Erasmus MC
Universitair Medisch Centrum Rotterdam

THORAXCENTRUM

# Thoraxchirurgische ingrepen bij Marfan-patiënten

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(Congenitaal) Cardio-thoracaal Chirurg
Erasmus MC

# Richtlijn Marfan

European Heart Journal (2014) **35**, 2873–2926
doi:10.1093/eurheartj/ehu281

ESC GUIDELINES

## 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases

**Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult**

**The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC)**

**Table I** Classes of recommendations

| Classes of recommendations | Definition | Suggested wording to use |
|---|---|---|
| Class I | Evidence and/or general agreement that a given treatment or procedure in beneficial, useful, effective. | Is recommended/is indicated |
| Class II | Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. | |
| *Class IIa* | *Weight of evidence/opinion is in favour of usefulness/efficacy.* | Should be considered |
| *Class IIb* | *Usefulness/efficacy is less well established by evidence/opinion.* | May be considered |
| Class III | Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. | Is not recommended |

**Table 2** Levels of evidence

| | |
|---|---|
| Level of evidence A | Data derived from multiple randomized clinical trials or meta-analyses. |
| Level of evidence B | Data derived from a single randomized clinical trial or large non-randomized studies. |
| Level of evidence C | Consensus of opinion of the experts and/or small studies, retrospective studies, registries. |

## Recommendations on genetic testing in aortic diseases

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| It is recommended to investigate first-degree relatives (siblings and parents) of a subject with TAAD to identify a familial form in which relatives all have a 50% chance of carrying the family mutation/disease. | I | C |
| Once a familial form of TAAD is highly suspected, it is recommended to refer the patient to a geneticist for family investigation and molecular testing. | I | C |
| Variability of age of onset warrants screening every 5 years of 'healthy' at-risk relatives until diagnosis (clinical or molecular) is established or ruled out. | I | C |
| In familial non-syndromic TAAD, screening for aneurysm should be considered, not only in the thoracic aorta, but also throughout the arterial tree (including cerebral arteries). | IIa | C |

[a]Class of recommendation.
[b]Level of evidence.
TAAD = thoracic aortic aneurysms and dissection.

## Recommendations for surgical techniques in aortic disease

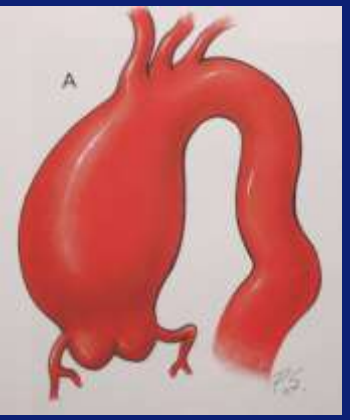
| Recommendations | Class[a] | Level[b] | Ref.[c] |
|---|---|---|---|
| Cerebrospinal fluid drainage is recommended in surgery of the thoraco-abdominal aorta, to reduce the risk of paraplegia. | I | B | 126–127 |
| Aortic valve repair, using the re-implantation technique or remodelling with aortic annuloplasty, is recommended in young patients with aortic root dilation and tricuspid aortic valves. | I | C | |
| For repair of acute Type A AD, an open distal anastomotic technique avoiding aortic clamping (hemiarch/complete arch) is recommended. | I | C | |
| In patients with connective tissue disorders[d] requiring aortic surgery, the replacement of aortic sinuses is indicated. | I | C | |
| Selective antegrade cerebral perfusion should be considered in aortic arch surgery, to reduce the risk of stroke. | IIa | B | 139,131, 134,141 |
| The axillary artery should be considered as first choice for cannulation for surgery of the aortic arch and in aortic dissection. | IIa | C | |
| Left heart bypass should be considered during repair of the descending aorta or the thoraco-abdominal aorta, to ensure distal organ perfusion. | IIa | C | |

## Recommendations on interventions on ascending aortic aneurysms

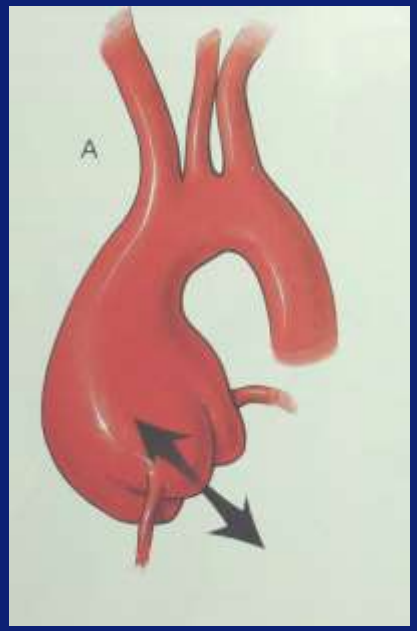
| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Surgery is indicated in patients who have aortic root aneurysm, with maximal aortic diameter[c] ≥50 mm for patients with Marfan syndrome. | I | C |
| Surgery should be considered in patients who have aortic root aneurysm, with maximal ascending aortic diameters:<br>• ≥45 mm for patients with Marfan syndrome with risk factors.[d]<br>• ≥50 mm for patients with bicuspid valve with risk factors.[e,f]<br>• ≥55 mm for other patients with no elastopathy.[g,h] | IIa | C |
| Lower thresholds for intervention may be considered according to body surface area in patients of small stature or in the case of rapid progression, aortic valve regurgitation, planned pregnancy, and patient's preference. | IIb | C |
| **Interventions on aortic arch aneurysms** | | |
| Surgery should be considered in patients who have isolated aortic arch aneurysm with maximal diameter ≥55 mm. | IIa | C |
| Aortic arch repair may be considered in patients with aortic arch aneurysm who already have an indication for surgery of an adjacent aneurysm located in the ascending or descending aorta. | IIb | C |
| **Interventions on descending aortic aneurysms** | | |
| TEVAR should be considered, rather than surgery, when anatomy is suitable. | IIa | C |
| TEVAR should be considered in patients who have descending aortic aneurysm with maximal diameter ≥55 mm. | IIa | C |
| When TEVAR is not technically possible, surgery should be considered in patients who have descending aortic aneurysm with maximal diameter ≥60 mm. | IIa | C |
| When intervention is indicated, in cases of Marfan syndrome or other elastopathies, surgery should be indicated rather than TEVAR. | IIa | C |

[a]Class of recommendation.
[b]Level of evidence.
[c]Decision should also take into account the shape of the different parts of the aorta. Lower thresholds can be used for combining surgery on the ascending aorta for patients who have an indication for surgery on the aortic valve.
[d]Family history of AD and/or aortic size increase >3 mm/year (on repeated measurements using the same imaging technique, at the same aorta level, with side-by-side comparison and confirmed by another technique), severe aortic or mitral regurgitation, or desire for pregnancy.
[e]Coarctation of the aorta, systemic hypertension, family history of dissection, or increase in aortic diameter >3 mm/year (on repeated measurements using the same imaging technique, measured at the same aorta level, with side-by-side comparison and confirmed by another technique).
[f]Pending comorbidities in the elderly.
[g]See text in section 8.
[h]For patients with LDS or vascular type IV Ehlers-Danlos syndrome (EDS), lower thresholds should be considered, possibly even lower than in Marfan syndrome. There are no data to provide figures and a sensible case-by-case approach is the only option.

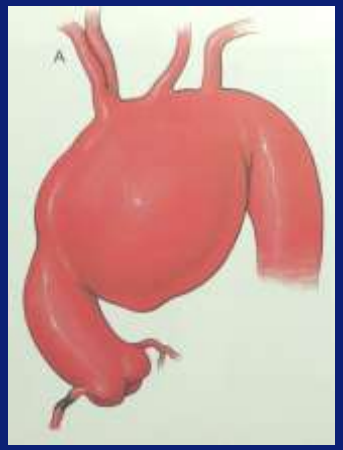
# Aneurysma van de aorta




*ascendens*




*aortawortel*

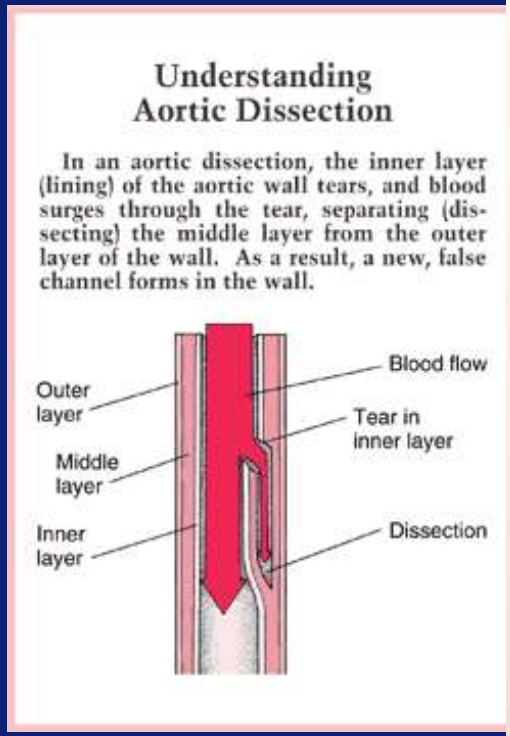


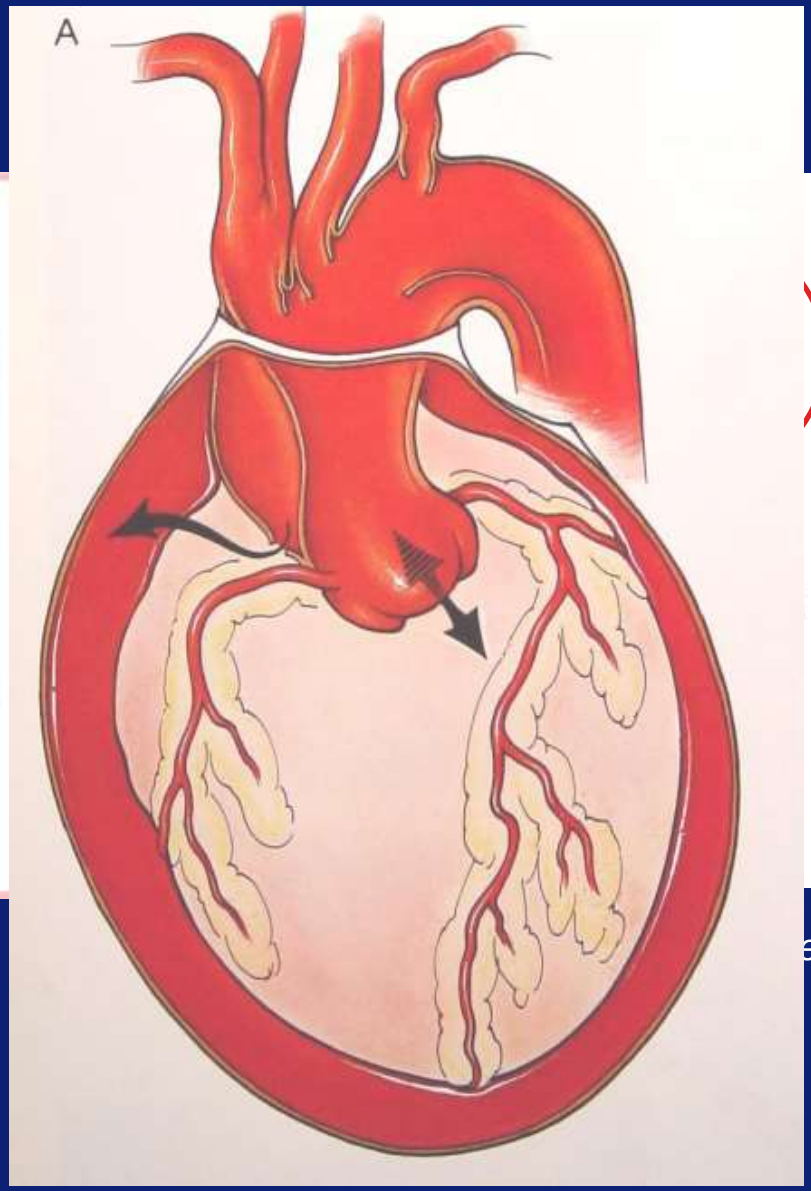

*boog*

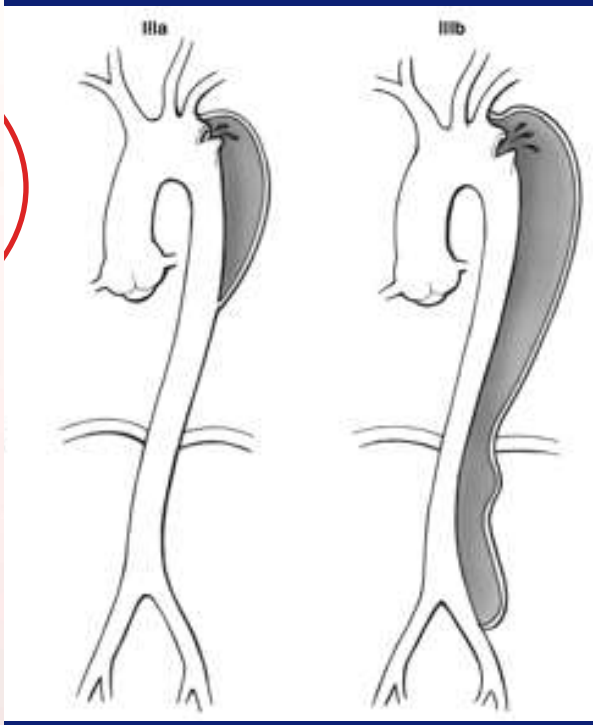
*descendens*


*thoraco-abdominaal*

# Aorta dissectie




*ens DeBakey*

Perspective

# Genes in thoracic aortic aneurysms/dissections - do they matter?

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Table 1 TAAD with their corresponding genes and clinical features

| Disorder | Gene(s) | Main cardiovascular features | Additional clinical features |
|---|---|---|---|
| Syndromic TAAD | | | |
| Marfan (1,7,8) | *FBN1* | Aortic root aneurysm, aortic dissection, mitral valve prolapse, main pulmonary artery dilatation, left ventricular dysfunction | Lens luxation, skeletal features (arachnodactylia, pectus deformity, scoliosis, flat feet, increased armspan, dolichocephalia) |
| Ehlers-Danlos (9-11) (vascular, valvular) | *COL3A1*, *COL1A2* | Arterial rupture and dissection without preceding dilatation/aneurysm, severe valvular insufficiency | Translucent skin, dystrophic scars, facial characteristics (Madonna face, thin lips, deep set eyes) |
| TGFβ-related vasculopathies | | | |
| Loeys-Dietz (2,12) | *TGFBR1/2* | Aortic root aneurysm, aortic dissection, arterial aneurysms and dissections, arterial tortuosity, mitral valve prolapse, congenital cardiac malformations* | Bifid uvula/cleft palate, hypertelorism, pectus abnormalities, scoliosis, club feet |
| Aneurysm-Osteoarthritis (13-15) | *SMAD3* | Aortic root aneurysm, aortic dissection, arterial aneurysms and dissections, arterial tortuosity, mitral valve prolapse, congenital cardiac malformations* | Osteoarthritis, soft skin, flat feet, scoliosis, recurrent hernia's, hypertelorism, pectus abnormalities |
| *TGF$_{\beta}$2* (16,17) | *TGF$_{\beta}$2* | Aortic root aneurysm, aortic dissection, arterial aneurysms and dissections, arterial tortuosity, mitral valve prolapse, congenital cardiac malformations* | Club feet, soft translucent skin |
| Arterial tortuosity syndrome (18) | *SLC2A10* | Arterial tortuosity, arterial stenoses and aneurysms | Hyperlax skin and joints |
| Cutis laxa syndromes (19) | *FBLN4* | Aortic root aneurysm, arterial tortuosity | Hyperlax skin and joints, mild emphysema |
| Non syndromic TAAD | | | |
| Familial thoracic aortic aneurysm syndrome (FTAA) (20-22) | *TGFBR1/2* (3-5%) | Thoracic aortic aneurysm/dissection | Lack of syndromal features |
| | *ACTA2* (10-14%) | Thoracic aortic aneurysm/dissection, cerebrovascular disease, coronary artery disease | Lack of Marfanoid skeletal features, livedo reticularis, iris flocculi, coronary artery/cerebrovascular disease) |
| | *MLCK* | Thoracic aortic aneurysm/dissection | Gastro-intestinal abnormalities |
| | *SMAD3* (2%) | Intracranial and other arterial aneurysms | |
| | *TGF$_{\beta}$2* | Mitral valve prolapse | |
| FTAA with bicuspid aortic valve (BAV) (23,24) | *ACTA2* | | Lack of Marfanoid skeletal features, livedo reticularis, iris flocculi |
| | *NOTCH1* | Highly calcified valve | |
| FTAA with patent ductus arteriosus (PDA) (6) | *MYH11* | Patent ductus arteriosus | |

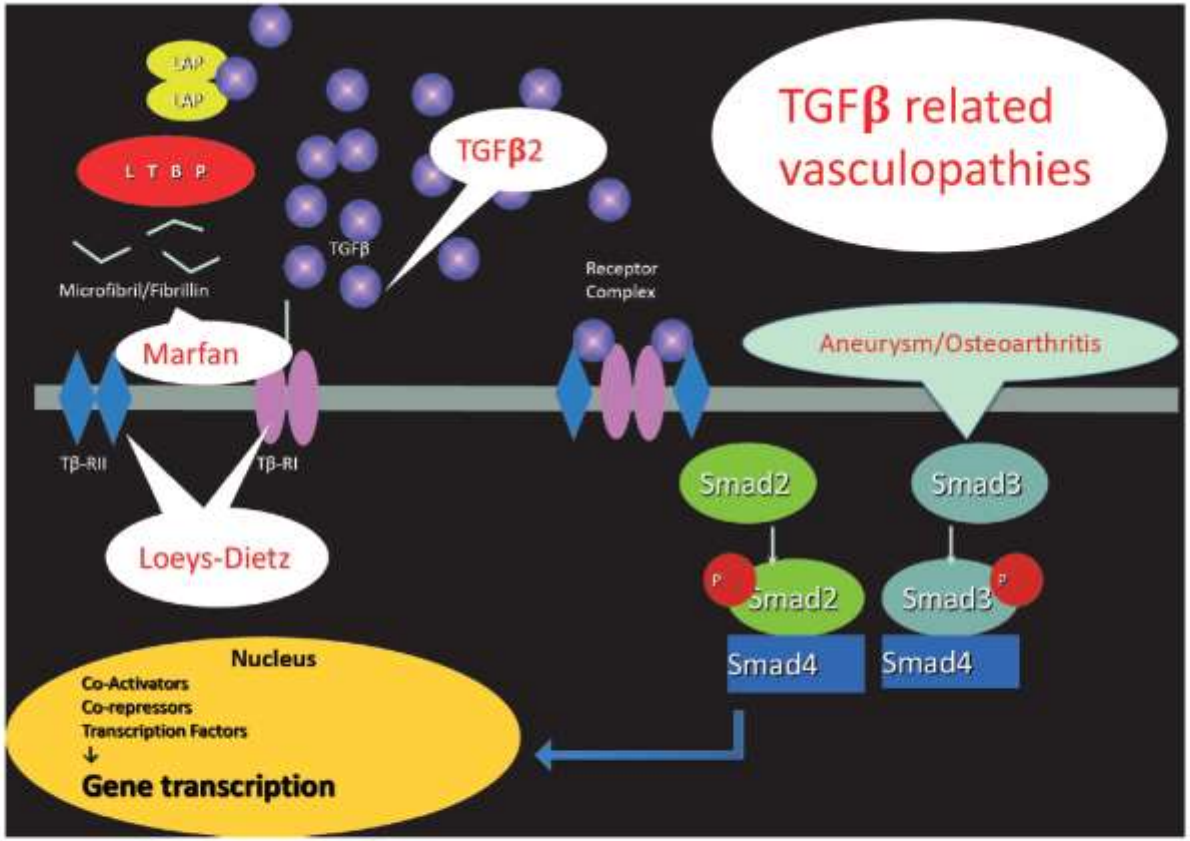
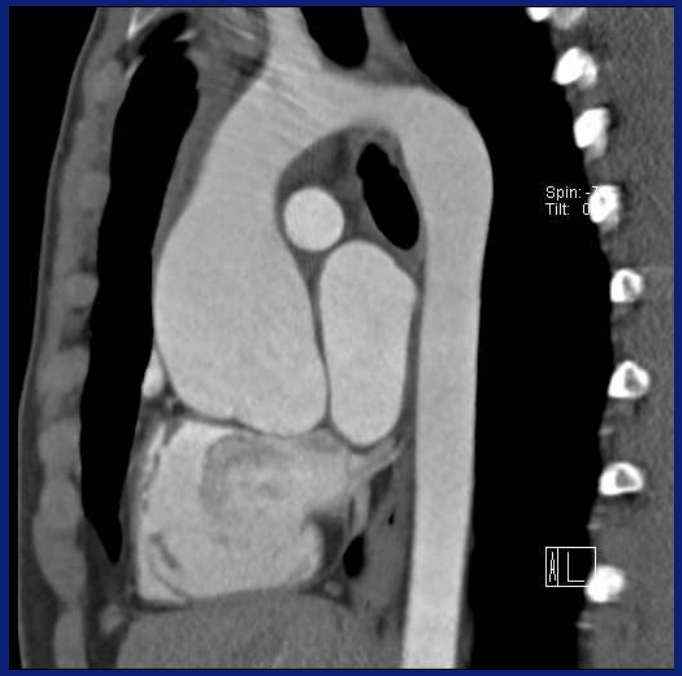
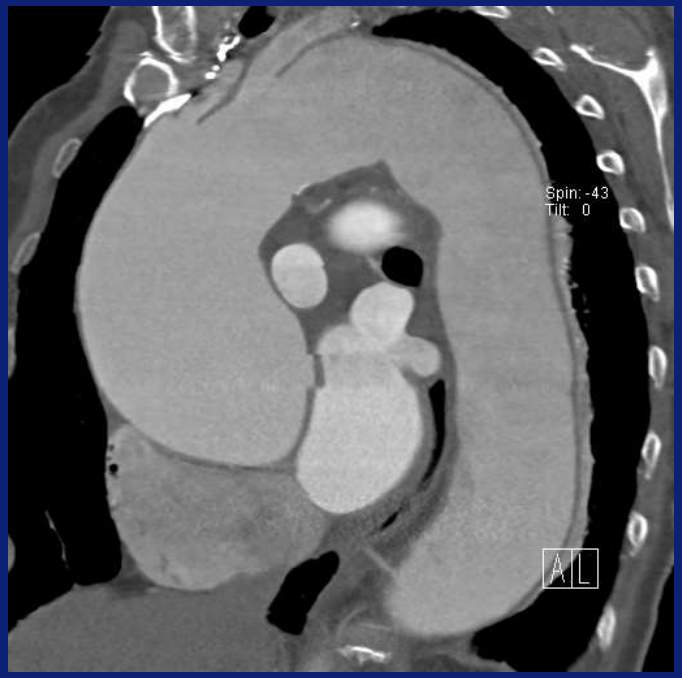


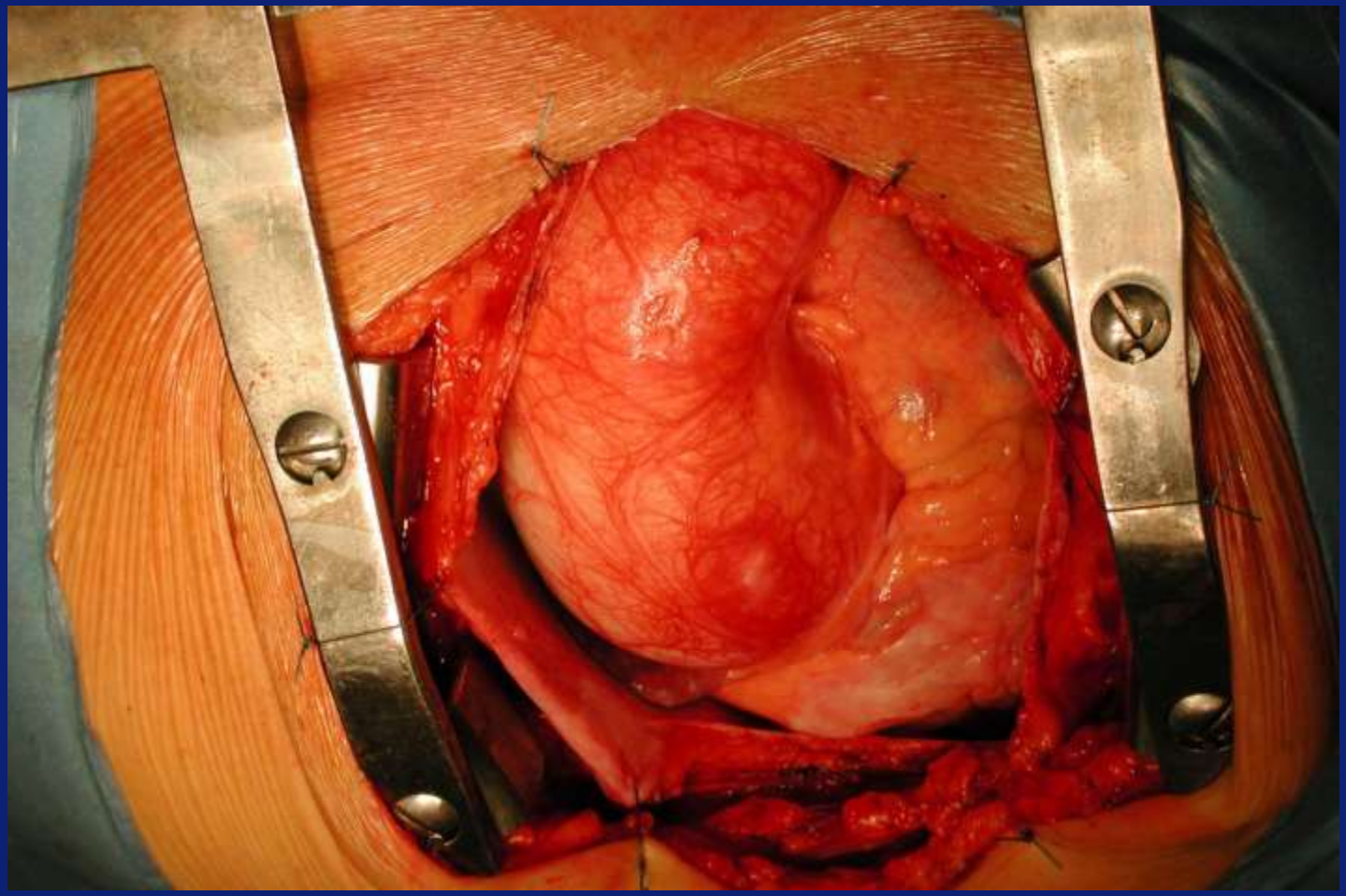

**Figure 3** The TGFβ pathway and related vasculopathies. Following its release from the Extracellular Matrix, TGFβ binds to its type II cell surface receptor (TβRII), which recruits and phosphorylates the type I receptor (TβRI). TβRI then recruits and phosphorylates SMAD2 and/or SMAD3. These P-SMADs then bind to the common SMAD (co-SMAD) SMAD4 to form a heterodimeric complex. This complex enters the cell nucleus where it acts as a transcription factor for various TGFβ-dependent genes, such as connective tissue growth factor (CTGF), plasminogen activator inhibitor-1 (PAI-1) and multiple collagens

# Syndroom van Marfan

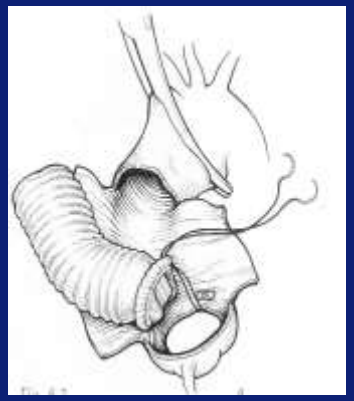


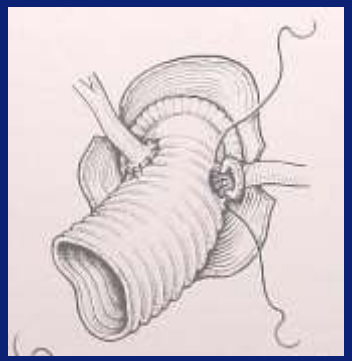


# Aneurysma aorta ascendens



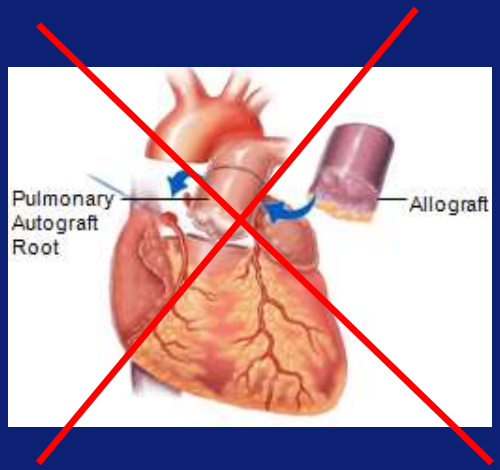
# Aortawortelvervanging



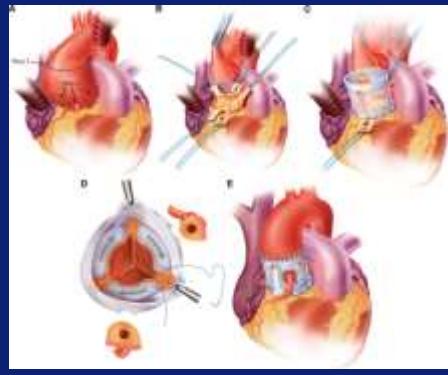


*klepdragende vaatprothese*

*donorklep*

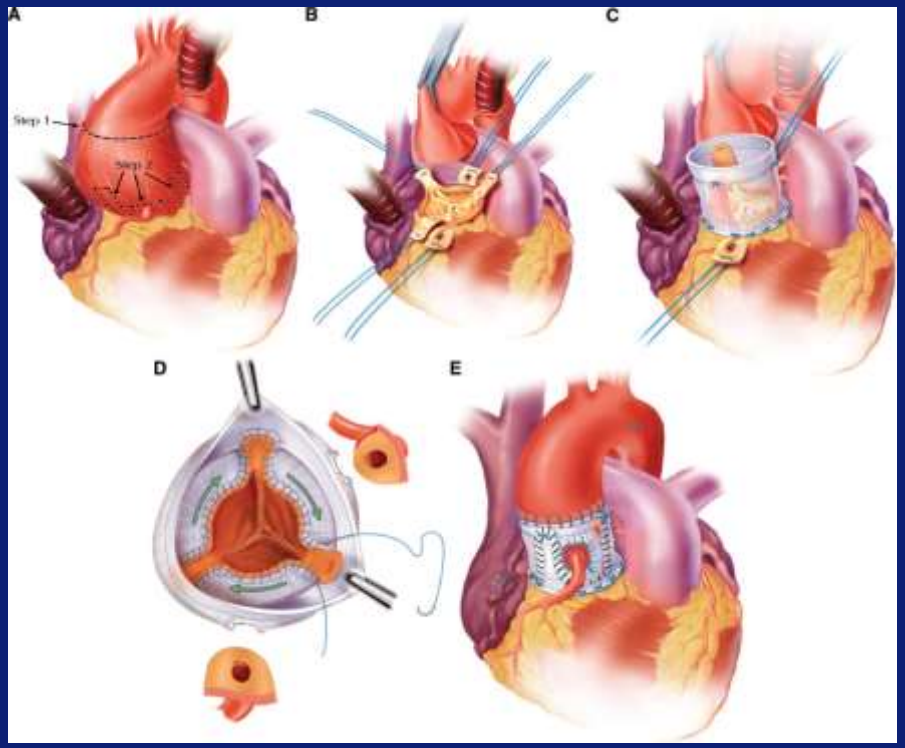


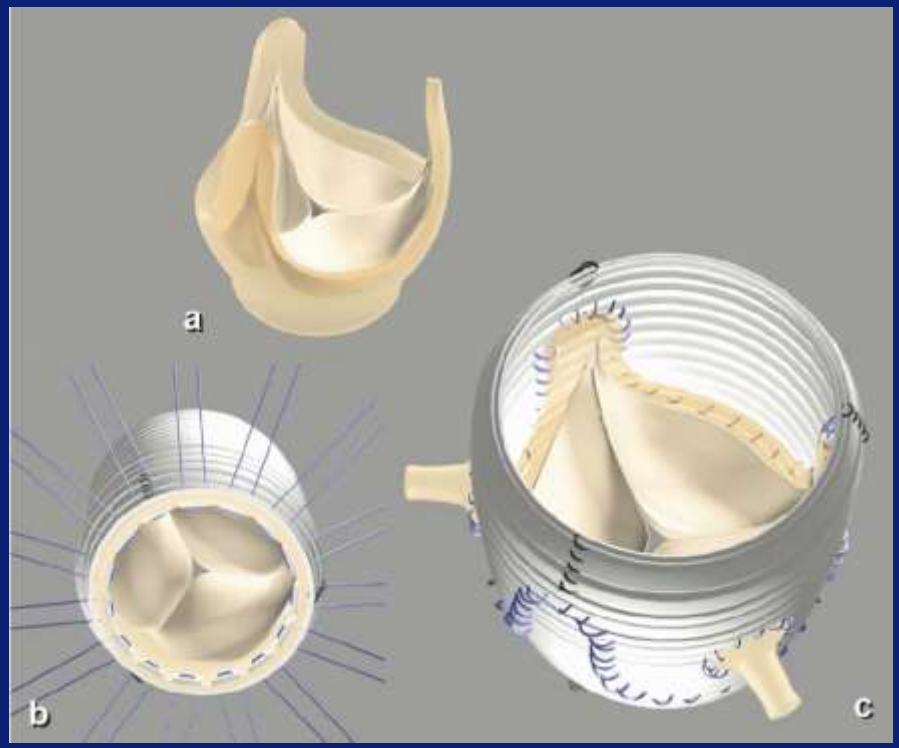

*pulmonalis autograft*



*klepsparend*

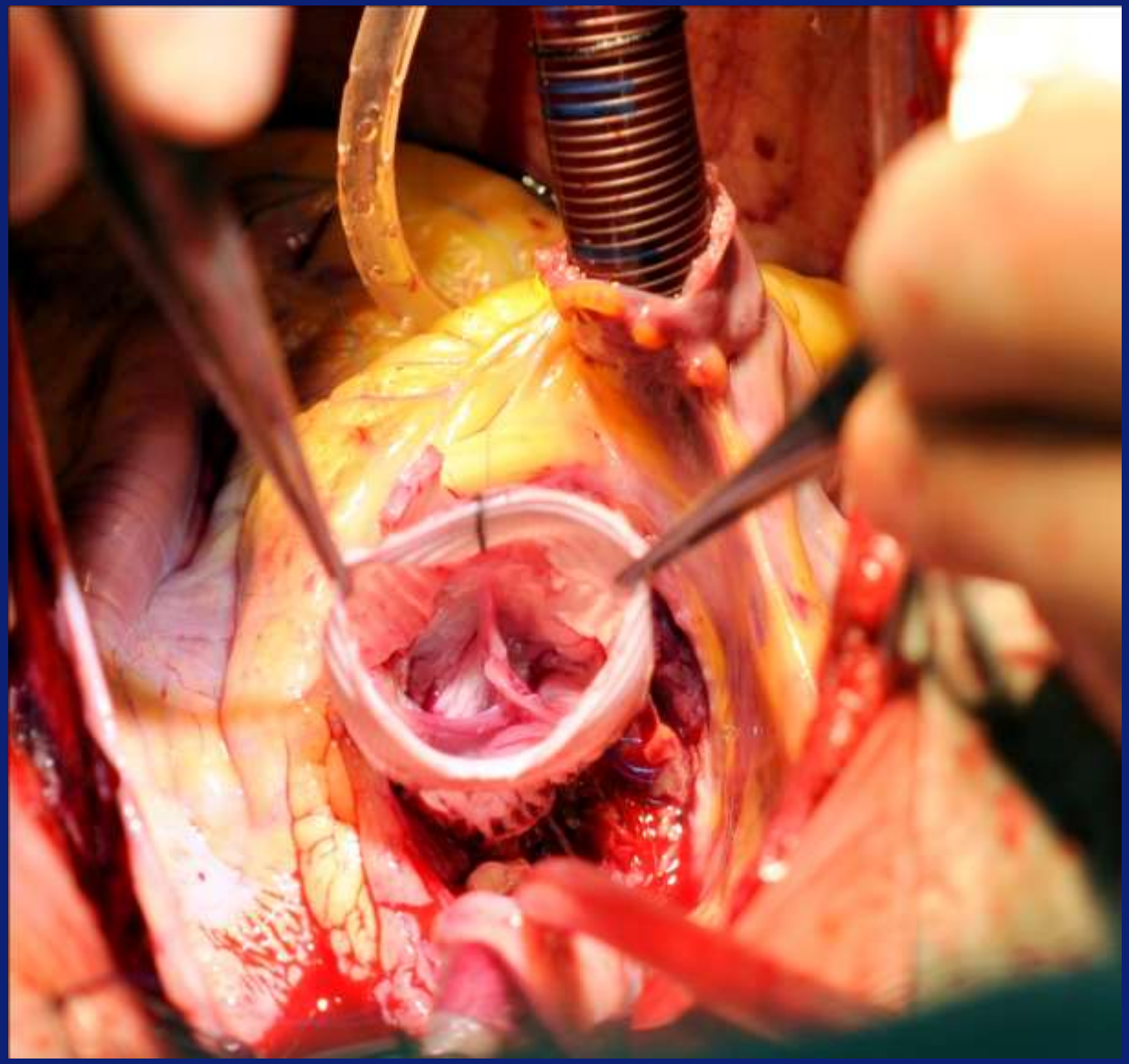
# Klepsparende aortawortel vervanging



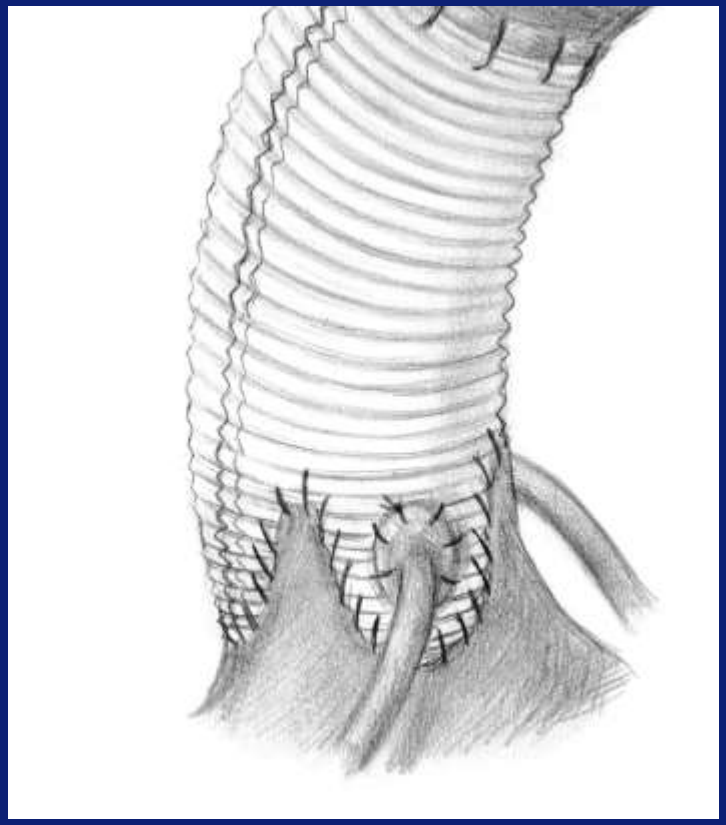




`*Techniek volgens Tirone David*

# Klepsparende aortawortel vervanging



# Aortawortel vervanging (Yacoub)



# Early and 1-year outcomes of aortic root surgery in patients with Marfan syndrome: A prospective, multicenter, comparative study

Joseph S. Coselli, MD,[a] Irina V. Volguina, PhD,[a] Scott A. LeMaire, MD,[a] Thoralf M. Sundt, MD,[b] Heidi M. Connolly, MD,[c] Elizabeth H. Stephens, MD, PhD,[d] Hartzell V. Schaff, MD,[e] Dianna M. Milewicz, MD, PhD,[f] Luca A. Vricella, MD,[g] Harry C. Dietz, MD,[h] Charles G. Minard, PhD,[i] and D. Craig Miller, MD,[d] on behalf of the Aortic Valve Operative Outcomes in Marfan Patients Study Group

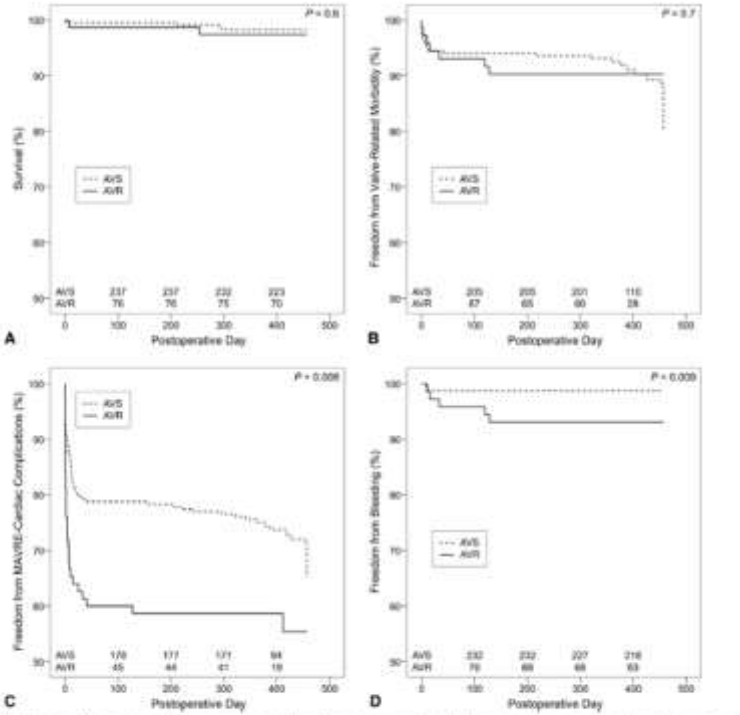



**FIGURE 2.** Kaplan-Meier analysis of 1-year overall survival and freedom from valve-related events comparing patients who underwent aortic valve-sparing (*AVS*) and aortic valve-replacing (*AVR*) root replacement. The *P* value was obtained by computing the log-rank statistic. A, Overall survival. B, Freedom from valve-related complications. C, Freedom from combined major adverse valve-related events (*MAVRE*) and cardiac complications. D, Freedom from bleeding.

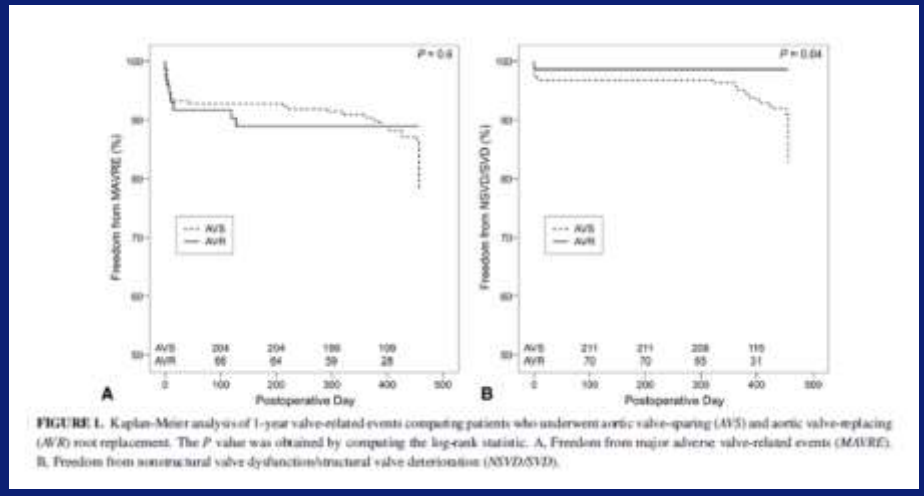
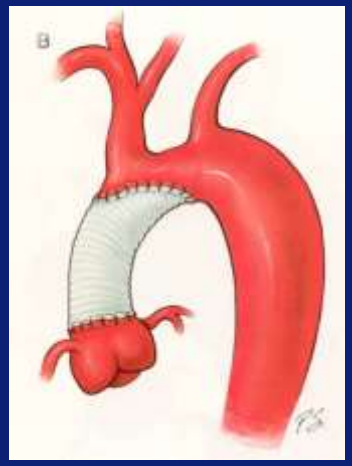
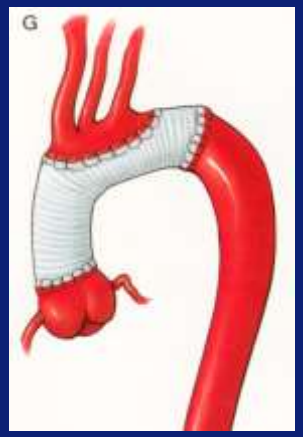


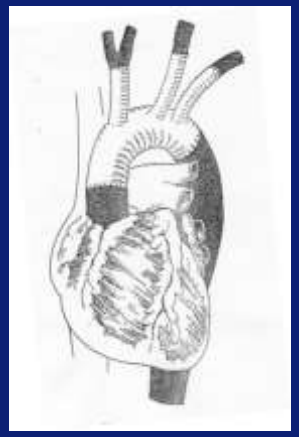

**FIGURE 1.** Kaplan-Meier analysis of 1-year valve-related events comparing patients who underwent aortic valve-sparing (*AVS*) and aortic valve-replacing (*AVR*) root replacement. The *P* value was obtained by computing the log-rank statistic. A, Freedom from major adverse valve-related events (*MAVRE*). B, Freedom from nonstructural valve dysfunction/structural valve deterioration (*NSVD/SVD*).

# Aorta vervanging



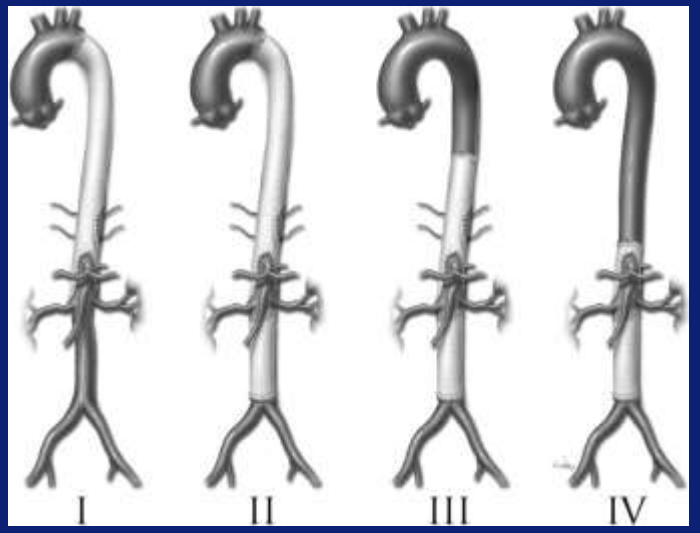
*ascendens*





*boog*

*descendens*




*Thoraco-abdominaal*

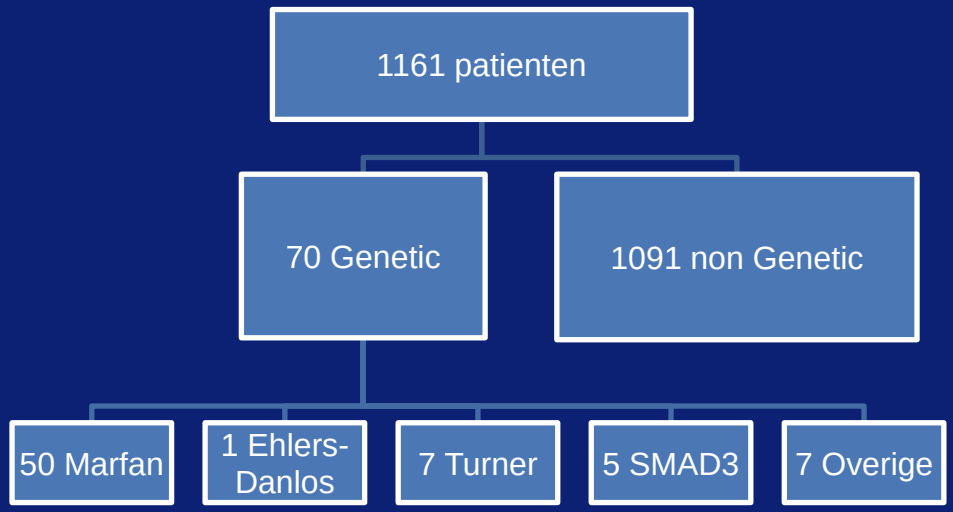
# Aorta database Erasmus MC

Periode 1972-februari 2013

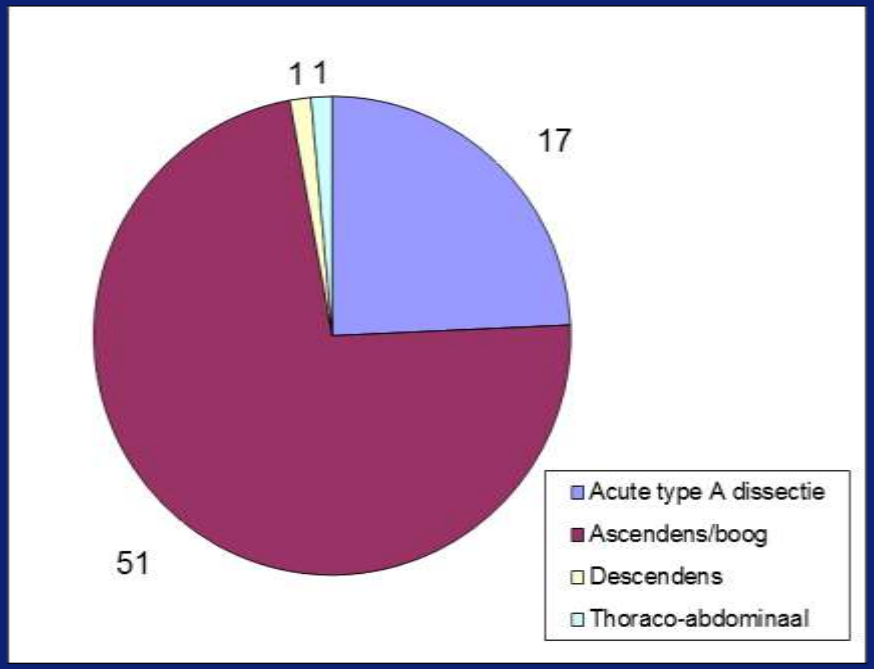
1256 operaties

1161 patienten

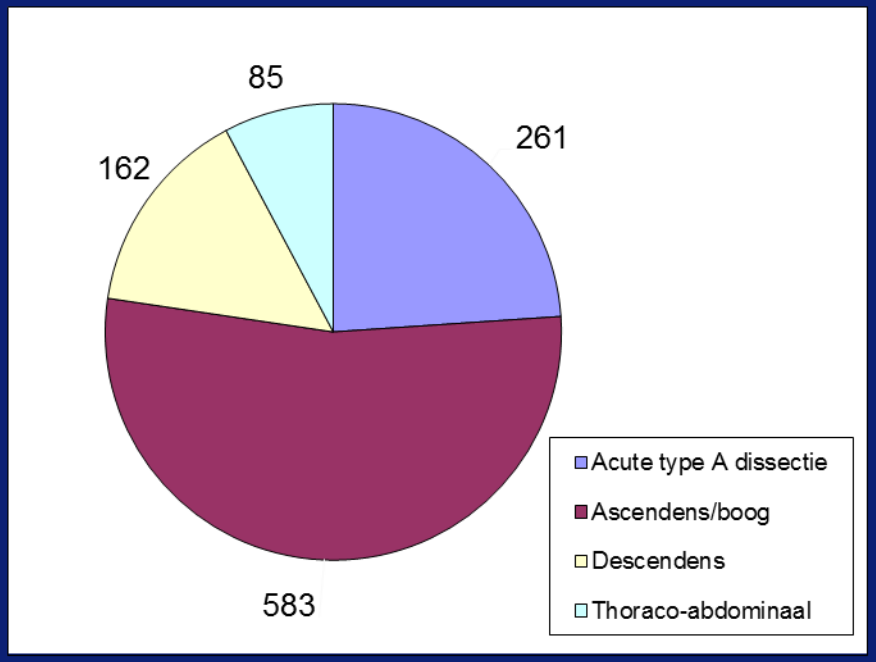
Complete follow-up via GBA



# Diagnose bij eerste operatie




*Genetic N=70*




*Non-Genetic N=1091*

# Patient characteristics

| | Genetic | non-Genetic | p value |
|---|---|---|---|
| | | | |
| | 70 | 1091 | |
| | | | |
| Age, mean | 34,5 | 57,5 | <0,001 |
| Age range | 10-76 | 8-85 | |
| M/F | 57%/43% | 69%/31% | 0,037 |

# Eerste operaties bij genetische aortasyndromen

## Acute type A dissectie

N=17

| | |
|---|---|
| Ascendens vervanging | 2 |
| Bentall + ascendens | 7 |
| Allograft +ascendens | 7 |
| T. David | 1 |

## Ascendens/boog aneurysma

N= 51

| | |
|---|---|
| Ascendens ± boog vervanging | 6 |
| Bentall + ascendens | 19 |
| Allograft + ascendens | 7 |
| Pulmonalis autograft | 1 |
| T. David | 18 |

| | |
|---|---|
| *Descendens aneurysma* | *1* |
| *Thoraco-abdominaal aneurysma* | *1* |

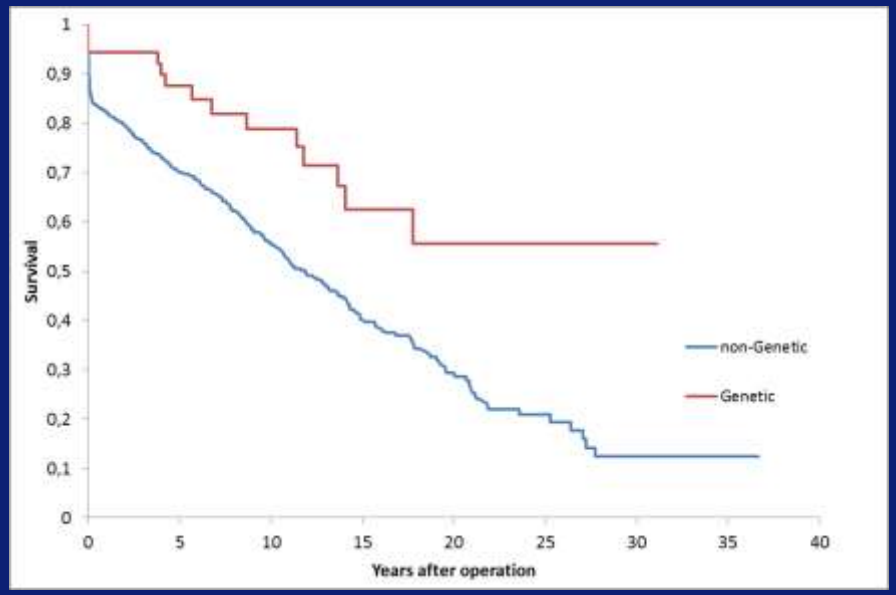
# Mortaliteit aorta ascendens/boog chirurgie 1972-2013

| | All | Genetic | non-Genetic | p value |
|---|---|---|---|---|
| | | | | |
| N | 912 | 68 | 844 | |
| | | | | |
| Overall | 9,80% | 5,90% | 10,10% | 0,263 |
| Acute type 1 dissectie | 20,50% | 11,80% | 21,10% | 0,357 |
| Asc/boog aneurysma | 5,50% | 3,90% | 5,10% | 0,702 |

*Mortaliteit niet acute ascendens/boog chirurgie na 2000: 2,2%*

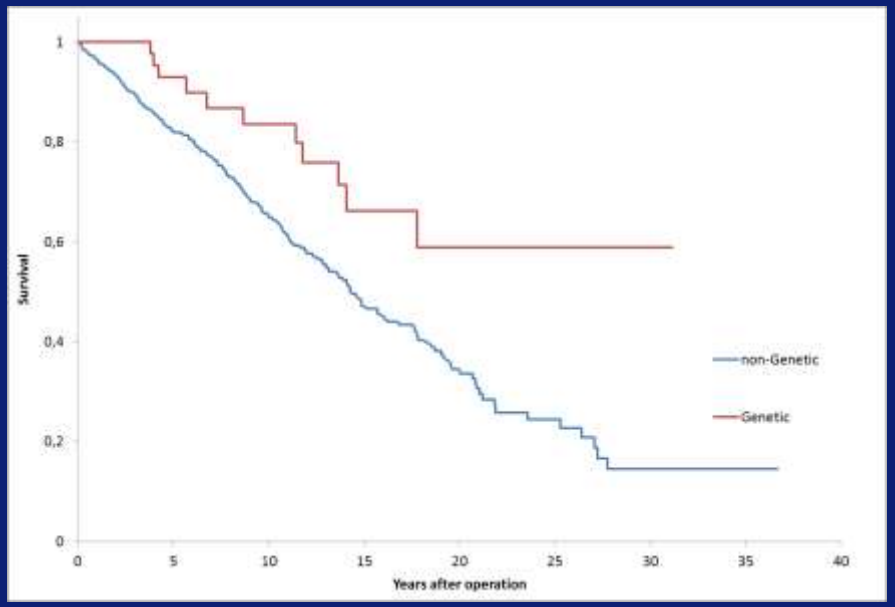
# Lange termijn overleving na eerste operatie

*All patients*




*P<0,001*

*Hospital survivors*




*P=0,004*

*Cox-regressie: na correctie voor leeftijd: niet significant*

# Vervolg operaties

Genetic aortic disease:

15/70

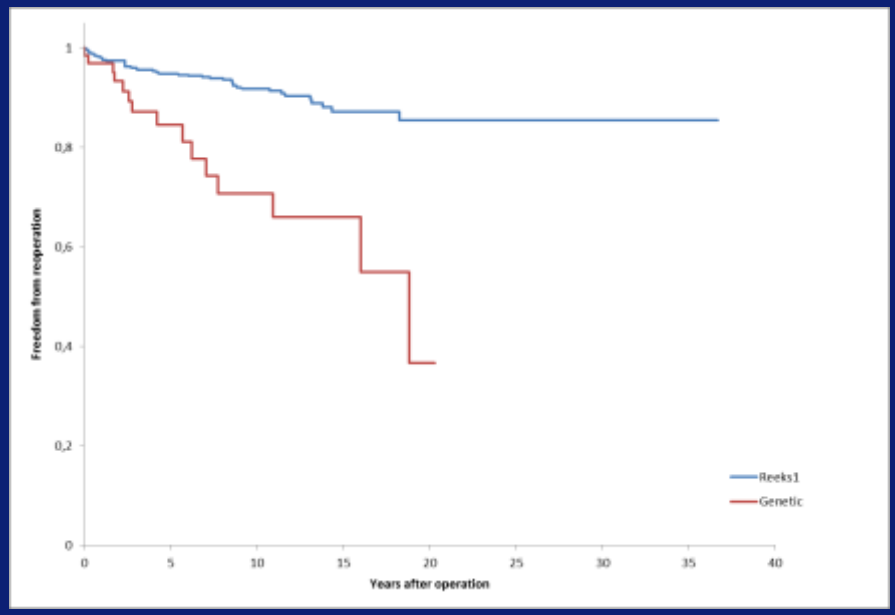
21,4%

Non-genetic aortic disease:

59/1091

5,4%

p<0,001

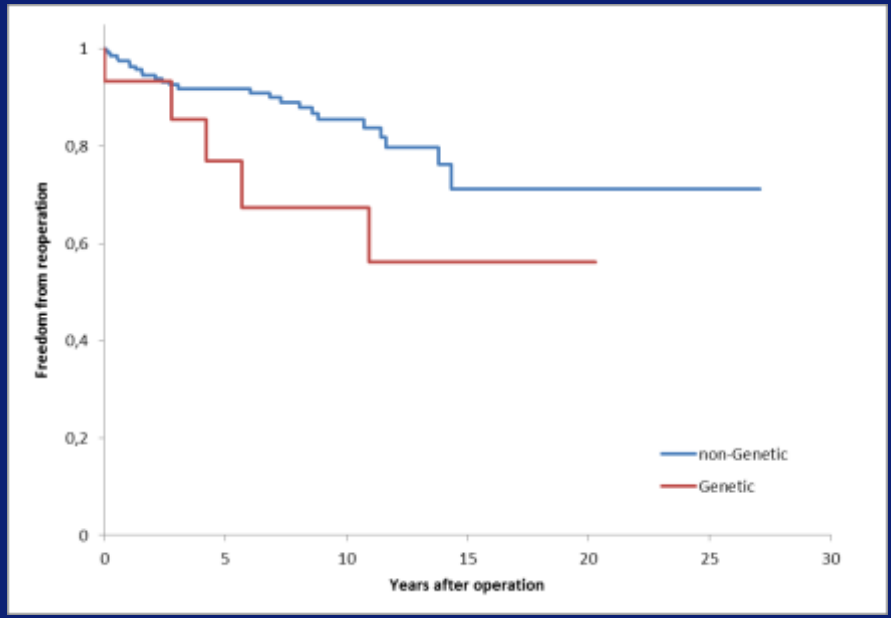



*P<0,001*

# Vervolg operaties na acute type 1 dissectie

5/17 patienten met genetische oorzaak dissectie

| | |
|---|---|
| Boogvervanging | 1 |
| Descendens vervanging | 1 |
| Thoraco-abdominaal | 3 |

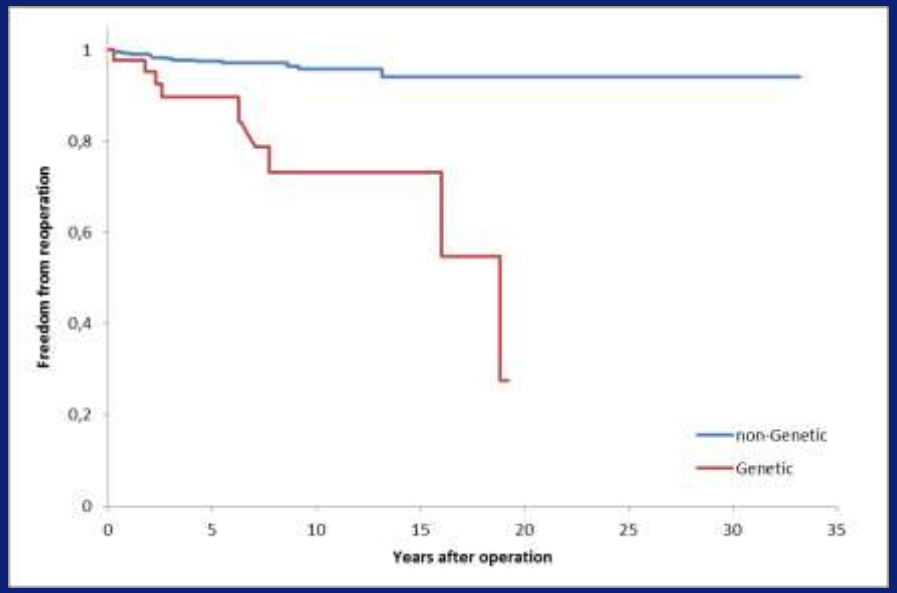



*P=0.086*

# Vervolg operaties na Ascendens/boog aneurysma

10/51 patienten met genetische oorzaak dissectie

| | |
|---|---|
| Boogvervanging | 4 |
| Descendens vervanging | 1 |
| Thoraco-abdominaal | 4 |
| Abdominaal | 1 |




*p<0,001*

# Indicaties voor chirurgie bij asymptomatische patienten

Degeneratief: ≥ 55 mm

Bicuspide aortaklep: ≥ 50 mm

M. Marfan: ≥ 50 mm.

- Bij positieve familie anamnese voor dissecties of snelle groei eerder.

Loeys-Dietz syndroom: ≥ 45 mm

Familaire aneurysma's: ≥ 45 mm

- Bij positieve familie anamnese eerder
- SMAD 3 mutatie !!

# Conclusies

Frequent erfelijke factor van belang bij aortale aandoening

Vooral ascendens/ boogpathologie

Lagere leeftijd bij eerste operatie

Iets meer vrouwen bij genetische origine aorta aandoening

Operatie sterfte bij genetische aorta aandoeningen niet hoger dan bij niet-genetische aandoening

Lange termijn overleving bij genetische aorta aandoening na eerste operatie beter dan bij niet genetische aandoening, echter na correctie voor leeftijdsverschil niet meer

Frequent vervolgoperaties, zowel na acute dissectie, als na electieve ascendens chirurgie

Zo mogelijk indicatie stelling voor operatie op maat, rekening houdend met diagnose, familie-historie, groeisnelheid