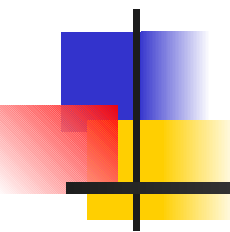


# The impact on function of currently available drug treatments for Neuromuscular disorders



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Michelle Eagle  
Newcastle Muscle Centre  
UK



# What is already Available

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- Steroids in Duchenne Muscular Dystrophy
- Cardiac treatment ACE inhibition/Beta blockers for cardiomyopathy
- Modafinil in myotonic dystrophy
- Enzyme replacement therapy for Pompe Disease
- Emerging therapies for SMA

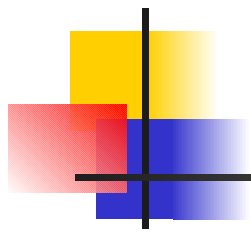


# Steroids and DMD

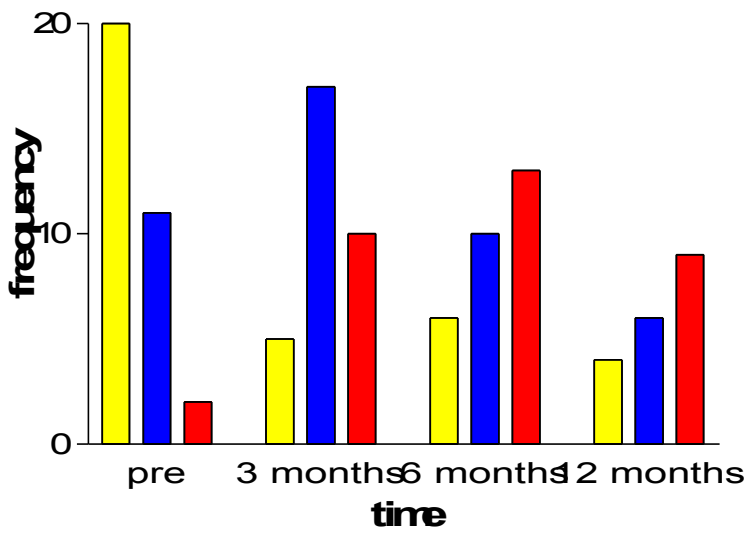
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Daily corticosteroids are now the gold standard treatment for ambulant boys with DMD.

- Full motor potential is best reached when steroids are started when the child is still ambulant.
- Starting steroids when ambulation is difficult will not improve walking ability and weight gain may be a major problem
- However starting daily steroids between 4-7 years will improve
  - Gross Motor Function
  - Respiratory function
  - Strength
  - Independence skills

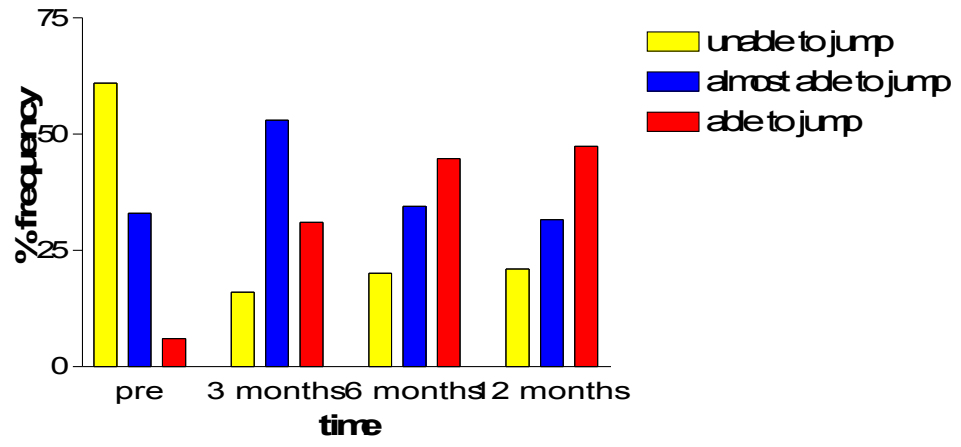


### frequency of jumping ability pre and post steroids



able almost unable

### %frequency of jumping ability pre and post steroid use



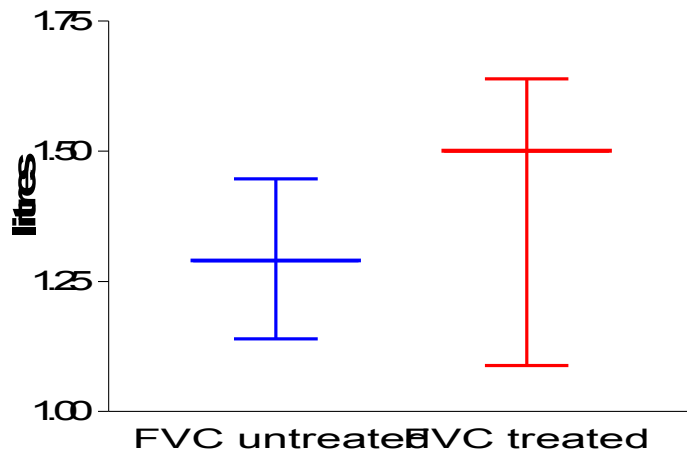
unable to jump almost able to jump able to jump

# Steroids and respiratory function

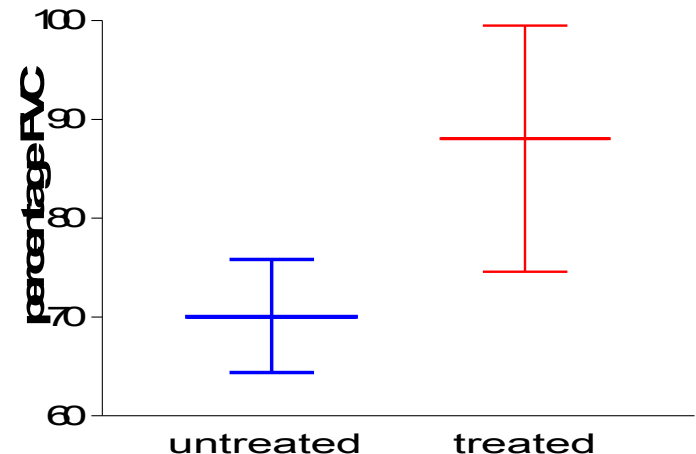
Continuous steroids improve the forced vital capacity (FVC) in ambulant boys with DMD.

Of boys aged 8.7 & 8.6 years mean FVC in the treated group was 1.5 litres (88% predicted) compared with 1.29 litres (70% predicted) in the untreated group. % FVC was significantly greater in treated boys ( $p=0.0014$ )

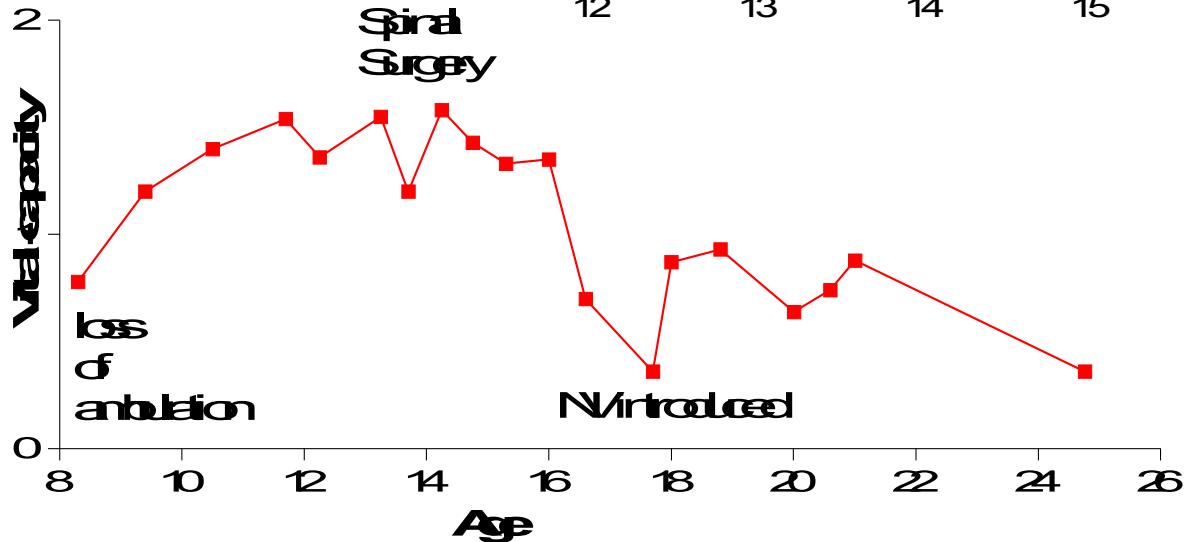
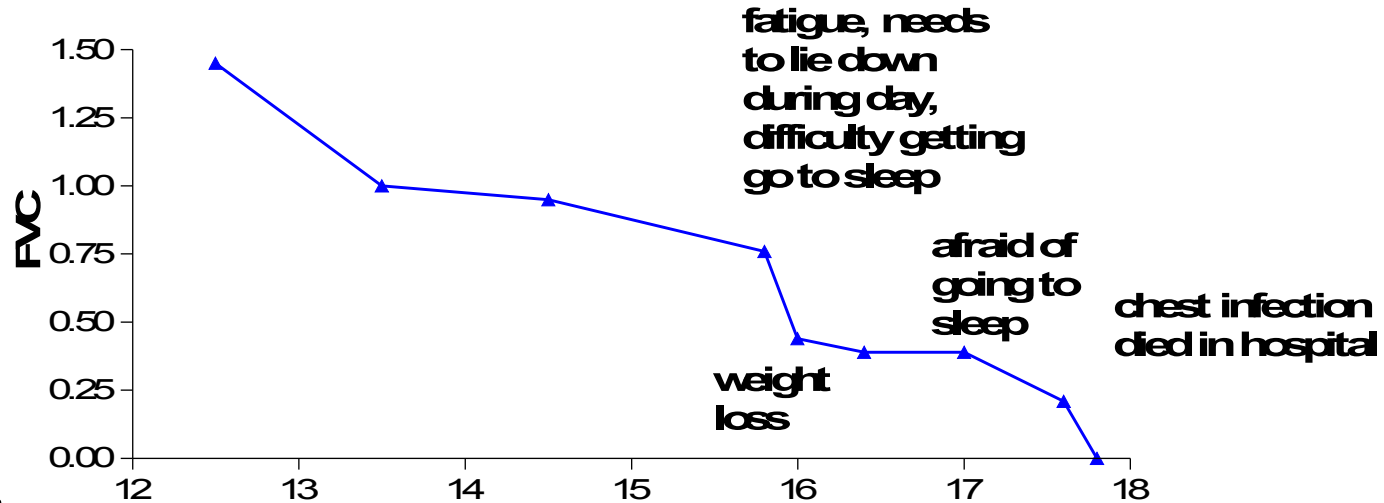
FVC in litres in age matched boys with DMD 18 months of steroid treatment v no treatment



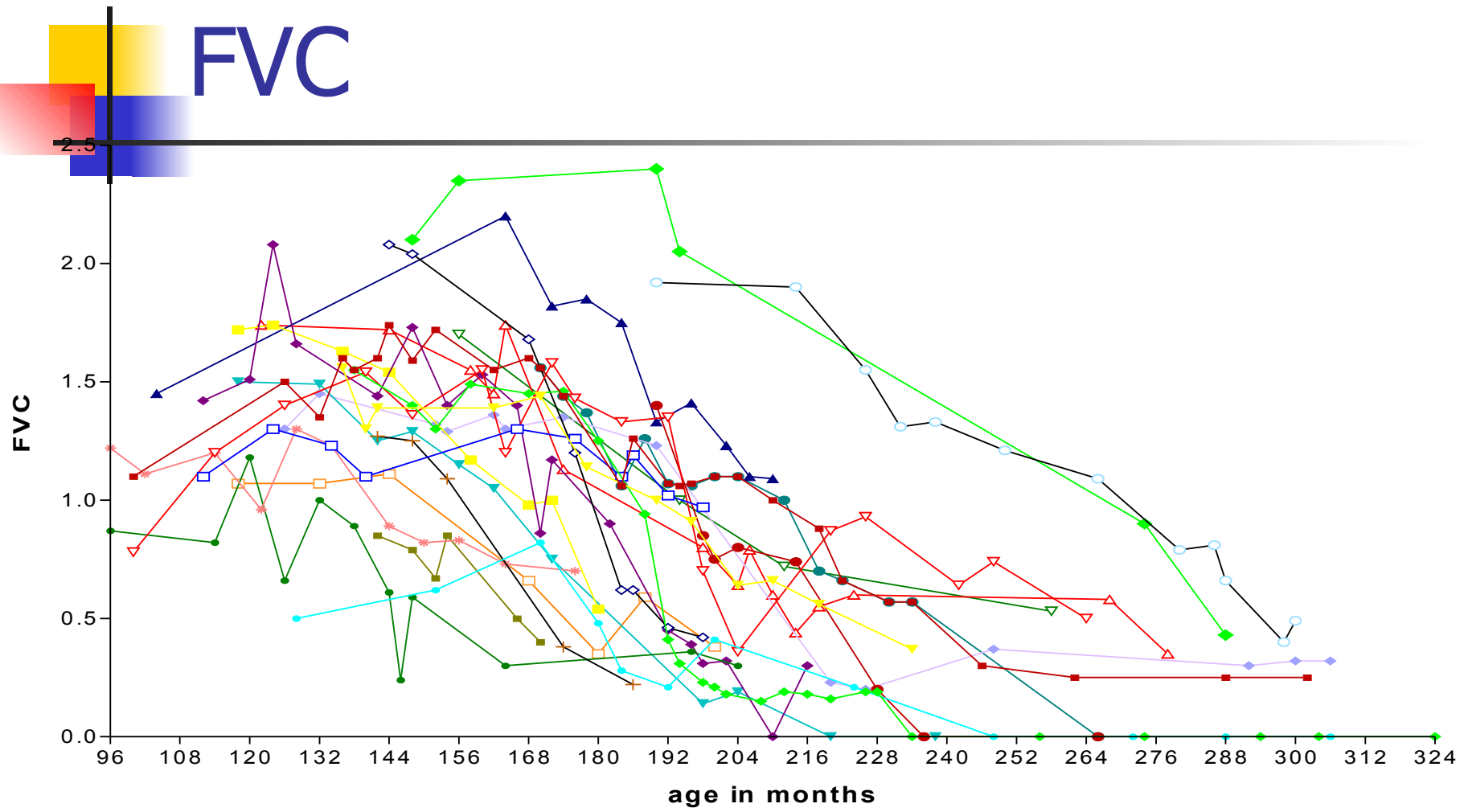
%FVC in age matched boys with DMD 18 months of steroid treatment v no treatment



# Untreated course of the FVC



# FVC

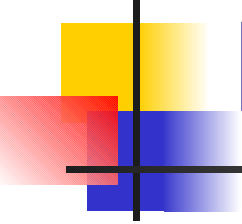


- |           |            |            |            |            |            |            |
|-----------|------------|------------|------------|------------|------------|------------|
| —○— no 57 | —□— no 132 | —■— no 25  | —▲— no 35  | —◇— no 68  | —△— no 126 | —◆— no 134 |
| —▽— no 2  | —▽— no 42  | —●— no 114 | —●— no 131 | —◆— no 145 | —■— no 175 | —●— no 110 |
| —◇— no 75 | —□— no 124 | —■— no 99  | —+— no 152 | —◇— no 4   | —*— no 53  | —▽— no 160 |
| —●— no 37 | —▽— no 168 |            |            |            |            |            |

# FVC in boys started on daily DFZ whilst ambulant



Doug  
Biggar



# Steroids in non-ambulatory boys with DMD- Pilot study

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## **Aims**

- To evaluate the impact of steroids on forced vital capacity in non-ambulant boys with Duchenne muscular dystrophy (DMD).
  
- To evaluate impact on functional ability and muscle strength



# Open label pilot study

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- prednisolone at 0.75mg/kg/day was prescribed for non ambulant boys.
- A pre-treatment assessment period of three months was followed by 6 months treatment and then a further three months without treatment.
- DEXA, ECHO, overnight oxymetry, manual muscle testing, functional testing, well being scales assessed 6 weekly



# Preliminary Results

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- 48 not ventilated patients were identified from our clinic population
- Two were excluded with severe cardiomyopathy, 4 patients approaching ventilation, 2 very obese and one diabetic were also excluded.
- 39 patients were asked to participate and 12 agreed. One patient died suddenly after the first baseline assessment.

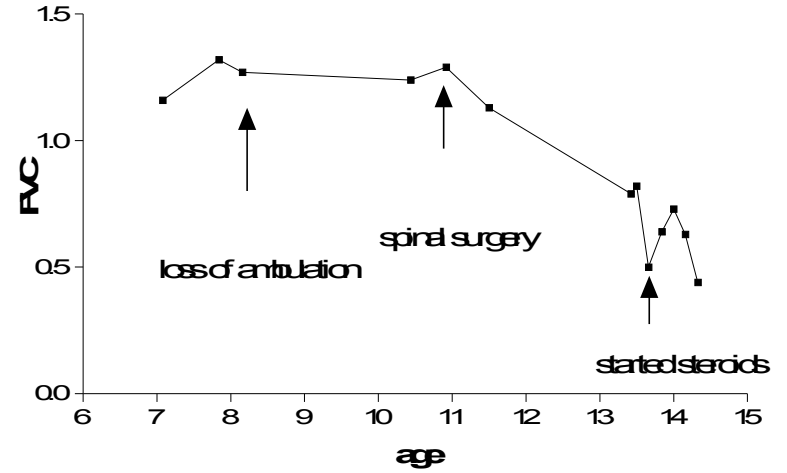
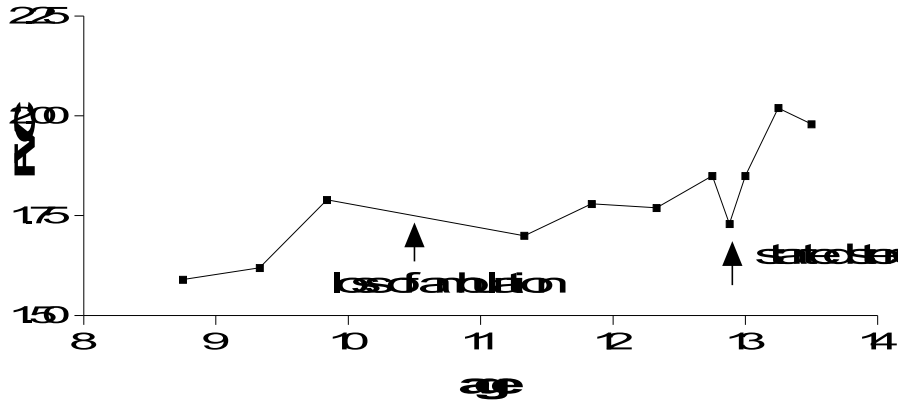


# Results

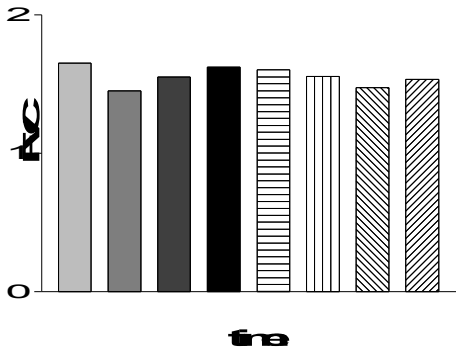
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- FVC deteriorated in all patients prior to starting steroids
- FVC improved with treatment to more than the baseline level except those whose pre treatment FVC was below one litre (although they still improved)
- FVC deteriorated to below the baseline when treatment was stopped
- 11 patients have completed 6 months on steroid Rx and 8 have requested to restart steroids.
- Reasons include deteriorating motor ability, weight loss, recurrence of hip pain and loss of ability to lift arms when steroids were stopped.

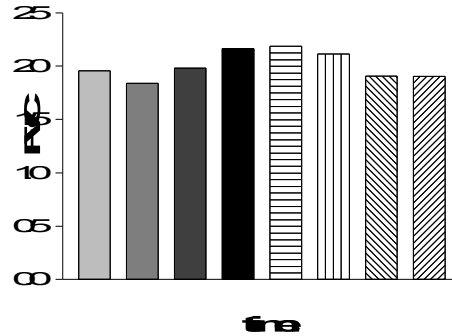
# FVC



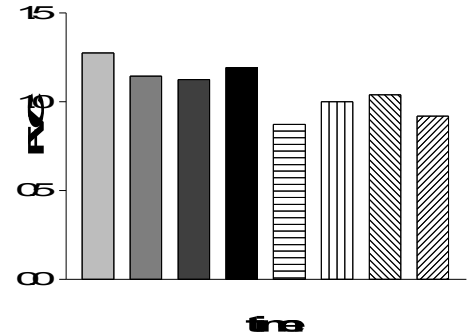
narFVCe1na  
petehatdirgalle  
tetahviltadck



narFVCe15

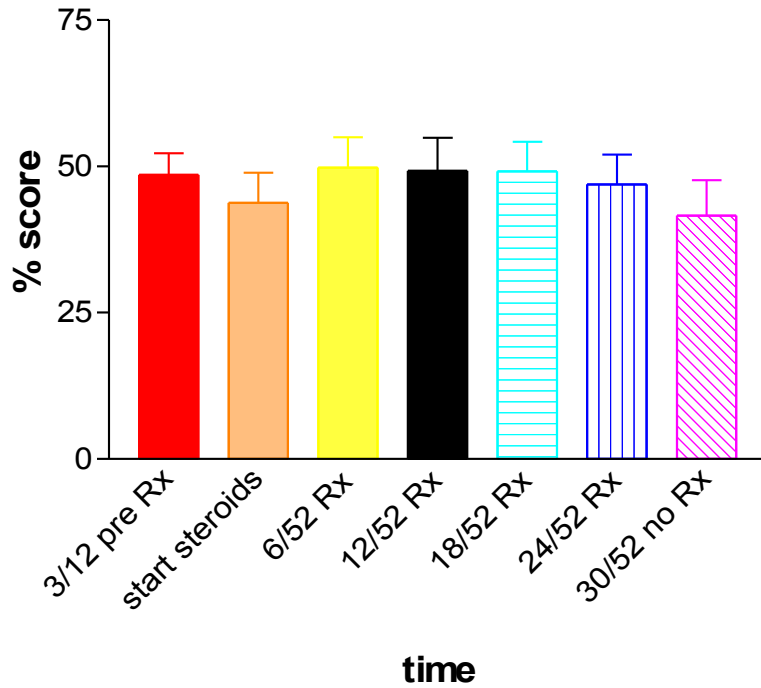


narFVCe1an15

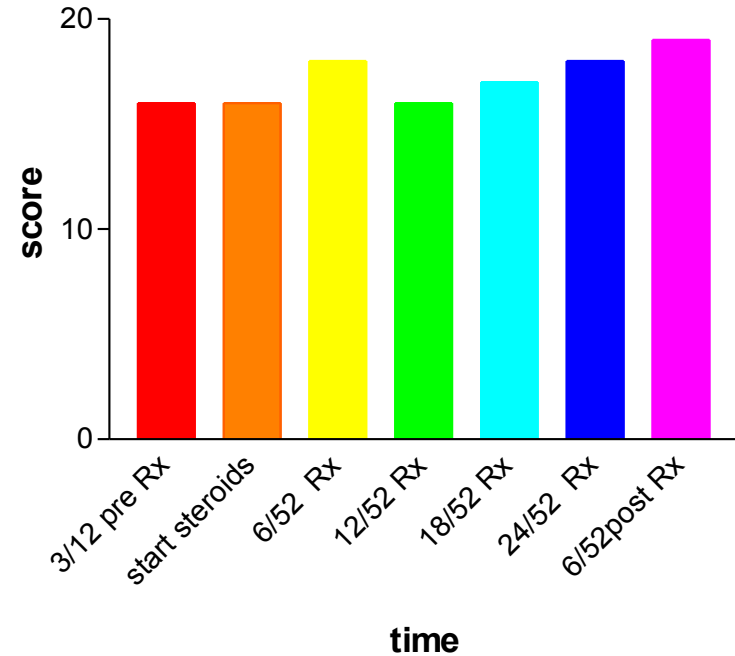


# Muscle strength and Functional Ability

**muscle strength**



**EK Functional scores pre and post steroid**

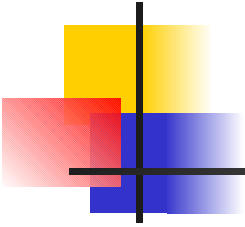




# Summary

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- FVC improves then plateaus over a 6 months period whilst taking steroids and deteriorates when steroids are stopped.
- The peak improvement in FVC is seen within 6 months in some patients but others are still improving at 6 months
- Patients with an FVC below 1 litre do not show as much benefit as those with an initial FVC over 1 litre and may deteriorate rapidly when steroids are withdrawn.
- Some non-ambulant patients benefited from increased weight but weight gain may be an undesired side effect.
- There were no reported behavioural or emotional disturbances over a 6 month period.



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- There appears to be a stabilisation of strength over a 6 month period.
  - Functional improvement lags a little behind the stabilisation in power
  - These changes are not statistically significant and further trials are still needed.



# Preliminary Conclusions

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- Steroids should be considered for non-ambulant patients with DMD with an FVC over 1 litre
- Further research is required to determine optimum dose and side effect/efficacy balance



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

# Goals of heart failure management

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*Traditionally*

*Symptom relief*



*Current emphasis*

*Prevent / slow progression*

*Prolong survival*



# Asymptomatic LV dysfunction

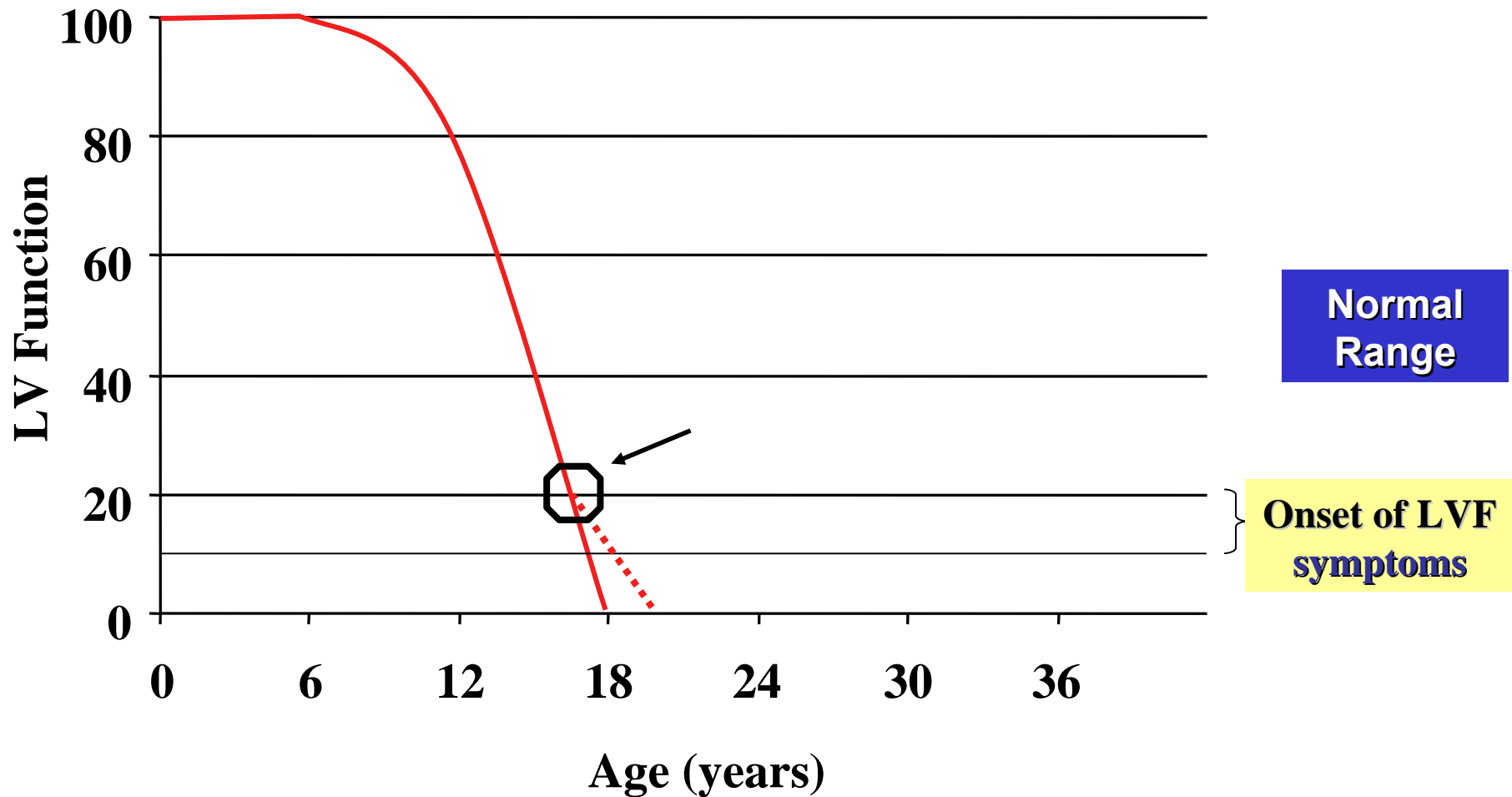
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ACE-inhibitors & ACE II blockers

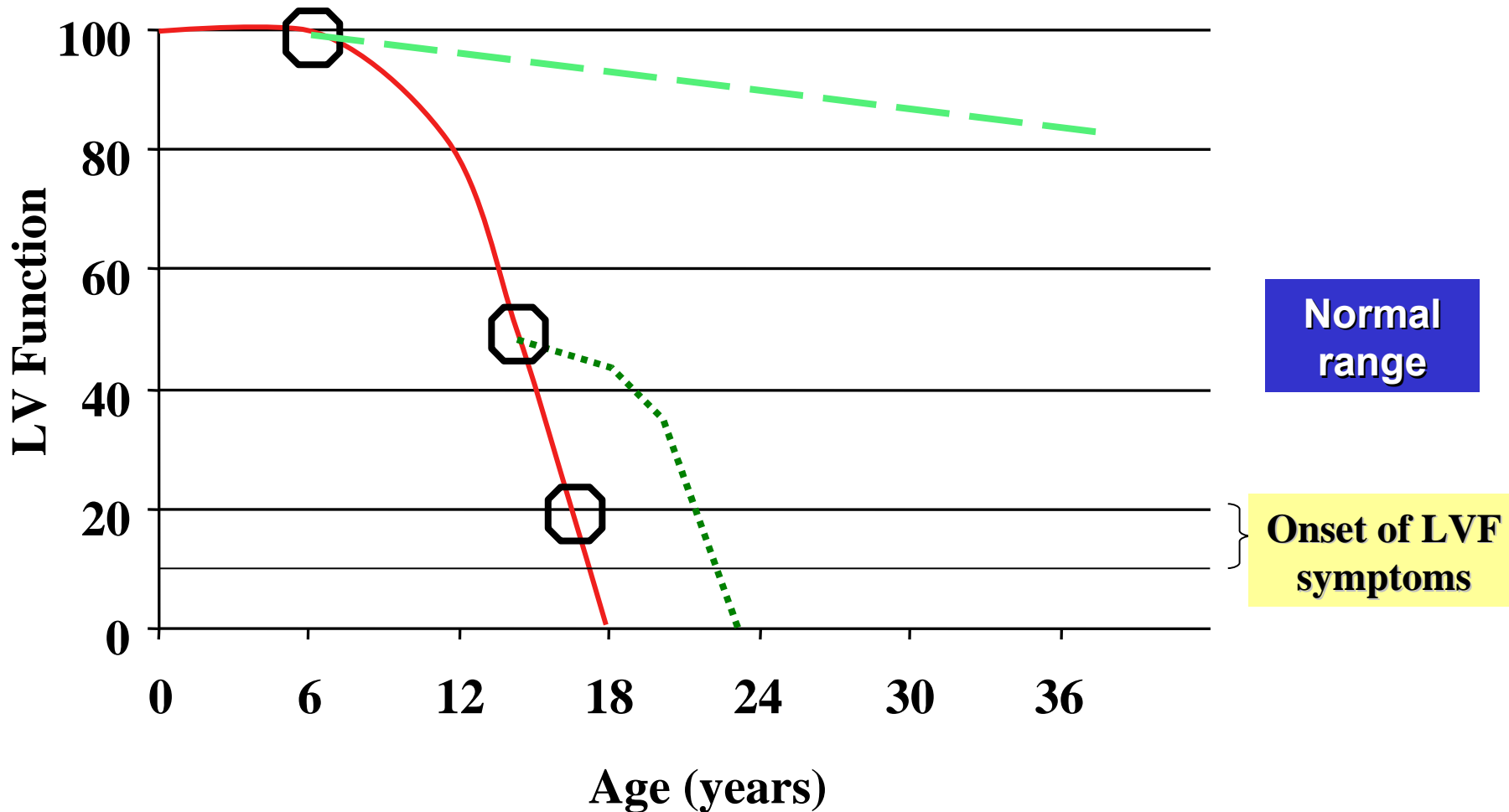
♣ Beta-blockers (metoprolol / bisoprolol / carvedilol)

♣ Anti-fibrosis agents (spironolactone / eplerenone)

# Cardiac involvement in DMD / BMD



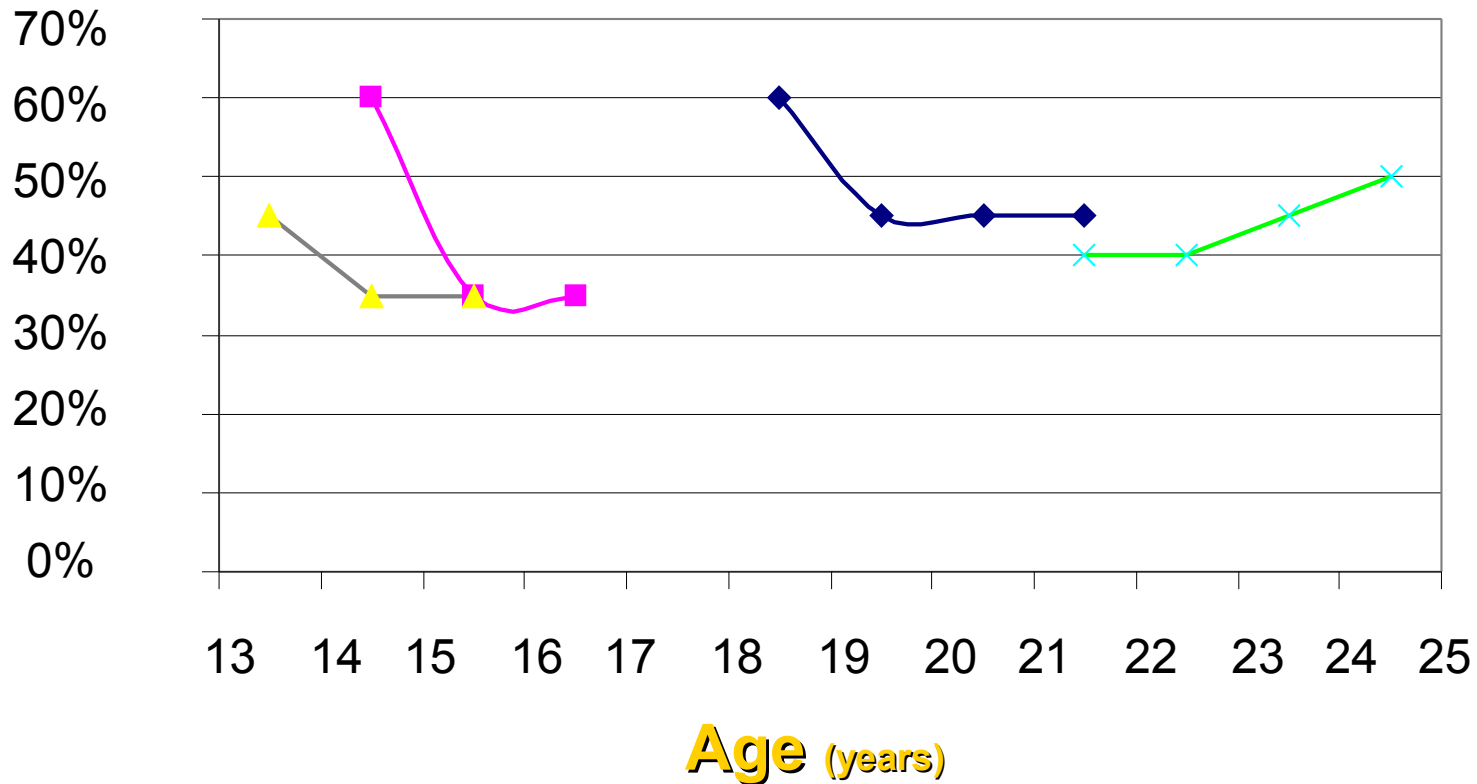
# Prophylactic cardiac treatment



# Effect of treating asymptomatic cardiomyopathy

## Stabilising Effects of ACE & BB therapy

LVEF%





***The Newcastle BHF-funded 'DMD Heart-Protection Study' - Aims .....to***

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**determine whether starting**

**♣ combination therapy with ACE-inhibitor & beta-blocker**

**♣ before the onset of echo-detectable LV dysfunction**

**♣ delays onset or slows cardiomyopathy progression rate**

**♣ five-UK-centre, double-blind, randomised, placebo-controlled trial**

**♣ over 5 years**



# future

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- Antisense oligonucleotides
- Myostatin inhibition
- Gene replacement?
- ????????



# Implications for the therapist

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- Paediatric therapists new learning curves
- Uncertainty
  - Progression
  - Impact of treatment
  - Changing objectives not simply preventing deterioration but really reaching potential
  - Assessment of ability even more valuable for the whole MDT e.g. role in changing dose of medication or information on when to start medication
- Adult therapist involvement in diseases
  - New pathways of referral
  - Clinical education



# Planning services

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- Wheelchair services
- Housing adaptations
- School and educational choices
- Adult employment



# conclusions

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Relearning patterns of disease progression

New assessment techniques have to be nationally and internationally applied

Global network of rehabilitation to ensure equality of standards

Maintaining high standards of continued professional development have never been so important in this changing world