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Study Design

Feasibility and Utility of Anatomical and Physiological Evaluation of Coronary Disease With Cardiac CT in Severe Aortic Stenosis (FUTURE-AS Registry): Rationale and Design

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ABSTRACT

Background: Coronary artery disease (CAD) in patients with severe aortic stenosis (AS) is common and may be associated with worse outcomes. Computed tomography coronary angiography (CTCA) and fractional flow reserve derived from computed tomography (FFR_{CT}) are tools for comprehensive coronary assessment. The utility and safety of CTCA and FFR_{CT} in the work-up for transcatheter aortic valve replacement (TAVR) is not established, especially in an evolving landscape that involves younger TAVR patients. The FUTURE-AS Registry will assess the utility and safety of cardiac-optimized CTCA and FFR_{CT} to evaluate CAD and guide referral for downstream invasive coronary angiography (ICA) in patients with severe AS being considered for TAVR.

Methods: FUTURE-AS is an international, prospective, multicenter registry of patients with severe AS referred for TAVR being assessed for CAD with CTCA and FFR_{CT}. The primary end point is the per-patient sensitivity and negative predictive value of CTCA and FFR_{CT} for identifying anatomical and physiologically significant CAD compared to ICA and invasive FFR. The safety end point is the incidence of symptomatic hypotension or bradycardia requiring intervention following the administration of nitroglycerin or β-blocker medications. Feasibility end points include the incidence of noninterpretable CTCA scans and CTCA scans not adequate for FFR analysis. Other utility end points include specificity, positive predictive value, and accuracy of CTCA and FFR_{CT}. Lastly, the potential of a CTCA and FFR_{CT} guided strategy to defer pre-TAVR ICA will be assessed.

Conclusions: FUTURE-AS will characterize the utility, safety, and feasibility of CTCA and FFR_{CT} for coronary assessment pre-TAVR.

Introduction

Minimally invasive, percutaneous transcatheter aortic valve replacement (TAVR) is a viable and increasingly utilized alternative to the traditional surgical treatment of patients with severe aortic stenosis (AS).[1-3] Coronary artery disease (CAD) is frequently observed in severe AS, with invasive coronary angiography (ICA) prior to TAVR a routine diagnostic practice.[4] Despite the uncertainty regarding the indication and prognostic value of revascularization in this cohort, an invasive procedure to identify

Abbreviations: AS, aortic stenosis; CAD, coronary artery disease; CCT, cardiac computed tomography; CT, computed tomography; CTCA, computed tomography coronary angiography; FFR, fractional flow reserve; FFR_{CT}, fractional flow reserve derived from computed tomography; ICA, invasive coronary angiography; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement.

Keywords: aortic stenosis; computed tomography coronary angiography; coronary artery disease; fractional flow reserve derived from computed tomography; transcatheter aortic valve replacement.

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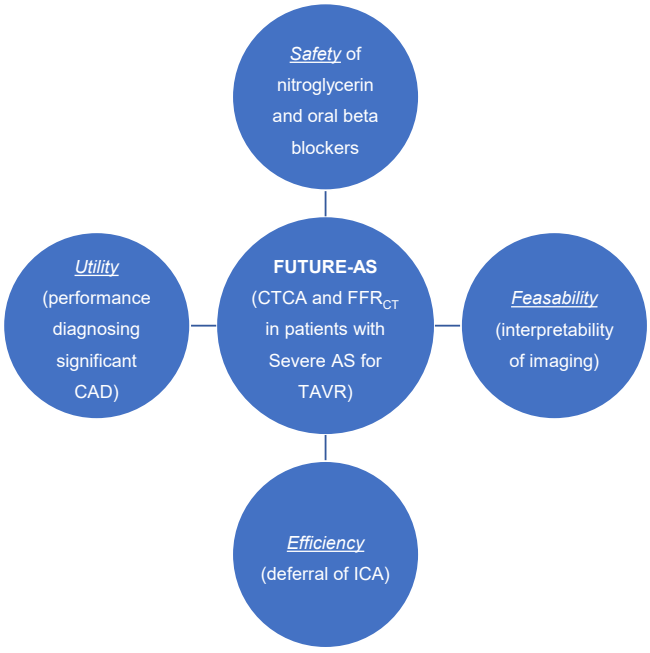
CAD remains a key aspect of the patient's journey toward TAVR.[5,6]

Cardiac computed tomography (CCT) is recognized as the gold standard tool for annular sizing, determining the risk of annular injury, and identifying the coplanar fluoroscopic angle prior to TAVR.[7] Computed tomography coronary angiography (CTCA) is increasingly utilized as a first-line noninvasive modality to identify the presence of anatomical CAD in patients with new-onset chest pain.[8] In severe AS, preliminary studies have demonstrated the feasibility of CTCA; however, its widespread adoption has been limited by reluctance to optimize image quality with nitroglycerin and β-blockers.[9] As well, although the requirements for anatomical evaluation in high-risk patients were commonly limited to the proximal coronary arteries, with a shift in the risk profile of TAVR patients, more complete CAD evaluation is needed, particularly given concerns regarding coronary reaccess in younger patients.

The use of physiology by means of fractional flow reserve (FFR) to diagnose hemodynamically significant CAD is superior to anatomical stenosis alone in identifying patients most likely to benefit from revascularization.[10,11] Although the level of evidence to support the physiological assessment of CAD in AS is less established, preliminary clinical data are promising and highlight its potential role in the risk stratification of CAD in this cohort.[12,13]

Patients with anatomically significant CAD on CTCA are often assessed with further stress testing or ICA to determine severity.[14,15] Advances in computational fluid dynamics, image processing, and artificial intelligence now permit severity assessment through the computation of noninvasive FFR from a standard CTCA.[16] There is well-established evidence supporting the diagnostic accuracy, prognostic value, and clinical utility of FFR derived from CT (FFR_{CT}) in real-world practice.[17-20] A recent study demonstrated acceptable diagnostic performance of FFR_{CT} in a cohort of patients with severe AS with a high burden of coronary calcification.[21]

The integration of CTCA optimized for anatomical and physiological assessment of CAD in a real-world setting is yet unknown. Therefore, the aim of the FUTURE-AS Registry is to assess the utility, safety, and feasibility of preprocedural CTCA with FFR_{CT} to evaluate CAD and guide referral for downstream ICA in patients with AS being considered for TAVR (Central Illustration).



Central Illustration.
The FUTURE-AS Registry will characterize the utility, safety, and feasibility of computed tomography coronary angiography (CTCA) and fractional flow reserve derived from computed tomography (FFR_{CT}) to evaluate coronary artery disease (CAD) and guide referral for invasive coronary angiography (ICA). AS, aortic stenosis; TAVR, transcatheter aortic valve replacement.

Materials and methods

Design

The FUTURE-AS Registry is an international, multicenter, prospective open-label observational registry of patients with severe AS designed to evaluate the safety, utility, and accuracy of CTCA and FFR_{CT} in guiding referral for ICA and optimizing efficiency in the clinical work-up of patients being considered for TAVR (Figure 1).

Hypothesis

In patients with AS being considered for TAVR, CTCA is a safe, feasible, and accurate noninvasive modality to identify the presence and severity of CAD and can identify patients who can be safely deferred from ICA prior to TAVR.

Objectives

The primary objective of this registry is to assess the diagnostic performance of CTCA and FFR_{CT} for identifying anatomical and physiologically significant diseases in comparison with ICA in patients with severe AS being considered for TAVR. Secondary objectives include assessing the safety of sublingual nitroglycerin and oral β-blocker therapy aiming for a target heart rate of <70 beats per minute prior to CTCA acquisition. Other objectives include assessing the feasibility of pre-TAVR CTCA and FFR_{CT}, as well as the potential clinical utility of a CTCA and FFR_{CT} guided strategy to defer pre-TAVR ICA.

Registry end points

The primary end point of the FUTURE-AS Registry is the per-patient sensitivity and negative predictive value of CTCA for identifying anatomical and physiologically significant CAD compared to ICA and invasive FFR.

Secondary end points include:

Safety. Incidence of symptomatic hypotension or bradycardia requiring intervention following administration of nitroglycerin or β-blocker medications.

Feasibility.

1. Incidence of noninterpretable CTCA scans due to heavy coronary calcification and/or inadequate image quality.
2. Incidence of CTCA scans not feasible for FFR analysis.

Utility.

1. Per-patient specificity and positive predictive value of CTCA and FFR_{CT} for identifying anatomical and physiologically significant disease compared with ICA and invasive FFR.
2. Per-vessel diagnostic performance of CTCA and FFR_{CT}.
3. Efficiency, defined as the potential of a CTCA and FFR_{CT} guided strategy to defer pre-TAVR ICA.

Setting

This international study involves centers from Canada, Australia, the United States, and the United Kingdom. The geographies

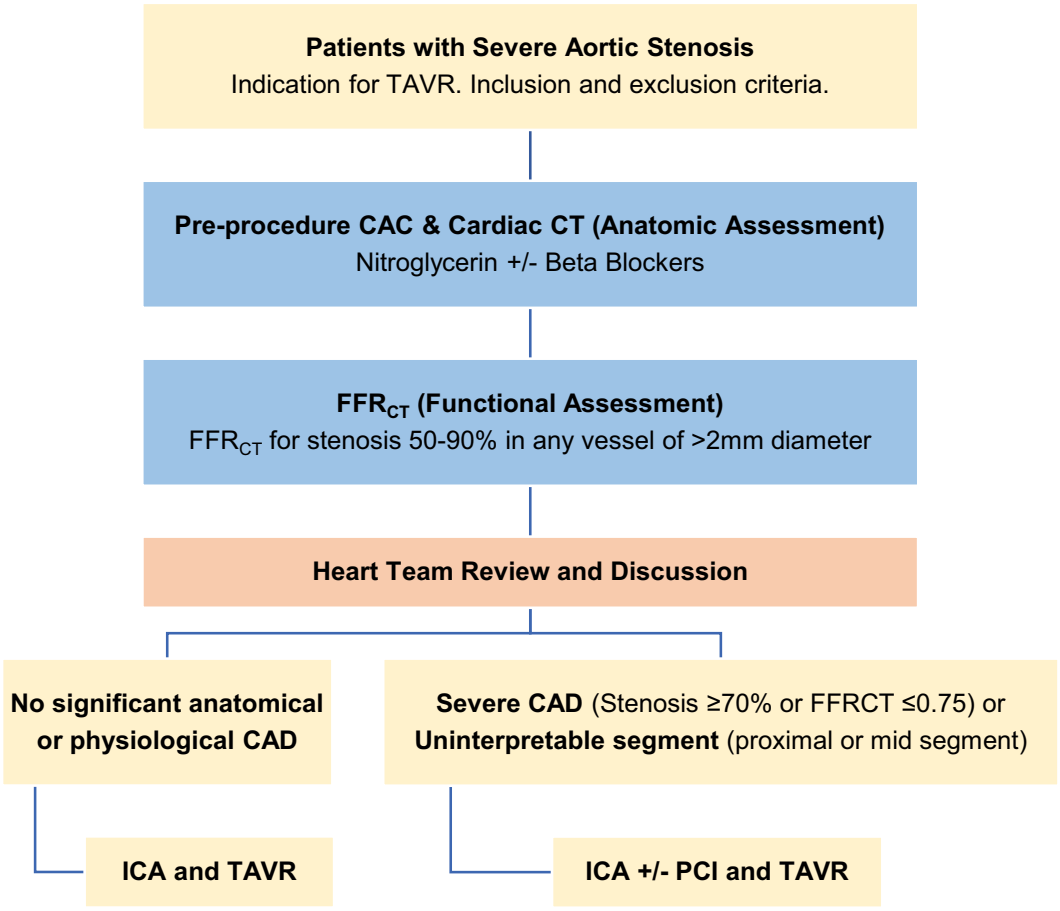


Figure 1.
Study flow diagram. Recruitment of severe aortic stenosis (AS) patients being considered for transcatheter aortic valve replacement (TAVR) to evaluate the utility of computed tomography coronary angiography (CTCA) and fractional flow reserve derived from computed tomography (FFR_{CT}) in the pre-TAVR clinical work-up. CAC, coronary artery calcium score; CAD, coronary artery disease; CT, computed tomography; ICA, invasive coronary angiography; PCI, percutaneous coronary intervention.

include socially diverse populations. Potential participants will be identified from referrals to each institution's structural heart disease service. Participants will be screened at the point of care for the TAVR planning CT and invited to give informed consent. This enrollment is done before the CT is performed, mitigating the possibility of bias related to the CT findings. Any patients who do not proceed to TAVR as per the institutional heart team decision or end up having surgical aortic valve replacement will still be included in the registry for analysis.

Eligibility criteria

Stable patients with severe AS being considered for TAVR will be eligible for enrollment in the FUTURE-AS Registry. Exclusion criteria for the study are related to mitigating the potential risk of decompensation from optimizing CTCA with nitroglycerin and β-blockers. These include:

1. Severe left ventricular dysfunction with ejection fraction <30%.
2. Critical AS (aortic valve area <0.6 cm^2, indexed aortic valve area <0.4 cm^2/m^2, peak velocity >5 m/s, mean pressure gradient >60 mm Hg, or dimensionless index <0.20)
3. Decompensated heart failure symptoms.
4. Syncope within the past 90 days.
5. Moderate or greater chronic renal impairment (estimated glomerular filtration rate ≤30 mL/min/1.73 m^2).
6. History of coronary revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting.
7. Inability to provide written informed consent.

CT acquisition and analysis

Imaging will be performed using third-generation or more recent scanners as per the recommendations of the Society of Cardiovascular Computed Tomography.[7] CTCA will be acquired in the same setting as the routine electrocardiogram-gated, multiphasic, contrast-enhanced chest, abdomen, pelvis CT used for planning TAVR procedures. CTCA acquired in isolation will be permitted if performed prior to preoperative ICA and/or TAVR. Patients will receive sublingual nitroglycerin (0.4-0.8 mg) and additional β-blockers (or any other medication for rate control) aiming for a prescan heart rate of <70 beats/min in accordance with Society of Cardiovascular Computed Tomography guidelines.[22] Blood pressure will be recorded pre and post medications and any adverse events will be recorded (Supplemental Figure S1). CTCA acquisition parameters are at the discretion of participating sites. Prospective electrocardiogram-gated acquisition will be encouraged to minimize radiation dose. Contrast bolus delivery is as per local acquisition protocols. Noncontrast images will be included to facilitate coronary artery calcium scoring.

CTCA analysis will be conducted by experienced local readers blinded to ICA results. Image quality will be assessed according to a 5-

point Likert scale. Uninterpretable image quality is a subjective determination that the vessel lumen cannot be identified due to motion artifact, noise, beam-hardening, or poor contrast opacification. Luminal stenosis assessment will be performed in all coronary segments ≥2.0 mm, using the 18-segment coronary model.[23] Stenosis grading is in accordance with the CAD-RADS (Coronary Artery Disease – Reporting and Data System) guideline.[24] Anatomically significant disease includes left main stenosis ≥50% or stenosis ≥70% in other vessels >2 mm in diameter.

FFR_{CT} analysis

CTCA images will be submitted to an independent core laboratory (HeartFlow) for computation of FFR_{CT}. The decision to further investigate CTCA results with FFR_{CT} will be directed by local physicians interpreting the scan, with a recommendation to consider FFR_{CT} for stenoses in the 50% to 90% range in vessels >2 mm in diameter. Given the threshold for revascularization is typically higher in patients considered for TAVR,[25] a positive FFR_{CT} will be defined as ≤0.75. Patients in whom FFR_{CT} analysis is unachievable due to image quality will still be included.

ICA implementation

For each patient, the institutional heart team will review the clinical history, CTCA, and FFR_{CT} prior to recommending a management strategy. In patients with significant anatomical or physiological CAD, pre-TAVR ICA should be considered. Similarly, in patients with uninterpretable proximal or midvessel segments >2 mm in diameter, pre-TAVR ICA should be considered.

In patients without anatomically (<70% stenosis) or physiologically (FFR_{CT} > 0.75) significant CAD, consideration will be given to defer the pre-TAVR ICA (Supplemental Figures S2 and S3) and instead perform ICA at the time of the TAVR procedure. In patients without significant CAD on CT but with significant CAD on ICA, it will be at the discretion of the treating physician regarding whether to proceed with TAVR or to revascularize the CAD first. Final management decisions are at the discretion of local physicians.

Sample size calculation and statistical analysis

Among patients with severe AS, the prevalence of severe CAD is approximately 40% and the sensitivity of CTCA (using >64 slice CT scanners) ranges between 92% and 98%.[4] Assuming these estimations to be true, a total sample size of 318 (127 with severe CAD and 191 without severe CAD) achieves 90% power to detect that sensitivity is greater than 96% using a 1-sided binomial test with one-sided alpha of 0.025.

Comparison between groups will involve ANOVA for continuous variables and a χ^2 test for categorical variables. The per-patient and per-vessel diagnostic accuracy of CTCA and FFR_{CT} compared with ICA and FFR for identifying significant disease will include sensitivity, negative predictive value, specificity, and positive predictive value. A receiver operating characteristic curve will be drawn and the area under the curve will be used to assess performance. The efficiency of CTCA ± FFR_{CT} to defer pre-TAVR ICA will be assessed as the diagnostic agreement between CTCA and ICA in patients without significant CAD (<70% stenosis and >0.75 FFR_{CT}).

Discussion

Our study will provide information on the diagnostic performance and safety of CTCA and FFR_{CT} optimized with nitroglycerin and β-blockers in a population of patients with severe AS. This registry includes centers from 4 countries, thus broadening the generalizability of our findings. The registry is designed to provide real-world evidence that will inform clinical practice in the evolving field of TAVR.

CTCA from the pre-TAVR screening CT has been used increasingly over the recent years to provide coronary clearance prior to TAVR. This has been largely limited to the evaluation of the proximal coronary segments owing to limitations of image quality due to the lack of nitroglycerin and the absence of complementary noninvasive functional assessment.[4,9] As a result, many institutions rely on a confirmatory ICA prior to TAVR. This "invasive-first" approach is limited by cost and attendant risks, drawbacks which in a subset of patients are avoidable.[26,27] The high negative predictive value of CTCA can identify patients with definite mild or no coronary disease, avoiding ICA, reducing cost, mitigating risk, and expediting the TAVR work-up.[27,28] FFR_{CT} offers a functional assessment and identification of flow-limiting CAD, which increases the sensitivity and specificity of CT and may assist with ICA planning.[21,29]

Although consensus on the management of CAD prior to TAVR remains unclear, the presence of significant CAD may portend worse outcomes.[30] In a Danish registry, the leading cause of death up to a maximum of 9 years post-TAVR was CAD, responsible for 35.8% of mortalities compared with 26.8% in a matched control population.[31] At 2 years post-TAVR, the incidence of acute coronary syndrome has been reported at 10%.[32] Post-TAVR patients admitted with STEMI or NSTEMI have demonstrated high mortality at 30 days (31.4% vs 15.5%) and 1 year (51.2% vs 41.3%).[33] With increasingly younger patients being treated with TAVR, there is a greater lifetime exposure to developing CAD and acute coronary syndrome, making CTCA a readily available and accurate tool to assess both stenosis severity and underlying plaque composition.[26,34]

The management of obstructive CAD in TAVR remains a challenge.[30] In a single-center observational study, patients with obstructive CAD who were not revascularized compared with those revascularized before TAVR, showed no difference in long-term survival.[35] In the ACTIVATION trial, a randomized trial of patients with significant CAD in TAVR, the strategy of PCI pre-TAVI was compared to no PCI.[36] There was no difference in 1-year mortality or rehospitalization; however, bleeding events were significantly higher with PCI.[36] Bleeding was the focus of a recent international study of patients with significant CAD receiving PCI pre-TAVI.[37] Late bleeding events occurred with an incidence of 7.9% and were an independent predictor of mortality at 4 years.[37] Furthermore, there remains uncertainty regarding the approach to revascularization in terms of timing and completeness.[26]

There is growing awareness that a more complete assessment of CAD prior to TAVR may be warranted.[26] To this end, CTCA and FFR_{CT} offer valuable noninvasive data to inform risk stratification, revascularization decision-making, and PCI planning.[27,30] Physiology guidance has been shown to downgrade the number of diseased coronary vessels in patients with AS.[26] By association, FFR_{CT} may help reduce unnecessary PCI and avoid bleeding events resulting from antithrombotic therapy. Further, a deferral of invasive procedures may lead to lower iatrogenic complications and a reduction in cost.

Historically, there has been hesitancy by clinicians to use nitroglycerin and oral β-blockers to optimize image quality in advance of CTCA.[21] This has limited the use and evaluation of CTCA and FFR_{CT} in the coronary assessment of patients with severe AS.[21] Excluding patients with critical AS and severely reduced left ventricular systolic function may avoid the complications of decompensation and hypotension and this will be assessed in our study.

Conclusion

FUTURE-AS will provide important real-world data on the safety and utility of a CTCA and FFR_{CT} guided strategy to accurately characterize

CAD both anatomically and physiologically in severe AS patients and potentially facilitate safe deferral of pre-TAVR ICA.

Peer review statement

Guest Editor Jonathon Leipsic had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Guest Editor Natalia Pinilla-Echeverri.

Declaration of competing interest

Stephanie Sellers received institutional grants from Edwards Lifesciences, Medtronic, and HeartFlow; consulting fees from Edwards Lifesciences, Anteris Technologies, and Medtronic; and equipment loan agreement from ViVitro Labs. Venkateshwar Polsani is on the speaker bureau for HeartFlow. Janarthanan Sathananthan is an employee of Boston Scientific. Jonathon Leipsic received grants from GE HealthCare; consulting fees and stock options from HeartFlow and Circle Cardiovascular Imaging; personal core lab services from Arineta; and speaking fees from Philips and GE HealthCare. Abdul R. Ihdayhid received consultancy fees from Abbott Medical, Boston Scientific, and Artrya (including stock options). The other authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics statement and patient consent

The study is in accordance with Good Clinical Practice, the National Statement on Ethical Conduct in Human Research (2007), and regulatory requirements. The Human Research Ethics Committee and the Research Governance Office have approved the study protocol. All patients provided informed consent prior to being enrolled in this study.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2023.101293.

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