

*Action Duchenne Meeting, London Nov  
'10*

# ***Cardiac Involvement in Duchenne & Becker Muscular Dystrophy***

***John P. Bourke***

*Consultant & Senior Lecturer in Cardiology*



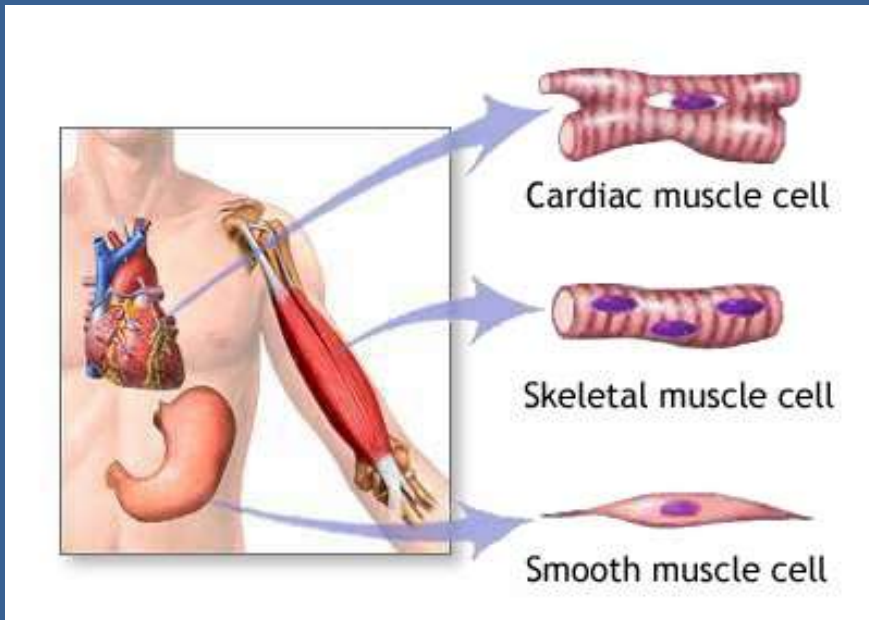
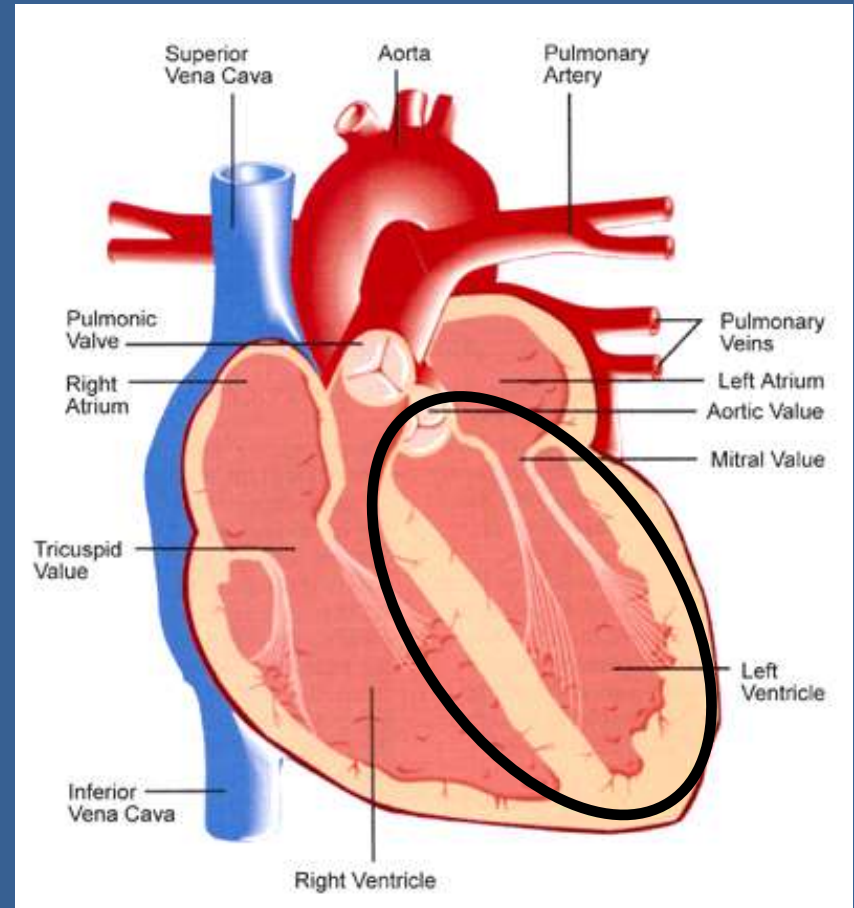
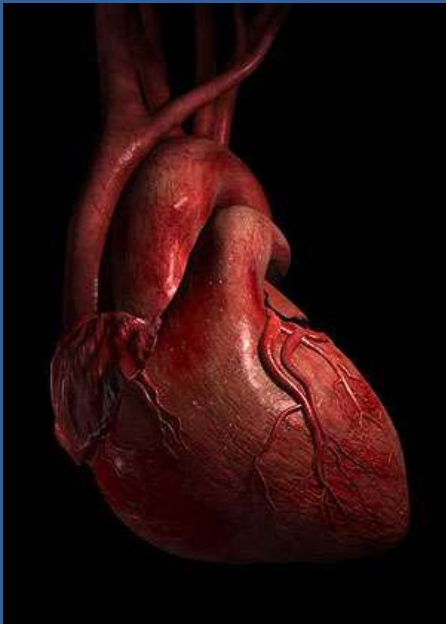
*Cardiology Department  
Freeman Hospital  
Newcastle upon Tyne*



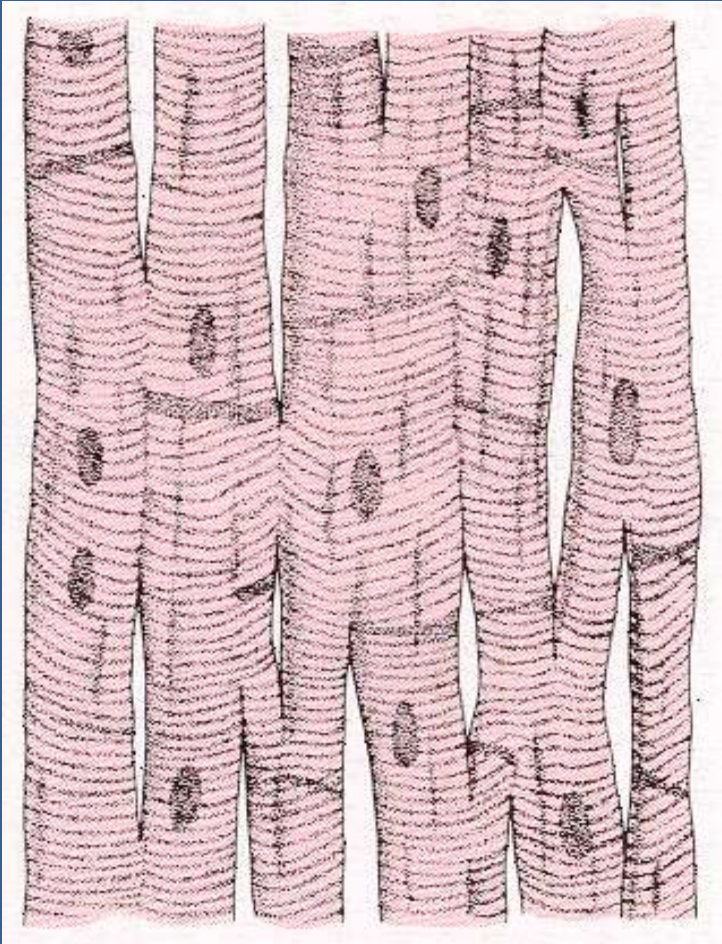
## Heart Involvement in DMD / BMD ...?

- ◇ The heart as another type of muscle
- ◇ Effects of DMD / BMD on the heart
- ◇ Natural history of heart involvement in DMD
- ◇ What supports for the heart are already available
- ◇ Do they work ?

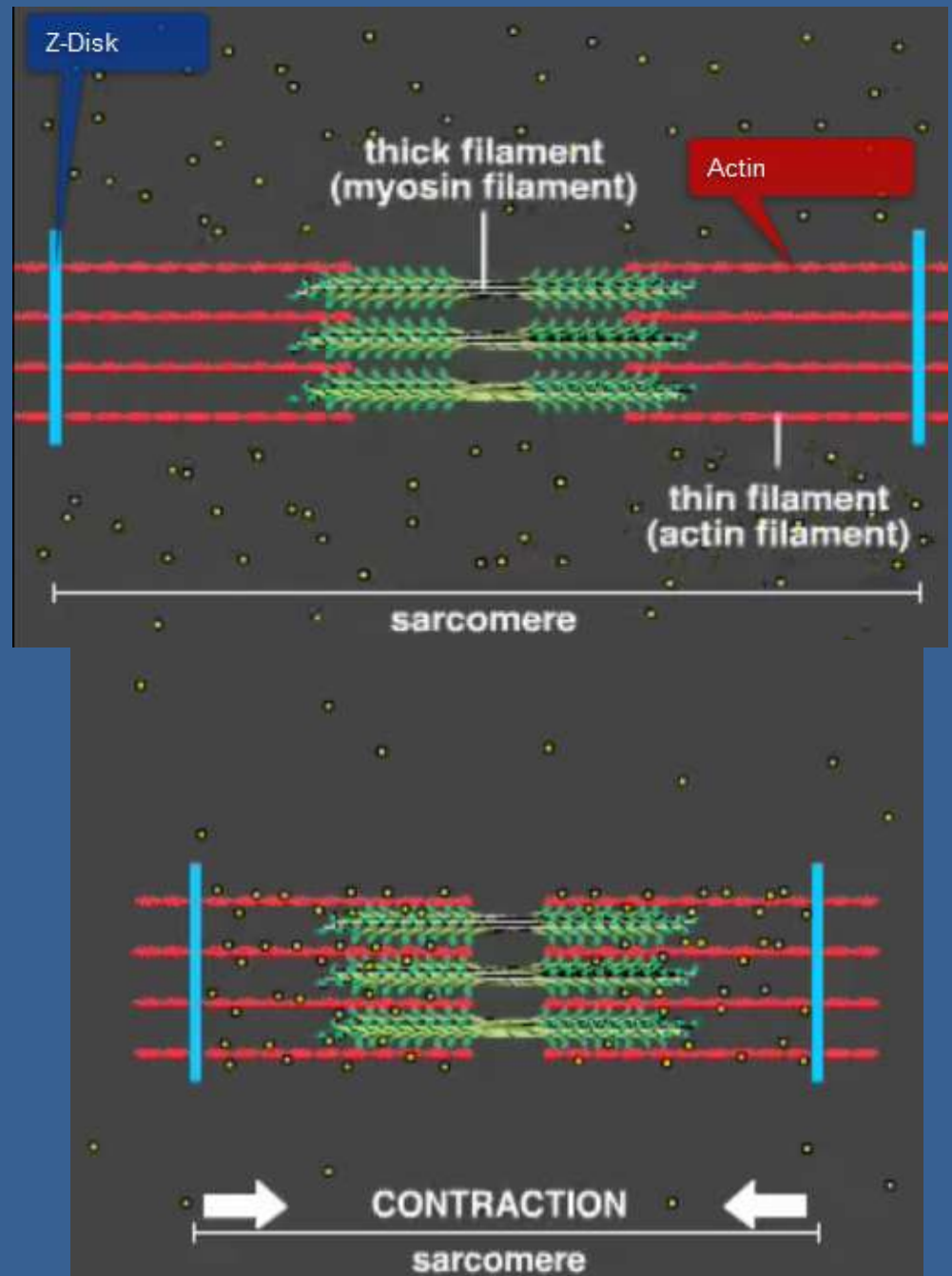
# Heart involvement in muscular dystrophy?



# How heart muscle contracts ...



**Heart muscle cells**



# Cardiac Involvement in inherited Muscle Disease

## ♥ **Cardiomyopathy**

- *Xp21 conditions (DMD / BMD / Female carriers)*
- *LGMD2I*
- *Congenital MD 1C*

## ♥ **Electropathy**

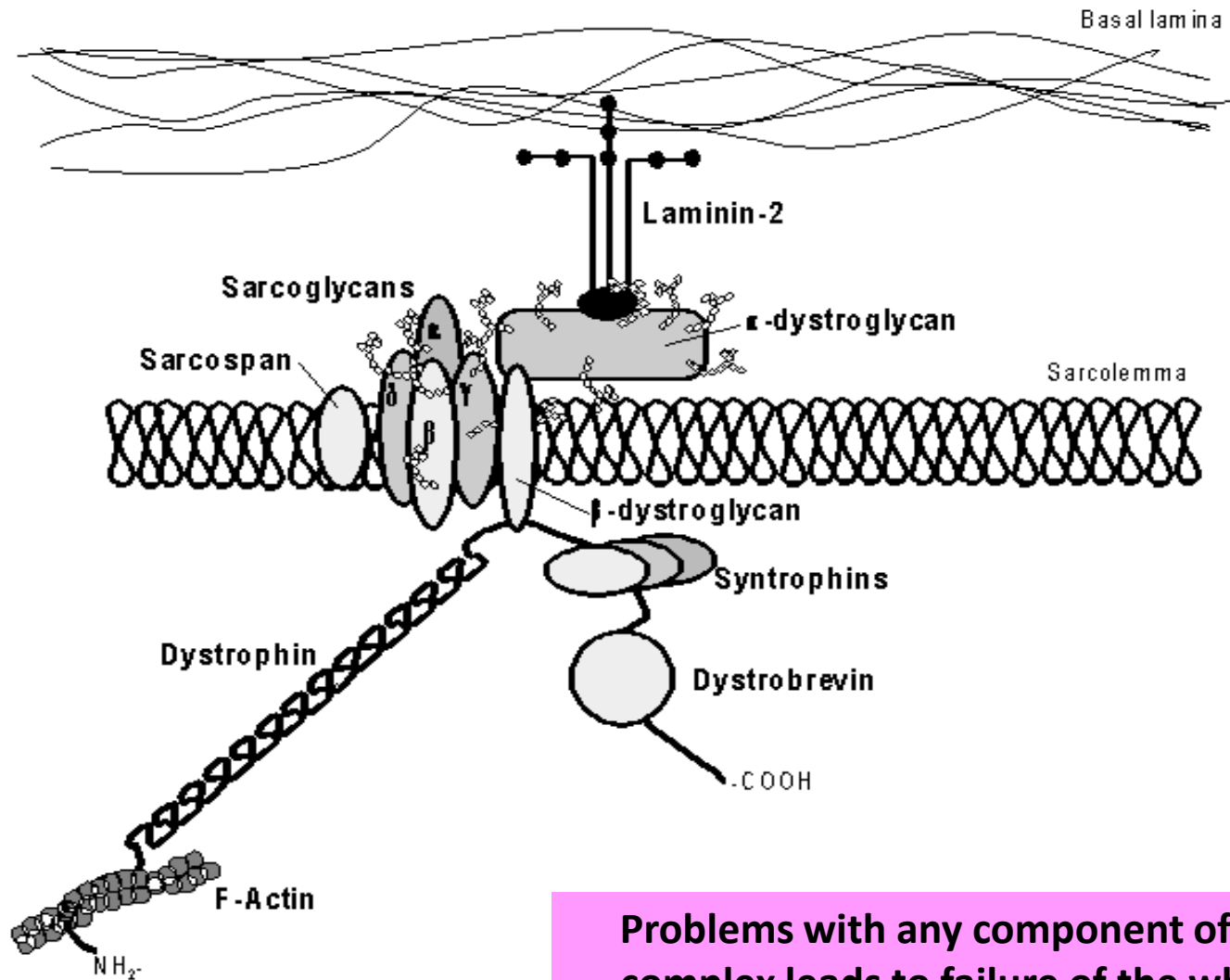
- **Conduction disease (sinus & AV-nodal disease)**
  - **Arrhythmias (AF & VT)**
- Myotonic dystrophy; XL-EDMD; LGMD; Laminopathies*

♥ **Both** - Damaged hearts become electrically unstable

# Cardiomyopathy in Inherited Neuromuscular Disorders

	<b>Nature of Cardiac Involvement</b>	<b>% Affected</b>	<b>Age range</b>	<b>Morbidity &amp; Mortality</b>
<b>DMD</b>	ECG Abnormalities HCM & DCM	Abnormal ECG > 90%  Abnormal Echo > 90%	ECG abnormalities progressive from 6 yrs	Cardiac death in 10 -20%
<b>BMD</b>	ECG abnormalities HCM & HCM	Abnormal ECG in 90%  Abnormal Echo = 65%	Variable, may be disproportionate to skeletal involvement	Cardiac death in up to 50%

# The cell membrane ...



Problems with any component of the complex leads to failure of the whole

# What happens to the heart in DMD / BMD ...?

## 1. *Causes* (lack of dystrophin)

- ◆ Cell membrane stability
- ◆ Extra- to intra-cellular force transduction
- ◆ Maintain local membrane components

**Repeated cell injury & repair**



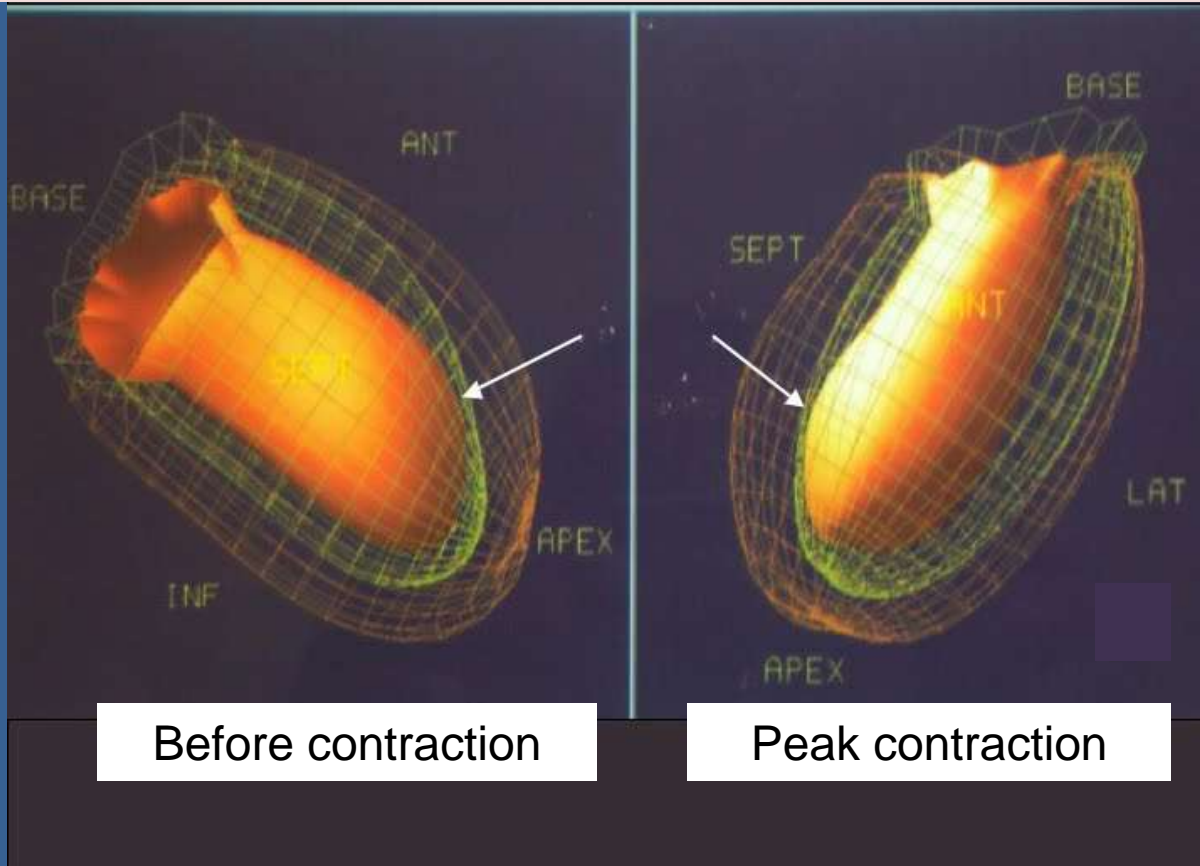
## 2. *Consequences*

- ◆ Loss of contractile function
- ◆ Secondary changes & the downward spiral in heart function  
(loss of muscle, scar formation, stretching)



# Measuring left ventricular pump function

## Contraction & Relaxation



**Ejection fraction** (global LV systolic function)  
& **Regional wall motion** (regional function)

# Echocardiographic quantification of ventricular function

Obtaining high quality images  
by echocardiography  
becomes increasingly difficult  
with age in boys with DMD

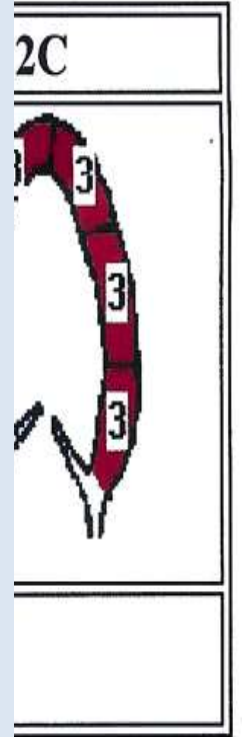
Patient positioning

Narrowing 'echo-window'

Operator expertise

'Simple' assessments probably sufficient ...

<b>I</b>	
WMSI	2.50
% Normal	19
X - Cannot Interpret	
4 - Dyskinetic	



Frac

D

e

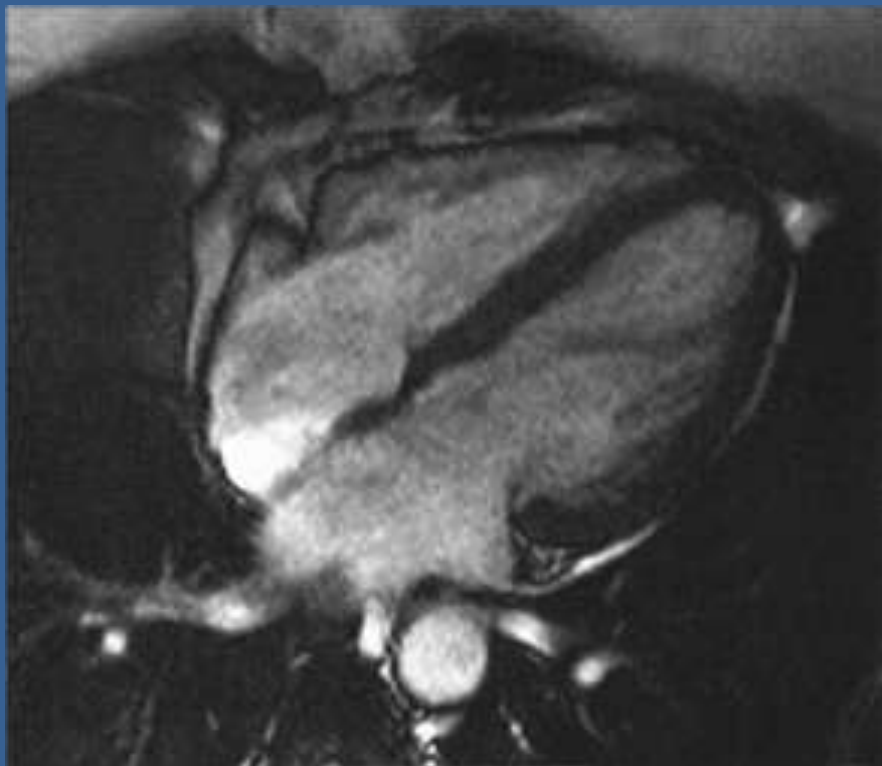
# DMD Boy: 12 Lead ECG

**No change in  
left ventricular systolic function  
at this stage**

- .... Epicardial changes initially
- .... Patchy process
- .... 'Electrical phase'
- .... ???

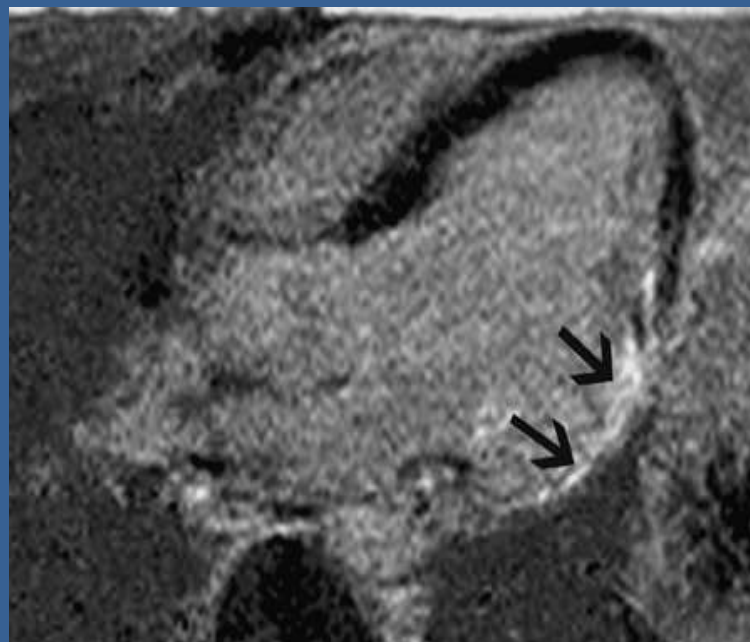


# Cardiac Magnetic Resonance Imaging



**Normal**

Scar Imaging with GAD



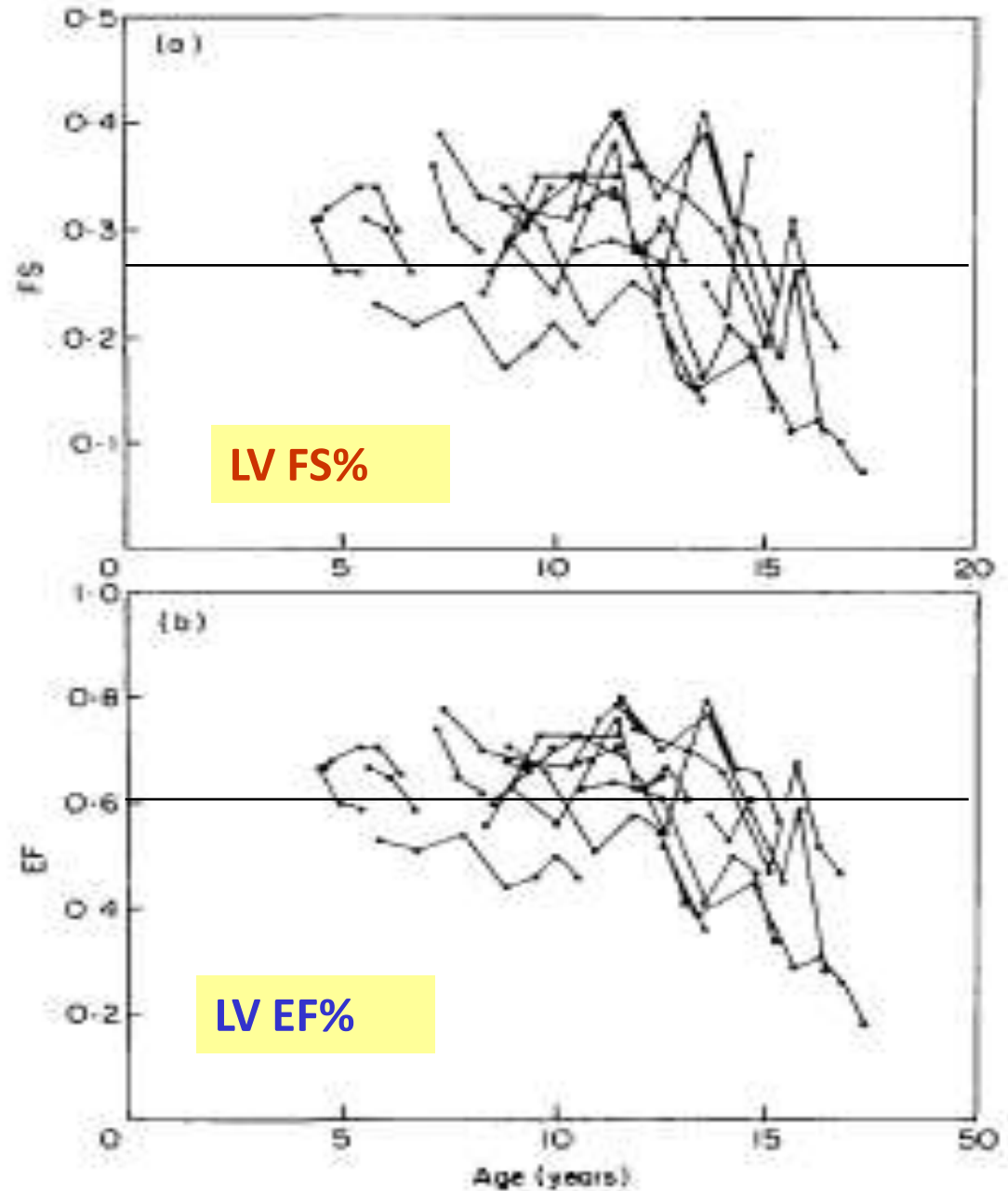
**DMD**

# Natural History of Heart Involvement in DMD

A non-invasive longitudinal study

Backman & Nylander

*Eur Heart J* 1992, 13:1239-1244



# Natural history studies of heart function in DMD

All point to progressive deterioration in LV function over time

1. Heymsfield SB, et al – *Am Heart J* 1978, 95:283-94
2. Ahmad M, et al – *Br Heart J* 1978, 40:734-40
3. Farah MG, et al – *Am J Med* 1980, 69:248-54
4. Goldberg SJ, et al - *Neurology* 1982, 32:1101-05
5. Hunsaker RH, et al – *Am J Med* 1982, 73:235-8.
6. Backman & Nylander - *Eur Heart J* 1992, 13:1239-1244
7. Kazuya S, et al - *Am Heart J* 1998, 135:937-44



PERGAMON

Neuromuscular Disorders 13 (2003) 166–172



[www.elsevier.com/locate/nmd](http://www.elsevier.com/locate/nmd)

Workshop report

107th ENMC International Workshop: the management of cardiac involvement in muscular dystrophy and myotonic dystrophy. 7th–9th June 2002, Naarden, the Netherlands

K. Bushby\*, F. Muntoni, J.P. Bourke

*Neuromuscular Disorders* 2003,13:166-172

**Steroid therapy  
for muscle strengthening**

**Cardiac benefits**

# Steroid effects & the heart in DMD

	Silversides et al 2003	Markham et al 2005
Steroid agent	Deflazacort vs Never	Any steroid vs Never
Design	Retrospective	Retrospective
Age of starting Rx	8.4 ± 2 yrs	≤ 21 yrs
Duration of Rx	> 3 yrs	---
Patient Number	33	111
Evaluation method	Echocardiogram	Echocardiogram

Results	Steroid (+) vs (-)	Steroid (+) vs (-)
Lost ambulation	48% vs 100%	
Cardio-active Rx	10% vs 42%	
LVEF < 45%	5% vs 58%	
LVFS%	33 ± 7% vs 21 ± 8%	
LVESD (mm)	30 ± 6 vs 37 ± 8	
Freedom from cardiomyopathy		Lower if steroid (-) ≤ 10 yrs x 4.4 } FS% < 28 > 10 yrs x 15 }
		93% vs 53%

# **ACE-inhibitors & Beta-blockers in DMD / BMD**

**Benefits when heart involved**

# Remodelling of DCM in DMD-BMD

Jefferies JL, et al Circulation 2005,112:2799-2804

- **76 [69 DMD & 7 BMD] boys** - **12.9 ± 13.7 yrs**

- **Review Schedule:**

Annual review until echo abnormal - 3 monthly thereafter

ACE-inhibitor or B-blocker added at time of first abnormal echo

B-blocker added to ACEi if no improvement after 3 mths

- **DCM+ in 31** - All started on therapy (mean age 14 yrs)  
ACEi alone 13 (42%); ACEi & BB 18 (58%)

- **Follow-up in 29** (ACE 2.7 & BB 1.6 yrs duration)

LV stable	2
LV improved	8
LV Normalised	19

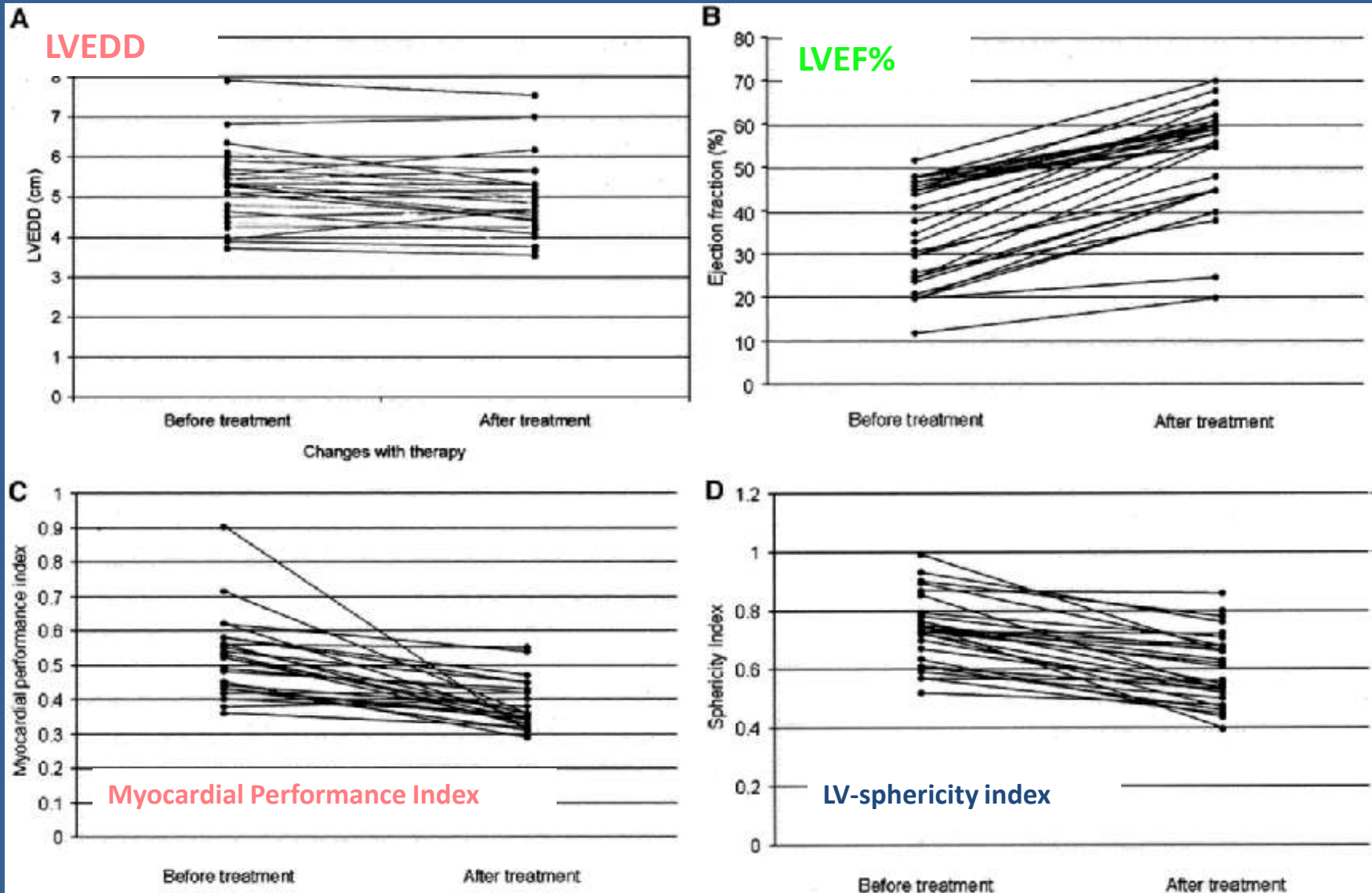
- **DNA Analysis**

Exon mutations 12 & 14-17 = Associated with DCM

Exon mutations 51-52 = ?? No DCM

# Remodelling of DCM in DMD-BMD

Jefferies JL, et al *Circulation* 2005,112:2799-2804



# Response of LV-function to *enalapril* in DMD during the second decade of life

Ramaciotti et al, Am Heart J 2006, 98:825-827

- ♥ Aim: describe the response & relationship to mutation type, ventricular size & age of DCM onset
- ♥ Serial echos in 50 DMD pts (aged 10-20 yrs) reviewed
- ♥ **27(46%) developed LV dysfunction** ( $13.2 \pm 2$  yrs)  
10 (43%) responded to enalapril (? Dose) & normalised FS%
- ♥ **Responders vs Non-responders**
  - No difference in age of starting therapy ( $p = 0.91$ )
  - Ventricles not more dilated in non-responders
  - Enalapril benefit maintained in 7 (70%) during 5-58 mths follow-up
- ♥ **No specific mutation associated with LV dysfunction**

# Newcastle Experience (1997-2009)

Applying evidence from other LV-dysfunction contexts to DMD / BMD

Step 1:

**ACE-inhibitor** (perindopril)

- preferably long-acting / once daily
- confirm tolerability

Step 2:

**Beta-blocker** (bisoprolol / carvedilol / metoprolol)

- added after a few days

Step 3:

Step 4:

**Appropriate dose up-titration**

- over few weeks & assess therapy response

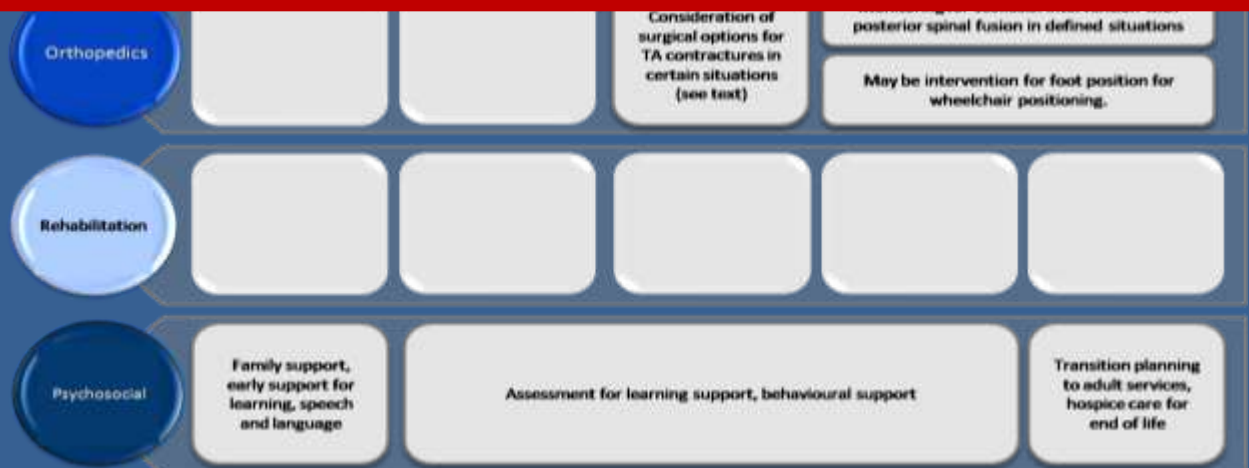
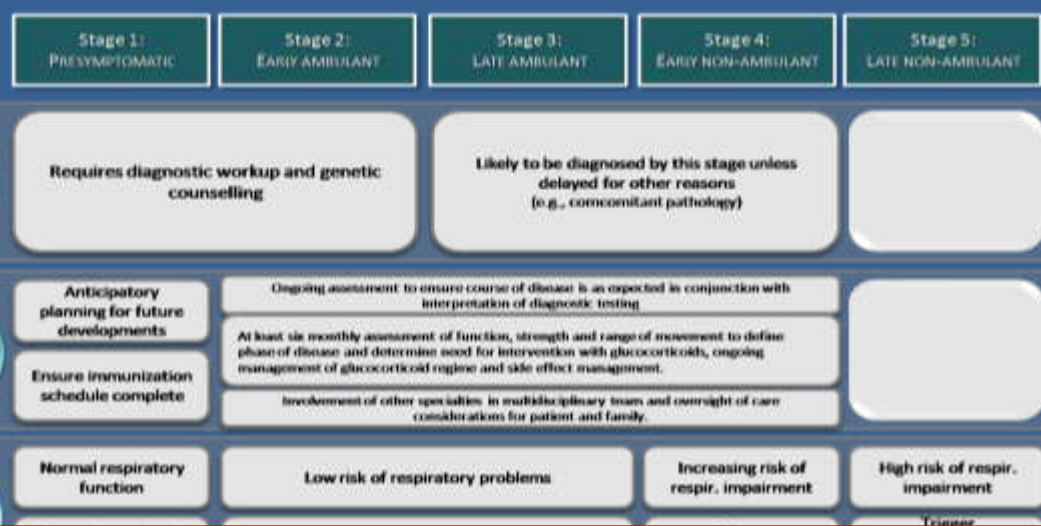
# Cardio-active therapy in DMD

## Benefits confirmed – 3 year data

	<b>Affected</b> N = 27	<b>ACE &amp; BB</b>	<b>Unaffected</b> N = 6	<b>No therapy</b>
	Baseline	Treated	Baseline	Latest
LVEDD cm	<b>4.7 ± 0.8</b>	4.6 ± 0.7	3.8 ± 0.5	4.1 ± 0.4
LVESD cm	<b>3.6 ± 1.0</b>	3.5 ± 0.8	2.9 ± 0.4	2.7 ± 0.4
LV-EF%	<b>53 ± 12</b>	55 ± 16	71 ± 9	70 ± 6
LV-FS%	<b>23 ± 7</b>	25 ± 9	34 ± 6	33 ± 5

# The diagnosis & management of DMD:

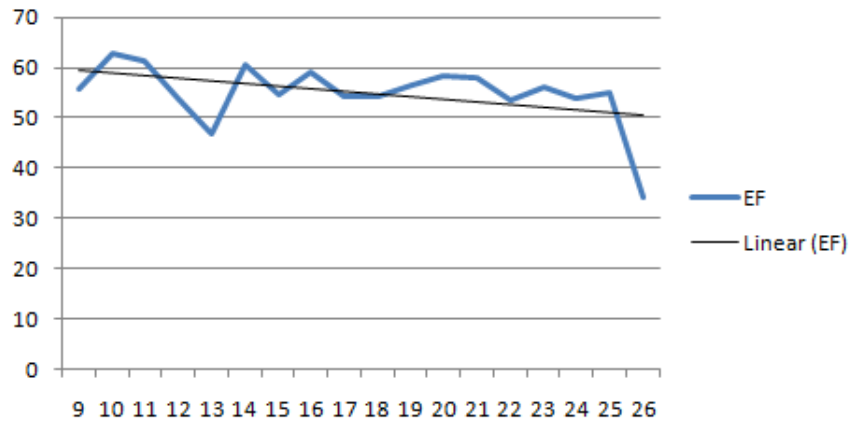
## An international consensus on care consideration



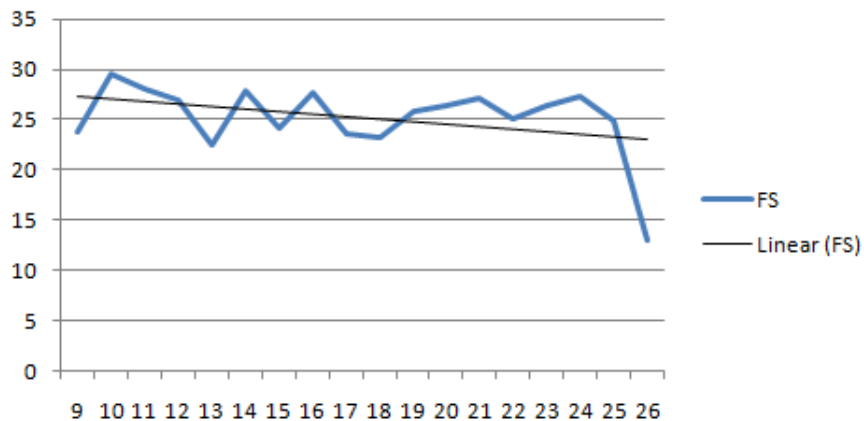
# Newcastle Experience (1997-2009)

## Long term follow-up

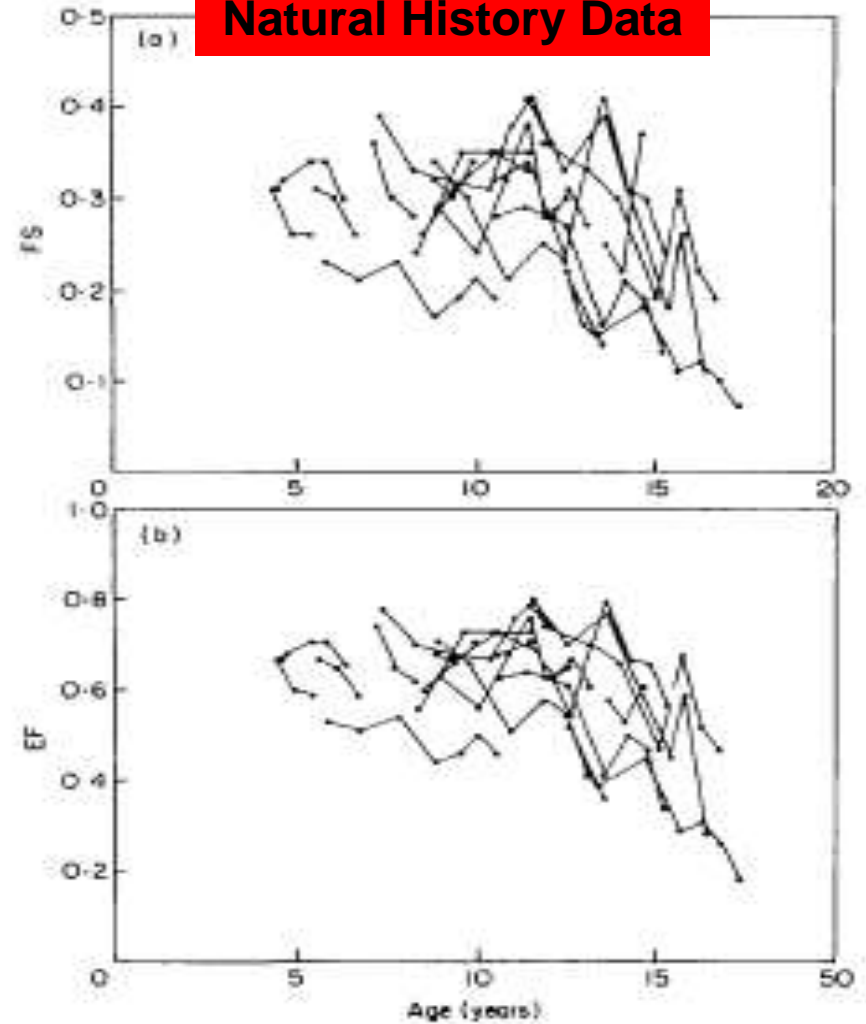
EF



FS



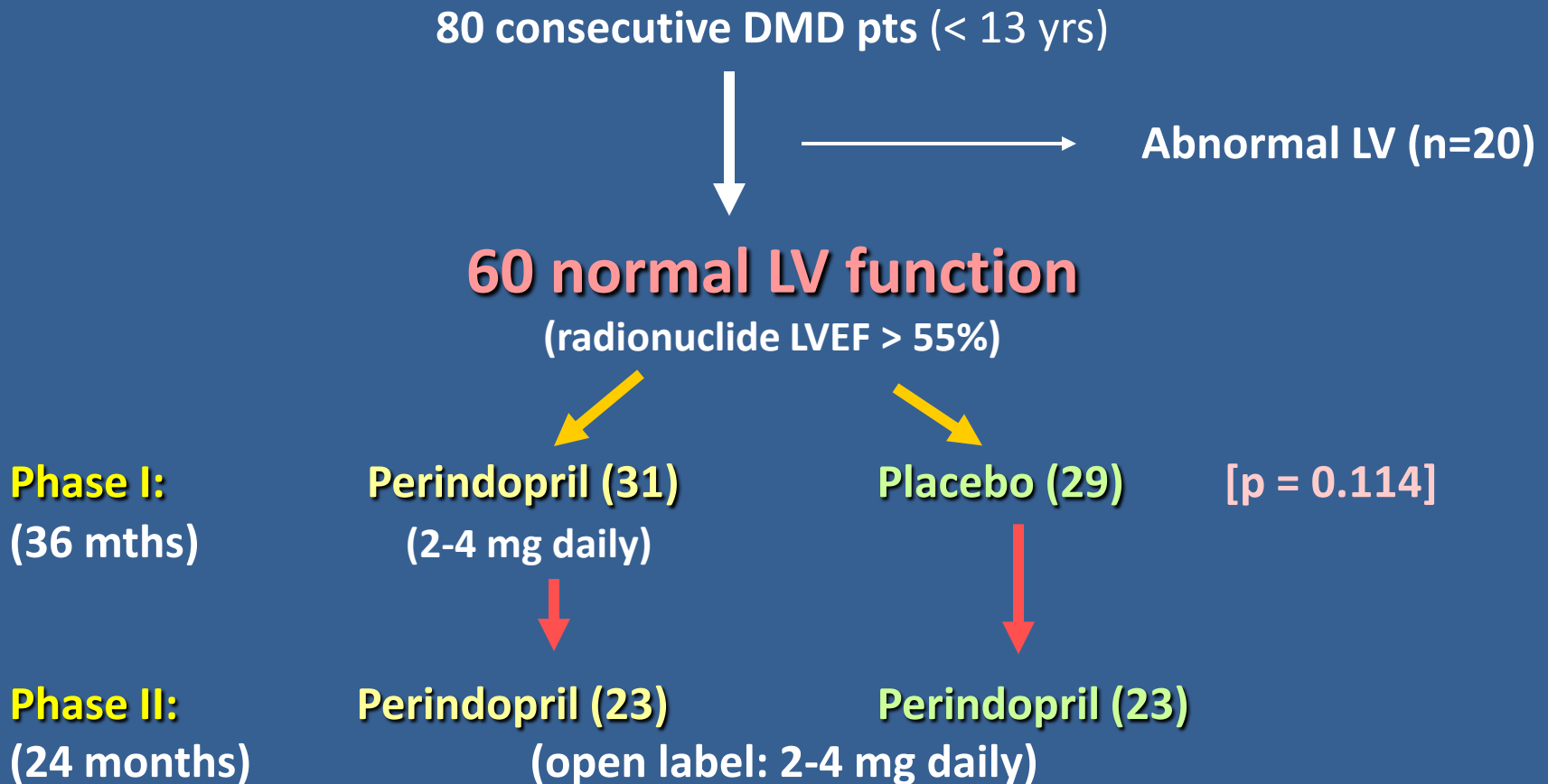
Natural History Data



**ACE-inhibitors & Beta-blockers  
before LV-dysfunction in DMD / BMD**

**Can DCM be prevented?**

# 'Effect of Perindopril on the Onset & Progression of Left Ventricular Dysfunction in Duchenne Muscular Dystrophy'



## Perindopril preventive treatment on mortality in DMD: 10-year follow-up

- ♥ DMD boys 9.5 to 13 yrs & normal LV function
- Randomised to perindopril (2-4 mg) or placebo x 3 yrs
- Open-label perindopril to all thereafter for  $\leq 10$  yrs

	<b>Perindopril Throughout (n=28)</b>	<b>Placebo Initially (n=29)</b>	<b>p</b>
<b>Baseline characteristics</b>	---	---	<b>NS</b>
<b>Alive at 10 yrs</b>	<b>26 (93%)</b>	<b>19 (66%)</b>	<b>0.02</b>
<b>Kaplan-Meier plot</b>	---	---	<b>0.013</b>

## Other drugs for the heart ...

◇ **Anti-scar agents** (spironolactone / eplerenone)

◇ **Ivabradine** (sinus node slowing agent)

### In heart failure:

◇ **Diuretics** (furosemide / bendroflumethiazide)

◇ **Nitrates** (venodilators)

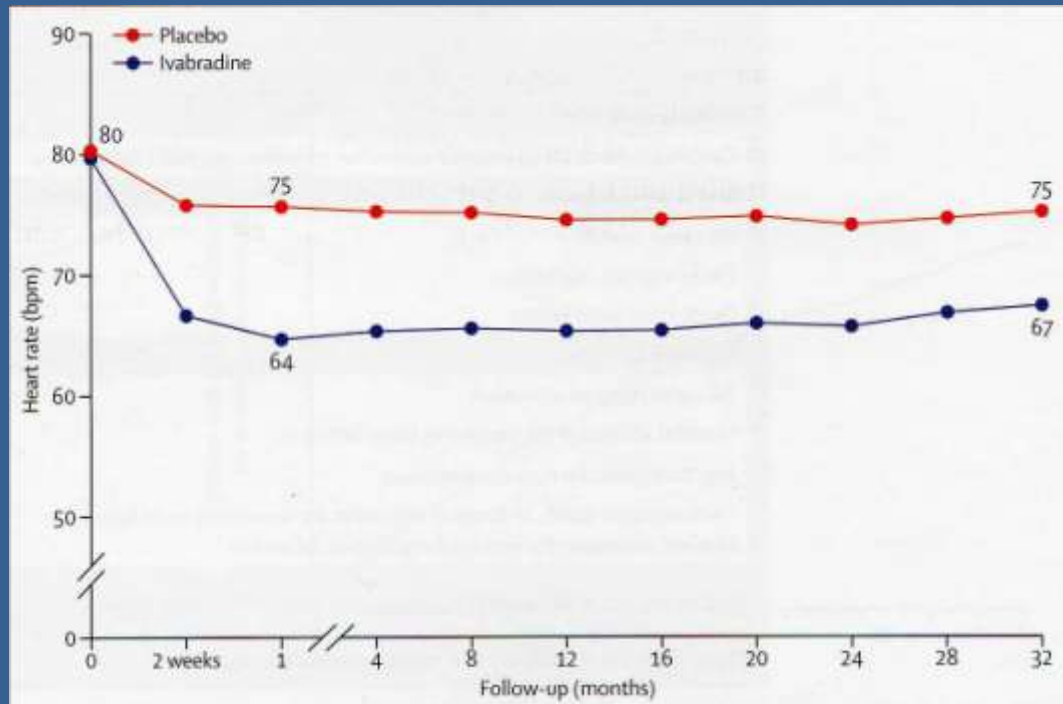
◇ **Phosphodiesterase inhibitors** (milrinone)

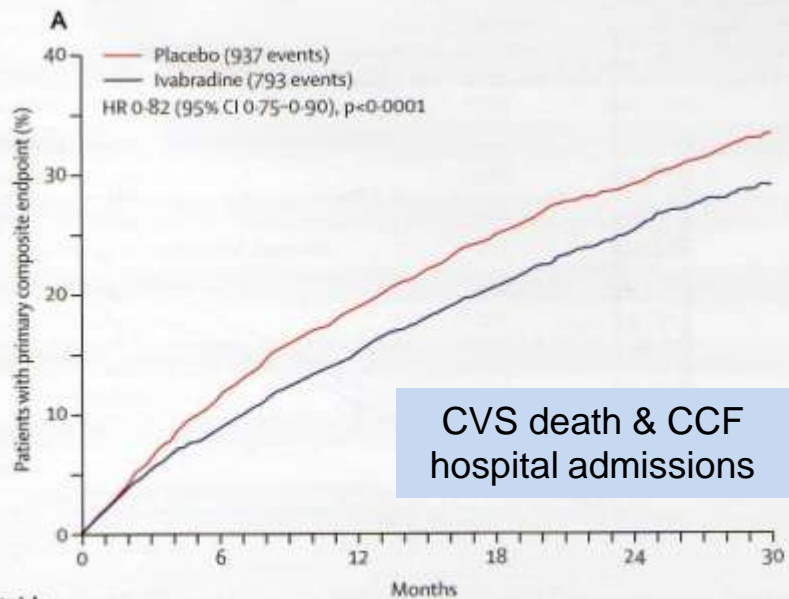
# Ivabradine & outcomes in chronic heart failure

## Addition of ivabradine to optimum medical therapy

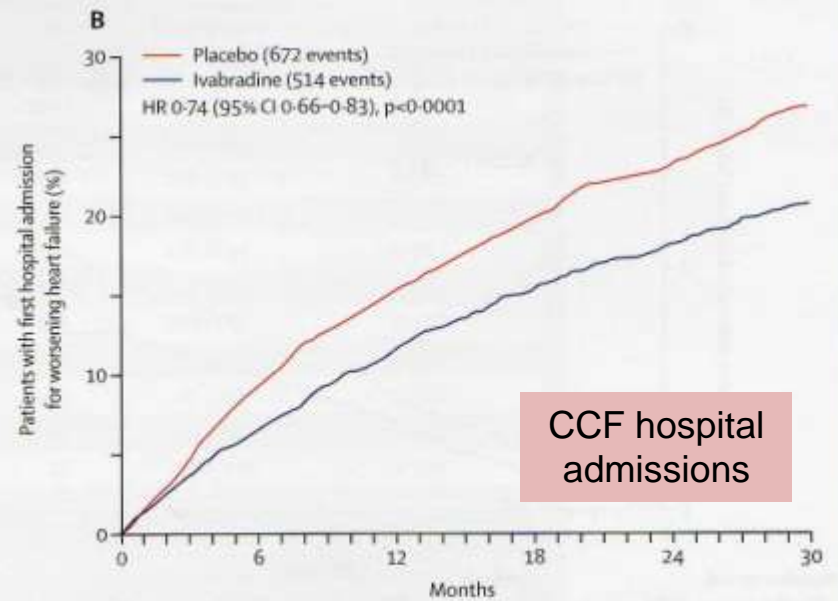
### Treatment at randomisation

β blocker	2897 (89%)	2923 (90%)
ACE inhibitor	2565 (79%)	2551 (78%)
ARB	455 (14%)	472 (14%)
Diuretic drugs (excluding antialdosterone)	2719 (84%)	2695 (83%)
Antialdosterone agents	1981 (61%)	1941 (59%)
Cardiac glycosides	706 (22%)	710 (22%)
Devices	110 (3%)	134 (4%)
CRT	28 (1%)	44 (1%)
ICD	92 (3%)	115 (4%)

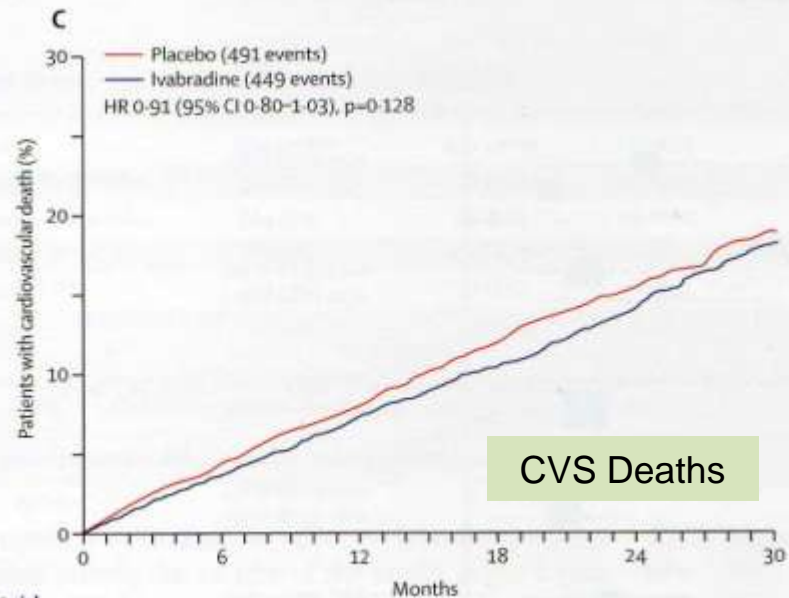




Number at risk	0	6	12	18	24	30
Placebo group	3264	2868	2489	2061	1089	439
Ivabradine group	3241	2928	2600	2173	1191	447



Number at risk	0	6	12	18	24	30
Placebo group	3264	2868	2489	2061	1089	439
Ivabradine group	3241	2928	2600	2173	1191	447



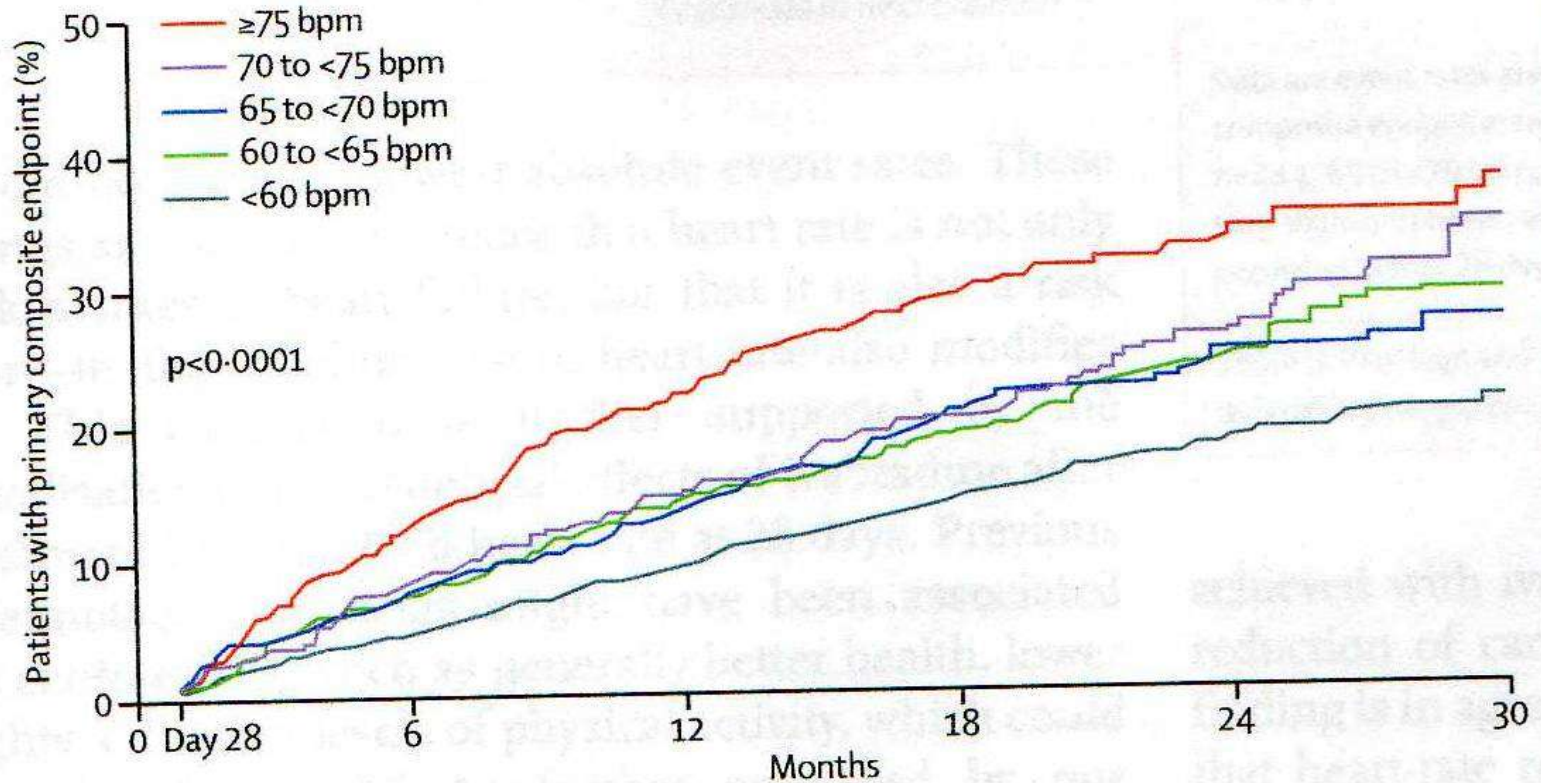
Number at risk	0	6	12	18	24	30
Placebo group	3264	3094	2817	2391	1318	534
Ivabradine group	3241	3085	2818	2428	1376	531

## Ivabradine & Outcomes in chronic heart failure [SHIFT]

Swedberg K, et al. Lancet 2010

# Heart rate as a risk factor in chronic heart failure [SHIFT]

Bohm M, et al. *Lancet* - Aug 2010



## Number at risk

	0	6	12	18	24	30
≥75 bpm	527	451	376	291	141	47
70 to <75 bpm	344	314	276	221	116	41
65 to <70 bpm	444	404	358	287	149	62
60 to <65 bpm	605	556	488	407	176	59
<60 bpm	1192	1132	1004	842	414	162

# Fatal arrhythmias in LV-dysfunction

FREEMAN ANALYSIS SERVICE

**Severely damaged hearts become progressively more unstable electrically ...**

**Occurs later in the natural history of DMD cardiac involvement...**

**Prevention through preservation of heart mechanical function ...**

## Heart Involvement in DMD / BMD ...?

- ◇ The heart as another type of muscle
- ◇ Effects of DMD / BMD on the heart
- ◇ Natural history of heart involvement in DMD
- ◇ What supports for the heart are already available
- ◇ Do they work ?

Heart protection & support is *already available*  
for patients with DMD / BMD ...

While we await the availability of  
more definitive / 'curative' therapies ...