

Stabilization of Early Duchenne Cardiomyopathy With Aldosterone Inhibition: Results of the Multicenter AIDMD Trial

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Background—Duchenne muscular dystrophy incurs nearly universal dilated cardiomyopathy by the third decade of life, preceded by myocardial damage and impaired left ventricular strain by cardiac magnetic resonance. It has been shown that (1) mineralocorticoid receptor antagonist therapy with spironolactone attenuated damage while maintaining function when given early in a mouse model and (2) low-dose eplerenone stabilized left ventricular strain in boys with Duchenne muscular dystrophy and evident myocardial damage but preserved ejection fraction. We hypothesized that moderate-dose spironolactone versus eplerenone would provide similar cardioprotection in this first head-to-head randomized trial of available mineralocorticoid receptor antagonists, the AIDMD (Aldosterone Inhibition in Duchenne Muscular Dystrophy) trial.

Methods and Results—This was a multicenter, double-blind, randomized, noninferiority trial. Subjects were randomized to eplerenone, 50 mg, or spironolactone, 50 mg, orally once daily for 12 months. The primary outcome was change in left ventricular systolic strain at 12 months. Among 52 enrolled male subjects, aged 14 (interquartile range, 12–18) years, spironolactone was noninferior to eplerenone (Δ strain, 0.4 [interquartile range, -0.4 to 0.6] versus 0.2 [interquartile range, -0.2 to 0.7]; $P=0.542$). Renal and pulmonary function remained stable in both groups, and no subjects experienced serious hyperkalemia. Infrequent adverse events included gynecomastia in one subject in the spironolactone arm and facial rash in one subject in the eplerenone arm.

Conclusions—In boys with Duchenne muscular dystrophy and preserved left ventricular ejection fraction, spironolactone added to background therapy is noninferior to eplerenone in preserving contractile function. These findings support early mineralocorticoid receptor antagonist therapy as effective and safe in a genetic disease with high cardiomyopathy risk.

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Duchenne muscular dystrophy (DMD), the most common severe form of muscular dystrophy, is an X-linked disorder in which the sarcolemmal protein dystrophin is effectively absent. Male patients with DMD typically die in the third and fourth decades of life of cardiopulmonary disease.¹ Mouse models of DMD, autopsy data, and in vivo human

studies using cardiac magnetic resonance (CMR)-based late gadolinium enhancement (LGE) imaging have all shown that progressive myocardial damage occurs well before left ventricular ejection fraction (LVEF) becomes abnormal.² Decline in cardiac function portends complications, such as heart failure, arrhythmias, and sudden death.

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Clinical Perspective

What Is New?

- In this first head-to-head study of available mineralocorticoid receptor antagonist drugs, spironolactone was noninferior to eplerenone in preserving cardiac contractility in boys with Duchenne muscular dystrophy.

What Are the Clinical Implications?

- In patients at high genetic risk of dilated cardiomyopathy, initiation of a mineralocorticoid receptor antagonist while ejection fraction is preserved may stabilize cardiac function and attenuate progressive myocardial damage.

Patients with DMD do not manifest clinical signs of cardiomyopathy until LV dysfunction and myocardial fibrosis are advanced. Thus, sensitive biomarkers are required to afford timely therapy that preserves function and prevents complications. Echocardiography is widely used to assess LV function in patients with DMD; reproducibility is impacted by acoustic window that may be limited, particularly as body habitus changes over time, reducing its appeal for rare disease clinical trials of modest sample size.³ CMR with LGE offers high reproducibility and identifies myocardial injury before decline in EF is apparent.^{4,5} LV strain by CMR is a sensitive and early marker of LV systolic dysfunction in DMD and is measurably abnormal before EF declines.⁶

Treatment of DMD cardiomyopathy with agents, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEIs/ARBs), typically starts when LV dysfunction is apparent. This strategy, however, may not be sufficient: prior studies have shown that cardiac function continues to decline with or without such therapy.^{7,8} As DMD is a genetic condition of nearly inevitable progression to dilated cardiomyopathy (DCM) and in which abnormal strain precedes EF decline,⁶ adding the mineralocorticoid receptor antagonist (MRA) drug spironolactone to ACEI was tested when EF was still normal in a mouse model.⁹ This combination significantly reduced myocardial injury and improved LV circumferential strain (Ecc). We then showed, in a double-blind, randomized, clinical trial, that the MRA drug eplerenone, 25 mg, orally once daily was superior to placebo in attenuating decline in both Ecc and EF in boys with DMD¹⁰; the benefit appeared sustainable in a 24-month open-label extension study.¹¹

Current care guidelines, however, do not recommend MRA therapy for DMD cardioprotection,^{12–14} yet reducing progression of cardiomyopathy in DMD remains a significant unmet clinical need. Recognizing that (1) eplerenone remains less available and costlier worldwide compared with spironolactone and (2) prior heart failure clinical trials of MRA endorsed titration to 50 mg daily for maximum effectiveness, we evaluated spironolactone versus eplerenone, 50 mg, once daily in patients with DMD in this first head-to-head comparison of MRA drugs. The primary objective of this study, the AIDMD (Aldosterone Inhibition in Duchenne Muscular

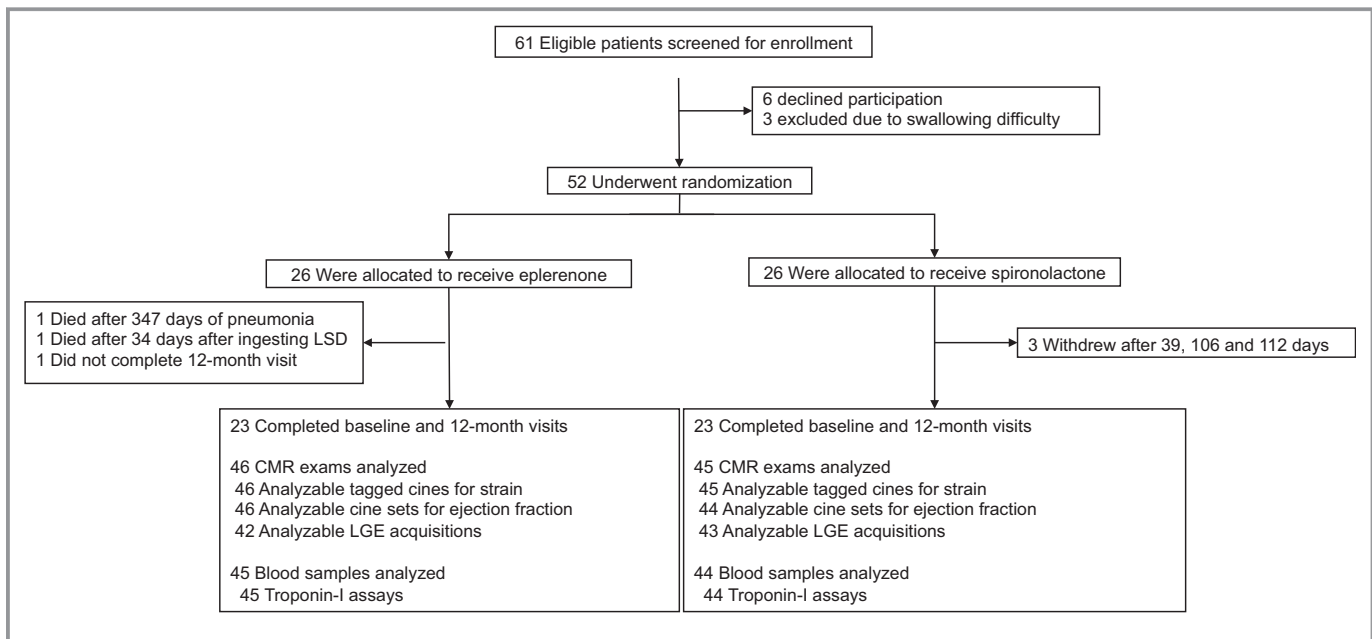


Figure 1. Screening, randomization, assessment, and follow-up. A total of 52 boys underwent randomization, with 26 assigned to receive eplerenone and 26 assigned to receive spironolactone in addition to background therapy. A total of 23 boys in each arm completed 12-month follow-up visits. CMR indicates cardiac magnetic resonance; LGE, late gadolinium enhancement; LSD, lysergic acid diethylamide.

Dystrophy) trial, was to test the hypothesis that spironolactone is noninferior to eplerenone in preserving cardiac function in patients with DMD. The primary end point was the 12-month change in LV strain.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. Boys with DMD confirmed clinically and by mutation analysis, aged ≥ 7 years, and able to undergo CMR without sedation were prospectively enrolled from 7 collaborating centers with clinical programs dedicated to cardiomyopathy in neuromuscular disease: Ohio State University Wexner Medical Center, Nationwide Children's Hospital, University of California, Los Angeles, Vanderbilt University Medical Center, University of Utah, University of Colorado, and University of Kansas Medical Center. All enrollment and follow-up visits were completed between March 2015 and April 2018. The study was approved by all participating institutional review boards in compliance with the Declaration of Helsinki. Written informed consent was obtained before treatment in all cases. For subjects aged ≥ 18 years, consent was obtained directly from the participant. For subjects aged 10 to 17 years, permission from a parent or guardian was also obtained. An independent data safety monitoring board provided continuous oversight from initial study design through study completion, and the data safety monitoring plan was approved by all participating centers' institutional review boards. Study data were collected and managed with electronic data capture tools hosted at The Ohio State University.¹⁵ S.V.R. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors edited and approved the article and assume full responsibility for the fidelity of this report to the study protocol.

Included were individuals with LVEF $\geq 45 \pm 5\%$ by clinically acquired echocardiography, cardiac nuclear scan, or CMR done within 2 months of enrollment. Excluded were those with (1) non-magnetic resonance compatible implants, (2) severe claustrophobia, (3) allergy to gadolinium-based contrast agents, (4) kidney disease, (5) prior use of or allergy to MRA, or (6) use of other investigational therapy. Subjects could not be taking nor take for the duration of the study potassium supplements, other potassium-sparing diuretics, or any CYP3A4 strong inhibitor, such as clarithromycin, telithromycin, itraconazole, ketoconazole, and protease inhibitors.

Randomization, Masking, and Study Drug

Enrolled subjects were randomized to receive either eplerenone, 50 mg, or spironolactone, 50 mg, orally once daily on top of background therapy in identical-appearing capsules

using a block randomization scheme. Computer-generated randomization was performed centrally using blocks of 4, and only the study statistician and the investigational pharmacies had the preset randomization assignments. The rest of the study personnel who enrolled participants were blinded to study drug. Approval for use of eplerenone and spironolactone outside their labeled indications for the purposes of this trial was obtained as a US Food and Drug Administration exemption from an investigational new drug application.

Cardiac Magnetic Resonance

CMR examinations were performed on a 1.5-T scanner at each center (Siemens Avanto; General Electric Optima). The identical acquisition protocol acquired at baseline and 12-month follow-up included the following: (1) mid-short axis grid tagged cine imaging; (2) long-axis and contiguous short-axis steady-state, free-precession cine imaging spanning the LV; (3) LGE using inversion-recovery gradient echo acquisitions in the identical long- and short-axis planes, with inversion time optimized to null normal myocardium and acquired 10 to 15 minutes after IV administration of 0.1 mmol/kg gadobenate dimeglumine; (4) precontrast and post-LGE T1 mapping in a mid-short axis plane; and (5) precontrast mid-short axis T2 mapping.¹⁶

Core laboratory investigators (S.V.R., W.M.) and staff blinded to clinical data performed all image analyses. According to the large body of literature endorsing Ecc as the most sensitive parameter to detect early LV alterations in DMD,^{3,17–22} we focused on this biomarker for our study. Midwall LV systolic Ecc was computed from each mid-LV short-axis tagged cine acquisition (HARP; Diagnosoft), noting more negative values indicate better contractile function. Excellent interobserver agreement has been previously shown by our laboratory and others.¹⁰ LV mass, volumes, and EF were measured from short-axis cines [EF=(end-diastolic volume–end-systolic volume)/end-diastolic volume]; and extent of myocardial damage by LGE was calculated as a percentage of LV myocardium using the full-width half-maximum technique (CMR42; Circle Cardiovascular Imaging). Myocardial T1 and T2 values were recorded, and myocardial extracellular volume fraction (ECV) was computed using precontrast and postcontrast T1 values measured in myocardium and blood along with hematocrit recorded on the day of CMR with this formula:
$$ECV = (1 - \text{hct}) \times (1/T1_{\text{myocardium}_{\text{post}}} - 1/T1_{\text{myocardium}_{\text{pre}}}) / (1/T1_{\text{blood}_{\text{post}}} - 1/T1_{\text{blood}_{\text{pre}}}), \%$$
²³

Safety Measures and Health Status

Baseline serum potassium level < 5.5 mmol/L was documented in all subjects on enrollment. Blood was drawn for potassium measurement at baseline and at 1, 2, 3, 6, 9, and

12 months; study drug was withheld or discontinued for serious hyperkalemia, defined as potassium level >5.5 mmol/L. Estimated glomerular filtration rate was computed using cystatin C given superiority over creatinine as a reliable measure of renal function in boys with DMD, according to subject age, as follows: $39.8 \times (\text{height}/\text{creatinine})^{0.456} \times (1.8/\text{cystatin C})^{0.418} \times (30/\text{blood urea nitrogen})^{0.079} \times (1.076^{\text{male}}) \times (\text{height}/1.4)^{0.179}$ for those aged <18 years and $70.69 \times (\text{cystatin C})^{-0.931}$ for subjects aged ≥ 18 years.²⁴

Given concern about treatment effect on cardiopulmonary status, spirometry was performed, and the largest forced vital capacity (FVC) and maximal inspiratory pressure were recorded over at least 3 trials. FVC as a percentage predicted value was computed using equations from the Global Lung Function Initiative with sex, age, height, ethnicity, and absolute FVC as input variables²⁵; an estimate of stature based on ulnar length was used in place of height when needed.²⁶ Subjects' self-perceived health was measured at baseline and 12-month visits using the EQ-5D-5L system and visual analogue scale for mobility, self-care, usual activities, pain/discomfort, and anxiety/depression,^{27,28} recording a composite index value.²⁹

Outcomes

The primary outcome was 12-month change in LV Ecc. Adverse events were recorded as worsening of pulmonary or health status measures, occurrence of any heart failure hospitalizations, documented arrhythmias, death, or hyperkalemia (potassium level ≥ 5.5 mmol/L).

Statistical Analysis

Analysis used a modified intention-to-treat approach, noting that subjects without a postbaseline CMR were not included in the analysis. Descriptive statistics for the baseline characteristics of the study patients were summarized by the treatment group. The χ^2 or Fisher exact tests were performed for categorical variables. For continuous variables, Shapiro-Wilk tests were first used to assess whether the normality assumption was violated. If there was sufficient evidence of violation of this assumption based on the observed data, nonparametric Wilcoxon rank sum tests were conducted. Otherwise, the more powerful independent 2-sample t tests were performed. Similar analyses were conducted to compare the baseline with 12-month changes in imaging and blood biomarkers between the eplerenone and spironolactone arms. Within each arm, repeated measures were compared using paired t tests or Wilcoxon signed-rank tests (if the normality assumption was violated). In our prior randomized controlled trial comparing eplerenone, 25 mg, daily with placebo in boys with DMD,¹⁰ we observed an average increase of 1.15 in Ecc

with an SD of 2.38 in the eplerenone group. Using a type I error rate of 5%, we conducted a power calculation using a noninferiority test on 12-month change in Ecc. If there is truly no difference in the 12-month Ecc change between the spironolactone and eplerenone groups, 46 patients (23 in each group) would result in at least 80% power to ensure that the lower limit of a 1-sided 95% CI for the true difference between the spironolactone and eplerenone groups to be above the noninferiority limit of -1.75 . This is a clinically acceptable tolerance for noninferiority based on prior studies showing a significant difference of -2 to -4 strain units across groups with similar SDs.⁶ Significance for this intention-to-treat analysis was set for $P < 0.05$. Linear regression models were used to examine the associations between baseline LGE score and 12-month change in strain. All statistical analyses were performed with STATA, version 15.0 (StataCorp, College Station, TX).

Results

Between February 2015 and May 2017, 61 eligible boys were identified for screening, and 52 were enrolled across 7 sites (Figure 1). Of 26 randomly assigned to receive eplerenone and 26 randomly assigned to receive spironolactone, 23 in each group completed baseline and 12-month visits. Table 1 summarizes baseline characteristics of the enrolled cohort by assignment group. Three subjects in the spironolactone group withdrew (2 because of difficulty arranging follow-up blood draws and 1 after a sibling's death). One subject in the spironolactone group completed 12-month follow-up but chose not to undergo follow-up CMR. Most subjects' background therapies included corticosteroids, and approximately two thirds were on background ACEI or ARB. Concomitant use of other medications was common and included vitamins, calcium supplements, proton pump inhibitors, and antidepressants. No subjects were receiving any other experimental agent, and all subjects were nonsmokers.

Safety

Two deaths occurred, both in the eplerenone arm and both deemed unrelated to study medication by the data safety monitoring board. The first was a 20-year-old patient with severe baseline restrictive lung disease (FVC, 13% predicted) who experienced respiratory syncytial virus pneumonia with respiratory failure; the second patient, aged 18 years, experienced accidental drowning after ingesting lysergic acid diethylamide. No other deaths and no symptomatic heart failure or cardiac arrhythmias occurred during the study. Gynecomastia was reported by one subject in the spironolactone arm, and one subject taking eplerenone developed a

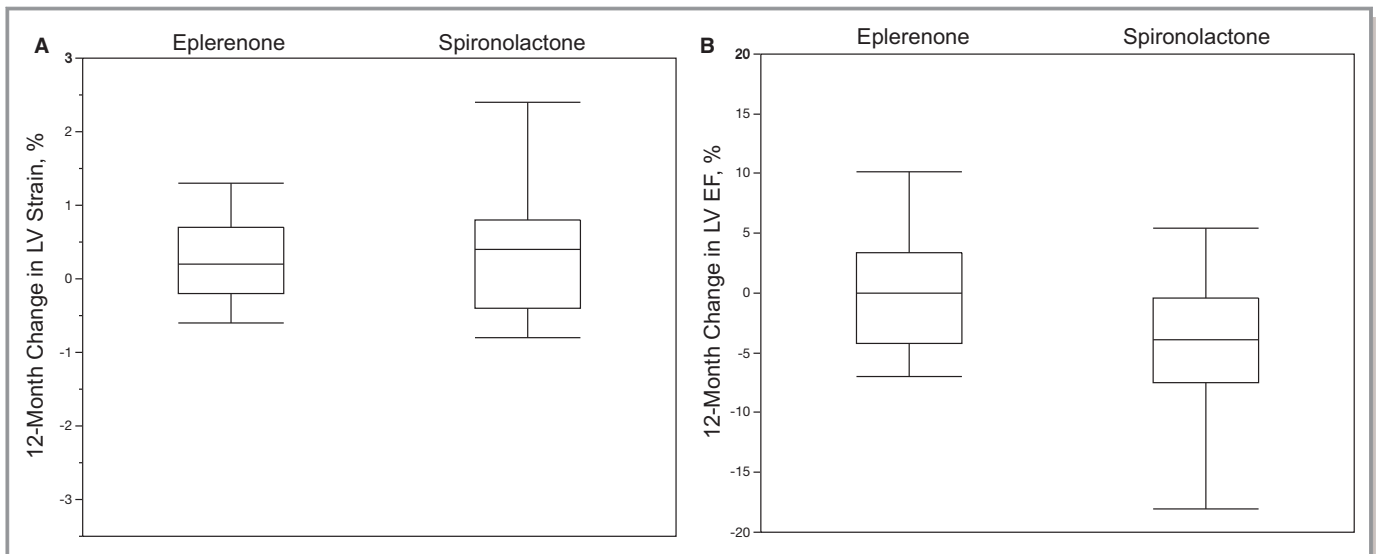


Figure 2. Stabilization of left ventricular (LV) strain with mineralocorticoid receptor antagonist therapy. **A**, Box plots show similar stabilization in LV strain over 12 months with spironolactone compared with eplerenone when added to background therapy. A more negative strain value indicates better contractility. **B**, There was also similar stabilization in the secondary end point of LV ejection fraction (EF) with eplerenone compared with spironolactone. The horizontal lines (from top to bottom) represent the upper adjacent value (UAV), upper quartile (75th percentile), median, lower quartile (25th percentile), and lower adjacent value (LAV). The UAV represents the largest observation less than or equal to the upper quartile plus 1.5 times the interquartile range (IQR). The LAV represents the smallest observation that is greater than or equal to the lower quartile minus 1.5 times the IQR. All values, including those outside these ranges, were included in the analytic sample.

facial rash (Table 2). Worse pulmonary function by FVC as a percentage predicted value and worse cardiac function by Ecc interacted to predict worse reported health status ($P=0.023$). However, pulmonary function remained stable over 12 months in both arms, with no significant change in FVC (eplerenone versus spironolactone change in FVC as a percentage predicted value, -4.0 [interquartile range {IQR}, -12.5 to 1.0] versus -6.0 [IQR, -14.0 to -1.0]; $P=0.667$) or maximal inspiratory pressure (eplerenone versus spironolactone change in maximal inspiratory pressure, -4.0 [IQR, -13.0 to 2.0] versus 3.0 [IQR, -2.1 to 9.0] mm Hg; $P=0.134$) over 12 months of therapy. Health status also remained stable over 12 months. Estimated glomerular filtration rate was normal at baseline and remained normal in all subjects at follow-up in both the eplerenone (137 [IQR, 122–181] versus 133 [IQR, 110–175] mL/min per 1.73 m²; $P=0.563$) and spironolactone (144 [IQR, 119–178] versus 122 [IQR, 102–159] mL/min per 1.73 m²; $P=0.242$) arms. Twelve-month changes in potassium were negligible, averaging 0.06 ± 0.59 mmol/L versus -0.12 ± 0.51 mmol/L in those randomized to spironolactone versus eplerenone, respectively ($P=0.291$). No subjects experienced serious hyperkalemia.

Outcomes

Ecc remained stable between baseline and 12 months (Δ Ecc) in both groups (Table 2; Figure 2A). LVEF also remained stable over 12 months in both the eplerenone and

spironolactone arms (Table 3, Figure 2B). Myocardial damage by LGE was also stable over 12 months in both the spironolactone-assigned subjects and those assigned to eplerenone (Table 3). Of 52 subjects, 12 had no evident myocardial damage by LGE at baseline; a median of 2 LV segments were LGE positive in the remaining subjects. In this cohort with less myocardial damage by LGE as a percentage of LV mass compared with those enrolled in our prior trial,¹⁰ baseline LGE was not a significant predictor of 12-month change in LV strain ($P=0.865$; $R^2=0.0008$). Myocardial T1 and T2 values did not change significantly with therapy (Δ T1= 11 ± 38 ms versus -8 ± 61 ms for eplerenone and spironolactone, respectively; $P=0.335$; Δ T2= 0.1 ± 9.6 ms versus -4.4 ± 9.7 ms for eplerenone and spironolactone, respectively; $P=0.326$), nor did myocardial ECV (Δ ECV= $0.7\pm3.7\%$ versus $0.9\pm3.3\%$ for eplerenone and spironolactone, respectively; $P=0.904$).

Discussion

In this double-blind randomized trial, we compared available MRA drugs eplerenone and spironolactone in boys with DMD and early cardiomyopathy (abnormal myocardial strain with preserved EF and relatively little evident myocardial damage). In a disease in which DCM and its complications are nearly universal later in life, early intervention with spironolactone was noninferior to eplerenone when added to common background

Table 1. Baseline Characteristics of the Study Patients

Characteristics	Eplerenone Group (N=26)	Spironolactone Group (N=26)	P Value
Age, median (IQR), y	14 (13–18)	13 (12–19)	0.361*
White race, N (%)	24 (92)	25 (96)	>0.999†
Ambulatory, N (%)	4 (15)	6 (23)	0.482†
Nocturnal ventilatory support, N (%)	7 (27)	6 (23)	0.749†
Forced vital capacity, mean±SD, L	1.7±0.8	1.9±0.8	0.634‡
Dystrophin mutation type, N (%)			0.717†
Exon deletion	16 (62)	15 (58)	
Exon duplication	4 (15)	3 (12)	
Other	5 (19)	8 (31)	
Point mutation	1 (4)	0 (0)	
LVEF, mean±SD, %	54.5±9.7	55.0±7.6	0.826‡
LV strain (Ecc), median (IQR), %	−16.9 (−18.0 to −12.4)	−15.4 (−17.3 to −12.2)	0.553*
LGE, median (IQR), % of LV mass	7.6 (0–17.1)	11.8 (0.6–26.4)	0.284*
Blood pressure, mm Hg			
Systolic, mean±SD	112.6±14.1	118.5±14.7	0.144‡
Diastolic, median (IQR)	66 (59–81)	67.5 (65–77)	0.453*
Heart rate, mean±SD, beats/min	95±14	100±12	0.217 ^c
Weight, mean±SD, kg	55.6±15.1	55.8±20.9	0.969‡
Serum potassium, mean±SD, mmol/L	4.1±0.5	4.1±0.5	0.978‡
Background medical therapy, N (%)			
ACEI	15 (58)	15 (58)	>0.999†
ARB	2 (8)	0 (0)	0.490†
β Blocker	3 (12)	7 (27)	0.159†
Steroid	21 (81)	23 (88)	0.703†
Prednisone	15 (58)	11 (42)	
Deflazacort	6 (23)	12 (46)	
None	5 (19)	3 (12)	

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Ecc, circumferential strain; IQR, interquartile range; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, LV ejection fraction.

*On the basis of the Wilcoxon rank sum test.

†On the basis of the χ^2 or Fisher exact test.

‡On the basis of a 2-sample *t* test.

therapy over 12 months to preserve LV strain. Furthermore, the 50-mg dose tested in this trial achieved better stabilization in LV strain regardless of MRA used (median 12-month changes in Ecc of 0.2 and 0.4 units [%] with eplerenone and spironolactone, respectively) compared with the 25-mg dose of eplerenone that achieved a more modest effect over 1 to 3 years in our prior trials that involved boys with DMD of similar age and in whom LV strain worsened by an average of 2.2 units (%) in the placebo arm.^{10,11}

In addition to being the first head-to-head clinical trial of 2 available MRA drugs, this trial offers several novel and important advances. A prior longitudinal study of boys with DMD not treated with MRA showed that LV strain declines

over 9 to 36 months, even if EF remains normal.⁷ On the basis of our findings, a case may be made for starting eplerenone or spironolactone in boys with DMD when only LV strain is abnormal and before other evidence of cardiac deterioration is apparent given the strain-stabilizing benefit demonstrated herein. As the prototypical disease in which genetics dictates nearly universal DCM, the concept of early intervention with MRA therapy is also novel and warrants consideration in other genetic mutations conferring high risk of DCM and its sequelae.³⁰ Insurance coverage and availability of eplerenone vary widely around the world, and cardiac care costs add to expenditures for a range of noncardiac healthcare requirements for those dealing with this disease.

Table 2. Adverse Events

Adverse Event	Eplerenone Group (N=23)	Spironolactone Group (N=23)
Death (unrelated)	2	0
Serious hyperkalemia (potassium >5.5 mmol/L)	0	0
Nonfatal pneumonia	1	0
Fall/fracture	1	2
Nausea	0	2
Gynecomastia	0	1
Nephrolithiasis	1	0

Thus, noninferiority of spironolactone in the primary end point of LV strain stabilization supports its use as a cost-effective alternative when needed. Our prior study indicated stabilized cardiac function by adding MRA to standard therapies^{10,11}; this study demonstrates that spironolactone and eplerenone are roughly equivalent in cardioprotection and, therefore, more patients (including those for whom access to eplerenone is problematic) can benefit. The value of timely cardiac magnetic resonance imaging, not consistently used by providers or covered by payors for early DMD cardiomyopathy evaluation, should also be recognized as it affords early detection of myocardial disease and institution of medication that can slow progression of cardiomyopathy.

Limitations

Because hard events like heart failure and cardiopulmonary death may not occur for a decade or more after detection of myocardial disease in boys with DMD, our study remains limited by use of surrogate end points. However, the inexorable progression of DMD cardiomyopathy, from abnormal strain to overt LV dysfunction, supports our focus on early disease and suggests stabilization of function should ultimately reduce

Table 3. Baseline to 12-Month Changes in Outcomes by Treatment Group

Biomarker	Eplerenone Group	Spironolactone Group	P Value
LV strain (Ecc), median (IQR), %	0.2 (−0.2 to 0.7)	0.4 (−0.4 to 0.6)	0.542*
LVEF, mean±SD, %	2.01±9.1	1.1±7.5	0.634†
LGE, mean±SD, % of LV mass	−0.53±1.98	0.50±1.47	0.958†

Ecc indicates circumferential strain; IQR, interquartile range; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, LV ejection fraction.

*On the basis of the 1-sided Wilcoxon rank sum test for noninferiority.

†On the basis of the 1-sided 2-sample *t* test for noninferiority.

event rates. Some measures, such as ambulatory status, atypical dystrophin mutation, and requirement for nocturnal ventilatory support, might indicate potentially less severe disease in the subjects randomized to spironolactone; although none of these differences was statistically significant, evaluation in larger sample size studies would help ensure noninferiority. Further trials could also vet a possible trend toward less progression in myocardial damage with eplerenone, suggested by 12-month change in LGE, noting that follow-up CMR data were missing in 6 of 52 subjects. Both ACEI and ARB may offer antifibrotic and antiremodeling benefits; the present trial design precluded quantification of MRA therapy's incremental antifibrotic and antiremodeling benefits over background ACEI/ARB use, although we note greater magnitude of strain stabilization in this higher-dose MRA study compared with the prior lower-dose MRA trial in DMD in the presence of similar background ACEI/ARB use in the study groups. Further studies of differential cardioprotection by type of background steroid therapy are needed, noting similar proportions of background corticosteroid use in this trial. Patients and families seek opportunities to participate in other therapeutic trials, such as those offering potential restoration of the underlying genetic defect; we were careful not to compete for enrollment in such studies while requiring 12 months of participation in this trial when other therapies could not be tested.

Conclusions

In summary, spironolactone, a lower-cost MRA drug with greater availability worldwide, appears to be noninferior to eplerenone in preserving cardiac function in boys with DMD at high risk of DCM and its complications. The low incidence of even minor adverse events in this population, plus ready availability of these medications at low cost compared with other DMD therapies, should support wider and earlier adoption of this therapeutic drug class.

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References

- Romfh A, McNally EM. Cardiac assessment in Duchenne and Becker muscular dystrophies. *Curr Heart Fail Rep*. 2010;7:212–218.
- Verhaert D, Richards K, Rafael-Fortney JA, Raman SV. Cardiac involvement in patients with muscular dystrophies: magnetic resonance imaging phenotype and genotypic considerations. *Circ Cardiovasc Imaging*. 2011;4:67–76.
- Soslow JH, Xu M, Slaughter JC, Stanley M, Crum K, Markham LW, Parra DA. Evaluation of echocardiographic measures of left ventricular function in patients with Duchenne muscular dystrophy: assessment of reproducibility and comparison to cardiac magnetic resonance imaging. *J Am Soc Echocardiogr*. 2016;29:983–991.
- Puchalski MD, Williams RV, Askovich B, Sower CT, Hor KH, Su JT, Pack N, Dibella E, Gottliebson WM. Late gadolinium enhancement: precursor to cardiomyopathy in Duchenne muscular dystrophy? *Int J Cardiovasc Imaging*. 2009;25:57–63.
- Grothues F, Smith G, Moon J, Bellenger N, Collins P, Klein H, Pennell D. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol*. 2002;90:29–34.
- Hor KN, Wansapura J, Markham LW, Mazur W, Cripe LH, Fleck R, Benson DW, Gottliebson WM. Circumferential strain analysis identifies strata of cardiomyopathy in Duchenne muscular dystrophy: a cardiac magnetic resonance tagging study. *J Am Coll Cardiol*. 2009;53:1204–1210.
- Hor KN, Mazur W, Taylor MD, Al-Khalidi HR, Cripe LH, Jefferies JL, Raman SV, Chung ES, Kinnett KJ, Williams K, Gottliebson WM, Benson DW. Effects of steroids and angiotensin converting enzyme inhibition on circumferential strain in boys with Duchenne muscular dystrophy: a cross-sectional and longitudinal study utilizing cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2011;13:60.
- Silva MC, Magalhaes TA, Meira ZM, Rassi CH, Andrade AC, Gutierrez PS, Azevedo CF, Gurgel-Giannetti J, Vainzof M, Zatz M, Kalil-Filho R, Rochitte CE. Myocardial fibrosis progression in Duchenne and Becker muscular dystrophy: a randomized clinical trial. *JAMA Cardiol*. 2017;2:190–199.
- Rafael-Fortney JA, Chimanji NS, Schill KE, Martin CD, Murray JD, Ganguly R, Stangland JE, Tran T, Xu Y, Canan BD, Mays TA, Delfin DA, Janssen PM, Raman SV. Early treatment with lisinopril and spironolactone preserves cardiac and skeletal muscle in Duchenne muscular dystrophy mice. *Circulation*. 2011;124:582–588.
- Raman SV, Hor KN, Mazur W, Halnon NJ, Kissel JT, He X, Tran T, Smart S, McCarthy B, Taylor MD, Jefferies JL, Rafael-Fortney JA, Lowe J, Roble SL, Cripe LH. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2015;14:153–161.
- Raman SV, Hor KN, Mazur W, He X, Kissel JT, Smart S, McCarthy B, Roble SL, Cripe LH. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: results of a two-year open-label extension trial. *Orphanet J Rare Dis*. 2017;12:39.
- Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, Case LE, Cripe L, Hadjiyannakis S, Olson AK, Sheehan DW, Bolen J, Weber DR, Ward LM; DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol*. 2018;17:347–361.
- Feingold B, Mahle WT, Auerbach S, Clemens P, Domenighetti AA, Jefferies JL, Judge DP, Lal AK, Markham LW, Parks WJ, Tsuda T, Wang PJ, Yoo SJ; American Heart Association Pediatric Heart Failure Committee of the Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; Council on Cardiovascular Radiology and Intervention; Council on Functional Genomics and Translational Biology; and Stroke Council. Management of cardiac involvement associated with neuromuscular diseases: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e200–e231.
- McNally EM, Kaltman JR, Benson DW, Canter CE, Cripe LH, Duan D, Finder JD, Groh WJ, Hoffman EP, Judge DP, Kertesz N, Kinnett K, Kirsch R, Metzger JM, Pearson GD, Rafael-Fortney JA, Raman SV, Spurney CF, Targum SL, Wagner KR, Markham LW; Working Group of the National Heart, Lung, and Blood Institute; Parent Project Muscular Dystrophy. Contemporary cardiac issues in Duchenne muscular dystrophy: working group of the National Heart, Lung, and Blood Institute in collaboration with Parent Project Muscular Dystrophy. *Circulation*. 2015;131:1590–1598.
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–381.
- Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E; Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized Protocols. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. *J Cardiovasc Magn Reson*. 2013;15:91.
- Ashford MW Jr, Liu W, Lin SJ, Abraszewski P, Caruthers SD, Connolly AM, Yu X, Wickline SA. Occult cardiac contractile dysfunction in dystrophin-deficient children revealed by cardiac magnetic resonance strain imaging. *Circulation*. 2005;112:2462–2467.
- Mertens L, Ganame J, Claus P, Goemans N, Thijs D, Eyskens B, Van Laere D, Bijmens B, D'Hooge J, Sutherland GR, Buyse G. Early regional myocardial dysfunction in young patients with Duchenne muscular dystrophy. *J Am Soc Echocardiogr*. 2008;21:1049–1054.
- Hagenbuch SC, Gottliebson WM, Wansapura J, Mazur W, Fleck R, Benson DW, Hor KN. Detection of progressive cardiac dysfunction by serial evaluation of circumferential strain in patients with Duchenne muscular dystrophy. *Am J Cardiol*. 2010;105:1451–1455.
- Bilchick KC, Salerno M, Plitt D, Dori Y, Crawford TO, Drachman D, Thompson WR. Prevalence and distribution of regional scar in dysfunctional myocardial segments in Duchenne muscular dystrophy. *J Cardiovasc Magn Reson*. 2011;13:20.
- Hor KN, Kisson N, Mazur W, Gupta R, Ittenbach RF, Al-Khalidi HR, Cripe LH, Raman SV, Puchalski MD, Gottliebson WM, Benson DW. Regional circumferential strain is a biomarker for disease severity in Duchenne muscular dystrophy heart disease: a cross-sectional study. *Pediatr Cardiol*. 2015;36:111–119.
- Lang SM, Shugh S, Mazur W, Sticka JJ, Rattan MS, Jefferies JL, Taylor MD. Myocardial fibrosis and left ventricular dysfunction in Duchenne muscular dystrophy carriers using cardiac magnetic resonance imaging. *Pediatr Cardiol*. 2015;36:1495–1501.
- Kellman P, Wilson JR, Xue H, Ugander M, Arai AE. Extracellular volume fraction mapping in the myocardium, part 1: evaluation of an automated method. *J Cardiovasc Magn Reson*. 2012;14:63.
- Viollet L, Gailey S, Thornton DJ, Friedman NR, Flanagan KM, Mahan JD, Mendell JR. Utility of cystatin C to monitor renal function in Duchenne muscular dystrophy. *Muscle Nerve*. 2009;40:438–442.
- Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J; ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40:1324–1343.
- Gauld LM, Kappers J, Carlin JB, Robertson CF. Height prediction from ulna length. *Dev Med Child Neurol*. 2004;46:475–480.
- EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199–208.
- Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, Swinburn P, Busschbach J. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. 2013;22:1717–1727.
- van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012;15:708–715.
- Rafael-Fortney JA, Chadwick JA, Raman SV. Duchenne muscular dystrophy mice and men: can understanding a genetic cardiomyopathy inform treatment of other myocardial diseases? *Circ Res*. 2016;118:1059–1061.