Endocrine Update in Turner Syndrome

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Pediatric Endocrinologist
Children’s Mercy Hospital
Conflict of Interest

• Speakers Bureau
  – Novo Nordisk
  – Pfizer
Objectives

• At the conclusion of the session, participants should:
  – Understand diagnostic features and karyotype abnormalities found in TS
  – Be aware of the multi-disciplinary medical needs in girls with TS
  – Appreciate existing controversies in care of girls with TS
Background

• Definition: loss of all or part of one sex chromosome with physical features in a phenotypic female

• Occurs in 1 in 2000 live born females
Estimated 80,000 affected in the U.S.
CLINICAL PRACTICE GUIDELINE

Care of Girls and Women with Turner Syndrome: A Guideline of the Turner Syndrome Study Group

Carolyn A. Bondy for the The Turner Syndrome Consensus Study Group*

National Institutes of Health, National Institute of Child Health and Human Development, Bethesda, Maryland 20892

Objectives: The objective of this work is to provide updated guidelines for the evaluation and treatment of girls and women with Turner syndrome (TS).

Participants: The Turner Syndrome Consensus Study Group is a multidisciplinary panel of experts with relevant clinical and research experience with TS that met in Bethesda, Maryland, April 2006. The meeting was supported by the National Institute of Child Health and unrestricted educational grants from pharmaceutical companies.

Evidence: The study group used peer-reviewed published information to form its principal recommendations. Expert opinion was used where good evidence was lacking.

Consensus: The study group met for 3 d to discuss key issues. Breakout groups focused on genetic, cardiological, auxological, psychological, gynecological, and general medical concerns and drafted recommendations for presentation to the whole group. Draft reports were available for additional comment on the meeting web site. Synthesis of the section reports and final revisions were reviewed by e-mail and approved by whole-group consensus.

Conclusions: We suggest that parents receiving a prenatal diagnosis of TS be advised of the broad phenotypic spectrum and the good quality of life observed in TS in recent years. We recommend that magnetic resonance angiography be used in addition to echocardiography to evaluate the cardiovascular system and suggest that patients with defined cardiovascular defects be cautioned in regard to pregnancy and certain types of exercise. We recommend that puberty should not be delayed to promote statural growth. We suggest a comprehensive educational evaluation in early childhood to identify potential attention-deficit or nonverbal learning disorders. We suggest that caregivers address the prospect of premature ovarian failure in an open and sensitive manner and emphasize the critical importance of estrogen treatment for feminization and for bone health during the adult years. All individuals with TS require continued monitoring of hearing and thyroid function throughout the lifespan. We suggest that adults with TS be monitored for aortic enlargement, hypertension, diabetes, and dyslipidemia. (J Clin Endocrinol Metab 92: 10–25, 2007)
Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting

On behalf of the International Turner Syndrome Consensus Group

www.eje-online.org
DOI: 10.1530/EJE-17-0430
Definition of Turner Syndrome

• Phenotypic female

• Complete or partial absence of the second sex chromosome

• Associated with one or more clinical manifestations of TS.
**Clinical Features**

**Table 3** Indications for chromosome analysis to diagnose Turner syndrome.

<table>
<thead>
<tr>
<th>As the only clinical feature:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal cystic hygroma, or hydrops, especially when severe</td>
</tr>
<tr>
<td>Idiopathic short stature</td>
</tr>
<tr>
<td>Obstructive left-sided congenital heart defect&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Unexplained delayed puberty/menarche</td>
</tr>
<tr>
<td>Couple with infertility</td>
</tr>
<tr>
<td>Characteristic facial features in a female&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>At least two of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal anomaly (horseshoe, absence, or hypoplasia)</td>
</tr>
<tr>
<td>Madelung deformity</td>
</tr>
<tr>
<td>Neuropsychologic problems, and/or psychiatric issues</td>
</tr>
<tr>
<td>Multiple typical or melanocytic nevi</td>
</tr>
<tr>
<td>Dysplastic or hyperconvex nails</td>
</tr>
<tr>
<td>Other congenital heart defects&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hearing impairment &lt;40 years of age together with short stature</td>
</tr>
</tbody>
</table>
NOT Turner Syndrome

- Phenotypic males with 45,X/46,XY (or other variant)
- Women >50 years with less than 5% 45,X (Russell et al., Cyto Gen Res, 2007).
- Very low (<5%) 45,X, in general
- SHOX deficiency
- Distal deletions Xq (del Xq26-28)
  - premature ovarian failure (POF) (Mercer et al., EJMG, 2012)
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Gene (candidate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stature, skeletal anomalies</td>
<td>SHOX</td>
</tr>
<tr>
<td>Stature, gonadal failure, minor physical features</td>
<td>(ZFX)</td>
</tr>
<tr>
<td>Viability</td>
<td>(USP9X)</td>
</tr>
<tr>
<td>Gonadal failure</td>
<td>(RPS4X)</td>
</tr>
<tr>
<td></td>
<td>(DIAPH2)</td>
</tr>
</tbody>
</table>
How to Diagnose

• Standard 20-cell karyotype which can identify at least 10% mosaicism with 95% confidence (ACMG Guideline: Wolff D, et al., Genet Med, 2010).

• If mosaicism is strongly suspected, additional metaphases may be counted or FISH studies performed.

• Consider a second tissue may be examined if there is a strong clinical suspicion of TS despite a normal blood karyotype or if there is low level mosaicism
  • Fibroblast
  • Cheek cells
Repeat Karyotype

- Infants who were diagnosed prenatally should have a postnatal karyotype
- Women diagnosed by a buccal swab only,
- Original karyotype performed in the distant past
- Original report not available for review
Recent Email

• “I got a phone call from the family of a patient diagnosed with Turner syndrome based on FISH studies which showed 4.2% mosaicism for 45,X. The family had questions about this wording from the paper (page G9):
  – ‘In women less than 50 years of age, there is no specific lower limit for 45,X that defines TS, although many have used 5%.’

• The family’s question was, does Olivia still have a diagnosis of Turner syndrome based on these guidelines?”
Non-invasive testing

- Insufficient evidence to recommend screening by sequencing or SNP array analysis of cell-free fetal DNA (cfDNA) in maternal blood. A meta-analysis of 37 studies showed that the detection rate (90%) and positive predictive value (23%) of cfDNA analysis was relatively low.

(Gil et al., Ultrasound Obstet Gynecol, 2015)
Y Material

• Found in about 10% of females with TS

• FISH with X and Y centromere probes is recommended to determine the origin of rings or small marker chromosomes

• FISH with the centromere probe DYZ3 is clinically indicated to exclude cryptic Y material associated with gonadoblastoma risk in individuals with 45X
  – Not SRY probe

• Routine molecular screening for Y-chromosomal sequences is recommended in TS patients with masculinization who are negative for Y sequences by conventional cytogenetic and FISH analysis.
Cytogenetic Findings in TS

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>45,X</td>
<td>54.6%</td>
</tr>
<tr>
<td>46, X,i(Xq)</td>
<td>16.6%</td>
</tr>
<tr>
<td>45,X/46,XX</td>
<td>12.6%</td>
</tr>
<tr>
<td>46,X,r(X)</td>
<td>5.3%</td>
</tr>
<tr>
<td>45,X/46,XY</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

Diagnosis

• Typically diagnosed at the following times
  – Prenatally- incidental or due to US findings
    • 90+% of 45X abort spontaneously
  – Neonatal period- heart defects or edema
  – Childhood- short stature
  – Teens- pubertal delay
  – Adulthood- infertility
    • 38%! 
Diagnosis

• Average age at diagnosis is about 6.5 years and is trending younger
  – 9 years for those not diagnosed in infancy
  – Average delay in diagnosis is 5 years after height drops below normal
Phenotype/Karyotype Generalizations

- **45,X compared to 45,X/46,XX mosaicism** is associated with
  - More severe phenotype, more CHD
  - More frequent early miscarriage.
- **45,X/46,XX mosaicism diagnosed postnatally**
  - More severe presentation than in patients identified prenatally.
- **45,X/46,XX mosaicism**
  - Varies with tissue type and patient age
- **45,X compared to 45,X/47,XXX mosaicism**
  - More severe phenotype
- **45,X with a Y chromosome** detected by standard karyotype or FISH:
  - Associated with an increased risk of gonadoblastoma.
- **Ring X chromosome**
  - Not always associated with severe intellectual disability.
# Physical Findings in TS

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Stature</td>
<td>100</td>
</tr>
<tr>
<td>Short neck</td>
<td>40</td>
</tr>
<tr>
<td>Abnormal US/LS ratio</td>
<td>97</td>
</tr>
<tr>
<td>Cubitus valgus</td>
<td>47</td>
</tr>
<tr>
<td>Short metacarpals</td>
<td>37</td>
</tr>
<tr>
<td>Madelung deformity</td>
<td>8</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>13</td>
</tr>
<tr>
<td>Genu valgum</td>
<td>35</td>
</tr>
<tr>
<td>Characteristic facies with micrognathia</td>
<td>60</td>
</tr>
<tr>
<td>Webbed neck</td>
<td>25</td>
</tr>
<tr>
<td>Low posterior hairline</td>
<td>42</td>
</tr>
<tr>
<td>Rotated ears</td>
<td>Common</td>
</tr>
<tr>
<td>Edema of hands/feet</td>
<td>22</td>
</tr>
<tr>
<td>Severe nail dysplasia</td>
<td>13</td>
</tr>
<tr>
<td>Strabismus</td>
<td>18</td>
</tr>
<tr>
<td>Ptosis</td>
<td>11</td>
</tr>
<tr>
<td>Multiple pigmented nevi</td>
<td>26</td>
</tr>
</tbody>
</table>


**Skeletal Growth Abnormalities**

**Lymphatic Obstruction Abnormalities**
GROWTH
Growth

• On average, girls with TS are 20 cm shorter than expected (8 inches)
  – Average untreated adult height is 4’ 8”
• Growth failure begins in utero and continues into childhood
  – No pubertal growth spurt
Body Proportions (Untreated Adults)

Gravholt CH, Naeraa RW 1997 AJMG 72:403–408
Growth Hormone

• GH therapy improves final height
  – Generally not deficient in GH

• Goal of therapy is to normalize height as early as possible
  – Normalize height in childhood and adulthood
  – Allows initiation of puberty at appropriate age
  – Cheaper?
Effectiveness of GH

- A randomized study showed a 7.2 cm gain over 5.7 years of treatment
  - Range 2-17 cm
  - 45mcg/kg/day
Adult Height Data:
Placebo-controlled Trial, Mean Data

Mean GH treatment effect at adult height = 5.0 cm

Ross JL et al. 2011 NEJM 364(13): 1230-42
Baseline Age and Gain in Height SDS

Quigley CA et al. 2002 J Clin Endocrinol Metab 87(5): 2033-41
Predictors of Taller AH

• Taller height at initiation
• Taller MPH
• Young age at initiation
• Longer period of treatment before puberty induction
• Long duration of tx
• Higher GH dose
Growth

• Looking at national GH database
  – Mean height SDS at initiation of rGH in girls with TS was -3 SDs
  – Mean age at initiation of rGH in girls with TS was 8.5 years

Differences in Children Treated With Recombinant Human Growth Hormone (rhGH): Have They Changed Over Time? Data From the Genentech National Cooperative Growth Study (NCGS)
Cernich J, Frane J, Lippe B
What dose to use?

Sas TC et al. 1999 J Clin Endocrinol Metab 84: 4607-12
van Pareren YK et al. 2003 J Clin Endocrinol Metab 88: 1119-1125

- Baseline age 2-11 yr (mean 6.5-6.9 yr)
- Also treated with low dose estrogen
IGF-1 levels in Dutch cohort

GH Recommendations

• Begin GH tx at 4-6 years of age if:
  – Evidence of growth failure
  – Already short or high likelihood of short stature
• Initial dosing of 45-50 mcg/kg/day
  – May increase to 68 mcg/kg/day
• Measure IGF-1 at least annually
  – Decrease dose if above 3 SDs from mean
  – Use clinical judgment if 2-3 SDs above mean
• Treat until growth slows- no need for “adult” tx
Growth

• GH risks in TS- studies not powered
  – Scoliosis
  – Diabetes- unclear
  – SCFE
  – Benign intracranial hypertension
  – Pancreatitis- possible

• No adverse effects on:
  – Cardiac size, aortic diameter, or CV function

Bell J et al. 2010 J Clin Endocrinol Metab 95(1): 167-77
Darendeliler F et al. 2007 Horm Res 68 Suppl 5: 41-7
GH and Diabetes in TS

• Studies show baseline insulin resistance and increased insulin levels on GH
• Glucose levels remain unchanged

Van Pareren YK et al. 2002 J Clin Endocrinol Metab
Bannink et al. 2009 Horm Res
Oxandrolone

• Adding oxandrolone 0.03-0.05 mg/kg/d to GH resulted in mean incremental height gain between 2.3 and 4.6 cm vs. GH alone
  – mild dose-dependent virilization
  – delayed breast development during treatment but no differences in adulthood
  – no negative effects on body proportions, carbohydrate metabolism, bone mineral density, psychosocial outcomes

Zeger MP et al. 2011 Horm Res Paediatr
Menke LA et al. 2010 JCEM
Freriks K et al. 2013 Eur J Endocrinol
PUBERTAL INDUCTION
Puberty

• Up to 30% of girls with TS have some spontaneous pubertal development
  – 2-5% achieve spontaneous pregnancy
• But, 90% eventually have gonadal failure
• If estrogen is needed, try to mimic normal puberty
  – What age?
  – What formulation?
Puberty

• What age should puberty be induced?
  – Early recommendation was 15 years
    • Increase final height by delaying epiphyseal fusion
    • Mostly ignored psychosocial aspects of delayed puberty
Puberty

• Other benefits to earlier start of estrogen
  – Cognitive
  – Hepatic
  – Quality of life
  – Possible benefit on bone density
Puberty

- What estrogen formulation?
Oral Estrogen

• Reaches systemic circulation after absorption into portal venous system and metabolism by liver
  – Exposing liver to a greater dose of estrogen than rest of body
  – Metabolized by liver to estrone and other metabolites before reaching systemic circulation
    • Associated with a pro-coagulable state, and increased risk of stroke

Mohammed JCEM 2015
Canonico Stroke 2016
Systemic Estradiol Options

• Transdermal
  – Can be cut into smaller doses

• Depot
  – Not preferred by most patients when transdermal option available

• Transvaginal
  – Not recommended in prepubertal girls
Oral contraceptive pills

• Not recommended to induce puberty
  – Estrogen dose too high
  – Growth deleterious effects
• May be used in girls with spontaneous puberty and secondary amenorrhea
• May be used for adult estrogen dosing
Monitoring treatment

• Routine monitoring of serum LH or FSH not recommended as levels remain elevated until higher levels of estrogen given

• Determinants for dose increase
  – Physiologic progression
  – Clinical assessment
  – Patient satisfaction
  – Growth potential
  – If girls are already older at initiation, the duration of time until adult dosing may be shortened

Torres-Santiago 2013
AMH as Predictor of Ovary Function

AMH < 4 pmol/L (<-2 SD) predicted no ovarian function

Lunding 2015 JCEM
## Recommended Estrogen replacement

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Pubertal Initiation dose</th>
<th>Adult dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transdermal E₂</strong></td>
<td>Equivalent of 3-7 µg/d</td>
<td>50-150 µg/d</td>
</tr>
<tr>
<td><strong>Micronized 17β oral E₂</strong></td>
<td>0.25 mg/d</td>
<td>1 - 2 mg/d</td>
</tr>
<tr>
<td><strong>Ethinyl Estradiol</strong></td>
<td>2 µg/d</td>
<td>10 - 20 µg/d</td>
</tr>
<tr>
<td><strong>Depot E₂</strong></td>
<td>0.2 mg/m</td>
<td>2 mg/m</td>
</tr>
</tbody>
</table>

CEE not recommended in view of thromboembolic risks in postmenopausal women, although there have been no studies in children.
Breast Development with Induction

• Onset breast buds within 6 m
  • Depot E₂ dosing → slightly slower
  • Oral E₂ → slightly faster

• Stage 4 breasts in avg of 2.25 yr
  • Similar to TS girls with spontaneous puberty (1.9 yr)
  • Similar to avg breast development in girls

• Increase every 6 m by 25-100% for 4 -6 dose changes

Ankarberg-Lindgren JCEM 2001
van Pareren YK JCEM 2003
Bannink Clinical Endocrinology2009
Perry RJ Horm Res Paediatr 2014
Oral vs. Transdermal Estradiol

Only one study has directly compared oral vs. transdermal, using E₂ itself

- 40 girls with TS followed for 1 year
- Plasma E₂ titrated to levels of normally menstruating adolescents
- No differences in:
  - body composition
  - bone mineralization
  - plasma lipids
- However, oral E₂:
  - Increased estrone, estrone sulfate and serum estrogenic bioactivity
  - Concerning for thromboembolic risk

Torres-Santiago JCEM 2013
Bone

• Delaying estrogen replacement harmful to bone health
• TD E2 (25-37.5 µg/) reported better than CEE (0.3-0.45 mg/d) for spine BMD in one study
• No differences were observed in another study in which TD and oral E2 doses were titrated to similar levels

Nabhan JCEM 2009
Torres-Santiago JCEM 2013
Ultra-low Dose Estrogen at Young Age

- Baseline age 5.0-12.9 yr
- GH 100 µg/kg 3 x week or placebo
- Half also received ultra low-dose EE2 from age 5
- Modest synergistic effect of childhood EE2 with GH

Ross JL et al. 2011 NEJM
Risk of Thrombosis

• Assessment of risk should be performed if personal or family hx of thrombosis
• Primarily to educate family on risks
  – Not to delay estrogen tx
Example

- RESULTS:
- Factor V Leiden: ABNORMAL. This patient is heterozygous of the factor V Leiden mutation, 1691G>A. This genotype is associated with a 5-10x increased risk for venous thrombosis. Recommend genetic counseling and DNA studies for at-risk family members.

- Prothrombin gene (factor II) ABNORMAL. This patient is heterozygous for the prothrombin variant, 20210G>A. Patients with this genotype have a 3 to 6 fold increased risk for venous thrombosis. Other factors, both environmental and genetic, may further increase this risk. DNA studies for at-risk family members, genetic counseling, and clinical correlation are recommended.
Puberty

• Bottom line
  – Begin tx at 11-12 years of age
  – Transdermal estradiol is preferred
  – Start low-dose
    • i.e. ¼ of a 25 mcg patch
  – increase over 2-4 years to adult dose
  – Add progestin after 2 years or at time of breakthrough bleeding
PREGNANCY
General recommendations

• Taking into account the positive outcomes after OD, we conclude that TS *per se*, is not a contraindication for pregnancy.

• Only after thorough screening and appropriate counseling should a woman with TS be considered for treatment with OD
  – Single embryo transfer is mandatory in TS recipients

• Even if all pre-screening results are normal, the maternal risks are still increased
Contraindications to pregnancy

- Significant cardiovascular abnormalities including a history of aortic surgery or aortic dissection
- Coarctation of the aorta
- Aortic size index > 2.5 cm/m²
- Uncontrolled hypertension
- Other major cardiac anomaly
Recommendations for follow-up during pregnancy

- Should be followed by a multidisciplinary team including maternal fetal medicine specialists, and cardiologists with experience in managing women with TS.
- An echocardiogram or MRI should be performed two to three times during pregnancy.
- Hypertension should be treated aggressively aiming at having blood pressure <140/90
# Co-Morbidities

Table 6. Recommendations for screening in Turner syndrome at diagnosis and throughout life (excluding those covered elsewhere, i.e. cardiac and neuropsychological).

<table>
<thead>
<tr>
<th>Test</th>
<th>At diagnosis</th>
<th>After diagnosis (childhood)</th>
<th>After diagnosis (adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight/BMI</td>
<td>Yes</td>
<td>Every visit</td>
<td>Every visit</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Yes</td>
<td>Every visit</td>
<td>Anually</td>
</tr>
<tr>
<td>Thyroid function (TSH and (free) T4)</td>
<td>Yes</td>
<td>Anually after 10 years of age</td>
<td>Anually</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminotransferase, GGT and alkaline</td>
<td></td>
<td>Anually after 10 years of age</td>
<td>Anually</td>
</tr>
<tr>
<td>phosphatase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c with or without fasting plasma</td>
<td></td>
<td>Anually after 10 years of age</td>
<td>Anually</td>
</tr>
<tr>
<td>glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-Hydroxyvitamin D</td>
<td></td>
<td>Every 2–3 years after</td>
<td>Every 3–5 years</td>
</tr>
<tr>
<td>Celiac screen</td>
<td></td>
<td>9–11 years of age</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Starting at 2 years; thereafter every two years</td>
<td>With suggestive symptoms</td>
</tr>
<tr>
<td>Renal ultrasound</td>
<td>Yes</td>
<td>Every 3 years</td>
<td>Every 5 years</td>
</tr>
<tr>
<td>Audiometric evaluation</td>
<td>Yes*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmological examination</td>
<td>Yes*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental evaluation</td>
<td>Yes, if no previous care has been established</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical investigation for congenital hip dysplasia</td>
<td>Yes, in newborns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin examination</td>
<td>At diagnosis</td>
<td>Anually</td>
<td>Anually</td>
</tr>
<tr>
<td>Bone mineral density</td>
<td></td>
<td>5–6 years and 12–14 years (see 6.1.10)</td>
<td></td>
</tr>
<tr>
<td>Skeletal assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CARDIAC
Cardiovascular

- Patients with TS have a 3-fold increased mortality vs. the general population
  - Roughly 40% of that increase is due to cardiovascular disease
- Structural abnormalities
- Conductive abnormalities
- Aortic Dissection
Structural Abnormalities

• Most common findings are
  – Bicuspid aortic valve
    • RR 180 compared to 46,XX
  – Coarctation of the aorta
    • 4-fold increase in pts. with webbed neck
    • ? Lymphatic obstruction causative
Aortic Dissection

• Relatively rare (40 per 100,000 TS patient years)
• Usually associated with risk factors:
  – BAV
  – Coarctation
  – Aortic dilation
  – Hypertension
    • Seen in about 25% of girls with TS
• Some cases have occurred without risk factors
Aortic Dissection

• Occurs earlier than general population
  – Average age is mid-30’s in TS
• Occurs at a smaller aortic diameter
  – >2.5 cm/m² in teens
• Pregnancy may also be a risk factor
  – 2% incidence of maternal death by aortic rupture
Cardiac Monitoring Youth

Infancy – 16 years: Cardiology exam, TTE, CMR, ECG

No CoA, BAV, HTN
- TSZ ≤ 3: Low risk
  - Repeat TTE or CMR every 5 years by primary managing clinician
- TSZ > 3: Moderate risk
  - Repeat TTE or CMR every 1 year by pediatric cardiologist

CoA, BAV, and/or HTN
- TSZ ≤ 3: Moderate risk
  - Repeat TTE or CMR every 1-2 years by pediatric cardiologist
- TSZ > 3: High risk
  - Repeat TTE or CMR every 6 months -1 year by pediatric cardiologist
Cardiac Monitoring Older

Above 16 years:
Cardiology exam, TTE, CMR, ECG

No CoA, BAV, HTN

ASI ≤ 2.0 cm²/m²
- Low risk
  - Repeat TTE or CMR every 5-10 years by cardiologist

ASI 2.0–2.3 cm²/m²
- Moderate risk
  - Repeat TTE or CMR every 3-5 years by cardiologist

ASI > 2.0–2.3 cm²/m²
- Moderate risk
  - Repeat TTE or CMR every 1 year by cardiologist

CoA, BAV, and/or HTN

ASI ≤ 2.3 cm²/m²
- Moderate risk
  - Repeat TTE or CMR every 2-3 years by cardiologist

ASI ≤ 2.3 cm²/m²
- High risk
  - Repeat CMR every 6 months - 1 year by cardiologist
Hypertension

- HTN may be present in 20-40% of pediatric age
  - 60% of adults with TS
- Should be assessed annually
- Treat with Beta blocker and/or ARB
  - > 16 with ascending ASI of ≥ 2.3 cm/m2
  - < 16 with ascending with TS z-score of > 3.0
- Neither BP threshold nor best anti-HTN regimen is established
Thank You