Losartan treatment in adult patients with Marfan syndrome: can we finally COMPARE?

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This editorial refers to ‘Losartan reduces aortic dilatation rate in adults with Marfan syndrome: a randomized controlled trial’†, by M. Groenink et al., on page 3491

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder with a prevalence of ~1 in 5000 individuals. The syndrome results from mutations in the fibrillin-1-encoding gene (FBN1). As > 600 mutations in FBN1 have been reported, a great variety of phenotypes are encountered. Hence, MFS is a systemic disorder which may differently affect the cardiovascular, ocular, and musculoskeletal systems. The cardiovascular manifestations, including progressive aortic root dilatation, or aortic dissection or rupture, are the leading cause of mortality in MFS. Myxomatous mitral valve changes may also be present and contribute to an adverse outcome.

The diagnosis of MFS continues to rely on a clinical assessment, as molecular testing for FBN1 mutations is neither sensitive nor specific. Accordingly, the established Ghent criteria use a combination of clinical findings in the various organ systems, the family history, and an FBN1 mutation to make the diagnosis of MFS.

Currently, the medical management of MFS patients employs serial cardiac imaging studies to measure aortic dimensions and pharmacological treatment to reduce the haemodynamic stress on the aortic wall. Once the aortic diameter reaches a certain threshold, prophylactic aortic root replacement, either by a composite valve graft repair or by an aortic valve-sparing operation, is undertaken. This strategy has extended the average life expectancy from ~40 years before the era of open heart surgery, up to ~70 years in patients with MFS. However, in spite of this progress, morbidity in patients with MFS remains high as the great majority will suffer an adverse cardiovascular event, such as surgical repair of the aortic root, fatal or non-fatal aortic dissection, or mitral valve surgery.

The pharmacological treatment for aortic root dilatation has relied until recently on beta-adrenergic-blocking drugs as several trials have shown that they reduce the rate of aortic growth. The invoked mechanisms of action have included reduction in aortic shear stress, in ejection impulse, and in heart rate. When beta-blocker therapy was not tolerated, clinicians have turned to calcium channel blockers or angiotensin-converting enzyme inhibitors, even though the evidence in favour of these molecules has been less.

Recent studies from basic science have improved our understanding of the pathogenesis of MFS. Derived from several observations, it is postulated today that abnormal fibrillin in MFS causes insufficient sequestration and consequent excessive activation of transforming growth factor-β (TGF-β), a pluripotential cytokine, involved in cellular migration, proliferation, and programmed cell death.

Based on the ability of the angiotensin receptor blocker, losartan, to inhibit TGF-β signalling, Dietz and colleagues used a mouse model with a fibrillin-1 mutation of MFS to examine the effect of losartan on aortic growth. In the losartan-treated animals, aortic growth was comparable with that of wild-type controls, and this effect extended beyond the modification of haemodynamics. Furthermore, when compared with propranolol-treated mice, losartan was also significantly more effective. Even more notably, the aortic wall architecture in losartan-treated animals was indistinguishable from that of wild-type littermates.

These experimental results were so convincing that physicians and patients worldwide did not wait for the results of prospective clinical trials before starting to use losartan to prevent progressive aortic root dilatation in MFS. Hence, there was some matter of urgency to perform clinical trials to test the efficacy of losartan in humans, and to adjust to a reality which was being dictated by the terrain.

Groenink et al. now present the first prospective, multicentre, randomized, controlled trial indicating a beneficial effect of losartan in adults with MFS. COMPARE (COzaar in Marfan PAtients Reduces Aortic Enlargement) was designed to test the hypothesis of whether losartan reduces the aortic dilatation rate at any of six pre-defined aortic levels in adults with MFS. Additional aims of the study were to examine the effect of losartan on aortic volume and incidence of aortic dissection, on elective aortic surgery, or cardiovascular death. The authors screened 797 patients from four Dutch University Marfan Clinics and used the Dutch national database of adults with congenital heart disease (CONCOR registry) to enrol 233 operated and unoperated patients who were randomized to losartan or no
additional treatment. All previously prescribed medication, including beta-blockers and calcium channel blockers, was continued after inclusion. Importantly, by design, the trial was open label with blinded assessment of endpoints. At baseline, patients would undergo magnetic resonance imaging (MRI) or exceptionally computed tomography (CT) of the entire aorta and again at 3 years of follow-up. Clinical assessment and transthoracic echocardiography were performed on an annual basis.

The authors were able to evaluate the aortic root dilatation rate in 145 patients with a native aortic root, and show that after 3 years of follow-up, the aortic root dilatation rate was significantly lower in the losartan group compared with the control group, with a number-needed-to-treat of 5.3 patients. Regression analysis showed further that change in mean arterial blood pressure or change in systolic blood pressure was not correlated with aortic root dilatation rate in patients treated with losartan or controls. In patients with prior aortic root replacement, the aortic arch dilatation rate was significantly lower in the losartan group. However, no significant differences in separate clinical endpoints or the composite clinical endpoint could be shown between groups.

The investigators of COMPARE should be congratulated on having tried to fill the gap between novel insights into the pathogenesis of MFS, lessons learnt from animal models, and their application in the clinical arena.

Some comments on the trial design have to be made. (i) The authors chose an open label protocol, in their opinion in order not to introduce the additional delay of a double-blinded study, but possibly also because it would have been very difficult to mask drug assignment on all occasions; nevertheless, in our view, the blinded assessment of endpoints by physicians not involved in treatment assignments allows for a valid treatment comparison. (ii) The decision to opt for an ‘add-on’ therapeutic strategy, without a placebo arm, might be criticized by some; however, current practice tells us that for many patients and caregivers beta-blocker therapy in MFS patients is considered standard of care (in the study >70% of patients were on beta-blockers), and discontinuation of this therapy would have been viewed as unethical. (iii) Finally, arguments could be made regarding the choice of the primary endpoint which is a surrogate endpoint and not a clinical endpoint per se; notwithstanding, the clinical endpoints of aortic dissection, elective aortic surgery, or cardiovascular death being rare, a far larger sample size with longer follow-up would have been required to document an effect of losartan treatment. Such a scenario would have been totally impractical. Moreover, as losartan delays aortic growth in the experimental mouse model, the investigators’ choice can be fully supported.

The results of COMPARE also highlight the importance of using modern cardiovascular imaging techniques (MRI or CT), which give unrestricted access to the chest and provide a comprehensive and accurate assessment of the aorta in different tomographic planes. This is of particular relevance in an adult patient population, such as in COMPARE, as the acoustic windows might be suboptimal, and the echocardiographic measurements thus unsatisfactory. It must also be stated that different imaging methods perform aortic measurements differently, and that consequently the dimensions are not interchangeable across techniques. In order to ensure a meticulous longitudinal follow-up of the aorta, specification of planes and lines of measurement have been published and should be followed accordingly.

Although the reduction of mean aortic root dilatation rate in the losartan group was present, irrespective of age, sex, blood pressure, aortic root size, presence of an FBN1 mutation, and concomitant beta-blocker use, the authors invite us to interpret these results with caution because of the small subgroups. Limited sample size did not allow the teasing out of the effects of losartan monotherapy on aortic root dilatation either. Finally, the expected aortic root dilatation rate was overestimated in the original sample size analysis (dilatation rate 1.35 mm/3 years as opposed to the expected 2.7 mm/3 years). Are these observations all linked together? One tentative explanation might be the age of the study cohort (mean age ~37 years), as the study enrolled per protocol individuals older than 18 years. Older individuals with MFS, who have not required surgery, probably suffer from milder variants of the disorder, making it more difficult to detect an effect of a pharmacological intervention. Be that as it may, future trials are eagerly awaited to provide answers to these questions.

In summary, the results of COMPARE provide additional evidence in favour of the efficacy and safety of losartan in MFS patients, by delaying aortic root dilatation of the native aortic root and by decreasing aortic arch dilatation in patients with prior aortic root replacement. Future studies, such as the Pediatric Heart Network Investigators Trial (results due in 2014), will hopefully inform us on the effects of losartan as a monotherapy on the aortic root dilatation rate and, hence, finally allow us to COMPARE different molecules in the treatment of MFS.

Conflict of interest: none declared.

References


**CARDIOVASCULAR FLASHLIGHT**

Vertebral artery pseudoaneurysm complicating transaxillar aortic valve implantation

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An 86-year-old female patient was admitted because of exertional dyspnoea and severe symptomatic aortic stenosis with a mean gradient of 46 mmHg and a valve area of 0.61 cm². The patient had a predicted operative mortality undergoing cardiac surgery as assessed by the logistic Euroscore II (58.9%). In the light of this, transcatheter aortic valve implantation using a 29-mm diameter device (CoreValve™, Medtronic, Inc., CV) was performed with a good function of the graft as assessed by echocardiography. Owing to severe kinking of the abdominal aorta a left subclavian artery approach was preferred. Early after the procedure the patient complained of a globus sensation and dysphagia. An abnormal pulsatile mass was palpable at the left cervical region. Computed tomography of the chest and the cervical region demonstrated a large retropharyngeal and mediastinal haematoma as well as a pseudoaneurysm originating from the proximal left vertebral artery (Panel A, Supplementary material online, Video S1) suggesting iatrogenic vessel perforation. The patient underwent immediate endovascular exclusion by stenting of the ostial region of the left vertebral artery using a covered coronary stent graft (Jostent Graftmaster™ 5.0 × 23 mm, Abbott Vascular) (Panels B and C, Supplementary material online, Video S2 and S3). After the procedure the patient recovered adequately. Follow-up examination by duplex ultrasound after 6 months demonstrated a regular Doppler-flow in the the left vertebral artery (Panel D). In certain circumstances, endovascular stenting may be a preferred treatment option for a vertebral artery pseudoaneurysm, particularly in patients with an increased risk for operative repair.

Supplementary material is available at *European Heart Journal* online.

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