essential component in the chain of survival. We believe that this study[12] should further stimulate efforts by those in positions of influence to facilitate widespread access to public-access defibrillation in the general community.

Aung Myat, Andreas Baumbach
Division of Clinical and Experimental Medicine, Brighton and Sussex Medical School and Sussex Cardiac Centre, Brighton and Sussex University Hospitals NHS Trust, Brighton BN2 5BE, UK (AM); and William Harvey Research Institute, Queen Mary University of London and the Bart's Heart Centre, London, UK (AB)
a.myat@nhs.net

We declare no competing interests.

1 Perkins GD, Travers AH, Berg RA, et al. Part 3: adult basic life support and automated external defibrillation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Resuscitation* 2015; **95:** e43–69.
2 Hallstrom AP, Ornato JP, Weisfeldt M, et al. Public-access defibrillation and survival after out-of-hospital cardiac arrest. *N Engl J Med* 2004; **351:** 637–46.
3 Bækgaard JS, Viereck S, Møller TP, Ersbøll AK, Lippert F, Folke F. The effects of public access defibrillation on survival after out-of-hospital cardiac arrest a systematic review of observational studies. *Circulation* 2017; **136:** 954–65.
4 Holmberg MJ, Vognsen M, Andersen MS, Donnino MW, Andersen LW. Bystander automated external defibrillator use and clinical outcomes after out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Resuscitation* 2017; **120:** 77–87.
5 Moran PS, Teljeur C, Masterson S, O'Neill M, Harrington P, Ryan M. Cost-effectiveness of a national public access defibrillation programme. *Resuscitation* 2015; **91:** 48–55.
6 Smith CM, Lim Choi Keung SN, Khan MO, et al. Barriers and facilitators to public access defibrillation in out-of-hospital cardiac arrest: a systematic review. *Eur Heart J Qual Care Clin Outcomes* 2017; **3:** 264–73.
7 Hansen SM, Hansen CM, Folke F, et al. Bystander defibrillation for out-of-hospital cardiac arrest in public vs residential locations. *JAMA Cardiol* 2017; **2:** 507–14.
8 Sondergaard KB, Hansen SM, Pallisgaard JL, et al. Out-of-hospital cardiac arrest: probability of bystander defibrillation relative to distance to nearest automated external defibrillator. *Resuscitation* 2018; **124:** 138–44.
9 Zijlstra JA, Koster RW, Blom MT, et al. Different defibrillation strategies in survivors after out-of-hospital cardiac arrest. *Heart* 2018; **104:** 1929–36.
10 Deakin CD, Shewry E, Gray HH. Public access defibrillation remains out of reach for most victims of out-of-hospital sudden cardiac arrest. *Heart* 2014; **100:** 619–23.
11 Kitamura T, Kiyohara K, Sakai T, et al. Public-access defibrillation and out-of-hospital cardiac arrest in Japan. *N Engl J Med* 2016; **375:** 1649–59.
12 Nakashima T, Noguchi T, Tahara Y, et al. Public-access defibrillation and neurological outcomes in patients with out-of-hospital cardiac arrest in Japan: a population-based cohort study. *Lancet* 2019; published online Dec 17. https://doi.org/10.1016/S0140-6736(19)32488-2.

Angiotensin-II receptor blockade in Marfan syndrome


Ian Hooton/Science Photo Library

Published Online
December 10, 2019
https://doi.org/10.1016/S0140-6736(19)32536-X

See Articles page 2263

Because aortic root dilatation and resulting dissection are the most life-threatening problems in patients with Marfan syndrome, research has focused on mitigating the risk for these complications. Whereas surgical replacement of the dilated aorta remains the most effective intervention, medical treatment aimed at reducing aortic root growth also contributes to improved outcome. β blockers are considered the gold standard for this purpose, with an effect most likely achieved by reducing aortic wall shear stress.[1]

A major discovery in the research to unravel the underlying pathogenesis of this condition was the demonstration of the transforming growth factor β (TGF-β) pathway involvement.[2] This opened-up perspectives for new treatment options through blockade of TGF-β, where angiotensin-II receptor blockers (ARBs) seemed an attractive option. The precise contribution of TGF-β has still not been fully elucidated. It has been shown that TGF-β has dual effects and should be regarded as a marker rather than a cause of pathology.[3] Nevertheless, the publication of the remarkable results, showing that losartan, an ARB, improved aortic growth in a mouse model of Marfan syndrome, had an impact in the Marfan syndrome community.[4] At least eight studies with losartan have been done.[5-8] Albeit with variable study design and populations, these studies showed that the results achieved in animal models could not be replicated in humans, leading to further speculation about possible explanations.

One of the hypotheses was that the lower bioavailability (33%) and short half-life (2 h)[9] of losartan might provide insufficient protection. Therefore, irbesartan, an ARB with longer bioavailability (up to 80%) and half-life (up to 15 h),[9] could result in a better outcome. For this reason, the study by Michael Mullen and colleagues[10] in *The Lancet* is very interesting. This randomised placebo-controlled trial shows that the intake of irbesartan significantly reduced aortic root dilatation in patients with Marfan syndrome (mean aortic root growth 0·53 mm per year [95% CI 0·39 to 0·67] in the irbesartan group *vs* 0·74 mm per year [0·60 to 0·89] in the placebo group; difference –0·22 mm per year [–0·41 to –0·02]; p=0·030). This moderate effect was mainly achieved during the first year of treatment and was maintained throughout the 4 subsequent years. A parallel effect was observed on blood pressure, suggesting a possible association

between lowering blood pressure and aortic growth. On the basis of these findings, previous conclusions are confirmed: the use of ARBs to inhibit aortic growth in patients with Marfan syndrome can certainly be considered.

Several recurring and unresolved questions in the design and interpretation of studies of ARBs have unfortunately not been clarified by this study either. First, many such studies are confronted with the issue of difficult patient recruitment. In the study by Mullen and colleagues,[10] not even half of the anticipated number of patients was achieved. This difficulty has to do with the rarity of the condition and with the difficulty of convincing patients to participate in research after the publication of preclinical trials.

Second, another limiting factor is the low hard event rate (aortic dissection and death), which forces all studies to rely on indirect outcome parameters, such as aortic root growth. Furthermore, an additional limitation of this study is the inclusion of both children and adults (192 patients with Marfan syndrome with a median age of 18 years [IQR 12–28]). Apart from somatic growth in half of the study population, which is difficult to account for, there is the problem of the measurement of the aorta itself and the calculation of the Z scores. Although aortic Z score values were used as a secondary outcome in this study, applying methods for Z score calculation based on data obtained in different age populations and using different echocardiographic methods is cumbersome. The authors sought to solve this difficulty by calculating the Z score according to the Devereux method[11] (developed for application in adult patients) while using the Pettersen reference[12] (developed for application in paediatric patients) as a sensitivity analysis.

A final consideration is that 108 (56%) patients in the cohort were taking β blockers. The authors tried to account for the confounding effect of β blockers through conventional stratified analysis, but the study was underpowered to perform meaningful subgroup evaluation (especially given the drop-out rate of 24% in the irbesartan group and 15% in the placebo group). Subsequently, evaluation of how the observed effect should be interpreted is difficult. Is the effect of the irbesartan better in comparison to no treatment or in comparison to β blocker treatment? What is the effect of combined treatment?

Despite these limitations, the study by Mullen and colleagues[10] is valuable and certainly adds to the ongoing discussion on how to best treat patients with Marfan syndrome. A planned meta-analysis of trials done thus far[13] will hopefully provide some answers that are urgently needed for this community.

Laura Muiño-Mosquera, Julie De Backer
Department of Paediatrics, Division of Paediatric Cardiology (LM-M), Centre for Medical Genetics (LM-M, JDB), and Department of Cardiology (JDB), Ghent University Hospital, Ghent 9000, Belgium
laura.muinomosquera@uzgent.be

We declare no competing interests.

1 Shores J, Berger K, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term β-adrenergic blockade in Marfan's syndrome. *N Engl J Med* **330:** 1335–41.
2 Neptune ER, Frischmeyer PA, Arking DE, et al. Dysregulation of TGF-β activation contributes to pathogenesis in Marfan syndrome. *Nat Genet* 2003; **33:** 407–11.
3 Cook JR, Clayton NP, Carta L, et al. Dimorphic effects of transforming growth factor-β signaling during aortic aneurysm progression in mice suggest a combinatorial therapy for Marfan syndrome. *Arterioscler Thromb Vasc Biol* 2015; **35:** 911–17.
4 Habashi JP, Judge DP, Holm TM, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science* 2006; **312:** 117–21.
5 Chiu H-H, Wu M-H, Wang J-K, et al. Losartan added to β-blockade therapy for aortic root dilation in Marfan syndrome: a randomized, open-label pilot study. *Mayo Clin Proc* 2013; **88:** 271–76.
6 Muiño-Mosquera L, De Nobele S, Devos D, Campens L, De Paepe A, De Backer J. Efficacy of losartan as add-on therapy to prevent aortic growth and ventricular dysfunction in patients with Marfan syndrome: a randomized, double-blind clinical trial. *Acta Cardiol* 2017; **72:** 616–24.
7 Teixido-Tura G, Forteza A, Rodríguez-Palomares J, et al. Losartan versus atenolol for prevention of aortic dilation in patients with Marfan syndrome. *J Am Coll Cardiol* 2018; **72:** 1613–18.
8 Li L, Yamani N, Al-Naimat S, Khurshid A, Usman MS. Role of losartan in prevention of aortic dilatation in Marfan syndrome: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2019; published online July 1. DOI:10.1177/2047487319861231.
9 Abraham HMA, White CM, White WB. The comparative efficacy and safety of the angiotensin receptor blockers in the management of hypertension and other cardiovascular diseases. *Drug Saf* 2015; **38:** 33–54.
10 Mullen M, Jin XY, Child A, et al. Irbesartan in Marfan syndrome (AIMS): a double-blind, placebo-controlled randomised trial. *Lancet* 2019; published online Dec 10. https://doi.org/10.1016/S0140-6736(19)32518-8.
11 Devereux RB, de Simone G, Arnett DK, et al. Normal limits in relation to age, body size and gender of two-dimensional echocardiographic aortic root dimensions in persons ≥15 years of age. *Am J Cardiol* 2012; **110:** 1189–94.
12 Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of Z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. *J Am Soc Echocardiogr* 2008; **21:** 922–34.
13 Pitcher A, Emberson J, Lacro RV, et al. Design and rationale of a prospective, collaborative meta-analysis of all randomized controlled trials of angiotensin receptor antagonists in Marfan syndrome, based on individual patient data: a report from the Marfan Treatment Trialists' Collaboration. *Am Heart J* 2015; **169:** 605–12.