

The PARTNER II Trial: Cohorts A and B University of Washington Medical Center Facts for the Referring Provider

1. What is the PARTNER II trial and what are the objectives?

The PARTNER II trial is a national study determining the safety and effectiveness of transcatheter aortic valve replacement (TAVR) using the Edwards SAPIEN XT (2nd generation) device and either the NovoFlex or Ascendra 2 delivery system. Entry criteria include both high-risk operable (Cohort A) and inoperable (Cohort B) patients with symptomatic critical aortic stenosis.

2. What are the two cohorts for enrolling patients?

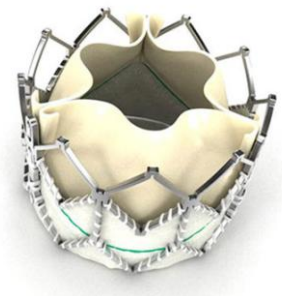
Patients enrolled into the Cohort A arm will first be determined to have adequate transfemoral access or inadequate transfemoral access. They will then be randomized 1:1 in a blinded manner to TAVR (either transfemoral or transapical access) vs. open Aortic Valve Replacement (AVR). Patients enrolled in the Cohort B arm will be randomized 1:1 in a blinded manner to TAVR using either the Edwards SAPIEN XT device and NovoFlex delivery system or the Edwards SAPIEN THV device and RetroFlex 3 delivery system that was studied in the PARTNER I trial. There will also be a small registry of inoperable patients who do not have transfemoral access who may be eligible for the transapical approach.

3. What are the differences between PARTNER I AND PARTNER II?

The PARTNER II trial is the follow-up trial to the recently completed PARTNER I trial which demonstrated the safety and effectiveness of the Edwards SAPIEN THV (1st generation) in both high-risk operable and inoperable patients with symptomatic critical aortic stenosis.

In the Cohort B population, the PARTNER II trial is designed to study and compare the safety and effectiveness of the second generation valve (SAPIEN XT) and delivery system (NovoFlex) to the first-generation valve (SAPIEN) and delivery system (RetroFlex3). The lower profile of the second generation valve, allows it to be implanted using a lower profile transfemoral system (18/19 F with NovoFlex vs. 22/24 F with RetroFlex 3), which is expected to further reduce vascular and access complications with TAVR.

In the Cohort A population, the trial is designed to compare the second generation valve (SAPIEN XT) and delivery system in intermediate risk (lower than PARTNER I) patients to traditional, open heart surgery.



*Edwards SAPIEN XT
Transcatheter Heart Valve*

4. Why is this trial significant for the future of treating patients with symptomatic critical aortic stenosis?

The results of both Cohort A and B arms of the PARTNER I trial were recently published in the New England Journal of Medicine (June 9, 2011). One-year results of PARTNER I Cohort A demonstrated that in selective high-risk operable patients, TAVR was non-inferior to traditional AVR in terms of all-cause mortality. In addition, TAVR was associated with significantly lower incidences of both major bleeding and new-onset atrial fibrillation, but statistically higher incidences of major stroke/TIA and vascular complications when compared to traditional AVR. One-year results of PARTNER I Cohort B demonstrated that in non-operable patients with critical aortic stenosis, TAVR was associated with significant reductions in both all-cause death and the composite endpoint of death or re-hospitalization, but higher incidences of vascular complications when compared to best medical therapy (including balloon aortic valvuloplasty).

5. Who are the physicians involved and who are the sponsors?

University of Washington Medical Center is the only site in Washington for the PARTNER II trial as its Cardiology and Cardiac Surgery services met the comprehensive selection criteria required for participation. Mark Reisman, M.D.

(Interventional Cardiology) and Edward Verrier, M.D. (Cardiac Surgery) are the local Co-Principal Investigators for the study. Additional local Sub-Investigators include: Gabriel Aldea, M.D. (Cardiac Surgery), Larry Dean, M.D. (Interventional Cardiology), Creighton Don, M.D. (Interventional Cardiology), Michael Kim, M.D. (Interventional Cardiology), Steve Goldberg, M.D. (Interventional Cardiology), Nahush Mokadam, M.D. (Cardiac Surgery) and Jack Sun (Cardiac Surgery). Rebecca Letterer, R.N. and Angela Hein, N.D. are the local research coordinators. The trial is sponsored by Edwards Lifesciences, LLC (Irvine, CA). The national Co-Principal Investigators are Martin Leon, M.D. and Craig Smith, M.D., both from Columbia University Medical Center.

6. What are the inclusion criteria for patients to be considered for trial enrollment?

The major inclusion criteria for enrollment into the PARTNER II trial are:

1. Patient has senile degenerative aortic valve stenosis with the following echocardiographic criteria: initial aortic valve area (AVA) of ≤ 0.8 cm² **or** indexed EOA < 0.5 cm²/m² **and** either a mean gradient > 40 mmHg **or** jet velocity greater than 4.0 m/s.
2. For the Cohort B population-A study-related interventional cardiologist and two cardiovascular surgeons agree that medical factors preclude operation, based on a conclusion that the probability of death or serious irreversible morbidity exceeds 50%.
3. For the Cohort A population an STS score of ≥ 4 .
4. Patient is symptomatic from his/her aortic valve disease, as demonstrated by NYHA Functional Class II or greater.
5. The study patient agrees to comply with all required post-procedure follow-up visits including annual visits through 5 years.

As with all studies performed by UWMC providers, we are committed to the highest quality of care to your patient with the patient's best interests in mind. In keeping with this commitment, potentially positive and negative aspects of participation in this study will be discussed with patients in detail before asking if they wish to participate in this study.

7. What are the major exclusion criteria?

Candidates will be excluded from the study if **any** of the following conditions are present:

1. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified or a previous valve in any position.
2. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (i.e. PCI). Implantation of a permanent pacemaker is not excluded.
3. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of screening evaluation.
4. Severe ventricular dysfunction with LVEF $< 20\%$.
5. Renal insufficiency (creatinine > 3.0 mg/dL) and/or end-stage renal disease requiring chronic dialysis at the time of screening.
6. Estimated life expectancy < 24 months due to non-cardiac co-morbid conditions.

(Note: the complete list of exclusion criteria is available at the website listed at the end of this document.)

8. If I refer my patient for evaluation for the trial will his or her prior tests/diagnostics be used for consideration or will new tests need to be conducted? Will those have to be conducted at UWMC?

Echocardiograms, carotid duplex, pulmonary function tests, and cardiac catheterizations performed at your facility can all be used for review of patient eligibility and may not need to be repeated. If coronary angiography reveals one or more hemodynamically significant stenoses, patients may require percutaneous coronary intervention (PCI), which can be performed either at your local medical center or at UWMC prior to study enrollment. Certain new tests, including CTA of the chest and iliofemoral vessels should be performed at UWMC. In addition, patients who are found upon initial screening to meet criteria for study inclusion will undergo a repeat study-mandated echocardiogram at UWMC.

9. How long does it usually take for a patient to be evaluated and considered for enrollment in the trial?

In order to determine eligibility to enroll into the PARTNER II trial, patients must be evaluated by two local site investigators (one interventional cardiologist and one cardiac surgeon) and undergo additional screening tests (study-mandated echocardiogram and/or transesophageal echocardiogram, CTA,). Once local investigators determine eligibility for enrollment, the case is presented to the PARTNER II trial executive committee for final approval. If final approval is achieved, the wait time to TAVR ranges from two to four weeks (on average).

10. How will I be notified if my patient is accepted or not for enrollment, and if my patient is accepted how will I stay informed of his or her status?

If you refer a patient for the trial we will call and/or send you a letter after your patient is evaluated and to inform you of your patient's enrollment status. We will send you copies of our clinical evaluation, and a letter about your patient's enrollment, screen failure, or choice to decline participation. In addition, we will discuss final enrollment status with the patient directly. If your patient is found to be ineligible for the trial, we will contact you to both discuss possible alternative therapies (i.e., balloon aortic valvuloplasty) as well as clarify details of long-term patient follow-up.

11. If my patient is enrolled in the trial, what role will I have in ongoing care and management of that patient?

We are required to have a regimen of follow-up care for patients enrolled in the study, but we also want to ensure our referring providers that we will return their patients to their care to whatever extent they wish.

12. How is payment for patient tests, visits and procedures handled?

There are no stipends or other forms of financial assistance associated with this trial. Billing for medical visits, procedures, tests and other associated care will follow our standard procedures. The study has been approved by CMS.

13. What are the endpoints of the study?

The primary safety and effectiveness endpoint is a non-hierarchical composite of death, major stroke, and for Cohort B re-hospitalization for symptoms of AS and/or complications of the valve procedure. The major secondary procedure-related complication endpoint is a non-hierarchical composite of adverse events both acute and long term and includes major vascular complications, and major bleeding.

14. Who do I contact for more information or to refer my patient for evaluation for the trial?

Rebecca Letterer, R.N.

PARTNER II Trial Coordinator

Phone: 206-543-6850

Email: rebeccal@cardiology.washington.edu

Mark Reisman, M.D.

PARTNER II Co-Principal Investigator

Phone: 206-861-8550

Email: mark.reisman@swedish.org

Edward Verrier, M.D.

PARTNER II Co-Principal Investigator

Phone: 206-598-3636

Email: edver@uw.edu

Gabriel Aldea, M.D.

PARTNER II Sub-Investigator

Phone: 206-598-3636

Email: aldea@uw.edu

Larry Dean, M.D.

PARTNER II Sub-Investigator

Phone: 206-598-5762

Email: lsdean@uw.edu

For more information please go to: <http://clinicaltrials.gov/ct2/show/NCT01314313?term=PARTNER+II&rank=1>