OVERVIEW OF **CARDIAC MANAGEMENT** IN MARFAN SYNDROME

AORTIC DISSECTION IS THE MAJOR CAUSE OF PREMATURE MORBIDITY AND MORTALITY IN MARFAN SYNDROME

KEYS TO SURVIVAL

- Enhanced awareness with early diagnosis
- Diligent long-term surveillance of aortic root diameter
- Surveillance of the entire aorta (descending thoracic and abdominal aorta) by the appropriate non-invasive imaging[1,2,3]
- Prophylactic surgery to replace the aortic root or other dilated aortic segments **before** dissection occurs is absolutely critical for survival

DIAGNOSIS

Aortic root aneurysm or aortic dissection and ectopia lentis are cardinal features of Marfan syndrome based on the 2010 Ghent nosology[4]. For the full diagnostic criteria, please visit MarfanDX.org.

CARDIAC MANIFESTATIONS INCLUDED IN 2010 DIAGNOSTIC CRITERIA[4]

- Dilation of the ascending aorta with a z-score greater or equal to 2, with or without aortic regurgitation, and involving at least the sinuses of Valsalva
- Dissection of the ascending aorta
- Mitral valve prolapse (MVP) with or without mitral regurgitation

OTHER CARDIAC FEATURES THAT MAY BE SEEN

- Dilation of the main pulmonary artery
- Calcification of the mitral annulus
- Primary dilation and/or dissection of the descending thoracic or abdominal aorta (approximately 10% of the Marfan population)
- Tricuspid valve prolapse

IMAGING STUDIES

- Standard chest radiograph is **inadequate** to detect aortic root enlargement[5]

- Initial evaluation should include two-dimensional echocardiogram to determine aortic diameter, which is measured at the sinuses of Valsalva and related to normal values based on age and body surface area[1,3,6]
- Two-dimensional echocardiograms should be performed at least annually. A six monthly interval between echo exams is recommended for the following:
    - After initial visit, unless the aorta has been documented to be stable in size
    - Aortic dimension change since last evaluation
    - Absolute size of aorta >4.5 cm
    - Severe valvular regurgitation
- Either magnetic resonance angiography (MRA) or multi-detector row computerized tomography (MDCT) are excellent modalities to image the entire thoracic and abdominal aorta[2,7]
- Transesophageal echocardiography (TEE) is useful for evaluation of aortic root, the descending aorta, and cardiac valves.
    - Serial TEE imaging is generally not routinely performed for aortic surveillance because the procedure is invasive and requires sedation
- Routine CTA or MRA imaging of the entire aorta is recommended if:[1,3]
    - The descending thoracic aorta, arch, or abdominal aorta are enlarged
    - The aorta has dissected
    - The aortic root and extent of aortic enlargement are not adequately visualized by transthoracic echocardiogram
    - Periodic imaging of the descending and abdominal aorta may be considered to evaluate for the presence of distal aortic aneurysm disease
- After aortic root surgery
    - Annual CTA or MRA imaging of the thoracic aorta is generally recommended
    - More frequent imaging is recommended if the enlarged aortic segment demonstrates progressive dilatation, if aorta >4.5 cm, unless documented to be stable at that size
- After aortic dissection
    - Long-term imaging of the aorta following aortic dissection is necessary to evaluate for progressive aneurysmal enlargement of the remaining aortic segments and to detect any complications
    - Typical imaging protocol following aortic dissection may include MRA at 1–3 months, 6 months, 12 months, 18 months, 24 months, and yearly[8] thereafter (more frequent imaging may be performed depending upon the aortic diameter and rate of growth)
- Accurate measurements of the aortic diameter, perpendicular to its walls, with comparison to prior studies of aortic dimension and body surface area are critical

MEDICAL MANAGEMENT OF MARFAN SYNDROME

- It is recommended that medical therapy utilizing adequate dosages of either a beta blocker or angiotensin receptor blocker (ARB) be initiated at the time of diagnosis of Marfan syndrome with the goal of reducing the rate aortic root dilation. Doses suggested are those given in randomized trials.
- The recent NHLBI Pediatric Heart Network trial[9,10] demonstrated equivalence of therapy with atenolol or losartan regarding aortic root growth rate and clinical outcomes in children and young adults with Marfan syndrome who had significant aortic dilatation (mean aortic root z-scores at enrollment of 4.2 and 4.4, respectively). Both treatment arms were associated with a decline in aortic root z-score over time (-0.141±0.013 and -0.116±0.013 z/year, respectively) with both slopes significantly different from 0.00 ($p<0.001$ for both arms) at the doses being tested.
- A notable difference from previously suggested medical therapy is the higher dose of atenolol that is currently being recommended. Based on trial results, atenolol should be uptitrated based on hemodynamic response to a maximum dose of 4 mg/kg/day (not to exceed 250 mg/day) with a goal of a 20% or greater decrease in mean heart rate measured on a 24-hr recording. This high dose of atenolol is generally well tolerated.
- Alternatively, in patients with contraindications to beta blockade, angiotension receptor blockers provide a similar amount of protection against aortic enlargement. Losartan should be started at an initial dose of 0.4 mg/kg/day and increased based on weight to a maximum dose up to 1.4 mg/kg/day, not to exceed 100 mg.
- Since the trial data provides evidence that in younger patients both drugs are associated with a greater decrease in aortic-root z-score over time, beta blockers or angiotension receptor blockers should be prescribed at the time of diagnosis even in the youngest children. Therefore, it is recommended that once a diagnosis is made, with or without aortic dilation, medical therapy should be started, maintained and continued after surgery indefinitely.
- For patients with an established descending or abdominal aortic dilation or dissection, aggressive blood pressure control should be maintained (aim for BP 120/80 or less if tolerated among with frequent imaging to document stability/instability of aorta (see imaging recommendations).
- Based on the patient's history, individualized treatment plans must be developed when deciding on which medical therapy to utilize (beta blocker [atenolol] or ARB [losartan]). However, since the NHLBI trial only investigated monotherapy of either atenolol or losartan that is the only evidenced based recommendation that can be made at this time. There are other ongoing trials which may provide additional information about combination therapy with both ARB drug and beta blocker. A meta-analysis of all worldwide trials of beta blocker and ARB therapy in Marfan syndrome[11,12] will be performed, and may provide additional evidence regarding optimal therapies.
- There has been a small study of ACE-inhibitor therapy in Marfan syndrome; more information is needed before recommending the use of this class of agents for the prevention of aortic disease in Marfan syndrome.[13]

SURGICAL MANAGEMENT OF AORTIC DILATION

- Prophylactic replacement of dilated ascending aorta when size threshold is reached[3,13,14,15]
- Determination of size threshold for aortic root replacement in Marfan syndrome
    - For aortic dimension greater than or equal to 5 cm, prophylactic aortic root replacement is recommended in patients with Marfan syndrome
    - Consider prophylactic aortic root replacement when aorta is 4.5–5 cm if aortic valve-sparing procedure is an option
    - Other factors that may significantly influence timing of aortic surgery are:
        - Rate of growth greater than 0.5 cm per year
        - Presence of severe aortic regurgitation (AR) or worsening AR over time
        - Family history of dissection, especially if dissection occurred at aortic dimension less than 5 cm
        - Need for another cardiac operation, such as mitral valve repair for mitral valve prolapse and regurgitation
- Prophylactic aortic root replacement carries a risk of 1 to 2 percent operative mortality at experienced centers[8]
- Surgical options include composite valve graft using mechanical valve, valve-sparing root replacement procedure, and bio-prosthetic/tissue valve composite graft[8,16–19]
    - Composite mechanical valve graft has excellent durability, but carries the risks of anti-coagulation, thromboembolism, and endocarditis
    - Valve-sparing root replacement procedures are available for most patients if the aortic valve is functioning normally. The major risk is re-operation due to leaking of the aortic valve in the future, as long-term durability of repair is not known.
- Medical therapy with beta-blocker or ARB should be continued after surgery indefinitely
- One may consider also using ARB therapy such as losartan after aortic root replacement surgery. One study reported that after root replacement, patients taking losartan in addition to standard therapy (beta blocker) had a slower growth of the aortic arch than those on standard therapy (beta blocker) alone.[11]
- After repair of ascending aorta, one must follow the distal aortic segments over time for late-onset aneurysm formation
- Patients who have undergone valve surgery require endocarditis prophylaxis (see Guidelines on Endocarditis Prophylaxis)

SURGICAL INDICATIONS FOR DESCENDING/ABDOMINAL AORTIC REPAIR INCLUDE[1]

- Change in size is sudden and exceeds 0.5 cm in a year

- When aorta exceeds 5.0–6.0 cm, or twice diameter of contiguous normal aorta
    - The increased risk of complications related to elective descending thoracic aortic surgery and the lower risk of death related to descending aortic dissection compared to ascending aortic disease explains the rationale for intervention of the descending thoracic aorta at a larger size

ENDOVASCULAR STENT-GRAFTING OF THE AORTA[1,20,21]

- Data on stent-grafts (TEVAR) in patients with Marfan or other related connective tissue disorders is limited. Therefore, there is insufficient information available to guide decisions regarding its safety and efficacy in people with these conditions.
- There is limited information regarding the impact of persistent radial forces of the stent-graft in the abnormal aortic tissue in patients with Marfan syndrome. Although stent grafting in patients with Marfan syndrome—who have chronic aortic dissections—is feasible, post-intervention surveillance confirms that the aorta continues to expand despite successful endograft deployment, even when the false-lumen is thrombosed.[20,21]
- Marfan syndrome and related connective tissue disorders remain a contraindication for stent-graft repair in all FDA investigational device exemption protocols
- Endovascular stent-grafts have been used successfully by experienced operators when surgical graft landing zones are present proximally and distally to anchor the endograft, and in the setting of life-threatening emergencies, such as aortic rupture

MEDICAL MANAGEMENT OF CHILDREN

- Beta-blockers or losartan are prescribed at the time of diagnosis (see above)
- Careful monitoring of dose is necessary during rapid body growth
- Reduced or divided dosing or substitution with an ARB can be considered when complications due to aggravation of asthma or lethargy-induced interference with learning are associated with beta-blockers[1]

SURGICAL MANAGEMENT OF CHILDREN[1]

- Symptomatic MVP with mitral regurgitation is a leading indication for cardiovascular surgery in a pediatric population
- Both composite graft repair and the valve-sparing procedure have shown good results in children with Marfan syndrome[19]
- Indications for aortic root replacement in the pediatric population include:
    - Rapid ascending aorta growth rate (>1 cm per year)
    - Significant aortic regurgitation
    - Need for mitral valve or other cardiac surgery in a patient with substantial aortic enlargement
- Use adult criteria when assessing the need for surgery in adolescents

MANAGEMENT OF PREGNANT WOMEN

- All pregnancies should be considered **high risk** and multi-disciplinary evaluation is required (cardiologist and high risk obstetrician)
- Risk of dissection is lower if the aortic root diameter is less than 4.0 cm[22]
- Beta-blockers should be continued during pregnancy and continued after delivery because of heightened risk of dissection post-partum
- Losartan cannot be taken during pregnancy. The drug influences kidney development in the developing fetus and is related to an increased risk of fetal loss.
- One may consider gradual tapering of losartan dosage to off over several weeks before planned pregnancy/conception
- Echocardiograms are recommended at least once during each trimester of pregnancy and once during the two months following pregnancy
- For pregnant women with aortic dilation, the 2010 Thoracic Aortic Disease guidelines[8] recommend monthly to bimonthly echocardiograms during pregnancy
- Surgical repair for substantial aortic root dilation should be done pre-partum whenever possible

ACTIVITY/LIFESTYLE MODIFICATIONS

- Competitive and collision contact sports are contraindicated.[23]
- Static (isometric) exercise is contraindicated (i.e., avoid heavy weight lifting, gymnastics, and pull-ups)
- Certain dynamic (isokinetic) exercise at decreased level of intensity is permitted with individualized heart rate limits used to determine acceptable intensity
- Exercise should be individually determined with particular attention to variation in intensity, even in the same type of activity, among different people
- Endocarditis prophylaxis is recommended for patients as advised by the ACC/AHA guidelines on endocarditis prophylaxis. Patients with a history of mitral or aortic valve surgery should receive antibiotic prophylaxis before certain procedures. Whether or not Marfan patients with mitral valve prolapse (MVP) also benefit from endocarditis prophylaxis is not known.

RELATED CONDITIONS ASSOCIATED WITH AORTIC ROOT ANEURYSM AND DISSECTION

- Bicuspid aortic valve[24–26]
    - Present in 1 percent of the population with significant proportion having aortic dilation
- Familial thoracic aortic aneurysm and dissection[27–32]
- Loeys-Dietz syndrome[33–36]
- Vascular Ehlers Danlos syndrome[37]

- Shprintzen Goldberg Syndrome[38]
- MASS
- Mitral valve prolapse

EVALUATION OF FIRST-DEGREE RELATIVES

- Screening of all first-degree relatives of people with Marfan syndrome, bicuspid aortic valve, or familial thoracic aortic aneurysm and dissection is warranted because of genetic predilection for aortic root and or ascending aortic aneurysm
- Screening should involve aortic imaging if the genetic testing has not been performed or the gene has not been identified

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