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de transparence (HAS).

Financial disclosure declaration on the  
HAS Website (*French High Authority of Health*)

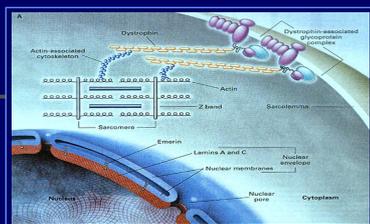
- Subvention association de recherche sur les myopathies sans contre partie , *Menarini*
- Conseil scientifique non rémunéré sur coversyl et myopathie de Duchenne, *Servier*
- Advisory board sur les biothérapies , *Lily*
- Granted by AFM (*French muscular dystrophy association*)

Angiotensin Converting  
Enzyme (ACE) inhibitors and  
muscle dystrophies .Past  
,Present and Future .

- Pr Denis Duboc, Hospital Cochin ,Paris ,France .
- Prague 2011

### Duchenne muscular dystrophy

- X-linked disease (Xp21), 1/3000 male births
- Gene codes for dystrophin



Fatkin d. *N Engl J Med.* 1999;341:1715-1724

All patients will develop **left ventricular dysfunction**,  
and more than 40% will die from heart failure.

Myocardial dysfunction due to  
the absence of an essential protein.

### The best treatment?

- To replace the gene, **gene therapy!**
- To repair the gene, **exon skipping!**
- To replace the tissue, **cell therapy!**
- To replace the protein, **recombinant enzyme administration!** (for lysosomal diseases, Fabry, Pompe,..)

Or a classical pharmacological approach based  
on the knowledge of the natural history and  
the pathophysiology of the disease?

### ACE inhibitors and DMD.

- Past : The curative treatment of HF
- Present : The preventive treatment of HF in DMD
- Future : The prevention of skeletal **muscle fibrosis** in muscular dystrophies
- PRAGUE 2011.  
Denis Duboc, Karim Wahbi, Henri Marc Bécane.  
Dep of Cardiology, Hop Cochin, Paris, France.

Present :Heart involvement in  
DMD: focus on **preventive  
therapeutic approaches.**

Baltimore 2011.  
Denis Duboc, Karim Wahbi, Henri Marc Bécane.  
Dep of Cardiology, Hop Cochin, Paris, France.

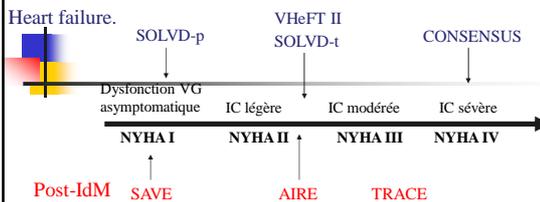
Heart involvement : 2 major problems

- 1- Heart Failure
- 2- Sudden cardiac Death

■ **Heart Failure - Molecular defects**

- decrease in cardiac muscle strength
- asymptomatic left ventricular dysfunction (NYHA 1)
- symptomatic heart failure (NYHA 2 to 4)
- **end stage Heart Failure . .**

Past ;Years 1985-1995: ACE inhibitors



Réduction du risque de mortalité : ~20%  
 (soit 4 vies sauvées pour 100 patients traités pendant 30 mois)  
 Réduction des réhospitalisations pour IC : 33%

0022-2923/92/0404022-0  
 THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS  
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Vol. 262, No. 4  
 Printed in U.S.A.

Effects of Perindopril on Myocardial Inotropy, Lusitropy and Economy, and on Diaphragmatic Contractility in the Cardiomyopathic Syrian Hamster<sup>1</sup>

DENIS CHEMLA, ELIZABETH SCALBERT, PIERRE DESCHE, JEAN-CLAUDE POURNY, FRANCINE LAMBERT and YVES LEGARPIENTIER  
 INSERM U275-Lisa-Ersta-Ecole Polytechnique, Palaiseau, France (D.C., J.-C.P., F.L.); IIR, Courbevoie, France (E.S., P.D.); and Service de Physiologie, Université Paris Sud, Hôpital de Bicêtre, Le Kremlin-Bicêtre (N.L.), France  
 Accepted for publication April 8, 1992

intrinsic contractility, and 2) that early therapy with angiotensin-converting enzyme inhibitor helped to preserve myocardial contractility and economy, and diaphragm contractility.

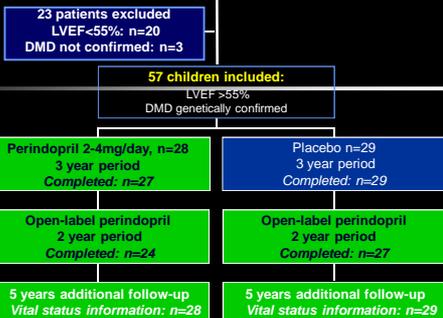
Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy

D. Duboc, C. Meune, G. Lerebours, JY. Devaux, G. Vaskzman, H-M Becane.

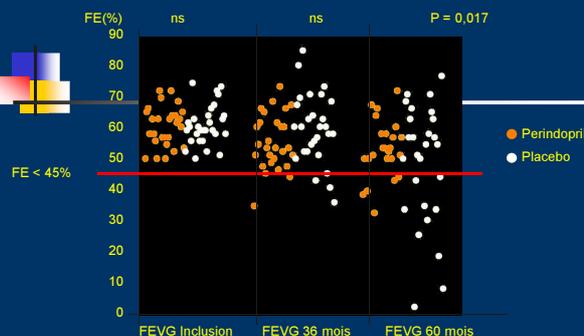
*J Am Coll Cardiol.* 2005;45:855-857.

Study protocol

Total of 80 children presenting with Duchenne disease



Evolution de la FEVG après 60 mois



**Left ventricular function and response to enalapril in patients with Duchenne muscular dystrophy during the second decade of life.**  
 Ramaciotti C, Heistein LC, Coursey M, Lemler MS, Eapen RS, Iannaccone ST and Scott WA. Am J Cardiol 2006

Journal of Cardiology (2009) 55, 72-78  
 ELSEVIER  
 ORIGINAL ARTICLE  
**Beneficial effects of beta-blockers and angiotensin-converting enzyme inhibitors in Duchenne muscular dystrophy**  
 Hitoko Ogata (MD, FJCC)<sup>a,\*</sup>, Yuka Ishikawa (MD)<sup>b</sup>, Yukitoshi Ishikawa (MD)<sup>b</sup>, Ryoji Minami (MD)<sup>b</sup>

**Genetic predictors and remodeling of dilated cardiomyopathy in muscular dystrophy.**  
 Jefferies JL, Eiden BW, Belmont JW, Craigen WJ, Ware SM, Fernbach SD, Neish SR, Smith EO, Towbin JA. Circulation 2005

« **ACE inhibitor therapy** was safely initiated either alone or in combination with b-bloker therapy. Although the use of carvedilol and metoprolol in our study was not randomized, both drugs appeared to have the desired effects on cardiac function »

**Editorial : Evolving Therapeutic Strategies for Dystrophinopathies.**  
 Potential for Conflict Between Cardiac and Skeletal Needs  
 Steven D Colan. Circulation 2005

From the Department of Cardiology, Children's Hospital Boston, Department of Pediatrics, Harvard Medical School, Boston, Mass.

« It is therefore reasonable to speculate that attenuation of the mechanical forces on the sarcolemma by means of pharmacological afterload reduction would reduce the rate of cell loss. The article by Jefferies et al does not permit any conclusions in this regard, but a recent study by Duboc et al provides some support to this hypothesis. »

**SCIENTIFIC LETTER**  
**Reliable detection of early myocardial dysfunction by tissue Doppler echocardiography in Becker muscular dystrophy**  
 C Meune, O Pascal, H M Bécane, F Héloire, D Christoforou, P Laforet, B Eymard, P Gueret, F Leturcq, D Recan, J Y Devaux, S Weber, D Duboc  
 Heart 2004;90:947-948. doi: 10.1136/hrt.2003.021113

840  
**SCIENTIFIC LETTER**  
**Cardiac tissue velocities and strain rate in the early detection of myocardial dysfunction of asymptomatic boys with Duchenne's muscular dystrophy: relationship to clinical outcome**  
 N Giatrakos, M Kinali, D Stephens, D Dawson, F Muntoni, P Nihoyannopoulos  
 Heart 2006;92:840-842. doi: 10.1136/hrt.2005.067710

**Journal of Cardiovascular Magnetic Resonance** 

Research **Open Access**

**Early manifestation of alteration in cardiac function in dystrophin deficient mdx mouse using 3D CMR tagging**  
 Wei Li<sup>1,4</sup>, Wei Liu<sup>5</sup>, Jia Zhong<sup>1,4</sup> and Xin Yu<sup>\*1,2,3,4</sup>  
Journal of Cardiovascular Magnetic Resonance 2009, 11:40

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**Circumferential Strain Analysis Identifies Strata of Cardiomyopathy in Duchenne Muscular Dystrophy**  
 A Cardiac Magnetic Resonance Tagging Study

Kan N. Hor, MD,\* Janaka Wansapura, PhD,† Larry W. Markham, MD,‡ Wojciech Mazur, MD,§ Linda H. Cripe, MD,\* Robert Fleck, MD,† D. Woodrow Benson, MD, PhD,\*  
(J Am Coll Cardiol 2009;53:1204-10)

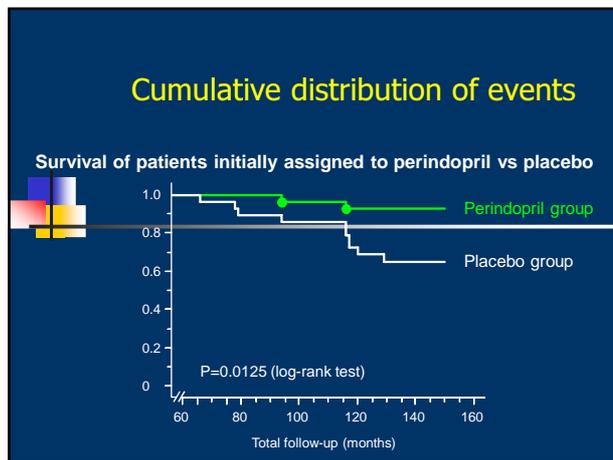
**Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up**

D. Duboc, C. Meune, B. Pierre, K. Wahbi, B. Eymard, A. Toutain, C. Berard, G. Vaskman, S. Weber, H-M Becane.  
*American Heart Journal*. 2007;154:596-602

**Results: deaths after up to 10 years of follow-up**

Cumulative number of deaths:	Group 1 (perindopril)	Group 2 (placebo)	P
7 years	0	3	0.080
8 years	1	5	0.159
9 years	1	5	0.159
10 years	2	10	0.009

Chi-square for comparisons



Early (9.5 to 13 years) administration of *perindopril* is associated with a significant decrease in 10-year mortality in Duchenne Muscular Dystrophy

NB :No patients has been treated by steroids during this study

It is probably beneficial to treat preventively these patients, before *heart failure* and before *left ventricular dysfunction* (before **apoptosis** initiation, before **TGF beta** pathway activation, before **fibrosis** process initiation, before molecular, tissular and cavity **remodeling**..)

**Update on the management of Duchenne muscular dystrophy**

A Y Manzur, M Kinali and F Muntoni

*Arch Dis Child* 2008 93: 986-990 originally published online July 30,  
**MANAGEMENT OF CARDIAC COMPLICATIONS**

clearly superior to late therapy.<sup>34</sup> Indeed, considering the well-described incidence and clinical course of DCM in DMD, and the recent claims of several groups that therapeutic intervention has a positive effect, the most logical approach appears to be to intervene before severe damage has occurred.

**ACE inhibitors and DMD**

- Future : the skeletal muscle

Sarika Arora, MD, Senior Editor

**Role of the renin-angiotensin system in diabetic nephropathy**

**The role of the renin-angiotensin system in liver fibrosis**

**Angiotensin-Converting Enzyme Inhibitor Therapy Improves Respiratory Muscle Strength in Patients With Heart Failure\***

**SARCOPENIA**  
**Losartan Restores Skeletal Muscle Remodeling and Protects Against Disuse Atrophy in Sarcopenia**

**CHEST**  
 Official publication of the American College of Chest Physicians

**Angiotensin-Converting Enzyme Inhibitor Therapy Improves Respiratory Muscle Strength in Patients With Heart Failure\***

Catherine Colrault, Albert Hagège, Denis Chemla, Marie-Dominique Fratacci, Claude Guérot and Yves Lecarpentier

*Chest* 2001; 119:1755-1760  
 DOI 10.1378/chest.119.6.1755

**Conclusions:** In patients with chronic heart failure, long-term therapy with the ACE inhibitor perindopril improved respiratory muscle strength, as indicated by significant increases in P<sub>max</sub> and P<sub>EMax</sub>.  
 (CHEST 2001; 119:1755-1760)

**Decreased muscle ACE activity enhances functional response to endurance training in rats, without change in muscle oxidative capacity or contractile phenotype**

Estelle Habouzit, Hélène Richard, Hervé Sanchez, Nathalie Kaulmann, Bernard Serrurier, Rachel Monnet, René Ventura-Clapier and Xavier Bigard  
*J Appl Physiol* 107:346-353, 2009. First published 30 April 2009; doi:10.1152/jappphysiol.91413.2008

	Sed-Ct (n = 8)	Sed-Per (n = 8)	Tr-Ct (n = 8)	Tr-Per (n = 8)
Running time to exhaustion, min				
Before protocol	187 ± 16	187 ± 18	182 ± 13	179 ± 20
After protocol	86 ± 6*	88 ± 14*	398 ± 20*†	<u>454 ± 16*†‡</u>

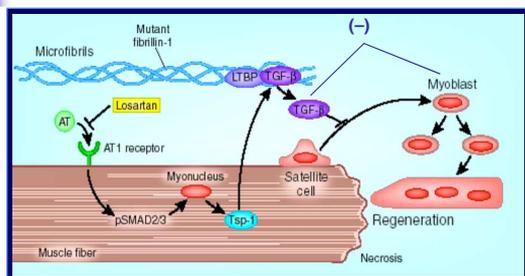
**Per (Perindopril)**

**Angiotensin II type 1 receptor blockade attenuates TGF- $\beta$ -induced failure of muscle regeneration in multiple myopathic states (4)**

Cohn RD, et al. *Nature Medicine* 2007

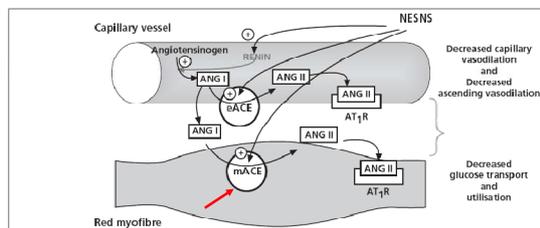
### ACE inhibitor bulks up muscle.

Jeffrey S Chamberlain  
Nature Medicine 2007



### Angiotensin-converting enzyme in skeletal muscle: sentinel of blood glucose homeostasis

Guenther J Dietze and Erik J Henriksen  
Journal of Renin-Angiotensin-Aldosterone System 2008 9: 75



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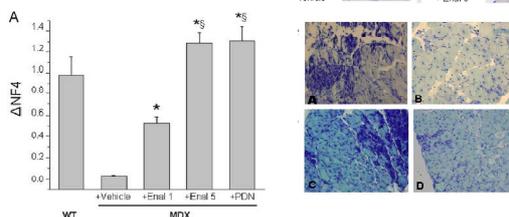
#### Perspective

Enalapril treatment discloses an early role of angiotensin II in inflammation- and oxidative stress-related muscle damage in dystrophic mdx mice<sup>☆</sup>

Anna Cozzoli<sup>1</sup>, Beatrice Nico<sup>1</sup>, Valeriana Teresa Sblendorio<sup>1</sup>, Roberta Francesca Capogrosso<sup>1</sup>, Maria Maddalena Dinardo<sup>1</sup>, Vito Longo<sup>1</sup>, Sara Gagliardi<sup>2</sup>, Monica Montagnani<sup>2</sup>, Annamaria De Luca<sup>3,\*</sup>

<sup>☆</sup>Unit of Pharmacology, Department of Pharmacology-Biology, Faculty of Pharmacy, University of Bari, Italy  
<sup>1</sup>Department of Human Anatomy and Histology, Faculty of Medicine, University of Bari, Italy  
<sup>2</sup>Department of Biomedical Sciences and Human Oncology, Faculty of Medicine, University of Bari, Italy

### Enalapril treatment discloses an early role of angiotensin II in inflammation- and oxidative stress-related muscle damage in dystrophic mdx mice<sup>☆</sup>

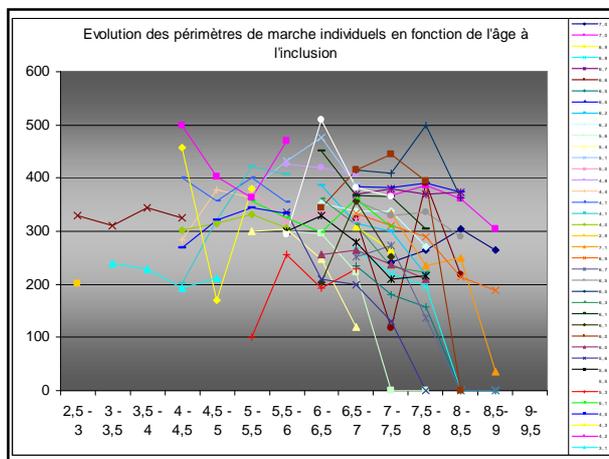
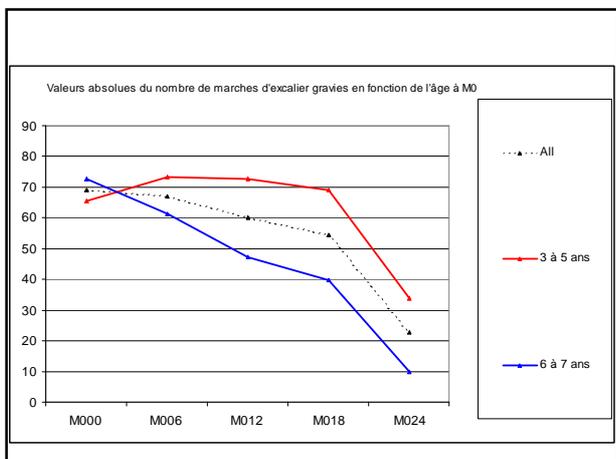
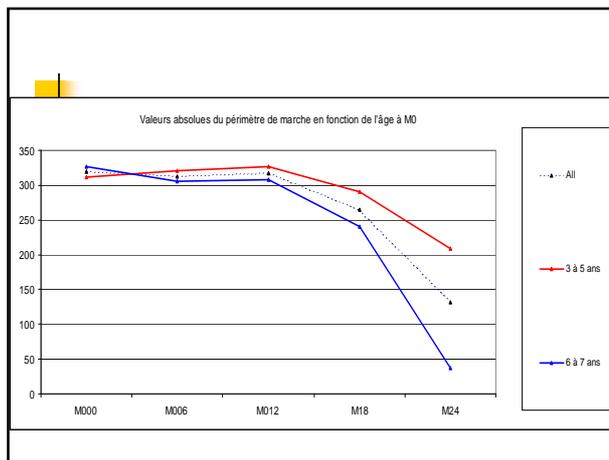
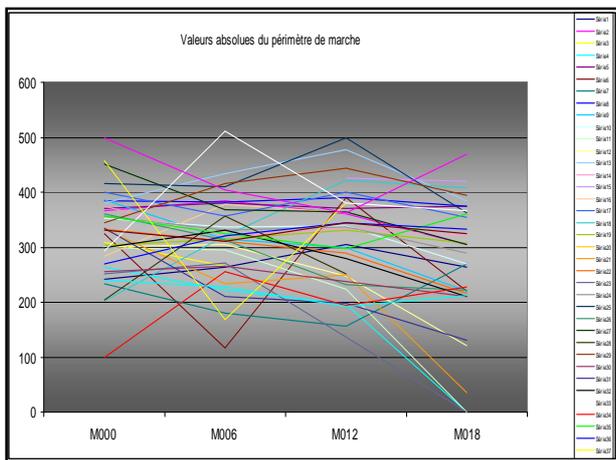
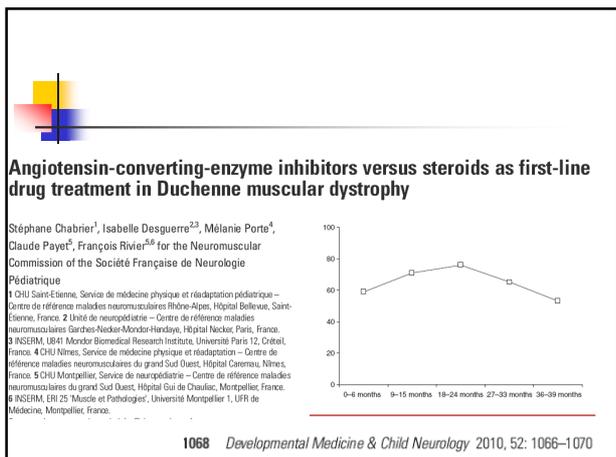


### A new trial

- Perindopril very early in the disease
- Randomized versus placebo
- Before the child has lost walking ability
- Between 3 to 8 years old
- First end point : walking distance
- Secondary end points : cardiac and muscle fibrosis
- Final Results : november 2011

### A New Trial

- Preliminary results
- All the patients were included in three months
- No direct side effect
- Blinded global results at 18 months
- 24 months of follow up for unblinded



Skipping toward Personalized Molecular Medicine  
 Hoffman EP  
 N Engl J Med, 2007

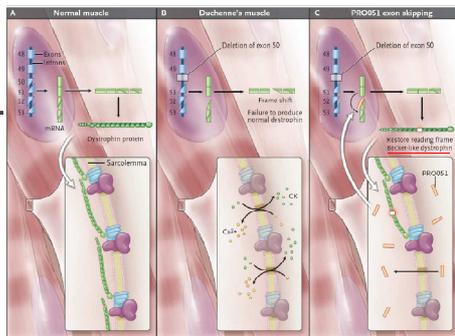


Figure 1. Mechanism of PROQS1 in the Restoration of Dystrophin Expression through Exon Skipping.