Randomised placebo-controlled trial of combination ACE inhibitor and beta-blocker therapy to prevent cardiomyopathy in children with Duchenne muscular dystrophy? (DMD Heart Protection Study): a protocol study

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ABSTRACT

Introduction Although cardiologists were ‘late-comers’ to the multidisciplinary team—contributing to the complex care of patients with Duchenne muscular dystrophy (DMD), they now recognise the importance of systematic cardiac surveillance and timely therapy to prolonged survival in patients with DMD. Empirical deployment of cardioactive medications has already improved outcomes, but the evidence base for clinical decision making is weak. Fundamental questions remain as to whether prophylactic therapy is justified and convincingly superior to prompt deployment of the same therapies once left ventricular (LV) dysfunction is detected. Even if it were, at what age should therapy be introduced and with what specific drugs?

Methods and analysis We are conducting a multicentre, parallel group, randomised, placebo-controlled study of combination therapy with an ACE inhibitor (perindopril) and a beta-blocker (bisoprolol) in boys with DMD aged 5–13 years, with normal LV function by echocardiographic criteria at the time of recruitment. Boys are being followed-up for a minimum of 3 years and a maximum of 5 years and undergo repeat assessments of LV function, heart rate and ECG, forced expiratory volume in the 1 s and forced vital capacity, adverse event reporting and quality of life at 6 monthly intervals. The primary outcome is change in LV function between active and placebo-treated participants over the course of the study.

Ethics and dissemination The study was approved by ‘NRES Committee East Midlands – Derby’. The results will be disseminated through manuscript publications, an international workshop and presentations to scientific meetings and parent forums.

Translational aspects The study seeks to establish the evidence for prophylactic heart therapies for children with DMD, define the optimum age for their introduction and identify any safety concerns.

Strengths and limitations of this study

- Double-blind, multicentre, randomised, placebo-controlled study design.
- Participants studied 6 monthly for a minimum of 3 years.
- Largest study to date of prophylactic therapy for cardiac dystrophinopathy.
- Use of echocardiographic assessments for primary endpoint measures.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is an X-linked recessively inherited neuromuscular disorder caused by a deficiency in the expression of the protein dystrophin on the inner aspect of muscle cell sarcolemma.1 Its clinical course has traditionally been characterised by weakness of proximal limb muscles and calf muscle hypertrophy and progresses to involve all body muscles.2 Affected individuals
typically lose ambulation and become wheelchair-dependent before the age of 13 years and die from cardiorespiratory failure in their third to fourth decade of age.3,4 From the cardiology perspective, some 90% of men with DMD develop a severe, progressive form of cardiomyopathy. Twenty per cent to 30% have evidence of left ventricular (LV) impairment on echocardiography by age 10 years.5–8 Subtle abnormalities in LV function are evident in an even larger proportion of patients at all ages when more sensitive imaging techniques, such as tissue Doppler, magnetic resonance or metabolic imaging, are deployed.9,10 Despite the prevalence of cardiac involvement, until recently cardiologists were not included in the multidisciplinary team managing patients with DMD. Historically, this was because survival in DMD was determined predominantly by respiratory muscle weakness and consequent respiratory failure. Despite the severity of underlying cardiomyopathy, patients with DMD remain asymptomatic because their limited physical activity, due to generalised muscle weakness, means that cardiac symptoms only emerge with the onset of heart failure. Even then, when cardiac medications were introduced, they were usually deployed tentatively and without any expectation that they would improve survival.

However, life expectancy in DMD has improved over recent decades, primarily as a result of three changes: routine use of corticosteroid therapy for muscle strengthening, non-invasive ventilation for respiratory muscle weakness and wider multidisciplinary care arrangements.11–13 This has meant that patients with DMD are now surviving routinely to an age when cardiac involvement is more advanced and the heart more often contributes directly to death.6,12,15

The results of large randomised controlled trials in patients with idiopathic forms of dilated cardiomyopathy have established that cardioactive medications can reverse or change the trajectory of decline in LV dysfunction and so improve prognosis.14–16 Combination therapy with an ACE inhibitor (ACEi),17,18 beta-blocker19–21 and an aldosterone antagonist22,23 are now deployed routinely and well tolerated in adults. More recently, the findings from cohort series of patients with established cardiac dystrophinopathy have shown that the rate of decline in LV function can be slowed also by the same drug combinations.24–27 However, when introduced after the detection of early, asymptomatic, LV systolic dysfunction, these therapies do not seem to be able to prevent a slower rate of decline over a longer period of time.25

**METHODS AND ANALYSIS**

**Patient and public involvement**

The study was designed against the background of uncertainties recognised both by clinicians and patient support groups about the value of prophylactic, cardio-specific medications for children with DMD and the optimum age to start therapy. This issue was a common theme raised by parents of boys attending cardiac surveillance clinics. This prompted the development of this clinical trial and the aims, study duration and the therapies to be tested evolved in discussion with patients/patient groups (eg, Action Duchenne, UK; an ENMC workshop with patient representatives; and so on) and clinician experts over several years. The burden of testing for the study was not specifically assessed with patients/patient but was designed to be intentionally low.

**Objectives and hypotheses**

The aim of this randomised, multicentre, placebo-controlled trial is to determine whether the introduction of ACEi (perindopril) combined with beta-blocker (bisoprolol) therapy, before the onset of echo-detectable LV systolic dysfunction, can delay the age of onset and/or slow the rate of progression of cardiomyopathy compared with placebo in men aged 5–13 years with DMD. The study is being conducted at four National Health Service (NHS) specialist hospital sites. LV function will be assessed serially over a minimum of 3 years and a maximum of 5 years. The study was designed on the assumption that only one high-quality placebo-controlled trial of prophylactic cardioactive therapy is ever likely to be funded and brought to completion. Patient recruitment began in mid-2011 and the last participant was recruited in January 2015. Patient follow-up is ongoing.

**Primary hypothesis:** Starting the combination of perindopril and bisoprolol before there is any evidence of LV systolic dysfunction, detectable by echocardiography, in children with DMD will delay the onset and/or slow the rate of progression of cardiac dystrophinopathy compared with placebo.
entry as required by local regulations. A screening log was kept by each site of those approached but not recruited to the study. Permission to use their child’s NHS number for tracing in the case of loss to follow-up and for assessment of long-term survival status was also obtained from the parent(s)/legal guardian(s).

Boys then underwent baseline testing. This comprised an echocardiogram with tissue Doppler imaging, 12-lead ECG, vitalograph for forced vital capacity (FVC) and forced expiratory volume in the 1 s (FEV₁) and peak flow measurements as well as blood sampling for haematology and biochemistry parameters. A parent and the boy also completed core and Neuromuscular disease specific module (NMD) module PedsQual quality of life questionnaires. To be eligible for randomisation and study enrolment, LV ejection fraction (LVEF), calculated by the 16-segment wall motion score method, had to be ≥55%, fractional shortening (FS) ≥28% and there could not be any LV segmental hypokinesis on baseline echo imaging.

Additional inclusion/exclusion considerations

Current or recent inclusion in a separate natural history trial did not preclude participation in the DMD Heart Protection study. Patients with contraindications to either ACEi or beta-blocker medications were not recruited. Renal function was measured by plasma urea, creatinine and potassium prior to study entry. Patients with abnormal renal function (ie, creatinine>upper limit of local laboratory range; typically >60 μmol/L) or consistently abnormally high serum potassium level (K>upper limit of local laboratory range; typically 5 mmol/L) were also excluded. To achieve blinding throughout the study, participants had to be able to swallow an empty capsule identical in size, colour and shape to that to be used throughout the study at the screening visit to be enrolled in the trial.

Randomisation, blinding and enrolment

Randomisation and dosing

To ensure concealment of allocation, randomisation was performed using the web-based Newcastle Clinical Trials Unit’s Randomisation Service in variable blocks, blocked and stratified by centre. Boys fulfilling study entry criteria were randomised to receive capsules containing both active medications (ie, perindopril 2 mg and bisoprolol 1.25 mg) or an identical placebo capsule (ie, containing an inert filler). All participants took one capsule at bedtime for the first month and those weighing more than 30 kg then increased to two capsules at bedtime thereafter. If a participant’s weight increases to more than 30 kg at any scheduled review, study medication increases to two capsules per day for the remainder of the study.

Blinding

Randomisation to active or placebo combined capsule (1:1 ratio) is double blinded from the point of manufacture and identifiable only by a master code held at the Newcastle Clinical Trials Unit (NCTU). Participants, clinicians, pharmacy and other trial staff are also blinded to treatment allocation. Study drug and placebo capsules are identical in appearance and packaging, identifiable only through the study code numbers on the medication bottles. Following entry of a participant into the study, bottle numbers assigned to him are recorded on the prescription, and a list of bottles received by participants is maintained by the NCTU. Emergency code-break envelopes, one per participant, are stored in the trial pharmacy at sites to allow unblinding in the event of an emergency. Any unblinding is notified to the trial coordinating team and a record will be maintained in both the Trial Master File and the Investigator Site File. Code breaks will not be performed routinely for participants on study completion.

Evaluation and follow-up

All participants are being followed-up 6 monthly for a minimum of 3 years and a maximum of 5 years. At each attendance, participants have height and/or arm span, weight, blood pressure and heart rate measured, and the family is questioned about any adverse events, intercurrent illnesses and need for urgent or elective hospital admissions since last assessed. A list of all concomitant medications and any changes in doses are recorded. Boys have a repeat echocardiogram, 12-lead ECG, peak flow, FEV₁ and FVC measurements and both the boy and a parent complete age-appropriate PedsQL, quality of life questionnaires. Families are instructed to bring all used and unused containers of trial medications back with them at each assessment as a way of assessing compliance with their allocated treatment (Table 1).

To increase the sensitivity of testing, cardiac MRI (cMRI) will be offered once to each participant as they exit the trial. This will allow supplementary measures of LVEF%, wall thicknesses, chamber dimensions and volume for comparisons between active and placebo cohorts in those who consent to this additional test.

Primary outcome variable

The primary outcome variable is change in LVEF%, derived from the 16-segment regional wall motion scoring system, compared with baseline between those receiving combination therapy or placebo over the duration of study participation. To assess the robustness of the echo-derived EF% result, similar comparisons will be made for other parameters of LV size and function, end-systolic and end-diastolic dimensions, LV wall motion index and LV-FS%. Prevalence of segmental, as opposed to global, cardiomyopathy will be compared by tissue Doppler imaging. LV diastolic function will be assessed using mitral-flow-to-left-ventricular-tissue-Doppler ratios (E/E’ ratios).

Secondary outcome variables

cMRI measures of LV size and function as well as the presence, extent and distribution of intramyocardial fibrosis will be compared between active and placebo treated patients.
Table 1  Test schedule for participants in the DMD Heart Protection Trial

| Time   | 0 months | 6 months | 12 months | 18 months | 24 months | 30 months | 36 months | 42 months | 48 months | 54 months | 60 months |
|--------|----------|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Inclusion/exclusion screening | X | | | | | | | | | | |
| Parent/guardian written informed consent and participant assent | X | | | | | | | | | | |
| Randomisation | X | | | | | | | | | | |
| Weight (kg) | X | X | X | X | X | X | X | X | X | X | X |
| Height and arm span (cm) | X | X | X | X | X | X | X | X | X | X | X |
| Seated blood pressure (mm Hg) | X | X | X | X | X | X | X | X | X | X | X |
| Symptom/adverse events | X | X | X | X | X | X | X | X | X | X | X |
| QoL questionnaires (parent/guardian and participant) | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG | X | X | X | X | X | X | X | X | X | X | X |
| 2D echocardiogram | X | X | X | X | X | X | X | X | X | X | X |
| LV tissue Doppler imaging | X | X | X | X | X | X | X | X | X | X | X |
| FEV<sub>1</sub>/FVC | X | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ |
| Serum biochemistry (potassium, sodium, urea and creatinine) | △ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ |
| Biomarker blood sample | Once | at | any | time point | | | | | | | |
| MRI of heart (including late Gad sequences) | | | | | | | | | | | |

▲=performed if clinically indicated; △=baseline blood test taken to confirm eligibility, if recent results are not available at screening visit. A repeat blood sample may be drawn for the same measurements, when the patient is established on maintenance dosage for the trial, at the discretion of the local PI; X=measure to be performed at that interval.

DMD, Duchenne muscular dystrophy; FEV<sub>1</sub>, forced expiratory volume in the 1 s; FVC, forced vital capacity respectively; QoL, PedsQL quality of life assessments.
Changes in quality of life measures over the duration of study participation will be compared between active and placebo treated participants using generic and muscle-specific PedsQL questionnaires.29 30 The cause of any deaths will be recorded and compared between groups as will the development of symptoms and/or signs of congestive cardiac failure (CCF). For the purpose of this study, heart failure will be diagnosed by the onset of symptoms of orthopnoea with or without peripheral oedema and objective signs of heart failure—raised jugular venous pressure, third heart sound or gallop rhythm, pulmonary plethora on chest X-ray or similar—all in the context of known advanced LV dysfunction (ie, echocardiogram LVEF <25%). Patients who develop CCF will be withdrawn from intervention but invited to continue follow-up (as per protocol) and treated thereafter at the discretion of clinician managing the patient. However, given the age, study duration and requirement to have normal LV function by all criteria at study entry, it is not anticipated that any participant will meet this heart failure endpoint.

Participants who show a progressive reduction in LVEF% on at least two assessments at least 3 months apart, culminating in LVEF ≤35%, will be deemed to have reached a predefined study endpoint, mandating the introduction of active therapy. They will cease trial medications without being unblinded and convert to open-labelled ACEi and beta-blocker therapy. They will be asked to continue under study follow-up. This stipulation is to avoid participants being withdrawn on the basis of subtle changes in heart measures of dubious clinical significance that could subvert the aim of the study.

Definition of end of study
The end of study will be the last patient’s last visit, as agreed with the study sponsor.

Sample size calculation
The sample size was based on a composition of change in LVEF% over the 5-year term of the trial. A difference of 5% between active and placebo-treated groups was considered to be the smallest that would represent a clinically useful gain. The SD of LVEF% has been taken to be 10%, and this gives two groups of 64 subjects to yield a power of 80% at the 5% significance level.31 By recruiting 140 patients, allowance was made for an approximate 10% participant dropout rate from ‘ACE-inhibitor cough’. Since the age of onset of earliest detectable cardiomyopathy is variable, depending on age at recruitment, duration of follow-up, steroid use as well as any impact of specific DMD-mutations, it was not possible to factor these meaningfully into a power calculation.

Statistical Analysis Plan
Full details of statistical analysis will be documented in a Statistical Analysis Plan that will be signed off prior to database lock. Subgroup analyses will be used to adjust comparisons for baseline variables (eg, age at recruitment, duration of study participation and steroid use).

Secondary endpoints
ANOVA will be used to examine differences between treatment groups in terms of LV-FS%, end-diastolic dimension and wall motion scores, adjusted for baseline value, age, body surface area, steroid use and centre.

To assess robustness of LVEF% result, similar comparisons will be made for parameters of echo and MR-imaged LV end-systolic and end-diastolic dimensions, wall thicknesses, wall motion index and LV-FS%. ANCOVA will also be used to examine differences in regional LV systolic function between treatment groups in terms of tissue–Doppler ratios.

From late-Gad-enhanced cMRI images at study exit, measures of LVEF%, wall thicknesses, chamber dimensions and volume and presence/extent of LV myocardial fibrosis will be obtained and compared between active and placebo participants.

The age of onset of earliest definite, echo-detectable impairment of LV function (ie, wall motion abnormality in >2 contiguous LV segments, ejection fraction >2SDs below mean for age) will be plotted for each group over the 5-year course of the trial and active-treated and placebo-treated groups will be compared using Kaplan-Meier plots.

Changes in quality of life measures (core, NMD-specific and parent proxy PedsQL modules) within participants over the course of the trial and between participants in active-treated and placebo-treated arms will be assessed and resulting scores compared.

Safety endpoints will be presented descriptively; no formal testing will be performed.

Full details of statistical analysis will be documented in a Statistical Analysis Plan that will be signed off prior to database lock. Subgroup analyses will be used to adjust comparisons for baseline variables (eg, age at recruitment, duration of study participation and steroid use).

Ethics and dissemination
The results will be disseminated through various manuscript publications focusing on different outputs from the study and presentations of results at local, national and international scientific meetings. Headline results will be fed back to participant families shortly after they become available by letter, which will also provide links to more detailed results (eg, study-related publications). Patient support group (eg, Action Duchenne, UK; Duchenne UK) have already offered to assist in publicising the results (eg, via their websites and patient-focused events).

We also plan to convene an international workshop of experts, when all results are available, to discuss their implications and whether they should influence management recommendations.
Trial management and data monitoring and ethics committees

**Trial steering committee**

The Trial Steering Committee (TSC) is composed of an independent chair, independent statistician, the chief investigator/applicant and coapplicants, sponsor/funder representative and representatives of the clinical trials unit (statistician and trial manager). The TSC met twice in the first year and meets annually thereafter. Its role is to supervise the trial to ensure that it is conducted to high standards in accordance with the protocol, the principles of good clinical practice (GCP) and with regard to participant safety. The TSC also considers safety issues for the trial and relevant information from other sources, ensuring at all times that ethical considerations are met when recommending the continuation of the trial.

**Data monitoring committee**

A committee of three, comprising two clinicians and one statistician, all independent of the trial, act as the Data Monitoring and Ethics Committee. They met once at the beginning of the study to agree monitoring procedures, again in year 2 and are planned to meet finally in year 4. As well as overseeing safety aspects, its role includes arbitrating in the case of any disagreements between the Principle Investigators (PI) at site and the CI over serious adverse events.

**Trial management group**

A trial management group consisting of the chief investigator, senior trial manager, trial manager, statistician and trial data manager meets quarterly to discuss operational aspects of the trial.

**Internal and external inspection**

All aspects of the study are also subject to internal oversight by trial management team, internal inspection by representatives of the study sponsor and independent external inspection by regulatory authorities (eg, Medicines and Healthcare products Regulatory Agency (MHRA)) who dictate their own frequency and depth of audit and inspection throughout.

**Data handling**

A secure system of electronic case report forms is being used for data collection, management and monitoring. Only authorised users with appropriate access permissions are able to enter/view/edit data.

All echocardiograms undertaken at recruiting site are being stored locally, and the anonymised images can be made available, if required, to NCTU for later analysis and validation of locally reported results. The quality and retention of study data are the responsibility of NCTU. Data are being collected to standards required by the latest directive on GCP (2005/28/EC) and local policy and will adhere to the Data Protection Act 1998. All study data will be archived in line with sponsor policy (currently 15 years).

All investigators and their participating institutions are required to permit site monitoring, audits, Research Ethics Committee (REC) and MHRA review and must provide direct access to source data and documents as required for these purposes.

**Potential weaknesses in study design**

This protocol was conceived originally at a time when cardiac medications were not prescribed routinely even for patients with DMD before the onset of symptomatic heart failure in most hospitals. Although the results of a randomised, placebo-controlled trial of prophylactic perindopril in DMD were known, their clinical significance was debated. On this basis, it was concluded that another placebo-controlled study was both necessary and ethically justifiable.

Ideally, the study would have had four arms (perindopril alone, bisoprolol alone, perindopril and bisoprolol and placebo alone). However, it rapidly became apparent that there were insufficient potential participants available to recruiting sites to allow that design. Furthermore, the anticipated cost over the study duration planned would have been prohibitive. It was decided, therefore, that this protocol should build on the finding of the earlier perindopril study by recruiting a larger patient cohort and by testing combination (perindopril and bisoprolol) rather than single agent (perindopril) therapy.

The optimum age at which to start prophylactic heart therapy is unknown. By recruiting participants as young as 5 years of age, the study aimed to check for intolerance which might outweigh cardiac benefits, particularly in the very young. However, recognising that the youngest recruits were less likely to develop echo-detectable cardiac dysfunction over even the maximum study follow-up of 5 years, the protocol included a prespecified analysis of results by age.

The decision to use echo rather than MR assessments for the main outcome measures was discussed repeatedly at the planning stage. Ultimately, echo measures were adopted for the following reasons: (1) young children might not tolerate the length and nature of cMRI without sedation or general anaesthesia. Both were considered unreasonable in a research study planned in 2009; (2) towards the end of study participation, older subjects might not be able to fit comfortably into an MRI scanner due to steroid induced changes in body habitus, scoliosis or limb contractures; and (3) because of respiratory muscle weakness, older patients with DMD do not tolerate lying supine for long without assisted ventilation. Inability to breath-hold adequately and/or patient movement reduce the image quality of cardiac MR scans and so their sensitivity in detecting subtle abnormalities. Furthermore, although cMRI is now used more routinely for surveillance and is more sensitive in detecting cardiac abnormalities at earlier stages in DMD, it was not as widely available in many hospitals in 2009.

A further important consideration was that if the findings were ultimately to change the conservative approach to heart management that prevailed when the study was first approved, they would need to be sufficiently robust.
to convince non-specialists of the benefits of prophylactic therapy. Also, allowing for wide variations in age of onset of detectable cardiac changes in DMD, a study of longer duration using less sensitive heart measures was considered more likely to provide clinically relevant answers than one of shorter duration even using more sensitive assessments. With the increased use and availability of cMRI since the study was first conceived, participants are now being offered cMRI once as they complete follow-up. This will increase the study’s ability to detect subtle differences in cardiac function and in fibrosis between active and placebo arms.

Each of the decisions made in developing the final protocol involved compromises and several can legitimately be criticised. However, it is probably only after results become available that it will become clearer whether the best trade-offs were made and whether the protocol should have been optimised differently.

**DISCUSSION**

It has been known for decades that a progressive form of cardiomyopathy affects almost all patients with DMD. LV function deteriorates progressively without symptoms for most of its course but ultimately contributes to heart failure and premature death in these patients. Traditionally, cardiac-specific medications were not deployed, because it was assumed that they would be of little benefit except in alleviating heart failure symptoms. This was based on the knowledge that none of them could correct the underlying dystrophin deficiency, which results in progressive cardiac myocyte damage from cardiac contractions. However, various cohort series have established that glucocorticoid steroid therapy delays the onset of cardiac dystrophinopathy and that a range of cardiac-specific drugs can slow the rate of deterioration in ventricular function when introduced after cardiomyopathy is detected.

Based on current understanding of the cause and course of cardiomyopathy, therapies are more likely to be effective if started before the process has led to functional difficulties. Support for the prophylactic use of ACEi therapy (perindopril) comes from the results of the only randomised, placebo-controlled trial in children with DMD. This found that, although mean LVEF% did not differ between treated and placebo groups after either three or 5 years, LVEF% fell to less than 45% after 5 years in eight of those initially receiving placebo as compared with only one taking perindopril. Additionally, early perindopril seemed to be associated with improved survival after 10 years. The results are encouraging but the findings have been criticised for a number of shortcomings in study design and the small trial size was not powered to detect a mortality outcome.

Some clinicians found the results persuasive and began to deploy prophylactic ACEi therapy routinely. However, others found the available evidence insufficient to justify daily drug-therapy for an average of 5 years before asymptomatic LV dysfunction would usually be detectable. The effect is that although steroid therapy is now recommended routinely for children with DMD, prophylactic ACEi therapy is not, primarily because of the lack of convincing evidence of benefit. Furthermore, even if the benefits of prophylactic ACEi therapy are accepted, available evidence does not define the optimum age for their introduction. Nor is it established whether therapy should be with ACEi alone, ACEi and beta-blocker, aldosterone antagonist alone or a combination of ACEi, beta-blocker and aldosterone antagonist. It is even debated whether prophylactic cardiac therapy is really superior to the prompt introduction of combination cardiac therapies on detecting the earliest evidence of ventricular dysfunction.

This randomised placebo-controlled study protocol was developed in recognition of these therapeutic uncertainties and to improve the evidence base for clinical decision making about how best to protect the hearts of children with DMD using currently available medications.

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**Disclaimer**

The BHF have not had any role in the design of the study or its protocol. Nor will they play any part in analysis of results or have any influence/authority over presentation of findings. The study sponsor has not had any role in protocol design and will not play any part in the reporting of findings. Nor does it have ultimate authority over presentation of results.

**Competing interests**

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation other than from the British Heart Foundation [grant: SP/05/001] for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Patient consent for publication**

Not required.

**Ethics approval**

The study secured ethical approval from the Trent Research Ethics Committee (renamed: ‘NRES Committee East Midlands – Derby’) in 2009.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

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and imaging findings in children and teenagers. *Klin Padiatr* 2015;227:225–31.

11 Eagle M, Baudouin SV, Chandler C, et al. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscul Disord* 2002;12:926–9.

12 Eagle M, Bourke J, Bullock R, et al. Managing Duchenne muscular dystrophy—the additive effect of spinal surgery and home nocturnal ventilation in improving survival. *Neuromuscul Disord* 2007;17:470–5.

13 Passamano L, Taglia A, Paladino A, et al. Improvement of survival in Duchenne Muscular Dystrophy: retrospective analysis of 835 patients. *Acta Myol* 2012;31:121–5.

14 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;18:891–975.

15 Burnett H, Earley A, Voors AA, et al. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: a network meta-analysis. *Circ Heart Fail* 2017;10:e003529.

16 Heran BS, Musini VM, Bassett K, et al. Angiotensin-receptor blockers in heart failure. *Cochrane Database Syst Rev* 2012:CD0033040.

17 Yusuf S, Pitt B, Davis CE, et al. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293–302.

18 Konstam MA, Kronenberg MW, Rousseau MF, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. SOLVD (Studies of Left Ventricular Dysfunction) Investigators. *Circulation* 1993;88:2277–83.

19 Bisoprolol Study II (CIBIS-II). The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:138–42.

20 MacMahon S, Sharpe N, Dougherty R, et al. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Australia/New Zealand Heart Failure Research Collaborative Group. *Lancet* 1997;349:375–80.

21 Anonymous. Effects of metoprolol CR in patients with ischemic and diluted cardiomyopathy : the randomized evaluation of strategies for left ventricular dysfunction pilot study. *Circulation* 2000;101:378–84.

22 Zannad F, Alla F, Doussset B, et al. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study (RALES). RALES Investigators. *Circulation* 2000;102:2700–6.

23 Cicora M, Zancolla L, Franceschini L, et al. Relation of aldosterone “escape” despite angiotensin-converting enzyme inhibitor administration to impaired exercise capacity in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 2012;110:98–102.

24 Allen HD, Flanigan KM, Thrush PT, et al. A randomized, double-blind trial of lisinopril and isosorbide for the treatment of cardiomyopathy in Duchenne muscular dystrophy. *PLoS Curr* 2013;5:1–13.

25 Violett L, Thrush PT, Flanigan KM, et al. Effects of angiotensin-converting enzyme inhibitors and/or beta blockers on the cardiomyopathy in Duchenne muscular dystrophy. *Am J Cardiol* 2012;110:98–102.

26 Kwon HW, Kwon BS, Kim GB, et al. The effect of enalapril and carvedilol on left ventricular dysfunction in middle childhood and adolescent patients with muscular dystrophy. *Korean Circ J* 2012;42:184–91.

27 Raman SV, Hor KN, Mazur W, et al. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2015;14:153–61.

28 Bushby K, Finkel R, Binkrant JD, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. *Lancet Neurol* 2010;9:177–89.

29 Davis SE, Hyman LS, Limbers CA, et al. The Pediatric Angiotensin-Converting Enzyme Inhibitor Trials: cardiovascular effects in the Pediatr Health Outcomes in Children With End-stage Renal Disease (Pediatric Health Outcomes in Children With End-stage Renal Disease) Investigators. *Pediatrics* 2010;126:e559–e566.

30 Scientific Tables. Geigy scientific tables. , 8th edition, 1990:5. 96–7. (tables 6 & 10) & 120, (table 10).
32 Heysmfield SB, McNish T, Perkins JV, et al. Sequence of cardiac changes in Duchenne muscular dystrophy. Am Heart J 1978;95:283–94.
33 Perloff JK, Henze E, Schelbert HR. Alterations in regional myocardial metabolism, perfusion, and wall motion in Duchenne muscular dystrophy studied by radionuclide imaging. Circulation 1984;69:33–42.
34 Muroyama M, Kondo K, Hizawa K, et al. Life spans of duchenne muscular dystrophy patients in the hospital care program in Japan. J Neurol Sci 1987;81:155–8.
35 de Kermadec JM, Bécane HM, Chénard A, et al. Prevalence of left ventricular systolic dysfunction in Duchenne muscular dystrophy: an echocardiographic study. Am Heart J 1994;127:618–23.
36 Ferlini A, Sewry C, Melis MA, et al. X-linked dilated cardiomyopathy and the dystrophin gene. Neuromuscul Disord 1999;9:339–46.
37 Corrado G, Lissoni A, Beretta S, et al. Prognostic value of electrocardiograms, ventricular late potentials, ventricular arrhythmias, and left ventricular systolic dysfunction in patients with Duchenne muscular dystrophy. Am J Cardiol 2002;89:838–41.
38 Finsterer J, Stöllberger C. The heart in human dystrophinopathies. Cardiology 2003;99:1–19.
39 Muntoni F. Cardiomyopathy in muscular dystrophies. Curr Opin Neurol 2003;16:577–83.
40 Wargo KA, Banta WM. A comprehensive review of the loop diuretics: should furosemide be first line? Ann Pharmacother 2009;43:1836–47.
41 Burnett H, Earley A, Voors AA, et al. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: a network meta-analysis. Circ Heart Fail 2017;10.
42 Manzur AY, Kuntzer T, Pike M, et al. Glucocorticoid corticosteroids for duchenne muscular dystrophy. Cochrane Database Syst Rev 2008;23:CD003725.
43 Silversides CK, Webb GD, Harris VA, et al. Effects of deflazacort on left ventricular function in patients with Duchenne muscular dystrophy. Am J Cardiol 2003;91:789–72.
44 Schram G, Fournier A, Leduc H, et al. All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol 2013;61:948–54.
45 Biggar WD, Harris VA, Eliasoph L, et al. Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. Neuromuscul Disord 2006;16:249–55.
46 Barber BJ, Andrews JG, Lu Z, et al. Oral corticosteroids and onset of cardiomyopathy in Duchenne muscular dystrophy. J Pediatr 2013;163:1080–4.
47 Jeffries JL, Eidem BW, Belmont JW, et al. Genetic predictors and remodeling of dilated cardiomyopathy in muscular dystrophy. Circulation 2005;112:2799–804.
48 Ramaciotti C, Heistand LC, Coursaye M, et al. Left ventricular function and response to enalapril in patients with duchenne muscular dystrophy during the second decade of life. Am J Cardiol 2006:98:825–7.
49 Ogata H, Ishikawa Y, Ishikawa Y, et al. Beneficial effects of beta-blockers and angiotensin-converting enzyme inhibitors in Duchenne muscular dystrophy. J Cardiol 2009;53:72–8.
50 Allen HD, Flanigan KM, Thrush PT, et al. A randomized, double-blind trial of lisinopril and losartan for the treatment of cardiomyopathy in duchenne muscular dystrophy. PLoS Curr 2013;5.
51 Duboc D, Meune C, Lerebours G, et al. Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. J Am Coll Cardiol 2005;45:855–7.
52 Duboc D, Meune C, Pierre B, et al. Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years’ follow-up. Am Heart J 2007;154:596–602.
53 Blain A, Greally E, Laval SH, et al. Absence of Cardiac Benefit with Early Combination ACE inhibitor and beta blocker treatment in mdx mice. J Cardiovasc Transl Res 2015;8:198–207.