AVARIJN Study

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We hypothesize that a significant proportion of patients with severe aortic stenosis is not referred for surgical treatment because of co-morbidities and/or old age, or is operated late in the course of the disease due to underestimation of disease...

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON29060

Bron
NTR

Verkorte titel
AVARIJN (Aortic VAlve RIJNmond)

Aandoening

Aortic Valve Stenosis, prognostic research.

Ondersteuning

Primaire sponsor: Erasmus MC
Department of Cardiothoracic Surgery
Overige ondersteuning: Erasmus MC
Department of Cardiothoracic Surgery

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

- Death

Toelichting onderzoek

Achtergrond van het onderzoek

Background

Aortic stenosis is the most common valvular heart disease in developed countries. The cause is mostly degenerative 1, other causes are rheumatic aortic valve disease, congenital malformations, (bicuspid valve or malformed leaflets) and endocarditis. The genetic background is largely unclear although some involved genes have been identified. While aortic valve calcification increases with age the prevalence of severe aortic stenosis increases concomitantly. Estimates range from 1-2% in people aged 75 years to nearly 6% in people who are a decade older 2,3. Aortic stenosis is becoming an increasingly important health problem in developed countries as the life expectancy of the population continues to rise. Agreement on treatment exists in symptomatic patients with severe aortic stenosis 4; these should be treated aggressively to prevent sudden death and deterioration of left ventricular function. Prognosis of these patients is poor when treated conservatively 5. Surgical replacement by a mechanical or biological prosthetic valve offers excellent long-term results. Other less invasive treatment modalities are balloon valvuloplasty, which can temporarily relief symptoms, and new techniques as percutaneous aortic valve replacement 6-9. However, a significant proportion of symptomatic patients are denied AVR because of severe co-morbidities or due to underestimation of disease severity 10,11.

For asymptomatic patients the optimal treatment strategy is uncertain. Truly asymptomatic patients have a much better prognosis compared to symptomatic patients, with an incidence of sudden death of only 0,4% 4. These patients should not be confronted with the risks associated with AVR since these are considerably higher than the risks of conservative treatment: operative mortality varies from 1% in young patients up to 11% in octogenarians 12-17, and prosthetic valve-related morbidity and mortality occurs in 3-4% per year 4. However, according an European observational study, a significant proportion (up to 37%) of the patients who claim to be asymptomatic, are found to be symptomatic when an exercise test is performed 18. In The Netherlands this propotion is not yet established. Therefore the number of patients who could benefit from an aortic valve replacement is probably underestimated. Furthermore echocardiographic findings have shown rapid progression of pressure gradients and decrease of aortic valve area in some patients 19-21. This may be accompanied by a rapid progression from an asymptomatic into a symptomatic stage; 3% of the patients die within 3-6 months after the onset of symptoms 22. Often, when symptoms occur disease is more advanced, and left ventricular dysfunction is present. It would therefore be useful to have a better indicator of disease-severity, to be able to select those who are at risk of clinical deterioration, and to determine the threshold when surgery is indicated. Ideally this cut-off point would be just before LV dysfunction and symptoms occur. At present biomarkers are not routinely used for diagnosis and evaluation of patients with (asymptomatic) aortic stenosis. Recent studies have demonstrated several natriuretic peptides to be predictive of left ventricular failure. BNP is secreted mostly in the left ventricle, ANP mainly in the atria, in reaction on increased intra-ventricular and intra-atrial

pressure or stretch. BNP is useful in discriminating cardiac versus non-cardiac dyspnea 23, it is accurate in discriminating symptomatic and asymptomatic patients, and it is associated with outcome in both patient categories 24. Asymptomatic patients with high Nt-proBNP at baseline have a much higher risk of developing symptoms during follow-up than those whose levels are normal 25. Nt-proBNP is the N-terminal end of proBNP, the precursor of BNP, and is biologically more stable than BNP 26. Therefore Nt-proBNP is a more practical marker in clinical practice. Measurement of elevated plasma Nt-proBNP could be predictive for symptom development in asymptomatic patients, and poor outcome in both symptomatic and asymptomatic patients 24,25,27.

In this regard Tissue Doppler Imaging is a new emerging ultrasound techniques that provides a measure of left ventricular wall motion 28. Instead of high-frequency low-amplitude signals from moving blood cells in conventional echocardiography, it quantifies high-amplitude, low-velocity signals of myocardial tissue motion 29. Thereby it provides objective means to quantify global and regional left and right ventricular function even before the occurrence of (subjective) symptoms and improves accuracy and reproducibility of conventional echocardiography studies 28,30.

Hypothesis

We hypothesize that a significant proportion of patients with severe aortic stenosis is not referred for surgical treatment because of co-morbidities and/or old age, or is operated late in the course of the disease due to underestimation of disease severity and progression. Nt-proBNP, TDI and strain measurement may predict the onset of symptoms in asymptomatic patients and may predict outcome in symptomatic patients.

Study objectives

The goals of this prospective observational cohort study are:

1. To assess in patients who are echocardiographically diagnosed with severe aortic stenosis if they are truly asymptomatic or not, to document the selected treatment strategy, to investigate potential determinants of prognosis, and to measure 1 and 2-year survival, functional status and quality of life.

2. To investigate if Nt-proBNP, Tissue Doppler Imaging and measurement of strain can predict the course of the disease in symptomatic patients, and to investigate if they are of additive prognostic value in asymptomatic or suspected symptomatic patients.

Study design

Hospital-based prospective cohort study in the wider Rotterdam area (Rijnmond) in The Netherlands (including Erasmus MC and all referring hospitals in the Rotterdam area).

Methods

From May 2006, all adult patients who visit the Erasmus Medical Center or an outpatient Cardiology clinic in the wider Rotterdam area and are diagnosed with severe aortic stenosis will be provided with study information, and invited to the Erasmus Medical Center or the participating center to participate in the proposed study. Written informed consent will be obtained prior to participation. Patients with previous aortic valve surgery or balloon dilatation will be excluded.

Echocardiographic inclusion criteria are (minimal 1):

1. Peak aortic velocity ¡Ý 4,0 m/s 4

2. Aortic valve area ¡Ü 1,0 cm2

3. Aortic valve area adjusted for body surface area ¡Ü 0,6 cm2/m2 31

4. LVOT/AoV TVI ratio ¡Ü 0,25

Patient characteristics, functional status, quality of life and treatment strategy will be established at baseline. Also Nt-proBNP will be measured, and a Doppler echocardiography, including Tissue Doppler Imaging, will be performed. Additional to Nt-proBNP measurement, serum will be saved in order to be able to assess possible Nt-proBNP influencing factors such as renal function or to assess future biomarkers. Also DNA will be saved for gene research. In case of asymptomatic severe aortic stenosis, an exercise test will be done according to recommendations in recent literature 1,31. Follow-up will be at 6 months, 1 and 2 years if conservatively treated. If the patient underwent AVR during this follow-up, one year after AVR is the final follow-up. At these time points echocardiography (Tissue Doppler Imaging, strain, strainrate) and Nt-proBNP assessment will be repeated, and related to functional status and quality of life at that particular time. Endpoints are death or AVR. Total duration of the study will be 3-4 years.
Approximately 215 patients are operated for aortic stenosis in Erasmus MC each year. A significant proportion (33% up to 68%) of elderly patients do not receive surgery although they have severe aortic stenosis 11,32. We estimate this proportion to be approximately 50%. Based on these assumptions we estimate it should theoretically be possible to include approximately 430 patients during the period of 1 year.

Innovative aspects

Better timing of intervention and earlier detection of patients who might benefit from surgical

treatment are the key innovative goals of this study. Nt-proBNP measurements, Tissue Doppler Imaging and strain measurements are not routinely performed but can prove to be of significant value to cardiovascular medicine in the near future. To our knowledge there are no previous or ongoing studies on this subject. Furthermore the proposed study will provide important new insights into the characteristics of the substantial number of patients who require valve replacement but are currently rejected for surgery. This will be of value to determine which patients may benefit from less invasive techniques to replace the aortic valve that are currently under development but may prove to be a realistic alternative treatment option.

References

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Doel van het onderzoek

We hypothesize that a significant proportion of patients with severe aortic stenosis is not referred for surgical treatment because of co-morbidities and/or old age, or is operated late in the course of the disease due to underestimation of disease severity and progression. NtproBNP, tissue Doppler imaging and strain measurement may predict the onset of symptoms in asymptomatic patients and may predict outcome in symptomatic patients.

Onderzoeksopzet

Accrual time: May 1 2006 - May 1 2009.

Study end: May 1 2010.

Onderzoeksproduct en/of interventie

We establish patient characteristics, treatment strategy, functional status, quality of life, Doppler echocardiography, ECG and Nt-proBNP at baseline. After 6, 12 and 24 months, we repeat the echocardiography, ECG and Nt-proBNP and related that to the functional score and quality of life at that particular time point.

If the patient underwent aortic valve replacement, we repeat these assessments one year after AVR.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Adult patients with severe aortic valve stenosis, presented in the Erasmus medical Center or outpatient Cardiology clinic in the wider Rotterdam area.

2. Written informed consent.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Patients with previous aortic valve surgery or balloon dilatation.

2. Patients mentally disabled and/or suspect for senile dementia.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-05-2006

Aantal proefpersonen:	342
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	17-10-2008
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL1435
NTR-old	NTR1496
Ander register	: MEC 2006-066
ISRCTN	ISRCTN wordt niet meer aangevraagd

Resultaten

Samenvatting resultaten
N/A