European Reference Network
for rare or low prevalence complex diseases

Network Vascular Diseases (VASCERN)

HTAD PATIENT PATHWAY

Strategy for Diagnosis and Initial Management of patients and families with (suspected) Heritable Thoracic Aortic Disease (HTAD)

DISCLAIMER

This document is an opinion statement reflecting strategies put forward by experts and patient representatives involved in the HTAD rare disease group of VASCERN.

This pathway is issued on 26/04/2018 and will be further validated and adjusted where needed.

1 Defining HTAD

Heritable Thoracic Aortic Disease (HTAD) covers disease entities with as common denominator Thoracic aortic aneurysms or –dissections that are familial and/or caused by genetic defects. Both syndromic and nonsyndromic entities exist. Although the number of genes involved in HTAD is steadily increasing, a large number of patients/families with HTAD have no identifiable defect, indicating that other genes must be involved. Genetic defects identified so far have can be categorized into (1) genes encoding components of the extracellular matrix (FBN1, MFAP5, MAT2A); (2) genes encoding components of the TGF signaling pathway (TGFBR1/2, TGFB2/3, SMAD2/3); (3) genes encoding components of the smooth muscle cell contractile apparatus (ACTA2, MYH11, MYLK, PRKG1).

Clinical entities covered by this WG include:

- ***syndromic entities*** such as Marfan Syndrome (ORPHA558), Loeys Dietz Syndrome (ORPHA60030), Aneurysm Osteoarthritis syndrome (ORPHA284984), Arterial tortuosity syndrome (ORPHA3342), Multisystemic smooth muscle dysfunction syndrome (ORPHA404463) and Neonatal Marfan syndrome (ORPHA284979)
- As well as ***nonsyndromic entities*** such as Familial Thoracic Aortic Aneurysms Dissections (Familial TAAD) (ORPHA91387), Familial aortic dissection (ORPHA229), caused by mutations in
    - actin, alpha 2, smooth muscle, aorta – ACTA2
    - fibrillin 1 – FBN1
    - microfibrillar associated protein 5 – MFAP5
    - myosin, heavy chain 11, smooth muscle – MYH11

- myosin light chain kinase – MYLK
- protein kinase, cGMP-dependent, type I – PRKG1
- SMAD family member 3 – SMAD3
- transforming growth factor beta 2 – TGFB2
- transforming growth factor beta 3 – TGFB3
- transforming growth factor beta receptor I – TGFBR1
- transforming growth factor beta receptor II – TGFBR2
- …

2 Overall Purpose of the Patient Pathway

Provide a uniform and approved (by VASCERN[1]) pathway that can be used by specialized centers for the clinical and molecular assessment of patients and families with (a suspicion of) Heritable Thoracic Aortic Disease (HTAD).

3 Working Group composition and work-flow for the pathway

The HTAD Rare Disease Working Group is one of the five Rare Disease WG's of the European Reference Network on rare multisystemic cardiovascular diseases (VASCERN).

A total of 13 HCPs representing 8 EU countries are member of the WG, as well as one patient representative. 2 additional guest centers from 2 countries are cooperating with the WG. The full list can be found on the website.

The pathway was generated based on available guidelines when possible and on expert opinion in all other settings. Discussion items were listed and if necessary items were included in a questionnaire sent out for voting and discussion over monthly teleconference calls.

4 Setting for the use of the pathway

Specialized centers for diagnosis and follow-up of HTAD with clinical and molecular genetic facilities.

5 Aims

1) Primary

- ❖ Decrease delay time to diagnosis.
- ❖ Establish correct diagnosis with molecular confirmation if possible.
- ❖ Exclude diagnosis when appropriate (important for reassurance).

2) Secondary

Optimize the use of resources: avoid overconsumption of financial and personnel resources

1 European Reference Network on multisystemic vascular diseases

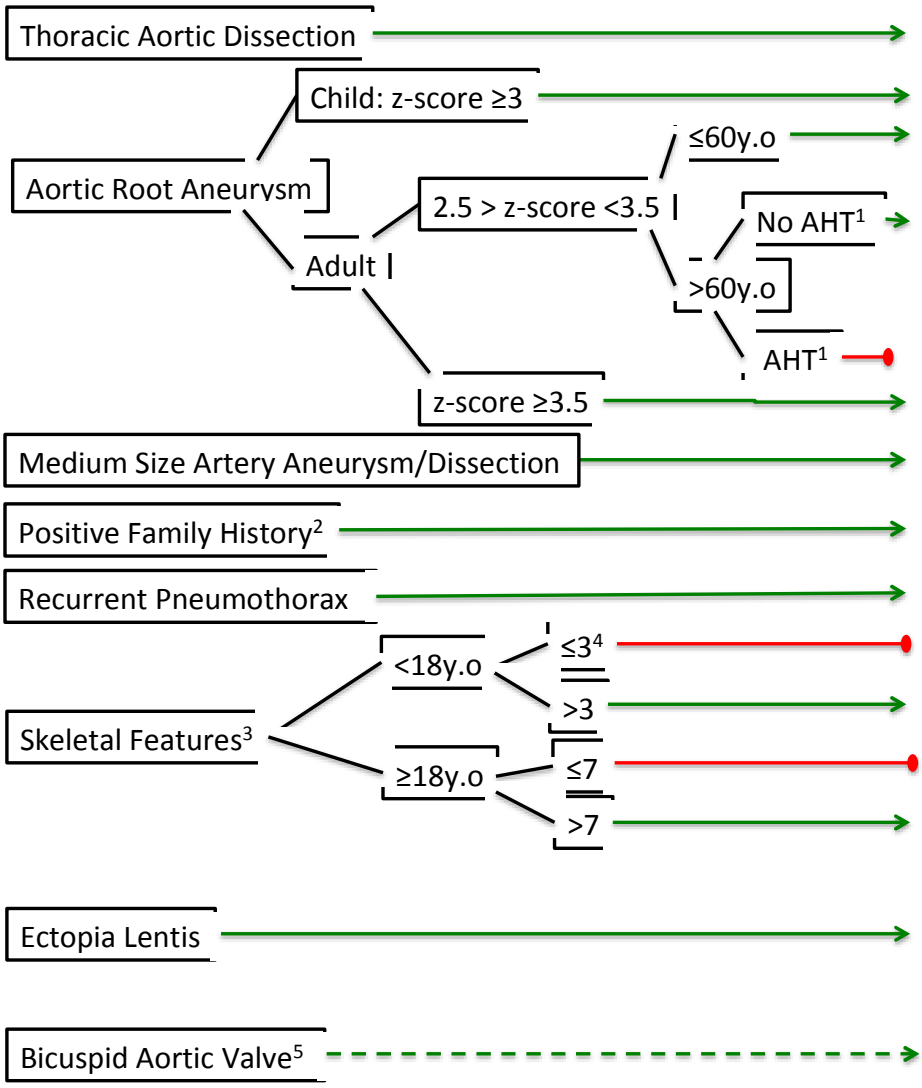
6 Pathway Elements

6.1 Presenting feature

Indicates the spectrum of presenting features for which patients are typically evaluated at the center.

According to the health care system and country specific rules for referral, some patients will undergo an initial screening outside the specialized center while other centers will offer this pre-screening themselves. In all cases, this pre-screening needs to be performed in close collaboration and under supervision of the regional HTAD center.

Patients considered eligible for further evaluations need clinical work-up and counseling at a specialized center where the indication for additional genetic testing will be considered.



[1]AHT-Arterial Hypertension = BP>140/90 or antihypertensive treatment
[2]Min 1 person first or second degree family
- TAA or dissection (suspicion) <60yr
- LVOT abnormality
- Sudden death <45yr

[3]systemic score and/or bifid uvula, hypertelorism, clubfoot, early onset and widespread ostoarthritis
[4]needs re-evaluation after 3-5yrs until age 18
[5] see below for further specifications

Specific considerations

1) Aortic Root measurements

❖ *Z-score*: according to the technique used (echo, CT, MRI) different reference values should be used. Transthoracic echocardiography is considered as the cornerstone study for measurement of the aortic root and for calculation of z-scores we recommend the formula's provided by Devereux (Devereux et al. 2012)(adults) and Campens (Campens et al. 2014)(adults and children) since these take sex into account.

❖ *Sex difference*: while sex definitely plays a role in the outcome and prognosis in HTAD patients with an established diagnosis – it is less an issue in the diagnostic setting since we agree to take all patients into account up to the age of 60y at which time almost 100% of men and women with HTAD will have developed AA dilatation(Detaint et al. 2010). Moreover, sex is included as a factor in the z-score calculation

2) **Age:** several features in the setting of HTAD are strongly age dependent.
   a. Aortic dilatation: may be absent in childhood / may be related to other factors at older age
      - Z-score takes age into account
      - Exclude patients >60 with hypertension and z-score <3,5 (unless positive family history – see below)
   - Skeletal features: may be mild in young children
      - Age distinction for the systemic score threshold

3) **Family History:** first or second degree relatives
   - TAA or aortic dissection <60yr. Aneurysm/dissection does not need to be formally proven in the family member

4) Skeletal features

SS >3 or >7 according to age. (SS= systemic score - see(Loeys et al. 2010))
- SS between 2 – 7 AND club feet, hypertelorism, bifid uvula; any age.

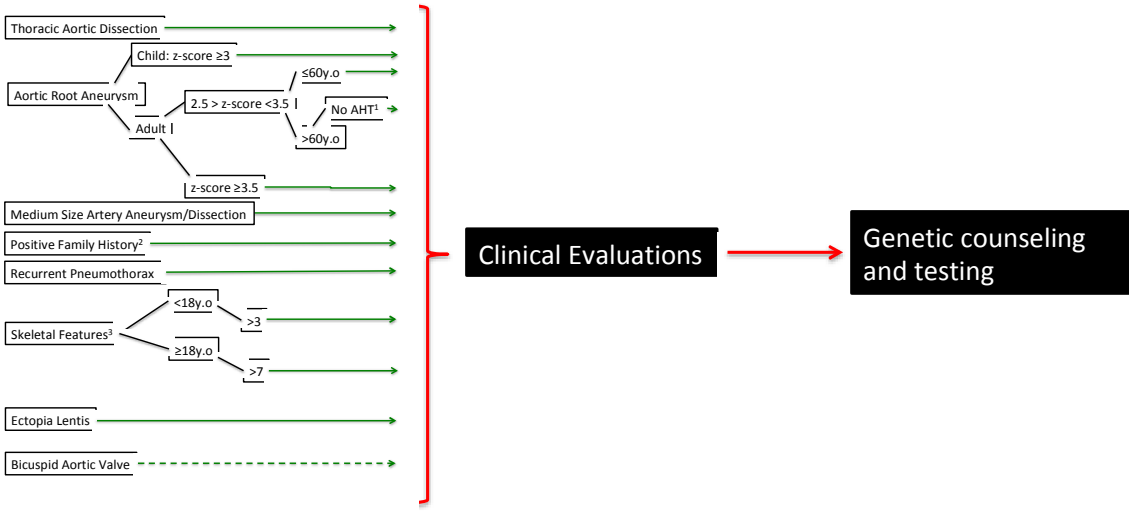
5) **Bicuspid Aortic Valve (BAV):** since BAV is a highly prevalent disease with low mutation detection rates at present. Therefor, we do not recommend genetic testing in all subjects and would limit this to
   - Familial cases
   - probands with additional systemic features
   - young probands with TAA and associated isolated AR

6.2 Clinical Evaluations

❖ Cardiovascular imaging
   - Cardiac ultrasound (TTE) is the cornerstone in diagnostic/screening setting and is necessary in all cases in whom the presenting feature is not a TAA or TAD.
   - In cases with documented TAA, additional imaging of the vascular system is indicated to exclude aneurysms at other locations and assess arterial tortuosity. Given the easier accessibility of CT in most centers, this is preferred over MRI in the screening setting – MRI is the preferred technique for follow-up.

- ❖ Ophtalmology (incl slit lamp examination)
    - Not indicated in all patients – restricted to those with a suspicion of classical Marfan Syndrome – slit lamp possible from the age of 3y
- ❖ Skeletal evaluation
    - Systemic score skeletal features to be assessed in all patients + hypertelorism, bifid uvula and (history of) club feet + (history of) early onset and widespread osteoarthritis
- ❖ Echocardiogram in first degree relatives

Results obtained from the clinical evaluations need discussion in a multidisciplinary setting at the specialized center after which the indication for additional molecular genetic testing will be evaluated



6.3 Genetic counseling and testing

Those patients in whom the clinical evaluations warrant further genetic testing will be sent for genetic counseling and consecutive testing at a center with expertise in the genes associated with HTAD

- ❖ FBN1: in clinical diagnosis of Marfan syndrome & ectopia lentis
- ❖ Panel in all others

Gene selection: Core genes listed in (Arslan-Kirchner et al. 2015). This list is dynamic and needs regular updating!

ACTA2 COL3A1 FBN1 FLNA MAT2A MFAP5 MYH11 MYLK NOTCH1 PRKG1 SMAD3 TGFB2 TGFB3 TGFBR1 TGFBR2

6.4 Family Follow-up

- ❖ Mutation known: cascade screening
- ❖ Mutation unknown in the index patient: follow-up depending on how many family members are affected. Start at 25y or 10y below the youngest TAA in the family, end at 65y (Dutch guidelines (Verhagen et al. 2018)).
    - 1 affected first/second degree relative: age dependent (both age of proband and family member!)
        - Proband <40y: repeat studies in family members
    - ≥2 affected first/second degree relatives: Echocardio. To repeat every 5y – every 2y in case of arterial hypertension

Arslan-Kirchner, M. et al., 2015. Clinical utility gene card for: Hereditary thoracic aortic aneurysm and dissection including next-generation sequencing-based approaches. *European Journal of Human Genetics*.

Campens, L. et al., 2014. Reference values for echocardiographic assessment of the diameter of the aortic root and ascending aorta spanning all age categories. *The American journal of cardiology*, 114(6), pp.914–920.

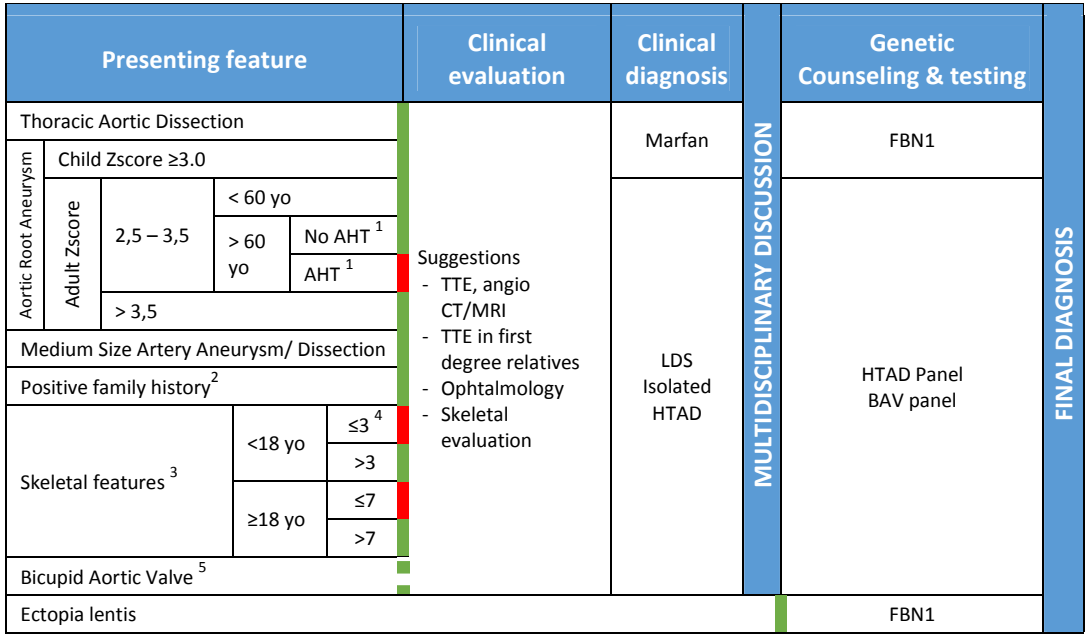
Detaint, D. et al., 2010. Cardiovascular manifestations in men and women carrying a FBN1 mutation. *European Heart Journal*, 31(18), pp.2223–2229.

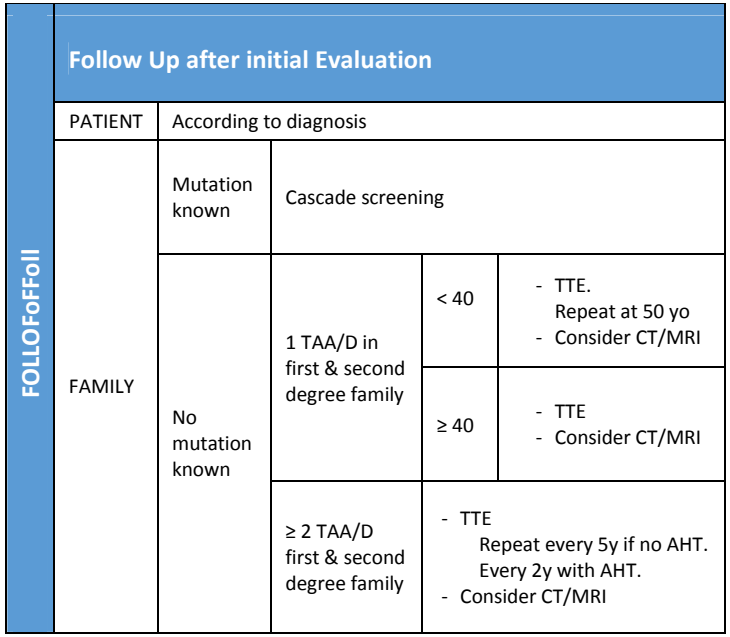
Devereux, R.B. et al., 2012. Normal limits in relation to age, body size and gender of two-dimensional echocardiographic aortic root dimensions in persons ≥15 years of age. *The American journal of cardiology*, 110(8), pp.1189–1194.

Loeys, B.L. et al., 2010. The revised Ghent nosology for the Marfan syndrome. *Journal of Medical Genetics*, 47(7), pp.476–485.

Verhagen, J.M.A. et al., 2018. Expert consensus recommendations on the cardiogenetic care for patients with thoracic aortic disease and their first-degree relatives. *International journal of cardiology*.

General overview





HTAD: Heritable Thoracic Aortic Disease; TAA/D: Thoracic Aortic Aneurysm/Dissection; TTE: transthoracic echocardiography

[1]AHT-Arterial Hypertension = BP>140/90 or antihypertensive treatment
[2]Min 1 person first or second degree family
- TAA or dissection (suspicion) <60yr
- LVOT abnormality
- Sudden death <45yr

[3]systemic score and/or bifid uvula, hypertelorism, clubfoot, early onset and widespread ostoarthritis
[4]needs re-evaluation after 3-5yrs until age 18
[5] see below for further specifications

ϕIncluding genes with an established association with HTAD
ϕϕ BAV panel including NOTCH1, SMAD6