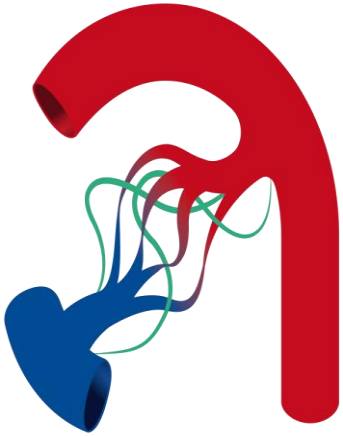
European Reference Network

for rare or low prevalence complex diseases

Network Vascular Diseases (VASCERN)

Heritable Thoracic Aortic Disease



Dr. Maryanne Caruana

Consultant Cardiologist

Lead for ACHD & Aortopathy Service

Clinical Focal Point for VASCERN HTAD RDWG

Mater Dei Hospital, Malta

SPTAR MATER DEI

Conflicts of Interest

Overview

- What is HTAD?
- Local experience

- Personal ERN experience

HTAD

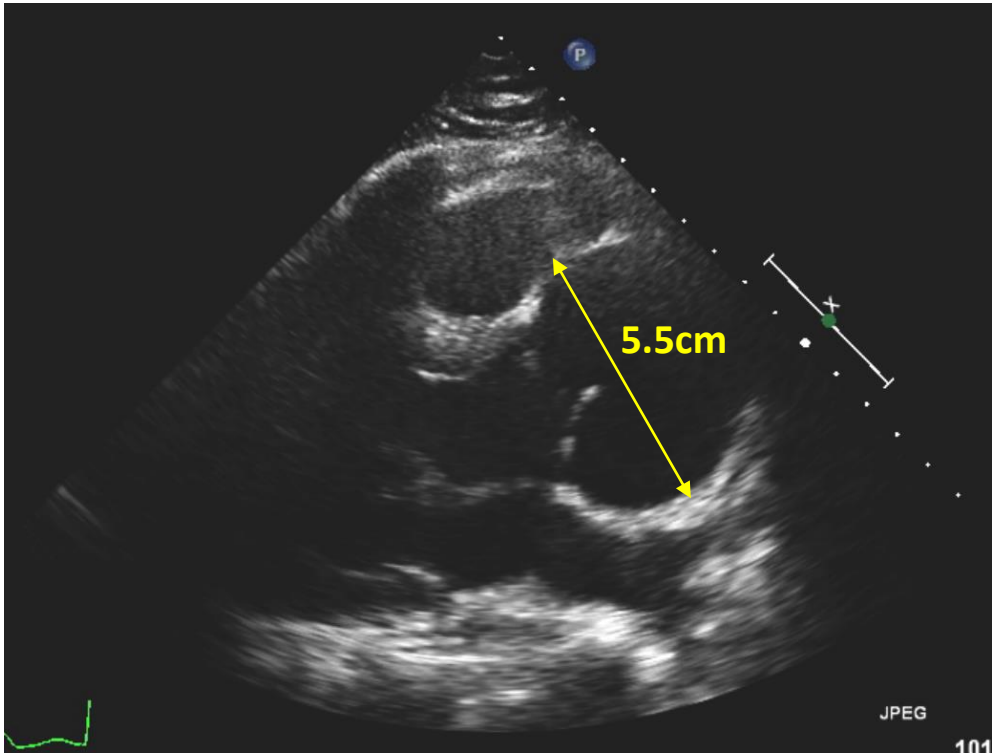
- Heritable Thoracic Aortic Disease
- Characterised by aortic aneurysm and aortic dissection
- Incidence = approximately 1 in 5000

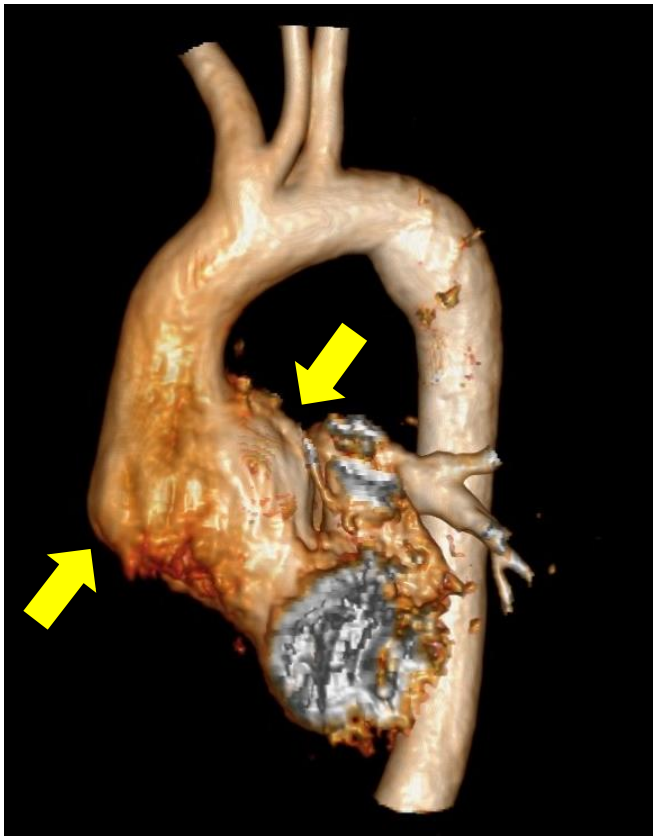
- Syndromic vs. non-syndromic
  - Syndromic e.g. Marfan, Loeys-Dietz, Aneurysm-Osteoarthritis, Arterial Tortuosity

- Sporadic vs. familial

- Most **autosomal dominant**

Aortic aneurysm

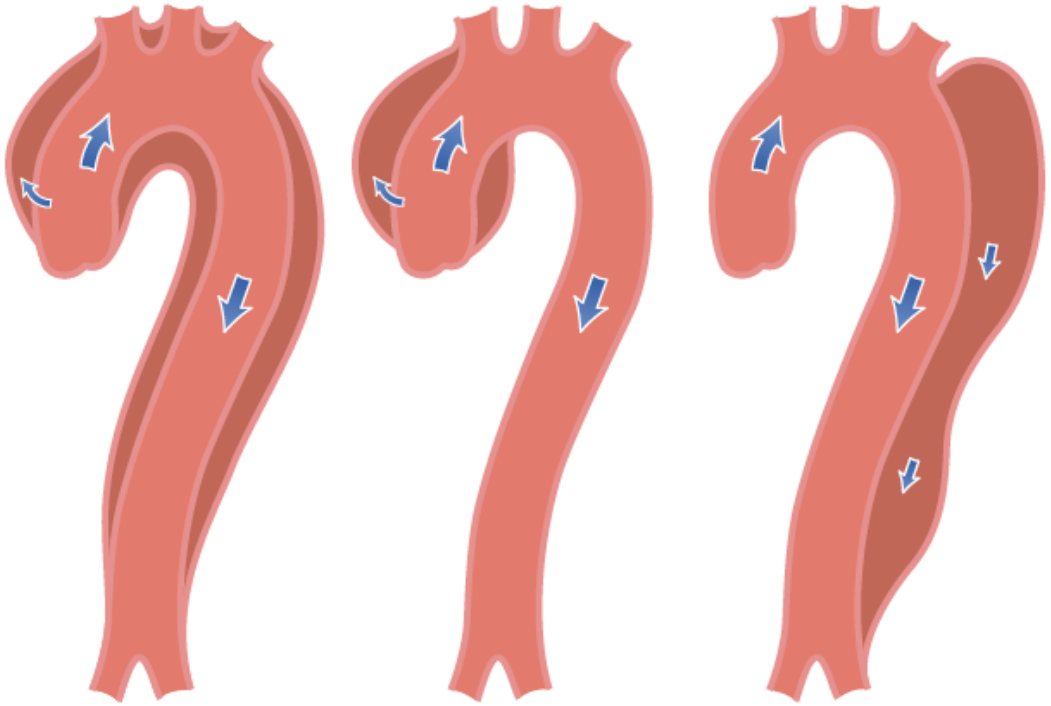




Aortic root aneurysm with subsequent diagnosis of Marfan syndrome

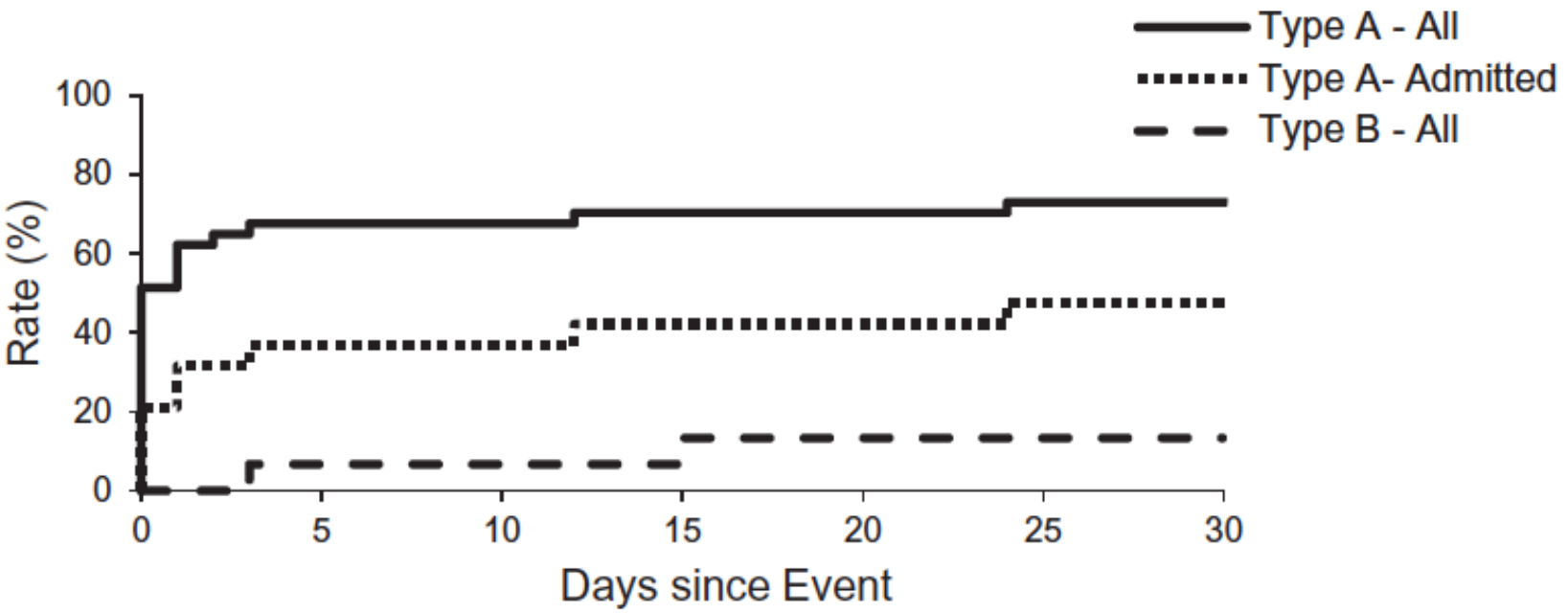
Aortic dissection classification

De Bakey	Type I	Type II	Type III
Stanford	Type A	Type A	Type B



Erbel R et al. Eur Heart J 2014;35:2873-926.

Aortic dissection mortality



Oxford Vascular Study

Howard DP et al. Circulation 2013;127(20):2013-7.

Genes involved

Encoding components of **extracellular matrix**

- *COL3A1*
- *FBN1*
- *LOX*

Encoding components of the **TGFβ pathway**

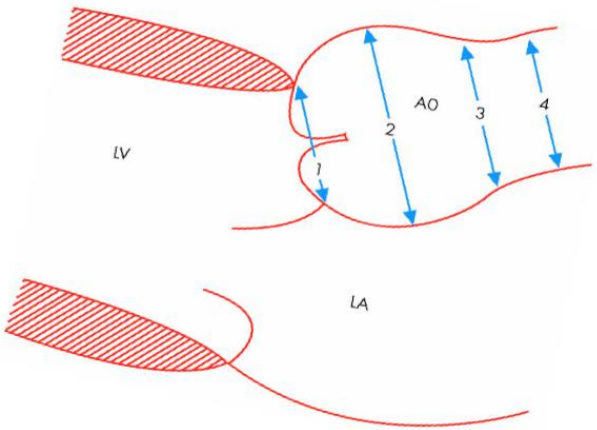
- *SMAD3*
- *TGFB2*
- *TGFBR1*
- *TGFBR2*

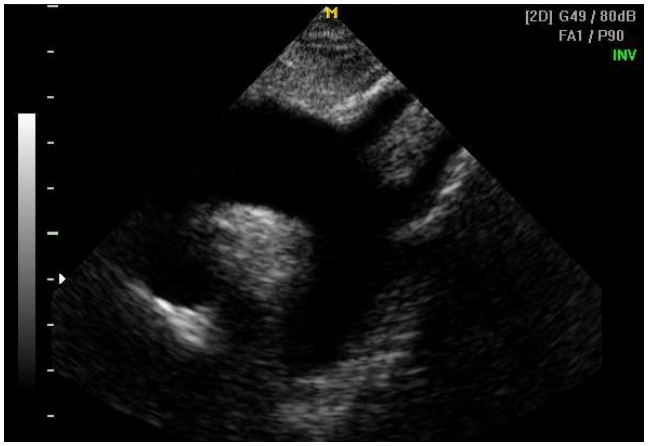
Encoding components of **smooth muscle cell contractile mechanism**

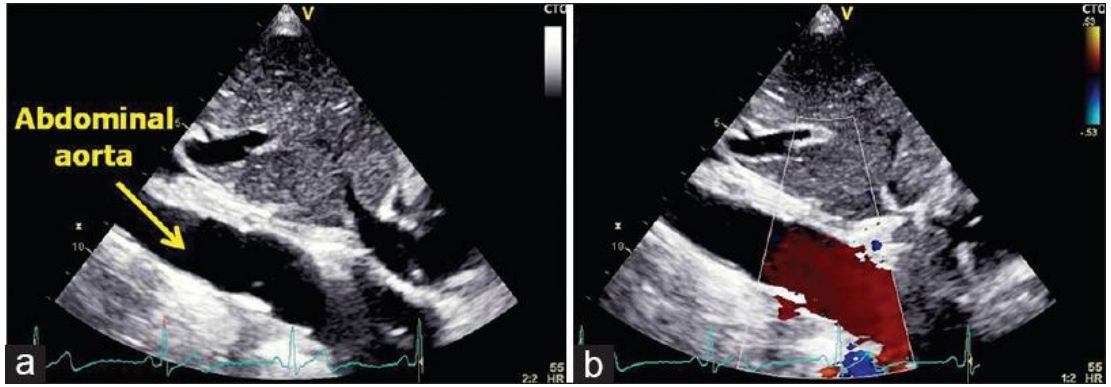
- *MYH11*
- *ACTA2*
- *MYLK*
- *PRKG1*

A causative variant remains unidentified in ~80% of non-syndromic HTAD!

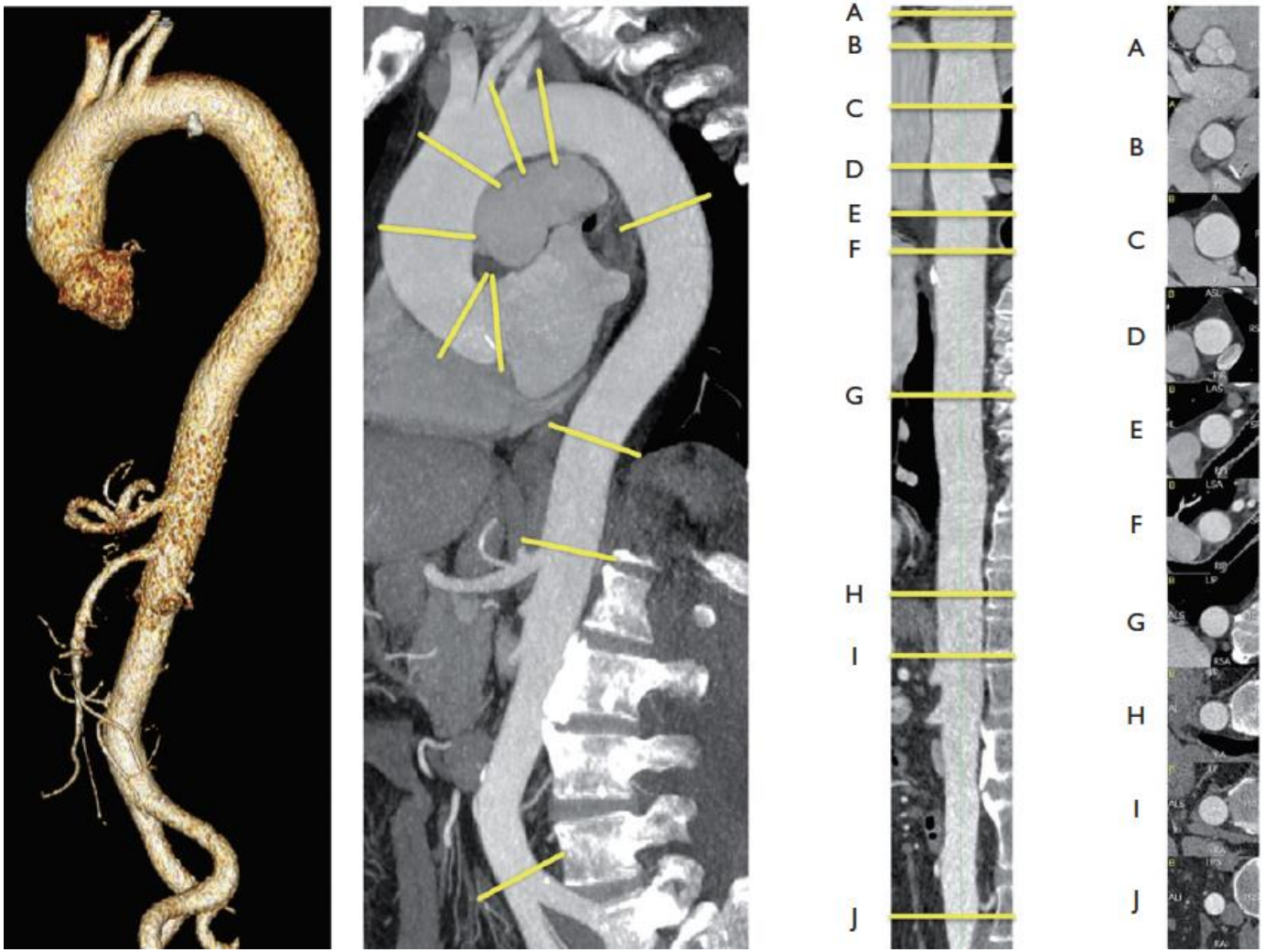
Serial imaging: echocardiography



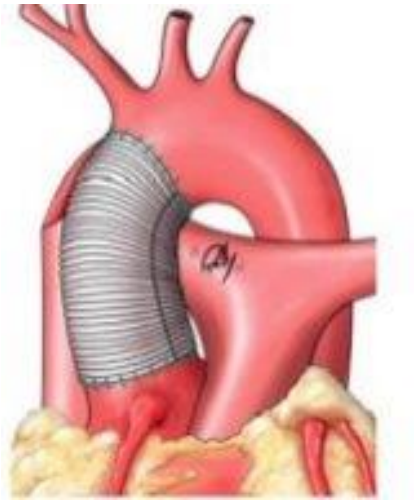


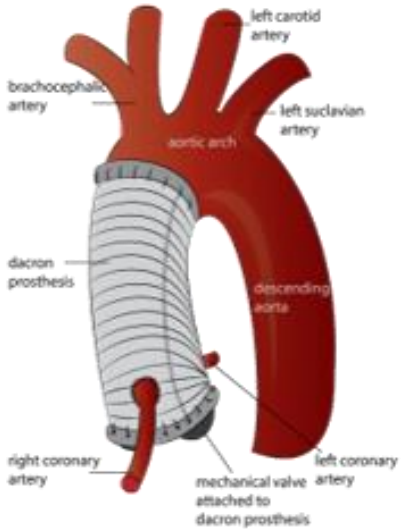


Serial imaging: CT / MRI

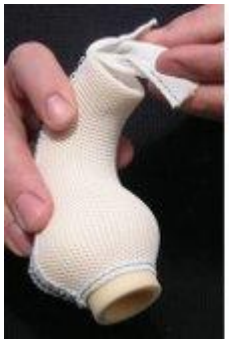


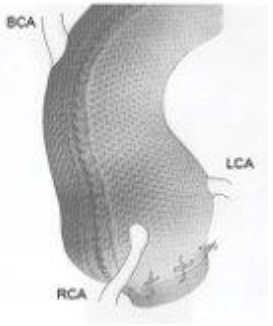
Prophylactic aortic surgery





Aortic valve-sparing root replacement operations: Yacoub procedure (labeled A and B) and David procedure (right).





Local experience

Some numbers according to my records:

- **Marfan syndrome** = 64 patients with 20 different confirmed likely pathogenic / pathogenic variants in *FBN1*
- **Loeys-Dietz syndrome** = 2 patients flagged up to me (never seen)
- 1 family with variants in *FBN1 and SMAD3*
- 66 patients with possible HTAD
  - Some with negative gene panel
  - Some awaiting genetics


6 RARE DISEASES WORKING GROUPS (RDWG)
HERITABLE THORACIC AORTIC DISEASES HTAD-WG
1 Chair
1 Co-chair
MEDIUM SIZED ARTERIES MSA-WG
1 Chair
1 Co-chair
NEUROVASCULAR WG
1 Chair
1 Co-chair
PATIENT GROUP (ePAG)
1 Chair
6 Co chairs
PEDIATRIC & PRIMARY LYMPHEDEMA PPL-WG
1 Chair
1 Co-chair
HEREDITARY HAEMORRHAGIC TELANGIECTASIA HHT-WG
1 Chair
1 Co-chair
VASCULAR ANOMALIES VASCA-WG
1 Chair
1 Co-chair
TRANSVERSAL WORKING GROUPS (WG)
Patient Registry WG
Pregnancy WG
Communication Advisory Task Force
Ethics WG

Meetings

1. **Monthly HTAD RDWG online meetings**
   - Every 4th Monday of the month
   - Updates on different projects
   - Case presentation
2. **Twice yearly face-to-face meetings**
   - HTAD RDWG spring meeting
   - VASCERN days every October

Statements

European Reference Network
for rare or low prevalence complex diseases
Network Vascular Diseases (VASCERN)

Stqarrija mill-VASCERN HTAD WG dwar il-COVID-19

Fdawn l-aħħar ġimgħat kien hawn xnigħat, speċjalment fuq il-midja socjali, li ACE-I/ARBs jistgħu iżidu kemm ir-riskju kif ukoll il-gravita' ta'infezzjoni bil-virus SARS-CoV2, filwaqt li sorsi oħra ssuġġerew li dawn il- medicini jistgħu jgħinu. Kif iddikjarat mill-European Society of Cardiology Council on Hypertension, **aħna nixtiequ ntennu li s'issa m'hemm l-ebda evidenza** li ACE-Is jew ARBs jistgħu jkunu ta'ħsara jew ta'għajnuna addizzjonali fil-kuntest ta'infezzjoni tal-COVID-19.

Flimkien mal-Council on Hypertension, **aħna nħeġġu kemm lit-tobba kif ukoll lill-pazjenti biex ikomplu jieħdu l-medicini tal-pressjoni bħas-soltu, għax s'issa m'hemm l-ebda evidenza klinika jew xjentifika li turi fiċ-ċert li dawn il-medicini għandhom jitwaqqfu fil-każ ta' infezzjoni tal-COVID-19.**

Research collaboration

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

HTAD patient pathway: Strategy for diagnostic work-up of patients and families with (suspected) heritable thoracic aortic diseases (HTAD). A statement from the HTAD working group of VASCERN

Maryanne Caruana [a], Marieke J. Baars [b], Evy Bashiardes [c], Kalman Benke [d], Erik Björck [e], Andrei Codreanu [f], Elena de Moya Rubio [g], Julia Dumfarth [h], Arturo Evangelista [i], Maarten Groenink [b], Klaus Kallenbach [f], Marlies Kempers [j], Anna Keravnou [c], Bart Loeys [k], Laura Muiño-Mosquera [l], Edit Nagy [m], Olivier Milleron [n], Stefano Nistri [o], Guglielmina Pepe [o], Jolien Roos-Hesselink [p], Zoltan Szabolcs [d], Gisela Teixidó-Tura [i], Janneke Timmermans [j], Ingrid Van de Laar [p], Roland van Kimmenade [j], Aline Verstraeten [k], Yskert Von Kodolitsch [q], Julie De Backer [l], Guillaume Jondeau [n,*]

Research collaboration

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Arrhythmia and impaired myocardial function in heritable thoracic aortic disease: An international retrospective cohort study

Anthony Demolder [a,m], Lisa Bianco [b], Maryanne Caruana [c,d], Elena Cervi [e], Arturo Evangelista [f,g], Guillaume Jondeau [g,h], Lisa Lauren Buttigieg [c,d], Ángela López-Sainz [f,g], Elena Montañés Delmás [i], Alessandro Pini [j], Anna Sabaté-Rotés [b], Katalin Szöcs [g,k], Maria Tchitchinadze [g,h], Gisela Teixidó-Tura [f,g], Yskert von Kodolitsch [g,k], Laura Muiño-Mosquera [a,g,l], Julie De Backer [a,g,l,m,1,*]

Exchange programme – Ghent 2022

Thank you!