# Evolut* EXPAND TAVR II Pivotal Trial

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The purpose of this trial is to evaluate the safety and effectiveness of the Medtronic Evolut PRO+ and Evolut FX TAVR system and guideline-directed management and therapy (GDMT) compared to GDMT in patients with moderate, AS. Data will be used to...

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

## Summary

### ID

NL-OMON53699

**Source**
ToetsingOnline

**Brief title**
Evolut* EXPAND TAVR II Pivotal Trial

### Condition

- Cardiac valve disorders

**Synonym**
Moderate aortic stenosis

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Medtronic Trading NL BV
**Source(s) of monetary or material Support:** Medtronic

### Intervention

**Keyword:** aortic stenosis, Evolut PRO + & Evolut FX TAVR system, Moderate, TAVI procedure

## Outcome measures

### Primary outcome

The primary safety objective is to demonstrate that the composite rate of all-cause mortality, all stroke, life-threatening or fatal bleeding (BARC Type 3 or 4), acute kidney injury (VARC 3 - Stage IV), hospitalization due to device or procedure-related complication, or valve dysfunction requiring re-intervention at 30 days in the device arm is less than the performance goal.
The primary effectiveness objective is to demonstrate the Medtronic TAVR system on the background of GDMT is superior to GDMT alone in the composite rate of all-cause mortality, heart failure hospitalization or event, or medical instability leading to aortic valve replacement or re-intervention at 2 years.

The primary effectiveness endpoint is defined as the composite of all-cause mortality, heart failure hospitalization or event, or medical instability leading to aortic valve replacement or re-intervention at 2 years.

### Secondary outcome

The following secondary endpoints will be hypothesis tested:

• Proportion of subjects alive and with moderately improved quality of life (>= 10 points in KCCQ summary score from baseline) at 1 year

• Composite of all-cause mortality and heart failure hospitalizations or events at 2 years

• Composite of all-cause mortality, all-stroke, or unplanned CV hospitalizations at 2 years

• Heart failure hospitalizations or events at 2 years

• All-cause mortality at 2 Years

• Unplanned cardiovascular hospitalizations at 2 years

• Days alive and free of unplanned cardiovascular hospitalizations at 2 years

Tertiary Endpoints

The following endpoints are descriptive and will not be hypothesis tested:

• Composite rate of all-cause mortality, heart failure hospitalization or event, or medical instability leading to aortic valve replacement or re-intervention at 30 days and 1 year

• Cardiovascular mortality at 30 days, 1 year, and annually through 10 years

• All strokes (fatal, disabling, and non-disabling) at 30 days, 1 year, and annually through 10 years

• All AVR at 30 days, 1 year, and annually through 10 years (GDMT arm only):

- Guideline indicated AVR at 30 days, 1 year, and annually through 10 years (GDMT arm only)

• Medical instability leading to aortic valve replacement or re-intervention at 30 days, 1 year, and annually through 10 years

• Total heart failure hospitalizations or events at 30 days, 1 year, and annually through 10 years

• Change in NYHA at 30 days, 1 year, and annually through 10 years

• Change in 6-minute walk test (6MWT) at 6 months, 1 year, and 2 years

• Health-related quality of life at 30 days, 6 months, 1 year, and 2 years by KCCQ

• Health-related quality of life at 30 days, 6 months, 1 year, and annually through 5 years by EQ-5D

• Change in the following left ventricular function parameters:

o Left ventricular mass (baseline to 1 year)

o Peak global longitudinal strain (GLS) (baseline to 1 year)

o E/e* (baseline to 1 year)

o NT-Pro BNP (baseline to 1 year)

• Aortic valve hemodynamic performance parameters (e.g., mean gradient, AVA, max aortic velocity, DVI, and aortic regurgitation) by echocardiography:

o TAVR + GDMT arm: 30 days, 6-months, 1 year, and annually through 10 years

o GDMT arm: 6-months, 1 year, and annually through 5 years

• Unplanned cardiovascular hospitalizations at 30 days, 1 year, and annually through 10 years

• Other echocardiographic variables (e.g., LV dimensions, LVEF, GLS, E/e*, LAVI, RV dimensions, CO, SVI, ZVA).

o TAVR + GDMT arm: 30 days, 6-months, 1 year, and annually through 10 years

o GDMT arm: 6-months, 1 year, and annually through 5 years

# Study description

**Background summary**

I refer to CIP version G dd 21.03.2024 page 17 to 20 for the complete background of the study protocol.

**Study objective**

The purpose of this trial is to evaluate the safety and effectiveness of the

Medtronic Evolut PRO+ and Evolut FX TAVR system and guideline-directed management and therapy (GDMT) compared to GDMT in patients with moderate, AS. Data will be used to support regulatory submissions to expand the current indications for the Evolut PRO+ and Evolut FX TAVR system to include patients with moderate AS.
*

**Study design**

This is a prospective, interventional, multi-center, randomized, pre-market, pivotal trial. The trial will involve up to 650 subjects randomized 1:1 to either TAVR + GDMT with the Medtronic TAVR system (TAVR + GDMT arm) or GDMT alone (GDMT arm). The trial will be conducted in up to 100 centers in the United States, Canada, Europe, Israel, Australia, New Zealand, and Japan. The study design and flow are outlined in Figure 1 of the CIP.

**Intervention**

Screening/Baseline Visit (30 days after initiation of GDMT and within 12 weeks of ERC review submission)
• Clinical assessment
• Medical history
• Transthoracic echo (TTE)
* For subjects with LVEF < 50%, SVI < 35 ml/m2, AVA < 1.0 cm2, and mean gradient > 20.0 mmHg and <40.0 mmHg OR max aortic velocity > 3.0 m/sec and < 4.0 m/sec, low dose DSEv may be performed to assess if they have moderate AS vs low-flow low gradient severe AS.
• pro B-type natriuretic peptide (NT-proBNP or BNP if NT-proBNP is not available)
• 6-minute walk test (6MWT)
* For subjects who deny symptoms, functional testing (6MWT or exercise tolerance test) may be performed per discretion of the investigative team. If testing reveals the presence of reduced functional capacity, the subject may go forward for further evaluation.
• Complete blood count (CBC)iv
• Serum creatinine
• 12-lead ECG
• Modified Rankin Scale
• Coronary arteriography (either selective or by computed tomography)v
• MDCT (peripheral vasculature and aortic annulus)
• Heart Valve Team assessment
• Quality of Life instruments:
o Kansas City Cardiomyopathy Questionnaire (KCCQ)
o European Quality of Life-5 Dimensions (EQ-5D-5L)
-GDMT Assessment
Index Treatment Visit: TAVR + GDMT Arm (between 1 to 21 days post randomization)

• Clinical assessment
• Index TAVR procedure
o Hemodynamics (Pre and final post-deployment LV and aortic pressures)
o Aortography (final result)
Index Treatment Visit: GDMT Arm (between 1 to 21 days post randomization)
• Clinical assessment
Discharge (TAVR + GDMT Arm only)
• Clinical assessment
• 12 lead ECG
30 days (between 30 to 45 days post index treatment visit)
• Clinical assessment
• 12 lead ECG
• TTE
• NT-proBNP (or BNP if NT-proBNP is not available)
• Quality of Life instruments:
o KCCQ
o EQ-5D-5L
6 Months (between 183 to 210 days post index treatment visit)
• Clinical assessment
• 12 lead ECG
• TTE
• NT-proBNP (or BNP if NT-proBNP is not available)
• Quality of Life instruments:
o KCCQ
o EQ-5D-5L
• 6MWT
1 Year (between 365 to 395 days post index treatment visit)
• Clinical assessment
• 12 lead ECG
• TTE
• NT-proBNP (or BNP if NT-proBNP is not available)
• Quality of Life instruments:
o KCCQ
o EQ-5D-5L
• 6MWT
18 months (between 550 to 580 days post index treatment visit)
• Clinical assessment
2 Years (between 730 to 760 days post index treatment visit)
• Clinical assessment
• TTE
• NT-proBNP (or BNP if NT-proBNP is not available)
• Quality of Life instruments:
o KCCQ
o EQ-5D-5L
• 6MWT
3 - 5 Years (between 60 days before and 60 days after the subject*s index treatment visit anniversary date)

• Clinical assessment
• TTE
• Quality of Life instrument:
o EQ-5D-5L
6 - 10 Years (between 60 days before and 60 days after the subject*s index treatment visit anniversary date)
• Clinical assessment
• TTE (TAVR arm only)
Other Evaluations

**Study burden and risks**

Subjects randomized to TAVR + GDMT will be exposed to the risks associated with the TAVR procedure and the risks associated with the device, as well as the study specific risks listed in section 9.1 of the protocol. However, the scientific literature shows that patients with moderate AS in this study are also exposed to the serious risks associated with their disease, including heart failure, irreversible ventricular functional disorders and death. Further, recent evidence indicates that the risks of the disease to the subjects in this study are similar to those with which TAVR has been shown to be effective in improving symptoms and survival. The established benefits of TAVR in patients with severe AS are hoped to be attributed to the subjects with moderate AS, and it is believed that the benefits of obstruction relief outweigh the risks of this intervention in these patients. Therefore, the risk-benefit ratio for the subjects is justified.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Elderly (65 years and older)

## Inclusion criteria

Please see pg 31 and 32 Key inclusion criteria
Prospective subjects must meet all the following inclusion criteria to be eligible for randomization:
1. Moderate aortic stenosis by TTE as assessed by the ECL:
o AVA > 1.0 and < 1.5 cm2; or
• AVA <= 1.0 cm2 with AVAI > 0.6 cm2/m2 if BMI < 30 kg/m2; or
• AVA <= 1.0 cm2 with AVAI > 0.5 cm2/m2 if BMI C30 kg/m2
and
o Max aortic velocity >= 3.0 m/sec and < 4.0 m/sec or mean aortic gradient >= 20.0 mmHg and < 40.0 mmHg

Subjects with low flow (SVI < 35 ml/m)2 and reduced LVEF (<50%), AVA <= 1.0 cm2, and max aortic velocity >= 3.0 m/sec and < 4.0 m/sec OR mean gradient >= 20 mmHg and < 40 mmHg can be included if low dose dobutamine stress echo (DSE) demonstrates all the following:
- SVI >= 35 ml/m2, and
- AVA > 1.0 cm2 and < 1.5 cm2, and
- Mean aortic gradient >= 20.0 mmHg and < 40.0 mmHg OR max aortic velocity >= 3.0 m/sec and < 4.0 m/sec
Subjects with normal flow (SVI >= 35 ml/m)2and preserved LVEF (>= 50%), AVA <= 1.0 cm2 and max aortic velocity >= 3.0 m/sec and < 4.0 m/sec OR mean gradient >= 20 mmHg and < 40 mmHg can be included if aortic valve calcium score is < 1200 AU for females and < 2000 AU for males.

2.(3) Listed in the CIP version F_18Sept2023 In the Symptoms of AS, defined as:
• NYHA > Class II, or
• Reduced functional capacity , defined as
o 6MWT < 300 meters118, 119, or
o < 85% of age-sex predicted metabolic equivalents (MET) on exercise tolerance testing (ETT)109

3. Any of the following:
• Documented heart failure event or hospitalization for heart failure within 1 calendar year prior to consent, or
• NT-proBNP >= 600 pg/ml (or >= BNP 80 pg/ml), or
• Persistent AF or Paroxysmal AF episode within 6 months prior to consent , , or
• Elevated aortic valve calcium score (> 1200 AU for females or > 2000 AU for males) as assessed by the MDCT core lab, or
• Any of the following on the qualifying TTE as assessed by the ECL:
o Global longitudinal strain (GLS) <= 16.0% (absolute value), or
o E/e* >= 14.0 (average of medial and lateral velocities), or
o Diastolic dysfunction > Grade II
o LVEF < 60%, or
o Stroke Volume Index < 35 ml/m2
4. Anatomically suitable for transfemoral TAVR using the Medtronic Evolut PRO+ or Evolut FX system
5. The subject and treating physician agree the subject will return for all required follow-up visits

## Exclusion criteria

Please see pg 32 and 33 Key exclusion criteria: * If any of the following exclusion criteria are present, the prospective subject is not eligible for randomization:
1. Age < 65 years
2. LVEF < 20% by 2-D echo
3. Class I indication for cardiac surgery
4. Contraindication for placement of a bioprosthetic valve
5. Documented history of cardiac amyloidosis
6. A known hypersensitivity or contraindication to any of the following that cannot be adequately pre-medicated:
• Aspirin, heparin, or bivalirudin
• Ticlopidine and clopidogrel
• Nitinol (titanium or nickel)
• Gold
• Contrast media
7. Blood dyscrasias as defined: leukopenia (WBC < 1000 cells/mm3), thrombocytopenia (platelet count <50,000 cells/mm3), history of bleeding diathesis or coagulopathy, or hypercoagulable states
8. Ongoing sepsis, including active endocarditis
9. Frailty syndrome per Heart Valve Team assessment
10. Coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft) within 30 days prior to randomization
11. In need of and suitable for coronary revascularization per Heart Valve Team
12. Chronic obstructive pulmonary disease (GOLD stage 3 or higher)
13. Symptomatic carotid or vertebral artery disease or successful treatment of

carotid stenosis within 70 days of consent
14. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support
15. Placement of cardiac resynchronization device within 90 days of consent
16. Recent (within 60 days of consent) cerebrovascular accident (CVA) or transient ischemic attack (TIA)
17. Child-Pugh class C liver cirrhosis
18. Gastrointestinal (GI) bleeding that would preclude anticoagulation
19. Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits)
20. Estimated life expectancy of less than 24 months due to associated non-cardiac co-morbid conditions
21. Other medical, social, or psychological conditions that in the opinion of the investigator precludes the subject from appropriate consent or adherence to the protocol required follow-up exams
22. Currently participating in an investigational drug or another device trial or study (excluding registries)
23. Evidence of an acute myocardial infarction <= 30 days prior to consent
24. Advanced renal impairment (defined as GFR < 30 mL/min) or need for renal replacement therapy
25. Need for emergency surgery for any reason
26. Subject is pregnant or breast feeding
27. Subject is less than legal age of consent, legally incompetent, unable to provide his/her own informed consent, or otherwise vulnerable as defined in Section *6.2.
Anatomical exclusion criteria:
28. Congenital unicuspid valve
29. Sievers Type 0 or Type 2 bicuspid aortic valve
30. Sievers Type 1 bicuspid aortic valve with ascending aorta diameter > 4.5 cm
31. Not anatomically suited for transfemoral TAVR with the trial device
32. Absence of calcified aortic valve
33. Severe LVOT calcification
34. Pre-existing prosthetic aortic valve
35. Severe mitral regurgitation by TTE as assessed by the Echo Core Lab
36. Severe tricuspid regurgitation by TTE as assessed by the Echo Core Lab
37. Moderate or severe mitral stenosis (mean gradient >= 5 mmHg, or valve area <= 1.5 cm2) by TTE as assessed by the Echo Core Lab 38
38. Hypertrophic obstructive cardiomyopathy
39. Severe aortic regurgitation by TTE as assessed by the Echo Core Lab
*

# Study design

## Design

| | |
|---|---|
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 30-11-2022 |
| Enrollment: | 100 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Generic name: | Medtronic Evolut PRO+ Evolut FX Transcatheter Aortic Valve (TAV) Bioprosthesis systems |
| Registration: | Yes - CE outside intended use |

# Ethics review

| | |
|---|---|
| Approved WMO Date: | 26-07-2022 |
| Application type: | First submission |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |

| | |
|---|---|
| Approved WMO Date: | 11-08-2022 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |

Approved WMO

| | |
|---|---|
| Date: | 02-01-2023 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 16-06-2023 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 10-04-2024 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 20-06-2024 |
| 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 | NCT05149755 |
| CCMO | NL79745.000.21 |