Circulation: Genomic and Precision Medicine

AHA SCIENTIFIC STATEMENT

Cardiovascular Health in Turner Syndrome

A Scientific Statement From the American Heart Association

ABSTRACT: Girls and women with Turner syndrome face a lifelong struggle with both congenital heart disease and acquired cardiovascular conditions. Bicuspid aortic valve is common, and many have left-sided heart obstructive disease of varying severity, from hypoplastic left-sided heart syndrome to minimal aortic stenosis or coarctation of the aorta. Significant enlargement of the thoracic aorta may progress to catastrophic aortic dissection and rupture. It is becoming increasingly apparent that a variety of other cardiovascular conditions, including early-onset hypertension, ischemic heart disease, and stroke, are the major factors reducing the life span of those with Turner syndrome. The presentations and management of cardiovascular conditions in Turner syndrome differ significantly from the general population. Therefore, an international working group reviewed the available evidence regarding the diagnosis and treatment of cardiovascular diseases in Turner syndrome. It is recognized that the suggestions for clinical practice stated here are only the beginning of a process that must also involve the establishment of quality indicators, structures and processes for implementation, and outcome studies.

Turner syndrome (TS) results from complete or partial absence of the second sex chromosome in either all or part of the cells of an individual. It is the most common chromosomal abnormality affecting females, occurring in 1 in 2500 live-born girls.[1] Characteristic clinical features include short stature, premature ovarian failure, and lymphedema. Early morbidity and mortality are increased in patients with TS compared with the general population and are related mainly to cardiovascular complications.[2] Congenital heart abnormalities occur in up to 50% of individuals, affecting mainly the left side of the heart and including bicuspid aortic valve (BAV), coarctation of the aorta, and thoracic aortic aneurysm. Mortality rates are 3-fold higher in women with TS compared with the general population, with the most common cause of death being cardiovascular disease.[3] Prompt recognition of the signs and symptoms of aortic dissection (AoD) and rupture depends on the awareness that these often-fatal complications occur primarily in young adult women with TS.[4–6]

It is important for healthcare professionals to recognize that hypertension in children with TS and coronary artery disease, myocardial infarction, and stroke in adults with TS[7] are exacerbated by an underlying predisposition to metabolic abnormalities, including dyslipidemia, type II diabetes mellitus, obesity, and hyperuricemia.[8]

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Given this broad spectrum of cardiovascular concerns, girls and women with TS require a continuum of care, counseling, and preventive management through their adult years. The specific management of many cardiovascular conditions, both congenital and acquired, is the same as in the general population. For these conditions, established guidelines should be followed. The purpose here is to highlight the instances in which there are unique cardiovascular risks involved in TS and to provide guidance for their monitoring and management.

WORKING GROUP

In July 2016, the Turner Resource Network hosted an international meeting of experts to make recommendations for the overall management of the numerous conditions affecting girls and women with TS, including cardiovascular health.[9] Attendees included most of the current working group who also contributed to that meeting and presented the suggestions for clinical practice that are reproduced in this document. The working group recognized that further context, details, and justification were needed. The suggestions for clinical practice stated here are the result of a comprehensive review and discussion of >1200 publications* in the medical literature and represent a consensus view based on the literature and practice experience of the working group members. It is understood that these suggestions for clinical practice are only the beginning of a process that must also involve the establishment of quality indicators,[11] structures and processes for implementation, and outcome studies.

In nearly all cases, Turner-specific medical evidence is very limited, especially as it relates to the scientific literature on the aorta. Further clinical and basic research is imperative. The working group's suggestions for clinical practice should be considered from that perspective and not taken as dogma. We view this report as a first step toward improving the cardiovascular health of girls and women with TS. Our plan is to review and revise this work as new evidence accumulates.

CONGENITAL HEART DISEASE

Congenital heart defects occur in 23% to 50% of individuals with TS and are the most frequent cause of early mortality.[12–14] The incidence is higher in individuals with 45X karyotypes compared with X mosaicism or other X structural abnormalities.[15,16] Left-sided obstructive lesions are most common, with a prevalence of 15% to 30% for BAV and 7% to 18% for aortic coarctation. Because BAV is likely to occur 30 to 60 times more frequently in TS than in females with 46,XX, it is possible that BAV in a female may be an independent marker for TS. Cross-sectional imaging modalities have unveiled an increased incidence of additional vascular anomalies that might otherwise have gone undetected by transthoracic echocardiography (TTE), including partial anomalous pulmonary venous connection,[17] left superior vena cava, an elongated transverse aorta, and dilatation of the head and neck arteries.[18,19] Neck webbing and an increased anterior-posterior thoracic diameter have been shown to be strong predictors of arterial and venous anomalies in TS.[20,21] Additional, but less frequent, anomalies include hypoplastic left-sided heart syndrome, mitral valve anomalies, interrupted inferior vena cava with azygous continuation, cardiac dextroposition, ventricular septal defect, atrioventricular septal defect, pulmonary valve abnormalities, and patent ductus arteriosus.[22–24]

Congenital coronary arterial anomalies are prevalent in TS.[25] The left coronary artery is most often affected, with an absent left main coronary artery being the most frequent anomaly.[25] In addition, single cases of coronary arterial anomalies have been reported, which include coronary arterial dilatation, single coronary ostium, coronary arteries originating from the thoracic aorta, and coronary artery–to–pulmonary artery fistulas.[22,26,27] Whether coronary arterial malformations increase mortality risk is unknown. The majority of the encountered coronary arterial anomalies in TS are benign or noninterarterial; however, it is important for the cardiothoracic surgeon to be aware of unusual coronary anatomy because it may necessitate modifications of the operative approach.

Suggestions for Clinical Practice

Diagnosis

- If TS is highly suspected or has been confirmed prenatally, a fetal echocardiogram should be performed. If congenital heart disease is confirmed, then follow-up care by a pediatric cardiologist is recommended to provide counseling on the anatomy and physiology of the specific defect, recommended site and mode of delivery, and postnatal multidisciplinary management plan.
- Diagnosis of a BAV or a left-sided obstructive lesion, whether prenatally or postnatally, in a female patient should prompt genetic evaluation for TS.
- All newly diagnosed individuals with TS should be evaluated by a cardiologist familiar with all aspects of cardiovascular disease seen in TS and undergo the following evaluation:
  - A comprehensive physical examination, including cardiac auscultation and assessment of femoral pulses and 4-extremity blood pressures (BPs), should be performed.

*An EndNote X7 library is available at the website of the Turner Syndrome Society of the United States[10] that contains the >1200 citations that helped to inform this work.

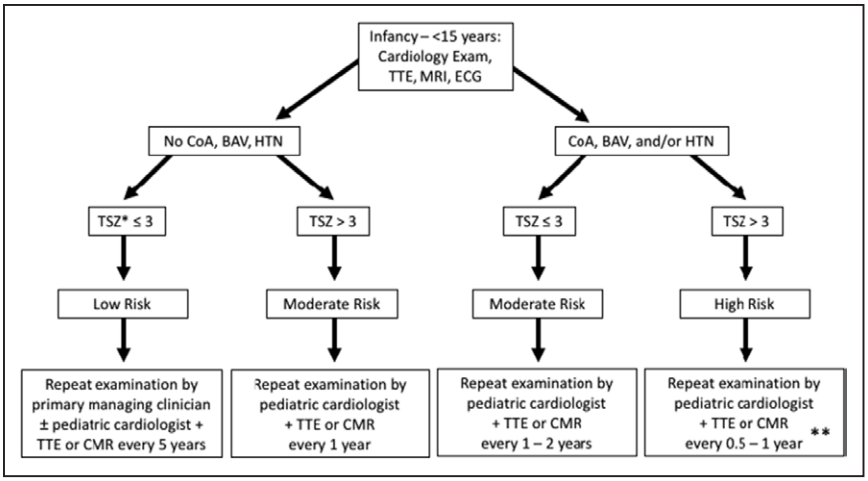

Figure 1. Suggested monitoring protocol for girls with Turner syndrome from infancy to 15 years of age.
BAV indicates bicuspid aortic valve; CMR, cardiac magnetic resonance; CoA, coarctation of the aorta; HTN, hypertension; MRI, magnetic resonance imaging; TSZ, Turner-specific *z* score; and TTE, transthoracic echocardiography. *Ascending aorta TSZ.[28] **It is important to remember that surveillance frequency may change with worse disease severity in terms of obstruction, regurgitation, or left ventricular hypertrophy. Modified from Gravholt et al.[9] Copyright ©2017, European Society of Endocrinology.

- A complete TTE, even in the presence of a normal fetal echocardiogram and cardiac examination, should be performed because certain cardiac abnormalities may be clinically "silent" or may not be recognized on a fetal echocardiogram.
- Visualization of the coronary artery anatomy should be attempted at the first encounter, by TTE in newborns and infants, or by cardiac magnetic resonance (CMR) or computed tomography (CT) in the adult population.
- An ECG should be done to assess for potential conduction and repolarization abnormalities.
- A CMR can be performed, as soon as it is feasible, without the need for general anesthesia.

Management

- For individuals with TS with congenital heart defects, management of their cardiac disease should be determined by their cardiologist according to previously described guidelines with the assistance of a multidisciplinary team.
- For individuals with no structural heart disease, annual assessment of BP should be performed.
- Clinicians should be vigilant when monitoring girls and women with TS for hypertension, which should be treated according to the standards set for the general population (see the High Blood Pressure section).
- Periodic surveillance imaging is recommended for those with normal-appearing aortas (see the suggestions for clinical practice in the Cardiac Imaging section).
- Clinicians should refer to the most recent guidelines by the American Heart Association for the prevention of infective endocarditis.

CARDIAC IMAGING

Figures 1 and 2 provide monitoring protocols.

Because of the high prevalence of congenital and acquired cardiovascular disease in TS, noninvasive cardiac imaging is critical for diagnosis, management, and risk assessment.[1,29,30] The most common modalities include TTE, CMR, and CT.[18,19,31–35] TTE is useful in the diagnosis of a BAV[36] and other congenital heart defects, as well as in the surveillance of aortic dilatation.[33] However, the high prevalence of undiagnosed abnormalities, such as elongation of the transverse aorta (defined as a relative increase in vertical distance from the top of the aortic arch to the origin of the innominate artery),[37] aortic coarctation, and partial anomalous pulmonary venous connection in TS, has led to increased use of CMR and CT as screening and surveillance tools.[18,31,32,35] CMR has been shown to be more accurate than TTE in adults with TS for the diagnosis of BAV.[19] CMR and CT are also more accurate for aortic size measurements and therefore more sensitive than TTE to changes in aortic size, particularly beyond the aortic root and in adults with TS, who often have limited echocardiographic windows.[38] Although serial surveillance with CT is an option, the risk of recurrent ionizing radiation should be recognized, and therefore, radiation should be used only when surveillance with CMR is not possible.

Cardiovascular disease is the major cause of death in TS, and death resulting from AoD is far in excess of that in the general population.[2,3] Predictors of AoD risk in TS have not been well studied. In the aortopathy associated with Marfan syndrome, risk factors include the degree of aortic dilatation and aortic growth rate. BAV is commonly present when AoD occurs in TS and should be considered a risk factor.[39] Risk assessment in TS may also include measures of aortic stiffness, distensibility,[40] and tortuosity, but these are currently not part of standard clinical imaging protocols.[41–43] The ascending aortic diameter divided by body surface area (BSA; the aortic size index [ASI][43]) may be useful in stratifying risk. The ASI has been the primary parameter used to assess AoD risk in TS and has known limitations in terms of the methodology for performing the measurement and for defining a dilated or aneurysmal aorta, particularly in children.[42,44,45]

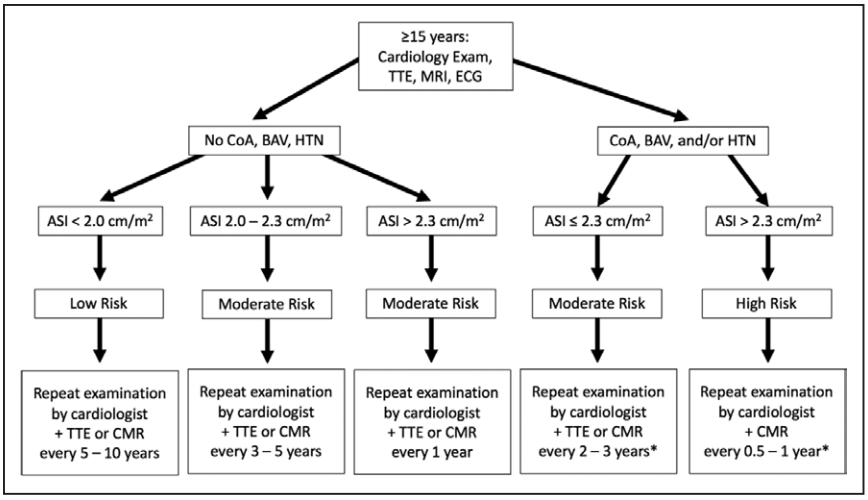

Figure 2. Suggested monitoring protocol for girls and women with Turner syndrome who are ≥15 years of age.
ASI indicates aortic size index; BAV, bicuspid aortic valve; CMR, cardiac magnetic resonance; CoA, coarctation of the aorta; HTN, hypertension; MRI, magnetic resonance imaging; and TTE, transthoracic echocardiography. *It is important to remember that surveillance frequency may change with worse disease severity in terms of obstruction, regurgitation, or left ventricular hypertrophy. Modified from Gravholt et al.[9] Copyright ©2017, European Society of Endocrinology.

Published guidelines recommend aortic diameter measurements at specified locations perpendicular to the vessel wall.[42,44,46–50] The optimal approach to aortic diameter measurements remains to be defined. Aortic diameters change over the cardiac cycle with the largest diameters observed in systole,[51,52] and systolic diameters may best reflect vascular function.[42] Conversely, diastolic diameters may be more reproducible.[30,44,45,53] In addition, pediatric TTE quantification guidelines recommend that measurements be made from leading edge to leading edge, whereas adult guidelines recommend measurements from inner edge to inner edge. Recently published normative TTE data for TS and most CMR studies have used inner edge to inner edge in TS,[18,28,31,54] which may therefore be preferable.

Furthermore, the aortic cross section may not be perfectly round along the entire aorta, particularly at the sinuses of Valsalva, where asymmetry can result in significantly varied measurements based on orientation along the axial plane.[55] Given these challenges, serial measurements must use the same modality and methodology to achieve the least possible measurement variability for the most reliable measurements of aortic size and growth.

Defining aortic dilatation is problematic because normal reference values must account for the effects of body size and age on the sizes of cardiovascular structures.[42,56] In the context of the smaller body sizes of individuals with TS, absolute aortic dimensions may not be as useful in identifying a dilated aorta. Data in children without TS suggest that aortic dimensions should be normalized to the square root of the BSA, and many published TTE and CMR *z*-score databases use this approach.[48,49,56,57] However, the outcome studies of ascending aortic size in TS normalize aortic dimensions to BSA[19] (ASI) and define dilatation as >2 cm/m^2 or >95th percentile on the basis of nomograms of children in the general population.[53,58,59]

An ascending ASI >2.5 cm/m^2 has been used to predict risk of AoD for girls and women >15 years of age (Figure 3).[39,54] Because there has been no prospective longitudinal study of AoD related to ASI in TS, causation is unproven. Therefore, further research is essential to know whether ASI or other factors are the best predictors of risk. The position of the working group is that the ascending ASI is currently the best method to adjust absolute aortic measurements for body size for those >15 years of age, but this remains to be proven. Therefore, it is useful to note that a woman with the average BSA for TS (ie, 1.6 m^2; Figure 3) has an absolute ascending aortic diameter of >4 cm when the ascending ASI is >2.5 cm/m^2. In addition, an ascending aorta ASI >2.5 cm/m^2 for a woman with average BSA corresponds to an ascending aorta Turner-specific *z* score of >4 (discussed below).[28] Before the age of 15 years, ascending ASI is often >2.5 cm/m^2 in healthy girls with TS (Figure 3), increasing the risk of false positives.[45] The age dependence of the ASI calculation is not specific to TS. Dividing by BSA is a simple way of indexing vascular dimensions and has been shown to be generally unreliable in children.[56]

Other studies use the ratio of the ascending to descending aortic diameters, defining a ratio of >1.5 as dilatation,[32] although this approach does not account for the fact that the descending aorta may not be normal. Given the limitations of the last 2 approaches (ASI and ascending/descending aorta ratio), a recent publication evaluated aortic diameters for healthy girls and women with TS (excluding subjects with a BAV), thereby providing normative *z* scores[60] based on a TS reference population.[28] The relationship between TS-specific *z* scores and *z* score referenced to the general pediatric/young adult population has been published.[45] TS-specific *z* scores are significantly lower than *z* scores based on a non-TS reference population.[45]

Suggestions for Clinical Practice

- When an infant or child is diagnosed with TS, TTE should be performed at the time of the diagnosis,

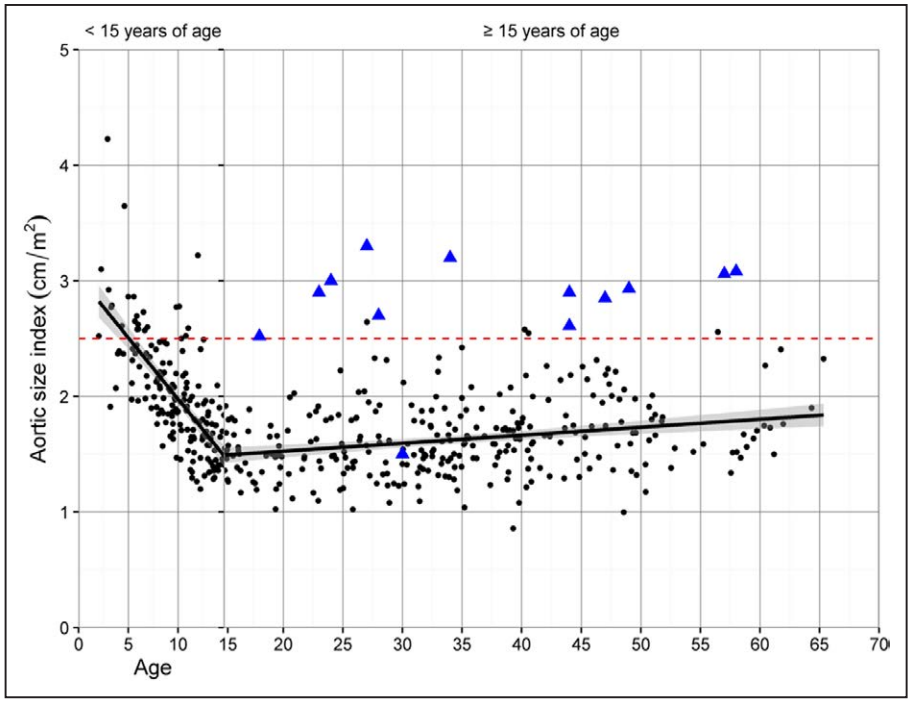

Figure 3. Relationship between ascending aortic size index (ASI) and age in individuals with Turner syndrome (TS) with or without aortic dissection (AoD).

Data were derived from references 39 and 54. Dots represent measurements determined by transthoracic echocardiography performed at study entry to the Healthy Heart Project during the annual meeting of the Turner Syndrome Society of the United States between 2003 and 2015 (n=458). For those who were ≥15 years of age (n= 212), the mean body surface area (BSA) was 1.62 m^2 and the mean absolute aortic size was 2.6±0.4 cm. At the time the study was performed, none of these individuals had either a history of AoD or an elective operation for an aortic aneurysm. Note that subjects <15 years of age with a negative history for AoD frequently have ascending ASI >2.5 cm/m^2, making ASI unreliable as a predictor of AoD in this age group.[45] Triangles represent echocardiographically determined ascending aorta ASI obtained before presentation with AoD in 13 individuals with TS reported in 2 studies[39,54] (absolute aortic size, 4.6± 0.7 cm; ascending ASI, 2.8±0.5 cm/m^2). Dashed line represents an absolute ascending aortic diameter of 4.1 cm, ascending ASI of 2.5 cm/m^2, and Turner-specific *z* score[28] of 4 based on the average BSA of 1.62 m^2 for the 290 women ≥15 years of age without aortic dissection (dots). Modified from Corbitt et al[45] with permission.

even if the fetal echocardiogram or postnatal cardiac examination was normal.

- When an infant or child is diagnosed with TS, CMR should be performed as soon as it is feasible without the need for general anesthesia.
- When an adult is diagnosed with TS, cardiovascular screening with TTE and CMR at the time of diagnosis is the preferred approach.
- When an adult or child diagnosed with TS cannot tolerate a CMR study, cardiovascular screening with electrocardiographically gated CT is a reasonable option.
- In the absence of a BAV or other significant disease at the initial screening, TTE or CMR surveillance studies should be performed every 5 years in children, every 10 years in adults, or before anticipated pregnancy to evaluate the aorta.
- If aortic dilatation or other AoD risk factors are diagnosed, timing of surveillance imaging should be guided by the knowledge that AoD occurs at smaller diameters than in non-TS genetic aortopathies, and follow-up should be guided by a multidisciplinary team under the supervision of a cardiologist with knowledge, experience, or special interest in the cardiovascular abnormalities in TS (see Figures 1 and 2 for suggested monitoring protocols).

MEDICAL AND OPERATIVE MANAGEMENT OF AORTIC ENLARGEMENT AND ANEURYSM THORACIC AoD IN TS

Gravholt et al[5] reported that in TS AoD occurs in ≈40 per 100 000 person-years compared with 6 per 100 000 person-years in the general population. The majority of AoDs originate in the ascending aorta (type A), whereas a smaller percentage (≈10%) originate in the descending thoracic aorta (type B).[5,6,39,54] When AoD occurs, it is a catastrophic and often fatal event. It is important to note that for women with TS, AoD appears to occur at smaller ascending aortic diameters than in those with other genetic aortopathies.[6,39,54] AoD in TS occurs at an age (median age, 29–35 years; range, 4–64 years) similar to that of others with genetic aortopathies.[39] Furthermore, in women with AoD, cardiovascular abnormalities such as BAV, coarctation of the aorta,

and hypertension are common.[6,31,39,54] Limited evidence suggests that growth hormone therapy is not a risk factor for aortic enlargement.[6,61] Aortic dilatation and enlargement of the brachiocephalic and carotid arteries may be present in TS even in the absence of structural heart disease, consistent with an underlying vasculopathy.[31,40,62–64] Although pregnancy is a rare event in TS, it is believed that pregnancy confers an additional risk for AoD in women with TS, particularly in those undergoing assisted reproductive therapy (ART) who also have a BAV, other cardiovascular malformations, aortic enlargement, or hypertension.[65]

Very limited data suggest that AoD usually (but not always) occurs at >15 years of age and appears to be more likely to occur with an ascending ASI ≥2.5 cm/m^2 (Figure 3).[39,54]

The mid ascending aorta is often dilated in TS. A global aortopathy is, however, evident by dilatation potentially involving the aortic root, distal ascending aorta, and descending aorta, as well as the proximal head and neck arteries.[18,31,66–68] Correspondingly, the risk of both Stanford type A and B AoD is increased.[6] No evidence exists to define comparable segment-specific ASI thresholds beyond the mid ascending aorta. A pragmatic approach must therefore be adapted to proposed surgical thresholds, and imaging must include the entire thoracic aorta in all girls and women with TS.

Definition of Aortic Enlargement and Aortic Aneurysm

The aorta is considered enlarged when the vessel diameter is larger than expected on the basis of age, sex, and BSA. An aortic aneurysm is generally defined as a localized dilatation having at least a 50% increase in diameter compared with the expected normal diameter.[41] When an aneurysm is diagnosed, medical or operative interventions may be necessary. Aortic enlargement of less than aneurysmal diameter may require changes in care such as limiting physical activity or additional monitoring. For growing girls and for women with TS who tend to have short stature, standardized scores (also called *z* scores) are typically used. In general, aortic enlargement has been defined as >2 SDs above the mean predicted diameter for a particular body size (or *z* score >2). Most measurements are obtained with 2-dimensional TTE according to endorsed standards.[42] Specifically, the ascending aorta is measured from an image of the ascending aortic diameter at the level of the right pulmonary artery.[42] TS-specific *z* scores have been established by Quezada et al[28] that are based on data suggesting that mild aortic enlargement occurs even in healthy individuals with TS who have no known risk factors for thoracic aortic enlargement.[69] Use of a Turner-specific *z* score[28,60] may be preferable to the general, population-based *z* scores because higher *z* scores derived from the non-Turner population could lead to overtreatment or stigmatization. Health professionals should be cognizant that TS-specific *z* scores are significantly lower than *z* scores derived from a general reference population.[45] For example, an ascending aorta TS-specific *z* score >3 is equivalent to a *z* score of >5 derived from the general reference population.

A TS-specific ascending aortic diameter *z* score of >3.0 generally fits the definition of an aneurysm, being at least 50% greater than the expected TS-specific mean normal diameter.

Using ASI has been proposed as a way to better predict risk for AoD in TS.[5,6,39,43,69] ASI is not applicable to those <15 years of age because girls with TS usually have relatively larger aortic diameters when indexed to body size compared with older individuals with TS (≥15 years of age). The ascending ASI decreases with body growth until the mid teenage years and remains relatively stable thereafter, making it a useful index beyond the age of 15 years (Figure 3). Although body mass index is not a predictor of aortic size,[28] BSA calculations include body weight. Therefore, decisions based on either *z*-score calculations or ASI in short-statured but obese individuals or those who weigh very little relative to their height should be made with caution.[70] In these cases, an absolute ascending aorta diameter of 4 cm in someone ≥15 years of age may be more accurate than ASI when determining AoD risk.

Medical Management

The approach to managing individuals with TS with aortic dilatation is a pragmatic one, recognizing the absence of clinical trials to guide pharmacological therapy. Cystic medial degeneration similar to other aortopathies has been documented in resected aortic tissue of women with TS.[5] Thus, using treatments that are typically a part of the treatment of Marfan syndrome or other genetic types of aortopathy may be reasonable. Because hypertension is common in TS, maintenance of normal BP may lessen the risk of aortic events.[71,72] De Groote et al[72] have proposed a practical algorithm for BP evaluation in adults. Because AoD appears to occur at a smaller absolute aortic dimension in TS than in other aneurysm disorders, it may be reasonable to begin prophylactic medical therapies earlier than what has been recommended for other conditions and to use ASI for the initiation of medication (see recommendations in the Medical Therapy section).

Operative Repair of Aortic Aneurysms and AoD

General technical concepts and perioperative care are not different from those for other patients with thoracic

aortic aneurysms and dissections. As with other aortopathies, the thresholds for considering elective operative repair are based on perceived risk for AoD. The diagnosis and management of AoD have been outlined in existing guidelines.[41]

Suggestions for Clinical Practice

Awareness of Risk for AoD

- Girls or women with TS and aortic enlargement and BAV should be counseled to seek prompt evaluation for any symptoms consistent with acute AoD such as unusual chest, neck, shoulder, back, or flank discomfort, particularly if it is sudden in onset and severe. They should be encouraged to provide information about their high-risk condition to healthcare providers.

Optimal Operative Management of Aortic Aneurysm in TS

- For women with TS who demonstrate an increase in either a TS-specific *z* score[60] of 1 or an increase in aortic diameter of >0.5 cm over a 1-year period, optimization of medical treatment and surgical consultation are recommended. The average aortic growth rate for adults with TS has been shown to be 0.1 to 0.4 mm/y.[66,73]
- Operative management of the aortic root and ascending aorta is reasonable for women with TS who are ≥15 years of age, have an ascending ASI ≥2.5 cm/m^2, and have associated risk factors for AoD, including BAV and hypertension.
- Operative management for an aneurysm of the aortic root or ascending aorta may be considered for women with TS who are ≥15 years of age, have an ascending ASI ≥2.5 cm/m^2, and do not have associated risk factors for AoD.
- Operative management for an aneurysm of the aortic root or ascending aorta may be considered for girls with TS who are <15 years of age and for whom the ascending aorta TS-specific *z* score is ≥4.0, with or without associated risk factors for AoD (ie, BAV and hypertension).

Optimal Medical Management of Aortic Aneurysm in TS

- Medical treatment of hypertension is recommended.
- Medical treatment that includes a β-blocker, angiotensin receptor blocker, or both may be considered in patients with TS in whom the aorta is dilated.

ELECTROCARDIOGRAPHY

Differences between the ECG in TS and in the general population can be roughly categorized into morphological issues (bundle-branch block, T-wave changes, P-wave changes) on the one hand and time intervals (PR interval, QT interval) on the other. The reported prevalence of these changes in girls and women with TS is ≈50%, which is higher than in control subjects without TS (30%).[74] Some changes such as P-wave and QTc dispersion and heart rate variability in TS can be attributed to an underlying autonomic effect.[75] Shortening of the PR interval (resulting from accelerated atrioventricular conduction) may be a consequence of excessive sympathetic drive.

The clinical relevance of these potential abnormalities may be 2-fold: Right-axis deviation in an individual with TS is correlated with the presence of partial anomalous pulmonary venous connection[76] and should trigger further diagnostic testing in those cases that are not already known, and QTc prolongation is associated with an increased risk for arrhythmias or even sudden cardiac death in the general population. It should be emphasized, however, that there is no published evidence to date for sudden cardiac death related to QTc prolongation in women with TS. Whether QTc prolongation should be considered an intrinsic feature of TS is unclear; a potential correlation with variants in the long-QT syndrome genes deserves further investigation.[77] Two observations suggest that prolonged QTc does not put girls and women with TS at risk: (1) No significant dysrhythmia has been documented in any girl or women with TS and prolonged QTc, and (2) in 1 TS study, QTc prolongation returned to normal in 40% of ambulatory ECGs[76] and returned to normal during exercise stress testing. Of note, QTc does not normalize during exercise in long-QT syndrome.[78]

Additional uncertainties include the threshold at which to define QT prolongation (now set at 440 milliseconds in many studies, which may be too low) and the calculation method used to define QTc interval in TS.

In view of the increased intrinsic heart rate in many individuals with TS,[79] the Hodges formula may be preferred over the Bazett formula because it takes the higher heart rate into account.[77] Finally, caution may be warranted with the use of QTc-prolonging drugs in women with TS. Careful assessment of the QTc interval before the initiation of such agents and electrocardiographic surveillance at least in those with preexisting QTc prolongation should be considered, as illustrated in a recent case report.[80] Decisions should be made on a case-by-case basis, balancing the benefits of these drugs against their potential risks. Because the arrhythmia torsades de pointes is the cause of sudden cardiac death in those with prolonged QTc in the setting of long-QT syndrome, postmortem assessment of women with TS who die suddenly would indicate that prolonged QTc may be the cause by excluding more common causes such AoD, stroke, myocardial infarction, or coronary malformations.

Suggestions for Clinical Practice

- Resting electrocardiographic recording with QTc measurement is reasonable in every individual with TS at the time of diagnosis.
- For QTc calculation, the Hodges formula [QTc=QT+ 0.00175 ([60/RR (R wave to R wave interval)]–60)] may be preferred over the Bazett formula.
- Exercise testing and 24-hour Holter monitoring might be considered for risk estimation in women with TS with QTc prolongation.
- In individuals with prolonged QTc (QTc >460 milliseconds), the following applies:
  - An ECG should be performed 1 to 2 weeks after the initiation of QT-prolonging drugs.
  - It is reasonable to avoid drugs that lengthen the QTc.

COMPETITIVE SPORTS PARTICIPATION

A safe level of exercise is important for a healthy lifestyle in girls and women with TS. Evidence is lacking on the cardiovascular and aortic risks for competitive athletics with TS. However, many of the same principles stated in the American Heart Association/American College of Cardiology scientific statement "Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities"[81] apply to girls and women with TS who have valvular, congenital heart, or aortic disease.[82,83]

Given the propensity for obesity and the metabolic syndrome in TS, healthcare professionals should be mindful of the significant benefits of having a heart-healthy lifestyle in light of the low risk of AoD in absolute terms (≈40:100 000 patient-years[5]) in this population. Therefore, consideration of the risk for AoD should be tempered by the importance of encouraging safe levels of physical activity in individuals with TS. In addition, there is no published evidence that contact sports represent a significant threat for AoD among girls and women with TS without significant aortic enlargement. Recreational (noncompetitive) exercise performed at low to moderate aerobic levels is considered to be low risk and beneficial for girls and women with TS unless significant cardiovascular or aortic disease is present (Figure 4[81]).

Because of short stature in TS, indexing the aortic size to the BSA (ascending ASI) may be a better predictor of aortic risk than aortic size alone. Consistent with information in earlier sections of this document, ascending ASI is age dependent for girls with TS who are <15 years of age (Figure 3). In girls with TS who are <15 years of age, an ascending ASI >2.5 cm/m^2 is relatively common, and as girls age, many "grow into" their aortas. Thus, for sports participation for girls <15 years of age, it is reasonable to use TS-specific *z* scores,[28] which are based solely on BSA, when determining eligibility for participation in competitive sports.[84] In women with TS who are ≥15 years of age, using the ascending ASI (or absolute aortic size) for determining eligibility and disqualification for sports participation is recommended. For certain women with TS and obesity, using absolute aortic diameter to guide sports participation and disqualification is reasonable.

Suggestions for Clinical Practice

- The function of the aortic valve and the presence of any other congenital heart defect or hypertension should be considered in determining participation recommendations for the athlete with TS and aortic dilatation.
- For girls and women with TS who are ≥15 years of age with a moderately dilated aorta (ascending ASI ≥2.0 cm/m^2), avoidance of intense weight training should be considered.
- For girls with TS who are <15 years of age, it is reasonable to participate in all sports if the aortic size has a TS-specific *z* score of <2.5.
- For girls and women with TS who are ≥15 years of age, participation in all competitive sports is reasonable if the ascending ASI is <2.0 cm/m^2.
- For girls with TS who are <15 years of age with a mildly to moderately dilated aorta (TS-specific *z* score, 2.5–3), participation in low and moderate static and dynamic competitive sports (classes IA, IB, IC, IIA, IIB, and IIC and certain types of gymnastics with lower isometric demands)[55] may be considered.
- For girls and women with TS who are ≥15 years of age with a moderately dilated ascending aorta (ASI, 2.0–2.3 cm/m^2), participation in low and moderate static and dynamic competitive sports (classes IA, IB, IC, IIA, IIB, and IIC and certain types of gymnastics with lower isometric demands) may be considered (Figure 4).
- Girls with TS who are <15 years of age with a TS-specific *z* score of >3 should not participate in any competitive sports.
- Girls or women with TS who are ≥15 years of age with an ascending ASI >2.3 cm/m^2 should not participate in any competitive sports.

TRANSITION

Transition is a process to optimize lifelong functioning and potential with high-quality, developmentally appropriate, and uninterrupted health care from adolescence to adulthood.[85] To be successful, this process should attend to the medical, psychosocial, educational, and vocational needs. Regional TS resource

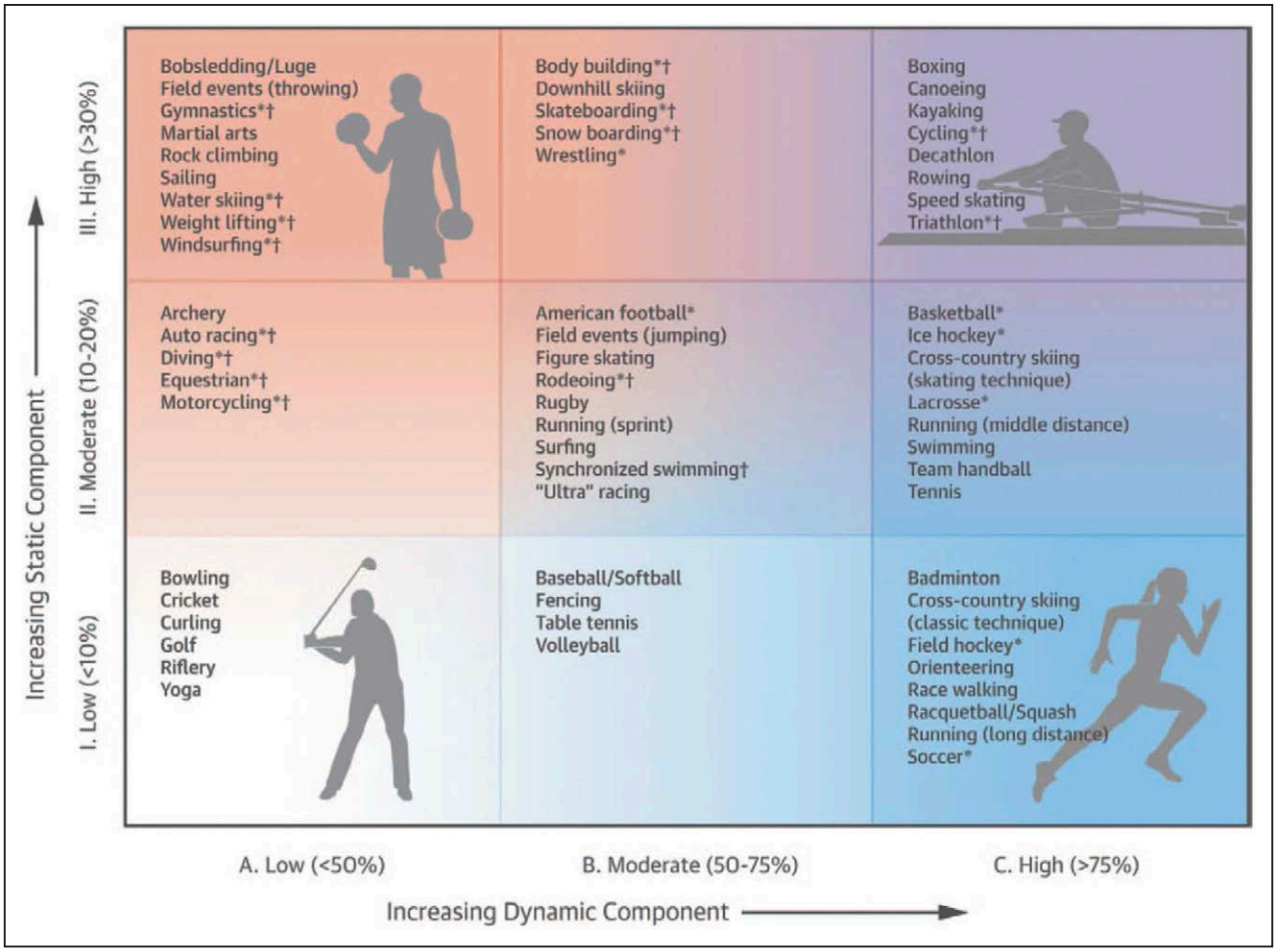

Figure 4. This classification is based on peak static and dynamic components achieved during competition; however, higher values may be reached during training.

The increasing dynamic component is defined in terms of the estimated percentage of maximal oxygen uptake ($\dot{V}o_2max$) achieved and results in an increasing cardiac output. The increasing static component is related to the estimated percentage of maximal voluntary contraction reached and results in an increasing blood pressure load. The lowest total cardiovascular demands (cardiac output and blood pressure) are shown in the palest color, with increasing dynamic load depicted by increasing blue intensity and increasing static load by increasing red intensity. Note the graded transition between categories, which should be individualized on the basis of player position and style of play. *Danger of bodily collision (see the Table for more details on collision risk). †Increased risk if syncope occurs. Modified with permission from Mitchell et al. Task Force 8: classification of sports. *J Am Coll Cardiol*. 2005:1364–1367. Copyright © 2005, Journal of the American College of Cardiology. Reproduced from Levine et al.[81] Copyright © 2015, American Heart Association, Inc.

centers (team clinics) are being organized by the Turner Syndrome Global Alliance. The Turner Syndrome Global Alliance, through its overall transition program, is helping to identify cardiologists who care for adults who also have expertise in congenital heart defects.

Current guidelines recommend that the transition process start at the age of 12 years with a written transition plan by 14 years of age[85–87] and with plans to transfer to adult congenital heart defect services by 18 years of age.[87] The transition process in this patient population should address the cardiovascular risks, associated congenital heart defects if applicable, and topics such as the educational and psychosocial needs. These topics are introduced gradually and reinforced in subsequent clinic visits and communications. Preparing the adolescent with TS for self-care and independence in adulthood is the goal.

Cardiovascular Health Care From Childhood to Adulthood

In addition to the congenital heart defects and aortopathy, girls with TS are at increased risk for obesity, abnormal triglycerides, diabetes mellitus, hypertension, stroke, and ischemic heart disease. The majority of the serious sequelae and increased mortality associated with these health risks are present in adults with TS.[3] Therefore, for all adolescents, a detailed transition strategy emphasizing an understanding of the cardiac status and the importance of lifelong care and prevention is critical. Discussion with girls independently and with their families should start as early as 12 years of age and should be age and developmentally appropriate.[85,86] The topics discussed[88] should be documented in the medical record and shared with the primary care provider and other subspecialists to ensure that the

individual and family hear consistent information and that this information is reinforced by all providers. During this transition period, the importance of preparation for adulthood cardiovascular care is emphasized with the aim of ensuring guideline-driven care, regular medical visits, and a reduction in morbidity.

Suggestions for Clinical Practice

- Lifelong cardiac follow-up is recommended for all individuals with TS, even in the absence of cardiovascular disease.
- Medical care during adulthood should be guided by a multidisciplinary team that includes a cardiologist with knowledge, experience, or a special interest in the unique cardiovascular issues facing women with TS.
- A heart-healthy lifestyle is essential and should be discussed with adolescents and young adults given the increased risk of obesity, abnormal triglycerides, diabetes mellitus, hypertension, stroke, and ischemic heart disease.
- Cardiovascular health-specific discussions with emerging adults should include the following:
  - Any residual hemodynamic considerations
  - Symptoms to be aware of
  - Diagnostic tests and potential management
  - Risks associated with noncardiac surgery
  - Life and health insurance
  - Education and employment
  - Need for lifelong cardiac care
  - Endocarditis symptoms and prophylaxis
  - Contraception/pregnancy including risks
  - Medications (indications and side effects)
  - Exercise and healthy diet
  - End-of-life issues

CARDIOVASCULAR RISKS DURING PREGNANCY

The rapidly evolving field of ART is increasing the childbearing potential for women with TS. Accordingly, it is imperative that reproductive health practitioners and obstetricians understand who might safely attempt pregnancy. Practitioners must become familiar with the special monitoring and management that women with TS might require during and after pregnancy. It should be noted that this document proposes that pregnancy can be undertaken safely by women with TS, even some individuals with known risk factors. The suggestions for clinical practice herein take a moderate stance on the advisability of pregnancy compared with the guidelines previously proposed by the American Society of Reproductive Medicine[89] that state that a significant cardiac malformation absolutely precludes pregnancy.

AoD During Pregnancy

Pregnancy in women with TS is associated with significant risks, including hypertensive disorders, preeclampsia, premature birth, low birth weight, and need for cesarean delivery.[90] Pregnancy in Marfan syndrome increases the risk of AoD or rupture.[91] Case reports,[6] but no controlled studies to date, suggest that pregnancy may increase the AoD risk in TS.

Structural changes in the intima and media have been described in pregnant women without aortic disease. Histopathology previously showed hypertrophy and hyperplasia of smooth muscle cells, fragmentation of reticular fibers, and less corrugated elastic fibers.[92] These changes may be driven not only by the increase in cardiac output and circulating blood volume but also by hormonal changes. Whether the alterations in the aortic wall lead to an increased risk of AoD in pregnant women remains undetermined.[6,39,65] There are case reports and AoD series that describe AoD during pregnancy, although low numbers and selection bias preclude any firm conclusions to be drawn. Patients derived from these reports may overrepresent those with unusual presentations of their disease.[93] In the GenTAC study (Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions) of 278 pregnancies in women with Marfan syndrome, an 8-fold increased risk of AoD was reported.[94] In addition, a population-based registry from Sweden reported a 25-fold increased risk of AoD related to pregnancy in TS.[95]

ART may pose additional risk for significant complications beyond those of a spontaneous pregnancy.[65] Type A and B AoDs have been described during ART-associated pregnancy in TS.[39] A comprehensive registry that includes all cases of pregnancy in women with TS is essential to answer the question of AoD risk in pregnancy in women with TS.[96] In TS cases in which the aorta is dilated, there are no studies that consider the advisability of elective aortic surgery before pregnancy. In women with other conditions associated with AoD such as Marfan and Loeys-Dietz syndromes, a dilated aorta is an indication to perform prepregnancy surgery. However, after aortic surgery in these conditions, women are still considered at risk for distal AoD, especially those with Loeys-Dietz syndrome.[97] Similarly, it is assumed that the risk of AoD is still present after elective aortic root replacement in TS. Apart from the risk of AoD, women with TS may have other cardiovascular abnormalities such as aortic valve stenosis or coarctation of the aorta. If prepregnancy aortic root surgery will include aortic valve replacement with a mechanical valve, the woman with TS will be put at risk of a valve thrombosis or bleeding. In a recent article on mechanical valves, only 58% of the pregnancies were without severe complication.[98] If a bioprosthetic aortic valve is used, the risk of throm-

bosis or bleeding is lower, but subsequent aortic valve interventions will be needed.[99] The guidelines for care in those with congenital heart defects are similar to those for women without TS.[100]

Cardiovascular Risks Beyond the Aorta

In addition to the increased prevalence of congenital heart defects and potentially increased risk of AoD, women with TS are at increased risk for diabetes mellitus and hypertensive disorders of pregnancy, including preeclampsia.[90,101,102] Preeclampsia and gestational hypertension in the general population are associated with several risk factors, including a family history of preeclampsia, nulliparity, older age, elevated body mass index, preexisting diabetes mellitus, chronic renal disease, antiphospholipid antibodies, multiple gestation, and preexisting hypertension.[103] Hypertension is more common in women with TS, which may contribute to the higher incidence of hypertensive complications during pregnancy. In addition, obstetric and fetal risks are higher, including a higher risk of miscarriage and fetal abnormalities.[104,105]

ART in Individuals With TS

Specific considerations and recommendations for ART in women with TS have been published.[9] In this document, aspects of ART that relate to cardiovascular health are addressed.

Most women with TS will not be able to conceive spontaneously or undergo ovarian stimulation because of reduced or absent ovarian capacity.[106] Women with mosaic TS are also likely to have reduced ovarian reserve. In women with normal ovarian reserve, stimulation has 3 potential adverse cardiovascular consequences: a prothrombotic effect,[107] a hemodynamic effect,[108–110] and the occurrence of ovarian hyperstimulation syndrome, which exacerbates these prothrombotic and hemodynamic changes and is further complicated by increased capillary permeability causing marked fluid shifts.[111] The risk of ovarian hyperstimulation syndrome is very low in women with TS and can be further reduced or even avoided altogether by altering the stimulation regimen used and avoiding the use of exogenous human chorionic gonadotropin.[112]

Because the majority of women with TS have no ovarian reserve, they will need to take estrogen to prepare the endometrium and subsequently the combination of estrogen and progesterone to maintain pregnancy. Hormone replacement therapy has prothrombotic effects and consequences.[113,114] However, hormone replacement therapy has not been studied specifically in TS. Prothrombotic effects are limited in the context of endometrial preparation and can be reduced by giving the estrogen component via the transdermal route.[113] Overall, the impact of the short-term exposure to exogenous estrogen is limited and minor compared with the prothrombotic effect of pregnancy.

No clear evidence is available on an association between ART and aortic dimension or AoD. Assisted conception seems to further increase the risk of hypertensive and cardiovascular complications compared with spontaneous conception. Associated older age at conception and a higher percentage of multiple pregnancies may contribute to these risks of assisted conception.[65]

Medical Treatment During Pregnancy

Medical treatment, specifically in terms of cardiovascular health, comprises antihypertensive treatment and prophylactic medication to prevent (further) aortic dilatation. Antihypertensive treatment recommendations are similar to those for pregnant women without TS. There is no clear evidence for prophylactic medication during pregnancy in women with TS who have aortic dilatation. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated in pregnancy because of potential detrimental fetal effects. β-Blockers may be considered and do not cause fetal abnormalities; however, some effect on fetal birth weight has been described.[115,116] This recommendation holds for any woman with aortic dilatation. The National Institute for Health and Care Excellence recommends 75 to 81 mg aspirin daily from 12 weeks of gestation until delivery for women at risk of preeclampsia.[117] This recommendation is based on data showing a benefit with aspirin use in patients with ≥2 moderate risk factors.[7] Oocyte donation is not given as a specific risk factor, but consideration should be given to prescribing aspirin in such pregnancies in a woman with TS.

Mode of Delivery in Women With a Dilated Aorta and TS

A delivery plan should be made by a multidisciplinary team consisting of at least an obstetrician, cardiologist, and anesthesiologist, all with expertise in pregnancy in the context of maternal heart disease or aortopathy. Vaginal delivery is the preferred mode of delivery in most women, according to the available literature. In the Registry of Pregnancy and Cardiac Disease, cesarean delivery was not superior to a vaginal delivery for the mother, whereas an increase in adverse fetal events was seen.[116] According to expert opinion, in women with a severely dilated aorta, a cesarean delivery is reasonable, although it also leads to hemodynamic changes. A cesarean delivery is recommended for women with a history of AoD. The short stature in TS predisposes for disproportion of the pelvis; cesarean delivery may be required for this reason.[105]

Suggestions for Clinical Practice

Imaging, Counseling, and Treatment in Women With TS Before Pregnancy or ART

- Imaging of the thoracic aorta and heart with TTE and CT/CMR should be performed within 2 years before pregnancy or ART in all women with TS.
- Exercise testing before pregnancy can be useful to reveal exercise-induced hypertension, especially in women with a history of coarctation of the aorta.
- All women with TS should be counseled about the increased cardiovascular risk of pregnancy.
- Women with aortic dilatation, BAV, elongation of the transverse aorta, coarctation of the aorta, or hypertension should be advised that pregnancy carries a high risk of AoD.
- Other options for motherhood such as adoption or using a gestational carrier should be discussed during preconception counseling.
- It is recommended that ART and spontaneous conception be avoided in women with TS with an ascending ASI of >2.5 cm/m^2 or (history of) AoD.
- It is recommended that ART or spontaneous conception be avoided in women with TS with an ascending ASI of 2.0 to 2.5 cm/m^2 and associated risk factors for AoD, which include BAV, elongation of the transverse aorta, coarctation of the aorta, and hypertension.
- If women with an ASI >2.5 cm/m^2 or a history of AoD do become pregnant, they should be followed up very closely at a specialized center and should deliver by cesarean delivery.
- Angiotensin inhibition (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) is contraindicated during pregnancy.

Monitoring, Therapeutic Management, and Delivery of Pregnant Women With TS

- During pregnancy, individuals with TS should be treated in specialized centers by a multidisciplinary team with knowledge of TS.
- In women with TS without aortic dilatation or other risk factors (hypertension, BAV, coarctation, elongation of the transverse arch, previous AoD, or surgery), it is reasonable to perform a TTE and clinical assessment at least once at ≈20 weeks of gestation.
- Women with TS with an ascending ASI >2.0 cm/m^2 or any risk factor (hypertension, BAV, coarctation, elongation of the transverse arch, previous AoD, or surgery) should be monitored frequently, including TTE at 4- to 8-week intervals during pregnancy and once during the first month after delivery, with subsequent imaging depending on the severity of aortic enlargement.
- CMR (without gadolinium) should be performed during pregnancy in the following circumstances: when there is concern of disease of the distal ascending aorta, aortic arch, or descending aorta; in cases of insufficient image quality of the ascending aorta; or when aortic dimensions are increasing.
- In pregnant women with TS, strict BP control is recommended.
- During pregnancy, prophylactic aortic surgery may be considered in the case of a dilated aorta (ASI ≥2.5 cm/m^2) with a rapid increase in diameter (>3 mm).
- The use of low-dose aspirin (75–81 mg) may be considered in pregnant women with TS.
- A vaginal delivery is reasonable in women with TS with an ascending ASI <2.0 cm/m^2.
- In women with TS with an ascending ASI of 2.0–2.5 cm/m^2, the following applies:
  - A vaginal delivery with epidural anesthesia and expedited second stage is reasonable.
  - A cesarean delivery may be considered.
- If women with TS with an ascending ASI >2.5 cm/m^2 become pregnant, a cesarean delivery is recommended.
- In women with TS with a history of AoD, a cesarean delivery is recommended.
- In case of an acute ascending AoD before the fetus is viable, it is recommended that emergency aortic surgery be performed with the understanding that fetal viability may be at risk.
- In case of an acute ascending AoD and a viable fetus, performing a cesarean delivery first, followed by urgent aortic surgery, should be considered.
- Aortic surgery in the pregnant patient should be performed under the following conditions: near normothermia, pulsatile perfusion or high pump flow, and avoidance of vasoconstrictors.
- In women with TS with an ascending ASI of >2.0 cm/m^2, postpartum monitoring is indicated for at least 48 hours.

HIGH BP

High BP is one of the most important modifiable risk factors for the cardiovascular risks in TS: AoD, stroke, and myocardial infarction. Although individuals with TS are frequently found to have hypertension, little has been documented about measurement, definitions, and management of hypertension specifically for women with TS. The subject has only recently been reviewed.[72]

Epidemiology and Pathogenesis

The prevalence of hypertension in individuals with TS is 20% to 40% in childhood[71] and up to 60% in adulthood. Hypertension may appear at early ages and continue through adulthood. Hypertension may be the result of renal anomalies that are frequently seen in TS or may be idiopathic.[71] Hypertension can persist after coarctation repair even in those without residual descending aortic pressure gradients. The intrinsic shape of the aorta in individuals with TS without coarctation may be a factor in the pathogenesis of hypertension for some.[118] Obesity, metabolic derangements, the lack of estrogen, the renin-angiotensin system, and abnormal vascular wall and vessel resistance have been identified as pathogenetic factors in hypertension in TS.[118] In addition to well-known end-organ damage in multiple systems, hypertension is a risk factor for aortopathy (specifically AoD) in individuals with TS, although AoD can occur without this risk factor.[6]

Identifying Hypertension and the Value of Ambulatory BP Monitoring

Several guidelines for the measurement and ascertainment of hypertension in infants, children, adolescents, and adults are available, but no guideline specifically addresses individuals with TS. De Groote et al[72] suggest a practical approach to hypertension identification and management for girls and women with TS, including an algorithm for BP evaluation in adult women.

Left ventricular hypertrophy (increased left ventricular mass) has been identified in TS even in those who are normotensive.[119] This could be an end-organ effect of hypertension that is masked during resting BP assessment, or it may relate to loss of diurnal variation (lack of nighttime dipping). Ambulatory BP monitoring (ABPM) has proved to be useful in demonstrating abnormal diurnal variation in BP values in women with TS.[120,121] In addition, because the vasculopathy of TS is characterized by increased vessel stiffness,[40] random resting BP measurement may not accurately reflect ongoing hypertensive stresses occurring throughout the day. Because other conditions associated with elevated arterial stiffness such as chronic kidney disease[122] are known to have a high prevalence of masked hypertension (normal in clinic and high on ABPM), women with TS may also be at increased risk of this abnormal BP pattern. ABPM is the best method to rule out masked hypertension and is the most sensitive method for predicting hypertension-induced left ventricular hypertrophy.[123] ABPM may be particularly valuable in those who are overweight or have prehypertension, conditions associated with a higher prevalence of masked hypertension.

Management

Recognition and treatment of hypertension in TS are similar to that in other individuals and include encouraging healthy lifestyle choices and aggressive management of obesity. Therefore, in all children, hypertension is diagnosed on the basis of percentile rank determined by sex, age, and height.[124] Adult guidelines suggest that BPs <130/80 mm Hg are desirable with >120 mm Hg considered borderline.[72] It is essential to diagnose secondary causes of high BP such as renal anomalies, obstructive uropathy, coarctation, sleep apnea, and hyperaldosteronism. Medication therapy is often used for women with TS with hypertension and includes the entire pharmacological armamentarium typically used for hypertension in patients without TS.[72] However, it is reasonable to treat high BP in TS with certain antihypertensive drugs such as β-blockers or angiotensin receptor blockers that are effective in slowing the rate of aortic dilatation in other genetic aortopathies such as Marfan syndrome.[125]

Women with TS have been recognized to have cellular and endothelial dysfunction that may be unique to the genotype and involves a variety of abnormal feedback and BP control mechanisms. Clues are emerging that give promise of better and more effective treatments. Individuals with TS have an aortopathy characterized by increased vascular stiffness and greater arterial medial thickness, suggesting a potential connection between abnormal vascular compliance/distensibility and childhood onset of essential hypertension. Paternal origin of the X chromosome appears to be associated with decreased aortic compliance.[108] New directions in biomarker detection and directed pharmacological therapy to specific pathogenic derangements are needed. Ultimately, the need to develop evidence-based treatments in the relatively small cohort of individuals with TS will require collaborative, multicenter efforts.

Suggestions for Clinical Practice

- Normal BP values should be defined on the basis of accepted guidelines for the general population.
- The diagnosis of hypertension should be considered in individuals with TS throughout the life span.
- ABPM should be considered in adults and children with normal resting BP, especially in the presence of unexplained left ventricular hypertrophy.
- Antihypertensive medication adequate to control hypertension with a greater emphasis on β-blockers or angiotensin receptor blockers, which may also be efficacious in decreasing aortic growth velocity, is reasonable.

LIPIDS AND THROMBOSIS

Adult women with TS have a high prevalence of ischemic heart disease and stroke.[3] The cardiovascular morbidity and mortality in adult life are significantly higher in women with TS compared with the general population.[2] Lean, normotensive woman with TS may never develop ischemic heart disease, whereas hypertensive patients with type 2 diabetes mellitus, obesity, and insufficient estrogen substitution are more likely to develop stroke or a myocardial infarction throughout life.[126] Therefore, it is important to assess the risk factors of a patient with TS in a multidisciplinary setup and to motivate the patient to exercise, to maintain normal weight, and to abstain from smoking.[127] There is not a specific dyslipidemia associated with TS,[128] but many patients develop an unhealthy lipid profile as a result of obesity, diabetes mellitus, or poor estrogen substitution.[129,130] There is no need for early lipid screening and intervention in childhood; instead, surveillance of risk factors such as obesity, diabetes mellitus, and hypertension is strongly advised. A multidisciplinary approach is important in patients with a high-risk profile, which often includes a cardiologist, an endocrinologist, and a dietitian. Attaining and maintaining a healthy weight through dietary and exercise modification should always be the primary approach. Medical treatment with statins should be implemented, if needed, as indicated by current guidelines.

Suggestions for Clinical Practice

- Lipids should be assessed in early adulthood (17–21 years) to rule out rare disorders in lipid metabolism. Additional assessment will depend on the general health of the patient (diabetes mellitus, hypertension, obesity, family history).
- Considerations for treating dyslipidemia should be based on current guidelines for the general population.

Stroke occurs in excess of the general population,[3] but whether this is simply related to the increased risk of hypertension or other TS-specific causes is unknown. Disturbances of thrombosis and fibrinolysis may increase the risk of thromboembolic stroke. The risk of thrombotic disease has not yet been formally addressed in outcome studies, but an increased risk of thrombus formation, even in the absence of a functional or morphological cardiovascular substrate, has been suggested.[131] Clotting factors and clotting times may be normal for cohorts with TS when assessed in total, but on the individual level, many will have procoagulant levels of clotting and fibrinolytic factors.[7] Fibrinogen has been found to be elevated in 65% of females with TS, and proteins C and S were reduced in a large fraction.[7] Conversely, clotting factors, fibrinolytic factors, fibrinogen levels, and clotting times have also been reported to be within the normal range in other cohorts with TS,[128,132] although high-normal values have been reported for some procoagulant factors.[133,134] The most common mutations associated with thrombus formation are more frequently reported in TS.[133,134] One study showed that factor V Leiden G1691A gene polymorphism heterozygosity is more prevalent in individuals with TS (13%) than in the general population (2%).[133]

Most patients with TS need hormone replacement therapy to induce puberty, to maintain female secondary sex characteristics, to obtain peak bone mass, and to normalize uterine growth,[9] and this treatment does not seem to be an issue in relation to venous thrombosis. The goal is to mimic physiological estrogen levels, and there are no studies that support that treatment with physiological doses increases the risk of thrombosis.[135] Therefore, screening for thromboembolic risk should be performed only in girls with a personal or family history of thromboembolism, and hormone replacement therapy can continue until the risk overshadows the benefits, which is around the usual age of menopause.[136] In summary, the clotting system appears to be excessively activated in some women with TS, but outcome data are lacking, and the common denominator has not yet been found. For this reason, no general recommendation can be issued, but certain awareness about thromboembolic disease in TS will help identify the few women with TS with coagulation disorders.

Suggestion for Clinical Practice

- No general recommendation can be issued for thromboembolic disease in TS. Awareness about the risk of thromboembolic disease in TS will help identify women with TS with coagulation disorders.

GENETICS OF HEART DISEASE

TS is characterized mainly by obstructive left-sided congenital heart defects that are rare in the general female population and should increase clinical suspicion for TS.[1] Congenital heart defects that are commonly diagnosed in TS include coarctation of the aorta, BAV, mitral valve anomalies, hypoplastic left-sided heart syndrome, and partial anomalous pulmonary venous connection.[17,19] Genetic testing for TS should be considered in female patients with any of these abnormalities. Regardless of the indication for genetic testing or specific result, genetic counseling by a geneticist or genetic counselor should be provided before and after any genetic test.[137]

A standard 20-cell karyotype remains the investigation of choice for molecular diagnosis of TS. Any adult woman with suspected TS who has no documented karyotype should be retested. If mosaicism is strongly suspected but not demonstrated with a standard karyotype, additional metaphases may be counted or fluorescence in situ hybridization studies performed.[138–141] Although a karyotype is preferred, TS will be detected on a comparative genomic hybridization microarray[142] (which is routinely performed in children with congenital heart defects). However, if diagnosed by comparative genomic hybridization microarray, a karyotype should subsequently be performed. 45,X/46,XX or 45,X/47,XXX mosaicism is associated with a milder cardiovascular phenotype, including less prevalent and less severe congenital heart defects and lymphatic abnormalities.[143,144] However, there is insufficient evidence to withhold routine surveillance from those with even low levels of mosaicism.

Suggestions for Clinical Practice

- The diagnosis of a BAV or an obstructive left-sided congenital heart defect in a female fetus, child, or adult should prompt a genetic evaluation for TS.
- The diagnosis of TS should be considered in any female with short stature and at least 1 additional characteristic clinical feature (ie, thyroid dysfunction, ovarian failure, Madelung deformity, renal anomalies, or hearing impairment) who also has an associated congenital heart defect.
- All individuals with suspected TS should have a standard 20-cell karyotype analysis because it will identify at least 10% mosaicism with 95% confidence in peripheral blood.
- Guidelines for surveillance and clinical management of cardiovascular disease should be applied equally to all patients with TS, regardless of karyotype.

FUTURE DIRECTIONS

Although the past 2 decades have seen significant advancements in our understanding of TS, many fundamental questions remain unanswered, and those that have been answered have also served to raise more questions. From the developmental origins of the cardiovascular manifestations seen in TS to the best approaches to clinical care for these girls and women, the field is wide open for clinical and basic researchers to make novel and meaningful discoveries. Given the broad scope of medical problems associated with TS, delineating key domains lacking evidence is essential. Therefore, the working group has identified research priorities in the field of TS (Table).

Table. Cardiovascular Research Priorities in TS

Molecular and developmental
Understand the biological and genetic determinants of aortopathy and congenital heart disease in TS.
Understand the impact of endogenous and exogenous hormones, including pregnancy and fertility treatments and growth hormone replacement, on aortic growth and the risk of aortic dissection.
Determine the extent of arterial pathology beyond the aorta.
Identify the role of tissue-specific mosaicism in the isolated cardiovascular phenotype.
Investigate the influence of the second sex chromosome on cardiovascular risk in the general population through the paradigm of TS.
Identify genetic profiles or serum biomarkers that will stratify individual risk.
Medical and surgical
Characterize and reduce the risk for aortic dissection with aortic enlargement in TS, including the use of specific biomarkers and functional imaging tools.
Develop new medical therapies that reduce the risk of cardiovascular complications in patients with TS (with or without aortic dilation).
Optimize risk stratification strategies and identify the ideal criteria for elective aortic surgery.
Elucidate the pathogenesis of increased cardiovascular morbidity and mortality in women with TS compared with the general population and determine the contributions of atherosclerotic disease, dyslipidemia, hypertension, and obesity.
Delineate the risk of stroke in TS.
Understand the pathophysiology of the QTc prolongation and what it means clinically for patients with TS.
Understand the role of estrogen replacement in early stroke risk.
Imaging protocols
Characterize the most accurate tool to define aortic enlargement and aneurysm (ie, TS-specific *z* score vs ASI vs absolute measurement).
Characterize the most accurate approach to measure the aortic diameter (eg, leading edge to leading edge vs inner edge to inner edge or measurements taken during systole vs diastole).
Pregnancy
Use the ROPAC registry to characterize the risk of pregnancy associated with TS (eg, aortic dissection, fetal growth restriction, preeclampsia).
Investigate the additional risk of ART.

ART indicates assisted reproductive therapy; ASI, aortic size index; ROPAC, Registry of Pregnancy and Cardiac Disease; and TS, Turner syndrome.

A better understanding of cardiovascular health in TS must overcome 2 fundamental challenges: A vast array of cardiovascular diseases significantly affect girls and women with TS, and TS is a rare condition, making the recruitment of large numbers of subjects for clinical studies difficult. Accordingly, significant advances will require collaboration across all the cardiovascular subspecialties and will need to engage research centers throughout the world. Clinical registries, such as the Turner Syndrome Research Registry, sponsored by the Turner Syndrome Society of the United States, and the Registry of Pregnancy and Cardiac Disease, sponsored by the European Society of Cardiology, that can recruit large numbers of potential research subjects, will be crit-

ical to the success of these projects. The topical areas of interest in terms of cardiovascular disease in TS include genetic and developmental factors affecting congenital and acquired disease, pathophysiological mediators and mitigators, clinical outcomes in operated and unoperated states, therapeutic strategies to improve clinical outcomes, and clinical management strategies to improve quality of life and attainment of full potential.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

†Significant.

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