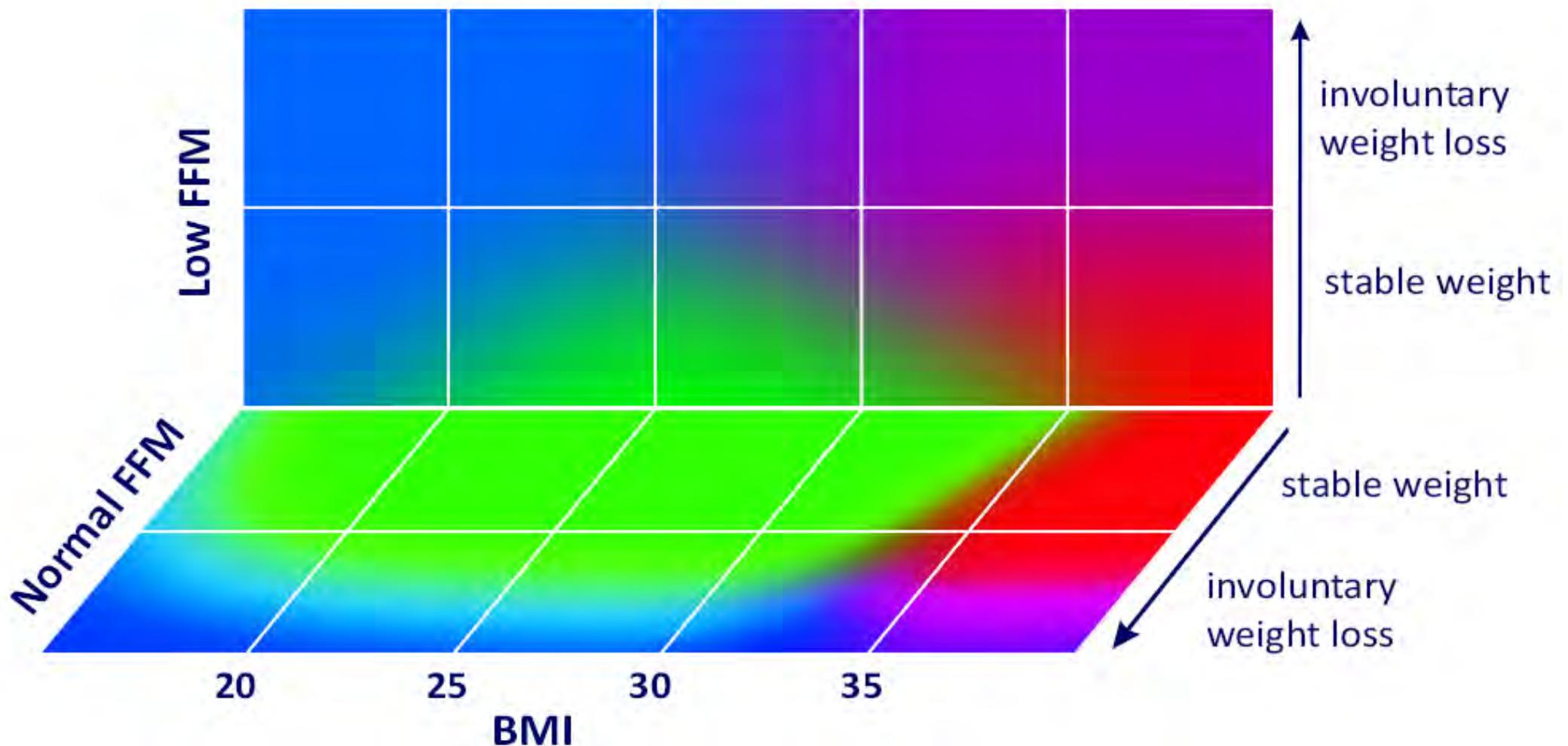
Low risk
Increased musculoskeletal risk
Increased cardiovascular risk
Increased cardiovascular & musculoskeletal risk

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Traitements multimodaux de l'IRC

- **IRAD2 study in Chronic Respiratory Failure**
 *Pison et al. Thorax 2011;66:953-60*
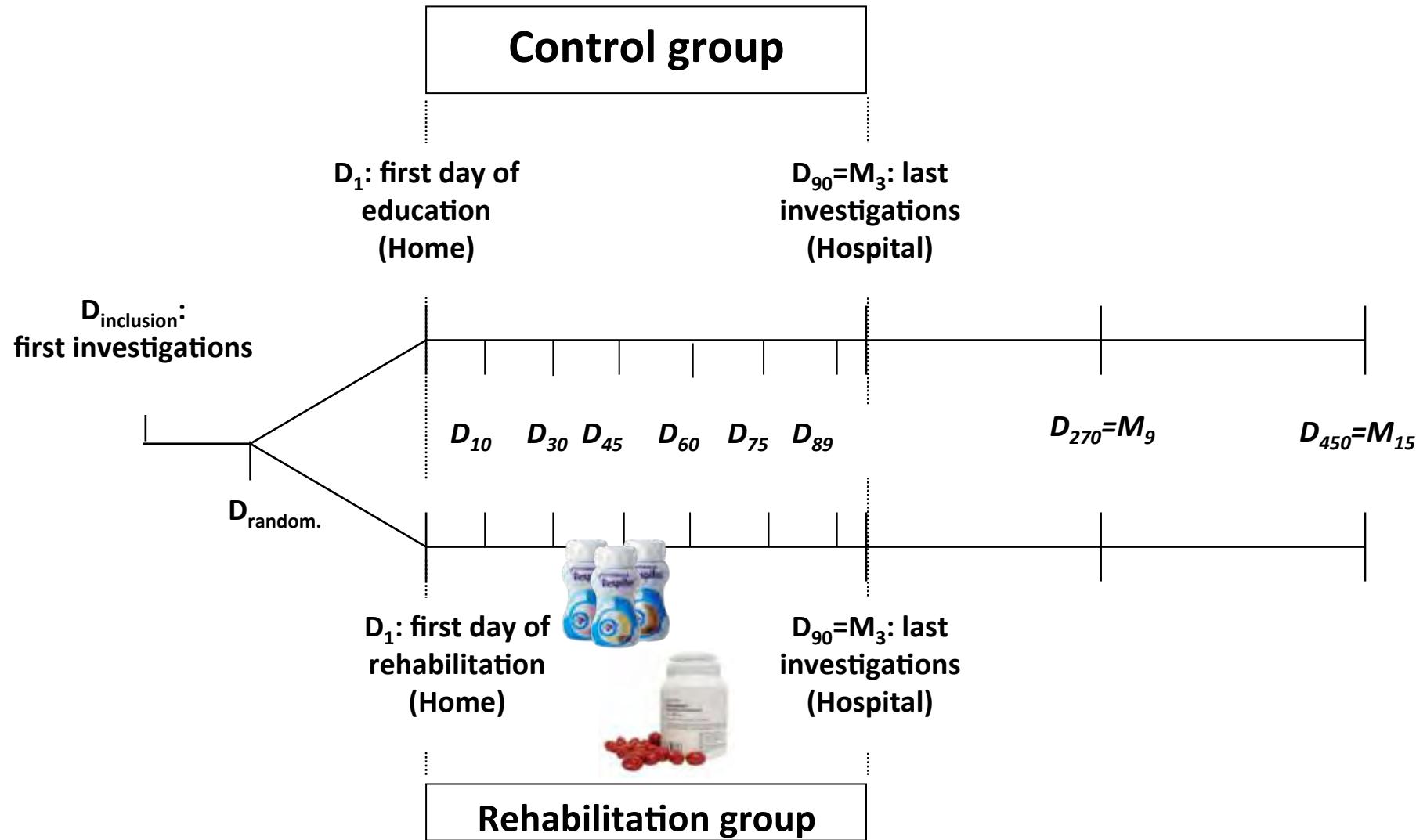
Traitements multimodaux de l'IRC

- **IRAD2 study in Chronic Respiratory Failure**
  Pison et al. Thorax 2011;66:953-60
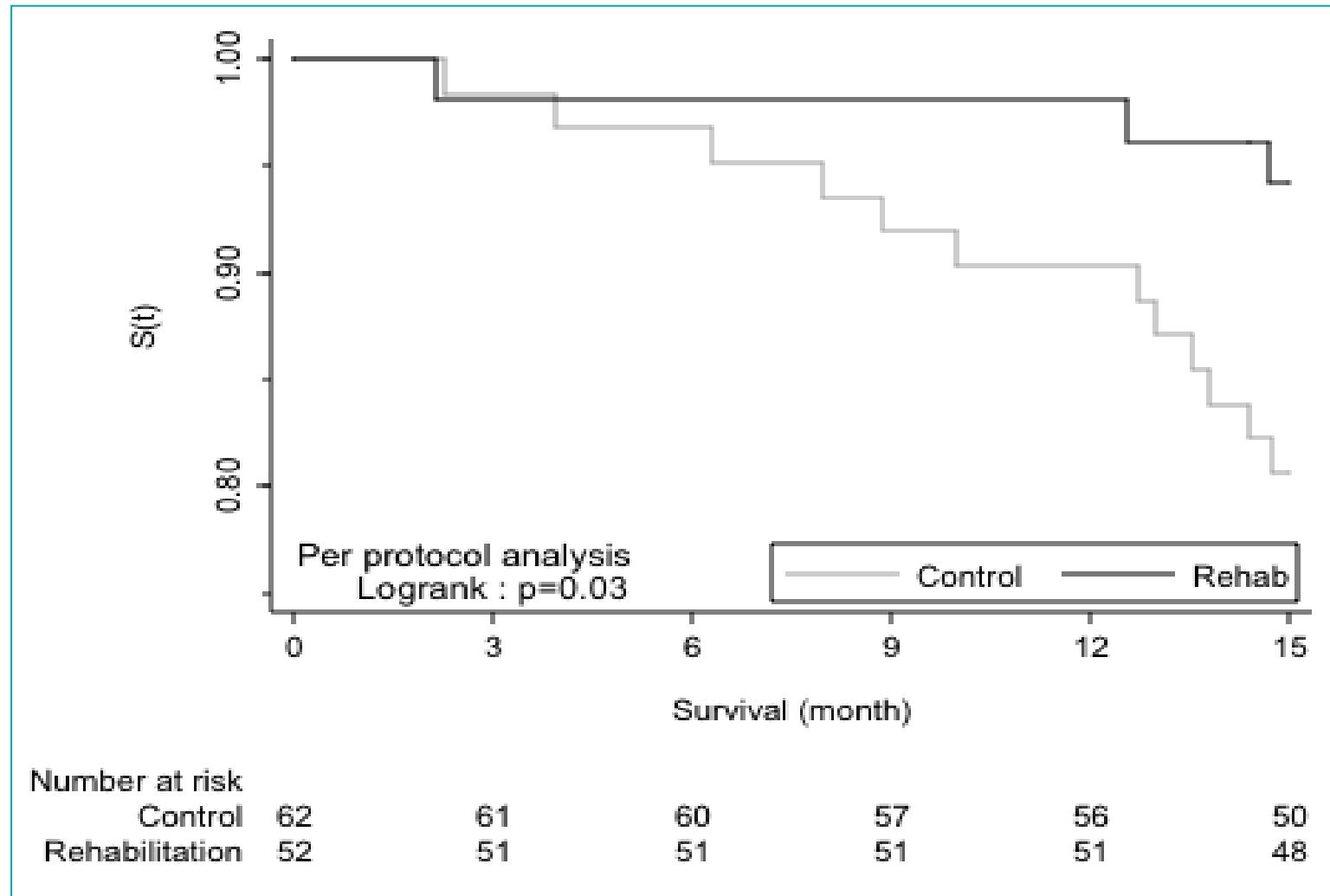
Comorbidité cardiovasculaire
Arterial stiffness and COPD
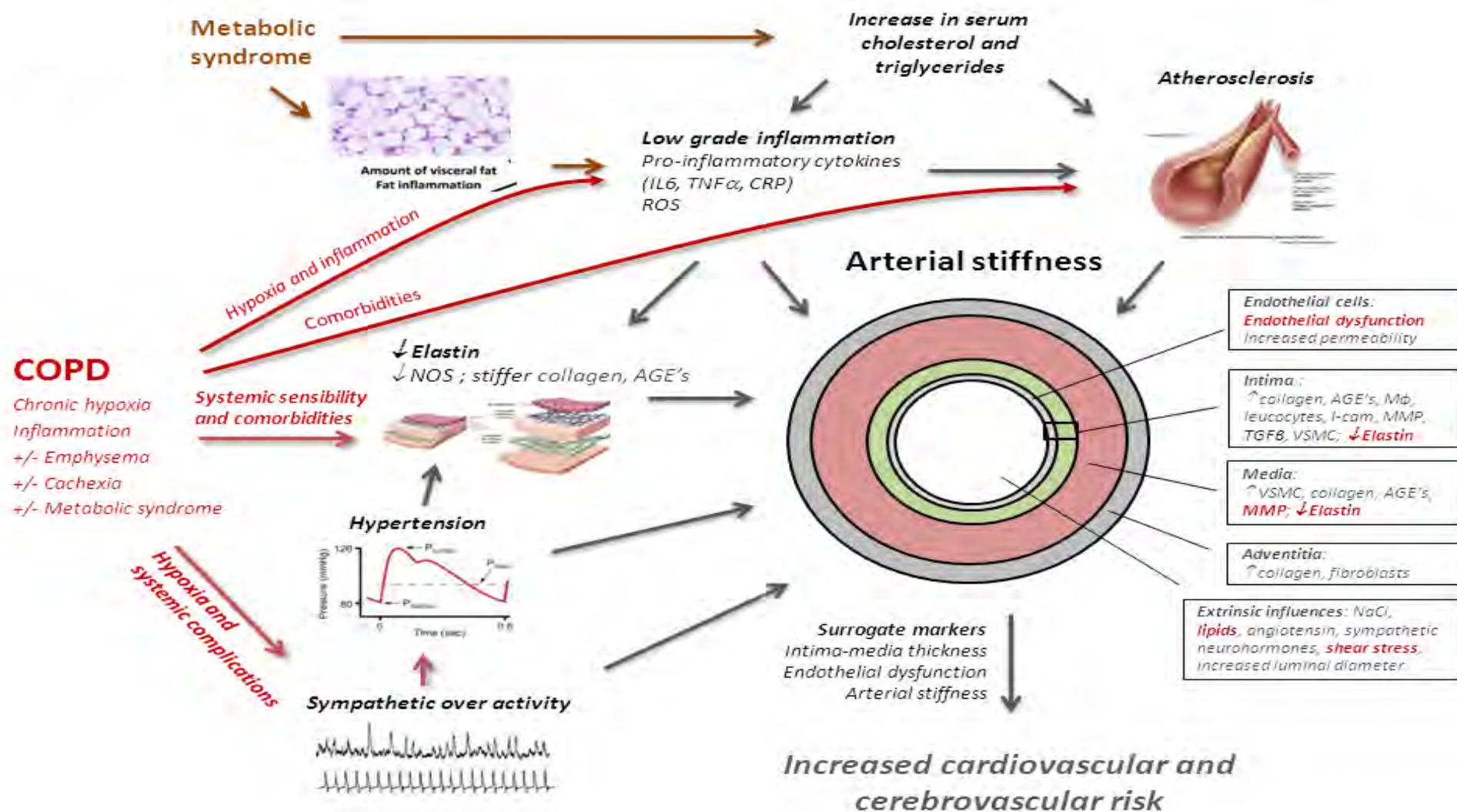
Long-acting Bronchodilators and Arterial Stiffness in Patients with COPD: A Comparison of Fluticasone Furoate/ Vilanterol with Tiotropium
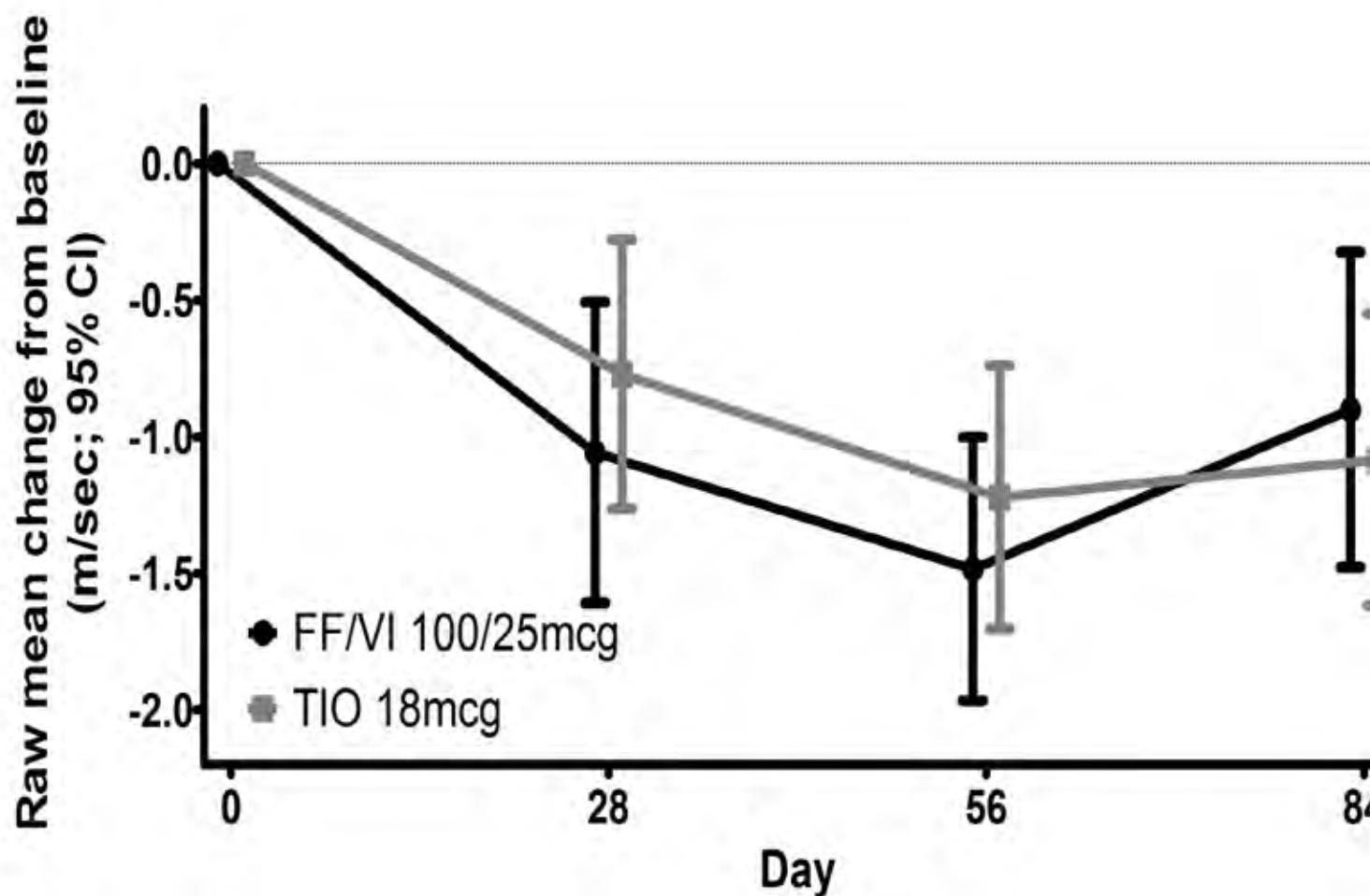

Vitesse d'onde de pouls: VOP
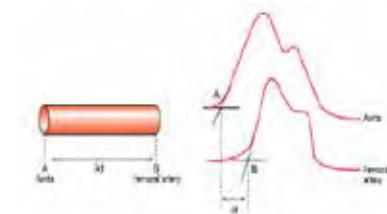
Pépin JL et al.   Chest 2013; Soumis

A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema

D   Upper-Lobe Predominance, Low Base-Line Exercise Capacity (N=290)

41
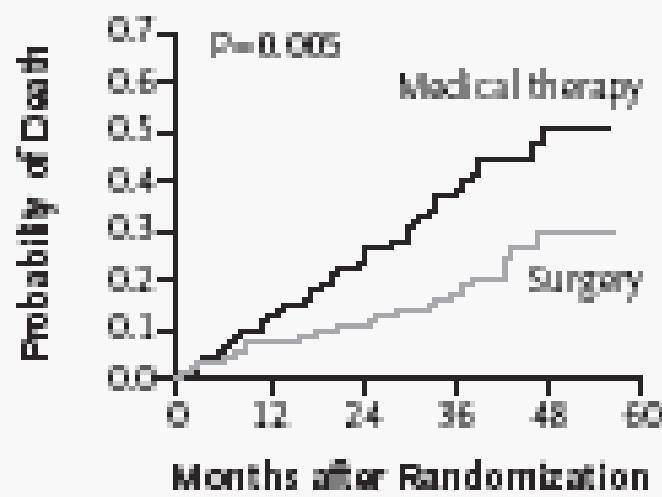
Réduction endoscopique de volume pulmonaire
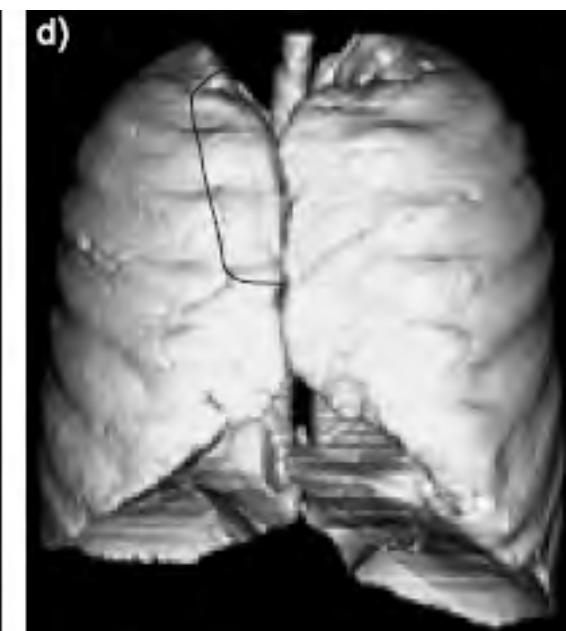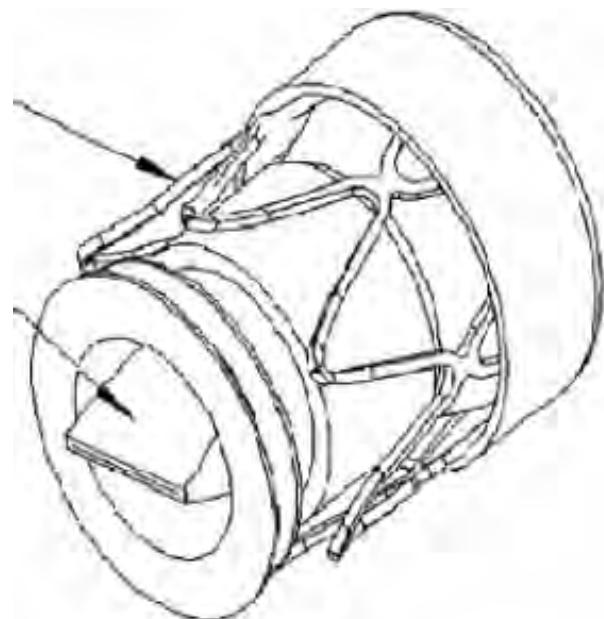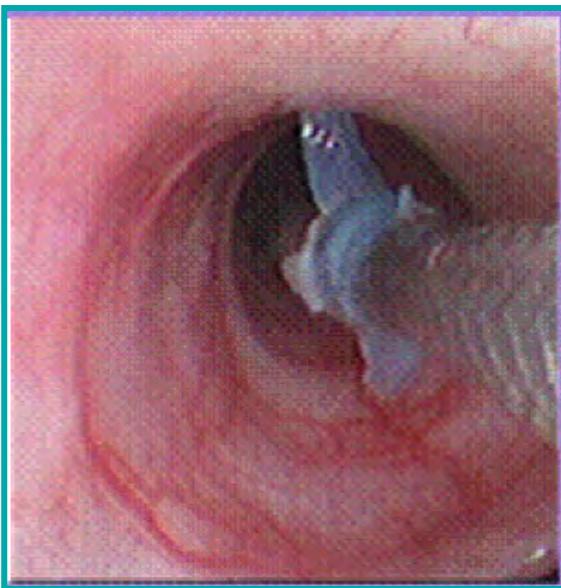
Survie ajustée sur la Qualité vie

Résultats de la transplantation pulmonaire, S. Quétant, T. Rochat, C. Pison. *RMR 2010;27:921-38*
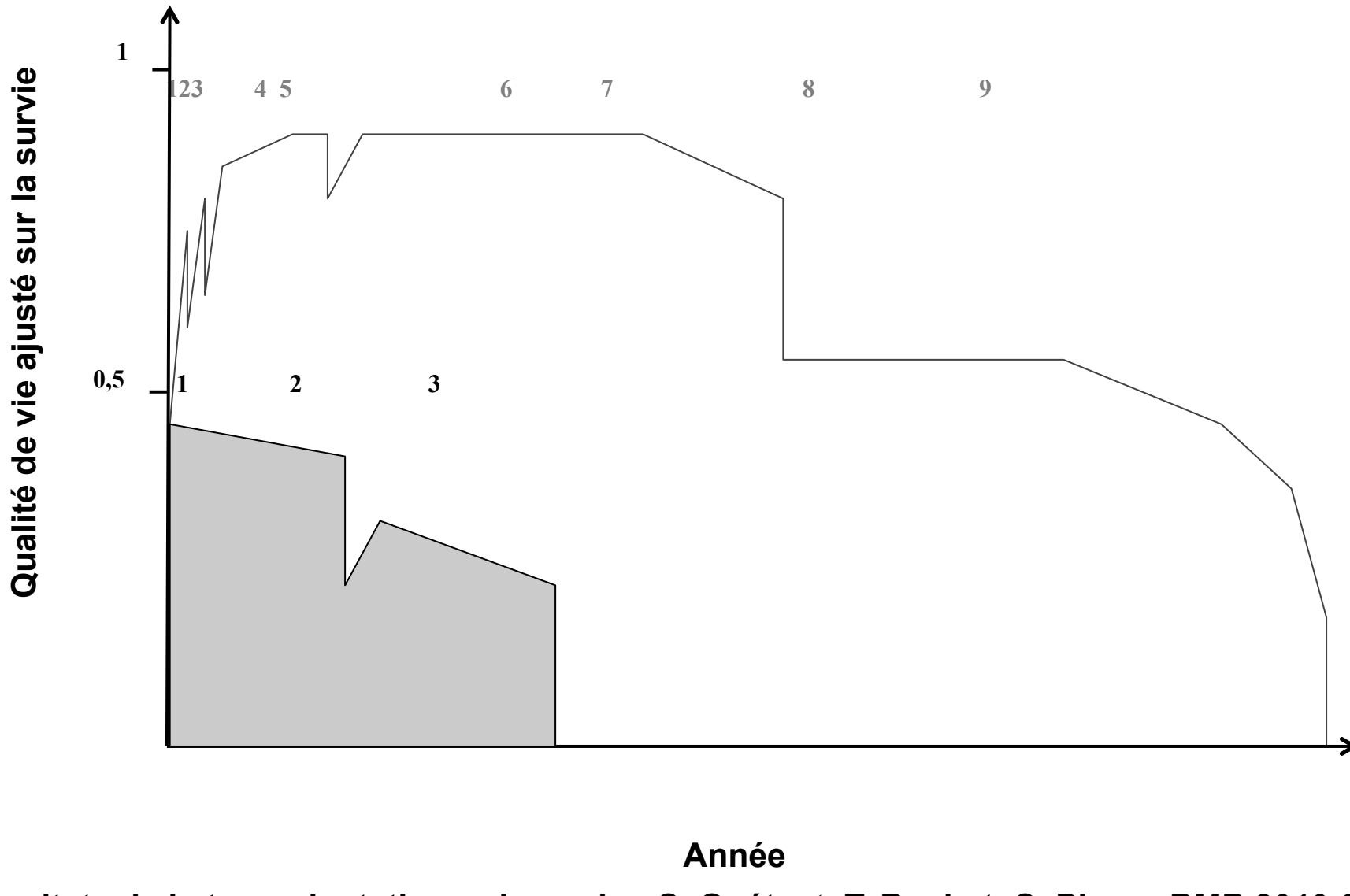
Indications BPCO

Guidelines for Referral

- BODE index exceeding 5.[16]

Guidelines for Transplantation

- Patients with a BODE index* of 7 to 10[16] or at least 1 of the following:
- History of hospitalization for exacerbation associated with acute hypercapnia (Pco_2 exceeding 50 mm Hg).[14]
- Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy.[18]
- FEV_1 of less than 20% and either DLCO of less than 20% or homogenous distribution of emphysema.[17]

Transplantation Pulmonaire à Grenoble

## Qui ?

BPCO   n = 90, 27 femmes, 54 ± 10 ans
Mucoviscidose   n = 54, 26 femmes, 28 ± 09 ans
Fibrose pulmonaire   n = 41, 27 femmes, 54 ± 11 ans
Hypertension pulmonairen = 16, 09 femmes, 43 ± 13 ans

## Donneurs : 39 ± 16 ans

Comment ?

101 patients sous ventilation non-invasive
103 avec CEC
33 jours au CHU
7 retransplantations, soit 3,4%

# Transplantation Pulmonaire à Grenoble
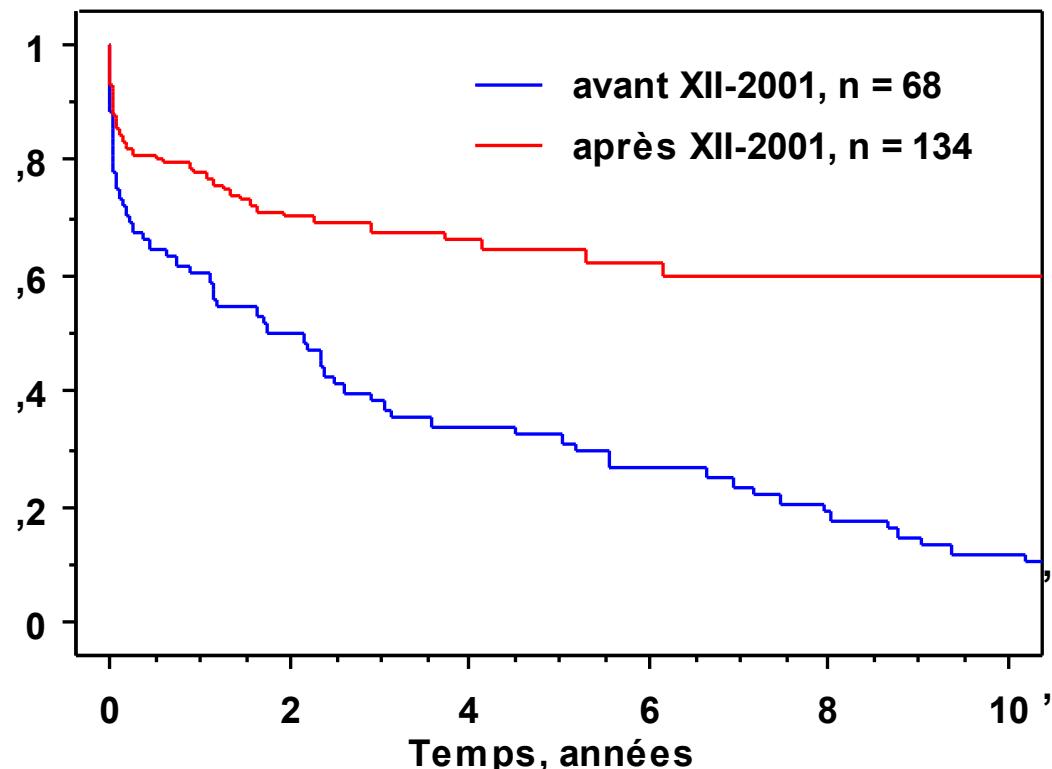
Toutes indications, n = 204

Mucoviscidoses, n = 54
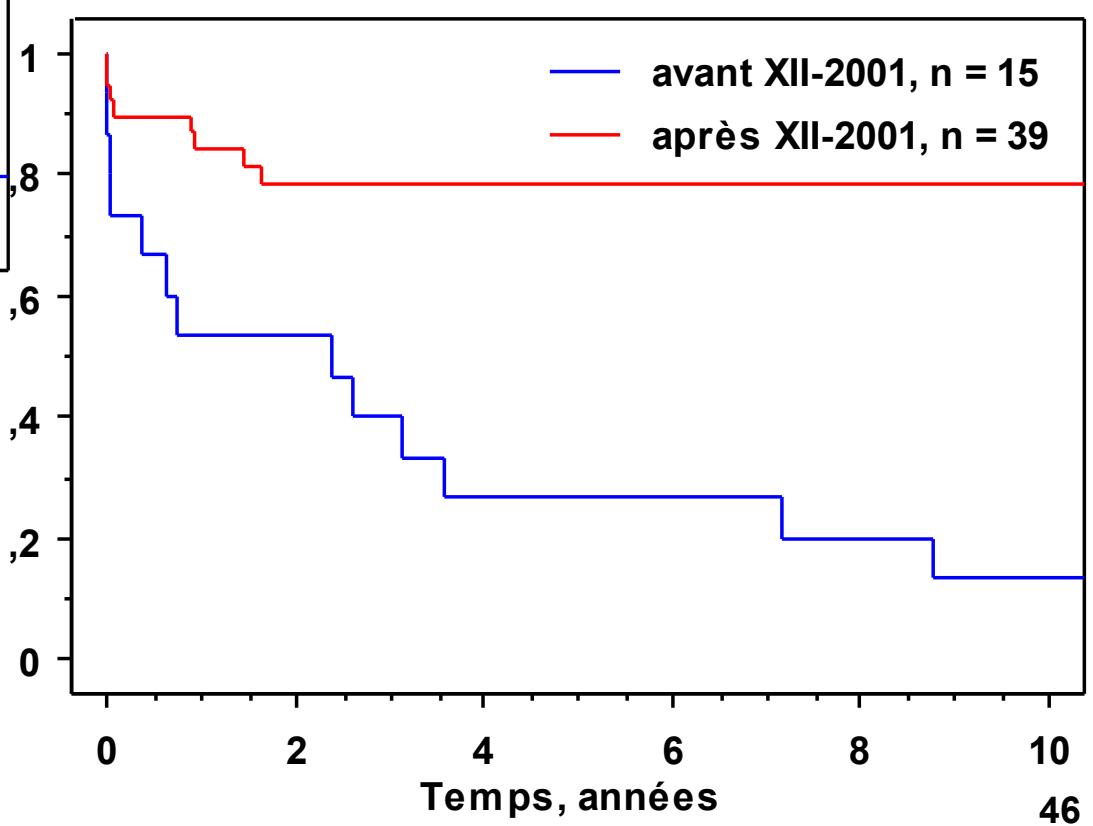
Traitements combinés

- 67 yr man with emphysema & PH, Home Nutritional rehabilitation, then LUL Endoscopic Volume Reduction 01-2010, Right Lung Tx 05-2010
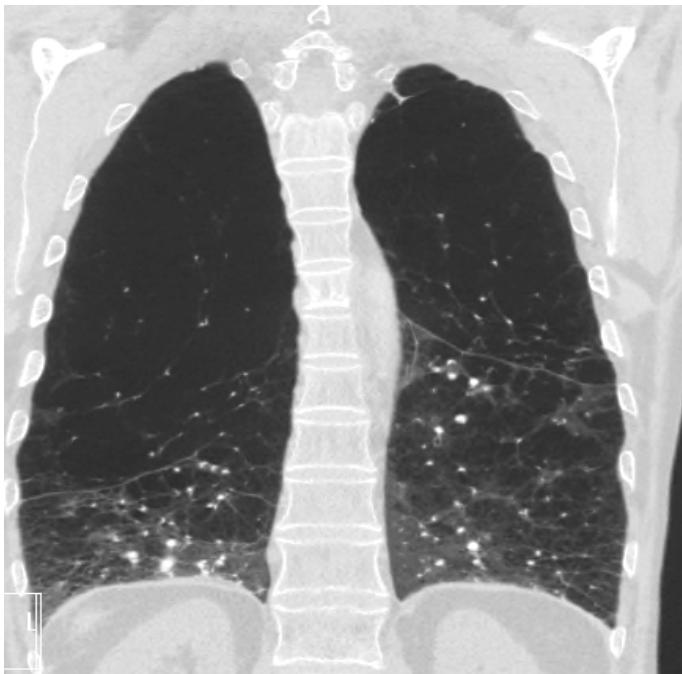
Date	09-2009	02-2010	07-2010
Weight, BMI	56, 21	61, 22.9	60, 22.6
FEV_1, L	0.77	1.17	2.25
FVC, L	2.27	2.86	3.31
PaO_2, kPa	5.36	6	12

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Faudra-t-il deux siècles pour généraliser l'usage du spiromètre ?


John Hutchinson
1811-1861

Charles Fletcher
1911-1995

Evolution prédite
de la prévalence BPCO
(Pays Bas), ‰
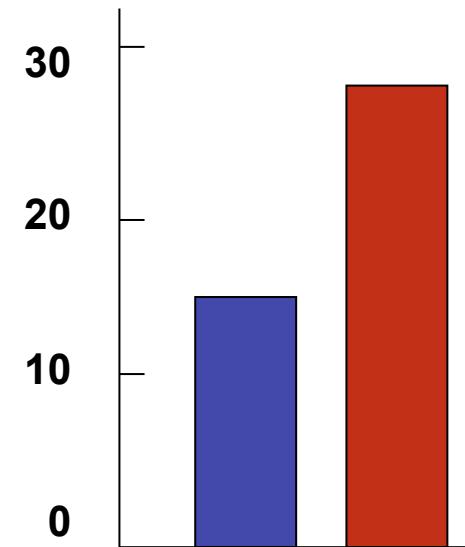
Fenstra, 2001

1994 -> 2015

Médicine Systémique & Soins innovants
Nouvelle Taxonomie & RCT multimodaux