





PHYSICAL ACTIVITY & COPD

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Statement on Potential Conflicts of Interest

No conflict related to the current presentation

Non-Restricted Research Grants	Advisory Committees
Menarini	AstraZeneca
	Boehringer Ingelheim
	GSK
	Teva

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Physical Activity: Body movements produced by skeletal muscles that involve energy expenditure

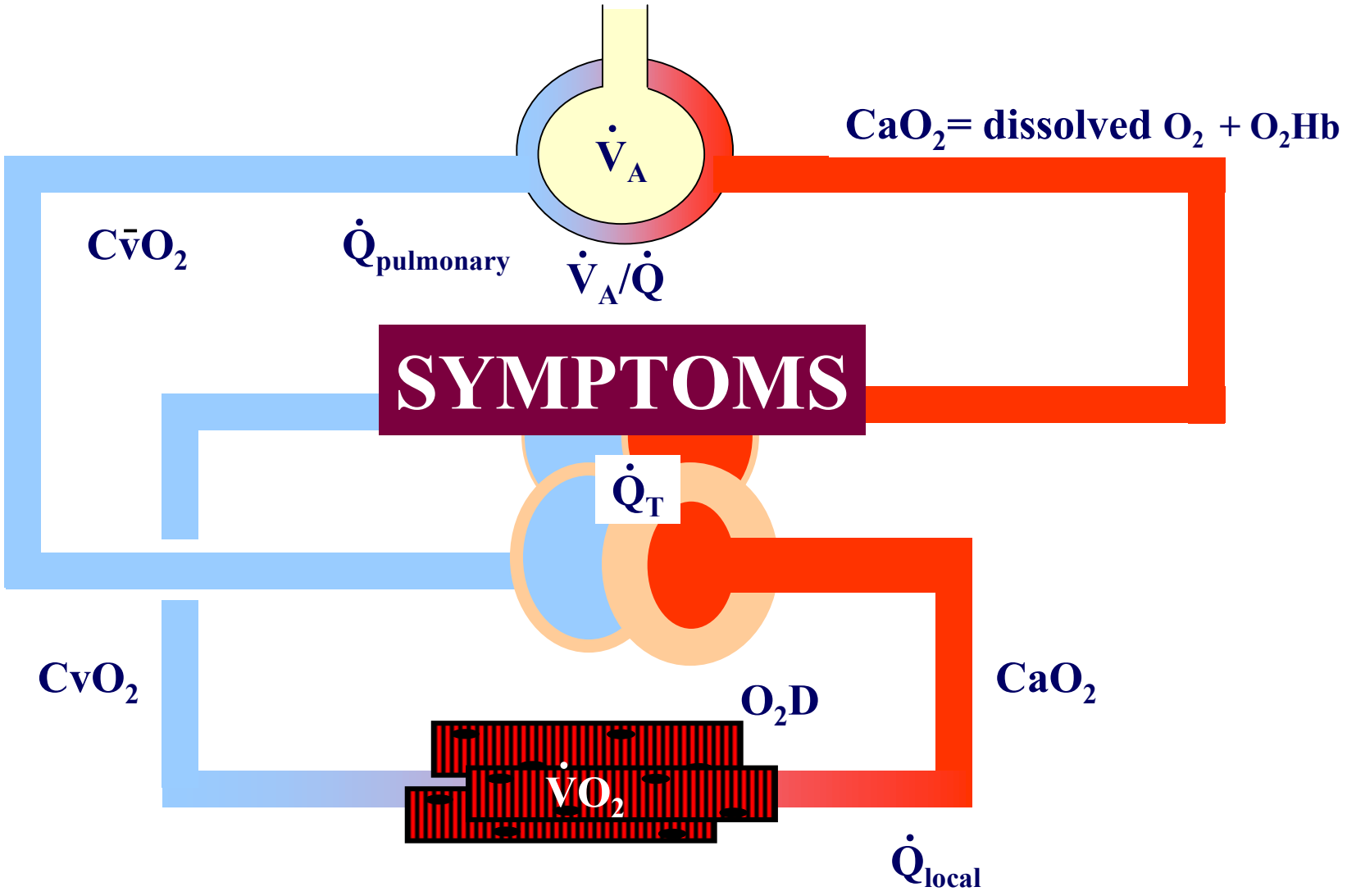
Caspersen CJ. Public Health Rep1985;100:131-46

Exercise: Is a physical activity that is planned, structured, and repetitive and has a purpose (conditioning, assessment)

Exercise Capacity or Tolerance: Is a Functional Capacity that allows maintenance of a specific level of Physical Activity

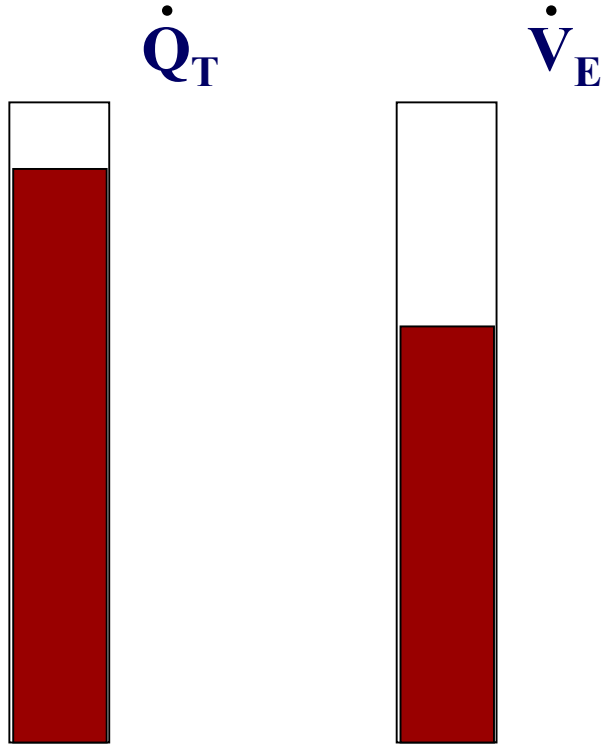
- **Incremental tests** (treadmill or cycloergometry, shuttle WT)
- **Submaximal tests** (6'WT, submaximal in treadmill or cycloergometry)

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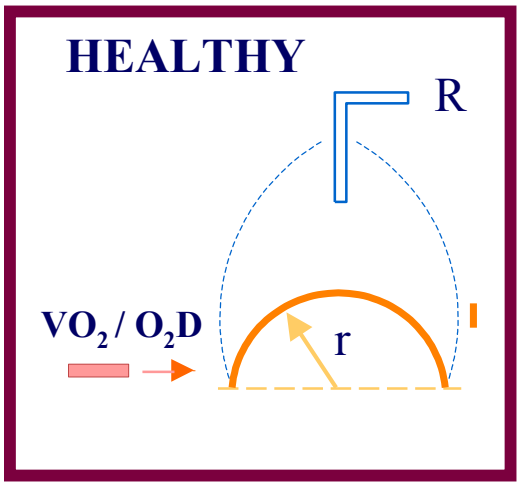


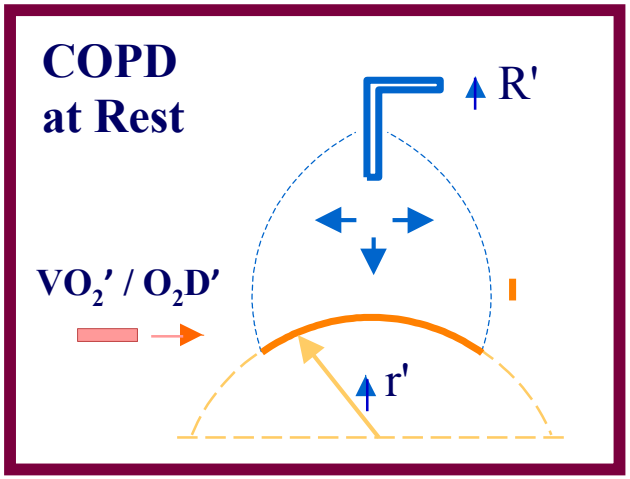


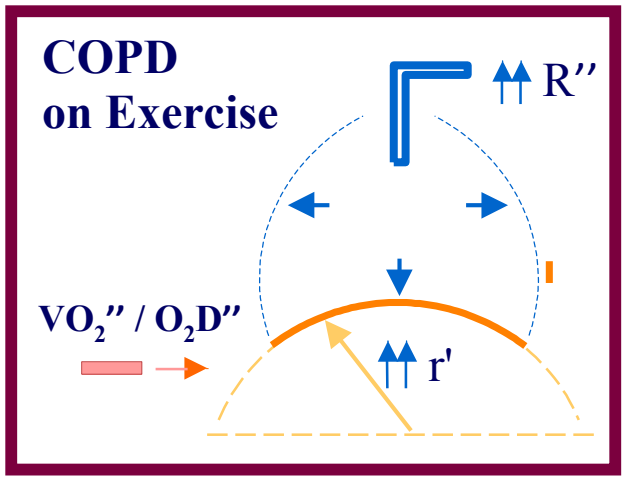
$\dot{Q}_T$ during exercise reaches 90 % of $\dot{Q}_T$ max (drugs)

$\dot{V}_E$ during exercise reaches only 65 % of $\dot{V}_E$ max (MVV)

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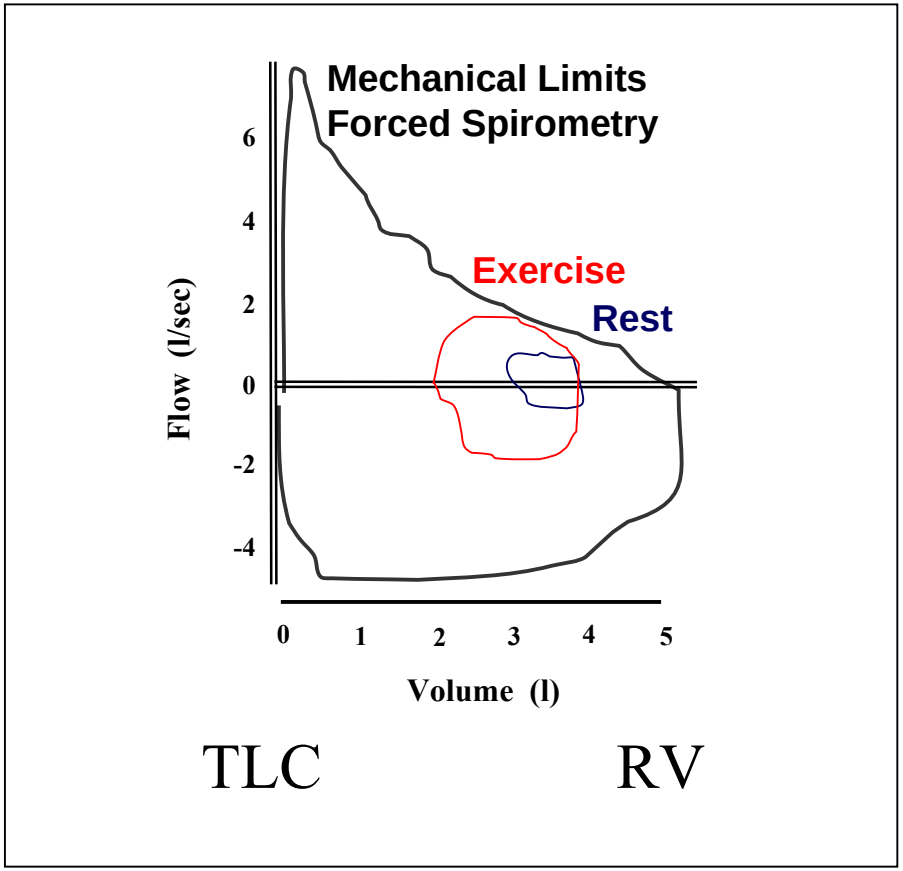




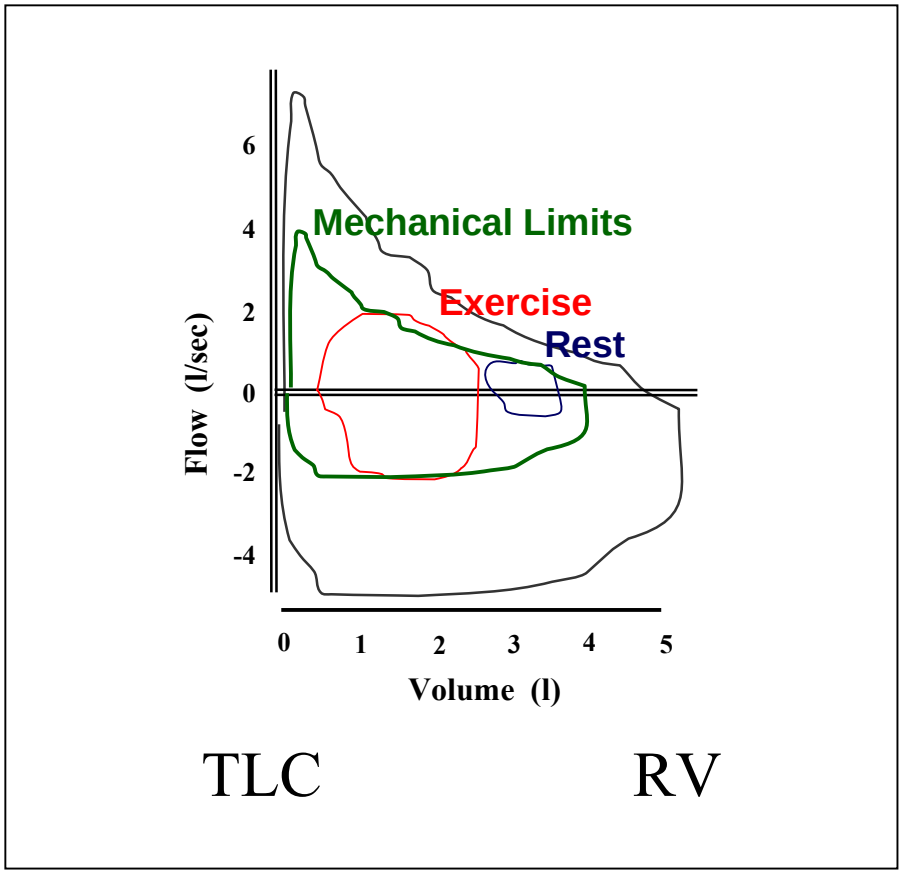
Airway Obstruction
Static Hyperinflation
Dynamic Hyperinflation

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DYNAMIC HYPERINFLATION

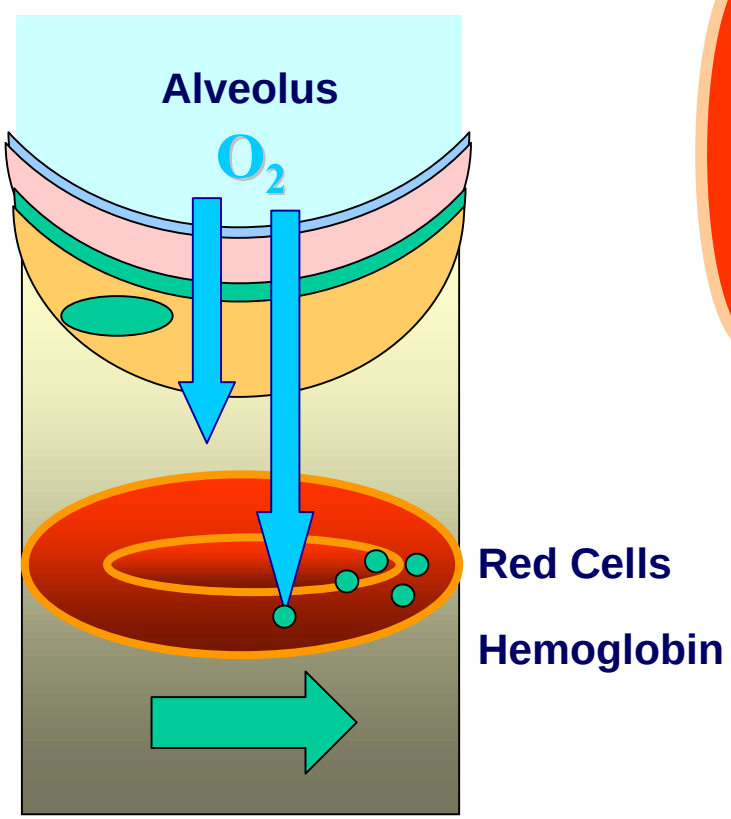


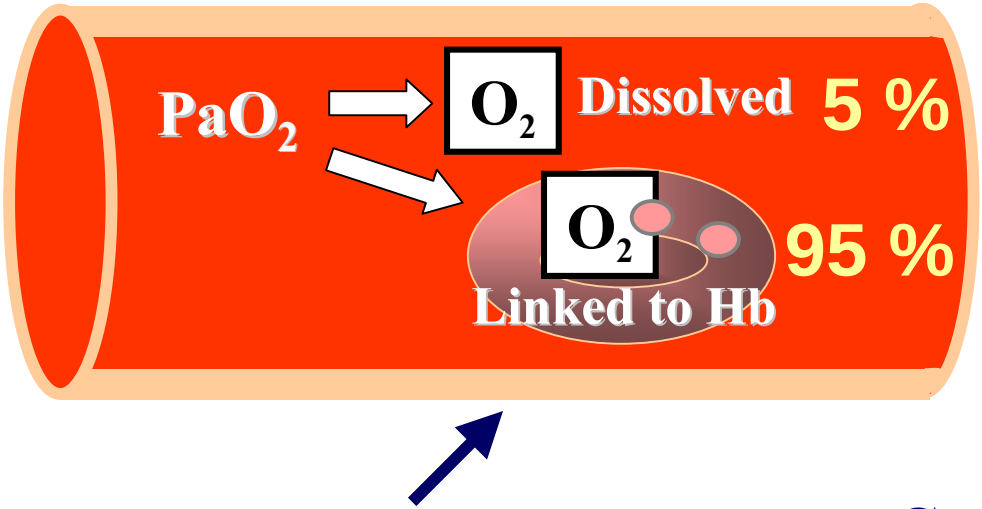
HEALTHY



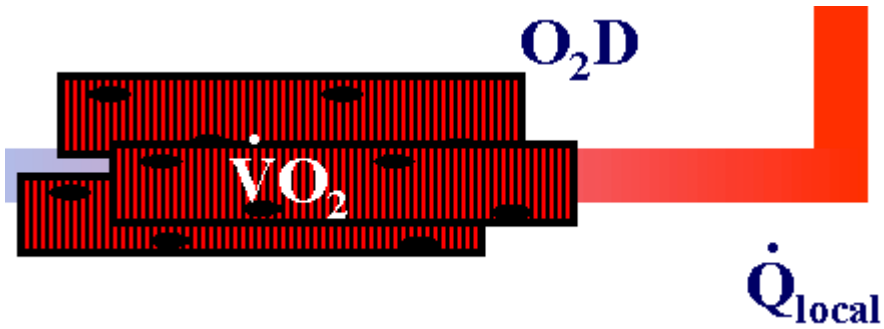
COPD

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CaO_2



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ANEMIA

Prevalence in COPD 17-23% (similar to other chronic diseases)

Variable	Anaemic	Nonanaemic	p-value#
Subjects n	116	561	
Age yrs	72.8±9.3	69.5±8.8	0.0003
Haemoglobin g·dL^{-1}	11.8±1.0	15.0±1.2	<0.0001
FEV$_1$ % pred	43.2±17.0	42.1±17.3	0.53
Pa,O_2 mmHg	72.1±13.3	71.9±11.9	0.87
MRC dyspnoea scale	2.8±0.9	2.6±0.8	0.04
6MWD m	265.4±122.1	325.1±124.4	<0.0001
CCI	6.5±3.5	4.8±2.4	<0.0001
BODE index	5.3±2.6	4.7±2.4	0.01

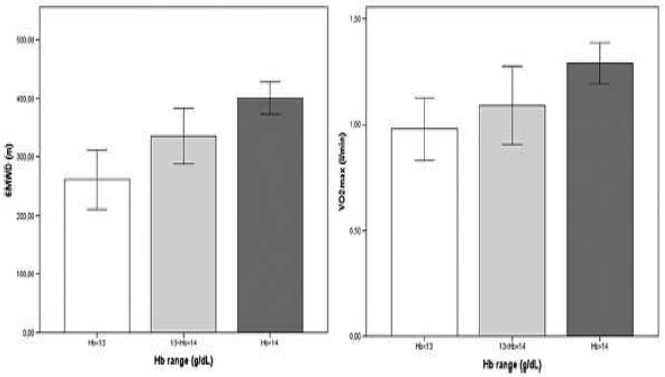
Independent risk factor for reduced functional capacity

Cote et al. ERJ 2007

Table 2 Exercise capacity, muscular strength, degree of dyspnoea and quality of life in COPD patients, divided according to the presence of anemia

	Total	Anemic	Non anemic	p-value*
6MWD (m)	360.0 ± 123.6	267.9 ± 86.7	373.0 ± 122.8	**0.001**
$VO2_{max}$ (l/min)	1.2 ± 0.4	0.9 ± 0.2	1.2 ± 0.4	**0.011**
Quadriceps Strength (Kg)	21.1 ± 7.4	21.3 ± 5.1	21.0 ± 7.7	0.853
MRC Dyspnoea scale	1.8 ± 1.4	2.8 ± 1.1	1.6 ± 1.3	**0.002**
SGRQ Total	41.4 ± 20.2	62.8 ± 20.9	38.7 ± 18.6	**0.005**

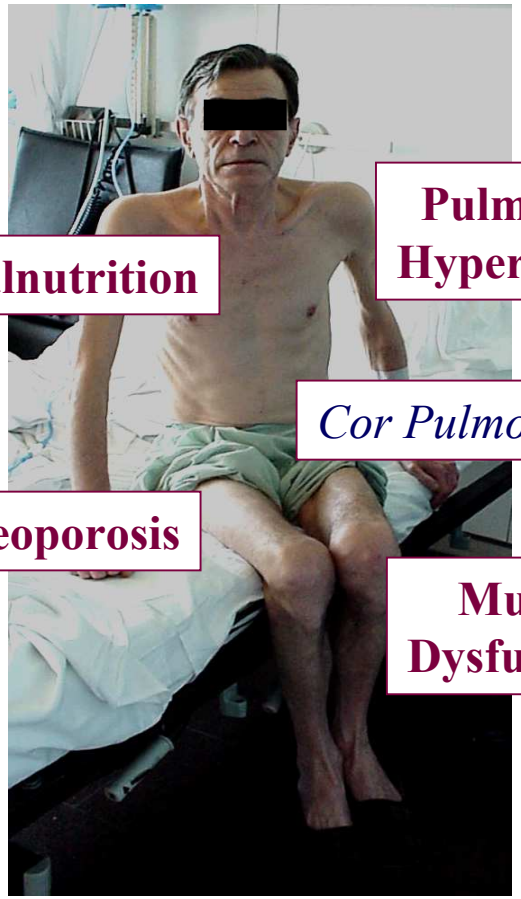
6'WD (m) **$\dot{V}O_2$max (l/m)**



Modified from Ferrari et al. BMC Pulmon Med 2015

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SYSTEMIC MANIFESTATIONS



Malnutrition

Pulmonary Hypertension

Cor Pulmonale

Osteoporosis

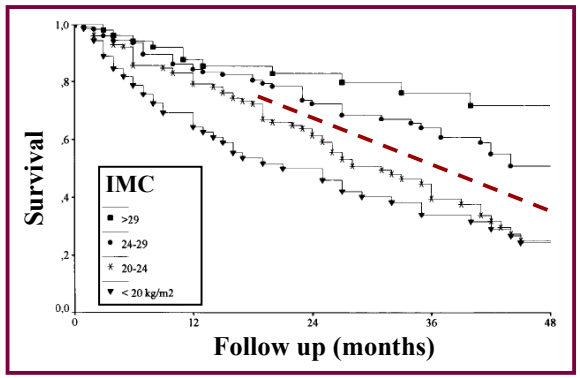
Muscle Dysfunction

NUTRITION - Body Composition

North America
Northern Europe
10-30%

Spain 3-5%

Life Style ?

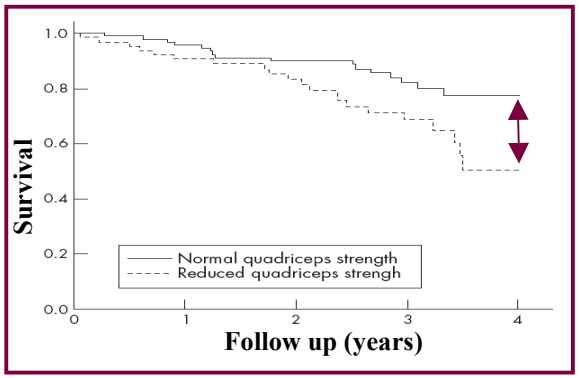


Schols A. AJRCCM 1998

MUSCLE DYSFUNTION

Obstruction Severity
- GOLD I-II, 29%
- GOLD III, 32%
- GOLD IV, 38%

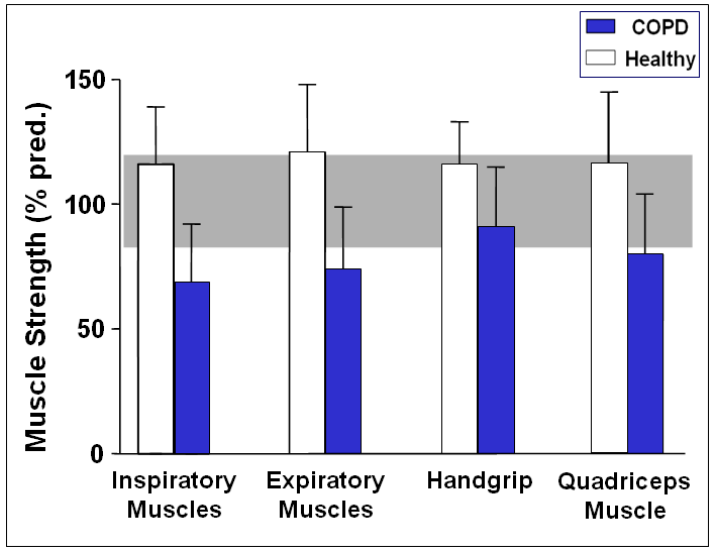
Dyspnea
- MRC 1-2, 26%
- MRC 3, 24%
- MRC 4-5, 43%



Swallow EB. Thorax 2007; Seymur JM. ERJ 2010

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Gosselink et al. AJRCCM 1996

AGE DIFFERENCES IN PERCEIVED LEG EFFORT AND DYSPNEA DURING EXERCISE*

Power Output (%)	Perceived Sensation	Age (yr) 20–30 (n = 55) Mean	SD	30–40 (n = 77) Mean	SD	40–50 (n = 104) Mean	SD	50–60 (n = 125) Mean	SD	60–70 (n = 99) Mean	SD
20	Dyspnea	0.3	0.66	0.3	0.56	0.4	0.65	0.4	0.71	0.3	0.56
	Leg effort	0.3	0.60	0.3	0.54	0.4	0.68	0.4	0.61	0.4	0.49
40	Dyspnea	1.1	1.09	1.1	1.15	1.1	1.11	1.3	1.17	1.4	1.13
	Leg effort	1.3	1.02	1.3	1.09	1.2	1.06	1.5	1.18	1.4	1.08
60	Dyspnea	2.4	1.32	2.3	1.55	2.2	1.45	2.5	1.43	2.5	1.56
	Leg effort	2.8	1.19	2.7	1.56	2.7	1.63	2.8	1.48	2.8	1.39
80	Dyspnea	4.0	1.76	3.8	1.56	3.6	1.80	3.9	1.70	4.0	1.96
	Leg effort	4.5	1.52	4.4	1.82	4.4	1.82	4.5	1.72	4.5	1.78
100	Dyspnea	6.8	2.40	6.3	1.95	6.5	2.37	6.5	2.33	6.6	2.28
	Leg effort	7.9	1.98	7.2	2.22	7.4	2.17	7.4	2.00	7.2	2.04

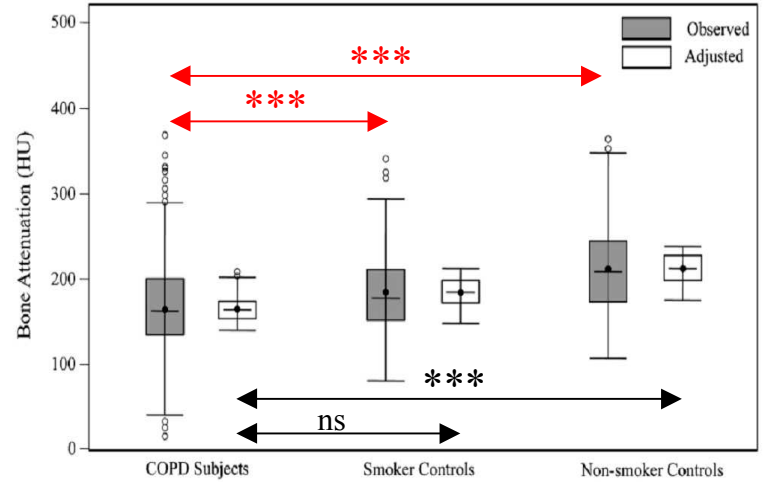
Killian KJ et al. ARRD 1992

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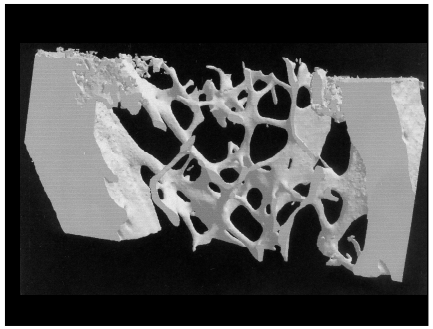
Table 1—*Prevalence of Osteoporosis and Vertebral Compression Fractures in COPD*

Study	Patient Group	Subjects	BMD Measure	Prevalence of Osteoporosis, %	X diagnosis of VCF	Prevalence of VCF, %
Osteoporosis						
Graat-Verboom et al[10]	COPD patients (GOLD I-IV) referred for PR	554	Whole-body B (DXA)		…	…
Ferguson et al[11]	COPD patients (GOLD II-IV)	658	BMD LS and (DXA)	21	…	…
Sin et al[12]	COPD patients (GOLD I-IV)	5215	BMD total fer (DXA)		…	…
Forli et al[13]	COPD patients awaiting LTX	40	BMD LS and (DXA)		…	…
Iqbal et al[14]	Patients with chronic lung disease	130	BMD LS and (DXA)	24	…	…
Sabit et al[15]	COPD patients (GOLD I-IV)	75	BMD LS and (DXA)		…	…
Bolton et al[16]	Respiratory outpatients referred for PR	81	BMD total bo and hip (DX	4-33	…	…
Compression fractures						
Jorgensen et al[17]	Ambulatory COPD outpatients (GOLD III-IV)	62	…	59	acic and lumbar spine liographs	24
Nuti et al[18]	Ambulatory COPD outpatients (GOLD I-IV)	2981	…	36	ral chest radiograph	41
Papaioannou et al[19]	COPD patients (GOLD not reported)	127	…	24	ral chest radiograph	27
McEvoy et al[20]	Male COPD patients (GOLD not reported)	312	…	32	ral lumbar and thoracic liograph	49-63

Lehouck et al. CHEST 2011



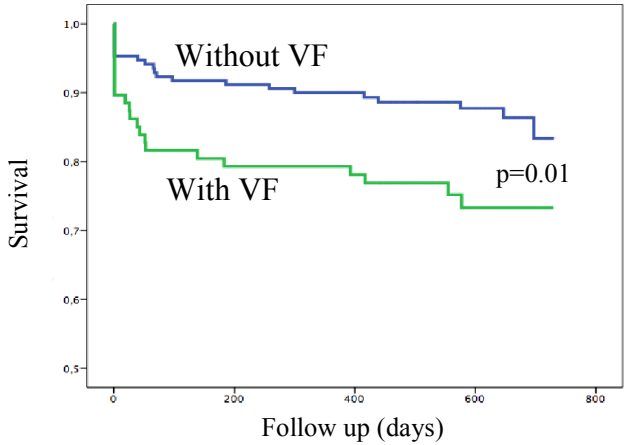
Romme *et al*. J Bone Min Res 2013



Factors involved

- Low physical activity
- Smoking
- Nutritional abnormalities
- Low Vit D levels
- Hypogonadism
- Steroids (systemic and inhaled)
- Systemic inflammation
- Hypercapnia

Biskobing, Chest 2002; Spurzem, Sem Respir Crit Care Med 2005;
Gan, Thorax 2004; Incalzi, Respir Med 2000



Pascual-Guardia *et al*. (submitted)

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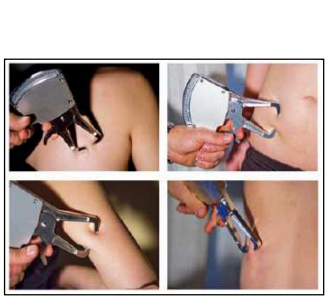
Tests related to Daily Activities

- 6’ Walking Test
- Shuttle Test
- Stairs, etc..



Cardiopulmonary Exercise Tests

- Cycloergometry (Incremental or Constant loads)
- Treadmill







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What is COPD ?

- A common, preventable and treatable disease, characterized by airflow limitation ($FEV_1/FVC < 70\ \%$)

- **Significant Extrapulmonary Manifestations**

- in Skeletal Muscles (Peripheral & Respiratory muscles)
- in Nutritional Status (Body Weight & Composition)
- in the Pulmonary Circulation and Blood
- in Bones and Phosphocalcic Metabolism
- in Kidneys and Water-Electrolyte Balance
- etc...

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What is COPD ?

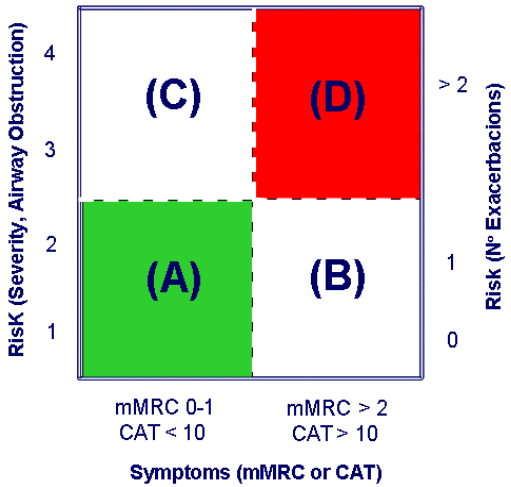
- A common, preventable and treatable disease, characterized by airflow limitation … exacerbations and **comorbidities** contribute to the overall severity in individual patients"

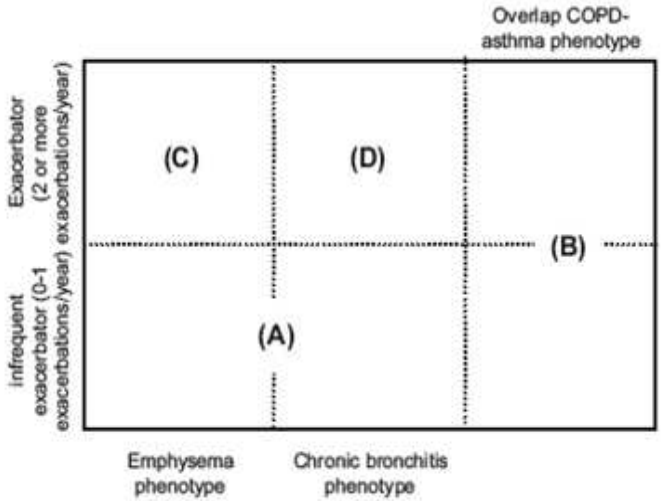
- **Frequent Comorbidities & Aging** →
  - **Reduced Physical Activity**
  - **Exercise Limitation**

- Coronary Heart disease, Arteriosclerosis, Stroke
- Cancer (Lung, Larynx, Oropharynx, Esophagus, Bladder, Kidney...)
- Diabetes, other endocrine disorders
- Rheumatoid Arthritis

- Physiological and Pathological Aging

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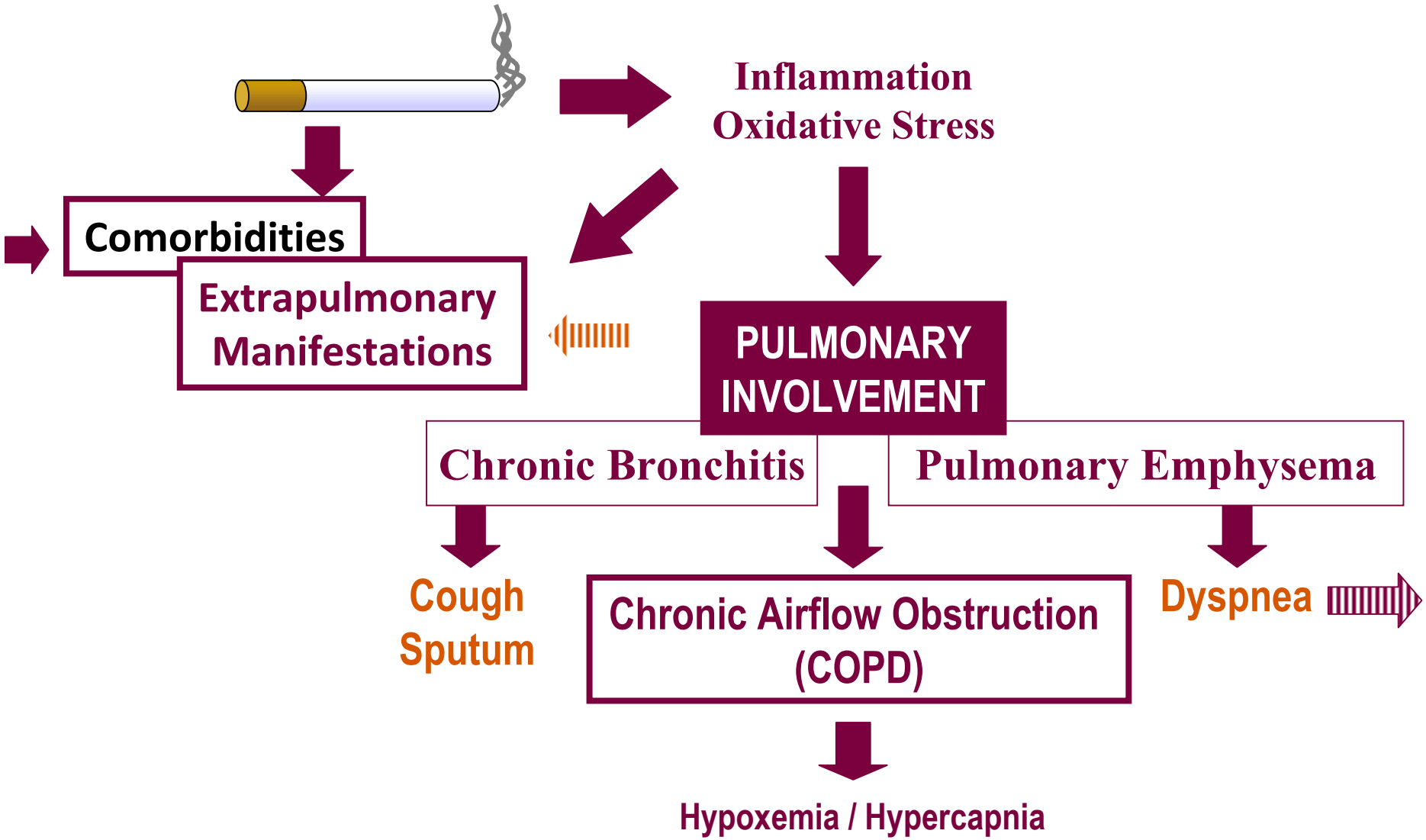


BODE Index

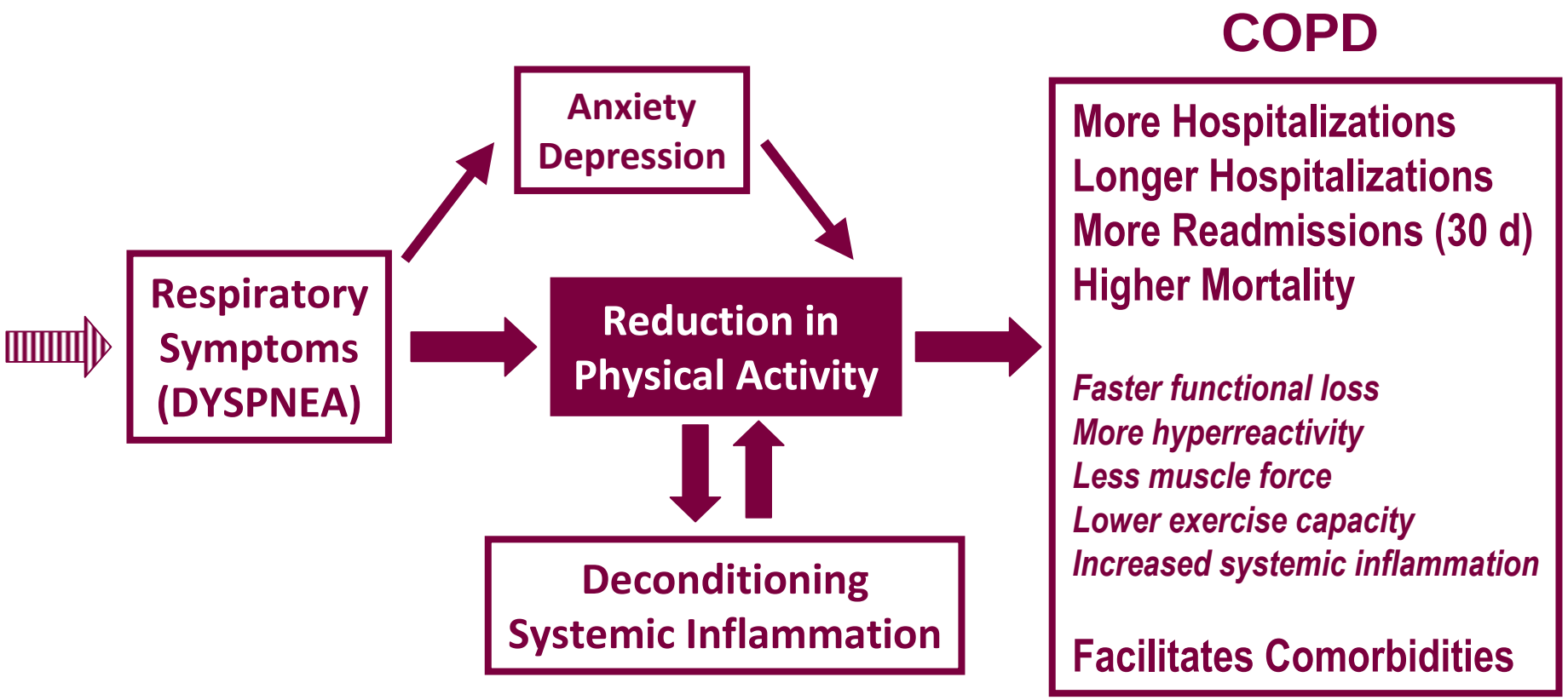
- B: **B***ody-mass Index*
- O: *Airflow* **O***bstruction*
- D: **D***yspnea*
- E: **E***xercise Capacity*

B. Celli et al. N Engl J Med 2004

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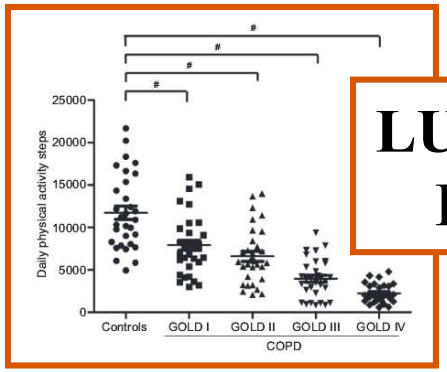


PHYSICAL ACTIVITY & COPD

Less PHYSICAL ACTIVITY

Dyspnea is the main symptom limiting exercise, which leads to reduced physical activity. The greater the dyspnea, the lower the levels of PA (ERS Statement 2104)

POOR CONTROL of SYMPTOMS



LUNG FUNCTION IMPAIRMENT

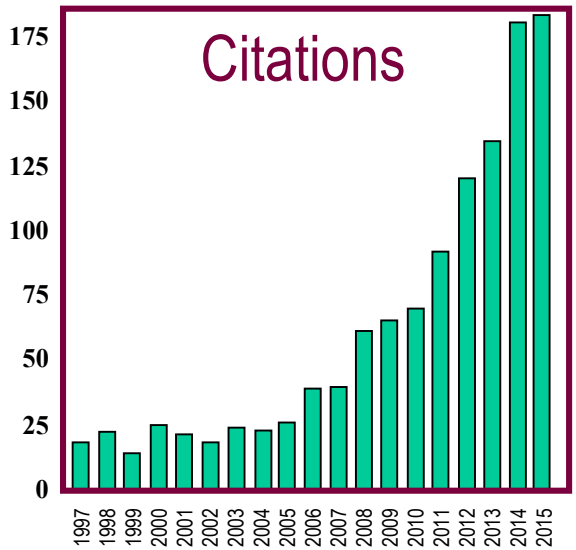
CARDIOVASCULAR DECONDITIONING

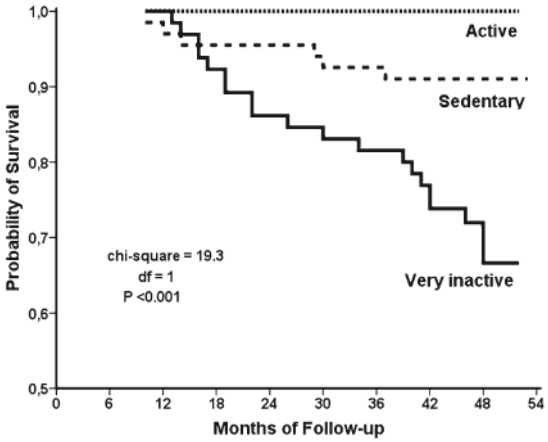
OSTEOPOROSIS MALNUTRITION

Muscle Mass Loss
SLELETAL MUSCLE DYSFUNCTION

Shrikrishna D. ERJ 2012

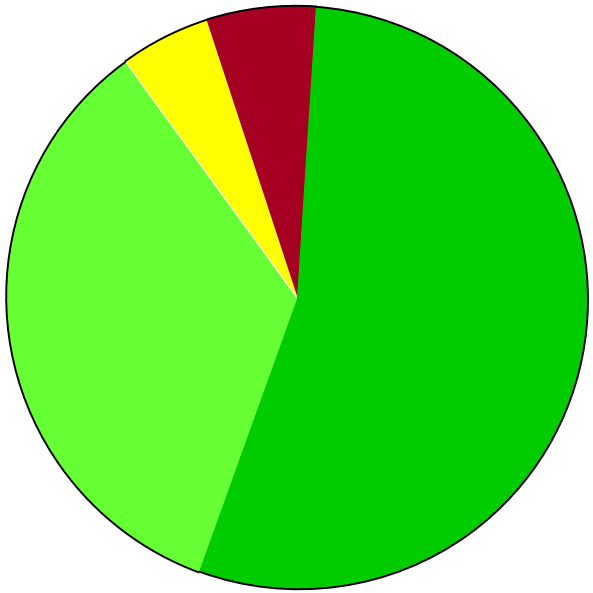
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Waschki B et al. Chest 2011; 140:331-342

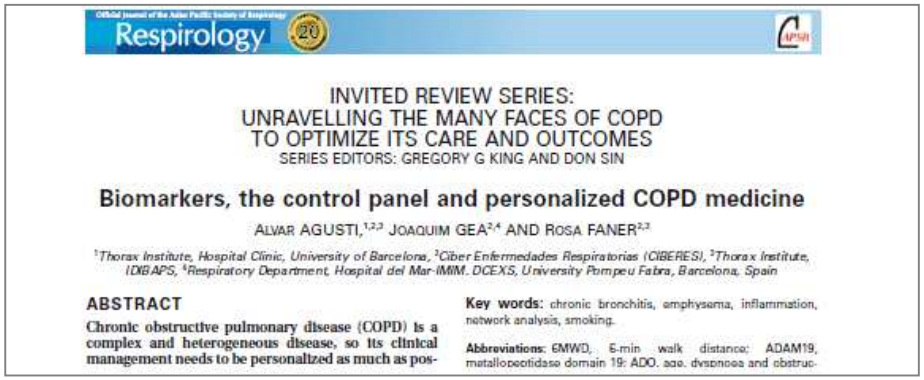
If a new treatment for COPD would improve your Physical Activity level you will consider it:



- The most important benefit
- A significant beneficial effect
- A beneficial but not very relevant effect
- I do not consider this as a beneficial effect

PROactive WP2

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Respirology

INVITED REVIEW SERIES:
UNRAVELLING THE MANY FACES OF COPD
TO OPTIMIZE ITS CARE AND OUTCOMES
SERIES EDITORS: GREGORY G KING AND DON SIN

Biomarkers, the control panel and personalized COPD medicine

ALVAR AGUSTI,[1,2,3] JOAQUIM GEA[2,4] AND ROSA FANER[2,3]

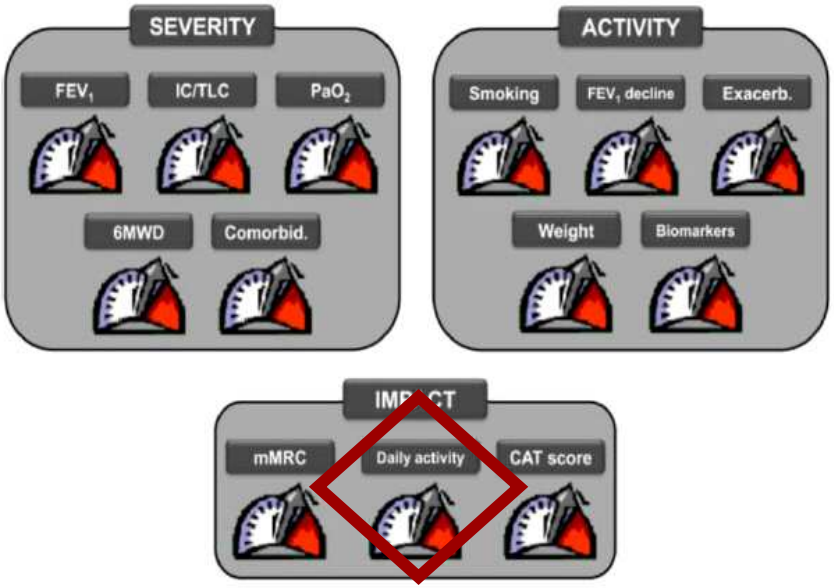
[1]Thorax Institute, Hospital Clínic, University of Barcelona, [2]Ciber Enfermedades Respiratorias (CIBERES), [3]Thorax Institute, IDIBAPS, [4]Respiratory Department, Hospital del Mar-IMIM. DCEXS, University Pompeu Fabra, Barcelona, Spain

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous disease, so its clinical management needs to be personalized as much as pos-

Key words: chronic bronchitis, emphysema, inflammation, network analysis, smoking.

Abbreviations: 6MWD, 6-min walk distance; ADAM19, metallopeptidase domain 19; ADO, age, dyspnoea and obstruc-



- ✓ **SEVERITY** (functional reserve)
- ✓ **ACTIVITY** (intensity of biological mechanisms)
- ✓ **IMPACT** (in the patient's life)

Questionnaires

- List of Activities
- MRF-28, PFSDQ, PFSDQ-M, UCDQ, FPI, CARS
- QoL-RIQ, DM Q, SOLQ, CCQ, CV -PERC, CSES
- PROactive

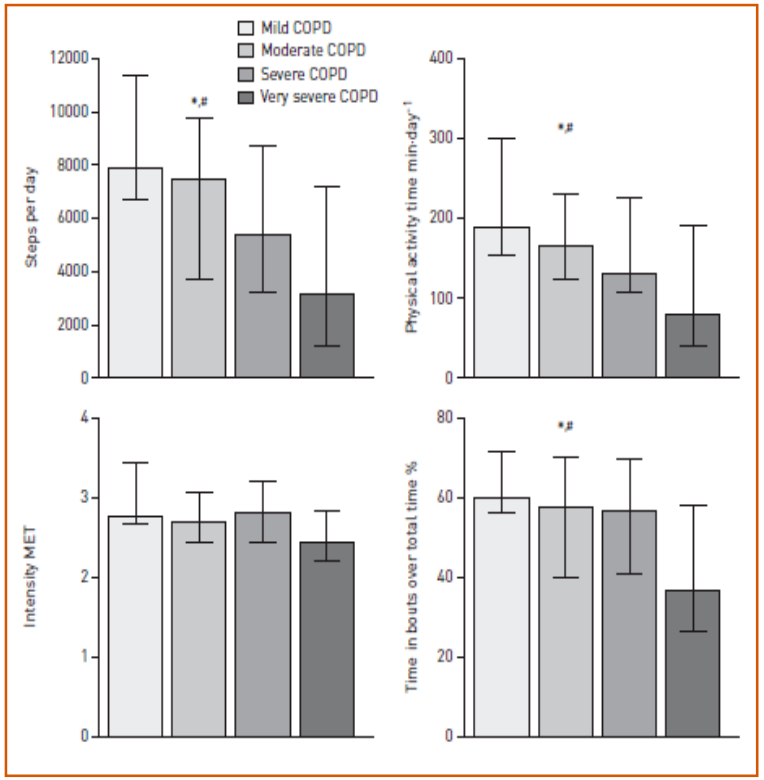
Other Instruments

- Pedometer (Step count)
- Accelerometers (Activity)
- Energy expenditure (doubly labeled water, DLW)

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PAC-COPD study, 342 patients

	Mild COPD	Moderate COPD	Severe COPD	Very Severe COPD
Subjects	9 (5)	87 (49)	64 (36)	17 (10)
Male	6 (67)	82 (94)	63 (98)	15 (88)
Age years	69±10	71±8	72±7	66±8
Working status: active	0 (0)	10 (11)	4 (6)	1 (6)
Low (IV, V) socioeconomic status	7 (78)	64 (82)	47 (80)	12 (75)
Current smokers	3 (33)	28 (32)	18 (28)	8 (47)
BMI kg·m^{-2}	28±4	30±5	28±4	25±5
Dyspnoea mMRC score	1.3±1.2	2.1±1.5	3.0±1.5	3.5±1.3
SGRQ total score	16±12	25±16	37±16	51±17
FEV$_1$ % pred	87±7	61±8	41±5	25±4
FEV$_1$/FVC %	67±7	60±9	47±11	35±8
RV/TLC %	46±5	54±8	62±8	69±7
Pa_{O_2} mmHg	81±8	76±10	72±10	69±9
6-min walking distance m	450±91	423±86	395±102	349±103



Donaire-González D. ERJ 2013

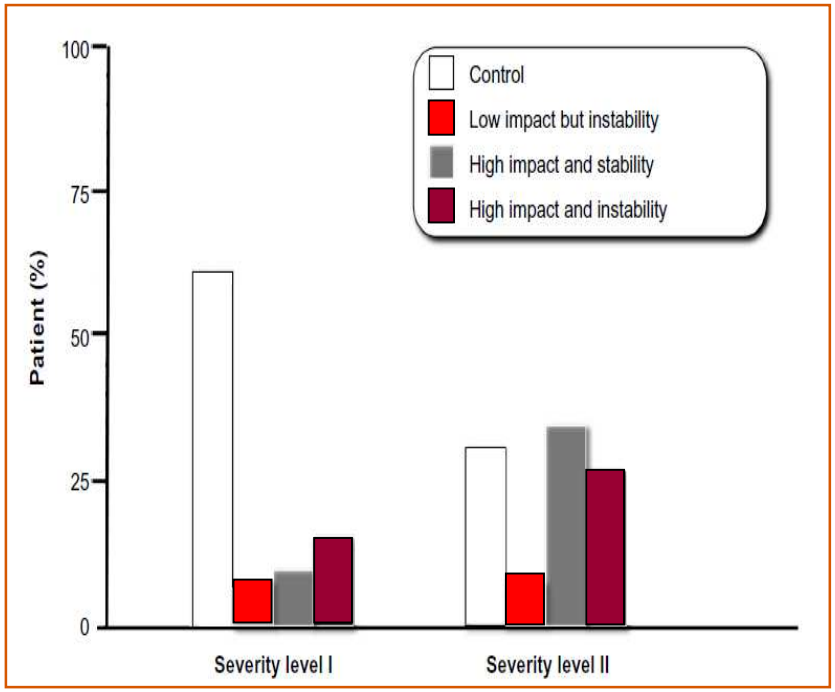
The greater the severity of the disease, more symptoms and the lower the level of Physical Activity (Less and Shorter efforts)

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DISEASE CONTROL

Static Control: Low Impact

Dynamic Control: Stability



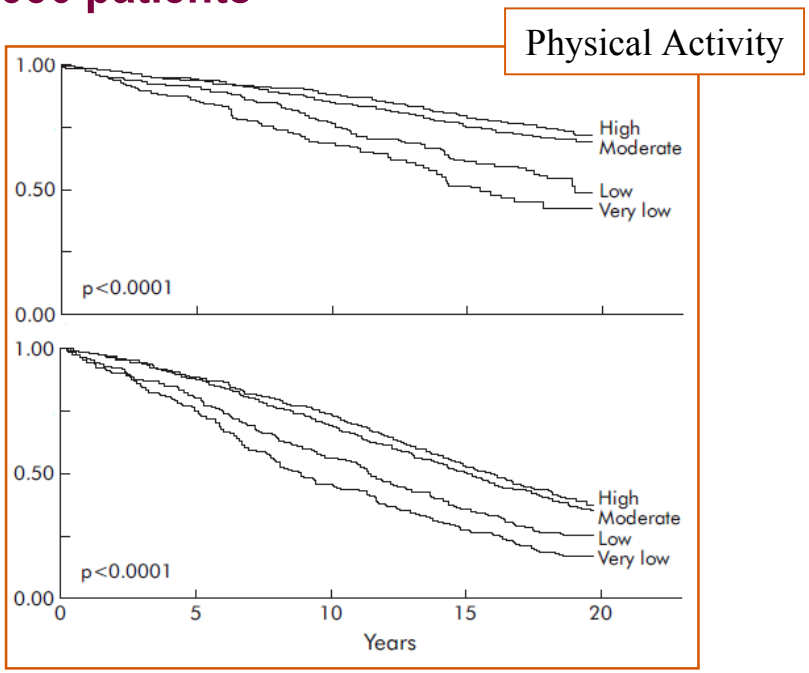
Soler-Cataluña JJ. IJCOPD 2014

Significant percentage with poor control

Symptom stability means good control
Can be further improved ?

PHYSICAL ACTIVITY & COPD

Copenhagen Population-based Register 2386 patients



Garcia-Aymerich J. Thorax 2006

EFRAM Study, 346 patients

Table 3 Multivariate adjusted risk factors of readmission to hospital for an exacerbation in a cohort of 312 patients with COPD (Cox regression)

	Adjusted HR (95% CI)	p value
⩾3 COPD admissions in the year before recruitment*	1.66 (1.16 to 2.39)	0.006
% predicted FEV_1	0.97 (0.96 to 0.99)	0.001
P_{O_2} (kPa)	0.88 (0.79 to 0.98)	0.024
Controlled by a:		
General practitioner	1.00	
Pulmonologist	1.66 (0.98 to 2.80)	0.058
Anticholinergics	1.81 (1.11 to 2.94)	0.017
Usual physical activity (in tertiles):		
<79 kcal/day	1.00	
79–232 kcal/day	0.87 (0.60 to 1.27)	0.469
>232 kcal/day	0.54 (0.34 to 0.86)	0.010

HR=hazard ratio; CI=confidence interval; FEV_1=forced expiratory volume in 1 second.
*HR for "COPD admissions as a continuous variable" 1.19 (95% CI 1.10 to 1.30), p=0.000.

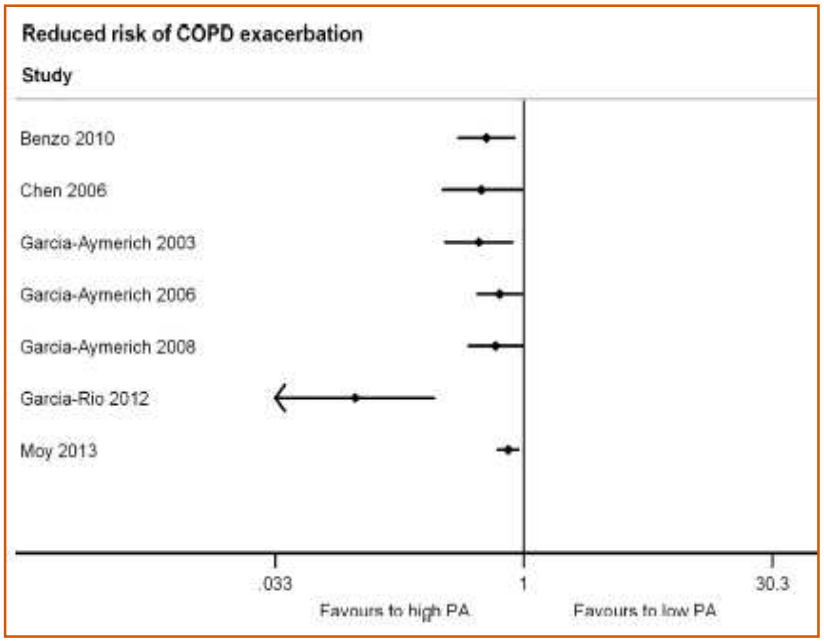
Garcia-Aymerich J. Thorax 2003

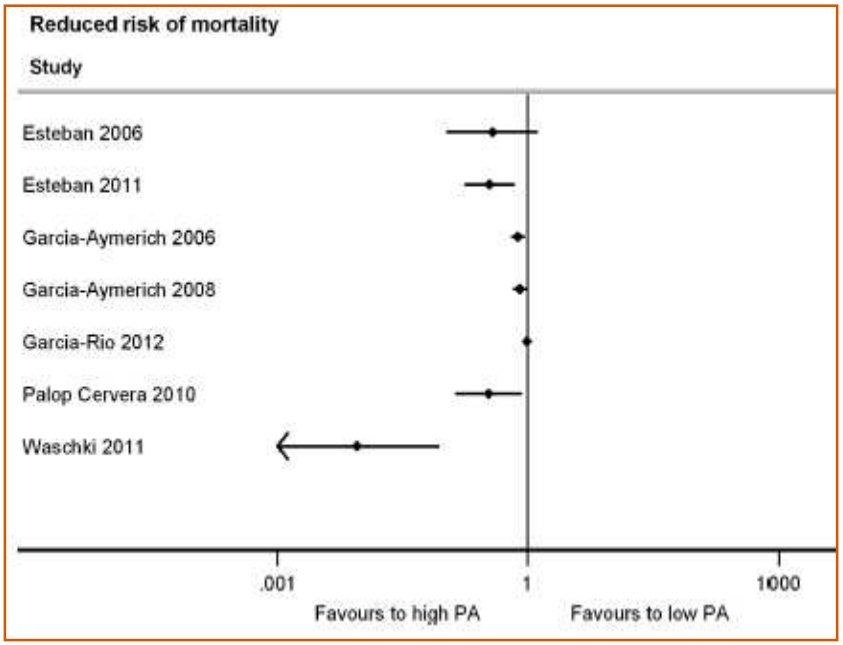
Moderate levels of regular physical activity results in lower risk of hospital admission and death

The higher the level of activity, the lower the risk of hospital admission

PHYSICAL ACTIVITY & COPD

Metaanalysis (86 studies)





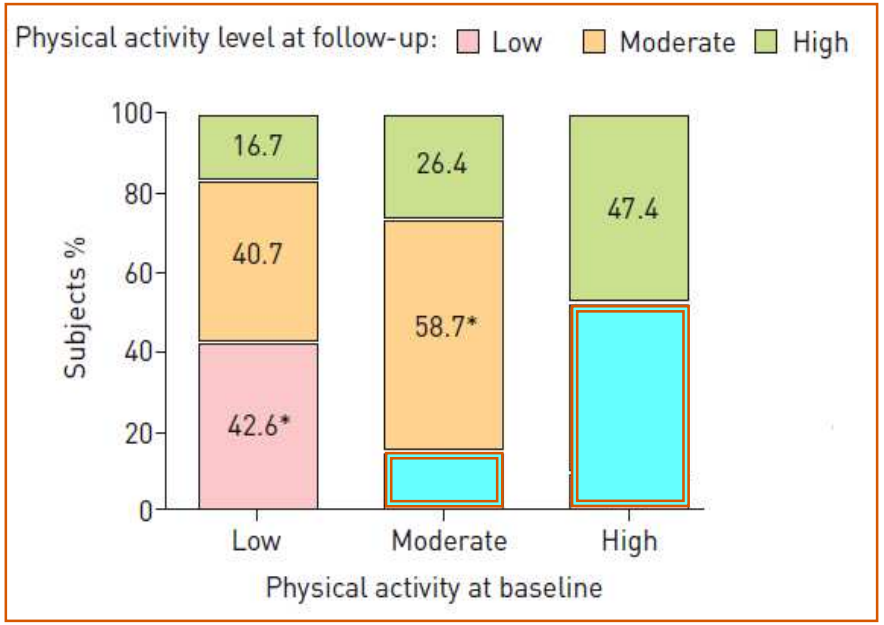
Gimeno-Santos E. Thorax 2014

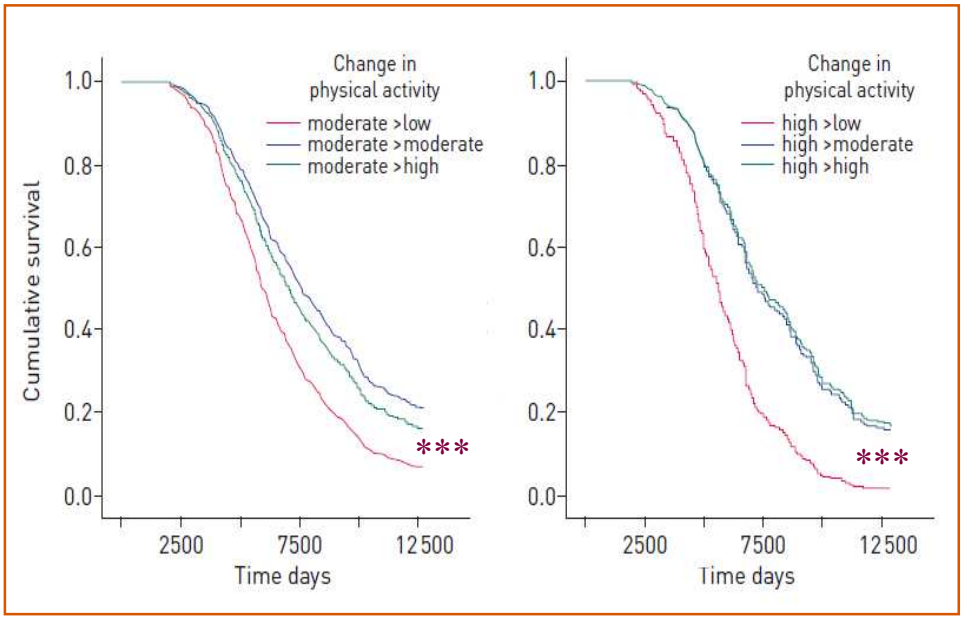
The level of Physical Activity is related to both nº of Exacerbations and Mortality

*"…this should attract attention since **some drug treatments could increase levels of physical activity**, for example, as a result of decreased hyperinflation, reduced symptoms and enhanced exercise capacity".*

PHYSICAL ACTIVITY & COPD

City of Copenhagen Heart Study (CCHS), 1270 patients





Vaes AW. ERJ 2014

If Physical Activity becomes reduced
(probably as a result of the evolution of the disease and its symptoms)
Mortality increases

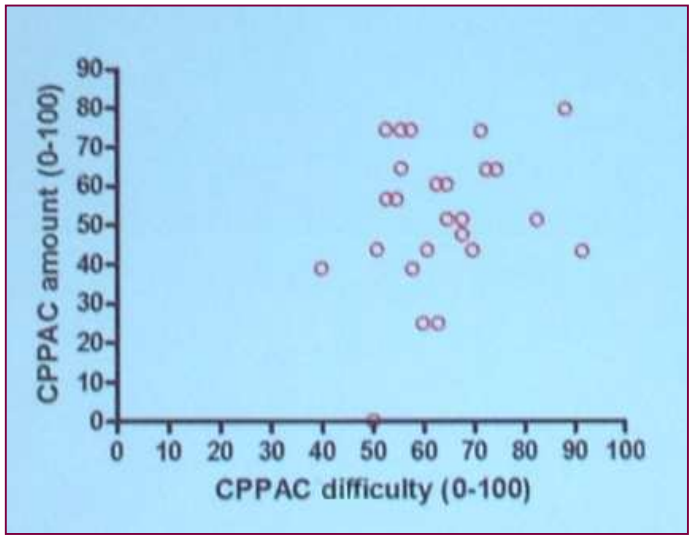
PHYSICAL ACTIVITY & COPD

Physical Activity is a Key factor for Health
There is a lack of validated instruments for its assessment

Dimensions of Physical Activity

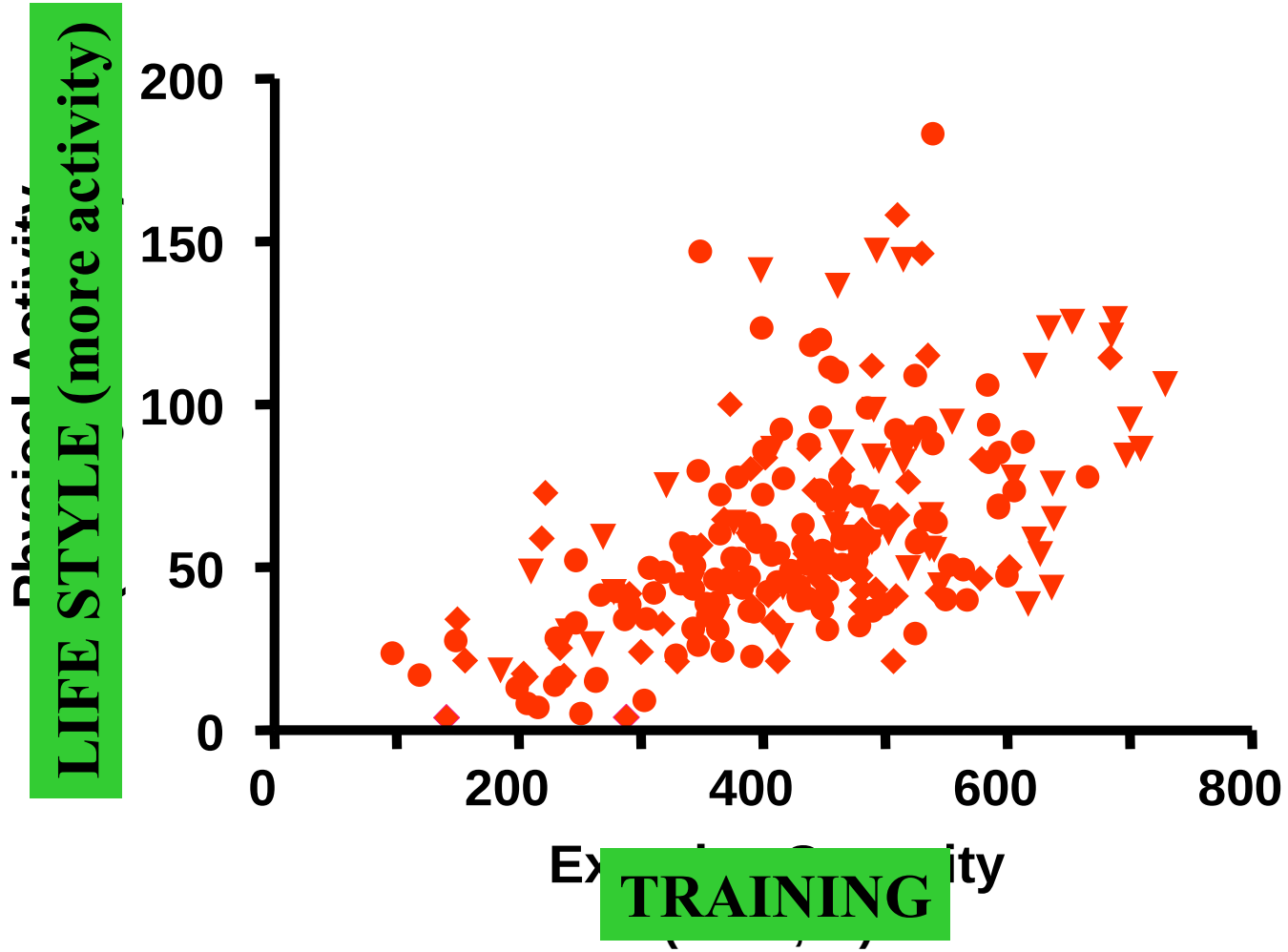
Amount of Activity
- How much I do ?

Limitations in doing Activity
- My troubles, my experience



Unfortunately, their relationship is low

PHYSICAL ACTIVITY & COPD



Data from PROactive Consortium

PHYSICAL ACTIVITY & COPD

To date there is a lack of instruments to assess appropriately Physical Activity

- Cross-sectional assesment
- Longitudinal assessment

  Evaluation of therapeutic interventions

Reference	**Drug**	**Time** (weeks)	Steps (Δ%)
DE O'Donnell et al. Respir Med 2011	Indacaterol	3	**-6**
T Troosters et al. NPJ PC Respir Med 2014	Tiotropium	24	**6**
H Watz et al. BMC Pulm Med 2014	Indacaterol	3	**10**
KM Beeh et al. BMC Pulm Med 2014	Aclidinium	3	**7**

Accelerometers

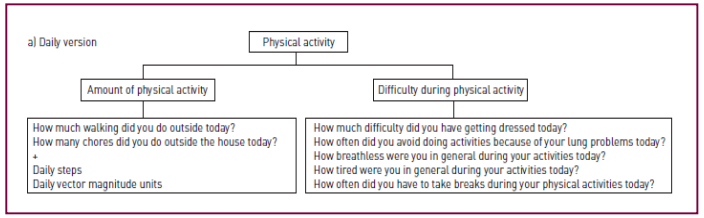
PHYSICAL ACTIVITY & COPD

Dimensions of Physical Activity

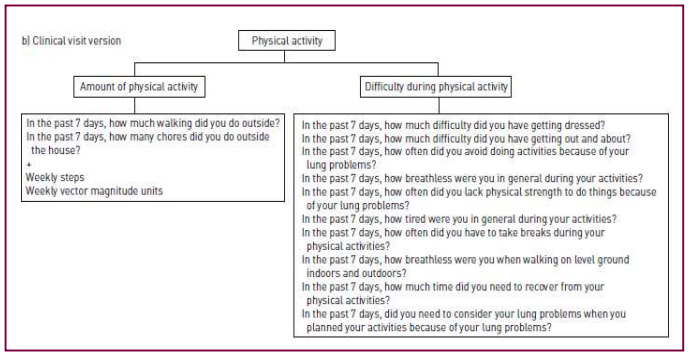
Amount of Activity
- 12 Possible items
- Instruments for Monitoring

Limitations in doing Activity
- 7 + 14 Possible items

→ Both daily 'PRO' and in the Clínical Visit:
- 2 Questions
- 2 Items from Monitors
  Steps & Vector Magnitude Units



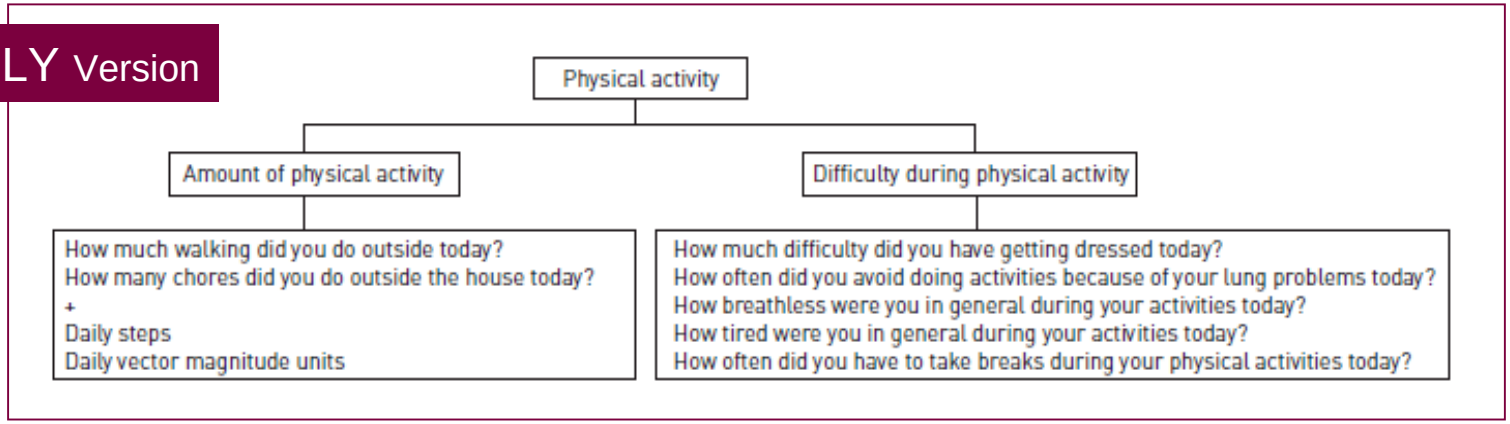
→
- Daily 'PRO': 5 Questions
- In the Clínical Visit: 10 Questions



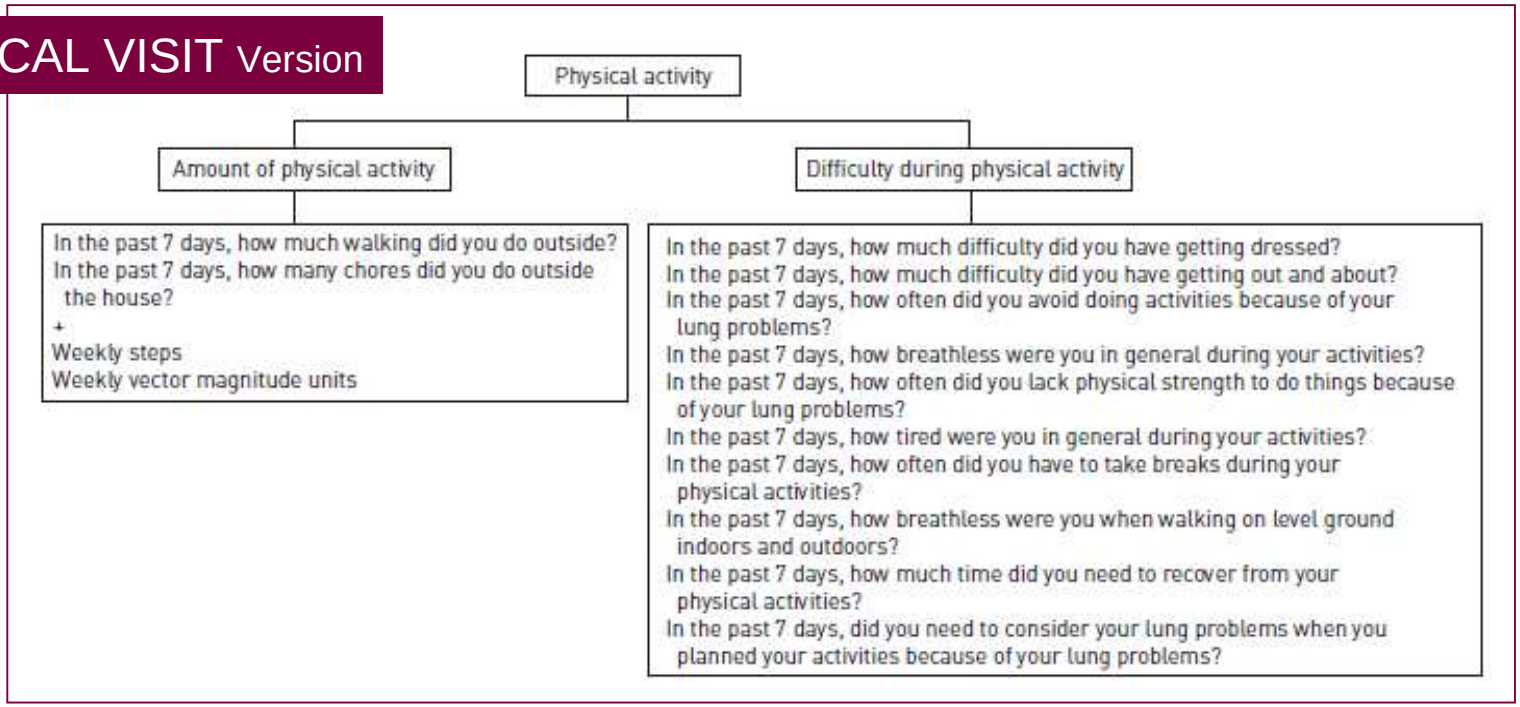
PROactive, Gimeno-Santos E. et al

PHYSICAL ACTIVITY & COPD

DAILY Version



CLINICAL VISIT Version

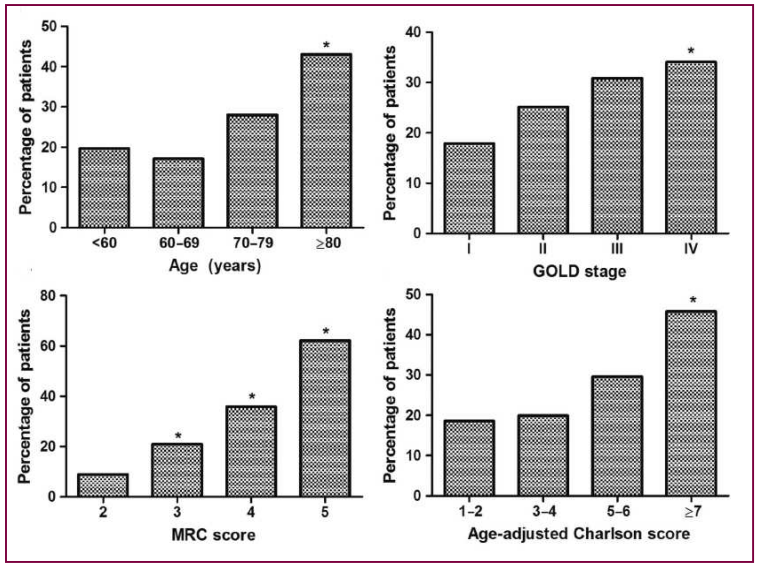


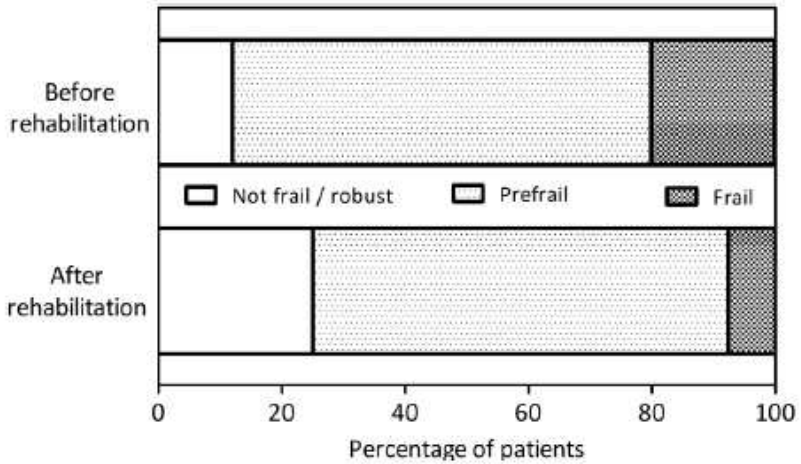
PHYSICAL ACTIVITY & COPD

Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study

Matthew Maddocks,[1] Samantha S C Kon,[2,3] Jane L Canavan,[2,4] Sarah E Jones,[2,4] Claire M Nolan,[2,4] Alex Labey,[2,4] Michael I Polkey,[2] William D-C Man[2,4]

Frailty: Low PA, weight loss, exhaustion,slowness, weakness
High prevalence in COPD (26%)





Frailty: Independent predictor of Rehab Program leaving
but Reversible with Rehab

Thorax 2016 [Epub ahead of print]

PHYSICAL ACTIVITY & COPD

INTERVENTIONS

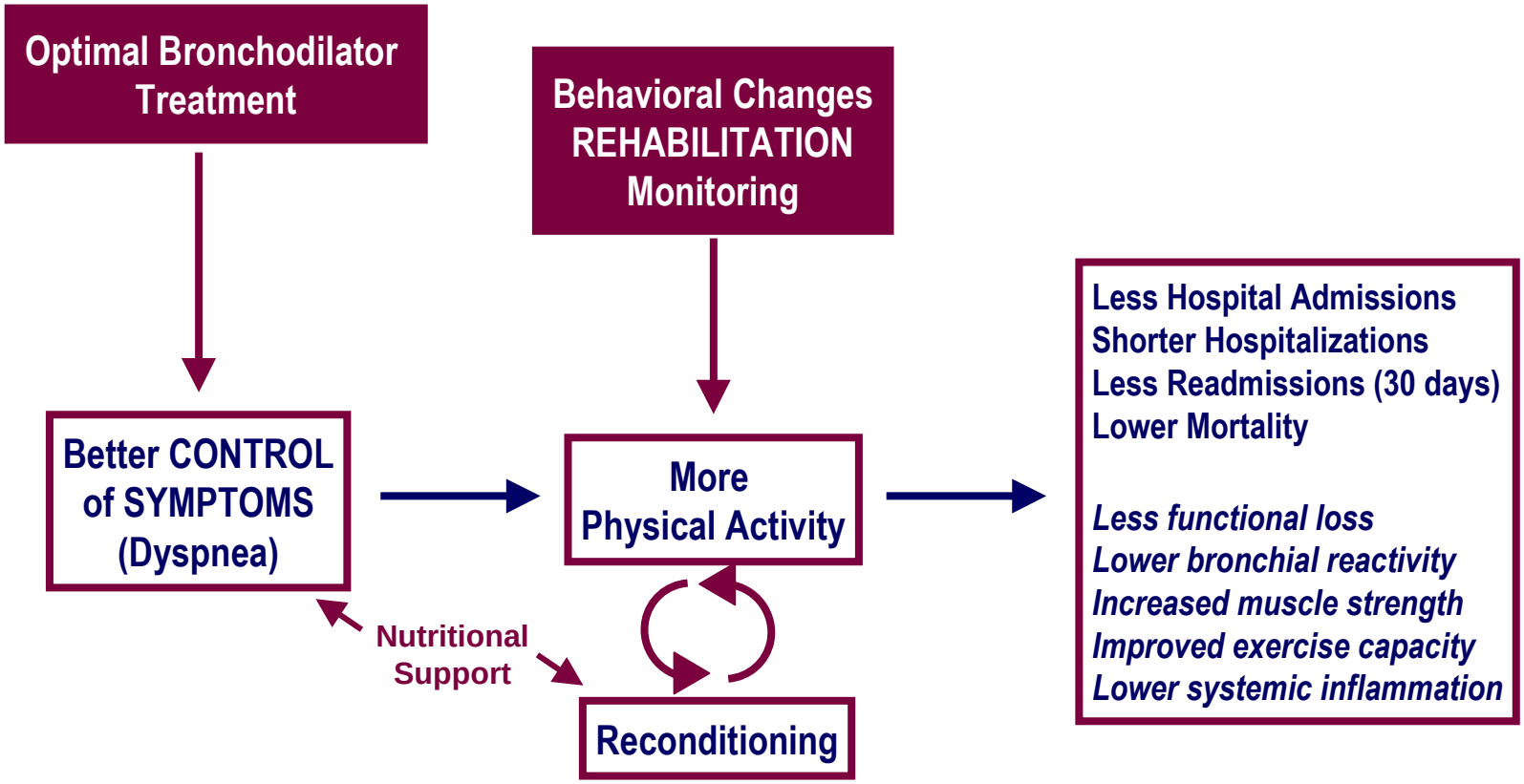
Amount of Activity
- How much I do ?

Limitations in doing Activity
- My troubles, my experience

Actions on the Patient Behaviour
- Steps Programs
- Telecoaching
- Interventions on the Environment
- Social Support Programs

Actions on the Patient Physiology
- General Training
- Bronchodilators (Optimization)
- Nutritional Support
- Other Drugs (?)
- Respiratory Muscle Training
- Oxygen Therapy

PHYSICAL ACTIVITY & COPD



PHYSICAL ACTIVITY & COPD

Pedometer-Directed Step Count Targets as an Adjunct to Pulmonary Rehabilitation in COPD: A Randomized Controlled Trial [Publication Page: A7862]

Claire M. Nolan[1], Matthew Maddocks[2], Jane L. Canavan[1], Sarah E. Jones[1], Samantha S.-C. Kon[1], Djeya Kaliaraju[3], Mike Polkey[4], William D.-C. Man[1].

[1]Respiratory Medicine, Nihr Respiratory Biomedical Research Unit Royal Brompton and Harefield NHS Foundation Trust and Imperial College, Harefield/United Kingdom, [2]Cicely Saunders Institute, King's College London, London/United Kingdom, [3]Harefield Pulmonary Rehabilitation Unit, Royal Brompton and Harefield NHS Foundation Trust, Harefield/United Kingdom, [4]Royal Brompton & Harefield NHS Foundation Trust, London/United Kingdom

The simple use of instruments (pedometer or accelerometers) and a specific objective (steps, min) is not enough to increase the level of Physical Activity in COPD













PHYSICAL ACTIVITY & COPD

The Effect of Indacaterol/ Glycopyrronium on Lung Function and Physical Activity in More Severe COPD - A Posthoc Subgroup Analysis of the MOVE Study [Publication Page: A6826]

Henrik Watz[1], Claudia Mailaender[2], Anne-Marie Kirsten[1].

[1]Pulmonary Research Institute at Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf/Germany, [2]Clinical Research, Novartis Pharma Gmbh, Nuremberg/Germany

Post-Hoc from the MOVE study (multicentric, randomized, crossover, placebo-controlled): 192 COPD patients, double bronchodilation (Indacaterol 110 µg & Glycopyrronium 50 µg / 24 h) in Lung Function and Physical Activity

Those with FEV_1> 62% pred. or IC>73% pred. vs. those with FEV_1<62% pred. ir IC<73% pred.

Both groups improved obstruction and air trapping

Only more obstructed and/or trapped patients improved physical activity (monitor metabolic-activity)



The Effect of Aclidinium Bromide 400 µg on Lung Function, Sleep Quality and Physical Activity in Patients with Chronic Obstructive Pulmonary Disease: Results of a Phase IV Pilot Study [Publication Page: A6820]

Helgo Magnussen[1], Michael Arzt[2], Stefan Andreas[3], Tanja Plate[4], Anna Ribera[5], Beatriz Seoane[5], Henrik Watz[1], Anne-Marie Kirsten[1].

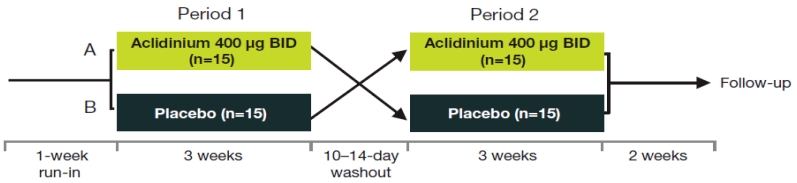
[1]Pulmonary Research Institute at Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf/Germany, [2]Usmz Universitäres Sleep Disorders Center, Regensburg/Germany, [3]Universitätsmedizin Göttingen, Göttingen/Germany, [4]Astrazeneca Gmbh, Hamburg/Germany, [5]Astrazeneca Plc, Barcelona/Spain

Pilot study (randomized, double-blind, crossover, placebo-controlled): 30 COPD patients (Aclidinium Bromure 400 µg / 12 h) in Lung Function, Sleep quality ans Physical Activity.

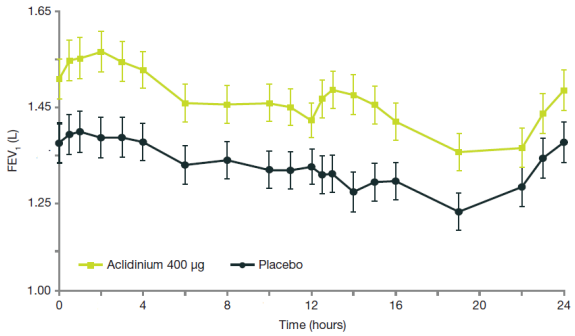
Airflow obstruction and the REM phase of sleep improved. Positive tendency in Sleep time & efficiency

Tendency for imporvement in moderate Physical Activity (Δ 18 min/day & Δ 246 steps/day)

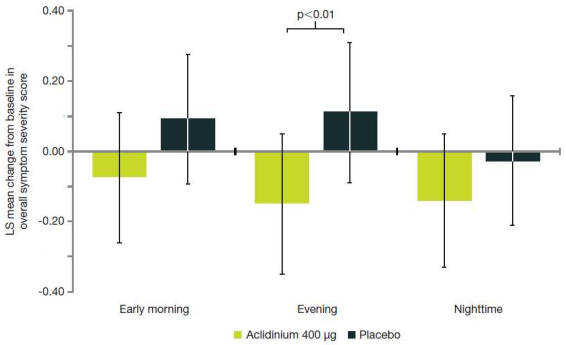
PHYSICAL ACTIVITY & COPD



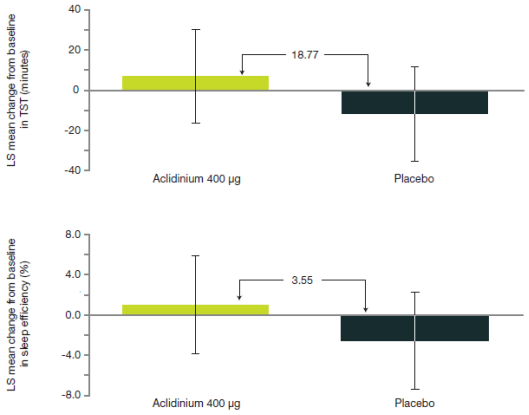
FEV$_1$ (3rd week)



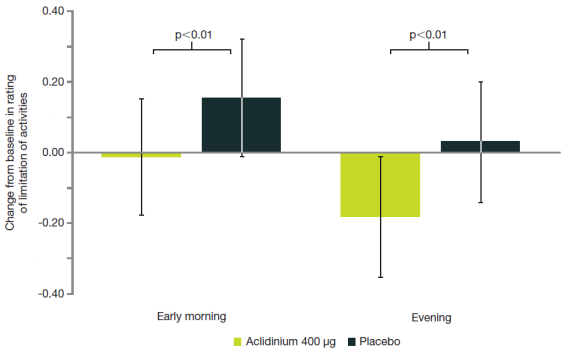
Symptoms (3rd week)



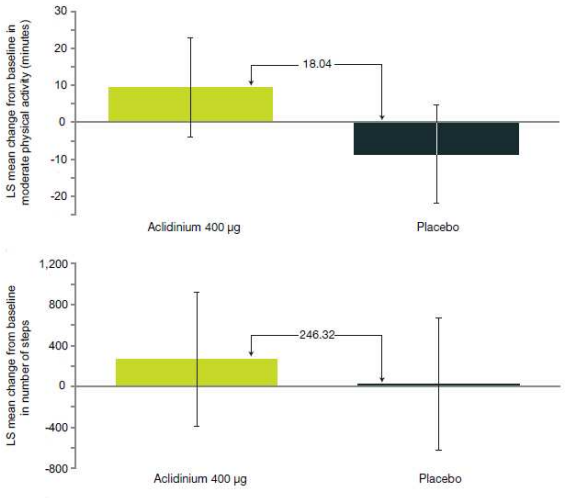
Sleep Quality (3rd week)



Limitation of Activities (3rd week)



'Amount' of Physical Activity (min & steps)



Magnussen H et al. ARRCCM 2016 (abstract)

PHYSICAL ACTIVITY & COPD

Physical activity is a prognostic marker in COPD

Two Dimensions in Physical Activity: Amount & Limitations
New assessment instruments

Patients consider very important that a treatment can improve their Physical Activity

Combination of Questionnaires & Monitors: better patient assessment and better prediction of response to treatment

Predictors of Physical Activity level: Sex, Symptoms (respiratory and depressive), Overweight and Social environment

Best results: Training + Behavioral Changes + Bronchodilators (x2)

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