



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

EMA Workshop:  
Ensuring safe and  
effective medicines for  
an ageing population

22-23 March 2012: European  
Medicines Agency, London, UK

# Frailty: Challenges and Possible Solutions

## Niccolò Marchionni

**Professor of Geriatrics**  
**University of Florence, Italy**

**EMA Geriatric Expert Group**

Joël Ankri	Antonio Cherubini
Adalstein Gudmundsson	Paul Jansen
Niccolò Marchionni ( <i>Chair</i> )	Susan Morgan
Mirko Petrovic	Michael Theodorakis
Hans Wildiers	

**... and Francesca Cerreta, EMA**

# Frailty: a definition

- Multi-factorial syndrome, caused by a reduction of physiological reserves and of the capability to resist stressful events (homeostatic capacity)
- Associated with an increased risk of unfavorable clinical events: disability, hospitalization, institutionalization, death
- Complex and dynamic condition, for which several models have been proposed

# Frailty: challenges

- How can frailty be practically measured in clinical settings?
- Are frailty measures useful to predict “hard” outcomes independently of co-morbidity and/or disability (a pre-requisite for adopting measures of frailty in RCTs)?
- Is frailty itself a potentially relevant outcome measure in RCTs?

# Frailty: challenges

- How can frailty be practically measured in clinical settings?

## Operative definition of **frailty** in a general older population – *The Cardiovascular Health Study*

1. Strength (handgrip) in lowest quintile
2. Gait speed in lowest quintile
3. Unintentional weight loss  $\geq 4,5$  kg during last year
4. Increased tendency to exhaustion
5. Usual physical activity in lowest quartile



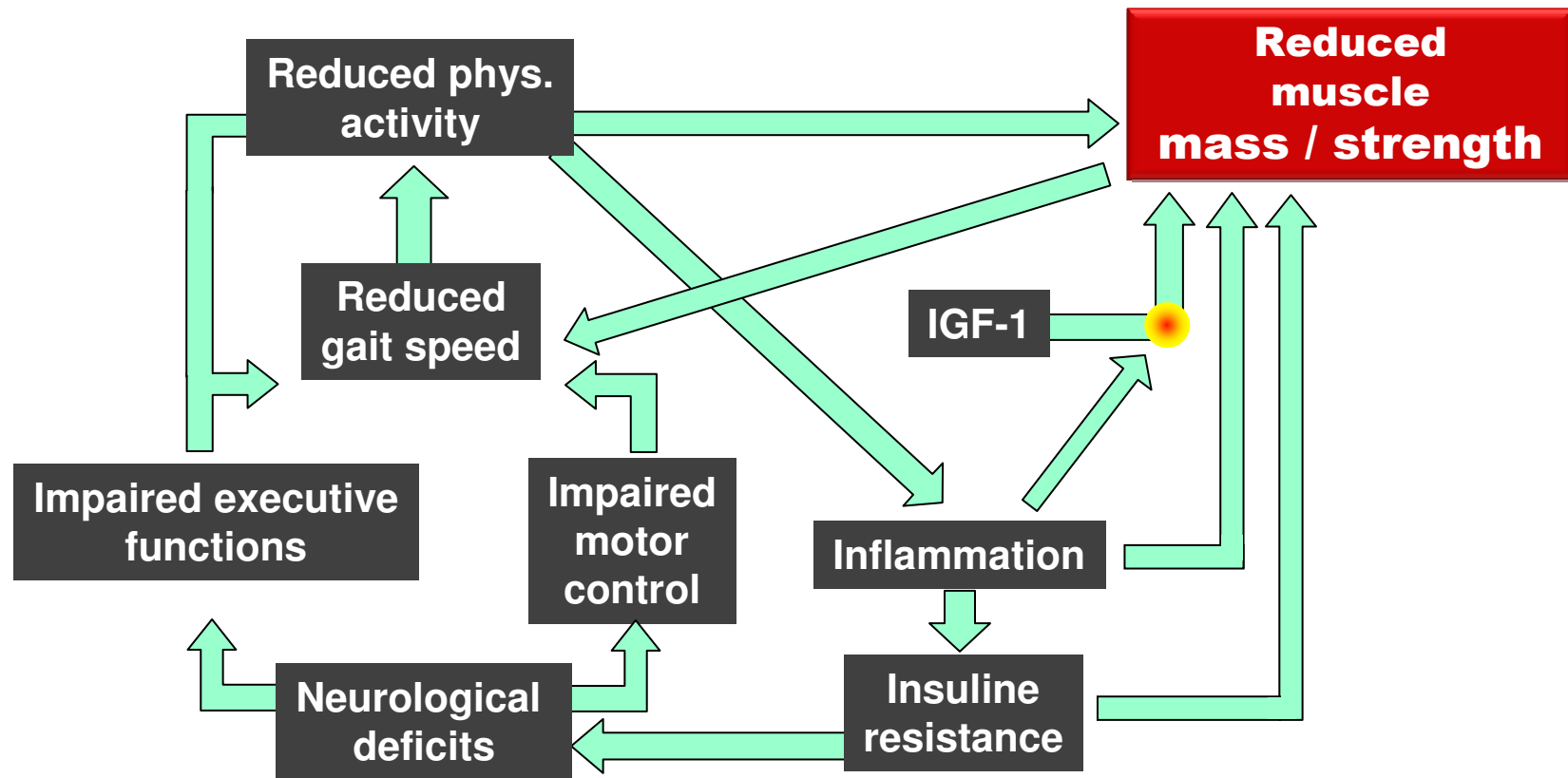
### **PHENOTYPE FRAILITY INDEX (PFI)**

**Frail:  $\geq 3$  components**

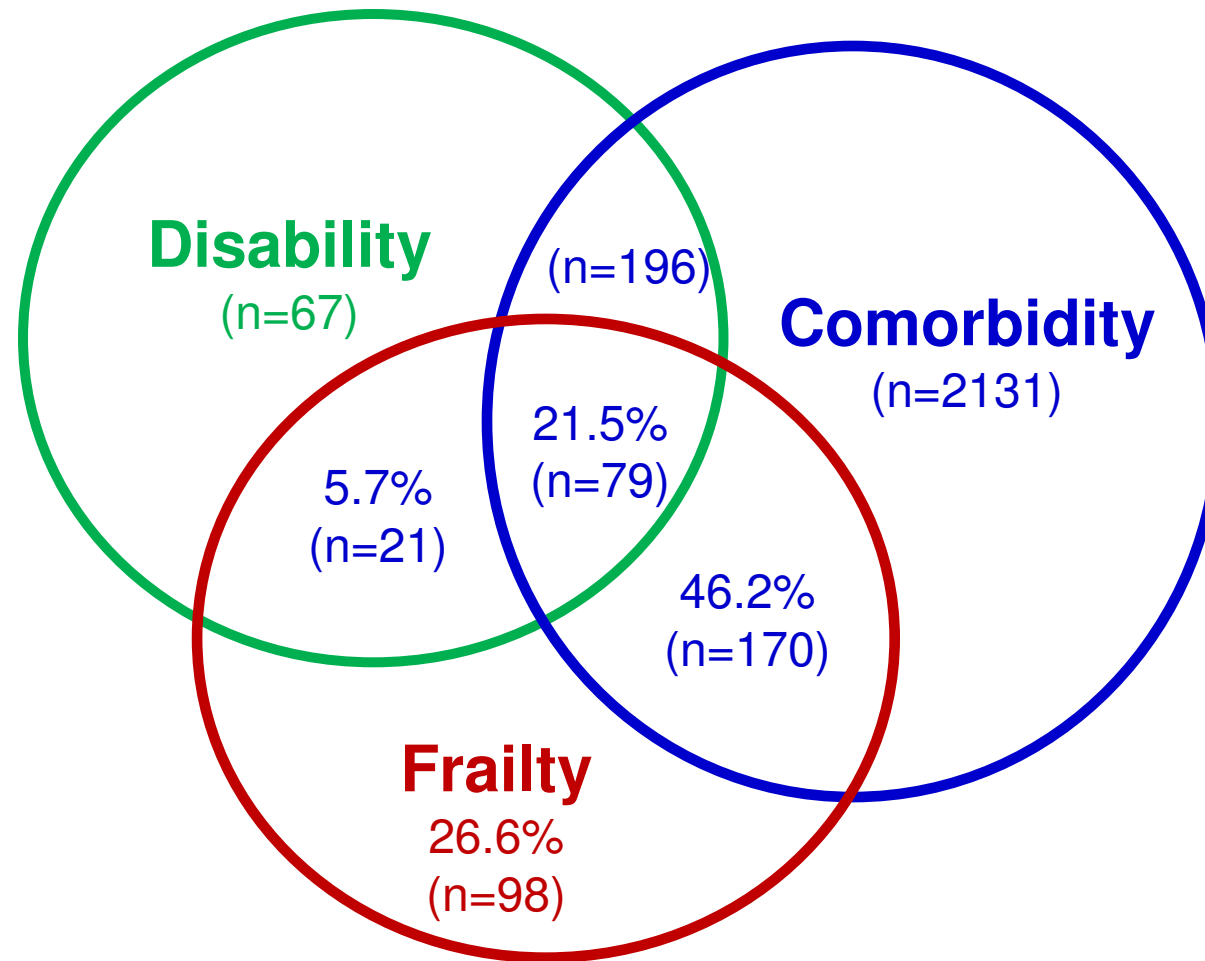
**Intermediate (pre-frail): 1 or 2 components**

**Non frail (robust): 0 components**

# Aging and the Pathogenesis of Sarcopenia: a Dimension of **Frailty** (?)



# The relationship of **frailty** with disability and comorbidity according to the PFI – *The Cardiovascular Health Study*

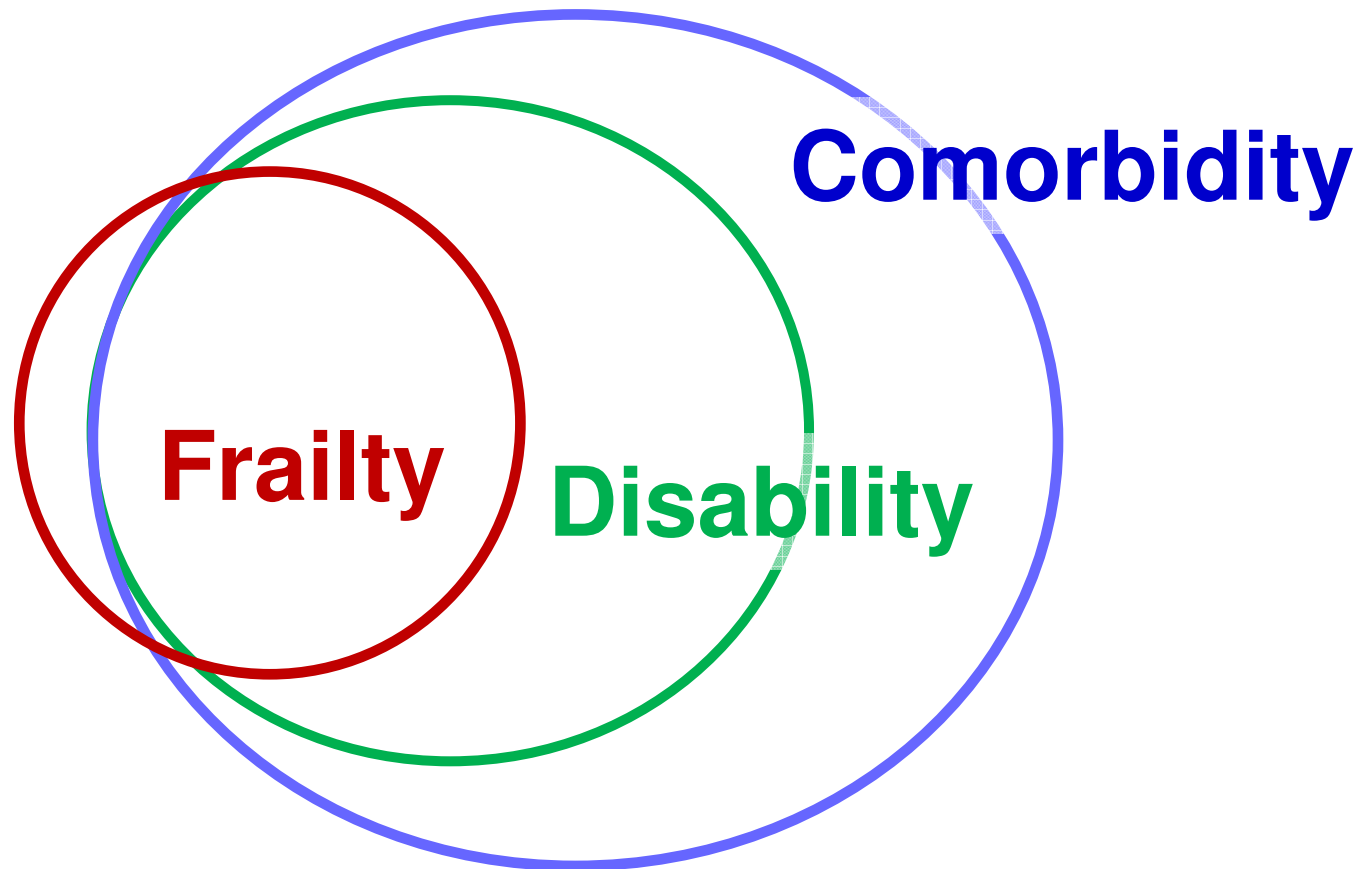


# Operative definition of **frailty** according to the Deficit Index (DI) - *Canadian Study of Health and Aging*

1. Very fit — robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
2. Well — without active disease, but less fit than people in category 1
3. Well, with treated co-morbid disease — disease symptoms are well controlled compared with those in category 4
4. Apparently vulnerable — although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms
5. Mildly frail — with limited dependence on others for instrumental activities of daily living
6. Moderately frail — help is needed with both instrumental and non-instrumental activities of daily living
7. Severely frail — completely dependent on others for the activities of daily living, or terminally ill



# The relationship of **frailty** with disability and comorbidity according to the DI



# Reduced physical performance and **frailty**: the *Short Physical Performance Battery (SPPB)*

– Includes three tests:

• **Standing balance** (up to 10 seconds for each item)

– Side-by-side → 

– Semi-tandem → 

– Tandem → 

• **Walking speed (4 meters)** → 

• **5 chair standing** → 

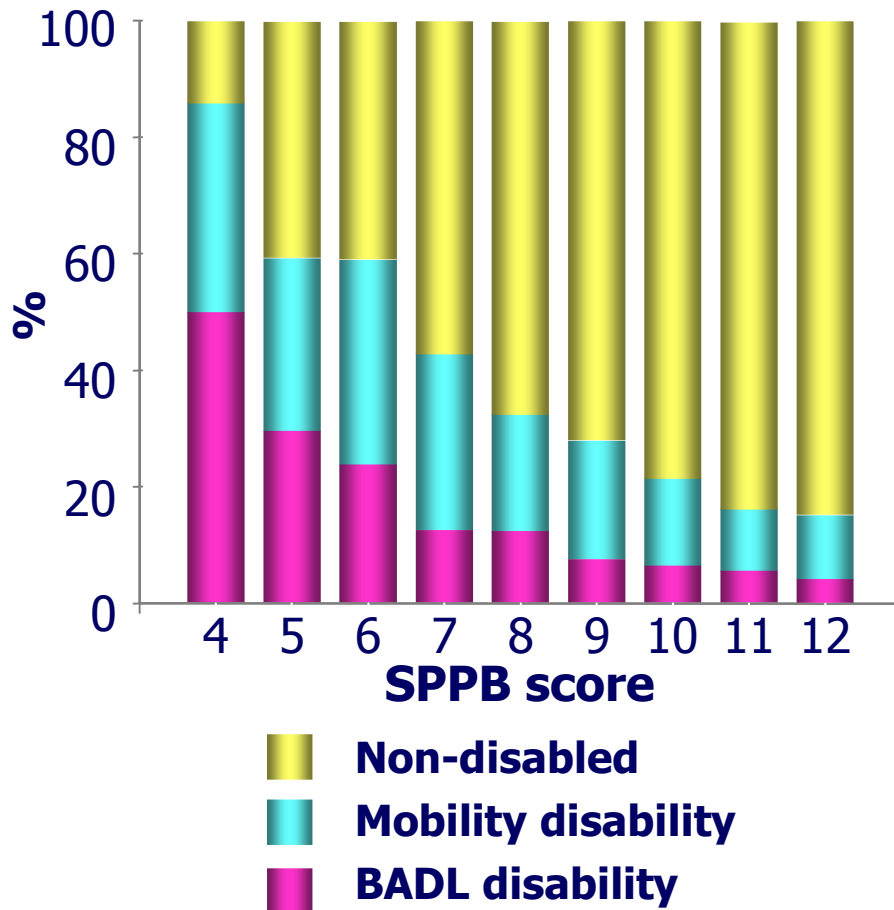
– Score 0-4 for each test, total 0-12 range

# Frailty: challenges

- How can frailty be practically measured in clinical settings?
- Are frailty measures useful to predict “hard” outcomes independently of co-morbidity and/or disability (a pre-requisite for adopting measures of frailty in RCTs)?
- Is frailty itself a potentially relevant outcome measure in RCTs?

# Predicting the risk of incident disability and death by SPPB score: population studies

N= 1122, FU 4 yrs.



N= 688, FU 8 yrs.

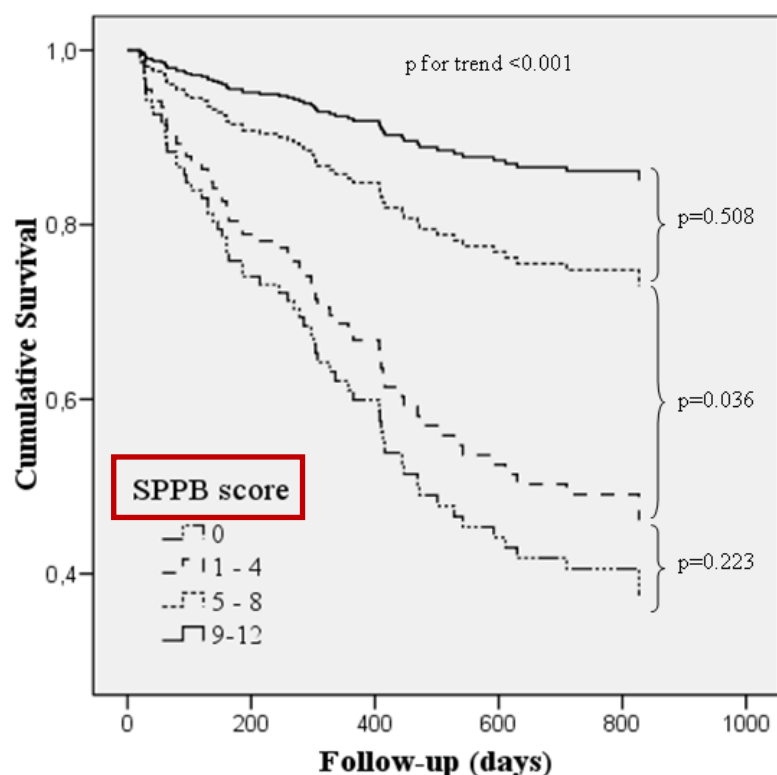
Table 4. Final Parsimonious Cox Proportional Hazard Models Predicting Death, Obtained Using Backward Deletion of Redundant Variables

Models and Variables	Hazard Ratio (95% Confidence Interval)	P-value
Model 3		
Index of Coexistent Diseases		.01*
Level 1	1	
Level 2	1.5 (0.9–2.4)	.10
Level 3	1.8 (1.1–3.1)	.02
Level 4	2.2 (1.3–3.6)	.002
Age	1.12 (1.11–1.15)	<.001
Sex (female vs male)	0.5 (0.4–0.6)	<.001
<b>SPPB score</b>	<b>0.93 (0.88–0.99)</b>	<b>.008</b>
MMSE	0.98 (0.94–0.996)	.03

# Lower Extremity Performance Measures Predict Long-Term Prognosis in Older Patients Hospitalized for Heart Failure

DANIELA CHIARANTINI, MD,<sup>1</sup> STEFANO VOLPATO, MD, MPH,<sup>2</sup> FOTINI SIOULIS, MD,<sup>2</sup> FRANCESCA BARTALUCCI, MD,<sup>1</sup> LAURA DEL BIANCO, MD,<sup>1</sup> IRENE MANGANI, MD,<sup>1</sup> GIUSEPPE PEPE, MD,<sup>3</sup> FRANCESCA TARANTINI, MD, PhD,<sup>1</sup> ANDREA BERNI, MD,<sup>4</sup> NICCOLO MARCHIONNI, MD,<sup>1</sup> AND MAURO DI BARI, MD, PhD<sup>1</sup>

(*J Cardiac Fail* 2010;16:390–395)

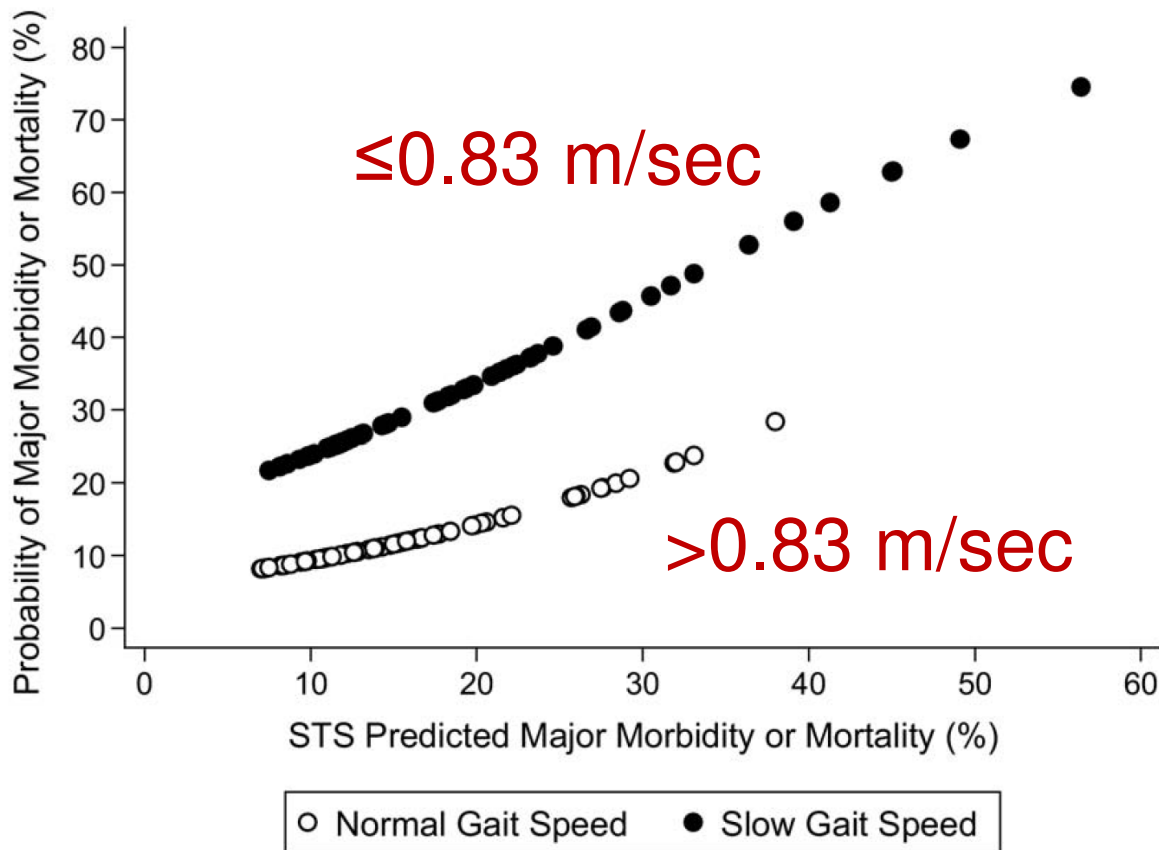


	HR (95% CI)	p value
<b>SPPB</b>		0.001*
<b>0</b>	6.1 (2.2-16.8)	0.001
<b>1-4</b>	4.8 (1.6-14.0)	0.004
<b>5-8</b>	2.0 (0.7-5.7)	0.223
<b>9-12</b>	Ref.	–
<b>Sex</b> (M vs. F)	1.2 (0.7-2.0)	0.583
<b>Age</b> (years)	0.98 (0.94-1.02)	0.355
<b>Site</b> (Ferrara vs. Florence)	1.9 (0.7-5.4)	0.216
<b>LVEF</b> (%)	0.97 (0.95-0.99)	0.005
<b>CIRS-C</b>	1.5 (1.1-1.98)	0.004
<b>NYHA class</b>	1.5 (1.1-2.2)	0.022

MMSE, depression, drug therapy and previous functional status deleted stepwise

\* For trend

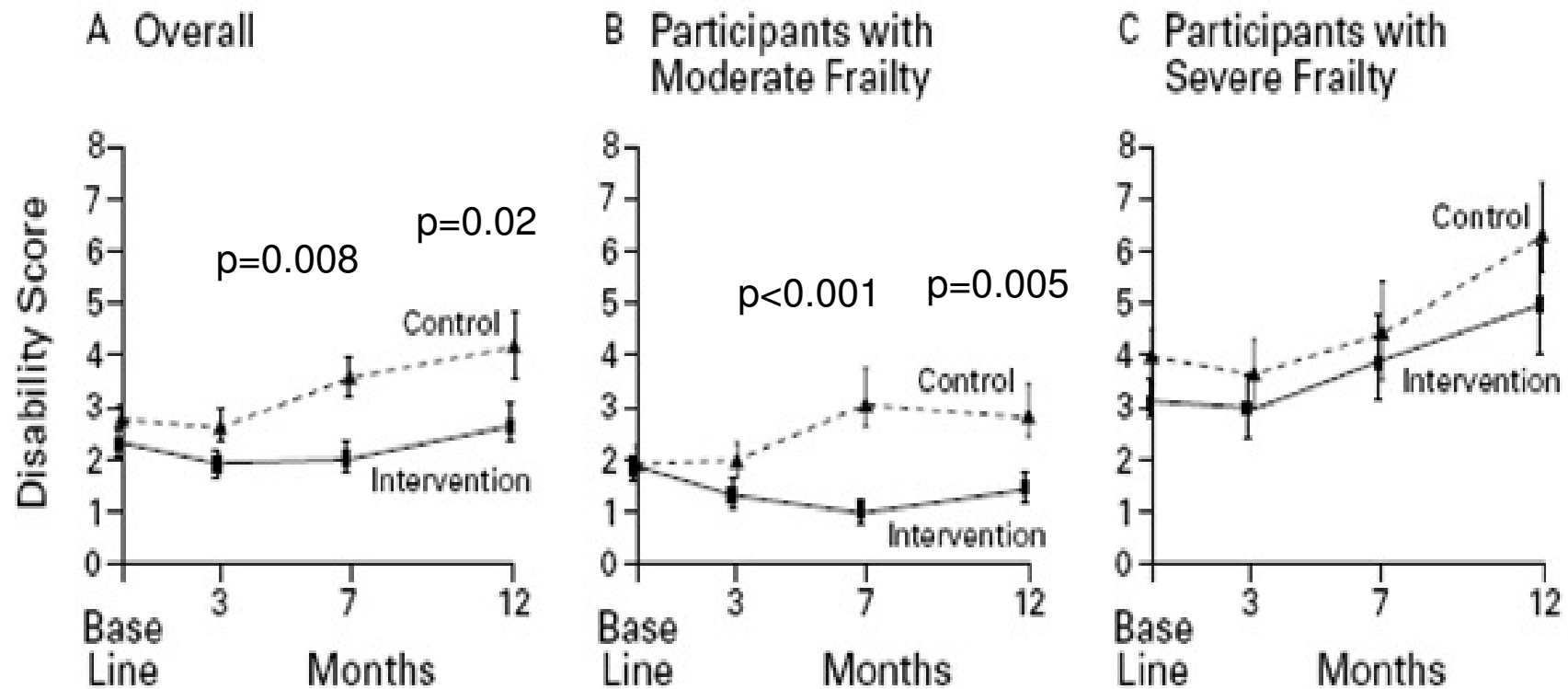
# Gait speed (5 meters) predicts the prognosis in older patients after cardiac surgery



- 131 pts., age 76 years
- Pre-operative assessed with Society of Thoracic Surgeons (STS) risk score

**$\leq 0.83$  vs.  $> 0.83$  m/sec:  
OR 3.1 (1.2-7.5),  
adjusted for STS score**

# Exercise intervention in **frail** (reduced gait speed or inability to stand from a chair) older persons

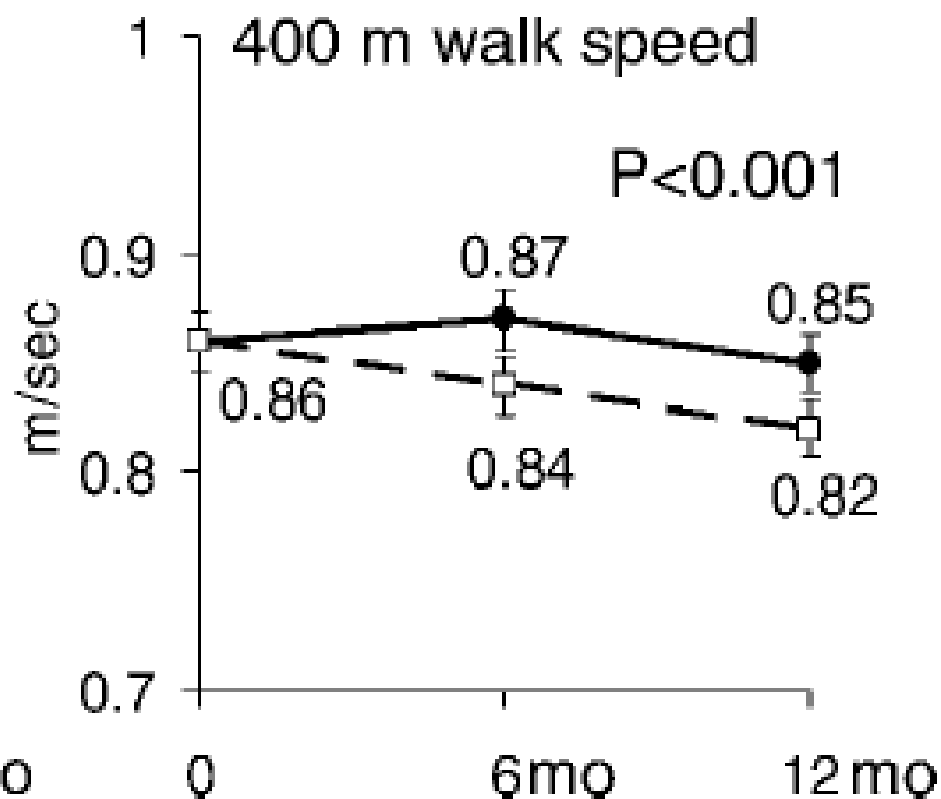
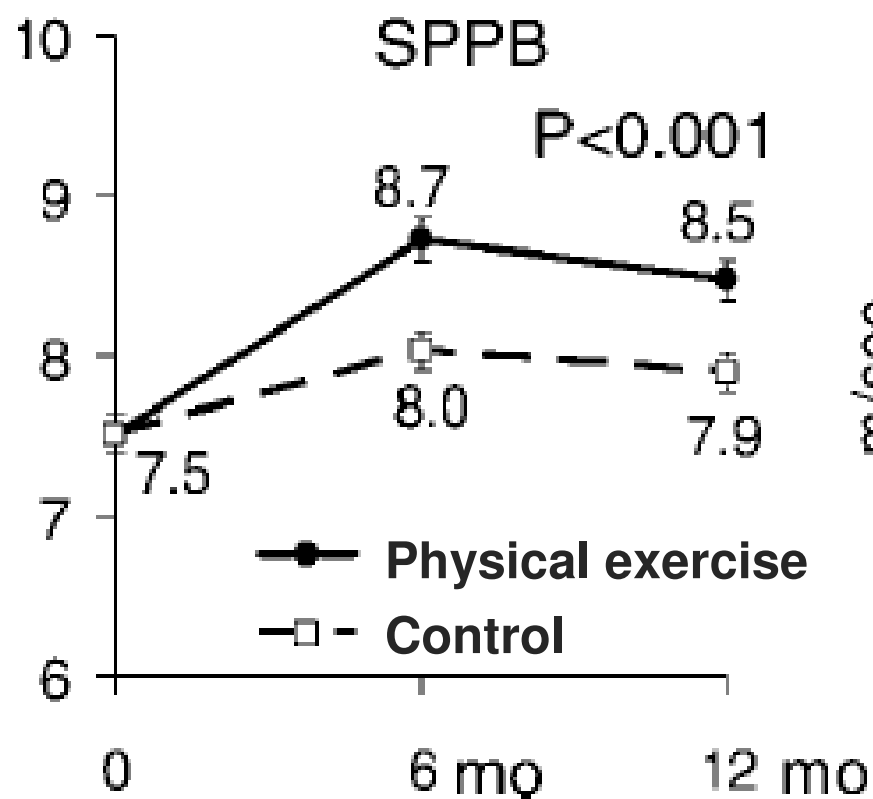


# Frailty: challenges

- How can frailty be practically measured in clinical settings?
- Are frailty measures useful to predict “hard” outcomes independently of co-morbidity and/or disability (a pre-requisite for adopting measures of frailty in RCTs)?
- Is frailty itself a potentially relevant outcome measure in RCTs?



# An RCT (LIFE study) of physical exercise in **frail** (SPPB 5-9) older persons



# Frailty: Challenges and Possible Solutions – Conclusion (1/2)

- **Frailty** (L. Fried's model) predicts clinically relevant outcomes (incident disability, death rate) in the general older population and in chronic conditions that are common in older persons, such as CHF
- The predictive value of frailty is **independent of comorbidity, disability and disease-specific severity indexes**

# Frailty: Challenges and Possible Solutions – Conclusion (2/2)

- In RCTs, frailty proved to be either a valid **selection** or a valid **outcome** measure
- Because of its independent prognostic power, measures of frailty could be proposed as **an adjustment variable** in pre- or post-registration pharmacological trials in older persons