# BIOTRONIK - Safety and clinical performance of the self-expanding transcatheter BIOVALVE prosthesis in subjects with severe symptomatic calcified aortic valve stenosis suitable for transfemoral transcatheter aortic valve implantation (TAVI)

Published: 05-04-2016
Last updated: 19-04-2024

To evaluate the safety and clinical performance of the BIOVALVE prosthesis in subjects presenting with severe symptomatic aortic valve stenosis, which are as judged by the heart team, indicated for transfemoral transcatheter aortic valve...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Cardiac valve disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON46183

**Source**
ToetsingOnline

**Brief title**
C1205 BIOVALVE

### Condition

- Cardiac valve disorders

**Synonym**
severe symptomatic aortic stenosis

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** BIOTRONIK AG
**Source(s) of monetary or material Support:** industry/company

## Intervention

**Keyword:** First-in-Human (FIH) Trial, self-expanding transcatheter prosthesis, TAVI, transfemoral

## Outcome measures

### Primary outcome

Early safety at 30 days (According to VARC-2; Kappetein et al. EuroIntervention 2012;8:782-795)

A composite of all-cause mortality, all stroke (disabling/non-disabling), life-threatening bleeding, acute kidney injury stage 2 or 3 (including renal replacement therapy), coronary artery obstruction requiring intervention, major vascular complication and valve-related dysfunction requiring repeat procedure (balloon aortic valvuloplasty (BAV), transcatheter aortic valve implantation (TAVI), or surgical aortic valve replacement (SAVR)).

### Secondary outcome

Combined safety endpoint at 30 days (Acc. to VARC-1; Leon et al. J Am Coll Cardiol 2011;57:253-269)

A composite of all-cause mortality, major stroke, life-threatening (or disabling) bleeding, acute kidney injury stage 3 (including renal replacement therapy), peri-procedural myocardial infarction, major vascular complication and repeat procedure for valve-related dysfunction (surgical or interventional

therapy)

Clinical efficacy after 30 days (Acc. to VARC-2):

A composite of all-cause mortality, all stroke (disabling and non-disabling), requiring hospitalizations for valve-related symptoms or worsening congestive heart failure, NYHA class III or IV, valve-related dysfunction (mean aortic valve gradient >=20 mm Hg, effective orifice area (EOA) <=0.9-1.1 cm2 * and/or Doppler velocity index (DVI) <0.35 m/s, and/or moderate or severe prosthetic valve regurgitation **).

* depending on body surface area

** refers to VARC-2 definitions

Assessment at 30 days, 3 months, 6 months, 1 year and annually thereafter through 5 years as applicable of

- life-threatening bleeding
- acute kidney injury
- coronary artery obstruction requiring intervention
- major vascular complication
- valve related dysfunction requiring repeat procedure
- peri-procedural myocardial infarction
- requiring hospitalizations for valve-related symptoms or worsening congestive heart failure
- NYHA classification
- valve-related dysfunction

Assessment of mortality and stroke at 30 days, 3 months, 6 months, 1 year and annually thereafter through 5 years

Conduction disturbances and arrhythmias at 30 days:

- New AV block (I, II, III, LBBB, RBBB)
- New permanent pacemaker implantation
- New onset of atrial fibrillation

Device success (Acc. to VARC-2):

Absence of procedural mortality and correct positioning of a single investigational prosthetic heart valve into the proper anatomical location and intended performance of the investigational prosthetic heart valve (no prosthesis-patient mismatch * and mean aortic valve gradient <20 mm Hg or peak velocity <3 m/s, and no moderate or severe prosthetic valve regurgitation *)

* refers to VARC-2 definitions

Time-related valve safety (Acc. toVARC-2):

A composite of structural valve deterioration (valve related dysfunction (mean aortic valve gradient >=20 mm Hg, EOA <=0.9-1.1 cm2 * and/or DVI <0.35 m/s, and/or moderate or severe prosthetic valve regurgitation **), requiring repeat procedure (TAVI or SAVR)), prosthetic valve endocarditis, prosthetic valve thrombosis, thromboembolic events (e.g. stroke) and VARC bleeding unless clearly unrelated to valve therapy (e.g. trauma)

* depending on body surface area

** refers to VARC-2 definitions

Assessment of

- structural valve deterioration

- prosthetic valve endocarditis

- prosthetic valve thrombosis

- thromboembolic events

- VARC bleeding

Echocardiograhic (ECHO) parameters at discharge, 30 days, 6 months, 12 months

and annually through 5 years

- Effective orifice area (EOA) and effective orifice area index (EOAI)

- Mean prosthetic valve gradient

- Prosthetic valve regurgitation (Acc. to VARC-1 and VARC-2)

Procedural success

A composite of device success without in-hospital occurrence of all-cause

death, myocardial infarction, all-stroke and re-intervention

# Study description

**Background summary**

Prolonged average life expectancy has resulted in an aging population and consequently, an increase in the number of patients with acquired, calcific, severe, symptomatic aortic valve stenosis. Aortic valve stenosis is a progressive, debilitating and life-threatening disease if left untreated.

Affected individuals are typically >65 years of age. The pathology involves progressive calcification of the leaflet bodies which limits normal cusp opening during systole. Cellular aging and degeneration have been implicated in this form of the disease and diabetes mellitus and hypercholesterolemia are risk factors. Aortic valve stenosis is the most frequent heart valve disease in Europe and North America and has a prevalence of 2-7% of the population beyond 65 years [1].

The standard of care therapy for patients suffering from severe symptomatic aortic valve stenosis is surgical aortic valve replacement. There is a consensus that early valve replacement should be performed in subjects with severe, symptomatic aortic valve stenosis [1], however, it has been investigated and found that surgery was denied in one third of patients with severe symptomatic aortic valve stenosis at an age >= 75 years [2]. Left ventricular dysfunction and age were the most striking characteristics of patients who were denied surgery.

To provide an option to treat high risk patients and to avoid under-treatment of aortic valve stenosis, the less invasive transcatheter heart valve therapy has been developed.

The first transcatheter heart valve implantation (TAVI) in human was conducted in 2002 [3] and in 2007 CE-certification was obtained for the CoreValve and SAPIEN transcatheter heart valves. Meanwhile, TAVI has proven to be feasible and safe in several studies and registries [4;5;6;7;8] and has become an established procedure [9].

In Europe replacement valves from different manufacturers are approved for the use in high-risk patients. New replacement valves are constantly under development to improve the safety and clinical performance [10].

To proof safety and efficacy of the newly developed BIOVALVE prosthesis in this First-in-Human clinical investigation the primary endpoint "early safety" (a composite of all-cause mortality, all stroke (disabling/non-disabling), life-threatening bleeding, acute kidney injury stage 2 or 3 (including renal replacement therapy), coronary artery obstruction requiring intervention, major vascular complication and valve-related dysfunction requiring repeat procedure (balloon aortic valvuloplasty, TAVI, or surgical aortic valve replacement at 30 days prost procedure) according to the Valve Academic Research Consortium (VARC-2 [11]) has been chosen.

For estimation of the rate of "early safety" events, an objective performance criterion (OPC) has been selected. The objective performance criterion is based on a historical control group derived from the results of a literature search.

The hypothesis is that the rate of "early safety" events in the BIOVALVE study population is non-inferior to the event rate of the historical control group.

For more details please refer to the statistical analysis plan (SAP, version 1.0, dated 06 August 2014) filed in standard research file section K6.

[1] Vahanian et al. Eur Heart J 2012;33:2451-2496
[2] Iung et al. Eur Heart J. 2005;26:2714-2720
[3] Cribier et al. Circulation 2002;106:3006-3008
[4] Smith et al. N Engl J Med 2011;364:2187-2198
[5] Adams et al. N Engl J Med 2014;370:1790-1798
[6] Thyregod et al J Am Coll Cardiol 2015;65:2184-94
[7] Mohr et al Euro J Cardio-Thoracic Surgery 2014;46:808-816
[8] Ludman et al. Circulation 2015;131:1181-119
[9] Cribier A. Arch Cardiovasc Dis 2012;105:146-152
[10] Taramasso et al. Nat Rev Cardiol 2014;11:157-167
[11] Kappetein et al. EuroIntervention 2012;8:782-795

**Study objective**

To evaluate the safety and clinical performance of the BIOVALVE prosthesis in subjects presenting with severe symptomatic aortic valve stenosis, which are as judged by the heart team, indicated for transfemoral transcatheter aortic valve implantation.

**Study design**

In a non-randomized, prospective, multi-center clinical investigation, approximately 113 eligible subjects will be enrolled at approximately 15 participating investigational sites.

To assure subject safety in this First-in-Human clinical investigation, the study is divided in 2 phases:
Phase 1: BIOVALVE-I feasibility clinical investigation
- Approximately 13 eligible subjects will be enrolled at one site
Phase 2: BIOVALVE-II pilot clinical investigation
- Up to 100 eligible subjects will be enrolled at approximately 15 sites

BIOVALVE-I/II subjects follow the same clinical investigation plan (CIP) in all aspects.

**Intervention**

The common name for the procedure which you will undergo is transcatheter aortic valve implantation (TAVI).
The procedure is performed in a specially assigned operating room with integrated heart catheterisation laboratory. You will receive anaesthesia adapted to your condition; however, you will not undergo a cardiopulmonary

bypass, since the implantation of the BIOVALVE prosthesis is performed on a beating heart. First, a catheter is pushed through your femoral artery into the left heart as you already know from the preliminary examination. A contrast medium is injected through this catheter before, during and after the implantation of the new aortic valve to monitor the individual steps of the implantation.
A guide wire is inserted through an introducer sheath at the opposite femoral aorta which is pushed forward through the aorta and aortic valve into the left heart chamber. A balloon catheter is pushed forward through this guide wire which is used to stretch the narrowed aortic valve.
Afterwards, the special catheter system containing the BIOLVALVE prosthesis is inserted, positioned and then the new cardiac valve is implanted step by step. For this purpose, the calcified valvular cusps are pushed to the wall by the metal structure (stent) of the BIOVALVE prosthesis, so that the new aortic valve can expand and immediately take up its function.

**Study burden and risks**

The nature and extend of the burden, risks and benefits associated with participation are described for baseline, procedure, discharge and follow-up.

A detailed overview of assessments performed is provided in the clinical investigation plan, page 18. A detailed description of risks and benefits is provided in the patient informed consent and in the clinical investigation plan, page 36-40.

Baseline
All baseline examinations are according to standard of care with the exception of assessing the stroke status and the quality of life status. The stroke scale assessment is done by using a) the National Institute of Health stroke scale questionnaire and b) the modified Rankin scale questionnaire. The stroke status is assessed by a trained and qualified site personnel. The quality of life status is assessed by using the EQ5D questionnaire.

Procedure
Implantation of the investigational device will not bring additional risk to the subjects, then otherwise experience in standard clinical care. None of the study patients will have any planned additional invasive or non-invasive examinations/procedures during the TAVI procedure.

Discharge
All post-procedure until discharge examinations are according to standard of care with the exception of assessing the stroke status. The stroke scale assessment is done by using a) the National Institute of Health stroke scale questionnaire and b) the modified Rankin scale questionnaire. The stroke status is assessed by a trained and qualified site personnel.

Follow-up after 1 month, 6 months and 12 months
During follow-up all patients are requested to return to the hospital after 1 month, 6 months and 12 months. All examinations are according to standard of care with the exception of assessing the stroke status and the quality of life status. The stroke scale assessment is done by using a) the National Institute of Health stroke scale questionnaire and b) the modified Rankin scale questionnaire. The stroke status is assessed by a trained and qualified site personnel. The quality of life status is assessed by using the EQ5D questionnaire.

Follow-up after 2, 3, 4 and 5 years
During follow-up all patients are requested to return to the hospital after 2, 3, 4 and 5 years. All examinations are according to standard of care.

Follow-up after 3 months
During follow-up all patients will be contacted by phone after 3 months. patients are asked for the health status and occurrence of adverse events.

Benefits
When receiving the investigational product, a patient's disease may be cured. Since the performance of the investigational product has not yet been proven in a lager patients population, it is also possible that a patient may not benefit from study participation.

Conclusion
To summarize, based upon the existing experience from preclinical data, data from the BIOVALVE-I First-in-Human study, and literature, it is expected that residual risks associated with the investigational device within its intended use are acceptable. Overall it is expected that the medical benefits will outweigh the residual risks.

## Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. The subject is >=65 years
2. The subject has provided written informed consent
3. Subject is willing to participate in the clinical investigation and to comply with all of the study procedures and follow-up visits
4. NHYA class >=II
5. High surgical risk: Logistic EuroSCORE-I >=20% (or equivalence of EuroSCORE-II) or STS score >=10% or co-morbidity judged by the heart team (consisting of at least one interventional cardiologist and one cardiac surgeon) to pose an absolute or relative contraindication for conventional aortic valve replacement according to VARC-2
6. Severe symptomatic calcific aortic valve stenosis characterized by mean aortic gradient >40 mm Hg or peak jet velocity >4.0 m/s or effective orifice area (EOA) of <1.0 cm2 (<0.6 cm2/m2 body surface area)
7. Annulus diameter as determined by multi-slice computed tomography (MSCT) from 20-26 mm

## Exclusion criteria

1. Trans-esophageal echocardiogram (TEE) is contraindicated
2. Congenital bicuspid or unicuspid valve
3. Left ventricular outflow tract (LVOT) obstruction such as hypertrophic obstructive cardio myopathy (HOCM) or subject presenting with systolic anterior motion (SAM). Evidence of intra cardiac mass, thrombus or vegetation
4. Transfemoral access vessel characteristics that would preclude safe placement of a 18 French sheath
5. Vessel and/or anatomical characteristics that would preclude safe delivery of the BIOVALVE

prosthesis to the ascending aorta and/or placement of the prosthesis
6. Anatomical restrictions such as shallow sinuses with heavily calcified leaflets, low height of coronary ostia, extreme tortuosity of the aortic arch, thoracic (TAA) or abdominal (AAA) aortic aneurysm, presence of endovascular stent graft
7. Severe mitral regurgitation grade >3
8. Severe mitral stenosis
9. Prosthetic mitral valve
10. Severe left ventricular dysfunction with left ventricular ejection fraction (LVEF) <20%
11. Hemodynamic instability
12. Percutaneous coronary intervention (PCI) within 30 days prior to index procedure and / or planned PCI during index procedure
13. Renal insufficiency (creatinine >2.5 mg/dl) or subject under dialysis and/or renal replacement therapy
14. Any cerebrovascular event or transient ischemic attack (TIA) within 180 days prior to TAVI procedure
15. Evidence of acute myocardial infarction (defined as >=2 fold CK level or in absence of CK a >=3 fold CKMB level above the upper range limit within <=30 days prior to TAVI procedure)
16. Blood dyscrasia defined as: leucopenia (WBC <1000 $mm^3$), thrombocytopenia (platelet count <50*000 cells/$mm^3$), history of bleeding diathesis requiring blood transfusion
17. Ongoing sepsis or suspected active endocarditis
18. Active peptic ulcer or gastrointestinal bleeding within last 3 months that would preclude anticoagulation
19. Subject refuses blood transfusion
20. Known hypersensitivity to, or contraindication to nitinol, anticoagulation/antiplatelet regimes, any other medications required for the procedure or post-procedure as determined by the heart team, or sensitivity to contrast media which cannot be adequately pre-medicated
21. Need for emergency TAVI intervention, or other medical, social, or psychological conditions that in the opinion of the heart team precludes the subjects from appropriate consent or adherence to protocol required follow-up exams
22. Expectation that subject will not improve despite treatment of aortic stenosis
23. Estimated life expectancy of less than 12 months due to associated non-cardiac co-morbidities
24. Severe pulmonary hypertension (> 60 mm Hg assessed by continuous wave Doppler, TTE) or clinical signs of acute severe right ventricular dysfunction
25. Currently participating in another investigational drug or device study where primary endpoint has not been reached yet

## Study design

## Design

**Study type:** Interventional

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 25-04-2017 |
| Enrollment: | 20 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Generic name: | BIOVALVE prosthesis |
| Registration: | No |

# Ethics review

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| Approved WMO Date: | 05-04-2016 |
| Application type: | First submission |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |

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|---|---|
| Approved WMO Date: | 25-08-2016 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |

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|---|---|
| Approved WMO Date: | 08-09-2017 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| ClinicalTrials.gov | NCT02249000 |
| CCMO | NL54588.100.15 |