European Review for Medical and Pharmacological Sciences 2023; 27: 8218-8224

Marfan syndrome and aortic involvement: a narrative review

R.G. CARBONE[1], A. MONSELISE[2], F. PUPPO[1]

[1]Department of Internal Medicine, University of Genoa, Genoa, Italy
[2]Clalit Health Services, Tel Aviv, Israel

Abstract. – Marfan syndrome (MFS) is a systemic connective tissue disease that commonly and most severely affects the ocular, skeletal, and cardiovascular systems.

The aim of the manuscript is to review the aortic involvement and complications in MFS, including aortal dissection, thoracic aortic aneurysm, abdominal aortic aneurysm, and acute aortic syndrome. Dissecting thoracic aortic aneurysm and progressing aortic root enlargement are the major causes of MFS morbidity and mortality. Guidelines on aortic disease endorsed by the American College of Cardiology, and the American Heart Association recommend the measurement of the external and internal aortic diameters perpendicular to the axis of blood flow when Computed Tomography, or Magnetic Resonance Imaging, or Cardiac Echography are performed. The pathophysiology, diagnosis, prevention, and medical and surgical treatments of MFS associated with aortic complications are reported in this narrative review. Development and strengthening of centers specialized in cardiovascular diseases and MFS, together with an improvement in the knowledge of its pathogenesis through genetics and proteomics investigations, can ameliorate the prognosis of this disease.

Key Words:
Marfan syndrome, Aorta aneurysm, Aorta dissection, Bicuspid aortic valve.

Introduction

Marfan syndrome (MFS) is a systemic connective tissue disease (CTD) that commonly and most severely affects the ocular, skeletal, and cardiovascular systems[1]. MFS is a congenital condition with a prevalence of 1 in 5,000[2].

The discovery of fibrillin-1, a constituent protein of elastin fibers, quickly led to the identification of the underlying genetic abnormality in MFS. MFS is an autosomal dominant disorder caused by a mutation in *FBN1* that encodes the gene for fibrillin-1 located in chromosome 15q21.1. In around 75% of cases, MFS is inherited from one parent[3-5].

Notably, selected clinical diagnostic criteria improved the detection of *FBN1* mutations in this autosomal dominant condition. Fibrillin-1 is a structural macromolecule that polymerizes into microfibrils which are the regulatory components of the extra-cellular matrix, contributing to the integrity and function of all connective tissues, including the aorta wall. *FBN1* gene mutations cause elastin and collagen destruction. This process leads to progressive dilatation of the proximal aorta predisposing the aorta to dissection[3-5] (Figure 1).

The classic MFS phenotype includes exaggerated long bone growth accompanied by scoliosis, pectus deformities, and increased joint laxity. Musculoskeletal abnormalities are often the first finding that raises suspicion for MFS. Abnormal osteogenesis and osteoclastic activity are associated with a higher fracture rate, presumably due to osteopenia[1].

Besides bones, other organs are involved in MFS, including skin, lungs with tracheomalacia, eyes, and skull, as well as neurological and cardiovascular systems. Vascular injury includes aneurysmal dilatation of the aortic root, thoracic aorta, and proximal pulmonary arteries predisposing to aneurysms and dissection. Cardiac damage leads to mitral and tricuspid valve prolapse, cardiomyopathy, and supraventricular arrhythmias[1] (Figure 2).

With the advent of prophylactic aortic surgery, the life expectancy of MFS patients has improved. Furthermore, pharmacologic therapy retards aortic aneurysm growth, especially when initiated at an early stage.

The aim of the manuscript is to review the aortic involvement and complications in MFS, including aortal dissection, thoracic aortic aneurysm, abdominal aortic aneurysm, and acute aortic syndrome.

Corresponding Author: Roberto G. Carbone, MD; e-mail: magister1@mail.com

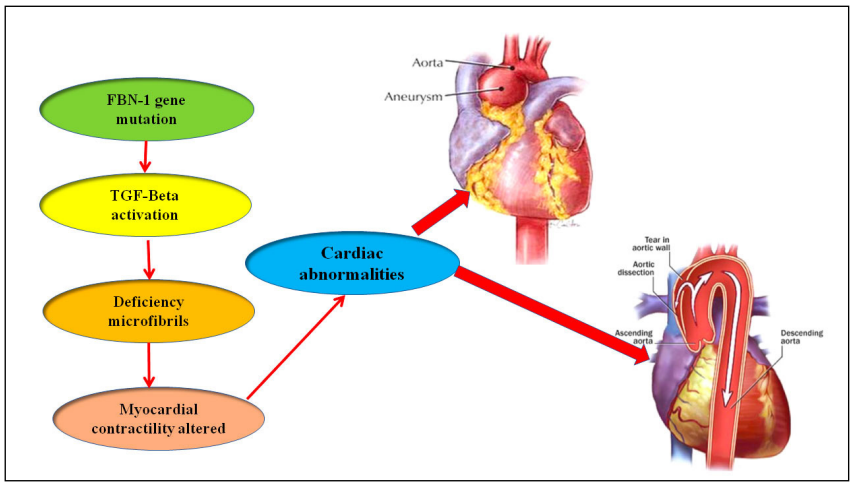

Figure 1. Picture describing multiple factors in the pathogenesis of Marfan syndrome and their relationship with aortic involvement.

Methods

A bibliographic search was performed applying the terms "Marfan syndrome", "aorta aneurism", "aorta dissection", "bicuspid aortic valve" in www.pubmed.gov from 2010 to 2022.

Marfan Syndrome and Aortic Disease

About 90% of patients with MFS develop changes in their heart and blood vessels, and about 40% die due to complete aortic rupture and bleeding. Aortic complications include aortic valve insufficiency, aortic root dilatation, and aortic aneurysm rupture[6].

Risk factors for aortic dissection include high blood pressure, atherosclerosis, aortic aneurysm, and aortic valve disease. Aortic dissection can lead to stroke and aortic valve damage[6].

Aortic diseases are classified as thoracic aortic aneurysm (TAA), abdominal aortic aneurysm (AAA), and acute aortic syndrome (AAS). Overall global death rates from aortic disease (including TAA, AAA, and acute aortic dissection) increased from 2.49 per 100,000 (95% CI 1.78-3.27) in 1990 to 2.78 per 100,000 (95% CI 2.04-3.62) in 2010. This increase seems to be more evident in non-developing countries, with a median death rate of 0.71 (95% CI 0.28-1.40) compared to 0.22 (95% CI 0.10-0.33) in developing countries. Overall increase in global death rates may be associated with an increasing mean age of the global population[6,7].

Aortic disease complications, such as dissecting TAA and progressing aortic root enlargement, are the major causes of MFS morbidity and mortality. Aortic involvement may be present either in neonatal life, where it is often fatal, or in adolescence and may worsen with age. TAA is more frequent in men, but women have worse outcomes.

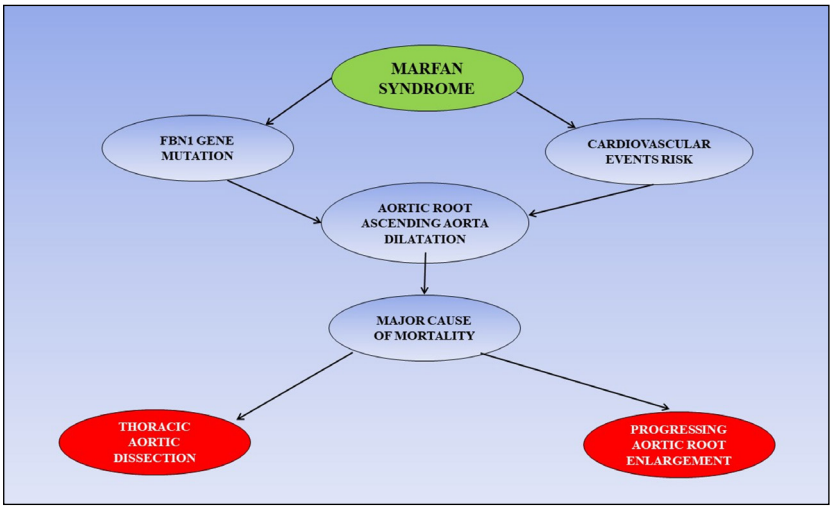

Figure 2. Flow chart showing Marfan syndrome pathophysiology associated with aorta complications.

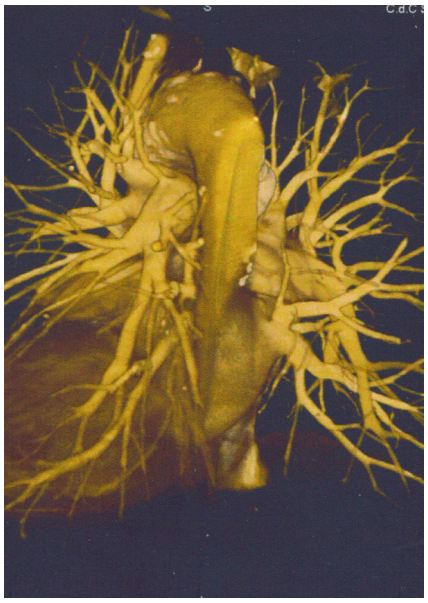

Figure 3. Cardiovascular magnetic resonance imaging showing aortic root enlargement in a patient with Marfan syndrome.

However, decreasing levels of estrogens associated with women aging and transitioning to menopause could lead to a loss of the protective effects of estrogens on the aortic wall and to the impairment of its elastic properties[6,7].

Diagnostic tools for the aortic involvement in MFS include family history, genetic testing, transthoracic echocardiogram (TTE), computed tomography (CT), and magnetic resonance imaging (MRI) of the entire aorta (Figure 3). Genetic testing is an essential diagnostic tool for the disease, with a 97% effectiveness in detecting *FBN1* mutations. Guidelines[8] on aortic disease endorsed by the American College of Cardiology (ACC) and the American Heart Association (AHA) recommend the measurement of the external and internal aortic diameter perpendicular to the axis of blood flow when CT, MRI, or trans thoracic cardiac echography (TTE) are performed. TTE is performed to screen, diagnose, or follow up on specific medical conditions, including aortic aneurysm or aorta dissection[8].

Multidisciplinary care of patients with MFS with more frequent surveillance and earlier prevention surgery led to increased longevity and decreased emergent operations. For patients with familial thoracic aortic aneurysms, monitoring every 5 years is prudent to prevent premature death. The life expectancy of patients suffering from MFS increased from 47 to 75 years thanks to the improvement of medical and surgical therapies for aortic dilation[9]. Of note, the most common abnormality associated with MFS is aortic root/valve dilatation, which over time may lead to dissection and rupture. In the last years, improvement in prophylactic surgical care of diseased aortic root/valve has led to an increased life expectancy among these patients[1]. Recently, Van Andel et al[10] proposed that aorta distensibility could be a predictor of aortic complications in MSF.

Aortic distensibility can be calculated according to the formula:

$$D = [(A_{max} - A_{min}) / A_{min}] / \text{pulse pressure}$$

Abbreviations:
D = distensibility (/mm Hg),
A_{max} = maximal (systolic) aorta area (mm^2),
A_{min} = minimal (diastolic) aorta area (mm^2),
Pulse pressure = systolic blood,
Pressure–diastolic blood pressure (mm Hg).

However, aorta distensibility was not confirmed to be a predictor of aortic events.

Bicuspid Aortic Valve

Bicuspid aortic valve (BAV) is the most common congenital aortic disease with a prevalence of 1-2% and a high incidence of adverse outcomes including aortic stenosis and aortic regurgitation[6].

Currently, the relation between BAV, aortic dilatation, and dissection risk among MFS patients with *FBN1* gene mutations is yet unknown. However, the prevalence of BAV is similar in subjects with MFS and *FBN1* gene mutation and the general population. Furthermore, the finding of BAV in association with the *FBN1* gene does not imply the need to lower the aortic diameter thresholds as a preventive measure of aortic root surgery[11].

Acute Aortic Syndrome

Acute aortic syndromes (AAS) are a group of interrelated, life-threatening conditions that include classic aortic dissection, intramural hematoma, aortic pseudo-aneurysm, and other aorta alterations. AAS are characterized by similar clinical manifestations and have shared diagnostic and management pathways[5-7].

AAS are characterized by classic aortic dissection leading to disruption of the medial layer

that results in the separation of the aortic wall layers and a subsequent formation of true and false lumens divided by an intimal flap. Intramural hematoma can develop in the media of the aortic wall in the absence of a false lumen and intimal tear, penetrating aortic ulcer (i.e., ulceration of an aortic atherosclerotic plaque, penetrating through the internal elastic lamina into the media), pseudo-aneurysm (i.e. dilatation of the aorta owing to disruption of all the aortic wall layers contained only by the periaortic connective tissue), and traumatic aortic injury (i.e. rupture of all aortic wall layers caused by trauma)[5-7].

The DeBakey classification evaluates the origin of intimal tear and extension of dissection. The Stanford classification divides AAS into two groups based on the site of origin: type A involving the ascending aorta and type B not involving the ascending aorta[5-7].

Acute Aortic Dissection

Classic acute aortic dissection (AAD) comprises 80-90% of all AAS and is typically characterized by the presence of an intimal flap separating the true lumen from the false lumen. Population-based studies[14] suggest an incidence of 2.6 to 3.5 cases per 100,000 subjects-years, including out- and in-hospital deaths.

Prevention

Primary Prevention

Primary prevention to reduce the risk of developing aortic disease in MFS includes healthy lifestyle measures from childhood, such as a healthy diet, ideal body mass index (BMI), regular physical activity, moderate alcohol consumption, and no tobacco use. Control of blood pressure, low-density lipoprotein (LDL) cholesterol levels and blood glucose are also considered essential prevention measures[11].

Furthermore, the search for optimal aortic diameter to avoid dissection risk and for diameter-independent markers of dissection risk continues[12].

Secondary Prevention

AAS and aneurysms are conditions that constitute a long-term high risk of severe complications such as aneurysm rupture, dissection, and hemorrhage.

TTE, CT and MRI are necessary measures to guarantee a correct patient follow-up. Periodical evaluation by a multidisciplinary team, including clinical and imaging surveillance, is an important addition to medical or surgical therapy[11,12].

Medical Treatment

Aortic aneurysm and dissection dramatically increase the risk of death in MFS. The most involved segment is the aortic root or ascending aorta which accounts for 60% of cases. Early diagnosis and management of thoracic aorta dilatation among MFS patients could prevent aortic rupture or dissection. Effective medical therapy could delay or prevent the need for surgery[3,5,6].

β-blockers and renin-angiotensin blockers, (angiotensin receptor blockers and angiotensin-converting enzyme inhibitors), are the mainstay of blood pressure control in patients with thoracic aortic dilatation[3,5,6].

The guidelines[13-17] consider the use of β-blockers a cornerstone therapy for MFS patients (class I - level of evidence: B). In fact, therapy reduces heart rate and blood pressure, increasing aortic tensile strength independently of their heart rate and blood pressure lowering effects. No consensus has been reached with regard to the dosage of β-blockers in MFS because clinical trial studies in the literature include a limited number of patients.

The discovery that transforming growth factor β (TGFβ) is involved in the pathogenesis of aortic aneurysms suggests that angiotensin receptor blockade (which attenuates TGFβ activity) could slow aortic root growth in MFS.

β-blockers should be administered to patients with MFS and TAA to control the rate of aortic dilatation unless contraindicated. Although the lack of randomized controlled trials demonstrating a reduction in mortality or dissection rates with β-blockers, they reduce wall shear stress and aortic growth rate. They are also the recommended drug class for antihypertensive treatment in patients with TAA. It should be noted that, although β-blockers should classically be used carefully in the setting of chronic severe aortic regurgitation because they may increase the hemodynamic load through prolonging diastole, an observational study[17] suggested that β-blockers may confer survival benefits in chronic severe aortic regurgitation patients[13-17].

Currently, no clinical trial suggests the role of angiotensin-converting enzyme inhibitors in the medical treatment of MFS or other causes of thoracic aortic dilatation. Indeed, studies on the use of angiotensin-converting enzyme inhibitors in

thoracic aortic dilatation are limited. Enalapril has been found inferior to losartan in reducing aortic root growth in an animal model of MFS. This finding was speculated to be related to the inhibition of angiotensin-II type 2 receptor signaling with enalapril, where its maintenance with losartan was shown to be protective against aortic aneurysm[17].

However, angiotensin-II type 2 receptor inhibition could be reasonable in MFS thoracic aortic disease patients intolerant to β-blockers to control the rate of aortic dilatation. Moreover, the combination of angiotensin-II type 2 receptor inhibitors with β-blockers may achieve a greater effect on aortic root size changes in patients with MFS[17].

Whereas no specific recommendations exist for statin therapy in MFS[18,19], dyslipidemia management should be performed according to the most recent guidelines.

Drugs to Avoid

Several investigations in literature indicate that calcium channel blockers therapy should be avoided in patients with MFS or related conditions. However, there are currently no official statements from the Food and Drug Administration (FDA) or European Medicines Agency (EMA) regarding this issue. Furthermore, detoxification therapy for drug abuse as fluoroquinolone antibiotics, which increase the risk of aortic aneurysm or dissection, should be performed in patients with thoracic aortic dilatation[20-22]. Finally, recent studies[23-25] regarding the negative impact of fluoroquinolones and calcium channel blockers in patients with connective tissue diseases require clinical caution because of the limitation of patients enrolled.

Surgical Treatment

There are non-surgical and surgical treatments for health problems associated with MFS. Surgery is recommended when: i) Aorta diameter is ≥ 5 cm, ii) Aorta expansion rate per year ≥ 0.5 cm (rapid expansion); iii) family members have undergone aortic repair[15].

Decision-making on timing and type of therapeutic intervention (thoracic endovascular aortic repair and/or open surgery) for TAA is dependent on clinical features and risk profiling, including MFS-related comorbidities, anatomy, location, size and growth rate of the aneurysm, and expertise of local aorta team[6,15].

Bossone and Eagle[6] showed that the high morbidity and mortality risk of AAA rupture requiring the elective repair of asymptomatic acute aneurysm aorta is associated with an aortic diameter > 5.5 cm in men or > 5 cm in women (maximum anterior-posterior aortic diameter on ultrasonography). Additionally, prompt referral to a surgeon should be considered if abdominal aneurysmal aorta growth rate is > 10 mm per year. Clinical trials, large observational studies, and meta-analyses in literature have demonstrated lower peri-operative morbidity and mortality with endovascular aneurysm repair than with open surgery, with an in-hospital mortality of 1.4% and 4.2%, respectively. However, the short-term survival benefit of endovascular aneurysm repair over open surgery is counterbalanced by higher rates of long-term complications and death. Patient factors favoring open repair of abdominal aortic aneurysm (the election strategy is reported in the 2020 NICE guideline[26]) include younger age, long life expectancy (> 10 years), some or no medical comorbidities, connective tissue disease and anatomy not suitable for endovascular aneurysm.

Conclusions

Development and strengthening of centers specialized in cardiovascular diseases and in the study of Marfan's syndrome complications, together with an improvement in the knowledge of its pathogenesis through genetics and proteomics investigations, can ameliorate the prognosis of this disease.

Informed Consent

Not applicable.

Ethics Approval

Approval from the Institutional Review Board (IRB) has not been requested as the study is a bibliographic review.

ORCID ID

Francesco Puppo: 0000-0002-5393-0071
Roberto G. Carbone: 0000-0002-6633-9707

Funding

No specific funding was received from any public, commercial or not-for-profit sources.

Conflict of Interest

The authors declare they have no potential conflicts of interest.

Authors' Contributions

All authors contributed to the study's conception.
The literature search was performed by RGC, who also wrote the first draft of the manuscript. AM and FP revised subsequent versions of the manuscript, and all authors read and approved the final version of the manuscript.

References

1) Aranson NJ, Patel PB, Mohebali, Lancaster RT, Ergul EA, Darrin Clouse W, Conrad MF, Patel VI. Presentation, surgical intervention, and long-term survival in patients with Marfan syndrome. J Vasc Surg 2020; 72: 480-489.
2) Keane MG, Pyeritz RE. Medical management of Marfan syndrome. Circulation 2008; 117: 2802-2813.
3) Asano K, Cantalupo A, Sedes L, Ramirez F. Pathophysiology and therapeutics of thoracic aortic aneurysm in Marfan syndrome. Biomolecules 2022: 12: 128.
4) Zeigler SM, Sloan B, Jones JA. Pathophysiology and Pathogenesis of Marfan Syndrome in: J. Halper (ed.), Progress in Heritable Soft Connective Tissue Diseases. Adv Exp Med Biol 2021; 1348: 185-206.
5) Milewicz DM, Braverman AC, De Backer J, Morris SA, Boileau C, Maumenee IH, Jondeau G, Evangelista A, Pyeritz RE. Marfan syndrome. Nat Rev Dis Primers 2021; 7: 64.
6) Bossone E, Eagle KA. Epidemiology and management of aortic disease: aortic aneurysms and acute aortic syndromes. Nat Rev Cardiol 2021; 18: 331-348.
7) Singh J, Wanjari A. Cardiac complications in Marfan syndrome: A review. Cureus 2022; 14: e29800.
8) Beetz NL, Trippel TD, Philipp K, Maier C, Walter-Rittel T, Shnayien S, Gehle P. Discrepancy of echocardiography and computed tomography in initial assessment and 2-year follow-up for monitoring Marfan syndrome and related disorders. Sci Rep 2022; 12: 15333.
9) Grygiel-Górniak B, Oduah MT, Olagunju A, Klokner M. Disorders of the aorta and aortic valve in connective tissue diseases. Current Card Rep 2020; 22: 70.
10) Van Andel MM, de Waard V, Timmermans J, Scholte AJHA, van den Berg MP, Zwinderman AH, Mulder BJM, Groenink M. Aortic distensibility in Marfan syndrome: a potential predictor of aortic events? Open Heart 2021; 8: e001775.
11) Milleron O, Ropers J, Arnoult F, Bouleti C, Delorme G, Langeois M, Tchitchinadze M, Guien C, Beroud C, Boileau C, Jondeau G. Clinical significance of aortic root modification associated with bicuspid aortic valve in Marfan syndrome. Circ Cardiovasc Imaging 2019; 12: e008129.
12) Roman MJ, Devereux RB. Aortic dissection risk in Marfan syndrome. J Am Coll Cardiol 2020; 75: 854-856.
13) Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwöger M, Haverich A, Lung B, Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ; ESC Committee for Practice Guideline 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J 2014; 35: 2873-2926.
14) Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S; ESC Scientific Document Group. 2016 European guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016; 37: 2315-2381.
15) Isselbacher EM, Preventza O, Hamilton Black J 3rd, Augoustides JG, Beck AW, Bolen MA, Braverman AC, Bray BE, Brown-Zimmerman MM, Chen EP, Collins TJ, DeAnda A Jr, Fanola CL, Girardi LN, Hicks CW, Hui DS, Schuyler Jones W, Kalahasti V, Kim KM, Milewicz DM, Oderich GS, Ogbechie L, Promes SB, Gyang Ross E, Schermerhorn ML, Singleton Times S, Tseng EE, Wang GJ, Woo YJ. 2022 ACC/AHA Guideline for the diagnosis and management of aortic disease: A report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation 2022; 146: e334-e482.
16) Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, Lung B, Kluin J, Lang IM, Meijboom F, Moons P, Mulder BJM, Oechslin E, Roos-Hesselink JW, Schwerzmann M, Sondergaard L, Zeppenfeld K; ESC Scientific Document Group 2020 ESC Guidelines for the management of adult congenital heart disease. Eur Heart J 2021; 42: 563-645.
17) Kocyigit D, Griffin BP, Xu B. Medical therapies for Marfan syndrome and other thoracic aortic dilatation in adults: A contemporary review. Am J Cardiovasc Drugs 2021; 21: 609-617.
18) Jovin IS, Duggal M, Ebisu K, Paek H, Oprea AD, Tranquilli M, Rizzo J, Memet R, Feldman M, Dziura J, Brandt CA, Elefteriades JA. Comparison

of the effect on long-term outcomes in patients with thoracic aortic aneurysms of taking versus not taking a statin drug. Am J Cardiol 2012; 109: 1050-1054.

19) Angeloni E, Vitaterna A, Pirelli M, Refice S. Effects of statin therapy on ascending aorta aneurysms growth: a propensity-matched analysis. Int J Cardiol 2015; 191: 52-55.

20) Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ Open 2015; 5: e010077.

21) Lee CC, Lee MT, Chen YS, Lee SH, Chen YS, Chen SC, Chang SC. Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. JAMA Intern Med 2015; 175: 1839-1847.

22) Lee CC, Lee MG, Hsieh R, Porta L, Lee WC, Lee SH, Chang SS. Oral fluoroquinolone and the risk of aortic dissection. J Am Coll Cardiol 2018; 72: 1369-1378.

23) US FDA. FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. FDA Drug Safety Communication. 2018. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures- or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics.

24) European Medicines Agency. Systemic and inhaled fluoroquinolones: risk of heart valve regurgitation/incompetence. 2020. Available at: https://www.ema.europa.eu/en/medicines/dhpc/systemic-inhaled-fluoroquinolones-risk-heart-valve-regurgitation-in-competence.

25) Dong YH, Chang CH, Wang JL, Wu LC, Lin JW, Toh S. Association of infections and use of fluoroquinolones with the risk of aortic aneurysm or aortic dissection. JAMA Intern Med 2020; 180: 1587-1595.

26) National Institute for Health and Care Excellence. Abdominal aortic aneurysm: diagnosis and management 2020 NICE. Available at: https://www.nice.org.uk/guidance/NG156.