ESC European Society of Cardiology
European Heart Journal (2021) **42**, 1985–1987
doi:10.1093/eurheartj/ehab152

EDITORIAL

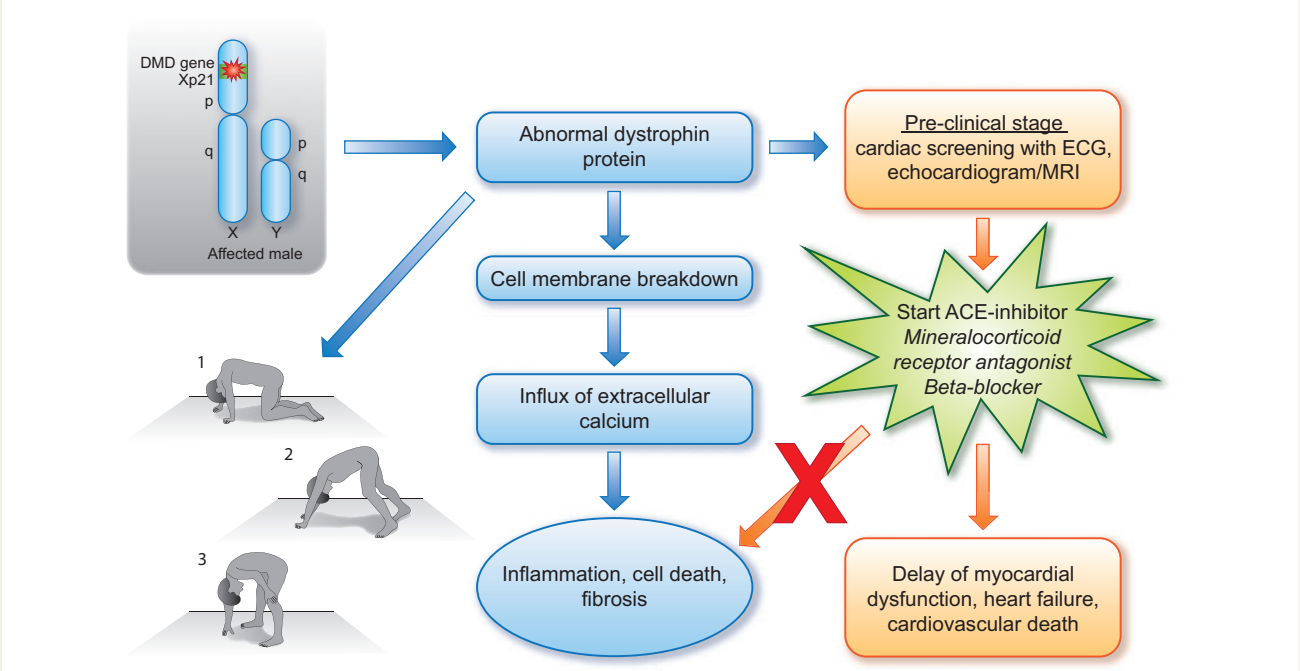
Cardioprotection in Duchenne muscular dystrophy

Anjali Tiku Owens [1]* **and Mariell Jessup** [2]

[1]Center for Inherited Cardiovascular Disease, Division of Cardiovascular Medicine, Perelman School of Medicine, University of Pennsylvania, 11th floor, 3400 Civic Center Blvd, Philadelphia, PA 19086, USA; and [2]American Heart Association, Dallas, TX, USA

Online publish-ahead-of-print 22 March 2021

This editorial refers to 'Association between prophylactic angiotensin-converting enzyme inhibitors and overall survival in Duchenne muscular dystrophy: analysis of registry data'†, by R. Porcher *et al.*, on page 1976.



Graphical Abstract Pathogenic variants in the dystrophin gene lead to progressive neuromuscular and cardiac dysfunction in patients with Duchenne muscular dystrophy. Diagnosis typically occurs when boys display signs of skeletal myopathy, such as Gowers' sign, the adoption of a prone position before standing to overcome pelvic muscle weakness. Lack of dystrophin protein leads to break down of myocyte cell membranes, inflammation and ultimately cell death and fibrosis. Cardiomyopathy is nearly inevitable and ongoing cardiac screening is recommended. The early initiation of angiotensin-converting enzyme (ACE) inhibitor therapy is life-saving. Concomitant therapy with mineralocorticoid receptor antagonists and betablockers may provide additional benefit.

† doi:10.1093/eurheartj/ehab054.
* Corresponding author. Email: anjali.owens@pennmedicine.upenn.edu

Duchenne muscular dystrophy (DMD) is an X-linked degenerative neuromuscular disorder with an incidence of 1 in every 3500–5000 live male births, resulting in the progressive loss of muscle function and cardiorespiratory death, typically by the third decade of life.[1] Mutations in the dystrophin gene are responsible for both DMD and a milder form of dystrophinopathy called Becker muscular dystrophy (BMD). Dystrophin is the largest gene in humans, ~2.4 Mb in size, with 79 exons. Pathogenic variants in dystrophin occur *de novo* in at least a third of affected patients, with the remainder of patients having a clear, familial pattern of disease. Exonic out-of-frame mutations in the gene dystrophin produce truncated or absent dystrophin protein, resulting in the loss of myocyte plasma membrane integrity and contractile dysfunction.[2] Clinical manifestations typically arise during the ages of 2–5 years, with falls, calf hypertrophy, gait disturbance, and the classic Gowers' sign (*Graphical Abstract*), followed by the loss of ambulation due to skeletal myopathy, respiratory impairment, and the nearly inevitable onset of dilated cardiomyopathy by age 18.[3]

Myocardial involvement of DMD remains under-recognized and undertreated. To date, the standard of care for DMD has included the use of anti-inflammatory glucocorticoid therapy, which has been associated with improvement in muscle function, albeit with the attendant morbidity of chronic steroid use. With recent advances in respiratory support, including 24/7 non-invasive ventilation, patients are now less likely to die of respiratory failure in their teenage years. Instead, DMD-associated cardiomyopathy and arrhythmia have emerged as a major cause of mortality in young adults, many of whom are transitioning from paediatric to adult cardiology care.[4]

Early detection of cardiomyopathy through clinical screening and subsequent treatment with angiotensin-converting enzyme (ACE) inhibitors is associated with attenuated progression of left ventricular dysfunction.[5] However, the diagnostic use of echocardiography is often hampered by difficult acoustic windows.[6,7] In addition, the very low cardio-metabolic requirement of patients who ambulate infrequently results in the masking of the clinical signs and symptoms of heart failure (HF). Cardiac magnetic resonance imaging (MRI) with assessment of late gadolinium enhancement has replaced echocardiography as the imaging modality of choice in the DMD Care Considerations Working Group recommendations from 2018[3]; however, cardiac MRI is not universally available, affordable, or easily performed in young children. MRI studies have demonstrated the clear presence of significant cardiac fibrosis even before the onset of overt left ventricular dysfunction,[8] prompting the question of the optimal time to initiate cardioprotective medications, including ACE inhibitors. Moreover, the potential impact of cardioprotective therapy on longer-term survival in patients with preserved ejection fraction by echocardiogram at the time of initiation has not been conclusively demonstrated.

In this issue of the *European Heart Journal*, Porcher *et al.* address this vital question—is ACE inhibitor therapy associated with improved survival and less HF hospitalization if started 'prophylactically', e.g. in a child with normal left ventricular ejection fraction (LVEF) and no HF symptoms? The study included 576 patients, aged 8–13 years, from the multicentre French DMD Heart Registry. Study design was complex, utilizing a non-intuitive emulated trial format to analyse a retrospective, observational cohort. In the absence of randomized data, the authors attempted to account for overt confounding factors that may have impacted the clinicians' decision to start ACE inhibitor therapy despite normal LVEF. MRI data were not reported. They used three statistical models: a Cox model with intervention as a time-dependent covariate; an emulated trial comparing ACE inhibitor treatment vs. no treatment; and a sensitivity analysis. The Cox model demonstrated a hazard ratio (HR) of 0.49 [95% confidence interval (CI) 0.34–0.72] associated with the use of ACE inhibitors and an HR of 0.60 (95% CI 0.39–0.93) for overall mortality after adjustment for baseline variables. In the emulated trial, ACE inhibitors significantly and profoundly reduced mortality (HR 0.39; 95% CI 0.17–0.92) and HF hospitalization (HR 0.16; 95% CI 0.04–0.62). The sensitivity analyses resulted in similar conclusions. Notably, discontinuation of ACE inhibitor therapy due to adverse events or side effects occurred in only 1.8% of the treated group.[9]

Three previous studies of ACE inhibitor therapy in DMD cardiomyopathy are consistent with the findings in the current analyses, demonstrating that ACE inhibition prevents progression of DMD cardiomyopathy.[5,10,11] In addition, the use of concomitant mineralocorticoid receptor antagonist therapy was investigated in another small trial in DMD patients and found to aid in the preservation of ventricular function.[12] Remarkably, there is a dearth of data on the use of beta-blockers in patients with DMD, despite the clear risk of fatal arrhythmic events in these individuals that might be mitigated by therapies targeting the adrenergic system. A final gap in the care of families with an affected DMD member is a focus on the mothers of these children, who are often carriers of DMD. Female carriers, many of whom are serving as the primary caregiver to their intensely disabled, non-ambulatory sons,[13] need to be screened for cardiac involvement and likewise treated.

In conclusion, cardioprotective strategies have been investigated in a number of cardiovascular disorders and successfully incorporated into treatment regimens for selected patients, including ACE inhibitors in patients with and without diabetes and coronary artery disease,[14] angiotensin receptor blockers and beta-blockers in Marfan syndrome,[15] and the use of ACE inhibitors and beta-blockers in patients at risk for chemotherapy-related toxicity.[16] Porcher *et al.* from the French multicentre DMD Heart Registry have now convincingly demonstrated that even very young patients with DMD can benefit from the life-saving intervention of ACE inhibition as well.

Funding

A.J.O. is supported by the Winkelman Family Fund in Cardiovascular Innovation.

Conflict of interest: A.J.O. is a consultant for MyoKardia and Cytokinetics. M.J. has no disclosures.

References

1. 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.
2. Kumar SH, Athimoolam K, Suraj M, Das Christu Das MS, Muralidharan A, Jeyam D, Ashokan J, Karthikeyan P, Krishna R, Khanna-Gupta A, Bremadesam Raman L. Comprehensive genetic analysis of 961 unrelated Duchenne Muscular Dystrophy patients: focus on diagnosis, prevention and therapeutic possibilities. *PLoS One* 2020;**15**:e0232654.

3. 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.
4. Buddhe S, Cripe L, Friedland-Little J, Kertesz N, Eghtesady P, Finder J, Hor K, Judge DP, Kinnett K, McNally EM, Raman S, Thompson WR, Wagner KR, Olson AK. Cardiac management of the patient with Duchenne muscular dystrophy. *Pediatrics* 2018;**142**:S72–S81.
5. Duboc D, Meune C, Lerebours G, Devaux JY, Vaksmann G, Bécane HM. Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. *J Am Coll Cardiol* 2005;**45**:855–857.
6. 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.
7. Spurney C, Shimizu R, Morgenroth LP, Kolski H, Gordish-Dressman H, Clemens PR; CINRG Investigators. Cooperative International Neuromuscular Research Group Duchenne Natural History Study demonstrates insufficient diagnosis and treatment of cardiomyopathy in Duchenne muscular dystrophy. *Muscle Nerve* 2014;**50**:250–256.
8. Hor KN, Taylor MD, Al-Khalidi HR, Cripe LH, Raman SV, Jefferies JL, O'Donnell R, Benson DW, Mazur W. Prevalence and distribution of late gadolinium enhancement in a large population of patients with Duchenne muscular dystrophy: effect of age and left ventricular systolic function. *J Cardiovasc Magn Reson* 2013;**15**:107.
9. Porcher R, Desguerre I, Amthor H, Chabrol B, Audic F, Rivier F, Isapof A, Tiffreau V, Campana-Salort E, Leturcq F, Tuffery-Giraud S, Yaou RB, Annane D, Amédro P, Barnerias C, Bécane HM, Béhin A, Bonnet D, Bassez G, Cossée M, de La Villéon G, Delcourte C, Fayssoil A, Fontaine B, Godart F, Guillaumont S, Jaillette E, Laforêt P, Leonard-Louis S, Lofaso F, Mayer M, Morales RJ, Meune C, Orlikowski D, Ovaert C, Prigent H, Saadi M, Sochala M, Tard C, Vaksmann G, Walther-Louvier U, Eymard B, Stojkovic T, Ravaud P, Duboc D, Wahbi K. Association between prophylactic angiotensin-converting enzyme inhibitors and overall survival in Duchenne muscular dystrophy: analysis of registry data. *Eur Heart J* 2021;**42**:1976–1984.
10. Duboc D, Meune C, Pierre B, Wahbi K, Eymard B, Toutain A, Berard C, Vaksmann G, Weber S, Bécane HM. Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up. *Am Heart J* 2007;**154**:596–602.
11. Silva MC, Magalhães 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.
12. Raman SV, Hor KN, Mazur W, Cardona A, He X, Halnon N, Markham L, Soslow JH, Puchalski MD, Auerbach SR, Truong U, Smart S, McCarthy B, Saeed IM, Statland JM, Kissel JT, Cripe LH. Stabilization of early Duchenne cardiomyopathy with aldosterone inhibition: results of the multicenter AIDMD trial. *J Am Heart Assoc* 2019;**8**:e013501.
13. Hor KN, Mah ML, Johnston P, Cripe TP, Cripe LH. Advances in the diagnosis and management of cardiomyopathy in Duchenne muscular dystrophy. *Neuromuscul Disord* 2018;**28**:711–716.
14. Bangalore S, Fakheri R, Wandel S, Toklu B, Wandel J, Messerli FH. Renin angiotensin system inhibitors for patients with stable coronary artery disease without heart failure: systematic review and meta-analysis of randomized trials. *BMJ* 2017;**356**:j4.
15. Tinkle BT, Saal HM; Committee on Genetics. Health supervision for children with Marfan syndrome. *Pediatrics* 2013;**132**:e1059–e1072.
16. Elghazawy H, Venkatesulu BP, Verma V, Pushparaji B, Monlezun DJ, Marmagkiolis K, Iliescu CA. The role of cardio-protective agents in cardio-preservation in breast cancer patients receiving anthracyclines ± Trastuzumab: a meta-analysis of clinical studies. *Crit Rev Oncol Hematol* 2020;**153**:103006.