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Association between prophylactic angiotensin-converting enzyme inhibitors and overall survival in Duchenne muscular dystrophy—analysis of registry data

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Aims To estimate the effect of prophylactic angiotensin-converting enzyme inhibitors (ACEi) on survival in Duchenne muscular dystrophy (DMD).

Methods and results We analysed the data from the French multicentre DMD Heart Registry (ClinicalTrials.gov: NCT03443115). We estimated the association between the prophylactic prescription of ACEi and event-free survival in 668 patients aged 8 to 13 years, with normal left ventricular function, using (i) a Cox model with intervention as a time-dependent covariate, (ii) a propensity-based analysis comparing ACEi treatment vs. no treatment, and (iii) a set of sensitivity analyses. The study outcomes were overall survival and hospitalizations for heart failure (HF) or acute respiratory failure. Among the 668 patients included in the DMD Heart Registry, 576 (mean age 6.1 ± 2.8 years) were eligible for this study, of whom 390 were treated with ACEi prophylactically. Death occurred in 53 patients (13.5%) who were and 60 patients (32.3%) who were not treated prophylactically with ACEi, respectively. In a Cox model with intervention as a time-dependent variable, the hazard ratio (HR) associated with ACEi treatment was 0.49 [95% confidence interval (CI) 0.34–0.72] and 0.47 (95% CI 0.31–0.17) for overall mortality after adjustment for baseline variables. In the propensity-based analysis, 278 patients were included in the treatment group and 834 in the control group, with 18.5% and 30.4% 12-year estimated probability of death, respectively. ACEi were associated with a lower risk of death (HR 0.39; 95% CI 0.17–0.92) and hospitalization for HF (HR 0.16; 95% CI 0.04–0.62). All other sensitivity analyses yielded similar results.

Conclusion Prophylactic ACEi treatment in DMD was associated with a significantly higher overall survival and lower rates of hospitalization for HF.

Graphical Abstract

Association between prophylactic angiotensin-converting enzyme inhibitors and overall survival in Duchenne muscular dystrophy.

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder that affects approximately 1 in every 3500 live-born male infants, making it the most common neuromuscular disease of childhood.¹ The disease is caused by mutations in the dystrophin gene (DMD), which lead to disruption of the open reading frame^{2,3} and dystrophin deficiency in muscle cells, resulting in decreased fibre stability and continued degeneration.⁴ The patients present with progressive muscle wasting and loss of muscle function, develop restrictive respiratory failure and dilated cardiomyopathy, and usually die in their late teens or twenties from cardiac or respiratory failure.^{5,6}

To delay the onset of cardiomyopathy, the majority of experts recommend the use of angiotensin-converting enzyme inhibitors (ACEi) in DMD patients by the age of 10 years, even in the presence of preserved left ventricular (LV) systolic function.^{7–13} A survival benefit conferred by this treatment has been suggested by a single randomized open-label trial, though this remains uncertain.¹⁴ Prophylactic ACEi are prescribed to the majority of patients in most neuromuscular referral centres; however, this strategy is not offered to most DMD patients anywhere else, including the USA.^{15,16}

In a clinical environment where randomized trials are precluded by practical and ethical reasons,^{17,18} we decided to perform a propensity-based analysis, using data from a large French multicentre DMD registry, to evaluate the effect of ACEi on overall survival.

Methods

The data, analytic methods, and study materials are not being made available to other researchers for the purposes of reproducing the results or replicating the procedure, because consent to participate in this study did not include public dissemination of patient data.

Patients

The patients included in this retrospective study were identified among the 668 patients entered in the DMD Heart Registry. This registry comprises patients who had been admitted between January 1986 and October 2018 to one of eight French medical centres for management of DMD (Cochin Hospital, Paris; Lille Hospital; Marseille Hospital; Montpellier Hospital; Necker Hospital, Paris; Pitié Salpêtrière Hospital, Paris; Raymond Poincaré Hospital, Garches; Trousseau Hospital, Paris) and fulfilled the following criteria: (i) a clinical profile consistent with a diagnosis of DMD; (ii) a mutation in the *DMD* gene, causing disruption of the reading frame or generation of a premature stop codon (verified in one of two specialized centres for *DMD* gene sequencing in France—Cochin Hospital and Montpellier University Hospital). The patients' medical records were reviewed and the following information was collected: results of genetic, neurological, and cardiac investigations; cardiovascular and respiratory events; drug treatments, doses, side effects; and dates and reasons for initiation, titration, or interruption of treatments.

Of the 668 patients included in the DMD Heart Registry, we excluded those (i) who had been diagnosed with DMD before January 1986, corresponding to prevalent cases; (ii) who had a concurrent illness that could also cause cardiac or respiratory disease or influence the vital prognosis;

or (iii) whose date of treatment initiation was unknown. The remaining patients were eligible for the present study.

This study complied with the ethical principles set out in the declaration of Helsinki. The local ethics committees approved the study and granted waiver of participant consent. The study was registered at ClinicalTrials.gov (NCT03443115).

Study outcomes

The primary study outcome was overall survival. Secondary outcomes were hospitalizations for heart failure (HF)¹⁹ and acute respiratory failure (ARF) during follow-up. We ascertained the survival of patients who were not followed beyond December 2016 by consulting the National Death Registry. An adjudication committee unaware of the patients' clinical status or outcomes, composed of three of the authors (KW, PL, AF), reviewed the data and classified the hospitalizations as HF- or ARF-related, according to pre-specified criteria.

Statistical analysis

Results are shown as means $\pm$ standard deviation, median and interquartile range (IQR), or counts and percentages, as appropriate. We estimated the overall survival curves and the cumulative incidence curves for hospitalization for HF and ARF.

In a first analysis, the effect of ACEi was estimated in a Cox model, with the introduction of prophylactic ACEi treatment as a time-dependent variable, without and with adjustment for baseline variables, including age, LV ejection fraction (LVEF), vital capacity (VC), systolic and diastolic blood pressure (BP), loss of ambulation, *DMD* mutation, and centre as a random effect. Glomerular filtration rate was not included in this model because its estimation is not currently performed in a routine setting.²⁰ This analysis has been shown to inappropriately correct for time-dependent confounding,²¹ though it is considered a standard approach for comparisons.

We then performed a propensity-based analysis and emulated a target trial with the inclusion of patients who fulfilled the following inclusion criteria: (i) age between 8 and 13 years, (ii) no previous ACEi treatment, and (iii) LVEF $\geq 55\%$, between January 1999 to December 2016. The inclusion process is illustrated in Figure 1:

We divided the overall inclusion period, from January 1999 to December 2016, into 72 consecutive, 3-month periods,^{22–26} identified all patients who met the inclusion criteria within each period, and included in the treatment group the patients whose treatment was introduced during that 3-month period. For each treated patient, we entered in a control group a random sample of three untreated patients, simulating a 1:3 randomization scheme, thus comparing patients-periods instead of individual patients, with regard to baseline characteristics and outcomes.

Patients in the control group were eligible for inclusion in the following 3-month periods, though no patients entered in the treatment group.^{24,27} The process was repeated over the 72 inclusion periods, before pooling all the data. Patients were followed from the date of inclusion to the date of death or until 31 December 2017, whichever occurred first. The date of 31 December 2017 guaranteed at least 1 year of theoretical follow-up for all patients. The follow-up of patients in the control group was censored when they were prescribed an ACEi.

Since treatment groups were not randomly assigned, the inverse probability of treatment weighting was used to correct for confounding by indication.^{28,29} The propensity score, i.e. the probability of receiving ACEi prophylaxis, was estimated by logistic regression with the following covariates: age, LVEF, VC, loss of ambulation, systolic and diastolic BP, non-invasive ventilation, spinal surgery, glucocorticoid and centre as a random effect, all measured at the time of inclusion in

the emulated trial. Each observation was weighted by the inverse of the predicted probability of receiving the treatment actually received, given these variables.^{28,29} This has been shown to theoretically balance the groups regarding these confounders. Balance was ascertained by calculating the standardized mean differences between groups before and after weighting; a < 10% standardized difference was considered to indicate successful balancing.^{30,31} In the control group (no ACEi prophylaxis), patients were arbitrarily censored when they received ACEi prophylaxis, and inverse probability of censoring weighting was used to correct for the induced time-varying selection.³² Inverse probability of censoring weights was proportional to the inverse of the probability of remaining uncensored until each timepoint, given the baseline and time-varying covariates.^{29,33} This probability was obtained by fitting a Cox model with age at inclusion in the emulated trial and centre as a time-fixed covariate, and with LVEF, VC, loss of ambulation, systolic and diastolic BP, non-invasive ventilation, spinal surgery, glucocorticoid as time-varying covariates. Stabilized weights, which usually increase the efficiency of estimates, were obtained by multiplying the weights by the overall probability of being uncensored at each timepoint, and the resulting weights were truncated at the first and 99th percentile to limit the influence of outlier observations.³⁴ Each observation was then weighted by the product of the inverse probability of treatment and the time-varying inverse probability of censoring weights, and overall survival curves and cumulative incidence curves

for hospitalization for HF and ARF were estimated while accounting for these weights. The treatment effect was summarized by the hazard ratio (HR), estimated in a Cox proportional hazards model, with baseline hazard stratified by 3-month inclusion periods to account for period effects. Standard errors and confidence intervals (CI) were obtained by bootstrapping. The proportional hazards assumption in Cox models was evaluated by examination of Schoenfeld residuals and Grambsch-Therneau lack-of-fit test.

To use values of LVEF, VC and BP at any arbitrary time while they were recorded at specific irregular timepoints, we used the best linear unbiased predictions obtained from flexible mixed-effect models.³⁵

Sensitivity analyses were carried out by repeating the propensity-based analysis, using a 1:1 allocation ratio and including a given individual only once.

We also assessed the sensitivity of the results to unmeasured confounding by computing the E-value when a non-null association was reached. The E-value measures the minimum strength of association needed between an unmeasured confounder and ACEi treatment and outcome, to fully explain the observed treatment effect or the upper confidence limit.³⁶ Pre-specified subgroup analyses were carried out for the 1:3 propensity-based analysis, according to treatment by glucocorticoids at study entry and inability to walk.

Table 1 Baseline characteristics of patients

	Patients included in the time-dependent treatment Cox analysis (n = 576)	Patients-periods included in the propensity-based analysisa		
		Not treated (n = 834)	ACEi-treated (n = 278)	SMD (%)
Age, years	6.1 ± 2.8	10.1 ± 1.6	10.2 ± 1.3	6.4
Study inclusion period, n (%)				
1986–1993	91 (15.8)	0	0	—
1994–1998	102 (17.7)	0	0	—
1999–2003	132 (22.9)	152 (18.3)	39 (14.2)	11.0
2004–2008	112 (19.4)	342 (41.0)	104 (37.3)	7.5
2009–2013	103 (17.9)	228 (27.3)	90 (32.2)	10.7
2014–2017	36 (6.2)	112 (13.5)	45 (16.3)	7.9
DMD gene mutation, n (%)				
N-terminal	54 (9.9)	87 (10.5)	35 (12.6)	6.8
Rod domain	448 (81.9)	676 (81.1)	223 (80.1)	2.4
CR domain	24 (4.4)	42 (5.0)	10 (3.5)	7.4
C-terminal	21 (3.8)	29 (3.5)	10 (3.7)	1.6
Left ventricular ejection fraction, %	64.6 ± 2.8	64.0 ± 3.2	63.8 ± 3.2	6.0
Vital capacity, % ^b	83.9 ± 12.9	75.7 ± 17.3	75.2 ± 15.9	2.7
Systemic blood pressure, mmHg				
Systolic	103.0 ± 7.2	103.9 ± 6.6	103.9 ± 7.0	<1.0
Diastolic	61.7 ± 6.2	62.8 ± 6.1	62.8 ± 6.0	1.0
Loss of ambulation	83 (14.4)	428 (51.3)	145 (52.3)	1.9
Spinal surgery	1 (0.2)	25 (3.0)	8 (3.0)	<1.0
Non-invasive ventilation	0	5 (0.6)	3 (1.2)	5.9
Glucocorticoids	18 (3.1)	224 (26.9)	77 (27.6)	1.6
Beta-adrenergic blocker	3 (0.5)	14 (1.7)	4 (1.5)	1.3
Mineralocorticoid receptor antagonist	1 (0.2)	1 (0.1)	1 (0.2)	1.6

Values are means±standard deviation, or number (%) of observations.
SMD, standardized mean difference computed as the absolute value of the mean difference divided by the pooled standard deviation, expressed as a percentage. SMDs <10% were considered to indicate a successful balance.
^aBaseline characteristics after inverse probability of treatment weighting. Number of patients in the weighted sample are rounded to the nearest integer to add to the total number.
^bVital capacity expressed as a percentage of predicted value.

All analyses were performed using R 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria). A P-value <0.05 was considered statistically significant.

Results

Patient selection

Figure 1 shows the selection of patients included in the present study. Of the 668 patients entered in the DMD Heart Registry between November 1986 and March 2017, 60 were excluded because the diagnosis of DMD was made before January 1986, 26 because the date of treatment initiation was not available, and 6 because they suffered from concomitant disorders. The remaining 576 patients (mean age 6.1 ± 2.8 years) were included in this study and were potentially eligible for the propensity-based analysis. Their baseline characteristics are presented in Table 1. The median follow-up was 13.5 years (range 4 months to 30.6 years). ACEi treatment was introduced in 390 patients (67.7%) of various ages with LVEF ≥55%, after a median treatment-free follow-up of 4.6 years (range 0 to 19.4).

The proportion of patients treated with ACEi was 62.5% at Cochin Hospital, 66.2% at Lille Hospital, 47.3% at Marseille Hospital, 60.3% at Montpellier Hospital, 72.9% at Necker Hospital, 67.2% at Pitié-Salpêtrière Hospital, 73.0% at Raymond Poincaré Hospital, and 88.2% at Trousseau Hospital.

Patient outcomes

Among the 390 prophylactically treated patients, 53 died (13.6%) at a median age of 20.0 years, vs. 60 (32.3%) at a median age of 21.0 years among the 186 untreated patients (Table 2). Among non-survivors, eight prophylactically treated patients (15%) died of HF, in contrast to 23 untreated patients (38%). ARF was the cause of death in 15 (28%) ACEi-treated patients and 17 (28%) untreated patients. Other causes of death were identified in 20 (38%) ACEi-treated patients and 9 (15%) untreated patients, while no cause of death was recorded in 10 (19%) and 11 (18%) patients, respectively. HF was the cause of hospitalization in 46 patients, 18 of whom were and 28 were not prophylactically treated with ACEi. ARF was the cause of

Table 2 Number of primary and secondary outcomes

	Patients included in the Cox model with intervention as a time-dependent covariate			Patients included in the propensity-based analysis (n = 1112 patients-periods, n = 412 unique patients)	
	All patients (n = 576)	Not treated (n = 186)	ACEi-treated (n = 390)	Control group (n = 834)	ACEi group (n = 278)
Person-year follow-up	7662.1	4189.0	3473.1	2164.5 ^a	2181.0 ^a
Deaths	113	60	53	55	29
Hospitalization for heart failure	46	28	18	31	9
Hospitalization for acute respiratory failure	178	76	102	68	67

^aWeighted person-year follow-up to match with cumulative incidence and HR estimation.

Table 3 Association between angiotensin-converting enzyme inhibitors and the primary and secondary outcomes estimated in a Cox model and a propensity-based analysis

	Cox model with intervention as a time-dependent covariate		Adjusted HR (95% CI)
	Propensity score-based analysis HR (95% CI)	Unadjusted HR (95% CI)	
Overall survival	0.49 (0.34–0.72)	0.47 (0.31–0.71)	0.39 (0.17–0.92)
Hospitalization for heart failure	0.37 (0.20–0.68)	0.50 (0.26–0.99)	0.16 (0.04–0.62)
Hospitalization for acute respiratory failure	0.76 (0.56–1.04)	0.98 (0.70–1.36)	0.78 (0.35–1.72)

No evidence for non-proportional hazards was found, except for the effect of angiotensin-converting enzyme inhibitors on hospitalization for acute respiratory failure in the propensity-based analysis ($P = 0.031$ for the proportional hazards), which is also displayed in Figure 2, where the curves of cumulative incidence cross.

hospitalization in 178 patients, 102 of whom were and 76 were not prophylactically treated with ACEi (Table 2).

Cox model with intervention as a time-dependent covariate

In a model with intervention as a time-dependent variable, the HR for overall mortality associated with the prescription of ACEi after adjustment for baseline variables was 0.49 (95% CI 0.34–0.72) and 0.47 (95% CI 0.31–0.71) in unadjusted and adjusted models, respectively (Table 3). An association was also observed between ACEi treatment and hospitalization for HF (HR 0.50; 95% CI 0.26–0.99), though not between ACEi treatment and ARF (HR 0.98; 95% CI 0.70–1.36) (Table 3).

Propensity-based analysis

Of the 576 eligible patients, 412 met the inclusion criteria (age between 8 and 13 years, no previous ACEi treatment, and LVEF ≥55%) at least once between January 1999 and December 2016. Of the 164 ineligible patients, 74 did not satisfy the age criterion, 20 received an ACEi before 1999 and 41 before the age of 8 years, and the 29 remaining patients had a LVEF <55% before satisfying the other inclusion criteria. Their baseline characteristics are presented in Table 1. Missing variables among those included in this model were VC for 42 patients and BP for 21 patients. The total follow-up for these 412 patients corresponded to 4209 patients-periods, including 278

patients-periods when treated and 3931 when not treated preventively with ACEi.

We included 278 patients in whom ACEi was introduced during the inclusion period in the treatment group and 834 patients-periods untreated with ACEi in the control group (Figure 1). The characteristics of patients-periods included in both groups before and after correction with the inverse probability of treatment weighting are shown in Table 1, respectively. The treated group was slightly older than the control group, had a lower LVEF and VC, and was more likely to have lost ambulation, as well as to have been previously treated with glucocorticoids and undergone spine surgery. The baseline characteristics of patients in the treated (mean age 10.2 ± 1.3 years) and control (mean age 10.1 ± 1.6 years) groups were successfully balanced after weighting. In the treatment group, ACEi were discontinued in 5 patients (1.8%) because of adverse events, including symptomatic hypotension in 2 (0.7%) and cough in 2 (0.7%); no patient experienced a life-threatening event.

Over a median follow-up of 8.2 years (IQR 5.4–10.8), 29 patients died in the treatment group, and 55 patients died in the control group over a median follow-up of 1.7 year (IQR 0.8–3.4), or 8.1 years (IQR 5.3–10.7) without artificial censoring when treated with ACEi (Table 2), corresponding to 18.5% and 30.4% 12-year estimated risk of death, respectively (Figure 2). Preventive treatment with ACEi was associated with a lower risk of death (HR 0.39; 95% CI 0.17–0.92) and hospitalization for HF (HR 0.16; 95% CI 0.04–0.62), but not with a lower risk of hospitalization for ARF (HR 0.78; 95% CI 0.35–1.72),

Figure 2 Incidence of primary and secondary outcomes in the propensity-based analysis. (A) All-cause mortality; (B) hospitalization for heart failure; (C) hospitalization for acute respiratory failure.

though there was some evidence of non-proportional hazards for the latter effect ($P = 0.031$; Table 3; Figure 2). There was no evidence of a differential association of preventive treatment with ACEi with death according to glucocorticoid use or loss of ambulation at inclusion (Figure 3).

The E-value for overall survival was 3.22, indicating that an uncontrolled confounder would need to be associated with both preventive treatment with ACEi and death by a relative effect of 3.22 each to explain the association. The E-value for the 95% upper confidence bound was 1.17, so the latter relative association would suffice to make the observed association appear non-significant. The E-values for hospitalization for HF were 12.8 and 2.61 for the estimated and the upper confidence bound, respectively

Figure 3 Exploratory subgroup analysis in the propensity-based analysis. HR are for the primary outcome (death). The numbers of events may not closely represent the HR because of the differential follow-up in each group.

All other sensitivity analyses yielded similar results for overall survival, including the propensity-based analysis with a 1:1 allocation ratio and unique inclusion of individuals (HR 0.49; 95% CI 0.24–0.96) and robust standard error estimation (HR 0.39; 95% CI 0.20–0.76), and for the secondary endpoints

Discussion

This analysis consistently revealed a significant overall survival benefit and lower risk of hospitalization for the management of HF associated with prophylactic ACEi treatment in DMD patients with preserved LV function (Graphical Abstract).

Most prior studies showed that prophylactic ACEi treatment of DMD patients is used mostly in neuromuscular tertiary medical centres, but not in all DMD patients anywhere^{15,16} despite the recommendations by most groups of experts.^{17,18,37,38} For example, a retrospective study in 17 centres across the USA reported the use of ACEi in <50% of DMD patients between 2005 and 2015.¹⁵ We observed that 67% of patients included in our study received ACEi prophylactically, with ratios ranging from 60% to 73% in six medical centres. This observation highlights the wide variability in the prescription of ACEi not only among medical centres, but also by individual physicians. This variability might be related to the intermediate level of evidence assigned to this treatment for this specific condition, leading to the implementation of general HF guidelines with treatment initiation in the presence of overt systolic dysfunction. In this context, where this treatment has been adopted in clinical practice, though not regularly offered to all patients, a randomized trial with mortality as the endpoint would be unethical as well as impractical because of the long follow-up and large sample size required. In such cases, a propensity-based analysis emulating a randomized trial is particularly useful to estimate a treatment effect in a real-life setting, and to mitigate confounding biases that arise in absence of random assignment.^{24,27} Our large patient sample allowed for the inclusion of all known prognostic factors in DMD in our analysis. Furthermore, our propensity-based analysis enabled a comparison of treated patients

and controls over the same time periods, which is particularly important in view of the major progress made in recent decades in the standard of care for this disorder. Since the potential for unmeasured confounding persisted, an E-value analysis was undertaken to quantify the minimum strength of association that an unmeasured confounder must have with both ACEi treatment and study outcomes to negate the observed associations, while simultaneously considering the measured covariates. We found that a residual confounding could explain the association if an unmeasured covariate exists that has a ≥ 3.78 relative risk association with total mortality and ≥ 12.0 with hospitalizations for HF, which seems unlikely in this setting. The magnitude of the prophylactic treatment effect of ACEi in this study is consistent with that observed in the only randomized study conducted to date in 57 patients suffering from DMD. In that study, the 10-year survival rates were 93% vs. 66% in patients randomly assigned to 3 years of perindopril vs. placebo, corresponding to an odds ratio of 0.15.¹⁴

As the clinical management of patients with DMD is heterogeneous,^{15,16} a propensity score analysis seems more likely to yield results that can be generalized than a randomized trial. Despite being based on observational data, our emulated trial was similar to a randomized, controlled target trial including, in particular, clear eligibility criteria. Confounding and time-varying selection biases were corrected by inverse probability weighting, and the design of the emulated trial prevented the introduction of immortal time biases.²⁷ In particular, the shorter follow-up of the control group, explained by artificial censoring at initiation of prophylactic treatment with ACEi, was corrected by inverse probability of censoring weighting. No intention-to-treat analysis was considered because of the high number of patients who received ACEi at some point during follow-up. Instead, patients who were prophylactically treated with ACEi were compared with patients who remained untreated. This is different from a per-protocol analysis, as patients in the treatment group who discontinued treatment for any reason (perhaps for toxicity) remained in that group, revealing treatment effects closer to real life.

In natural history studies, end-stage HF developed in up to 40% of DMD patients in the second or third decades of life,^{17,37} providing a strong impetus for the first randomized study of the prophylactic use of ACEi in this population, earlier than usually prescribed for dilated cardiomyopathy. A single, open-label, randomized trial in 57 patients revealed a lower incidence of dilated cardiomyopathy in patients aged 9 to 13 years treated prophylactically with perindopril compared with placebo, and suggested a higher survival at 10 years.¹⁴ The prevention of severe HF and higher overall survival observed in our study strongly support the widespread use of this treatment strategy in DMD patients, especially because its tolerance was excellent. In a broader perspective, these results suggest that HF treatments may be beneficial not only in patients with LV systolic dysfunction, but also at earlier stages of the disease characterized by malignant and progressive myocardial involvement, in order to delay the development of severe HF.

Study limitations

The main limitation of this study was the estimation of an association of prophylactic use of ACEi with outcomes, based on non-random assignments. However, the likelihood of differences exclusively due

to biases was limited by (i) the magnitude of the effect observed, (ii) the consistency of our results, and (iii) the application of the most effective methods of adjustment for selection biases and confounding factors. Another limitation was the absence of accounting for drug doses in our analysis of treatment efficacy. Finally, we allowed a 3-month grace period to classify the participants in the ACEi group, which may have created an immortal time bias. We could have (i) duplicated the participants and censored them if they deviated from the original assignment, or (ii) randomly assigned them to one of the study groups.^{22,39,40} However, given that a single patient was followed for <3 months and no event occurred during that follow-up, this had no practical effect on the results.

Emulating a target trial is, nevertheless, a complex task, and several statistical tools were used, which rely on assumptions. In particular, we had to assume that all relevant confounders were measured repeatedly during follow-up. Despite being cautious in our recording of prognostic variables, we cannot exclude having overlooked confounders. In addition, since physiological measurements were not made every 3 months, we predicted their values by modelling. Our analyses, therefore, rely on a sufficient accuracy of these predictions, as well as on a reasonable specification of the propensity score and censoring models. We believe, nevertheless, that a complex and imperfect emulated trial approach remains the most sensible means of obtaining reliable information on the potential effect of ACEi prophylaxis in this context, where large trials are not likely to be conducted. It also provides results emulating more traditional studies, despite time-varying treatments and confounding. Finally, it clearly defined the target population, in contrast with other modelling techniques, such as the Cox model with time-dependent variables that we used for comparison, where precise eligibility criteria that may change over time cannot be applied.

Conclusions

A significantly higher overall survival and lower rates of hospitalization for HF were observed with the prophylactic prescription of ACEi than without treatment in patients presenting with DMD and a preserved LV function.

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