The Cardiac Society of Australia and New Zealand

Update on the diagnosis and management of inherited aortopathies, including Marfan syndrome

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It was reviewed by the Quality Standards Committee and ratified at the CSANZ Board meeting held on Friday, 25th November 2016.

KEY POINTS:

1. A number of inherited conditions can predispose the aorta, and less commonly other blood vessels, to dilatation and/ or rupture

2. Broadly speaking, these conditions are recognised as syndromic when accompanied by a number of systemic features or non-syndromic when the aortic dilatation appears to exist in isolation

3. The commonest syndromic aortopathy is Marfan syndrome and the commonest non-syndromic aortopathy is that which accompanies congenital bicuspid aortic valve

4. Mutations in a number of genes have been identified, particularly in syndromic aortopathy

5. Although genotype-phenotype relationships exist, the phenotypes of the syndromic aortopathies may have significant overlap

6. When a syndromic aortopathy is suspected review by a clinical geneticist is instrumental in characterising the clinical signs and the family history

7. Confirmation of a diagnosis (either clinically or by gene testing) allows identification of individuals at increased risk of aortic sequelae who will benefit from active medical management

8. Medical management is usually undertaken by a cardiologist with referral to other specialists (eg cardiothoracic surgeons) as appropriate

9. At risk family members should be offered predictive testing if a mutation is identified, and should otherwise be screened in keeping with the presumptive clinical diagnosis and assessment of risk

10. Pregnancy and the post-partum period confer a higher risk for aortic complications.

    a. Women with a personal or family history of aortopathy need appropriate pre-conception screening and counseling.

    b. Intervention may be required pre-conception and they should be managed closely throughout pregnancy, ideally in a high-risk obstetric clinic.

    c. Management may include appropriate cessation and commencement/ continuation of medication ((ACE inhibitors and ARB are teratogenic and contraindicated in pregnancy, beta blockers can be used in pregnancy) and should include involvement of a cardiologist in the management and decision making for delivery

11. A clinical diagnosis of an inherited aortopathy can be made in the absence of a positive genetic test if the systemic features are consistent with a specific syndromic aortopathy. A familial history of aortic dissection in the absence of both a positive gene test and systemic examination findings may be more difficult to manage without a working clinical diagnosis. However, an inherited risk of dissection should nonetheless be considered in this setting, particularly if the process has affected young individuals and/or in the absence of traditional risk factors.

INTRODUCTION

The aortopathies encompass a number of conditions that result in an aorta that is structurally more susceptible to both dilatation and/ or dissection. There is no accepted definition for the term and it is broadly applicable to both inherited and acquired conditions. This update concentrates on the inherited syndromic and non-syndromic aortopathies. Acquired thoracic and abdominal aortic aneurysm and dissection occur particularly in the elderly; are associated with cardiac risk factors, especially hypertension and cigarette smoking, and not considered further in this document [1-3]. This update is intended as an overview, not an exhaustive literature review. Where guidelines exist, regardless of the often-limited evidence base, these will be recommended. Extensive discussion of each condition is also beyond the scope of the update and interested readers may find the references a useful resource.

CLINICAL CHARACTERISTICS

1.   Syndromic aortopathies

This term includes and this update will briefly discuss Marfan syndrome (MFS); Turner syndrome (TS); Loeys Dietz syndrome (LDS); Ehlers-Danlos, particularly type IV (vascular subtype); and arterial tortuosity syndrome (ATS).

Most of these conditions are characterised by autosomal dominant inheritance. Turner syndrome is due to sex chromosome aneuploidy with the loss of one of the X chromosomes (45,X). ATS is a rare autosomal recessive condition.

2.   Clinical presentation

The most serious complication of an aortopathy is an aortic dissection. Aortic dissection due to an underlying heritable disorder (whether syndromic or non-syndromic) presents in the same way as aortic dissection in the general community. Guidelines are available regarding investigation, diagnosis and treatment of this potentially life-threatening complication [4].

Consideration of an underlying heritable disorder should be given particularly in the setting of occurrence at a young age (<50), dissection during pregnancy or post-partum, when clinical examination uncovers clinical signs in keeping with one of the syndromic conditions (see below), or when there is a family history of dissection. A positive family history is an important clue. Taking a full family history is an essential part of clinical care, including following an emergent presentation.

The conditions that cause syndromic aortopathies may present to the clinician in a variety of other clinical settings reflecting other affected organ systems. It is important to note that the clinical features described below can occur in a spectrum from mild to severe, and a clinical cardiac genetic service may be best placed to make a detailed assessment of the patient and family.

SYNDROMIC AORTOPATHIES

1.   Marfan syndrome (MFS)

This is the best known and characterised inherited aortopathy. It is also the one most often genotypically positive in the setting of clinically diagnostic features. The revised Ghent Criteria [5] (see Table 1 below) allows a diagnosis to be made according to the presence or absence of family history and taking into account the aortic root size, ectopia lentis, a number of systemic features and the identification of an *FBN1* mutation.

Table 1: Revised Ghent Criteria for diagnosis of Marfan syndrome (MFS) (see original article for description of differential diagnoses [5])

	No family history (a)	Family history (b)
Diagnosis of MFS	1. AoD (Z ≥ 2) and EL = MFS 2. AoD (Z ≥ 2) and FBN1 = MFS 3. AoD (Z ≥ 2) and Syst ≥ 7 = MFS 4. EL + FBN1 + known AR = MFS	1. EL + FH* MFS = MFS 2. Syst ≥ 7 = MFS + FH* MFS = MFS 3. AoD (Z ≥ 2 if adult, Z ≥ 3 if < 20 yoa + FH* MFS = MFS
	Clinical sign	**Score**
Systemic (syst) features and scores for each feature (maximum 20)	1. Wrist + Thumb sign	3
	2. Wrist OR Thumb sign	1
	3. Hindfoot deformity	2
	4. Flat feet	1
	5. Pneumothorax	2
	6. Myopia (> 3 dioptres)	1
	7. Mitral valve prolapse	1
	8. Facial features (≥ 3/5) (dolicopcephaly, enopthalmus, downslanting palpebral fissures, malar hypoplasia, retrognathia)	1
	9. Pectus carinatum	2
	10. Pectus excavatum or chest asymmetry	1
	11. 11. Reduced US/LS AND increased AS/Ht (in the absence of severe scoliosis)	1
	12. Scoliosis, thoracolumbar kyphosis	1
	13. Reduced elbow extension	1
	14. Skin striae	1
	15. Dural ectasia	2
	16. Protrusio acetabuli	2

FH* = Family history of MFS, where diagnosis fulfils criteria in column titled (a)

AoD = aortic root dilatation

Z = Z-score, derived from the internet z score calculator: http://www.marfan.org

Syst = systemic features

EL = ectopia lentis

FBN1 = *fibrillin-1* mutation

yoa = years of age

US/LS = upper span: lower span ratio

AS/Ht = arm span: height ratio

2.   Loeys Dietz syndrome (LDS)

LDS was described recently, and clinically may appear as MFS or a marfanoid-like condition. It is now understood to be a clinical continuum due to dysregulation of TGF beta (TGFβ) signalling. Clinical features are present in the vascular, skeletal, craniofacial and cutaneous systems [6]. The vascular disease is widespread and manifests as arterial tortuosity, aneurysm formation and dissection. Early reports suggesting almost ubiquitous aortic root dilatation likely reflect ascertainment bias [6]. Skeletal involvement overlaps with the skeletal features of MFS and additionally may manifest as early onset osteoarthritis. Craniofacial features include hypertelorism, bifid uvula (see Figure 1), cleft palate, craniosynostosis and structural brain anomalies. Intellectual disability has been reported in severely affected children. Cutaneous features include hyperelastic and/or translucent skin, easy bruising and dystrophic scars.

Figure 1: Bifid uvula

(Image taken with patient consent)

3.   Ehlers Danlos syndrome (EDS)

The Ehlers Danlos syndromes are characterised by joint hypermobility, skin hyperextensibility and tissue fragility [7]. EDS Type IV (vascular subtype), is associated with rupture of organs and normally sized blood vessels, including the aorta [8]. Clinically, important clues are a history of an arterial/ intestinal/ uterine rupture, incidentally noted organ tissue fragility at operation and extensive easy bruising and translucent (thin) skin. Guidelines recommend surgical intervention in EDS Type IV only in the setting of life-threatening complications due to the increased surgical risk [4]. Aortic dilatation has been reported in the classic and hypermobile subtypes. However, most subtypes of EDS are a more benign condition with respect to aortic dissection risk [9]. The rarer (autosomal recessive) kyphoscolitic subtype of EDS has also been associated with vascular rupture[8].

4. Arterial tortuosity syndrome (ATS)

This is a very rare condition with marfanoid appearance, cutis laxa, hyperelastic soft skin, joint hypermobility and dislocations and herniae. Imaging reveals more widespread and tortuous involvement of the arterial tree [10].

5. Turner syndrome (TS)

TS is characterised by a woman of short stature who may present with delayed puberty and either reduced fertility or infertility. The incidence of bicuspid aortic valve (BAV) and coarctation of the aorta, as well as hypertension, are overrepresented in these women [11, 12].

6. Other

A number of other genetic syndromes have been reported in association with aortic disease, including but not limited to: Weill-Marchesani syndrome (*ADAMTS10* and *FBN1*)[13]; congenital contractural arachnodactyly (resembles MFS, is characterised by crumpled ears, scoliosis, joint contractures and *FBN2* mutations)[14]; Noonan syndrome (mutations in the RAS–MAPK signaling pathway) [15, 16]; Alagille syndrome (*JAG1*)[17] ; X-linked dominant periventricular nodular heteropia, EDS variant (*FLNA*)[18] and Shprintzen-Goldberg syndrome (*SK1*) [19].

1.2 Non-syndromic thoracic aortic aneurysms and dissection (TAAD)

Non-syndromic TAAD is recognised by the clustering of aortic sequelae in a family [20]. By definition, the clinical phenotype is otherwise normal. To date, mutations in these families have been identified in a number of genes (see Table 1, below). The proportion of families who will have an identifiable genetic mutation is unknown. Therefore, a positive family history is always significant even in the absence of a putative gene mutation.

1.3 Bicuspid aortic valve associated aortic aneurysm and dissection

Bicuspid aortic valve is the commonest condition in our community (1% prevalence) that can develop aortic dilatation and aneurysm formation (approximately 20-30% of subjects with BAV [21]). Though usually a sporadic finding, it can be inherited [20, 22], and thus guidelines recommend echocardiographic screening first-degree relatives to determine whether the aortic valve is bicuspid or tricuspid [23].
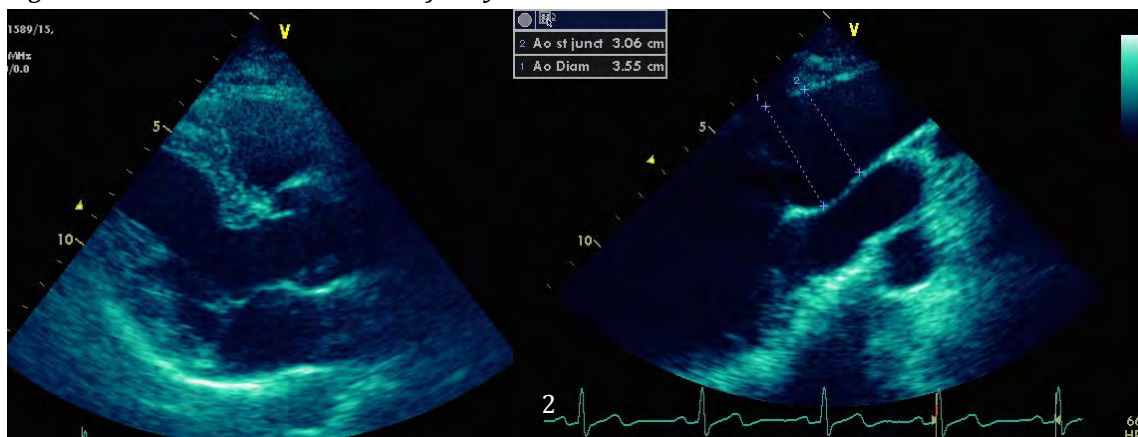
1.4 Clinical diagnosis

Ideally, consideration of an inherited aortopathy should prompt referral to a clinical or cardiac genetics service for a thorough specialised examination. Standardised examination protocols exist for determining the likelihood clinically of MFS [5] and EDS [24].

Assessment of the aortic root and ascending aorta is essential if there is clinical suspicion of an inherited aortopathy. Aortic root involvement is classically seen in MFS and EDS, but may also occur in the other syndromic aortopathies (Fig 1). The ascending aorta is the usual site of dilatation in BAV, TS and the non-syndromic aortopathies, but also may occur in other conditions, including MFS (Fig 2). Abdominal aortic aneurysms have been reported in both MFS and LDS. Involvement of vasculature throughout the body, including cerebral vessels, occurs in LDS [6, 25].

Clinical symptoms in other vascular beds should lead to directed imaging. Once a diagnosis of syndromic subtype is made, then imaging will need to be considered accordingly (see management). It appears prudent to image the entire aorta, though no evidence regarding the optimal interval between screening is available.

Involvement of other specialists will need to be considered on a case-by-case basis according to the likely diagnosis.

Figure 1 Dilated aortic root in Marfan syndrome

Transthoracic echocardiography long axis parasternal view showing a dilated aortic root (4.2 cm) in a 23 year old woman with a clinical diagnosis of MFS, awaiting genetic results (1) and a borderline dilated aortic root with a normally sized ascending aorta (2) in a woman with both clinical and genetic diagnosis (note the off axis imaging required in the setting of chest wall abnormalities).

Figure 2 Dilated ascending aorta associated with a bicuspid aortic valve
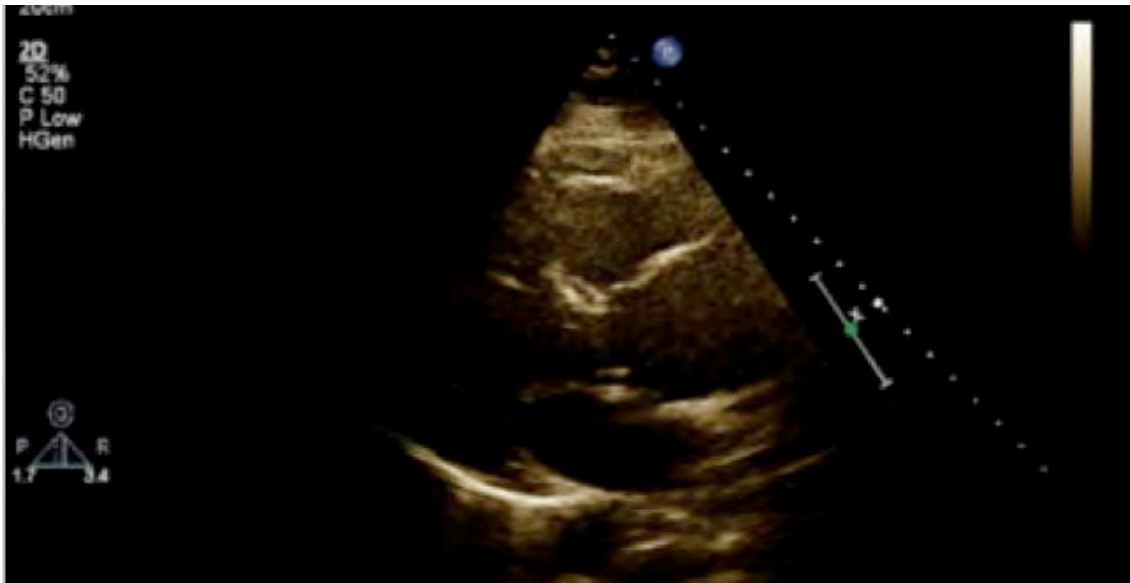
Transthoracic echocardiography long axis parasternal view showing a dilated ascending aorta (5.0 cm) in the setting of a bicuspid aortic valve with mild stenosis (mean gradient 13 mmHg) in a 40 year old woman. Note the relative preservation of the aortic sinus compared to the dilatation seen with MFS.

1.5 Family history

A detailed (three generation pedigree) family history is essential. A reported clinical or genetic diagnosis in a family member should be verified by obtaining relevant documentation, with consent as appropriate.

2.0 Molecular genetics

Molecular confirmation of a suspected clinical diagnosis is increasingly important for guiding patient management. As an example, an individual who looks marfanoid will have more extensive arterial imaging screening if identified to have a *SMAD3* mutation as opposed to an *FBN1* mutation.

2.1 Overview

Table 2 lists the genes identified most commonly for specific clinical phenotypes. The genotype-phenotype relationship is not absolute. Mutations in the same gene can cause variable clinical phenotypes. Fulfilment of the modified Ghent criteria does not necessarily imply a diagnosis of MFS, as patients with LDS may fulfil these criteria as well.

Table 2: Gene(s) most commonly identified for the different clinical 'classical' aortopathy diagnoses

Condition	Gene	Reference
Marfan syndrome	*FBN1*	[26]
Loeys-Dietz syndrome	*TGFBR2*	[25]
	TGFBR1	
	SMAD3	
	TGFB2	
Ehlers Danlos syndrome (vascular subtype)	*COL3A1*	[27]
Arterial tortuosity syndrome	*SLC2A10*	[10]
Non-syndromic TAAD (*Mutations in many of the genes identified in this table as causing syndromic aortopathy have also been identified in cases of non-syndromic aortopathy*)	*ACTA2*	[28] [29] [30]
	MYH11*	
	PRKG1	
	MYLK	
Bicuspid aortic valve#	*NOTCH1^*	[22]

* May be associated with a patent ductus arteriosus

Non-syndromic TAAD genes have been identified in individuals with BAV and aortic dilatation

^ Accounts for a small proportion of patients with BAV

2.2 Genetic testing

A definitive molecular genetic diagnosis can clarify an equivocal clinical picture or result in a diagnosis in an apparently phenotypically normal individual. It is unknown at this stage what proportion of patients with these different genetic mutations will develop aortic dilatation or dissection. Identification of a causal mutation allows for the provision of accurate genetic counselling, the screening of at-risk family members and offers the possibility of accurate prenatal or preimplantation genetic diagnosis.

2.2.1 Sanger sequencing of individual candidate genes

Sanger sequencing may be considered when there is no doubt about the clinical diagnosis. Despite clinical certainty however, a pathogenic mutation may not be found. Typically, exonic or whole-gene deletions and/or duplications are not detected by this method and require alternative technology e.g. quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes the relevant gene/chromosome segment. There are intrinsic hurdles, not least of all cost, of Sanger sequencing of consecutive candidate genes compared to multi-gene panel testing.

2.2.2 Multi-gene panels

Many clinical laboratories offer a multi-gene MFS/LDS/familial TAAD panel that includes *FBN1* and numerous other genes associated with aortic aneurysm and dissection disorders. This approach may be advantageous, given the known clinical and genetic heterogeneity of these disorders.

2.2.3 Limitations of genetic testing

It is important to recognise that no testing method guarantees a molecular diagnosis. The described limitation of Sanger sequencing to detect deletions and/or duplications may also occur in panel testing and should be discussed with the testing laboratory as appropriate. Both methodologies described above may result in the finding of a variant of uncertain/ unknown significance (VUS). Ideally, family studies to track the VUS genotype with phenotype may assist with clarification. Practically, however, this can prove difficult. Whilst functional studies to determine the molecular effect of the mutation may assist in interpretation of a VUS, these studies are not readily available.

3.0 Management

3.1 Affected individuals

Management of acute dissection is not dealt with in this document. Broadly speaking, management of patients at risk of aortic dilatation and dissection falls into the following categories:

1. Consideration of medical therapy
    a. There is data regarding medical prophylaxis of aortic dilatation, largely limited to individuals with MFS

    b. A number of trials have shown a positive effect on reducing aortic growth with the use of beta-blockers, angiotensin receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEI) [31, 32]. We are not aware of currently available data regarding the effect of medical therapy on mortality.

    c. Superiority of a medication class has not been established, and treatment should be individualised as tolerated. Future recommendations may suggest concomitant use of more than one class of medication.

    d. It is unknown whether clinicians should aim for the dose used in trials or measure effect on a physiological variable (e.g. heart rate at submaximal exercise) or both.

2. Surveillance for aortic dilatation
    a. Usual practice is clinical review with yearly echocardiogram in MFS

    b. 6 monthly echocardiogram if the aortic root is either close to surgical threshold or has increased significantly in size between prior imaging interval ($\geq$ 0.3 cm/year)

    c. If there is significant valvular disease (eg aortic or mitral regurgitation), then imaging frequency may be further individualised

    d. CTA or MRI of the entire aorta should be undertaken in MFS. The interval for repeat screening of a normally sized aorta is not stipulated in most publications [4, 5, 23]. The ESC Grown Up Congenital Heart Disease Guidelines suggest this be done on a 5 yearly basis [33]. More recent ESC and AHA multimodality imaging guidelines suggest a 3 yearly interval, but this statement is unreferenced in the document [34]. If relatively frequent serial imaging is to be undertaken, MRA may be preferable to CTA in order to minimise the risks associated with recurrent radiation exposure.

    e. CTA or MRA of the entire vasculature (cerebral to pelvic) should be undertaken in the syndromic aortopathies where more widespread vascular involvement has been documented e.g. LDS, ATS. The interval has been suggested to be 1 year in the first instance and then at least 2 yearly for LDS [25], though earlier recommendations had been for yearly MRA [23]. Abnormal results should translate into an increased screening frequency and referral as appropriate.

    f. The clinical picture of non-syndromic aortopathies remains to be fully elucidated, and therefore the optimal extent and frequency of vascular imaging is unclear. We would err on the side of caution and suggest imaging the entire vasculature, at least at baseline, in non-syndromic individuals with a genetic mutation.

    g. The extent of imaging that should be undertaken in non-syndromic individuals in whom genetic testing is uninformative is unknown.

3. Guidelines for aortic surgery

    a. Current guidelines recommend consideration of aortic surgery at varying thresholds. These are reproduced in table 3, below. Recommendations for the general population are included as a comparator.

    b. A lower threshold than in the guideline [4] has been proposed for women with TS. Data on 20 individuals with both TS and dissection (n = 17 Type A, of which n = 16 also had a BAV) proposed a lower cut off at > 25mm/m^2 [35].

    c. Data exists in an unselected population with thoracic aneurysms linking an increase in indexed aortic size (adjusted to body surface area) to risk of rupture and the combined endpoint of rupture, dissection and death [36].

Table 3: Guideline recommendations for surgical intervention

Surgical intervention recommended	ESC 2014 [4]	AHA 2010, 2014* [23, 37]
MFS	≥ 50 mm ≥ 45 mm[1]	> 50 mm[4] > 40 mm if contemplating pregnancy
LDS	Treat patients with marfanoid manifestations as per MFS thresholds	≥ 42 mm (TTE) ≥ 44 – 46 mm (CT)
TS	> 27.5 mm/m² *(NB other data suggests a cut off of > 25mm/m² should be utilised, see above)*	4.0 – 5.0 cm (not separated out in 2010 guideline from other conditions)
Non syndromic aortopathy	No specific data[2]	No specific data
BAV	≥ 55 mm	4.0 – 5.0 cm (not separated out in 2010 guideline from other conditions)
	≥ 50 mm[3]	2014* > 55 mm
		> 50 mm[5]
		> 45 mm[6]
General population	≥ 55 mm	≥ 55 mm

[1] = Risk factors: family history of dissection, size increase > 3mm/y, severe aortic regurgitation (AR) or mitral regurgitation, desire for pregnancy

[2] = Document suggests management according to family history

[3] = Risk factors: family history of dissection, hypertension, coarctation of the aorta, size increase > 3mm/y

[4] = Repair if family history of aortic dissection at < 50 mm, severe AR or rapid growth >5 mm/y

[5] = Risk factors: family history of dissection, growth ≥ 5 mm/y

[6] = If having surgery for severe AS or AR

    d. The potential role of pre-emptive and protective surgery, utilising a Personalised External Aortic Root Support (PEARS) polymer mesh, remains to be established [38]. This procedure currently appears to be available only in the UK and Belgium.

4. Associated complications and appropriate intervention

    a. Apart from aortic complications, the inherited aortopathies may result in a number of other health issues, which require referral to the appropriate specialty

5. Advice regarding exercise restriction

    a. Exercise carries risk to the aorta, therefore recommendations exist about

       i.   Avoiding participation in competitive sports or undertaking strenuous or highly exertive exercise in patients with a diagnosis of a syndromic aortopathy and in individuals with a dilated aorta [4] and

      ii.   Avoiding heavy weight lifting (requiring straining) in all individuals with a diagnosis of a syndromic or non-syndromic aortopathy or with a dilated aorta or a prior dissection [23, 39].

b. It is unknown whether patients who have a non-syndromic aortopathy diagnosis and a normal size aorta should be given the same advice, though this may be a reasonable approach

c. A comprehensive table for patients is available in an article by Maron et al, which outlines advice regarding different types of exercise in MFS [23, 40].

d. Some clinicians exclude patients from contact sport with a risk of collision [23]. This is recommended by the latest guidelines (see point e., below)

e. A recent AHA/ACC Scientific Statement has been published regarding exercise advice to competitive athletes with aortic diseases [41]. Although the introductory statement explains that the guidelines apply to competitive sports, and may not apply to those engaged in recreational activities, it is not entirely clear how these groups are defined

6. Pregnancy and the post-partum period confer a higher risk for aortic complications. Women with a personal or family history of aortopathy need appropriate pre-conception screening and counseling. Although the effect of pregnancy on the aorta may be mediated by female sex hormones, there is no known contraindication to available hormonal or non hormonal contraceptives for women with aortopathy. Prenatal or preimplantation genetic diagnosis is available if there is an identified mutation. Aortic intervention may be required pre-conception and these women should be managed closely throughout pregnancy, ideally in a high-risk obstetric clinic, with a multidisciplinary team. Management may include appropriate cessation and commencement/ continuation of medication ((ACE inhibitors and ARB are teratogenic and contraindicated in pregnancy, beta blockers can be used in pregnancy). A cardiologist should be involved in the management and decision making for delivery.

7. Advice regarding other lifestyle factors [4]
- Cessation of smoking is essential

- Prompt identification and treatment of hypertension
- Advise against use of cocaine

3.2 Asymptomatic family members

Aortic disease tends to be asymptomatic until a complication (usually dissection) occurs. Family members should be assessed as to whether they are at risk. This will depend on the family history, the biological relationship with the affected individual and whether a clinical diagnosis plus or minus a genetic diagnosis has been made in the proband.

If there is a clear genetic diagnosis, then first-degree relatives should be offered predictive testing. If the screened relative does not have the familial mutation they can be released from screening.

We advocate erring on the side of caution with respect to screening echocardiography of at-risk relatives. This is advised in

1. All family members who share the familial mutation and who therefore should be under clinical care, not screening,

2. At-risk family members where a clinical genetic diagnosis exists and

3. At-risk family members where no clinical genetic diagnosis is made but the dissection occurred in a young individual without an apparent risk factor e.g. long standing hypertension.

Current guidelines recommend a screening interval of 5 years in healthy at-risk relatives. Additionally, consideration of wider screening of the arterial tree in non-syndromic aortopathy is recommended, although no advice is given regarding frequency of more extensive arterial imaging [4].

3.3 Genetic counselling and psychological counselling

Genetic counselling is important for any family where a familial diagnosis is being considered. The circumstances in which the diagnosis was first raised can influence the way in which the family copes with diagnostic confirmation and the possibility of genetic testing. As aortic dissection can be unexpected and cause the rapid demise of a previously well young individual, there may be significant issues of grief, guilt and loss. Health and travel insurance, and career options may all be impacted by confirmation of an aortopathy diagnosis. The genetic counsellor is well placed to be an initial source of support and may liaise with other counsellors or psychologists to provide ongoing support.

3.4 Pre-natal and preimplantation genetic diagnosis (PND and PGD)

Prenatal and pre-implantation diagnosis is available when a definite genetic mutation is identified as causative of the aortopathy syndrome in the proband. Individuals with genetic changes that are not definitively pathogenic (e.g. VUS) cannot be offered PND or PGD. Decision-making regarding PND or PGD is a very personal process, and the role of the clinician is to provide information and obstetric or IVF referral, if appropriate from the genetic point of view, when desired by the patient.

3.5 Unresolved questions

1. The modified Ghent Criteria for MFS state that aortic size should be corrected for age and body size and expressed as a z-score[5]. Imaging guidelines highlight the concerns that indexation consistently allows a greater aortic size in larger individuals [34]. In contrast, surgical thresholds, other than for women with TS, are all expressed as absolute values. In practice, the authors often consider both absolute and indexed size and utilise the most concerning value to determine screening interval. Absolute size, rather than indexed, still guides surgical referral in practice other than in very small adults. There is a lack of consistency between these approaches; hopefully this will be clarified with time.

2. It is likely that further genes causing TAAD will be identified in the future.

3. Ideally, determination of genotype – phenotype correlations will allow individualised risk prognostication and treatment. This will require multinational and multicentre sharing of aortic surveillance and outcome data in a large number of individuals.

4. It is unknown whether a particular class of drug or indeed combination therapy will provide better morbidity and mortality benefit, and whether this will be uniform for all sub-types of aortopathies.

5. It is unknown whether medical therapy should commence at the time of diagnosis, regardless of age and aortic size. Although opinions and practices are by no means uniform nationally or internationally, we are aware that some experts in the field recommend medical treatment of an asymptomatic individual who is mutation positive in a family where another family member with the same mutation has had aortic dilatation and/or dissection.

3.6 Concluding remarks

The aortopathies encompass a group of phenotypically and genetically heterogeneous conditions. This update has described the classical clinical findings, which can be quite variable between and within families. Currently, management of these conditions is impacted by variable expression and penetrance. As such, the prediction of aortic sequelae in any affected individual is not possible. The

finding of a VUS may complicate diagnosis and create challenges both in clinical management and for the patients. Best care requires comprehensive cardiological and genetic evaluations and investigations, with the provision of an appropriate screening plan. Rarely, even despite this, affected individuals may dissect without prior aortic dilatation.

4.0 Further information

1. Available from the references below

2. Marfan support groups exist in Australia and overseas, and can be accessed on the Internet

3. Clinical and cardiac genetic services are available both in Australia and New Zealand for review of patients with a suspected or proven aortopathy diagnosis

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