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

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Background Duchenne muscular dystrophy (DMD), an X-linked disorder due to lack of dystrophin, is associated with muscle weakness and myocardial dysfunction. Although preliminary data support the efficacy of angiotensin-converting enzyme inhibitors on left ventricular (LV) function, our aim was to examine the long-term impact of a preventive treatment with perindopril on mortality in children with DMD.

Methods Patients with DMD between the ages of 9.5 and 13 years presenting with normal LV ejection fraction were included in this prospective study. They were randomly assigned for 3 years to perindopril, 2 to 4 mg (group 1), or placebo (group 2) in a double-blind protocol, followed by open-label treatment with perindopril for up to 10 years. Survival rate at 10 years in each group is reported.

Results There were 28 patients assigned to group 1 and 29 to group 2. Baseline characteristics were similar in both groups. At the end of the 10 years’ follow-up period, survival status was available for all included patients: 26 (92.9%) of 28 patients in group 1 were alive at 10 years versus 19 (65.5%) of 29 in group 2 (P = .02). Kaplan-Meier cumulative survival was significantly lower in group 2 than in group 1 (P = .013).

Conclusion Early initiation of treatment with perindopril is associated with a lower mortality in patients with DMD with normal LV ejection fraction at study entry. (Am Heart J 2007;154:596-602.)
included in a 2-phase prospective study. Left ventricular ejection fraction was ≤55% in 20 patients, and DMD was not confirmed in 3 patients. Additional inclusion criteria included tolerance of a 1-mg test dose of perindopril and a systolic blood pressure ≥80 mm Hg in the supine or >70 mm Hg in the sitting position. Patients with contraindications to treatment with an ACEI, treated with other cardioactive drugs, or who had a blood urea nitrogen level >7 mmol/L were not included in the study. The protocol was approved by the appropriate ethics review committees, and informed, written consent was obtained from the parents or legal guardians.

Randomization and follow-up

After their inclusion into the study, the patients were randomly assigned for 3 years (phase I), in a double-blind fashion, to either perindopril, 2 to 4 mg daily, as tolerated (group 1, n = 28), or placebo (group 2, n = 29). In phase II, all patients were observed during open-label treatment with perindopril, 2 to 4 mg daily for 2 additional years. Radionuclide ventriculography to determine LVEF was not performed in 1 patient at the end of phase I and in 6 children at the end of phase II for personal reasons; however, all patients complied with prescribed therapy. The development of LV dysfunction at 5 years, the main study end point, has been previously reported.

Thereafter, all patients remained on an open-label regimen of perindopril, 2 to 4 mg daily, for an additional 5 years of follow-up (extended period), to measure the 10-year survival rate, a prespecified secondary study end point. The prescription of other cardioactive drugs was allowed during both the phase II and the extended period of the study, at the discretion of the primary care physicians. Compliance to treatment was assessed during each visit by interrogation of both patients and parents or legal guardians.

Follow-up and outcome. Information pertaining to the vital status, ongoing therapy, and, when available, date of last medical visit of the 57 patients originally included in the study was gathered on a yearly basis by telephone communications with their relatives and primary care physicians. If necessary, the vital status was confirmed by consulting the administrative records kept in the city hall of the patient’s birthplace. In France, these records, which contain the dates and precise locations of birth and death, are regularly updated and may be consulted upon request. The absence of mention of death indicates that the person is alive.

All data prospectively collected yearly were entered in a computerized database by a clinical research assistant; statistical analysis was performed blindly (group 1 vs group 2) at the end of the 10-year study period.

Statistical analysis. Differences in baseline characteristics were examined using Student t tests for normally distributed continuous variables and χ² analysis for differences in frequencies. Survival was analyzed by the Kaplan-Meier method; the log-rank test was applied for the time to first occurrence of a primary end point, on an intention-to-treat principle. Although the number may appear as too few, we also analyzed data using a Fisher exact test on frequencies. Analysis of different criterion possibly influencing mortality was examined using χ² analysis or Fisher exact test when appropriate. All P values were 2-tailed, and P < .05 was considered statistically significant. The analyses were performed with the Staview software (Abacus concept, Berkeley, CA).

Results

The baseline characteristics of the study groups were similar (Table I). No other pharmaceutical agent than the study drugs was administered during phase I. During phase II, treatment with perindopril was continued; exact doses of perindopril were not recorded during that period, but all physicians reported that it was prescribed at maximum tolerated doses in all patients, as recommended. In addition, in the beginning of phase II, 4 patients in group 1 (initially allocated to perindopril) and 5 in group 2 (initially allocated to placebo) were treated with β-adrenergic blockers. No additional patient has been treated with β-adrenergic blockers during the extended follow-up period. At 10 years of follow-up, all patients were still treated with perindopril; 2 patients were still being treated with β-adrenergic blockers in group 1 versus none in group 2. The reasons for discontinuation of beta-adrenergic blockade during the extended period were not specified. No patient has been treated with digoxin.

### Table I. Baseline characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Perindopril (group 1, n = 28)</th>
<th>Placebo (group 2, n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>10.7 ± 1.2</td>
<td>10.6 ± 1.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>37.1 ± 10.1</td>
<td>37.5 ± 13.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>141 ± 10</td>
<td>139 ± 14</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>109 ± 12</td>
<td>105 ± 8</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>64 ± 9</td>
<td>61 ± 12</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>94 ± 12</td>
<td>99 ± 15</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65.0 ± 5.5</td>
<td>65.4 ± 5.5</td>
</tr>
<tr>
<td>Daily dose of assigned study drug, phase I period, 2/4 mg (n)</td>
<td>9/19</td>
<td>12/17</td>
</tr>
</tbody>
</table>

Unless specified otherwise, values are means ± SD.

### Table II. Deaths up to 10 years of followup

<table>
<thead>
<tr>
<th></th>
<th>Group 1—initially assigned to perindopril (n = 28)</th>
<th>Group 2—initially assigned to placebo (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative no. of deaths</td>
<td>7 yFS</td>
<td>0</td>
</tr>
<tr>
<td>8 y</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>9 y</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>10 y</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>
spironolactone, or steroids during any part of the study; none had implantable devices, including cardioverter/defibrillators or cardiac pacemakers. Compliance to prescription was fair in all patients; it was assessed during the double-blind period by pill count and by interrogation of both patients and families during the open phase. Adequate compliance, a key factor in therapeutics, is encouraged by the French Association Against Myopathies (AFM); families are invited to participate in the meetings of the AFM and do adhere to the edited recommendations. Lastly, a tracheotomy has been performed in 13 patients at the end of the extended period (5 in the perindopril group vs 8 in the placebo group, \( P = .38 \)). In France, a standard policy is applied for ventilatory support; it has been recommended by a consensus of national experts and promoted by the AFM for >10 years and has been recently approved by the French National Health System (Haute Autorité de Santé). A tracheotomy has to be performed when vital capacity is <300 mL, whereas noninvasive nocturnal ventilation is recommended in patients with vital capacity <500 mL and transient nocturnal hypoxia and/or \( \text{PCO}_2 > 55 \text{ mm Hg} \).

Patients’ survival

Vital status information was available at the end of the extended period in all of the 57 included patients. Vital status has been gathered by telephone communications with both the relatives and primary care physicians for 54 patients. For the 3 remaining (1 in the perindopril group and 2 in the placebo group), vital status was determined after physician interrogation and confirmed by city hall interrogation: all 3 were alive.

Table II summarizes the cumulative death during the extended follow-up period; the Kaplan-Meier cumulative survival in each study group is represented in Figure 1. Of 28 patients, 26 (92.9%) in group 1 were alive at 10 years versus 19 (65.5%) of 29 in group 2; early versus delayed initiation of treatment with perindopril conferred a 27.4% absolute risk reduction in all-cause mortality (\( P = .0125 \) for the log-rank test and \( P = .02 \) for the Fisher exact test). It is noteworthy that this effect became apparent after 7 years of treatment (Figure 1).

No difference between the patients who were alive versus those who died during the study could be demonstrated regarding age at randomization, \( \beta \)-blocker agent prescription, and perindopril dosage available at the end of phase I.

Most patients died at home, all of them from a cardiorespiratory mode of death. In fact, none of the patients died from any other cause including respiratory or nonrespiratory infectious disease, but a clear distinction between cardiac and respiratory failure cannot be ascertained. As expected, a depressed LV function was a predictor of poor outcome because 5 of 9 patients who had an LVEF \(<45\%\) at 5 years died during the subsequent 5 years’ extended period, versus 7 of 48 who had an LVEF \(>45\%\) (mortality rate of 55.6% in the group with LVEF \(<45\%\) vs 14.6% in patients with LVEF \(>45\%, P = .006\)). Lastly, 4 of 13 patients with a tracheotomy performed died versus 8 of 36 of those without a tracheotomy during the study period (\( P = .35 \)).
Discussion

This study documented a survival benefit conferred by the early, instead of delayed, administration of perindopril in patients with DMD between the ages of 9.5 and 13 years presenting with normal LVEF at entry in the study. Although several other studies have reported a lowering of mortality by ACEI in patients with congestive heart failure, or a preventive effect in patients at high risk of adverse cardiovascular events, ours is the first to demonstrate a survival benefit conferred by ACEI in patients with DMD, a population genetically determined to develop LV dysfunction.

Vital status information was available in all included patients at the end of the extended follow-up period; both the relative and physician telephone interrogation were done in 54 patients, whereas physician and city hall administrative records were consulted in the 3 remaining. These 3 patients were alive, and we assume that our information is valid because in France, an administrative authorization is mandatory before burial; administrative records are immediately updated in such cases.

Duchenne muscular dystrophy is characterized by cardiac involvement and progressive muscular weakness; progressive deficit of intercostal muscles and diaphragmatic function leads to severe, chronic respiratory insufficiency. As a consequence, both cardiac and respiratory failure are responsible for the observed mortality in patients with DMD. In our study, we report all-cause mortality; it was either sudden death or death due to a cardiorespiratory case in all patients. Interpretation of our results may be that early perindopril allocation, versus delayed, improves cardiac function and/or respiratory function and/or both functions. Furthermore, previous experimental studies have observed a beneficial effect of ACEI on diaphragmatic contractility.

However, we have reported that (1) perindopril delayed the onset and progression of LV dysfunction in the first 5 years of our study, (2) a reduced LVEF (LVEF <45% at 5 years' follow-up) was associated with increased mortality as demonstrated in the general population of the CHARM study and in the particular setting of DMD, and (3) the presence of tracheotomy was not associated with differences in mortality. One may therefore assume that cardiac mortality may be the major cause of death in our patients, and our findings of death in 10 of 29 in group 2 during the 10-year follow-up is in accordance with cardiac death rate estimated by previous studies.

In addition, all other potentially pertinent confounding factors, including other cardioactive drugs and the need for ventilatory support, were equally represented in both groups (group 1 vs group 2) and in patients who died or were alive during the study period, reinforcing our assumption of a survival benefit only conferred by early perindopril administration.

We have previously reported a beneficial effect of perindopril on LV function during the first 5 years’ follow-up of our study because in the actively treated group, a single patient had an LVEF <45% at 5 years, versus 8 in the group assigned to placebo (P = .02). The effect of treatment on survival seems to have begun at 7 years, beyond which mortality continued to increase in the group of patients who did not receive early perindopril therapy, and was significant at 10 years’ follow-up. This gradual onset of treatment effect and progressive benefit over time are consistent with a hemodynamic effect and/or a specific antifibrotic effect of perindopril and are concordant with experimental observations made in a model of progressive cardiomyopathy resembling Duchenne myopathy. In addition, one may explain the “relative lack of efficacy” of delayed perindopril administration by cardiac remodeling, which is a very prompt phenomenon after myocardial injury; therapeutics are more effective when administered very early in the course of the disease, before the fibrosis and remodeling process are established.

In fact, dystrophin plays a critical role in the myocardium by connecting the cytoskeleton to the external basement membrane. Its absence is responsible for membrane fragility, loss of transductional force, and, ultimately, myocyte necrosis promoted by mechanical stress. Thus, afterload reduction by perindopril may be a key factor in our study, which included children <11 years of age with DMD, on average. Some of the children were still capable of muscular exercise, and there is experimental evidence that the myocardium is vulnerable to pressure overload. The inhibition of aldosterone synthesis by ACEI might also prevent the development of fibrosis, and previous studies have demonstrated a beneficial effect of such inhibition. Finally, nitric oxide (NO), a powerful antioxidant, might also be involved in the development of cardiac dysfunction in DMD. Mutation of dystrophin is accompanied by loss of dystrophin-associated glycoprotein complex that includes neural NO synthase. The restoration of neural NO synthase activity in an animal model resulted in NO synthesis and limitation of myocardial fibrosis, without increasing the expression of membrane-associated cytoskeletal proteins. Because they stimulate the synthesis of NO by blocking the degradation of bradykinin by the direct promotion of the bradykinin type 2 receptor coupling to NO storage sites and by inhibiting aldosterone, ACEI may exert part of its beneficial effects via an NO-related pathway.

In their recent study, Cohn et al demonstrated that losartan, an angiotensin II type 1 receptor blocker, protects regenerative capacities and improves muscle...
function in an Mdx mouse model of DMD. Although regenerative capacities may not be considered as a major element for cardiac improvement, their results and ours may suggest that strategies based on angiotensin II blockade (ACE inhibitors and/or angiotensin II blockers) may have generalized clinical beneficial effects, both on skeletal muscle, diaphragm and intercostal muscles, and heart function.\textsuperscript{32-35}

Clinical implications

Our study may have important implications for the management of patients with DMD. In fact, we and others had already reported the preventive effect of ACEI against loss of LV contractility.\textsuperscript{14,34,35} However, there is still ongoing controversy as to whether patients with DMD should be treated early (preventively) by ACEI.\textsuperscript{36-38} We assume that our demonstration of a survival benefit reinforces the need for a rigorous cardiac screening in all patients with DMD and early use of ACEI in both patients with systolic dysfunction as well as in those with normal LVEF. However, because we limited study entry to patients between the ages of 9.5 and 13 years, the optimal age for initiation of therapy remains to be determined.\textsuperscript{14} The recent documentation of reduced myocardial performance (strain, a marker of contractility, determined by magnetic resonance imaging) in 13 children with DMD whose mean age was the same as that of our patients\textsuperscript{39} supports the earlier introduction of ACEI treatment. As suggested by Chamberlain,\textsuperscript{35} now is the time for clinical studies targeted at examining young children before the fibrosis process is established and evaluating the global effect of therapeutics.

Study limitations

The randomized, double-blind phase of our protocol was limited to 3 years, after which perindopril was dispensed in an open-label fashion. The doses of ACEI administered during the extended follow-up period were not recorded. However, therapy was prescribed at maximally tolerated doses in all patients; based on the balanced baseline characteristics in both groups, we expect that the doses of ACEI would probably have been similar during follow-up. Only few patients were treated with \(\beta\)-adrenergic blockers because this study had been planned before the demonstration and wide acceptance of their efficacy in the management of heart failure. In addition, respiratory insufficiency, often present in these patients, may be viewed as contraindication to beta-blockade, although we do not share this opinion.

We have reported all-cause mortality, hypothesizing that ACEI decreases the death rate by its effects on the cardiac involvement of the disease. Although our results may strongly suggest that the main cause of death was cardiac and may be prevented by perindopril, we cannot clearly distinguish between cardiac, respiratory, or both effects of ACEI. Such as in most studies, we assume that all-cause mortality may be the most appropriate end point; making a distinction between cardiac and respiratory failure and beneficial effect of ACEI is difficult and not clinically relevant. In addition, we focused on cardiac involvement; the age of loss of ambulation is an important parameter in DMD and may be influenced by ACE inhibitor (ref nature). However, it was not evaluated in our study.

No patient was treated with corticosteroids. In fact, steroids have demonstrated a preventive effect on muscle degeneration.\textsuperscript{40,41} In addition, a retrospective study also pointed out a considerable cardiac protective effect\textsuperscript{42}, the confirmation of such a beneficial effect and a possible additive effect to perindopril are to be demonstrated prospectively. Lastly, the present study reports a secondary end point; therefore, it may be considered as a preliminary report.

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References


Appendix A

The following French investigators and institutions participated in this study:

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