TAVR and CAD: Rationale and Design of the COMPLETE TAVR Trial

NYTV Virtual Dec 10th, 2020

David Wood MD
Janar Sathananthan MBChB, MPH
Centre for Cardiovascular Innovation– Centre d'Innovation Cardiovasculaire
Vancouver, BC, Canada

CCI-CIC

Centre for Cardiovascular Innovation

Centre d'Innovation Cardiovasculaire

Disclosures

- Dr. Wood is a consultant to Edwards Lifesciences, Medtronic and Abbott and has received unrestricted grant support funding from Edwards Lifesciences and Abbott.

- Dr. Sathananthan is a consultant to Edwards Lifesciences and Medtronic

COMPLETE TAVR

David Wood MD (PI)

John Webb MD (Co-PI)

ClinicalTrials.gov Identifier: NCT04634240

CCI-CIC.org

Centre for Cardiovascular Innovation

COMPLETE TAVR

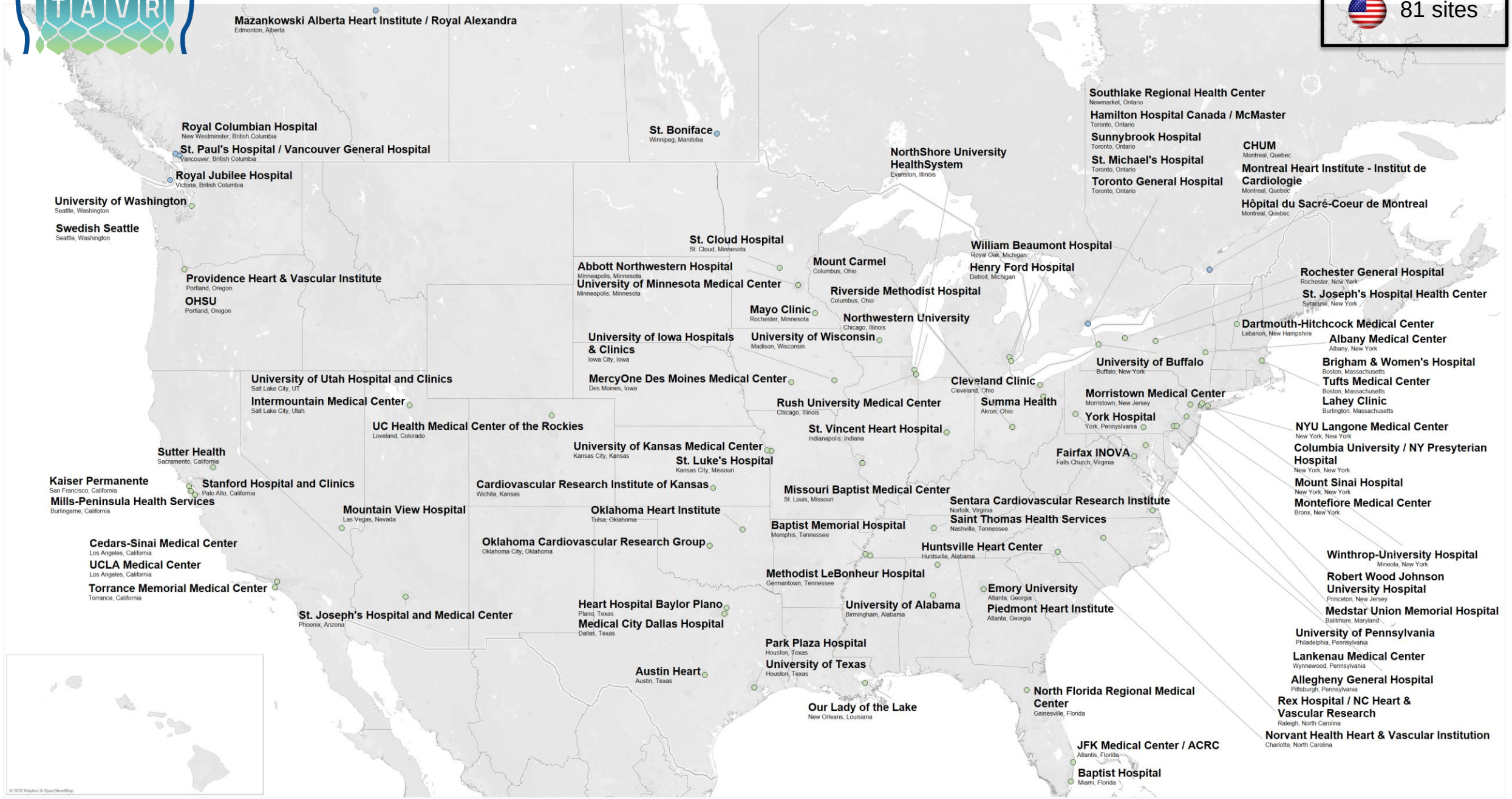
Steering Committee

- David A Wood MD (PI)
- John G Webb MD (Co-PI)
- John A Cairns MD (SCC)
- Martin B Leon MD
- Janar Sathananthan MBChB
- Shamir Mehta MD
- Roxana Mehran MD
- Dave Cohen MD
- G B John Mancini MD
- Tej Sheth MD
- Raj Makkar MD
- Vinod Thourani MD
- Michael Mack MD
- Mark Russo MD
- Sandra Lauck PhD
- Jonathon Leipsic MD
- Susheel Kodali MD
- Philippe Genereux MD
- Rob Welsh MD
- Anita Asgar MD
- Azeem Latib MD

COMPLETE TAVR Clinical Sites

13 sites

81 sites



Study Objective

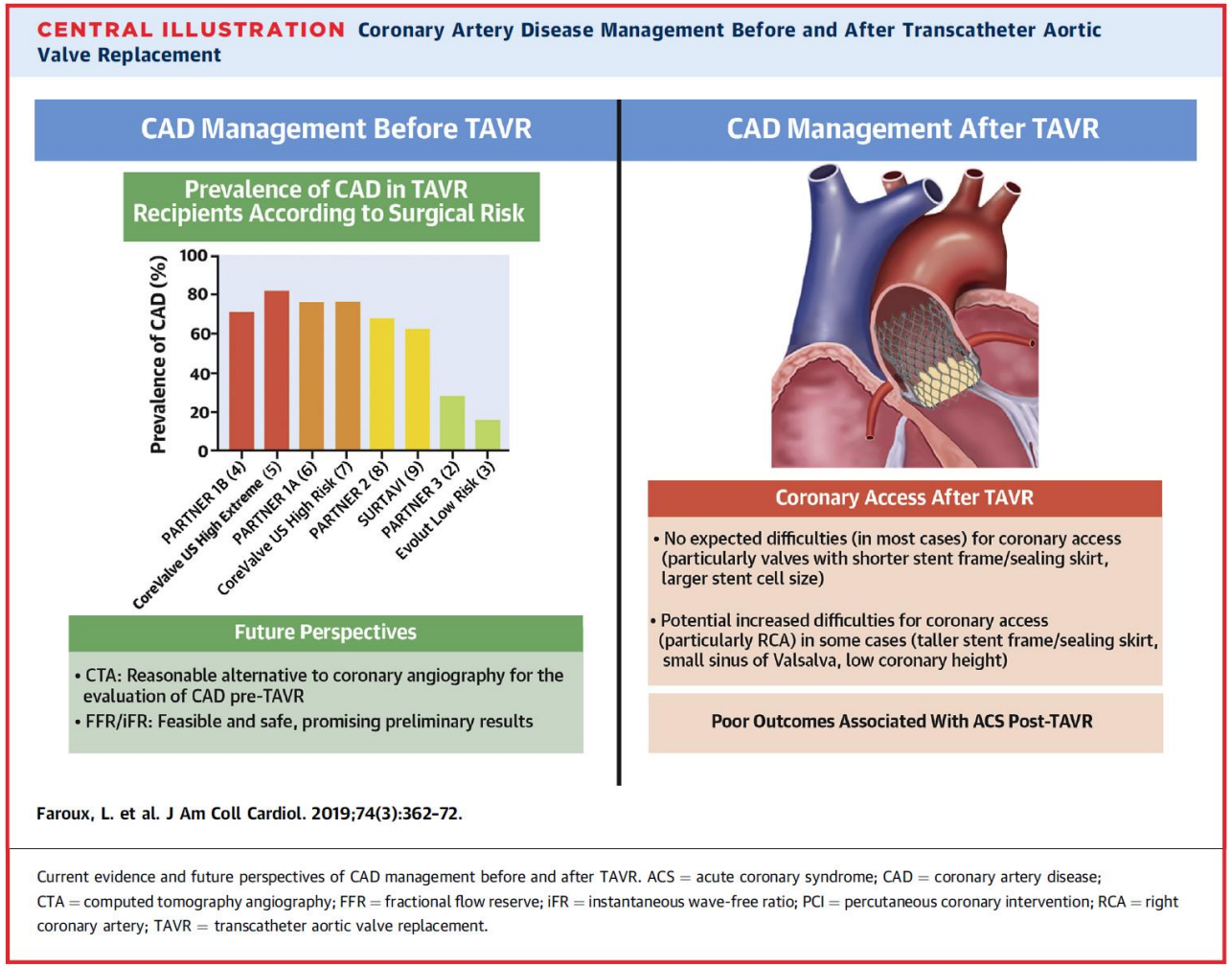
- Among patients who have undergone **successful elective transfemoral TAVR** with a balloon expandable transcatheter heart valve (Edwards Lifesciences, Irvine, CA) who are receiving guideline-directed medical therapy, is a strategy of **complete revascularization involving staged PCI** using drug eluting stents to treat all suitable coronary artery lesions (>70% visual angiographic stenosis in a vessel of at least 2.5 mm diameter) superior to a strategy of guideline-directed **medical therapy alone** in reducing the composite outcome of cardiovascular death, new myocardial infarction, ischemia driven revascularization, or hospitalization?

CCI Centre for Cardiovascular Innovation

COMPLETE TAVR

Background

- 50% concomitant CAD in “all-comers” TAVR population (15 - 81%)
- No Core Lab data
- 10% ACS post TAVR in > 700 patients after median follow-up of 2 years[1] (poor outcomes)
- Level of Evidence C for SAVR + CABG (ACC/AHA/ESC)
- Benefit and Optimal Timing of PCI unknown
- Challenges with coronary access post TAVR
- “Large appropriately powered RCT is needed”



1. Vilalta et al. JACC CVI. 2018

CCI Centre for Cardiovascular Innovation

COMPLETE TAVR

Faroux et al. JACC. July 2019

Meta-Analysis > Circ Cardiovasc Interv. 2018 Mar;11(3):e006000.
doi: 10.1161/CIRCINTERVENTIONS.117.006000.

Impact of Coronary Artery Revascularization Completeness on Outcomes of Patients With Coronary Artery Disease Undergoing Transcatheter Aortic Valve Replacement: A Meta-Analysis of Studies Using the Residual SYNTAX Score (Synergy Between PCI With Taxus and Cardiac Surgery)

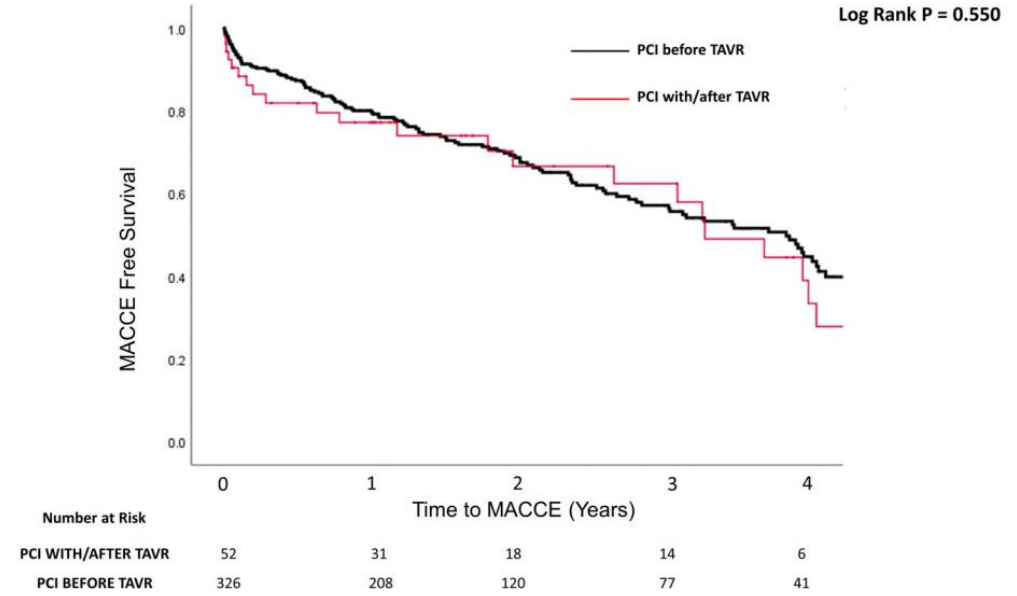
WHAT IS KNOWN

- Current data suggest that patients with severe coronary artery disease (as defined by the SYNTAX score [Synergy Between PCI With Taxus and Cardiac Surgery]) are at increased risk for mortality post–transcatheter aortic valve replacement.

CCI Centre for Cardiovascular Innovation

COMPLETE TAVR

FIGURE 5 MACCE-free survival rate between patients (n = 380) who received PCI before TAVR and PCI with/after TAVR (log rank p = .550). MACCE, major adverse cardiac and cerebrovascular events; PCI, percutaneous coronary interventions; TAVR, transcatheter aortic valve replacement [Color figure can be viewed at wileyonlinelibrary.com]



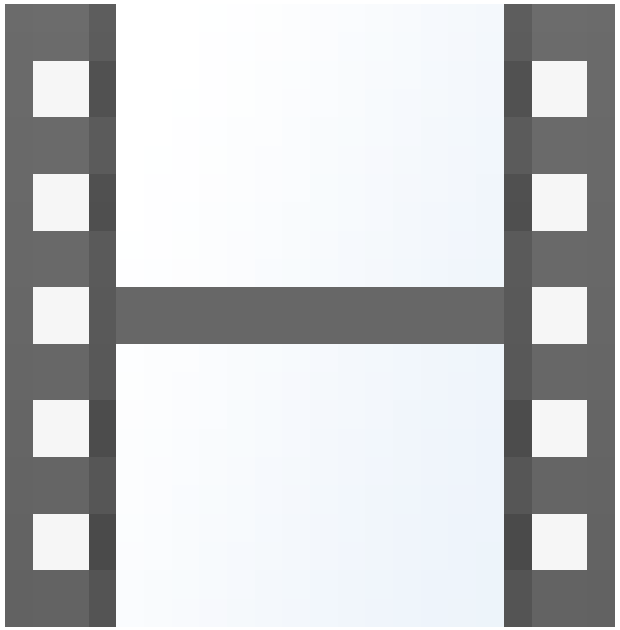
Received: 29 July 2020 | Accepted: 2 August 2020
DOI: 10.1002/ccd.29233

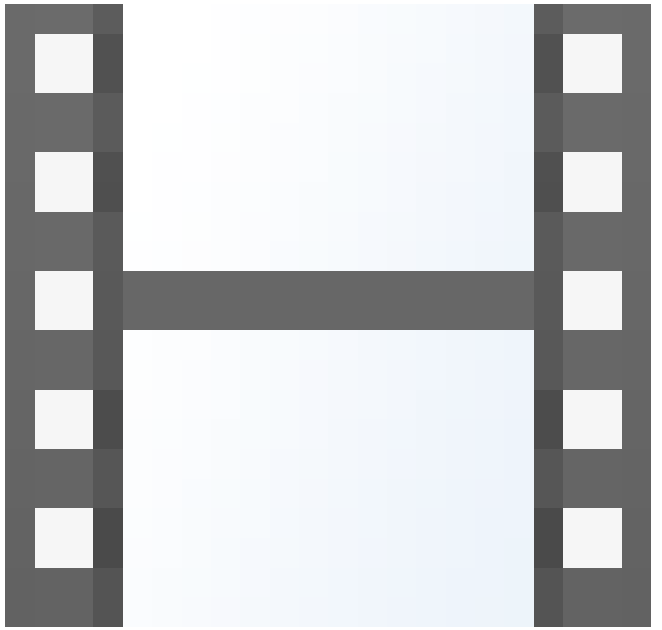
Conclusion: Among patients who underwent both PCI and TAVR, history of CABG, higher BMI, and statin therapy had lower, while those discharged on warfarin, had higher adverse event rates. Adverse events rates were similar regardless of timing of PCI.

CCI Centre for Cardiovascular Innovation

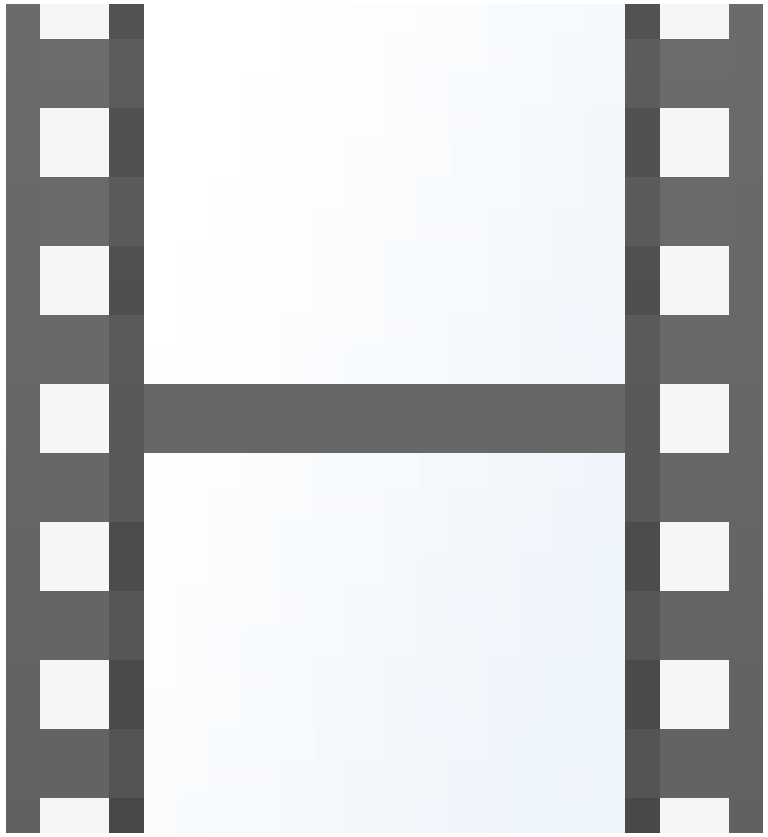
COMPLETE TAVR

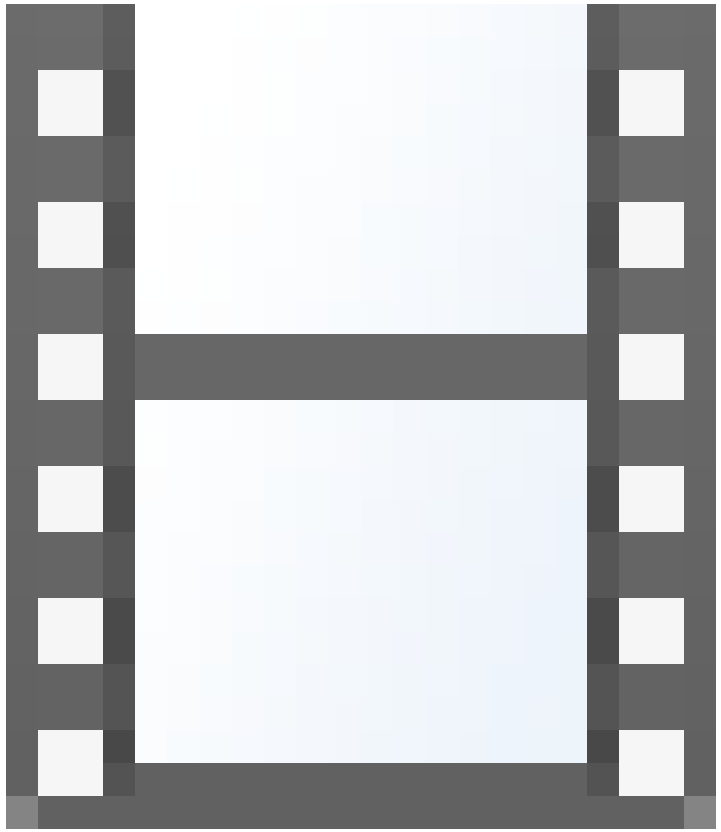
Patient A





Patient B



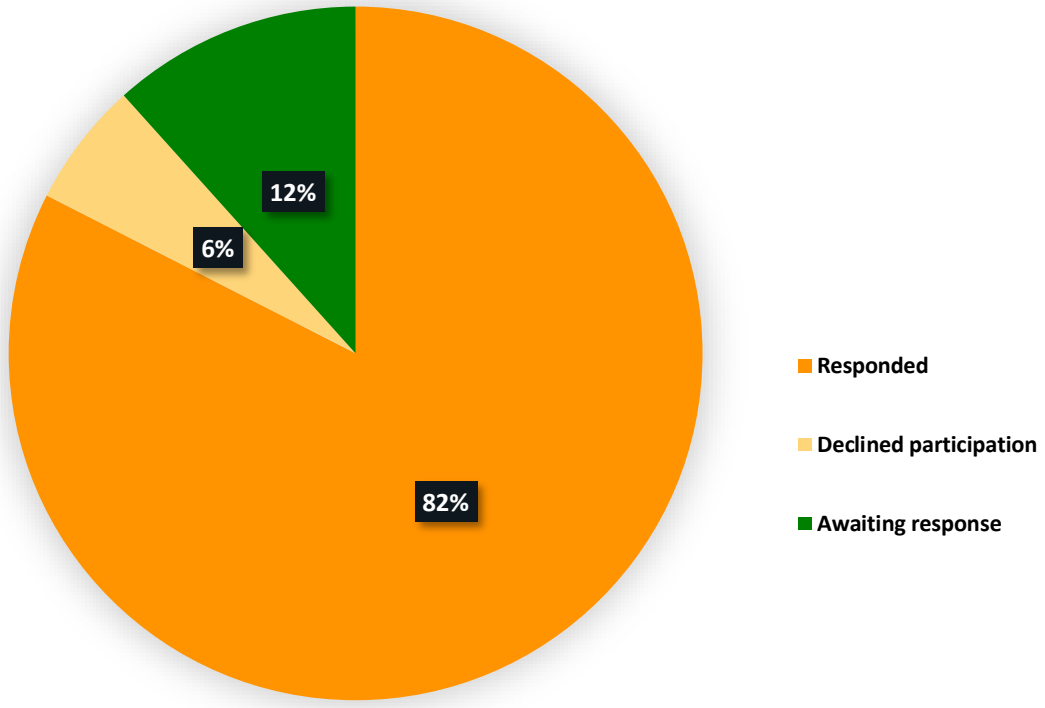


Site Feasibility Questionnaire Results

Centre for Cardiovascular Innovation

COMPLETE TAVR

SITE FEASIBILITY SURVEY RESULTS (18 days post Invitation)

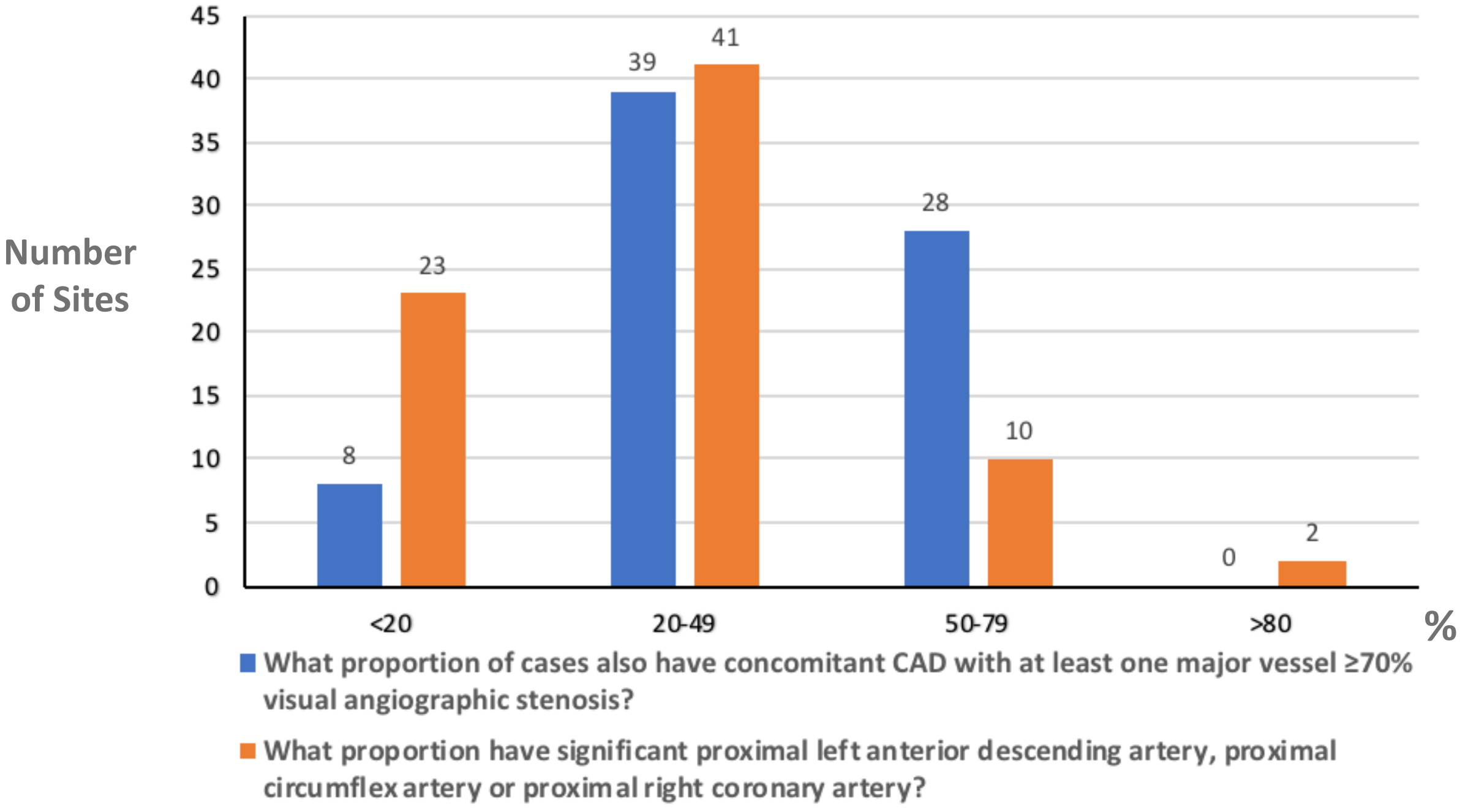


Question	Yes	No
Clinical equipoise?	74	4
Willing to randomize?	78	0
Influence clinical guidelines?	78	0

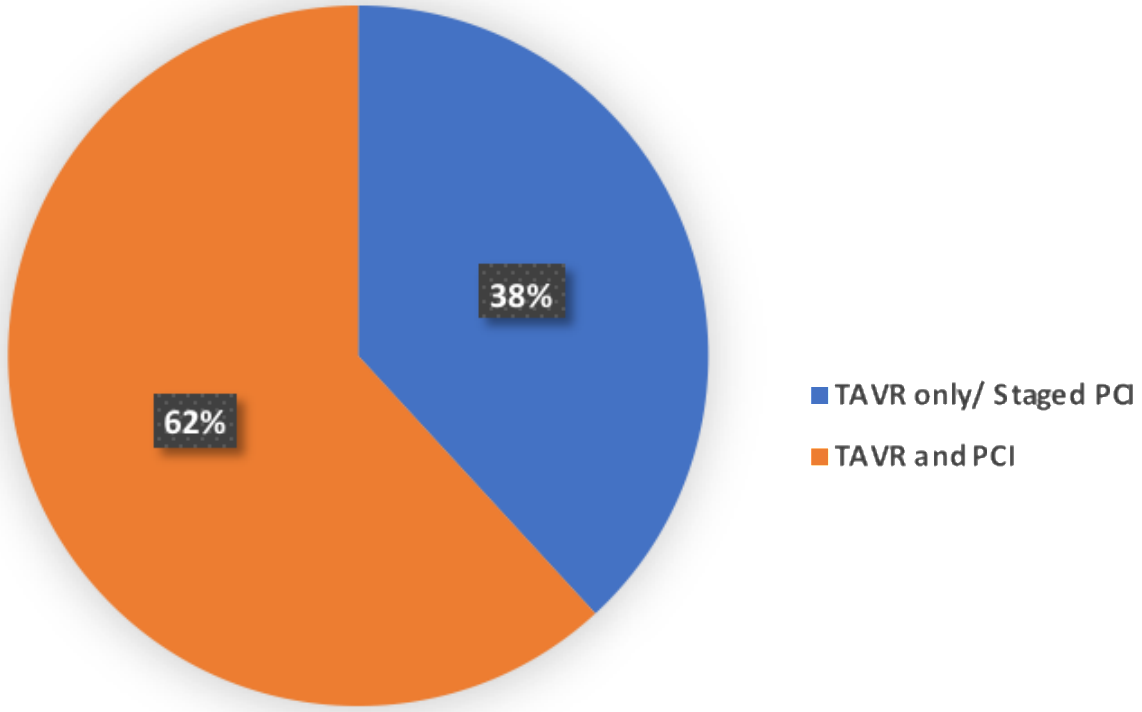
78 sites have already completed their Questionnaire

78 out of 103 sites have already agreed to participate

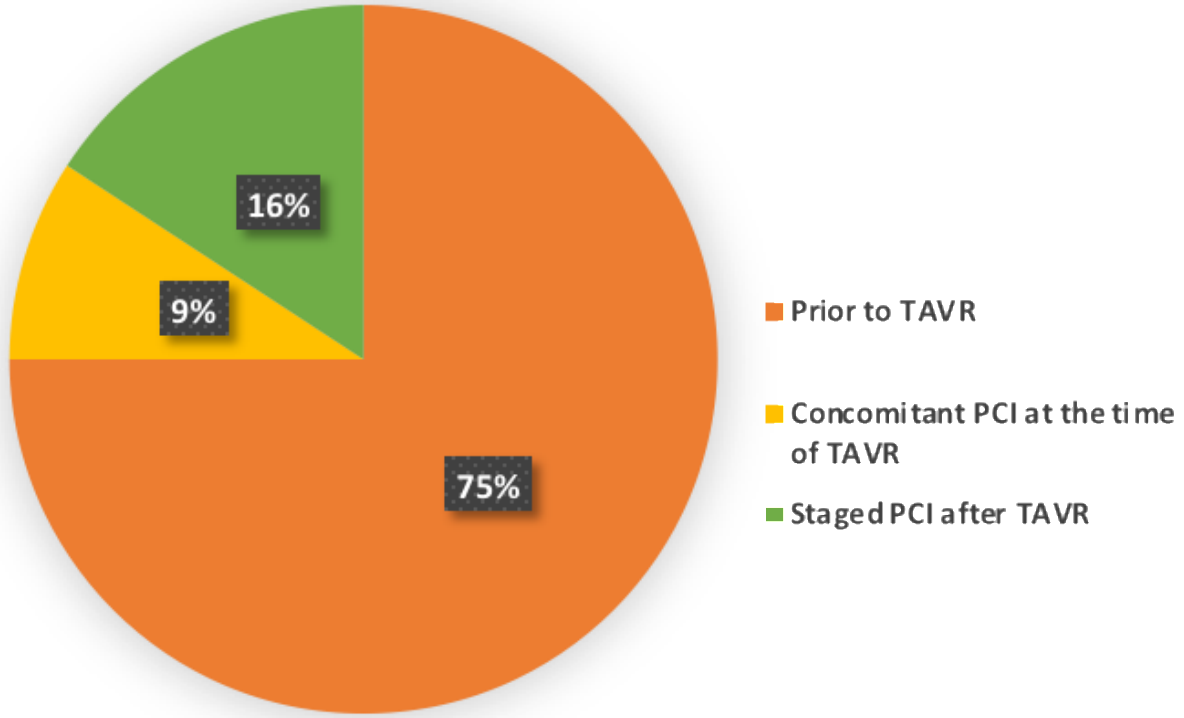
All 78 sites believe COMPLETE TAVR will influence global clinical guidelines. **All** 78 sites will randomize patients to Staged PCI vs Medical Therapy 1 – 45 days post successful TF TAVR


Number of Sites
45
40
35
30
25
20
15
10
5
0
8
23
39
41
28
10
0
2
<20
20-49
50-79
>80
%
What proportion of cases also have concomitant CAD with at least one major vessel ≥70% visual angiographic stenosis?
What proportion have significant proximal left anterior descending artery, proximal circumflex artery or proximal right coronary artery?

In your TAVR patients with concomitant coronary artery disease…preferred approach at your centre in 2019?



If a strategy of PCI is chosen to treat concomitant coronary artery disease, when is the PCI performed?



Currently 60% vs 40% at most North American Sites!

SYMPTOMATIC AS PATIENTS with at least 1 coronary artery lesion in a vessel that is **> 2.5 mm** in diameter with a **≥ 70%** visual angiographic* stenosis AND Heart Team Consensus they are suitable for transfemoral TAVR and would receive a bypass if they were undergoing elective SAVR

*CT and Angiographic Core Labs

SUCCESSFUL TF TAVR WITH A BALLOON EXPANDABLE THV

Exclusion Criteria: Intent to revascularize (PCI or CABG) or prior CABG or PCI within 90 days

COMPLETE TAVR

RANDOMIZATION within 24 hours
and Stratified for Intended Timing of PCI and Requirement for OAC:

COMPLETE REVASCULARIZATION	**MEDICAL THERAPY**
Guideline-directed medical therapy Staged PCI of all lesions (1 – 45 days post TAVR) Goal of complete revascularization in all qualifying lesions N=2000	Guideline-directed medical therapy alone No revascularization N=2000
Antithrombotic Therapy	
ASA 81 mg + Clopidogrel 75 mg for 6 months, then ASA alone lifelong	ASA 81 mg lifelong
If Requirement for OAC (usually AF)	
Rivaroxaban 15 mg + clopidogrel 75 mg for 6 months, then Rivaroxaban 20 mg alone lifelong	Rivaroxaban 20 mg lifelong

MEDIAN FOLLOW-UP: 3.5 YEARS

PRIMARY OUTCOME: Composite of CV Death, New MI, Ischemia-Driven Revascularization, or Hospitalization for Unstable Angina or Heart Failure

SECONDARY OUTCOMES: Each component of the primary outcome taken separately, Angina Status, All-cause Mortality, Stroke, Cost-effectiveness, QOL, Bleeding, Contrast Associated Acute Kidney Injury, and Fluoroscopic Time/Contrast Utilization for Staged PCI if randomized to Complete Revascularization

Inclusion

- Men and women with severe **symptomatic aortic valve stenosis** defined as: AVA ≤ 1.0 cm2 or AVA index ≤ 0.6 cm2/m2 AND Jet velocity ≥ 4.0 m/s or mean gradient ≥ 40 mmHg AND NYHA Functional Class ≥ 2 OR Abnormal exercise test with severe SOB, abnormal BP response, or arrhythmia AND
- **Coronary artery disease** defined as at least 1 coronary artery lesion in a vessel that is > 2.5 mm in diameter and that is amenable to treatment with PCI and has at least a 70% visual angiographic diameter stenosis AND
- Consensus by the Multidisciplinary Heart Team that the patient is suitable for elective transfemoral TAVR with a balloon expandable transcatheter heart valve AND would receive a bypass with an anastomosis distal to the coronary artery lesion(s) if they were undergoing SAVR

Exclusion

- PCI already performed within 60 days or during elective transfemoral TAVR
- Planned revascularization of coronary artery lesion(s)
- Planned surgical revascularization
- Non-cardiovascular co-morbidity reducing life expectancy to < 5 years
- Any factor precluding 5-year follow-up
- Prior Coronary Artery Bypass Graft Surgery

Anatomical Exclusion Criteria

1. Aortic annulus diameter < 16 mm or > 28 mm (3D imaging)
2. Severe AR (> 3+) or MR (> 3+)
3. Severe LV dysfunction (LVEF < 30%)
4. Severe calcification of aortic valvar complex (esp. LVOT)
5. Vascular anatomy not suitable for safe femoral access
6. Low coronary takeoff (high risk for obstruction)

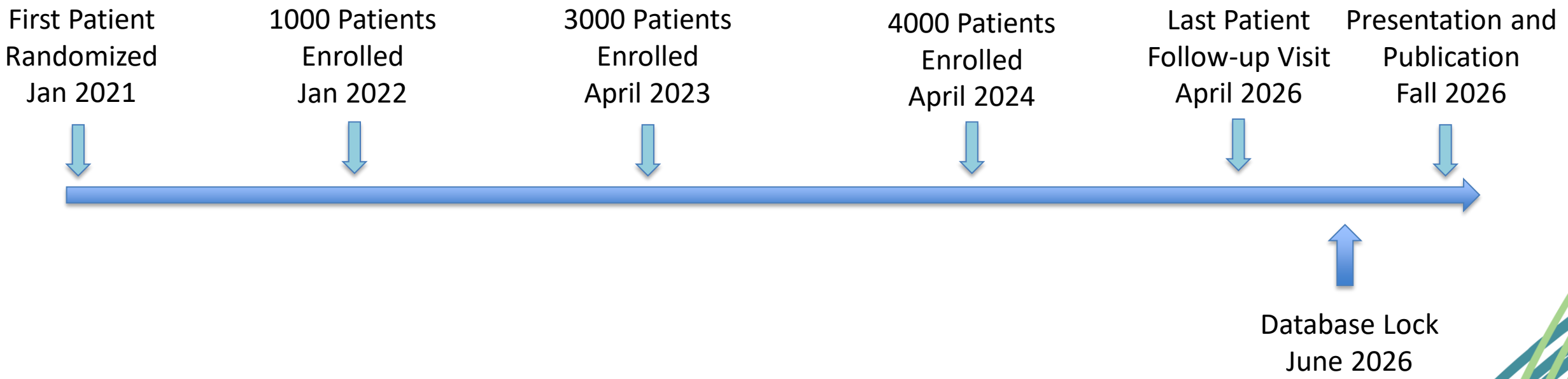
Clinical Exclusion Criteria

1. Acute MI within 1 month
2. Stroke or TIA within 90 days
3. Renal insufficiency (eGFR < 30 ml/min) and/or renal replacement Rx
4. Hemodynamic or respiratory instability
5. Frailty (objective assessment; > 2/4+ metrics)

Sample Size Calculation*

alpha:	**0.05 (two-sided)**
Power:	80%
Treatment allocation:	**1:1**
Annual control event rate:	6.2%
Treatment effect:	**Hazard ratio=0.8**
Recruitment period:	3 years (uniformly distributed)
Total follow-up time:	**5 years**
Loss to follow-up rate:	2% (by end of study)
Drop-in rate (Medical therapy alone to complete revascularization):	**2.5%**
Drop-out rate (Complete revascularization to medical therapy alone):	4%
Total sample size:	**4,000**

We will randomize 4000 patients at 103 North American sites with planned first randomization in January 2021, last patient enrolled in Spring 2024, and publication in Autumn 2026



CCI Centre for Cardiovascular Innovation

COMPLETE TAVR

Summary

1. This will be the largest TAVR study to date and will have a median follow-up of 3.5 years. In addition to the main findings, we envision more than 20 Substudies including coronary access (4000 baseline core lab CT scans and 6000 core lab angiograms), antithrombotic therapies, stenosis severity, lesion location, intracoronary imaging, CT FFR, QOL, and cost effectiveness.
2. We believe there is clinical equipoise with regard to the benefit/risk of PCI.
3. All patients enrolled in COMPLETE TAVR will be elective (no ACS) and will have symptoms (either from the AS or concomitant CAD or both).
4. We believe the trial will strongly influence global coronary, transcatheter and surgical guidelines in 2026 regardless of the outcome.

CCI Centre for Cardiovascular Innovation

COMPLETE TAVR

COMPLETE TAVR

David Wood MD (PI)

John Webb MD (Co-PI)

ClinicalTrials.gov Identifier: NCT04634240

CCI-CIC.org

Centre for Cardiovascular Innovation